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Abstract

Chronic subjective tinnitus is a widespread disorder. This perceptual anomaly is assumed to result from a dysbalance of excitatory and inhibitory mechanisms on different levels of the auditory pathways. However, the brain areas involved are still under discussion. Using resting-state functional magnetic resonance imaging, we investigate differences in cerebral regional homogeneity (ReHo) between patients with unilateral chronic tinnitus and nontinnitus control subjects. To our knowledge, our study is the first to investigate the intraregional connectivity of patients with unilateral tinnitus in relation to hearing loss. Our analyses, based on strict recruitment and characterization of the participants, showed reduced ReHo in the primary auditory cortex contralateral to the side of the perceived tinnitus percept in patients. Reduced ReHo in this same region was also correlated with increased Tinnitus Handicap Inventory and Visual Analogue Scale for loudness scores, reflecting an alteration of synchronization in this region related to the perceived loudness of the tinnitus and the related distress. Furthermore, increased ReHo in the supramarginal and angular gyri ipsilateral to the tinnitus side was correlated with increased tinnitus duration and hearing threshold at the tinnitus pitch. The correlations observed in these brain areas, which are normally related to the nontinnitus ear, could highlight compensatory mechanisms in these secondary auditory regions.

Keywords

brain regional connectivity, functional neuroimaging, magnetic resonance imaging, resting state, tinnitus

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Introduction

Chronic subjective tinnitus is a widespread disorder in industrialized countries, and its prevalence ranges from 5.1 to 42.7% depending on its definition and the measurements used (McCormack, Edmondson-Jones, Somerset, & Hall, 2016). Tinnitus can take many forms and is often described as a ringing, hissing, or buzzing sensation (Jastreboff, 1990). These perceptions can cause visible changes in behavior, a sharp deterioration of quality of life, and it has been linked to posttraumatic stress disorder and clinical depression (Berrios & Rose, 1992; Berrios, Ryley, Garvey, & Moffat, 1988; Reynolds, Gardner, & Lee, 2004). Tinnitus may originate from different peripheral nodes or central auditory pathways (cochlea, auditory nerve, cochlear nucleus, superior olivary nucleus, inferior colliculus, thalamus, auditory cortex, etc.). Most cases of chronic subjective tinnitus are associated with hearing loss, presbycusis, or exposure to noise (Eggermont & Roberts, 2004; Nicolas-Puel et al., 2006). Moreover, approximately 90% of people with chronic tinnitus have some form of hearing loss (Davis & Rafaie, 2000). Unfortunately, the physiopathology underlying tinnitus has remained poorly understood, involving a complex interplay of peripheral

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and central auditory mechanisms (Noreña & Farley, 2013).

Various functional magnetic resonance imaging (fMRI), electroencephalography, and magnetoencephalography (MEG) studies focusing on cerebral resting-state activity in targeted networks have shown alterations in functional connectivity or activity in different brain regions, including the auditory cortex (Burton et al., 2012; Kim et al., 2012; Maudoux et al., 2012a; Zhang et al., 2015), the prefrontal cortex (Kim et al., 2012, Maudoux et al., 2012a, 2012b; Vanneste & De Ridder, 2011), and the insula (Burton et al., 2012; Chen et al., 2015a; Vanneste, van de Heyning, & De Ridder, 2011) in tinnitus patients. Schmidt, Akrofi, Carpenter-Thompson, and Husain (2013) and Schmidt, Carpenter-Thompson, and Husain (2017) also observed a decreased functional connectivity in certain parts of the default mode network, particularly the prefrontal cortex and the cingulate posterior cortex with the precuneus.

More recently, data-driven developed models, such as amplitude of low-frequency fluctuations (Chen et al., 2014, 2015a) or regional homogeneity (ReHo; Chen et al., 2015b; Lv et al., 2016; Yang, Zheng, Ou, & Huang, 2014), allow comparisons of subjects without any prior choice of regions of interest. Increased ReHo values have been reported in several brain regions of subjects with tinnitus compared with nontinnitus control subjects, including the inferior frontal gyrus (Chen et al., 2015a, 2015b), the middle temporal gyrus, the postcentral gyrus, the insula, and the supramarginal gyrus (Yang et al., 2015). In contrast, decreased ReHo values have been reported in the cuneus (Chen et al., 2015b) and the anterior lobe of the cerebellum (Yang et al., 2014) in subjects with tinnitus. This has led to the conclusion that chronic tinnitus induces changes in many cerebral networks, including the attention network (Chen et al., 2015b), the default mode network (Chen et al., 2015a), and the basal ganglia and the auditory cortex (Yang et al., 2014).

There are, however, still too many unsolved questions and controversies in the literature to establish a valid physiopathological model of tinnitus associated with hearing loss (Leaver, Seydell-Greenwald, & Rauschecker, 2016), especially for unilateral tinnitus.

There are several reasons that may underlie the high variability between published results. First, results may be dependent on the data treatment method used. Indeed, most resting fMRI studies are based on the choice of *seeds* corresponding to different regions of interest (e.g., auditory cortex; Burton et al., 2012; Schmidt et al., 2013, 2017; Wineland, Burton, & Piccirillo, 2012) or on the comparison of functional connectivity patterns in a predefined network. In both cases, group differences will only be observed in the preselected regions, thus the a priori selection of regions of interest strongly influences the results (Leaver et al., 2016).

Second, in many publications, the population of interest is very heterogeneous, as tinnitus manifests itself in many different forms. Unfortunately, little importance has been placed so far on etiologies, hearing loss, lateralization, and perceptions of tinnitus. Considering this large variability, using narrower selection criteria might lead to a better understanding of the changes underlying tinnitus, with less variability between data and higher specificity.

Finally, the disparity between results could be due to the intense noise produced by the scanner during resting-state acquisitions and its impact on tinnitus. Although most investigators consider a *resting-state* fMRI experiment to be devoid of external stimulation, subjects are unavoidably under heavy acoustic noise produced by the equipment (Rondinoni et al., 2013). The residual noise in the ears of the subjects and its influence on tinnitus perception, taking into account the impact of any attenuation devices used, is still rarely the subject of investigation.

This study aims to better understand the physiopathological mechanisms of subjective tinnitus related to a hearing loss using resting-state fMRI. Our main objective is to identify differences in cerebral ReHo in patients with unilateral tinnitus compared with nontinnitus control subjects in a resting state. Our second objective is to highlight lateralized differences related to tinnitus lateralization. A strict inclusion protocol is used to ensure homogeneity of the subject population. Correlations between ReHo values and different clinical parameters characterizing tinnitus have also been assessed.

Materials and Methods

Population

Nineteen patients with unilateral chronic tinnitus and sixteen healthy nontinnitus control subjects were recruited from the ear nose throat (ENT) Consultation of the Montpellier University Hospital (France).

All tinnitus patients had tinnitus that was either perceived as a high-frequency pure tone or as a narrowband noise with a measured tinnitus pitch at 4 or 6 kHz.

Ten patients reported right-sided tinnitus and nine reported left-sided tinnitus; they all experienced a complete residual inhibition of their tinnitus for at least 30 s.

All participants were right-handed (Edinburgh Handedness Inventory; Oldfield, 1971). Tinnitus patients and control group were matched in age and education.

The Local Ethical Committee (Comité de Protection des Personnes Sud Mediterranée IV) approved the study.

Written informed consent was obtained from all subjects.

Psychoacoustical and Psychosocial Assessments

After an ENT consultation performed to exclude neurological, vascular, infectious, or drug-related causes and confirm an otologic (noise induced, presbycusis) etiology, patients with tinnitus underwent a complete psychoacoustical assessment to characterize their hearing function and tinnitus (Henry & Meikle, 2000; J. A. Vernon & Meikle, 1981). Psychoacoustic measurements included: pitch matching (PM), loudness matching, minimum masking level (MML; Feldmann, 1969), and residual inhibition (J. Vernon, 1977).

After pure tone audiometry testing, the PM of the tinnitus was assessed using a two-alternative forced-choice method (J. Vernon & Fenwick, 1984). For PM, pure tones were used for patients perceiving their tinnitus as a pure tone and narrow band noises (1/3-octave band) were used for patients perceiving their tinnitus as a narrow band noise. The center frequencies of stimuli used were 1, 2, 3, 4, 6, and 8 kHz.

The loudness matching of the tinnitus was evaluated using an ascending method (increment-2 dB) to avoid producing residual inhibition (J. Vernon & Fenwick, 1984). The type of stimulus (pure tone or narrow band noise) was the same as that used for PM.

The MML of the tinnitus patients was measured with a narrow-band noise centered at the frequency of the tinnitus (Feldmann, 1969). All tinnitus patients had an MML value greater than 40 dB hearing level. The main interest of this measure was to verify that the noise produced by the MRI scanner does not mask or change tinnitus perception during functional acquisition. Finally, a residual inhibition test was performed.

All these tests were performed on the ipsilateral ear, to avoid loudness or frequency distortions between ears (diplacusis; Tyler & Conrad-Armes, 1983).

The psychoacoustical assessments were completed by different psychosocial tests. The subjective loudness of the tinnitus was evaluated with the Visual Analogue Scale for Loudness (VAS-l; Esteve-Fraysse et al., 2012; Nicolas-Puel et al., 2006). Patients were asked to evaluate the intensity of their perceived tinnitus between 0 and 10, with 0 representing no perception and 10 the most intense experience of tinnitus imaginable.

An evaluation of the tinnitus severity and the related distress was realized using the Tinnitus Handicap Inventory (THI; Newman, Jacobson, & Spitzer, 1996). The duration was controlled; all patients with a tinnitus duration of less than 1 year were excluded.

The nontinnitus control subjects underwent a pure-tone audiometry assessment and an ENT examination. Participants were required to be free of neurological disorders, Meniere's disease, temporo-mandibular joint disorders, and other neurological issues or chronic physical diseases. None of the participants were undergoing treatment for tinnitus at the time of participation in this study. The characteristics of the participants are summarized in Table 1.

MRI Scanning

Neuroimaging data were acquired using a 3T magnet (Skyra, Siemens, Germany) with a 20-channel head coil from the I2FH platform in the neuroradiology department of Montpellier hospital.

An axial high-resolution 3DT1 MPRAGE was acquired with the parameters: repetition time (TR)/echo time (TE) = 1,690/2.54 ms, inversion time = 922 ms, flip angle = 9°, resolution = $1 \times 1 \times 1$ mm^3, and 176 slices.

For resting-state imaging, a T2*-weighted gradient echo-planar sequence was performed using axial slice orientation and the following parameters: TR/TE = 2,400/30 ms, flip angle = 90°, resolution = $2.39 \times 2.39 \times 3$ mm^3, 39 slices, 200 volumes, and total time = 8 min.

The resting-state paradigm was defined as follows: keep eyes closed, think about nothing in particular, and do not sleep.

A field map image was acquired with a gradient echo sequence in order to correct functional images for field inhomogeneity. The parameters were as follows: TR/TE1/TE2 = 487/4.92/7.38 ms, flip angle = 60°; resolution = $3.8 \times 3.8 \times 3$ mm^3, and 39 slices.

Our measurements showed a noise level of 75 dB sound pressure level (SPL) in the high frequencies during the resting-state acquisitions. To ensure that the perception of tinnitus was not disturbed by fMRI acquisition noise, subjects wore over-ear protection (NNL® headphones) that attenuated acoustic noise. The attenuation of the over-ear protection was tested using KEMAR® (Knowles Electronics Manikin for Acoustic Research, G.R.A.S) giving an attenuation of 35 dB in the high frequencies (Figure 1) and a residual noise of 40 dB SPL in the tinnitus frequency range.

Data Preprocessing

Data were preprocessed using MATLAB (The Mathworks Inc., MA) and SPM12 (see http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). All images were reoriented according to the anterior commissure, flipped to force the tinnitus to be on the left side. The 3DT1 images were segmented into six tissue classes using the DARTEL approach. Resulting segmentations were then used to create a dedicated DARTEL template. All T1 images were then normalized according to this template (Ashburner, 2007).

Table 1. Characteristics of the Participants.

Characteristics	Patients with unilateral tinnitus ($n = 19$)	Control subjects with no tinnitus ($n = 16$)	p
Age (year)	63 ± 10	59 ± 11	.3
Range (years)	44–82	39–78	
Gender			
Male	14	7	
Female	5	9	
Mean PTA (0.25, 0.5, 1, and 2 kHz; dB HL)			
Right ear	17 ± 4	15 ± 2	.83
Left ear	18 ± 4	14 ± 3	.92
Right ear average hearing threshold (dB HL)			
250 Hz	14 ± 9	13 ± 9	.58
500 Hz	15 ± 8	13 ± 9	.46
750 Hz	15 ± 6	13 ± 7	.29
1000 Hz	17 ± 7	15 ± 6	.40
1500 Hz	19 ± 8	16 ± 10	.83
2000 Hz	23 ± 12	18 ± 12	.89
4000 Hz	44 ± 16	20 ± 16	.00014
6000 Hz	47 ± 17	23 ± 14	.00008
Left ear average hearing threshold (dB HL)			
250 Hz	14 ± 7	12 ± 9	.43
500 Hz	17 ± 8	13 ± 10	.22
750 Hz	16 ± 6	11 ± 11	.14
1000 Hz	16 ± 7	11 ± 7	.06
1500 Hz	20 ± 10	16 ± 10	.28
2000 Hz	24 ± 10	18 ± 9	.06
4000 Hz	39 ± 16	20 ± 17	.003
6000 Hz	48 ± 17	28 ± 14	.0007
Tinnitus			
Right-sided tinnitus	11		
Left-sided tinnitus	8		
Duration (years)	12 ± 13		
THI	36 ± 13		
VAS-l	6 ± 1		
Tinnitus pitch (%)	4 kHz: $n = 9$; 6 kHz: $n = 10$		
HTTP (dB HL)	57 ± 10		
MML (dB HL)	59 ± 9		

Note. Mean values with according standard deviations are presented. THI = Tinnitus Handicap Inventory; VAS-l = Visual Analogue Scale for Loudness; HTTP = hearing threshold at the tinnitus pitch; MML = minimum masking level; dB HL = decibels, hearing level; PTA = pure tone audiometry.

Resting-state images underwent field map correction, slice timing, motion correction, coregistration with 3DT1, and finally normalization using the parameters estimated from 3DT1. All images were smoothed using a 6-mm full width at half-maximum kernel.

Structural Analysis

To search for anatomical differences between the two populations, a voxel-based analysis was performed on gray matter segmentation. A two-sample t test was used to compare between groups. The significance threshold was set at $p < .005$, uncorrected with a minimal cluster size of 25 voxels.

ReHo Analysis

ReHo analyses were performed using Resting-State fMRI Data Analysis Toolkit (REST) on Matlab® (http://www.restfmri.net). ReHo maps were generated after detrending the data (band-pass filter 0.01–0.08 Hz). Kendall's coefficient of concordance was computed to measure the local synchronization of a given voxel with the 26 nearest neighboring voxels in a voxel-wise way (Zang, Jiang, Lu, He, & Tian, 2004). The ReHo value was then assigned to the identified central voxel. Maps were compared between groups using a one-sided two-sample t test. A correction for multiple comparisons was performed by a Monte Carlo simulation using the AlphaSim program (https://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf), resulting in a corrected threshold of $p < .005$ and minimum cluster size of 25 voxels.

Regression Analysis

Correlations between MML, hearing threshold at the tinnitus pitch (HTTP), duration, and ReHo values were investigated in patients using the REST correlation tool (Pearson correlation). These analyses were performed only in the tinnitus patient group, as it was impossible to allocate any value to these parameters for subjects with no tinnitus. The correlation analysis of VAS-l and THI score was performed on all subjects including nontinnitus control subjects. As nontinnitus control subjects showed no tinnitus, their VAS-l and THI scores were set at zero. The significance threshold was set to $p < .005$ (AlphaSim correction, one-sided t test) with a minimal cluster size of 25 voxels.

Results

Audiometry

The mean audiogram for each group is presented in Figure 2. There were no significant differences between the hearing thresholds of the two groups for the frequency range of 0.25 to 2 kHz (Table 1). Tinnitus subjects showed significantly elevated hearing thresholds relative to the control group for 4 kHz and 6 kHz,

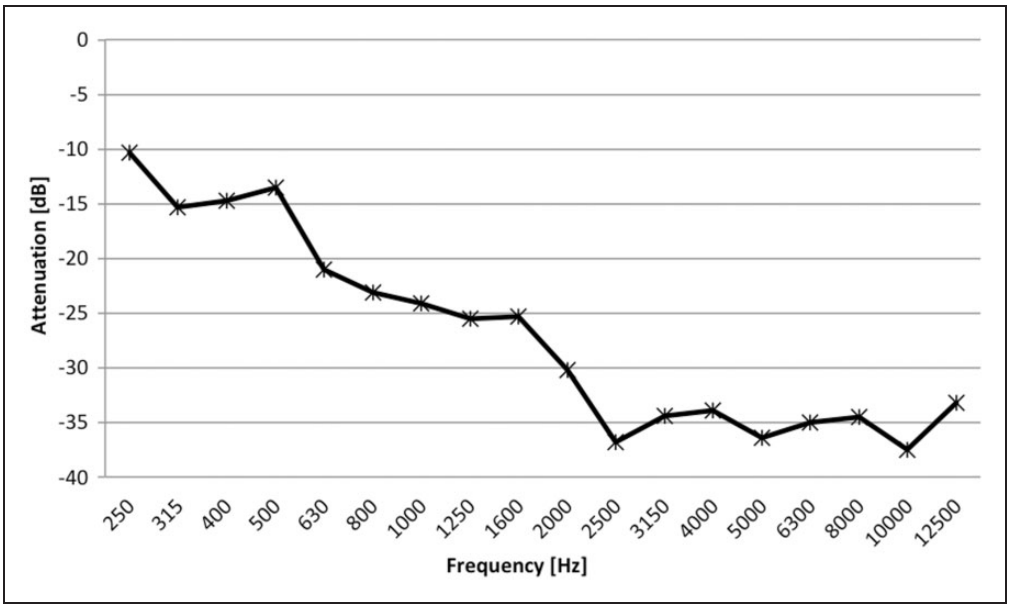

Figure 1. Attenuation of the NNL® headphones measured on KEMAR manikin (Knowles Electronics Manikin for Acoustic Research, G.R.A.S) for a white noise of 90 dB SPL.

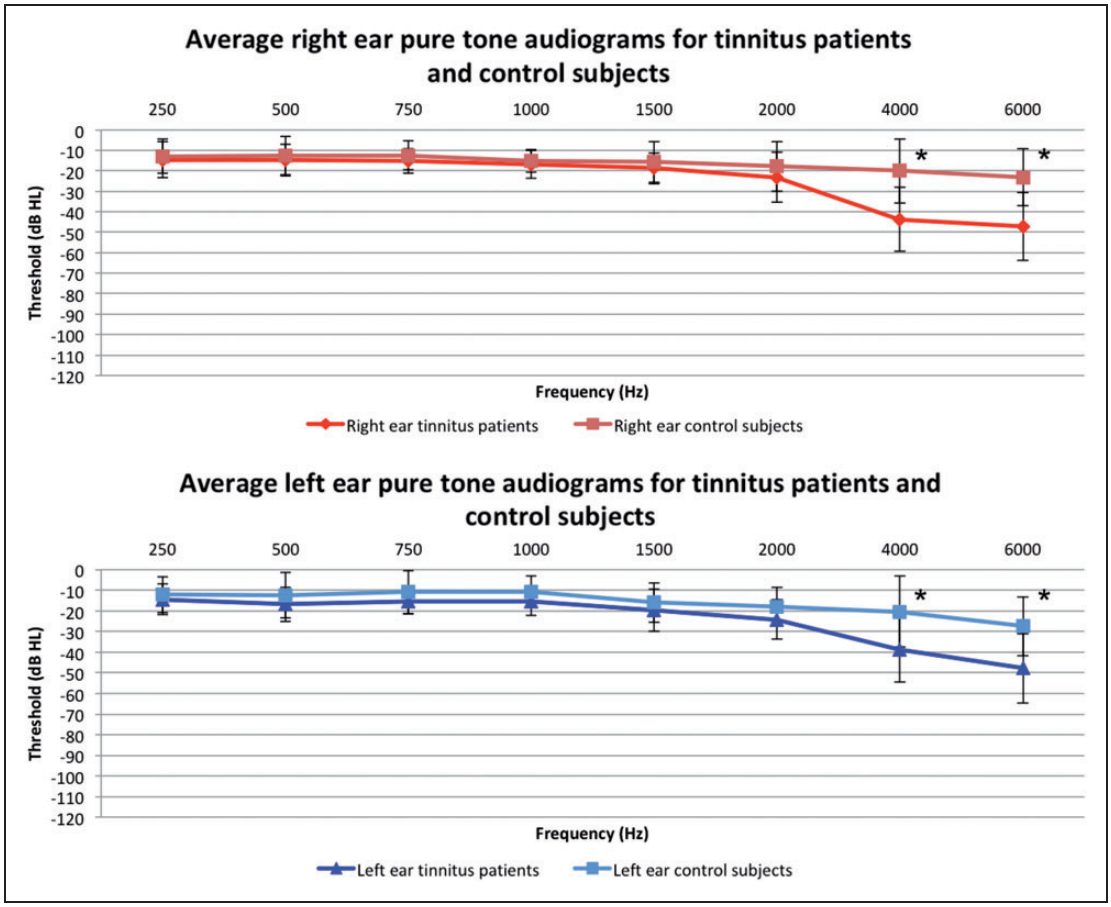

Figure 2. Mean pure tone audiograms for tinnitus patients and control subjects. Mean values and standard deviations are presented. *Indicates significant difference between tinnitus patients and control subjects. dB HL = decibels, hearing level.

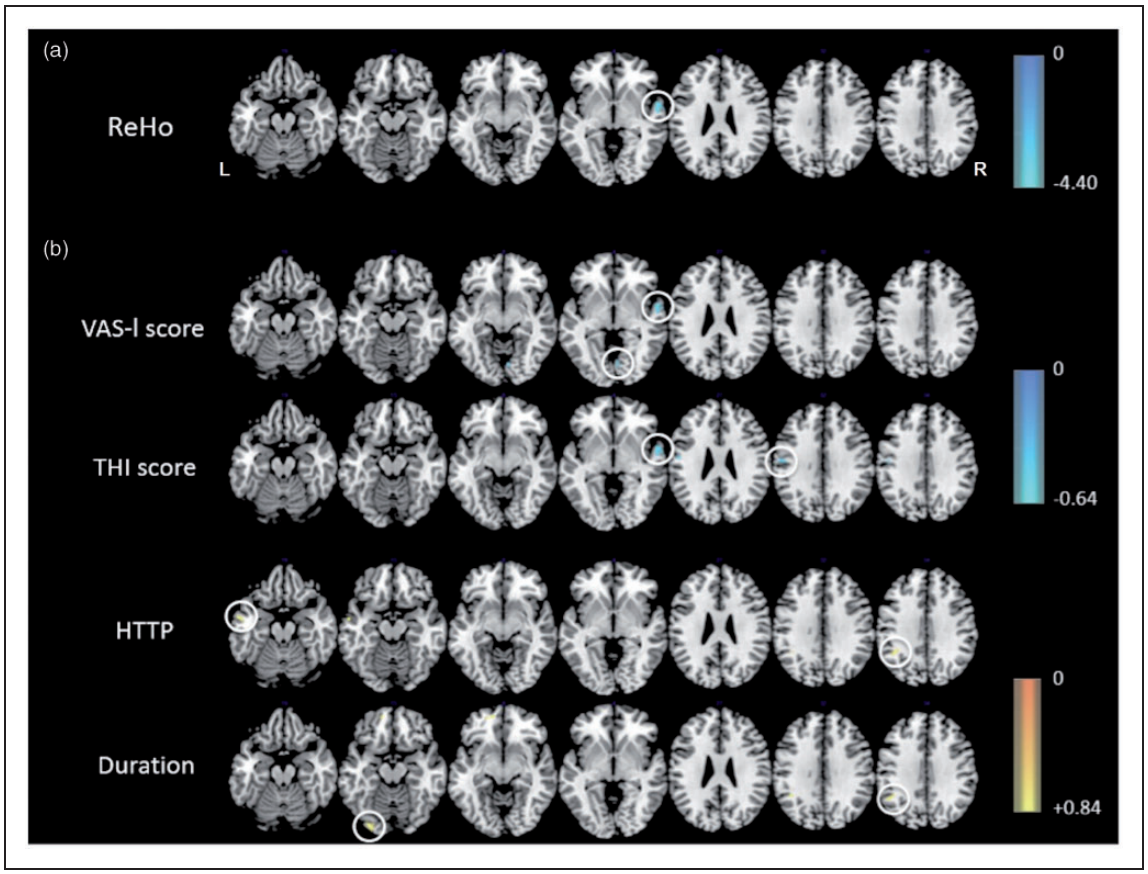

Figure 3. ReHo differences and correlations to clinical parameters in patients with tinnitus. (a) Regions of decreased ReHo in patients with tinnitus compared with nontinnitus control subjects (one-sided two-sample t test, $p < .005$, $k = 25$), whereby the blue spectrum shows the areas of decreased ReHo. (b) Regression analysis between clinical scores and ReHo values (Pearson correlation, $p < .005$, AlphaSim correction, $k = 25$). The blue spectrum highlights an inverse correlation, while the red spectrum shows a positive correlation. ReHo = regional homogeneity; VAS-I = Visual Analogue Scale for Loudness; THI = Tinnitus Handicap Inventory; HTTP = hearing threshold at tinnitus pitch. White circles indicate significant regions. Table 2 identifies regions where significant increases and decreases occurred.

which correspond to tinnitus frequencies. No differences were found between the two populations for the mean pure tone audiometry calculated for 0.25, 0.5, 1, and 2 kHz.

Structural Analysis

Voxel-based morphometry did not highlight any gray-matter differences between patients with tinnitus and nontinnitus control subjects ($p < .005$, uncorrected $k = 25$).

ReHo Analysis

Compared with nontinnitus control subjects, patients with chronic tinnitus had significantly decreased ReHo values in a cluster located between the contralateral superior and middle temporal gyri (Figure 3(a) and Table 2; $p < .005$, AlphaSim correction, $k = 25$). Separate analysis for right-sided and left-sided tinnitus patients both revealed decreased ReHo values in the same region contralateral to the tinnitus side.

Correlation Analysis

We performed a correlation analysis between ReHo and the following clinical parameters: VAS-I, THI score, HTTP, tinnitus duration, and MML ($p < .005$, AlphaSim correction, $k = 25$). Results are presented in Figure 3(b) and are discussed in greater detail later. Table 2 identifies the regions where significant correlations occurred. Correlation analyses for MML, HTTP, and tinnitus duration were only investigated in tinnitus patients, whereas VAS-I and THI were analyzed for both groups.

VAS-I. ReHo values were negatively correlated with VAS-I scores in two regions. The first was located between the contralateral superior and middle temporal

Table 2. Regions Showing Significant ReHo Decreases in Patients With Tinnitus Compared With Nontinnitus Control Subjects, and Significant Correlations Between ReHo Values and VAS-I Score, THI Score, HTTP, and Tinnitus Duration (One-Sided Two-Sample *t* Test, $p < .005$, $k = 25$).

	Brain region	MNI coordinates *x*, *y*, and *z* (mm)				Cluster size (mm^3)
ReHo analysis					Peak *T* score	
	Contralateral superior/middle temporal gyrus	58	2	−4	−4.3946	35
Correlation analysis					Correlation score *r*	
VAS-I	Contralateral superior/middle temporal gyrus	58	2	−4	−.6156	26
	Contralateral lingual gyrus	6	−76	−6	−.5806	27
THI score	Contralateral superior/middle temporal gyrus	58	2	−4	−.6336	25
	Ipsilateral precentral gyrus	−56	−14	32	−.5537	32
HTTP	Ipsilateral middle temporal gyrus	−58	−4	−18	.83704	34
	Ipsilateral supramarginal/angular gyrus	−40	−48	34	.7739	26
Duration	Ipsilateral lingual gyrus	−28	−90	16	.7974	43
	Ipsilateral superior frontal lobe	−6	49.5	7.5	.7898	30
	Ipsilateral supramarginal/angular gyrus	−48	−52	38	.7344	29

Note. VAS-I = Visual Analogue Scale for Loudness; THI = Tinnitus Handicap Inventory; HTTP = hearing threshold at the tinnitus pitch; MNI: Montréal Neurological Institute.

gyri, and the second in the lingual gyrus contralateral to the tinnitus. The former region also discriminated in the comparison analysis between patients with tinnitus and nontinnitus control subjects.

Tinnitus Handicap Inventory. Interestingly, ReHo values in the contralateral superior and middle temporal gyri were also negatively correlated with THI scores. An additional region also appears to be associated: the precentral gyrus ipsilateral to the tinnitus.

Hearing threshold at the tinnitus pitch. A positive correlation between ReHo values and the measured HTTP was observed for a cluster located between the supramarginal and the angular gyri ipsilateral to the tinnitus. In addition, a positive correlation was also found between ReHo values in the middle temporal gyrus ipsilateral to the tinnitus and the measured HTTP.

Tinnitus duration. Tinnitus duration was positively correlated with ReHo values in the lingual gyrus, frontal lobe, and supramarginal/angular gyri ipsilateral to the tinnitus.

Minimum masking level. No correlation was found between ReHo values and MML.

Discussion

The objective of this study was to better understand the physiopathological mechanisms of subjective unilateral tinnitus linked to a hearing loss and to evaluate the intraregional connectivity in patients with tinnitus compared with nontinnitus control subjects. The second objective of this article was to highlight lateralized differences related to tinnitus lateralization. Using a rigorous inclusion protocol and implementation of over-ear protection that limited the impact of fMRI noise on the auditory pathways and the perception of the tinnitus, we demonstrated differences in ReHo between tinnitus patients and control subjects in several brain regions, particularly in the auditory network.

ReHo Analysis

Decreased ReHo was found in the superior and middle temporal gyri (auditory cortex) contralateral to the tinnitus in patients with unilateral tinnitus. We did not detect any increases in ReHo values in the patients with tinnitus compared with the nontinnitus control subjects. Separate analysis for right-sided and left-sided tinnitus patients both revealed decreased ReHo values in the same region contralateral to the tinnitus side.

These results differ from those obtained in previous studies using a comparable type of analysis, which did not report any differences in the activity of the auditory cortex for patients with tinnitus (Chen et al., 2015b; Yang et al., 2014). This could, however, possibly be explained by the heterogeneity of the populations included in these previous studies, as patients with right-sided, left-sided, and bilateral tinnitus were included. Interestingly, despite the contrasting results, the authors came to similar conclusions. They argue

that tinnitus can disrupt the functioning of various networks and brain areas, especially in the auditory cortex, the limbic, and the attentional network (Chen et al., 2015b; Yang et al., 2014).

In contrast, other studies focusing on resting-state interregional functional connectivity highlighted observations concordant with our results. Numerous publications have demonstrated a decreased connectivity in the auditory cortex in tinnitus patient groups (Burton et al., 2012; Kim et al., 2012; Maudoux et al., 2012b; Zhang et al., 2015), particularly in relation to the thalamic regions (Zhang et al., 2015) and the occipital cortex (Burton et al., 2012).

ReHo analysis of neural tissue has been widely used to characterize changes in the functional integrity of brain regions that occur with aging and disease (Mankinen et al., 2011; Paakki et al., 2010; Wu et al., 2007; You et al., 2011; Zeng et al., 2015). Decreased ReHo reflects local disruption of the synchronization of spontaneous brain activity, implying a functional deficit (Chen et al., 2015b). Information coming from a sound perception is mainly processed by the auditory cortex located in the contralateral side to the perception. The decreased ReHo we observed in the auditory cortex contralateral to the tinnitus side reveals an alteration of the local functional connectivity (Jiang & Zuo, 2016) and thus the integrity of this region, which may be related to the tinnitus perception. Indeed, this result is in agreement with cortical tonotopic map reorganizations reported in animal studies (Eggermont & Komiya, 2000; Noreña, Tomita, & Eggermont, 2003), and MEG human studies reporting the frequency region corresponding to the tinnitus pitch is abnormally represented in auditory cortex (Mühlnickel, Elbert, Taub, & Flor, 1998). This disorganization we observed in the auditory cortex contralateral to the tinnitus side could be related to changes in the balance of excitation and inhibition at multiple levels of the projections pathway (Bauer, Brozoski, Holder, & Caspary, 2000).

Correlation Analysis

VAS-l and THI score. Our analysis showed an inverse correlation between both the THI and VAS-l scores and the ReHo values of a region located in the superior and middle temporal cortex (auditory cortex) contralateral to the tinnitus side. These results confirm those obtained in the comparison analysis, and the same region was also distinguished between patients with tinnitus group and nontinnitus control group. The altered synchronization of the auditory cortex contralateral to the tinnitus might be related to tinnitus perception and, in particular, to its loudness, as well as the distress it causes. It seems that the greater the distress or the perceived loudness is, the more the contralateral auditory cortex is desynchronized. This result is in agreement with previous MEG studies (Mühlnickel et al., 1998) showing that tonotopic changes appear to be correlated with the perceived strength of the tinnitus but not with the amount of hearing loss, which is the primary determinant of changes in tonotopic maps (Rajan, 1998).

Finally, the inverse correlation that was found between VAS-l scores and ReHo values in the contralateral lingual gyrus could suggest an implication of the auditory attention network in the perception of tinnitus, as suggested by some recent studies (Schmidt et al., 2017).

To verify whether this similarity of results could be explained by an underlying correlation between the clinical scores, a Pearson's correlation ($p < .05$) was performed and showed that the clinical scores were independent of each other. The independence between THI and VAS-l scores is in agreement with other studies, showing low correlation for these indicators (Fackrell, Hall, Barry, & Hoare, 2016). Indeed, the THI score evaluates the distress caused by tinnitus, whereas the VAS-l evaluates the perceived loudness of tinnitus. It is, therefore, not surprising that these parameters are not related. As we know, according to patient psychology, each individual's experience of tinnitus can be different. The perceived distress can differ widely for the same perceived loudness.

HTTP and tinnitus duration. A positive correlation was found between the HTTP and the ReHo values in the ipsilateral middle temporal gyrus. The HTTP and the tinnitus loudness have showed to be correlated in many publications (Moore, 2018; Wang & Yang, 2018).

This relationship between HTTP and the ReHo of the ipsilateral auditory cortex could indicate that the more the tinnitus is perceived (or the more the hearing loss is important at the tinnitus pitch) the more the ipsilateral auditory cortex intraconnectivity increases.

This result could indicate a compensatory mechanism of the auditory cortex that is primarily assigned to the processing of auditory information from the nontinnitus ear. This compensatory mechanism could be related to an alteration in the processing of information or tonotopic reorganization in the auditory cortex contralateral to the tinnitus side, which is mainly assigned to the tinnitus ear.

Both tinnitus duration and HTTP show positive correlations with ReHo values in the supramarginal and angular gyri ipsilateral to the tinnitus. Multiple studies using resting-state fMRI in tinnitus patients reported these two associated regions (Chen et al., 2015a, 2015b; Davies, Gander, Andrews, & Hall, 2014; Schmidt et al., 2013; Zhang et al., 2015). Increased ReHo was found in the supramarginal gyrus in patients with tinnitus compared with nontinnitus controls (Chen et al., 2015b) as well as increased functional connectivity in the angular gyrus (Zhang et al., 2015). In addition, our results are

consistent with those of Chen et al. (2014), who highlighted increased amplitude of low-frequency fluctuation in the angular gyrus in patients with tinnitus. Both cerebral areas have been shown to be involved in pitch recognition (Gaab, Gaser, Zaehle, Jancke, & Schlaug, 2003), memory (Grimault et al., 2009; Koelsch et al., 2009), and attentional modulation of an auditory stimulus (Corbetta & Shulman, 2002, 2011). These results may indicate that a longer tinnitus duration or a more pronounced hearing loss induce stronger changes in these regions. The correlation between the ReHo values in the ipsilateral secondary auditory cortex areas that are related to the nontinnitus ear and the tinnitus duration and the auditory threshold could also point toward compensatory mechanisms of the tinnitus-challenged brain.

It is important to highlight that we checked whether there was a correlation between the auditory threshold at the tinnitus frequency and the age of participants, which could somehow lead to misinterpretation of the data, but found no association (Pearson correlation, $p > .05$).

Conclusion

Cerebral activity and, particularly, the activity of the auditory pathways have been important topics in tinnitus research for many years. Unfortunately, despite a large number of studies, no consensus has been reached concerning how the activity of the auditory pathways or cortex is modified in tinnitus patients. We believe that this could be dependent on the analysis methods used and the heterogeneity of the populations included. We therefore used a data-driven approach to investigate tinnitus-dependent variations in ReHo in a uniform and well-described patient cohort.

We observed a decreased local functional connectivity lateralized in the auditory cortex contralateral to the tinnitus in patients with unilateral tinnitus. The contralateral auditory cortex is involved in processing most of the information that comes from the tinnitus ear. This disorganization of the auditory cortex contralateral to the tinnitus side is in agreement with tonotopic map reorganization related to tinnitus.

We argue that data-driven whole-brain ReHo analysis is a good method to reveal subtle changes in the auditory regions of patients with tinnitus when compared with other methods (such as resting-state activity or interregional connectivity measurement), which have shown divergent results in these regions.

The disorganization of the contralateral auditory cortex that we observed in tinnitus patients is supported by the fact that ReHo values in this region negatively correlate with VAS-l and THI scores. It seems that the greater the distress or the perceived loudness is, the more the contralateral auditory cortex is desynchronized. Interestingly, this decreased functional intraregional connectivity is accompanied by an increased connectivity in the ipsilateral primary and associative auditory cortex. This may indicate the development of compensatory processes, highlighting the adaptability of the brain in patients with tinnitus.

Our separate whole-brain analysis for right-sided and left-sided tinnitus patients both showed that changes in ReHo occurred in the same region with respect to the tinnitus side. Therefore, we choose to flip all the images acquired for right-sided tinnitus patients so to force the tinnitus to be on the left side for all analyses. In future studies, it could be interesting to increase the size of the populations and to observe whether new separated analyses reveal other regions of interest.

Limits

We did not integrate the total intracranial volume; this can be a limitation. However, the data set was normalized, every anatomical map was checked for atrophy, and structural analysis did not highlight any gray-matter differences between patients with tinnitus and nontinnitus control subjects. In future papers, it could be interesting to integrate this parameter in analyses.

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Author Contributions

Study design: A. Gentil, E. Le Bars, and F. Venail. Recruitment of participants: A. Gentil and F. Venail. Data acquisition: A. Gentil and E. Le Bars.

Quality control of data and algorithms: N. Menjot de Champfleur and J. Deverdun. Analysis and interpretation of data: A. Gentil, J. Deverdun, E. Le Bars, and F. Venail. Critical revision of the manuscript for important intellectual content: E. Le Bars, F. Venail, and N. Menjot de Champfleur. Obtained funding: F. Venail, J.-L. Puel, and E. Le Bars. Supervision of the study: E. Le Bars and F. Venail. Manuscript editing: A. Gentil and J. Deverdun. Manuscript review: E. Le Bars, F. Venail, and J.-L. Puel.

Data Availability

The raw datasets supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher, on request.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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