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ORIGINAL COMMUNICATION

Tinnitus distress: a paradoxical attention to the sound?

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Abstract

Tinnitus, the perception of sound in the absence of external stimuli, is often a disturbing symptom for which the underlying functional neuroanatomy still remains poorly understood. Most studies have focused solely on functional connectivity changes in the auditory cortex of tinnitus patients. The aim of this study was to investigate whether a correlation exists between tinnitus behavioural scores and functional brain connectivity of five resting-state networks comprising the auditory, the default mode, the external control left and right, and the salience network. For this purpose, a large sample of one hundred and thirty-five subjects underwent resting-state functional magnetic resonance imaging and their behavioural scores were obtained using clinical evaluations. Networks were extracted using independent component analysis, and functional connectivity patterns in the extracted networks were evaluated by a graph theoretical approach. The effects of tinnitus for each network were investigated by correlating the graph strength of all the regions with the tinnitus behavioural scores using stepwise fit regression analysis. Results indicated that alterations of functional interactions between key neural circuits of the brain are not limited to one single network. In particular, tinnitus distress showed a strong correlation with the connectivity pattern within and between the right executive control network and the other four resting-state networks, indicating that tinnitus distress is probably the consequence of a hyperactive attention condition. Among the behavioural scores, the strongest correlation was observed between age and hearing loss, while the tinnitus objective loudness was not correlated with any behavioural scores.

Keywords Tinnitus · Resting-state networks · Graph theory · Distress · Executive control network

Introduction

Tinnitus is defined as the perception of sound in the absence of any external sound source [1]. About 25% of the adult population has experienced one or more acute tinnitus

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episodes, and about 8% reports having daily or permanent tinnitus [2]. Although some patients benefit from audiological, psychological, pharmacological, or surgical therapies, a large fraction of tinnitus patients are left untreated and waiting for a treatment that would offer permanent relief [3]. Having a good understanding of the underlying neurophysiological mechanism of tinnitus is crucial for the development of specific treatments.

It is known that peripheral lesions in the cochlea or the auditory nerve produce dysfunctional input to central auditory structures and induce changes in the auditory system [4–11]. Associated with plastic changes in central auditory structures, extra-auditory regions have been implicated in the tinnitus pathophysiology [4, 8, 12, 13]. Recently, it has been proposed that the unified percept of tinnitus could be considered as an emergent property of multiple, overlapping dynamic brain networks, each encoding a specific tinnitus characteristic [4]. Indeed, more and more researches suggest that the cortex is organized into parallel, segregated systems of networks that are specialized for processing distinct forms of information [14].

Initially, functional brain imaging methods have emphasized task-induced increases in regional brain activity associated with the execution of a wide variety of tasks. More recently, however, a great interest has been developed to the study of the functional organization of the brain at rest [15, 16]. Indeed, being at rest does not mean that the brain is silent. In fact, during rest, the observed correlation of low-frequency fluctuations of the BOLD signal between brain regions indicates ongoing information processing and ongoing functional connectivity [17]. Associations of regions with synchronous activity are commonly called resting-state networks and are formed by patches of cortex with a well-defined spatial distribution consistently recognized in healthy awake subjects. Recent comprehensive surveys have shown that resting brain dynamics can be broken down into a relatively small set of consistently found resting-state networks (RSNs) [18, 19]. Examples of RSNs are: auditory network (Aud), default mode network (DMN), executive control network left (ECNL), executive control network right (ECNR), salience network (Sal), sensorimotor network (Sen), and the three visual networks (lateral, medial, and occipital).

Regarding tinnitus, preliminary evidence using EEG [20, 21], MEG [10], and PET [22] has indicated that specific clinical characteristics are correlated to specific brain area activations. These findings have been further confirmed by an fMRI study, focusing on the auditory resting-state network demonstrating a positive correlation between the connectivity in the posterior cingulate/precuneus region and a behavioural measurement of tinnitus [23]. These results have provided some insight into the role of network interaction for the emergence of clinical tinnitus characteristics. To date, the literature lacks a study that specifically addresses the issue of whether tinnitus is an emergent property of dysfunctional interactions within and between networks and whether these dysfunctional network interactions could be related to specific clinical characteristics. If the modification of connectivity leads to the tinnitus percept, a correlation between the strength of the functional inter-regional connectivity and clinical characteristics of tinnitus (e.g. tinnitus distress) should be found. This study addresses this supposition.

The aim of the present study was to investigate the neuronal activation patterns associated with clinical tinnitus characteristics (age, distress, loudness, intensity, duration, and hearing loss). We hypothesized that tinnitus clinical characteristics would be associated with specific resting-state activity and functional connectivity patterns and that this could be tested by looking at the spontaneous brain activity of 135 tinnitus patients using resting-state fMRI. All tinnitus subjects also received an in-depth clinical evaluation.

Additionally, we wanted to see whether the pathology is related solely to the auditory network or to higher-order networks responsible for auditory perception. To investigate this, we combined an individual independent component analysis (ICA) with an automated component selection method to select nine components of interest to be used in a second-level analysis. We performed an analysis to identify the correlation between different tinnitus characteristics and the graph strengths of the functional connectivity pattern of five resting-state networks (Aud, DMN, ECNL, ECNR, and Sal) relevant to tinnitus (out of these nine different networks) [4, 23, 24, 31, 34, 35]. For each resting-state component, the statistical analysis was not restricted to regions that are part of each network of interest but to the full brain.

Methods

Participants

We prospectively assessed 135 tinnitus patients (41 women; mean age 50 years, SD= 15) (ESM_1). Audiological and clinical examinations were performed. Hearing levels were assessed using audiological testing. Pure tones ranging from 250 Hz to 12.5 kHz were presented to each ear until the threshold of detection was reached. Tinnitus patients were tested to identify the best match to the perceived frequency of their tinnitus. They were also asked to identify the best match to the perceived intensity of their tinnitus; the intensity was corrected for the hearing threshold measured for the according frequency. Self-reported severity of tinnitus impact was measured using the Tinnitus Questionnaire (TQ) [25]. We asked the tinnitus patients to score the tinnitus intensity they experienced on a numeric rating scale,

ranging from 0 (none) to 10 (loudest imaginable tinnitus). Perceived intensity of the tinnitus during the scan was not asked. Exclusion criteria were contraindication for MRI (e.g. the presence of ferromagnetic aneurysm clips, pacemakers), hyperacusis, or phonophobia. All patients were free of major neurological, neurosurgical, or psychiatric history.

fMRI data acquisition and preprocessing

In all patients, functional MRI time series were acquired on a 3T head-only scanner (Siemens Trio, Siemens Medical Solutions, Erlangen, Germany) operated with a standard transmit–receive quadrate head coil. Two hundred multislice T2*-weighted functional images were acquired with a gradient-echo echo-planar imaging sequence using axial slice orientation and covering the whole brain (50 slices; voxel size: $2.5 \times 2.5 \times 2.8$ mm^3; matrix size $80 \times 80 \times 50$; repetition time = 3000 ms; echo time = 30 ms; flip angle = 90º; field of view = 200×200 mm^2). The three initial volumes were discarded to avoid T1 saturation effects. For anatomical reference, a high-resolution T1-weighted image was acquired for each subject (T1-weighted 3D magnetization-prepared rapid gradient-echo sequence). Initially, structural and functional data were manually coregistered into standard stereotactic Montreal Neurological Institute (MNI) space. They were then entered into an automatic pipeline in GraphICAr (BraiNet—Brain Imaging Solution Inc.—Sarnia, ON, Canada), which included further minute realignment and adjustment for movement-related effects, noise spikes, and spontaneous deep breaths (using ArtRepair toolbox for SPM (http://cibsr.stanford.edu/tools/ArtRepair/ArtRepair.htm) [26]. In GraphICAr, fine coregistration, segmentation of the structural data, spatial and functional normalization into standard stereotactic MNI space and spatial smoothing with a Gaussian kernel of 8 mm full-width at half-maximum of the fMRI data are performed as implemented in SPM8.

Extraction and identification of resting-state networks

For the RSN identification we used a multiple-template matching method which is inbuilt in GraphICAr [26]. Initially, the fMRI signal was decomposed into sources of neuronal/physiological origin using ICA, which aims to decompose the signal into a set of statistically independent components (ICs) and their associated time courses [27]. In ICA each spatial map (source) has an associated time course, which corresponds to the common dynamic exhibited by this component. The component images (spatial maps) were calibrated to the raw data, so the intensity values were in units of per cent signal change (PSC) from the mean [28]. For the ICA decomposition we used 30 components and the infomax algorithm as implemented in Group-ICA of fMRI toolbox (RRID: SCR-001953; http://mialab.mrn.org/software/gift/).

After the ICA decomposition, the nine different RSNs were identified at an individual level. For this, we ran a single subject ICA, and the set of ICs that maximized the goodness of fit (absolute value of average voxels falling to the template minus the average voxels outside the template) with a set of predefined binary RSN templates, while considering all the RSNs simultaneously was selected [29]. The predefined RSN templates were selected by an expert after visual inspection from a set of spatial maps resulting from a Group-ICA decomposition performed on 12 independently assessed controls and were confirmed by another expert for accuracy of structural labelling reported elsewhere [29]. This ICA approach is robust in non-homogenous populations and can be used directly for individual assessment of subjects in clinical applications [26, 33].

Applying graph theory

Once the ICs were identified as the RSNs of interest, a graph theoretical approach was applied on the ICs to visualize and calculate the graph properties of each network [26, 30, 31]. For this analysis, the cortex was parcellated into 1015 regions of interest (ROIs) with anatomical significance, using the Lausanne 2008 Atlas with functions from the Connectome Mapping Toolkit [32]. Each ROI is considered as a node of a graph; the connections between nodes typically carry weights describing the correlation, or the degree of connectivity between each pair of nodes. After decomposing the whole brain to components using ICA, the weighted matrices (w_{ij}) for each of the nine RSNs were obtained by calculating the edge weights using Eq. (1):

$$w_{ij} = |z_i| + |z_j| - |z_i - z_j|, \tag{1}$$

where w_{ij} represents the edge weight between nodes "i" and "j", with z_i *and* z_j the z-values which are obtained from the scalar map of the independent component of interest for the nodes "i" and "j", respectively [26, 33].

fMRI second-level statistical analysis

The w_{ij} matrices ("correlation matrices") of each network for all 135 subjects were obtained using GraphICAr. The w_{ij} matrices were thresholded from 0 to 1 in steps of 0.1, and subsequently, the mean over the thresholded w_{ij} matrices were obtained to create a threshold-independent quantity [33]. Graph strengths (GS) of each 1015 regions (S_i) for all subjects were calculated from the mean thresholded w_{ij} matrix using the formula $S_i = \sum_{j=1}^{N} w_{ij}$, where N is the number of regions. Then mean GS over the subjects were calculated, and the GS values greater

than the thresholded GS (values greater than half of the maximum GS value for the network) were plotted (Fig. 1). It is important to note that some brain regions may spatially belong to several RSNs (overlapping regions), while other, the isolated regions, only belong to one (supplementary figure ESM_2). This is explained by the fact that some regions have an associated BOLD signal that can fit the dynamic of different ICA components. Therefore, in the plots, regions belonging to the specific network were kept, while only the isolated regions of other networks were plotted. In our tinnitus population (Fig. 1), even though the networks are mainly defined by regions that belong to their particular network, there exist a few isolated regions belonging to other networks that contribute as well. Therefore, in all the plots we represent by a circle each region with a GS above threshold and used a different colour depending on their RSN of origin. The assigned RSN of origin of a particular region is based on GraphICA templates created from 12 normal subjects without tinnitus as mentioned in "Extraction and identification of resting-state networks" and shown in the supplementary figure (ESM_2). (The axial and sagittal views of the templates for the nine RSNs using the isolated regions (non-overlapping) and the overlapping regions are plotted.) The axial slices of the unthresholded mean GS on the normalized structure for each of these networks are shown in Fig. 2.

Pearson correlations among the six behavioural scores (BS) (i.e. age, tinnitus distress (TQ score), tinnitus duration, tinnitus subjective intensity (numerical rating scale from 0 to 10), tinnitus objective loudness (as measured during the audiological assessment and corrected for the hearing threshold measured for the according frequency), and hearing loss) were calculated (Table 1). First, to assess how the GS of each network varies with the BS, GS was averaged over the 1015 regions of each network (global GS) for each subject and correlations between the global GS and the BS were calculated (Table 2) for each of the five networks of interest. Stepwise fit regression analysis was performed to examine the relationship between clinical characteristics and BS with spontaneous BOLD activity. We used the default values of p entering = 0.05 and p exiting = 0.10 and performed the stepwise fit regression analysis on the GS of each region, network by network using the BS as the predictors. Before stepwise fit regression analysis was performed, we checked the multicollinearity among the BS by calculating the variance inflation factor (which should be < 5) and confirming that it can be neglected for the stepwise fit analysis to be performed [36]. T-statistics and p values for coefficient estimates (between the GS and each BS while keeping the other BS as covariates) were obtained from the

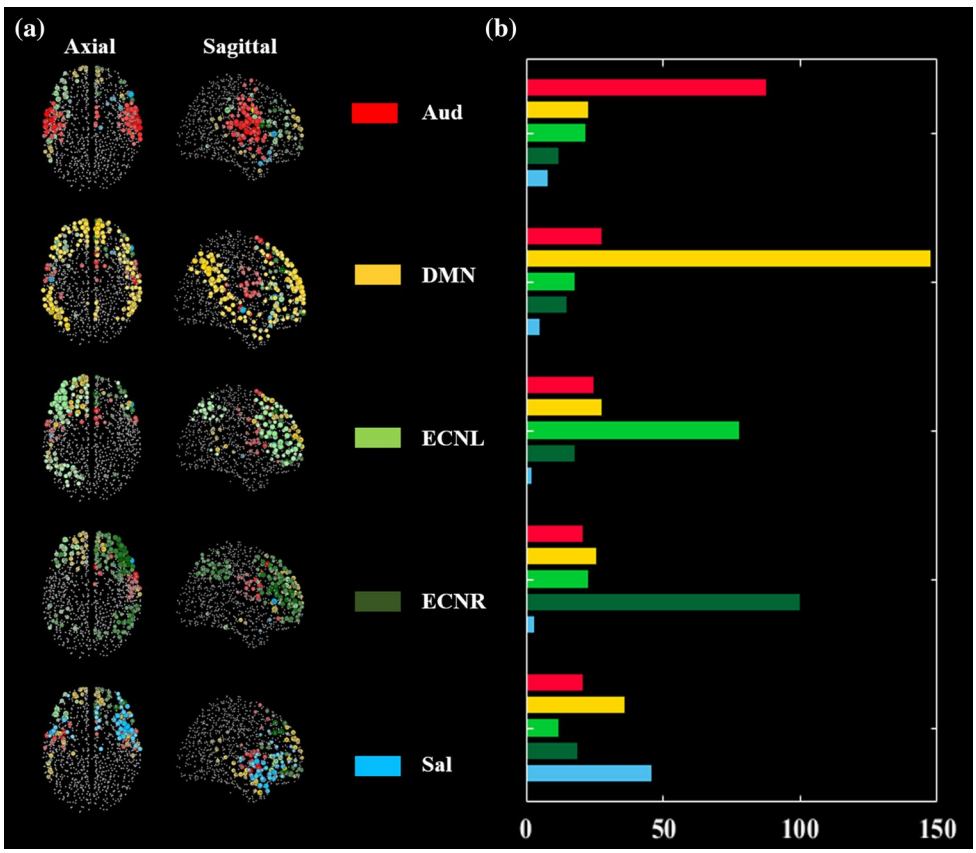

Fig. 1 Mean graph strength (GS) plots of auditory (Aud), default mode network (DMN), executive control network left (ECNL), executive control network right (ECNR), and salience (Sal) separated by different colours for each network for tinnitus patients. Only the GS values greater than 0.5 of the maximum GS value of that network are plotted. **a** Axial and sagittal plots of the networks. Size of the circle represents the value of the GS, and the darker the circle, the higher the GS. **b** Contribution of regions of each network in the mean GS plots of the overall network in tinnitus patients

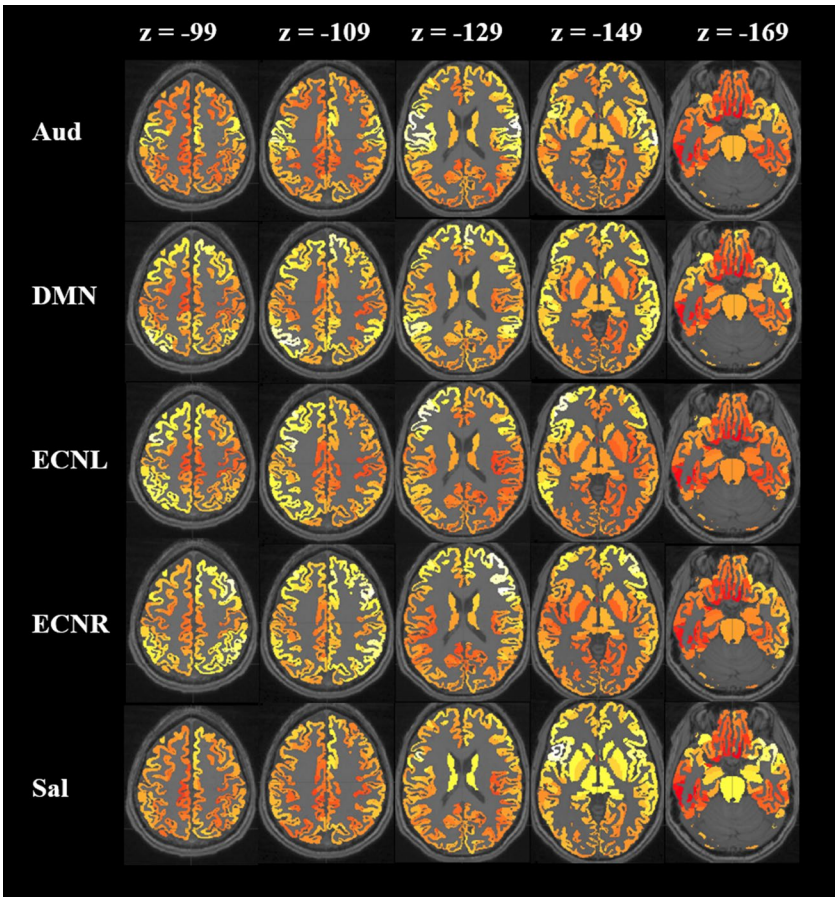

Fig. 2 Axial slices of the mean GS of tinnitus patients implemented on the normalized structure

Table 1 Correlation between the BS obtained from 135 patients

BS	Age		Distress		Loudness		Intensity		Duration		Hearing loss	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Age			0.17	0.06	0.09	0.30	0.20	0.02*	0.27	< 0.01*	0.67	< 0.01*
Distress					− 0.04	0.68	0.43	< 0.01*	0.12	0.18	0.35	< 0.01*
Loudness							− 0.06	0.52	− 0.01	0.95	0.02	0.80
Intensity									0.19	0.03*	0.34	< 0.01*
Duration											0.34	< 0.01*
Hearing loss												

*Statistically significant *p* values

Table 2 Correlation between the GS averaged over all 1015 regions with BS for tinnitus patients

	Age (years)		Distress (TQ score)		Objective loudness (dB SL)		Subjective intensity—VAS (dB)		Duration (years)		Hearing loss	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Auditory	0.11	0.19	− 0.07	0.42	− 0.07	0.43	− 0.13	0.14	− 0.06	0.52	0.00	0.98
DMN	0.18	0.03*	0.01	0.88	0.02	0.84	0.01	0.90	0.09	0.27	0.15	0.09
ECNL	− 0.01	0.95	0.16	0.06	0.04	0.67	0.14	0.10	− 0.01	0.90	0.03	0.76
ECNR	0.05	0.57	0.22	0.01*	0.05	0.55	0.13	0.12	0.05	0.59	0.03	0.73
Salience	− 0.04	0.64	0.02	0.84	− 0.08	0.33	− 0.04	0.68	0.02	0.80	0.01	0.88

*Statistically significant *p* values

stepwise fit analysis, for each region and for each network separately. We performed multiple comparisons test using the Benjamini–Hochberg procedure (using a false discovery rate of 0.25) for the whole-brain volume to control the false positives [37] (Tables 3 and 4, ESM_3a, ESM_3b, ESM_3c, and ESM_3d). We visualized the *t* values of the correlation plots using different colours for each network for the regions which survived the multiple comparisons test (Fig. 3 and ESM_4). We were interested in exploring the core networks' behaviour shared by all tinnitus patients, rather than the difference between the groups, irrespective of lateralization. However, given the importance of inter-hemispheric

Table 3 Correlation between the distress and GS on the ECNR network for tinnitus patients

ROI	*x*	*y*	*z*	*t* value	*p* value	Network
lh.insula	89.81	141.18	− 145.73	2.14	0.03	Aud
lh.postcentral	80.78	127.22	− 103.95	2.57	0.01	Aud
lh.posterior cingulate	121.75	141.84	− 109.17	3.30	< 0.01	Aud
lh.precentral	87.16	130.93	− 98.61	2.74	0.01	Aud
lh.superior frontal	116.40	143.20	− 103.17	2.07	0.04	Aud
lh.supramarginal	87.16	118.77	− 125.85	2.22	0.03	Aud
rh.insula	165.91	132.01	− 140.39	3.04	< 0.01	Aud
rh.postcentral	160.43	117.36	− 92.65	3.19	< 0.01	Aud
rh.posterior cingulate	135.89	139.00	− 107.71	3.43	< 0.01	Aud
rh.precentral	167.81	124.58	− 88.29	3.47	< 0.01	Aud
rh.superior frontal	137.35	143.51	− 99.02	2.64	0.01	Aud
rh.superior parietal	153.45	106.19	− 90.38	2.78	0.01	Aud
rh.supramarginal	183.16	125.28	− 111.46	2.41	0.02	Aud
Left hippocampus	103.15	121.51	− 160.17	3.69	< 0.01	DMN
lh.inferior parietal	80.00	90.89	− 120.21	2.12	0.04	DMN
lh.middle temporal	79.90	151.88	− 182.10	2.45	0.02	DMN
lh.superior frontal	115.90	170.90	− 88.55	2.50	0.01	DMN
lh.superior temporal	73.39	118.28	− 146.43	1.98	0.05	DMN
rh.precuneus	141.00	102.09	− 109.01	3.20	< 0.01	DMN
lh.fusiform	95.13	109.98	− 164.81	2.44	0.02	DMN
lh.caudal middle frontal	96.01	143.66	− 94.37	3.06	< 0.01	ECNL
lh.lateral orbitofrontal	91.90	170.14	− 154.68	2.30	0.02	ECNL
lh.pars triangularis	93.26	175.98	− 144.78	2.09	0.04	ECNL
lh.superior parietal	95.69	97.00	− 110.41	2.31	0.02	ECNL
lh.supramarginal	87.22	104.50	− 104.45	3.50	< 0.01	ECNL
lh.inferior parietal	76.28	91.69	− 100.74	3.05	< 0.01	ECNR
lh.superior frontal	109.78	177.55	− 94.91	2.15	0.03	ECNR
rh.inferior parietal	179.54	99.42	− 112.63	2.40	0.02	ECNR
rh.inferior temporal	186.97	97.09	− 166.99	− 2.08	0.04	ECNR
rh.precuneus	133.32	83.31	− 112.47	2.51	0.01	ECNR
lh.postcentral	71.87	133.26	− 105.16	2.23	0.03	ECNR
lh.supramarginal	79.82	99.20	− 96.02	2.79	0.01	ECNR
rh.posterior cingulate	135.66	115.42	− 107.26	2.99	< 0.01	ECNR
rh.precuneus	135.04	107.71	− 105.41	3.19	< 0.01	ECNR
rh.superior frontal	147.68	172.50	− 93.04	2.32	0.02	ECNR
rh.inferior parietal	183.76	93.97	− 109.69	2.37	0.02	ECNR
rh.supramarginal	186.11	105.45	− 103.50	1.99	0.05	ECNR
Left pallidum	109.77	140.49	− 149.54	2.58	0.01	Sal
lh.lateral orbitofrontal	99.18	163.96	− 168.91	2.37	0.02	Sal
lh.paracentral	114.97	117.77	− 103.58	2.01	0.05	Sal
rh.pars triangularis_	181.87	173.66	− 138.57	2.00	0.05	Sal
rh.posterior cingulate	140.15	121.11	− 109.82	2.85	0.01	Sal
Right thalamus proper	140.83	127.72	− 141.05	3.29	< 0.01	Sal

Table 4 Correlation between the age and GS on the DMN for tinnitus patients

ROI	*x*	*y*	*z*	*t* value	*p* value	Network
rh.posterior cingulate	135.57	129.46	− 107.88	2.79	0.01	Aud
Right thalamus proper	140.83	127.72	− 141.05	3.40	< 0.01	Sal
lh.isthmus cingulate	123.18	104.24	− 119.26	3.09	< 0.01	DMN
lh.medial orbitofrontal	120.68	173.01	− 161.79	2.89	< 0.01	DMN
lh.pars orbitalis	83.60	172.65	− 157.86	2.87	< 0.01	DMN
lh.precuneus	123.35	86.49	− 131.43	3.10	< 0.01	DMN
lh.superior parietal	110.63	65.89	− 100.52	2.96	< 0.01	DMN
rh.isthmus cingulate	134.68	104.58	− 120.94	3.02	< 0.01	DMN
rh.medial orbitofrontal	133.18	192.99	− 168.08	3.25	< 0.01	DMN
rh.precuneus	133.47	87.85	− 130.41	3.23	< 0.01	DMN

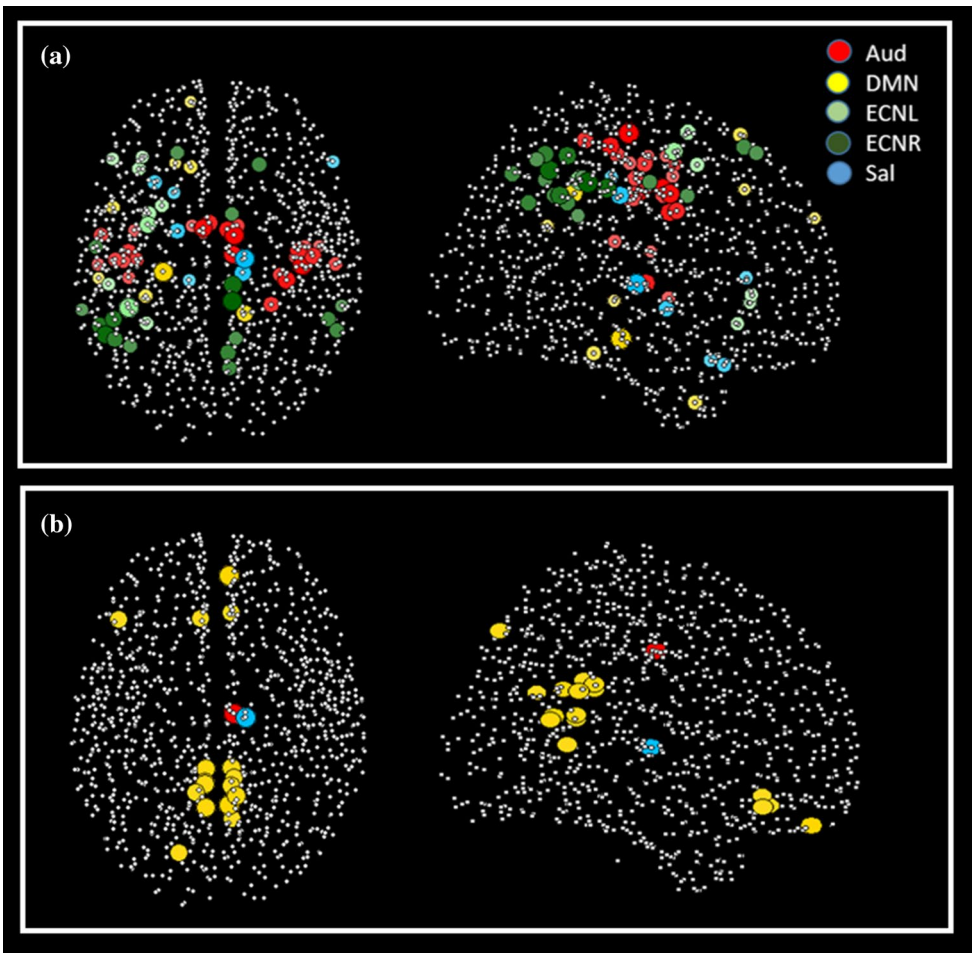

Fig. 3 Representation of the correlation between GS and behavioural scores (BS) of tinnitus patients for **a** ECNR and distress. **b** DMN and age

competition in high-order sensory perception, we performed analysis between unilateral (35 patients) and bilateral (100 patients) tinnitus for completeness and have reported the results in Appendix section (ESM_ 5 and ESM_6).

Results

Patients

Patients' demographic characteristics are summarized in ESM_1. Patients ranged in age from 15 to 81 (mean = 50, SD= 15) and had tinnitus for a mean period of 5.8 years

(SD = 7.2). Tinnitus-matched frequencies ranged from 250 Hz to 12.5 kHz (mean = 5000 Hz, SD = 3270 Hz). Corrected tinnitus-matched intensities (objective loudness) were 8 dB SL in mean (SD = 9 dB SL). Tinnitus Questionnaire (TQ) score varied across patients from 2 to 75 [25]. According to the TQ score, 56 tinnitus patients (41%) had slight (0–30 TQ score), 40 (30%) moderate (31–46 TQ score), 26 (19%) severe (47–59 TQ score), and 13 (10%) very severe distress (60–84 TQ score). Numeric rating of the tinnitus subjective intensity ranged from 0 to 10 (mean = 5, SD = 3). Hearing loss due to tinnitus had an average value of 32 dB with a standard deviation of 20 dB. According to the World Health Organization grades of hearing impairment [38], 89 (65%) tinnitus patients have a grade 0 impairment (no impairment, 25 dB or better—averages of values at 500, 1000, 2000, 4000 Hz—better ear), 30 (22%) have a grade 1 impairment (slight impairment, 26–40 dB, better ear), 17 (12%) have a grade 2 impairment (moderate impairment, 41–60 dB, better ear), and 1 (1%) has a grade 3 impairment (sever impairment, 61–80 dB, better ear).

Neural correlates of tinnitus characteristics

It is important to note that when we looked for correlation between clinical characteristics and brain connectivity in the five different resting-state networks of interest, the maps used for the second-level analysis were not thresholded. This implies that for each network, the statistical analysis was not restricted to regional parts of a thresholded map but rather performed on a whole-brain image.

The mean GS of the auditory, DMN, ECNL, ECNR, and salience networks and the contribution of each network to the mean for the tinnitus patients are displayed in Fig. 1a, b, respectively. Although the networks in our tinnitus population are defined to a certain extent by the characteristic region of each network, as shown by the highlighted regions of the colour of that particular network (Aud—58%, DMN—69%, ECNL—52%, ECNR—58%, and Sal—34%), a few regions belonging to other networks are participating as well (Fig. 1b). For example, when considering mean GS of the auditory network in our tinnitus population, although the main contribution comes from regions belonging to the auditory RSN template (58%), regions that are found to be part of DMN (15%), ECNL (14%), ECNR (8%), and salience (5%) in the GraphICA control population (ESM_2b) contributed as well.

Pearson correlations between the BSs are shown in Table 1. Age and hearing loss showed the strongest significant correlation ($r = 0.67$, $p < 0.01$). Interestingly, distress and tinnitus duration were not correlated, but were both significantly correlated with hearing loss ($r = 0.35$, $p < 0.01$ and $r = 0.34$, $p < 0.01$, respectively) and subjective tinnitus intensity ($r = 0.44$, $p < 0.01$ and $r = 0.19$, $p = 0.03$, respectively). Hearing loss was significantly correlated with all BSs except tinnitus objective loudness (Table 1). Age was correlated with duration of the tinnitus ($r = 0.27$, $p < 0.01$) and subjective tinnitus intensity ($r = 0.20$, $p = 0.02$), in agreement with previous studies [39], while the tinnitus objective loudness was not correlated with any BSs.

Among the correlations between the global GS for each network and BS, the strongest correlations were observed between distress and the ECNR ($r = 0.22$, $p = 0.01$), followed by age and the DMN ($r = 0.18$, $p = 0.03$) (Table 2). As described above in the methodology section, the variation inflation factors, which quantify the severity of multicollinearity between the BSs (age, distress, loudness, intensity, duration, and hearing loss) were 1.9, 1.3, 1.0, 1.3, 1.1, and 2.2, respectively. Since these values are smaller than 5, the multicollinearity among the BSs could be neglected, allowing for stepwise regression analysis to be implemented [36].

We then selected the ECNR and the DMN and looked at the correlation between distress and age, respectively, and the GS value of all 1015 regions for both networks. Regions with a correlation value which survived the multiple comparisons test are depicted in Fig. 3 and further listed in Tables 3 and 4.

In the ECNR the importance of the tinnitus-related distress correlates with the GS of many regions of the brain. The most significant regions are the part of right precuneus that overlaps with ECNR, left inferior parietal, right posterior cingulate, left and right posterior cingulate regions, right insula, right postcentral, right precentral, left hippocampus, left caudal middle frontal, left supramarginal and the right thalamus ($p < 0.01$). Although the effect of distress mainly affects the ECNR, based on the associated network of each significant region (see colour in Fig. 3a, and associated network listed in Table 3) it is mostly the interaction between the ECNR and the other resting-state networks that is disturbed. Similar results were obtained within the unilateral and bilateral groups, although the effect of distress on the ECNR on the bilateral group was milder affecting only few regions belonging to the auditory network than the unilateral group where many regions belonging to all the networks were affected (ESM_5a, ESM_5d, ESM_6a, and ESM_6d).

In the DMN the age correlates with the GS of many regions of the brain. Here the significant positive age effect is primarily seen in the network itself, mostly in the precuneus, cingulate, and orbitofrontal regions (see colour in Fig. 3b, and associated network listed in Table 4). These results were duplicated in the bilateral tinnitus group, where a positive correlation was obtained between age and DMN (bilaterally in the precuneus, cingulate, and inferior parietal regions) as well as with auditory network (ESM_5b, ESM_5c, ESM_6b, and ESM_6c).

Discussion

The implications and significance of clinical differences observed across patients as well as the neurological mechanisms involved in tinnitus remain unknown. The present study explored whether the clinical characteristics of tinnitus were associated with specific resting-state activity and connectivity patterns. While past fMRI, EEG, and MEG studies on tinnitus have analysed brain activity, they rarely have considered changes in connectivity [7, 9, 21, 29]. It appears that abnormal activities localized in specific brain areas are, however, not sufficient to fully explain tinnitus pathophysiology but that tinnitus and tinnitus characteristics are also related to the dysfunctional interaction between separable distributed networks, related to the distress, subjective loudness, and duration of tinnitus. Our findings support the hypothesis that the unified percept of tinnitus could be considered an emergent property of multiple overlapping dynamic brain networks [3]. When looking at the mean graphs of tinnitus patients (Fig. 1), we clearly see that networks are modified compared to the template created from the 12 independently assessed controls [26] (ESM_2). For example, in our tinnitus population, we observe that some auditory-related brain regions (in red, Fig. 1a) have their resting BOLD activity that are somehow more related to the associated time course of the DMN, ECNR, ECNL, and salience network than the control population (see the auditory contribution in each network, Fig. 1b). In fact, our observation fits the idea that the brain operates via functional interactions between distributed regions, or neural networks, and that the interaction between these networks is rather dynamic and can be reorganized in response to task, change in sensory input, cognitive overload or learning [40]. This explains why some neural regions can be coupled with a specific network at one time and with a different one if the situation changes (i.e. hearing tinnitus). Our results show that tinnitus is indeed associated with such a reorganization of functional connectivity.

As for the association between tinnitus characteristics and brain connectivity, our main finding is the correlation between tinnitus-related distress and the ECNR GS values. The ECN includes portions of the lateral prefrontal cortex and posterior parietal cortex and is thought to be important for externally oriented awareness [41, 42] and cognitive control abilities [40, 43]. This fronto-parietal network is believed to be involved in allocating top-down attentional resources [44]. It is, with the DMN and the salience network, considered a "higher-order" network or "control" network, as opposed to auditory, somatosensory or visual networks which are considered as "lower-order" or "processing" networks [45, 46]. Earlier, we mentioned that the brain can be viewed as a dynamic multinetwork interaction. This is especially true for these "higher-order" networks. Modification of the functional coupling of these control networks with the sensory cortical regions influences how the information is processed and even if the information is consciously perceived [47]. Functional connectivity analysis of human functional magnetic resonance imaging data revealed that sensory areas that selectively process relevant information are functionally connected with the fronto-parietal network, whereas those that process irrelevant information are simultaneously coupled with the DMN [48]. This shows that the processing of sensory cortical activity is greatly influenced by top-down modulations with the fronto-parietal network associated with top-down enhancement. Our results, by showing that tinnitus, and specifically tinnitus distress, is associated with a modification of functional connectivity not only within the regions of ECNR, but also between regions belonging to different networks, indicate that the burden of tinnitus can be linked to a paradoxical attention to the sound. This can explain the success of cognitive therapies aiming at helping patient to put their attention away from tinnitus and focussing on other matters [49]. This also stresses the importance of the control of associated factors like the level of alertness, attention or anxiety, as they play a role in the perceived tinnitus distress.

In accordance with previous studies, we show that age influences the DMN connectivity. Interestingly, the modulation of connectivity takes place mainly between regions of the DMN and not between the DMN and other resting-state networks. We show an increased GS value with age mostly in the posterior part of the DMN. These results conflict, however, with previous work showing decreased connectivity between the precuneus and prefrontal cortex with age [50] and should be explored further, while other showed increases or decreases in connectivity with age depending on the observed region of the DMN [51, 52].

Interestingly, there was no significant correlation between the tinnitus objective loudness, the tinnitus subjective intensity (VAS), the tinnitus duration and the mean GS of the five networks of interest. One hypothesis is that these tinnitus characteristics are mainly linked to modification of neuronal activity in specific brain area and less to modification of functional interaction between brain regions. Another hypothesis is that the tinnitus perceived loudness during the scanning session might have been a better factor to explore the brain functional activity linked to tinnitus loudness.

When looking at the correlation between the different behavioural scores, interestingly, we see that distress does not correlate with duration of tinnitus. This suggests that the long-term duration of the tinnitus percept does not ineluctably result in emotional distress and annoyance and that habituation might not necessarily be a matter of time. This

lends support to previous work suggesting distress and duration should be considered as two independent dimensions for tinnitus [53]. As opposed to previous studies, we do not find a correlation between the tinnitus distress and the age [54, 55]. However, we corroborate earlier works showing that tinnitus stress is positively correlated with hearing loss. Tinnitus loudness largely depends on the method used for its characterization. It can be assessed using psychophysical matching procedures or can be subjectively rated using VAS [56]. In agreement with previous work, our study confirmed that VAS intensity ratings correlated with tinnitus-related distress [49], whereas psychophysically determined tinnitus objective loudness does not [57]. This observation stresses the importance of proper selection of clinical measures when evaluating tinnitus and knowledge of what these measures represent. Certainly, the psychophysically determined tinnitus objective loudness does not give an accurate representation of the disturbance caused by the tinnitus.

Conclusion

Our findings provide evidence that alterations of functional interactions between key neural circuits of the brain can explain some tinnitus characteristics. Not only the auditory regions, but also the non-auditory regions are affected by tinnitus pathology. Specifically, the connectivity patterns of the right executive control network which is relevant for perception of external stimuli are mostly being affected by distress of patients with tinnitus. Also tinnitus appears to be a pathological condition which tends to produce hyperattention towards something that should not be salient to us. Therefore, all therapies that aim at modifying this abnormal state of alertness towards the tinnitus sound should be able to reduce its perception. Identifying the brain's intrinsic system responsible for the conscious perception of the tinnitus or for the reaction to the noise could help in designing new noise cancellation strategies and open avenues for treatment of tinnitus.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standards The study was approved by the Ethics Committee of the Antwerp University Hospital. Informed consent to participate in the study was obtained from the patients.

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