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Tinnitus-frequency specific activity and connectivity: A MEG study

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ABSTRACT

Tinnitus pathophysiology has been associated with an atypical cortical network that involves functional changes in auditory and non-auditory areas. Numerous resting-state studies have replicated a tinnitus brain network to be significantly different from healthy-controls. Yet it is still unknown whether the cortical reorganization is attributed to the tinnitus frequency specifically or if it is frequency-irrelevant. Employing magnetoencephalography (MEG), the current study aimed to identify frequency-specific activity patterns by using an individual tinnitus tone (TT) and a 500 Hz-control tone (CT) as auditory stimuli, across 54 tinnitus patients. MEG data were analyzed in a data-driven approach employing a whole-head model in source space and in sources' functional connectivity. Compared to the CT, the event related source space analysis revealed a statistically significant response to TT involving fronto-parietal regions. The CT mainly involved typical auditory activation-related regions. A comparison of the cortical responses to a healthy control group that underwent the same paradigm rejected the alternative interpretation that the frequency-specific activation differences were due to the higher frequency of the TT. Overall, the results suggest frequency-specificity of tinnitus-related cortical patterns. In line with previous studies, we demonstrated a tinnitus-frequency specific network comprising left fronto-temporal, fronto-parietal and tempo-parietal junctions.

1. Introduction

Tinnitus aurium or "ringing in the ears" is perceived in tinnitus patients unrelated to any external auditory stimulus. This so-called phantom sound is assumed to be prevalent in 10 to 15% of the adult population (Jarach et al., 2022). Currently, tinnitus is not assessable by any techniques besides the patients' self-reports. The health status of tinnitus patients has been studied intensively, revealing in parts of the population a high level of suffering, in addition to hearing problems: attentional and sleeping problems, a significant reduction in a patient's emotional well-being, including stress, depression and anxiety, and a reduced quality of life (Brueggemann et al., 2022; Dobie, 2003; Ivansic et al., 2017, 2019; Tyler & Conrad-Armes, 2009). Even though many different treatment approaches exist of which some can reduce tinnitus distress, there are many insufficient therapy outcomes and until now no curative treatment or licensed pharmacological therapy is available for subjective tinnitus (Baguley et al., 2013; Elgoyhen et al., 2015; Langguth & Elgoyhen, 2012). According to current guidelines, counselling, administration of hearing aids, behavioural therapy and self-help groups are recommended treatment strategies (Cima et al., 2019; Fuller et al., 2017; Mazurek et al., 2022). To advance diagnostical procedures and evaluation of treatment, an objective assessment of the individual tinnitus is desirable but hampered due to the subjective nature of tinnitus along with the high heterogeneity concerning its etiology, genetic contribution, and clinical phenotype (Elgoyhen et al., 2015).

Regarding neurophysiological correlates of tinnitus, a tinnitus-related increase in neural excitability reflected in the amplitude of the auditory N1 component was reported repeatedly (for review see Foxe et al., 2011; Tomé et al., 2015). This auditory evoked response is often used as an objective assessment to examine stimulus-associated EEG/

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MEG signal or as a biomarker to indicate typical and atypical cortical development. Similarly, a plethora of research employing electroencephalography (EEG) or MEG has examined the N1 component in relation to tinnitus, yet the findings are controversial throughout the literature. For instance, it has been shown that tinnitus patients compared to healthy-controls yield a higher N1 amplitude in response to a frequency-specific tone outside the region of hearing loss, typically 500 Hz or 1 kHz tones (Hoke et al., 1989; Pantev et al., 1989; Roberts et al., 2013; Weisz et al., 2005b), or in response to the tinnitus frequency (Kadner et al., 2002; Ku et al., 2017; Pineda et al., 2008). Yet other authors demonstrated significantly smaller N1 amplitudes in tinnitus patients in comparison to normal-hearing controls (Attias et al., 1993; Jacobson & McCaslin, 2003) or failed to exhibit any statistical difference in response to a 1 kHz tone (Colding-Jørgensen et al., 1992; Jacobson et al., 1991). The inconsistency of these outcomes is possibly caused by a relatively small sample size (<30 subjects) and different methodological strategies such as different and/or a varying number of a-priori-defined regions of interest or by varying restrictions of numbers of dipoles. Consequently, a consensus on the N1 amplitude in response to frequency-specific auditory stimulation in tinnitus patients has not been reached yet.

While these above-mentioned studies focused on auditory regions and mainly on N1 evoked response, other neuroimaging studies reveal that conspicuous activity is not restricted to the auditory system only, but comprises regions involved in non-auditory and higher-order functions such as the attention, memory, and emotion network (Husain & Schmidt, 2014). Hence, it is suggested that tinnitus involves top-down processes (Jastreboff, 1990) and a widespread network of cortical sources. In particular, there exists a growing body of literature pointing towards a differential brain network involving fronto-parietal, anterior cingulate cortex, subcortical regions and the auditory cortices in tinnitus patients as compared to healthy-controls. Such evidence has been provided by recording resting states and by different functional imaging techniques such as functional magnetic resonance imaging (fMRI), electro/magnetoencephalography (EEG, MEG), and positron emission tomography (PET) (Besteher et al., 2019; Maudoux et al., 2012; Mirz et al., 1999; Paraskevopoulos et al., 2019; Stein et al., 2015a, Stein et al., 2015b). Several authors assume that this is due to cortical reorganization (Eggermont & Roberts, 2004, 2012; Christo Pantev et al., 2012; Stein et al., 2015a, Stein et al., 2015b), by which each source contributes to a different extent (Maudoux et al., 2012; Mirz et al., 1999). Two reviews (Husain & Schmidt, 2014; Kok et al., 2022) supplied an overview over global changes in tinnitus patients and suggested that several resting-state brain networks such as the default mode network, auditory attention network, and functionally coupled regions in the limbic system among others are maladaptively reorganized in tinnitus patients. The principal brain structures involved in these networks comprise areas such as the posterior cingulate cortex, the medial prefrontal cortex, inferior frontal cortex, medial prefrontal cortex, the insula, and the *para*-hippocampus (see also Besteher et al., 2019).

To the best of our knowledge, most studies in the field used resting state measurements to investigate tinnitus-related cortical connectivity. Resting-state as a task-free measurement cannot directly relate neurophysiological findings to specific cognitive processes and draw conclusions from this relation. In addition, most of them employed ROI-based analyses, which define regions of interest a-priori and, as a consequence, areas important to the tinnitus network might have been neglected. Thus, a lack or replicability has been pointed out in a recent review (Kok et al., 2022). In our recent study (Paraskevopoulos et al., 2019), by using directed functional connectivity metrics, we applied a whole-head analysis and were able to investigate connectivity differences of intrinsic cortical networks underpinning tinnitus, without predefining the regions of the network. By studying 40 chronic tinnitus patients and 40 control subjects via open-eyes resting state MEG measurements, we were able to outline altered functional connectivity in intrinsic networks of the tinnitus population. We demonstrated increased connectivity between dorsal prefrontal and right medial temporal areas, as well as, increased engagement of other intrinsic networks such as the affective and attentional networks, along with an effect in the auditory domain. Additionally, the resting state networks showed maladaptive alterations, including a significant reduction in network efficiency, as well as increased characteristic path length in tinnitus patients correlating with tinnitus distress.

However, there is a growing body of research showing a larger scale network that functions in a dynamic state, thereby motivating to study evoked activity in tinnitus patients. As an example, tailor-made notched music training (TMNMT) significantly reduced tinnitus loudness being accompanied by decreased tinnitus-related auditory evoked fields at a latency of 100 ms after sound onset of the tinnitus tone (Stein et al., 2015a, Stein et al., 2015b). Through inducing inhibition on neurons coding the tinnitus frequency, by using appropriate auditory stimulation, the effects of maladaptive plasticity in chronic tonal tinnitus patients are reduced. Frequencies representing the subject's individual tinnitus pitch are extracted from the music's frequency spectrum by applying a notch filter. Thus, hyperactive neurons coding the tinnitus frequency get laterally inhibited by neurons coding the edge frequencies of the notch (Catz & Noreña, 2013). Due to these findings, we assume that specifically the neuronal populations in the auditory cortex that code the tinnitus frequency are involved in tinnitus perception (Diesch et al., 2004; Mühlnickel et al., 1998; Roberts et al., 2010).

Currently, it is still unknown whether the tinnitus network is attributed to the perception of the tinnitus tone per se or if it is frequency irrelevant. We hypothesize a tinnitus frequency-specific functional connectivity pattern. Methodologically, we followed the approach of Paraskevopoulos and coauthors (2019) by using magnetoencephalographic measurements, however in the current study we recorded evoked-related brain responses and not brain responses related to resting states. In particular, we applied functional brain connectivity and event-related source space analysis and provided a paradigm of frequency-specific auditory stimulation in contrast to a control stimulus. Thereby, we aimed at identifying frequency-specific activity patterns specifically attributable to an auditory stimulation using the individual tinnitus tone and a 500 Hz-control tone. The cortical responses of 54 tinnitus patients were additionally compared to a group of normal-hearing subjects not suffering from tinnitus that underwent the same paradigm in a control study, to eliminate frequency-specific differences in cortical activation as an alternative interpretation of our findings.

2. Methods

2.1. Participants

In total, 54 tinnitus patients (*mean age* = 52.98 years, *SD* = ±9.5 years, *age range* = 27–64 years; *gender* = 29 males, 25 females) with chronic (≥3 months) tonal (i.e. tone, peep- or whistle-like) tinnitus (23 bilateral, 14 dominant left, 15 dominant right; *mean tinnitus pitch-match frequency* = 6078.24 Hz, *SD* = ±2905.24 Hz) and 20 normal-hearing subjects (*mean age* = 31.50, SD = ± 7.89; *gender* = 12 male, 8 female) not suffering from tinnitus, were included in the main and the control study respectively. MEG measurements were performed at the Biomagnetic Center of the Hans Berger Department of Neurology, Jena University Hospital (JUH). Subjects were recruited from the pool of patients of the Tinnitus Center at the ENT department of the JUH. They were first selected from the database according to the following inclusion criteria: 1) chronic and tonal tinnitus with stable pitch, 2) no severe hearing loss (≤60 dB HL) in the frequency ranges of one half octave above and below the tinnitus pitch-match frequency as well as 3) tinnitus frequencies between 1 and 12 kHz; and following exclusion criteria 1) severe or acute neurological or psychiatric disorders, 2) otological diseases 3) other rehabilitation therapies, that might interfere with this study. In addition, each patient received an initial ENT evaluation by an oto-rhino-laryngologist, in order to exclude any potential

physiological disorder that could evoke tinnitus perception or might distort any threshold determination, such as excess earwax, irregularities of the tympanic membrane or the ear canal. The tinnitus was considered tonal when a patient described the sound as a "pure" tone, like a musical note, ringing, beeping or whistling, otherwise reports of hissing-like tinnitus sound lead to exclusion. The study was performed in accordance with the Declaration of Helsinki and approved by the ethics committee of the JUH (4883–07/16). All participants signed an approved informed-consent before being included in the study.

2.2. Behavioral measurements

2.2.1. Audiometry

Pure tone audiometry was performed by an examiner using the clinical audiometer Equinox 2.0 (Interacoustics A/S, Assens, Denmark). Standard clinical procedures were followed to assess pure tone hearing thresholds. During this procedure, air conduction thresholds (in dB sound pressure level (SPL)) of all subjects were determined for the following frequencies: 125, 500, 1000, 1500, 2000, 3000, 4000, 6000, 8000, 10000, 12000, 14,000 and 16000 Hz. The group mean average of these audiometry values is shown in Fig. 1.

2.2.2. Pitch matching

The tinnitus frequency was determined by using a self-administered automated iPod-based pitch-matching procedure comprising a recursive two-interval forced-choice test (RIFT) repeated for ten sessions. The test was performed running a Graphical User Interface (GUI) based application on an iPod Touch Model A1367. Patients wore stereo headphones (Sennheiser HD 201, Wedemark- Wennebostel, Germany) for testing. The application was developed for individual tinnitus pitch matching and was evaluated in relation to a standardized audiometric test and demonstrated equal reliability (for details see Wunderlich et al., 2015) as well as very high reliability across measures (Korth et al., 2020). The advantage of using a self-administered test is that it can be repeatedly performed at home without the supervision of an examiner. Initially, patients were instructed by the researcher how to use the application. They were required to do the test once a day on 10 consecutive days. Afterward, an automatically generated email was sent to the examiner including the outcome of all 10 pitch matching tests. The mean frequency across all sessions was calculated and used as the individual tinnitus pitch of each patient.

2.2.3. Questionnaires

A series of self-report psychometric questionnaires were provided in German language to assess anxiety, depression, somatic symptoms (SCL-90-R, BDI II, PHQ-D, WHODAS 2.0, KSE-G, STAI-G), as well as tinnitus severity (THI, THQ, TQ) (Beck & Steer, 1984; Goebel & Hiller, 1994; Goebel and Wolfgang, 1998; Kemper et al., 2012; Kuk et al., 1990; Newman et al., 1996; Schmitz et al., 2000; Spielberger et al., 1971; Spitzer et al., 1999; Üstün et al., 2010; Spielberger et al., 1983;). For the descriptive scores of all questionnaires, see Table 1..

2.3. Stimulation paradigm

The stimulus paradigm was performed via Presentation software (Version 18.0, Neurobehavioral system, Inc., Berkeley, CA, https://www.neurobs.com). It consisted of two different tone-stimuli: the 500 Hz tone representing the control condition for both the patients and the control group and the tinnitus tone which was the individual tinnitus frequency for the patients group, whereas for the control group in the control study, the TT was a randomly selected frequency by the pool of tinnitus frequencies (*mean* = 5600, *SD* = 2141.85) measured in the tinnitus patients. Each stimulus lasted 1000 ms with an inter-stimulus interval (ISI) between 3000 and 4000 ms, which was set to avoid rhythmicity and expectancy. In total, 150 stimuli (75 tinnitus tone (TT) and 75 control tone (CT) stimuli) were presented binaurally in a randomized order. Prior to the stimulation, patients were asked to match the intensity of the control tone to their perceived tinnitus tone, in order to ensure that the perceived loudness of both conditions was equal. During the experiments the intensity of the tones was set to 50 dB SPL above hearing threshold.

2.4. MEG recording

Magnetoencephalography (MEG) was recorded using a 306-channel helmet-shaped neuromagnetometer (Vectorview, Elekta Neuromag Oy, Helsinki, Finland), comprised of 102 magnetometers and 204 planar gradiometers, in a magnetically shielded room. MEG data were sampled

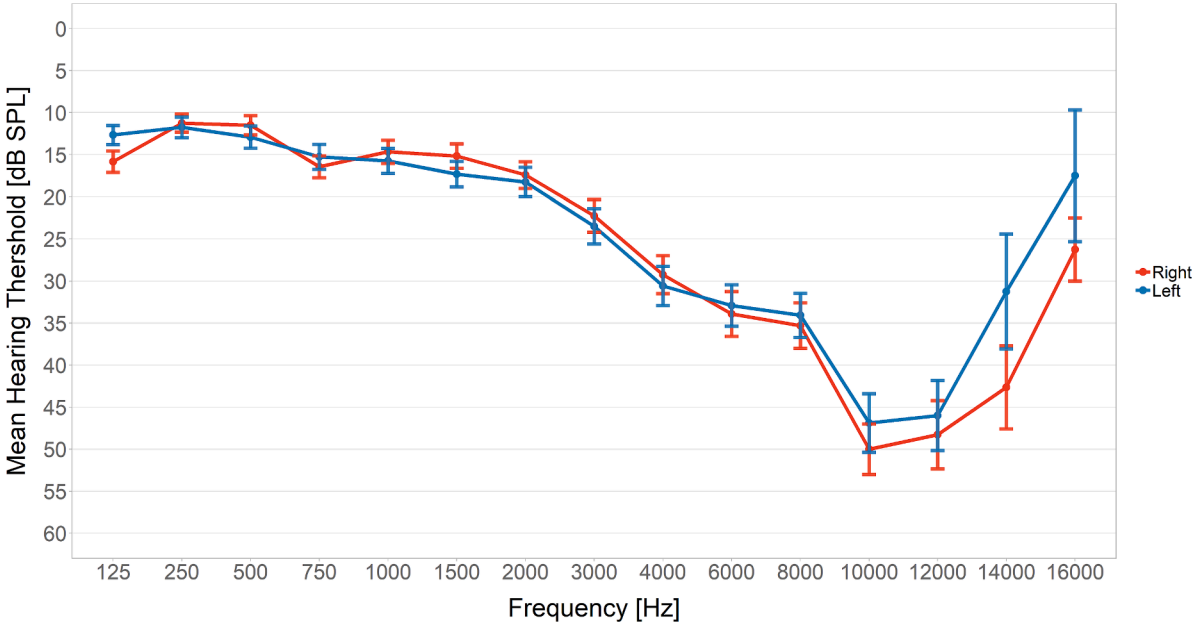

Fig. 1. Mean values pure-tone audiometry. The figure depicts the audiometric results across all subjects. The lines represent the mean hearing thresholds in dB sound pressure (SPL) at different frequencies in Hz and the vertical bars represent their corresponding standard deviation, for both ear sides.

Table 1
Descriptive scores.

	SCL-90	BDI II	PHQ							THI	WHODAS	THQ	TQ	KSE		STAI	
			so	dep	pan	anx	bul	bin	alc					PQ	NQ	S	T
p004	N/A	1	2	1	2	1	2	2	2	22	6	21.7	13	2	0.33	30	25
p005	0.24	6	2	2	2	2	2	2	2	40	19	30.4	22	2.33	1	36	41
p006	0.32	N/A	3	2	2	1	2	2	2	38	20	33.3	36	4	0	29	29
p007	0.14	0	1	1	2	1	2	2	2	6	6	3.3	7	2.66	0.33	31	26
p008	0.46	10	2	2	2	2	2	2	2	46	13	29.5	42	3	0.33	36	44
p010	0.28	6	1	1	2	1	2	2	2	24	9	20	27	2.33	0.66	27	36
p011	0.34	11	1	2	2	2	2	2	2	34	11	10.7	17	1.66	0.33	36	45
p012	0.28	6	3	1	2	1	2	2	2	10	2	5.55	9	3	0.33	36	34
p013	0.44	13	2	1	2	2	2	2	2	32	9	20.2	31	3.33	0	36	38
p014	0.1	1	1	1	2	1	2	2	2	6	1	3.3	7	2	0	20	21
p015	0.54	12	N/A	N/A	N/A	N/A	N/A	N/A	N/A	34	48	27.4	28	2	0.66	36	41
p016	0.78	18	2	3	2	2	2	1	2	28	40	28.1	34	2	0.33	33	31
p017	0.25	6	3	2	2	3	2	2	2	34	16	25.2	28	3.33	1	30	34
p018	0.44	11	1	1	2	1	2	2	2	71	49	35.6	35	2.33	1	48	50
p020	0.14	2	1	1	2	1	2	2	2	4	2	16.3	12	3	0.33	20	29
p021	0.32	5	2	1	2	2	2	2	2	30	24	23.7	13	2.66	0.66	35	33
p023	0.4	11	3	2	2	2	2	2	2	32	16	43	25	2.66	0.66	53	45
p024	0.51	7	3	1	2	2	2	2	2	16	15	14.8	10	3	0.66	33	36
p029	1.97	30	4	4	1	4	2	2	2	70	15	58	58	0.33	0	66	64
p030	0.77	25	2	3	2	1	2	2	2	66	32	67	46	3.67	0	30	49
p031	0.14	0	1	1	2	1	2	2	2	14	14	13.3	20	3	0.33	31	29
p032	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
p033	0.3	3	1	1	2	1	2	2	2	12	7	10.2	10	3	0	33	31
p034	0.61	23	1	4	2	4	2	2	2	72	22	61.1	59	1.33	0.66	55	54
p035	0.08	5	1	1	2	1	2	2	2	18	9	15.9	N/A	3	0.33	32	27
p036	0.45	6	1	1	2	2	2	2	2	26	10	25.9	39	3	0	34	39
p038	0.6	2	2	2	2	3	2	2	2	34	23	22.2	29	1.66	0.66	36	38
p039	0.37	14	3	3	2	2	2	2	2	38	36	29.3	33	2.33	1.33	45	49
p040	2.82	37	4	4	2	4	2	2	2	96	66	90.4	47	3	0	75	63
p041	0.16	3	3	2	2	1	2	2	2	24	10	29.9	41	3.33	0.33	26	33
p043	0.43	10	2	2	2	1	2	2	2	32	16	21.1	47	3	0.66	41	N/A
p044	0.24	8	2	2	2	N/A	2	2	2	40	22	27.4	42	3	1.33	31	34
p045	0.27	3	2	2	2	3	2	2	2	54	4	39	38	3.66	1.66	N/A	N/A
p046	1.24	30	1	4	2	3	2	2	2	66	38	65.2	N/A	N/A	0.67	56	61
p047	0.6	7	4	2	1	2	2	2	2	32	23	32.2	39	1.66	0	43	39
p048	0.41	6	13	N/A	N/A	2	2	2	2	28	37	33	46	2	2	43	42
p050	0.1	0	2	1	2	1	2	2	2	18	8	14.5	21	3.33	0	N/A	N/A
p051	0.21	0	2	1	2	1	2	2	2	18	10	21.5	11	3	0	26	32
p052	N/A	18	1	2	2	2	2	2	2	58	34	67.4	54	2	0	47	46
p053	0.32	8	1	2	2	2	2	2	2	44	22	43.7	41	3.66	0	31	32
p054	0.27	6	2	1	2	1	2	2	2	18	11	11.4	19	2.33	0.33	29	26
p055	1.16	20	3	3	2	2	2	2	2	60	13	45.6	40	2.33	0.66	61	58
p056	1.44	1	1	2	2	2	2	2	2	18	8	23.7	18	3.33	0	50	43
p057	0.33	2	1	1	2	2	2	2	2	34	17	34.4	26	3.33	0	31	34
p058	0.12	0	1	1	2	1	2	2	2	6	4	10	15	3	0.33	24	25
p059	0.38	17	2	2	2	2	2	2	2	44	45	33	33	1.66	0	43	45
p060	0.58	15	1	2	2	4	2	2	2	62	33	70.4	45	3.33	0	36	49
p061	0.01	0	1	0	2	1	2	2	2	14	2	6.48	8	2.66	0.66	36	29
p062	1.78	29	1	3	2	3	2	2	2	36	37	34.8	28	2.33	1	60	62
p063	0.1	4	1	1	2	1	2	2	2	20	5	68.6	36	3	0	22	26
p064	0.62	25	1	2	2	3	2	2	2	78	30	66.7	56	2	1	53	51
p066	0.11	1	2	1	2	1	2	2	2	20	3	39.1	24	3	0.67	27	28
p067	0.88	26	2	3	2	2	2	2	2	58	57	60.4	43	3	0.33	54	55
p068	0.5	14	1	3	2	1	2	2	2	58	43	49.6	39	2.66	0	38	55
Mean	0.51	10.07	1.82	1.84	1.96	1.84	2	1.98	2	35.71	20.22	32.72	32.45	2.46	0.62	38.23	39.72
SD	0.52	9.49	0.91	0.96	0.19	0.92	0.00	0.13	0.00	20.33	15.65	20.33	13.85	0.81	0.69	12.11	11.40

Note. BDI II = Beck Depression Inventory II: 0–12 = mini, 13–19 = mild, 20–28 = moderate, 29–63 = severe; PHQ-D = Patient Health Questionnaire: so = Somatic (1 = mini. 2 = low. 3 = medium. 4 = high), dep = Depression (1 = mini, 2 = mild, 3 = moderate, 4 = severe), pan = Panic (1 = yes, 2 = no), anx = Anxiety (1 = mini, 2 = mild, 3 = moderate, 4 = severe), bul = Bulimia (1 = Yes. 2 = No), bin = BingeEating (1 = Yes, 2 = No), alc = alcohol abuse (1 = Yes, 2 = No); THI = Tinnitus Handicap Inventory; WHODAS = World Health Organization Disability Assessment; THQ = Tinnitus Handicap Questionnaire; TQ = Tinnitus questionnaire Goebel and Hiller; KSE-G = Social Desirability–Gamma Short Scale: NQ (negative qualities), PQ (positive qualities); STAI-G = S (state anxiety), T (trait anxiety) Inventory: total score (20–37 = no, 38–44 = moderate, 45–80 = high).

at 1 kHz, applying an online low pass filter at 330 Hz and high pass filter at 0.1 Hz. A 3D Digitizer (3SPACE FASTRAK, Polhemus Inc., USA) was used to locate anatomical landmarks (nasion and preauricular points) and the MEG localization coil sets. Two bipolar channels recorded the electrooculogram (EOG), another two the electrocardiogram (ECG). During recordings, patients lay in supine position. They were instructed to stay relaxed with their eyes open and to fixate on a point on the ceiling of the MEG chamber. The auditory stimuli were delivered via silicon tubes of 60 cm length and an inner diameter of 13 mm ending with a silicon earpiece fitted individually to each subject's ear. The whole experiment lasted for approximately 30 min. Before analyzing the MEG data, a Signal Space Separation (SSS) provided by Elekta MEG system was implemented to reduce the external noise from the MEG signals within the helmet.

2.5. MEG data analysis

For the analysis of the data, we followed a previously developed pipeline that has been already used for auditory experiments (Paraskevopoulos et al., 2015, 2019; Salvari et al., 2019). Fig. 2 depicts the analysis step by step.

2.6. Statistical analysis

The BESA research software was used for the pre-processing of the data, which provides an adaptive artifact correction procedure to correct electrocardiographic (ECG) and eye-blink artifacts (Ille et al., 2002). Due to different sensor types, only the gradiometer channels were used to simplify the data analysis. Both sensor types produce similar results in source reconstruction (Garcés et al., 2017), though gradiometers are more sensitive to sources directly under the sensors. Data were down-sampled to 500 Hz and filtered offline with a low-pass filter of 35 Hz and a high-pass filter of 0.5 Hz, using this frequency range for the next processing steps. Channel-wise baseline correction was based on the mean evoked related fields (ERFs) in the time-window 100 ms before stimulus onset. Data were divided into epochs, including the 1000 ms post- and 500 ms pre-stimulus onset intervals. Trials exceeding an amplitude of 1200 fT/cm were considered artifacts and were rejected, and epochs that exceeded the 15% of rejected trials were excluded from further processing. Among the 54 subjects, none of them exceeded current exclusion numbers, and as such we ended up having at least the 85% of trials for each condition and each subject for analysis.

For the source space analysis within the tinnitus group, we first calculated the Global Field Power (GFP) in sensor space with a bootstrap algorithm, in order to roughly determine the time-windows of the auditory components a-priori to be used for further statistical analysis. Fig. 3 shows the Grand Average of the ERF time series after 1000 bootstrap sampling, along with their corresponding confidence intervals set at 95%. The time-windows were selected according to observed differences between the means that fall outside the confidence interval. Namely, the 20–60 ms, 80–120 ms, 140–220 ms and 220–300 ms time intervals.

For the forward solution, a standardized realistic head model of finite elements (FEM) was used, created from an averaged head using 50 individual MRIs in Talairach space, as provided by the BESA software. Due to the fact that most of the patients were not willing to undergo MRI scanning, we could not acquire individual head models for all patients. For source reconstruction, the original Low Resolution Electromagnetic Tomography (LORETA) was applied as the inverse solution for each subject and each condition. The current inverse solution is based on weighted minimum norm method and it provides a smooth distribution of sources with a solution space formed by a regular cubic grid (Pascual-Marqui et al., 1994). Current Density Reconstruction (CDRs) time series were extracted with 10 mm voxel size, for each time-window separately, as single images for each subject and each condition. The timepoint of each image was displayed at the maximum GFP within interval. For the source space analysis the images were then smoothed with 1x1x1 mm voxel size resolution. For the current analysis, the SPM12 running in Matlab environment (R2016b version; MathWorks Inc., Natick, MA, USA) was used. An explicit mask was set to exclude deeper regions from the current density estimation prior to statistics, which were out of interest, as well as, to decrease the search volume, as well. Paired-sample t-tests were run for between-conditions statistical differences and for each time-window separately. T-contrast matrix-tables were designed to test statistical differences for each side of the contrast ($TT > CT$, $CT > TT$). For the between-groups analysis we applied the same preprocessing procedure and run a factorial analysis of a 2-Group (control subjects, tinnitus subjects) × 2-Frequencies (CT, TT) design to test whether the differences in tones derive due to group differences. The Family Wise Error (FWE) was set for multiple analysis correction at 0.05 probability level (unless otherwise noted).

2.7. Connectivity analysis

As we were interested to examine functional connectivity without pre-defining specific cortical regions, we used a whole-head approach that included the complete time-interval after stimulus onset (1000 ms). The CDRs were extracted as 4D images that included a complete 3D space solution for each time point. The LORETA solution was again used, which generally divides the cerebral cortex into 2394 voxels of 7x7x7mm. Since we did not have individuals head model, and the inverse solution used (i.e. LORETA) is by definition smooth, we reduced the number of voxels by re-slicing the images into a voxel size of 10x10x10mm. We used a generic head model of 863 voxels, based on Talairach space, which includes the cortex and a few sub-cortical areas, while excluding deep sub-cortical regions. Each voxel represented the nodes in the network, comprising a 863-node network covering the whole head. This has been found in our previous work to have a good analogy for leaving the LORETA solution untouched (Paraskevopoulos et al., 2015, 2019; Salvari et al., 2019). An adjacency matrix of 863 × 863 × 108 (nodes × nodes × (54 subjects × 2 conditions)) was calculated via the HERMES toolbox and based on the Mutual Information (MI) algorithm, which detects mutual dependences between random variables (here the nodes in the network) non-linearly (Niso et al., 2013). To examine for statistically significant connections between conditions, a general linear model (GLM) for each pair of nodes was applied, with The False Discovery Rate (FDR) set for multiple comparisons correction of 0.05 significance level and 10.000 permutations (NBS toolbox; Zalesky et al., 2010). With regard to the control group analysis, it should be mentioned that we did not apply the same functional connectivity procedure, since it would have made our analysis more complex and also the source space analysis provided adequate results on our hypothesis of interest.

3. Results

3.1. Source space

Among the time windows selected for statistical analysis, only the 220–300 ms interval did not demonstrate statistically significant differences after the analysis in source space. Fig. 4 depicts the significant regions on a cortical surface as yielded by the analysis of between-condition comparisons in SPM, projected in Montreal Neurological Institute (MNI) brain coordinates.

With regard to the TT > CT contrast (see Table 2), the results revealed significant differences in the 80–120 ms time-interval involving the left fronto-parietal cortex with peaks of clusters in occipital cortex (peak cluster: x = -14, y = -78, z = 22, cluster size = 2403, t = 6.33, p <.05, FWE corrected), in left precentral gyrus (x = –22, y = -24, z = 50, cluster size = 1168, t = 6.23, p <.05, FWE corrected) and cingulate gyrus (peak cluster: x = -14, y = -26, z = 46, cluster size = 136, t = 5.74, p <.05, FWE corrected), as well as, in the right medial frontal gyrus (cluster peak: x = 10, y = 6, z = 54, cluster size = 136, t = 4.96, p <.05, FWE corrected). The region of anterior cingulate cortex was also obtained in the 140–220 ms time interval, with the peak of cluster located on the right side (peak cluster: x = 0, y = -12, z = 42, cluster size = 980, t = 5.35, p <.05, FWE corrected).

For the CT > TT contrast (see Table 3), statistically significant differences were demonstrated in the 20–60 ms interval which involved the left putamen (peak cluster: x = –32, y = -14, z = 16, cluster size = 885, t = 5.56, p <.05, FWE corrected at cluster level). In the 80–120 ms time-window, the results revealed statistically significant cortical activation in the temporal and frontal cortex bilaterally. The biggest in size cluster comprised the left temporal cortex and part of the left inferior frontal cortex, with the peak of the cluster placed in the left superior temporal gyrus (× = -52, y = -16, z = 4, cluster size = 2387, t = 6.80, p < 0.5, FWE corrected). Other significant regions were obtained in right inferior frontal gyrus (peak cluster: x = 50, y = 34, z = 4, cluster size = 1724, t =

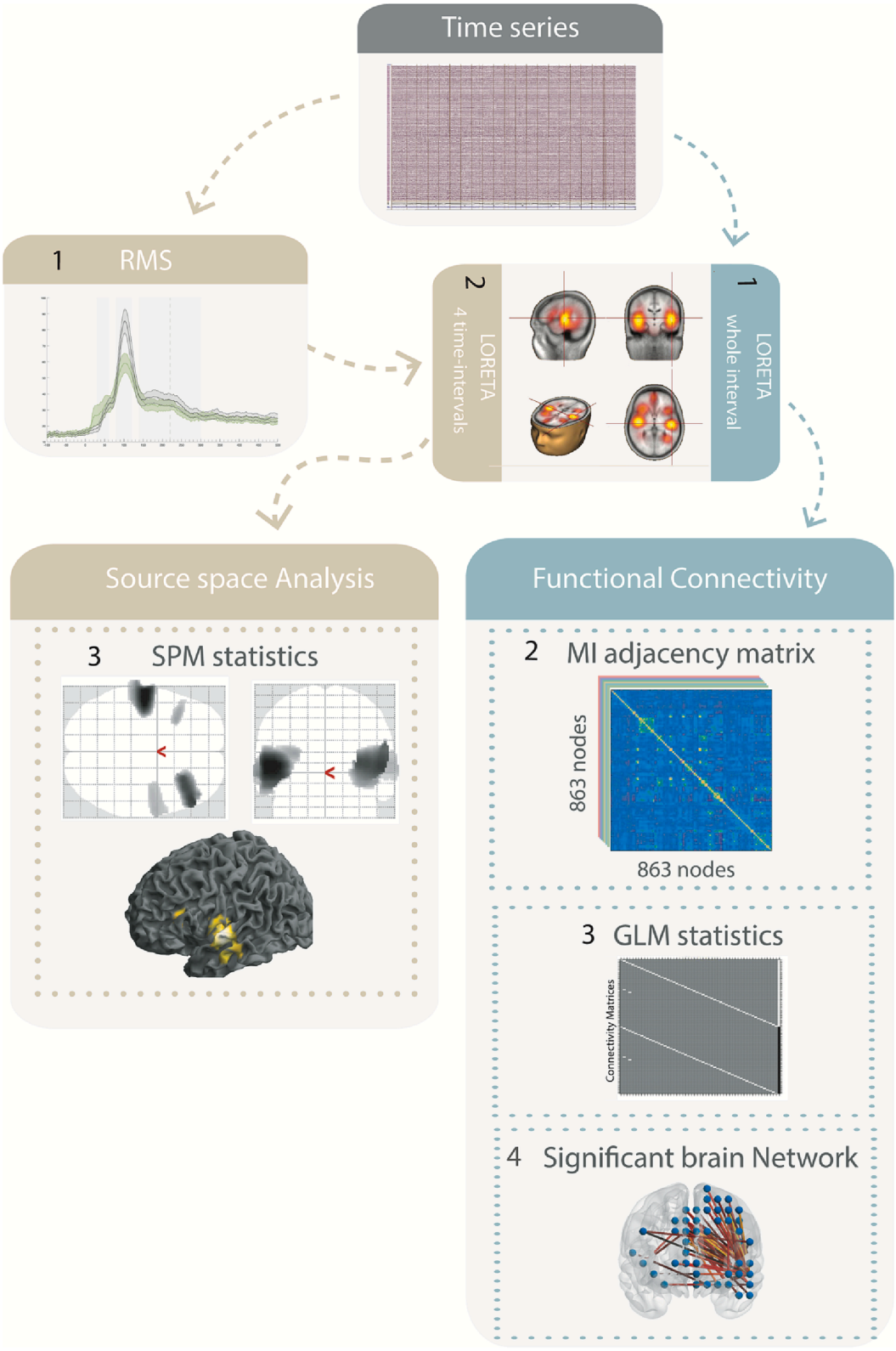

Fig. 2. Schematic illustration of the analysis. Time series pre-processing was applied in BESA research software. Source space analysis: 1) The Root Mean Square (RMS) was calculated to determine the time-intervals of interest, 2) The Low Resolution Brain Electromagnetic Tomography (LORETA) solution was applied on the averaged evoked fields for each time-interval, 3) Statistical analysis in source space was performed using Statistical Parametric Mapping in the form of the SPM12 toolbox for each time window and each side of the contrast (TT > CT, CT > TT), 4) The mean amplitude values of the significant regions were extracted for each condition and each time window, 5) Multiple linear regression analyses were run with the clusters as the dependent variables and the questionnaires and the demographics as the independent variables. Brain connectivity analysis: 1) The LORETA solution was applied on the averaged trials of the whole time-interval after stimulus onset (1 s), 2) Mutual Information (MI) adjacency-matrices construction in HERMES toolbox, 3) Statistical analysis of the adjacency matrices in NBS toolbox, 4) Visualization of the brain network graph performed by the BrainNet toolbox.

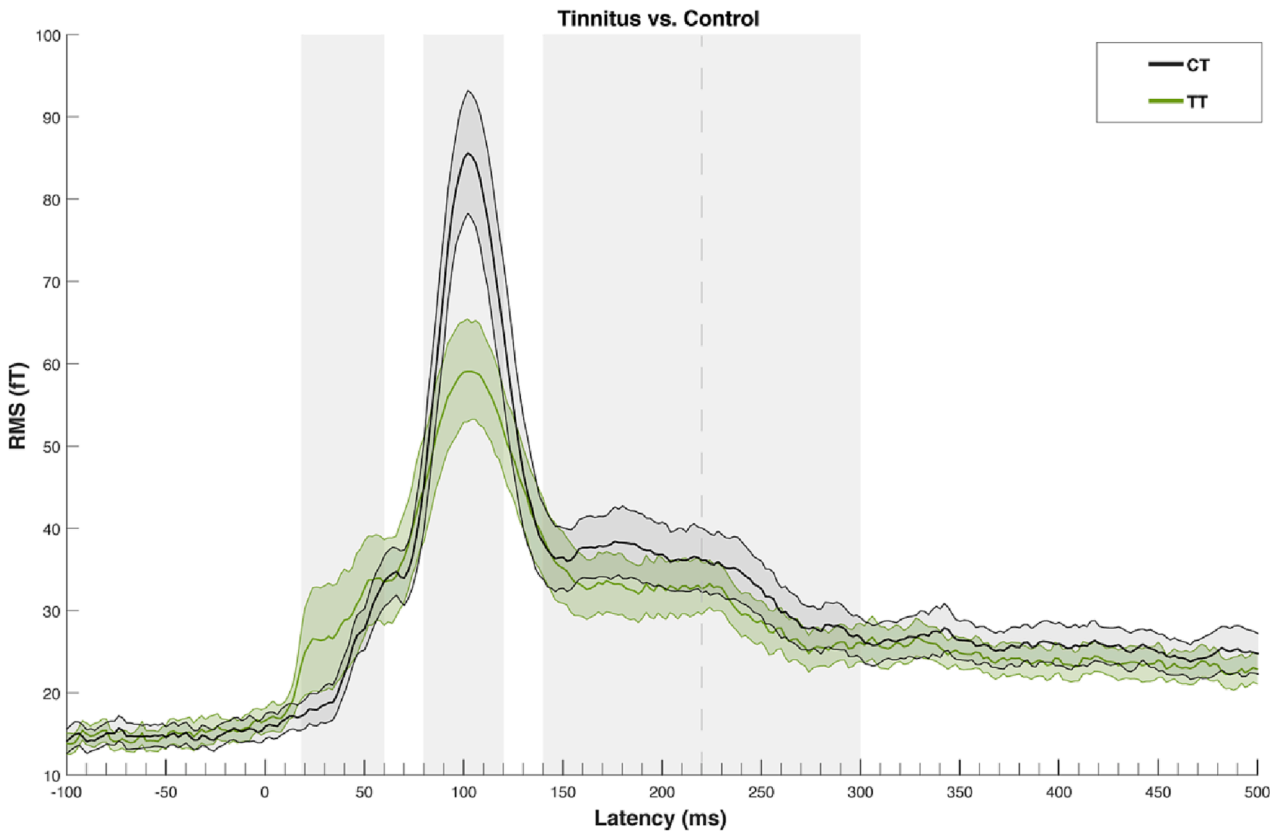

Fig. 3. Group Averages of Root Mean Square timeseries. The graph illustrates mean of the RMS time-series of each condition averaged across subjects. The means of each condition are identified by the thicker lines representing the TT in black and the CT in green color. Their corresponding confidence interval (set at 95 %) are depicted by the shaded color. The time-intervals selected for the analysis are also framed in grey-transparent color.

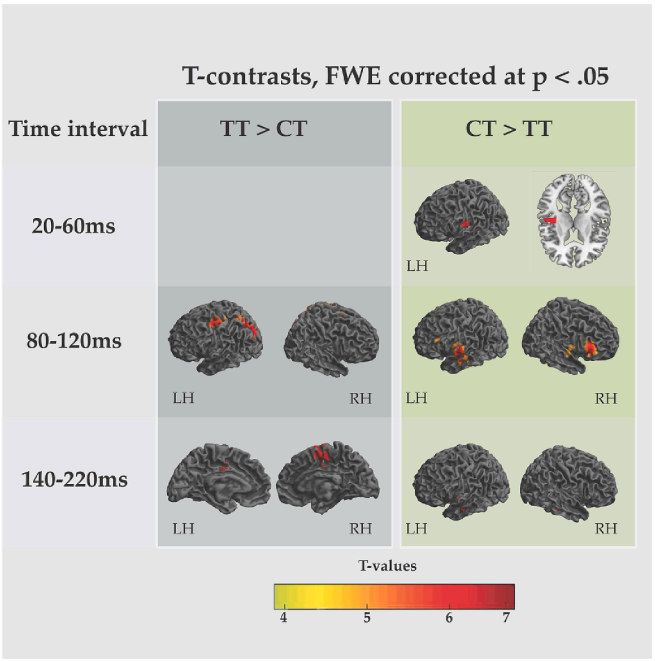

Fig. 4. Results of the statistical parametric mapping between conditions and on three different time-intervals. All the images depict the left and right-hemisphere view of the brain; also horizontal view in 20–60 ms time interval; the midsagittal view in 140–220 ms time interval on the TT > CT contrast. At the bottom, the color bar represents the T values of each peak cluster, as resulted from the analyses, FWE corrected at p <.05.

6.31, p <.05, FWE corrected), in right superior temporal gyrus (peak cluster: x = 62, y = -4, z = 6, cluster size = 738, t = 4.98, p <.05, FWE corrected) and left insula (peak cluster: x = –32, y = 18, z = 16, cluster size = 293, t = 5.17, p <.05, FWE corrected). Statistically significant activation was demonstrated in 140–220 ms time interval analysis, although, with very small clusters, namely in the left putamen (peak cluster: x = –32, y = -16, z = -10, cluster size = 138, t = 5.80, p <.05, FWE corrected), right parahippocampal gyrus (peak cluster: x = 48, y = -28, z = -14, cluster size = 118, t = 5.09, p <.05, FWE corrected) and left superior temporal gyrus (peak cluster: x = -48, y = -12, z = -10, cluster size = 225, t = 5.08, p <.05, FWE corrected).

3.2. Control study

The results of the interaction analysis Group × Frequency showed statistically significant differences between the factors in the right parahippocampal gyrus and left primary somatosensory cortex in the postcentral gyrus [corrected at p < 0.001 by taking into account peak voxel significance (threshold p < 0.001 uncorrected) and cluster size (threshold size > 210 voxels); Table 4,Fig. 5.

3.3. Functional connectivity

The analysis of functional connectivity yielded statistically significant differential brain network for the TT in comparison to the CT, which involved mainly the left hemisphere in the temporal, frontal and parietal lobe (p <.001, FDR corrected, 10.000 permutations). In total, 104 weighted edges were demonstrated representing the connectomes across the 81 nodes, that were found to be the statistically significant regions in the network. Fig. 6 shows the edges of the network that are colored relatively to the t-values indicating the strength of each

Table 2

Time window	Location of peak cluster	Tinnitus > Control MNI			Cluster size in voxel	T(1,54)	P FWE corrected
		x	y	z			
80–120 ms	Left occipital cortex	−14	−78	22	2403	6.33	0.000
	Left precentral gyrus	–22	−24	50	1168	6.23	0.000
	Left posterior cingulate gyrus	−14	−26	46	136	5.74	0.007
	Right frontal gyrus	10	6	54	136	4.96	0.007
140–220 ms	Right Anterior cingulate cortex	0	−12	42	980	5.35	0.000

The statistically significant regions in different time windows with corresponding locations and coordinates (MNI) as derived by the source space analysis of TT > CT. Cluster size and T- values are also depicted, FWE corrected at $p < 0.05$ level of significance.

Table 3

Control > Tinnitus							
Time window	Location of peak cluster	MNI			Cluster size in voxel	T(1,54)	P FWE corrected
		x	y	z			
20–60 ms	Left putamen	–32	−14	16	778	5.45	0.000
80–120 ms	Left superior temporal gyrus	−52	−16	4	2387	6.80	0.000
	Right inferior frontal gyrus	50	34	4	1724	6.31	0.000
	Left insula	–32	18	16	293	5.17	0.002
	Right superior temporal gyrus	62	−4	6	738	4.98	0.000
140–220 ms	Left putamen	–32	−16	−10	138	5.80	0.007
	Right parahippocampal gyrus	48	−28	−14	118	5.09	0.009
	Left superior temporal gyrus	−48	−12	−10	225	5.08	0.003

The statistically significant regions in different time windows with corresponding locations and coordinates (MNI) as derived by the source space analysis of CT > TT. Cluster size and T- values are also depicted, FWE corrected at $p < 0.05$ level of significance.

Table 4

Group × Frequency						
Location of peak cluster	MNI			Cluster size in voxel	F (1,20)	P value
	x	y	z			
Right parahippocampal gyrus	24	−24	30	400	19.90	0.000
Left primary somatosensory	–32	−34	52	597	16.23	0.000

The statistically significant regions with corresponding locations and coordinates (MNI) as derived by the source space analysis of Group vs Frequency. Cluster size and F- values are also depicted, $p < 0.001$ level of significance.

connectome in the network, as revealed by the statistical analysis.

In general, the network demonstrated left lateralization with most of the edges being concentrated in the left temporal regions connecting several areas throughout the brain, mainly in the dorsal frontal cortex and fewer regions in the parietal and occipital lobe. The results showed that the most significant regions in the network were the left superior and middle temporal gyrus, since they revealed the most connectomes in the network, as well as, the highest in strength based on the t-values. More specifically, the current regions were significantly connected to the left superior frontal gyrus, the middle frontal gyrus bilaterally, the medial frontal gyrus bilaterally, the anterior and posterior cingulate cortex, the left fusiform gyrus, the right precuneus and occipital areas. In addition, statistically significant connections were detected between the left inferior frontal gyrus and the right precentral gyrus, the left inferior temporal gyrus and the right precuneus extended to the right middle occipital gyrus, as well as, the left parahippocampal gyrus and the right precentral gyrus. The inverse side of the contrast was also calculated (CT > TT), though it did not yield any statistically significant differential brain network.

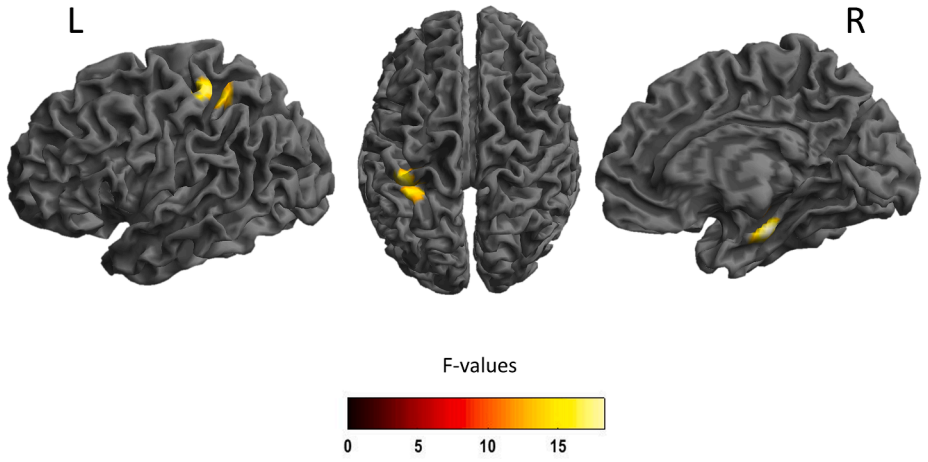

Fig. 5. Results of the statistical parametric mapping of the factorial Group by Frequency. All the images depict the left and right-hemisphere view of the brain. At the bottom, the color bar represents the F values of each peak cluster, as resulted by the analyses, $p < .001$.

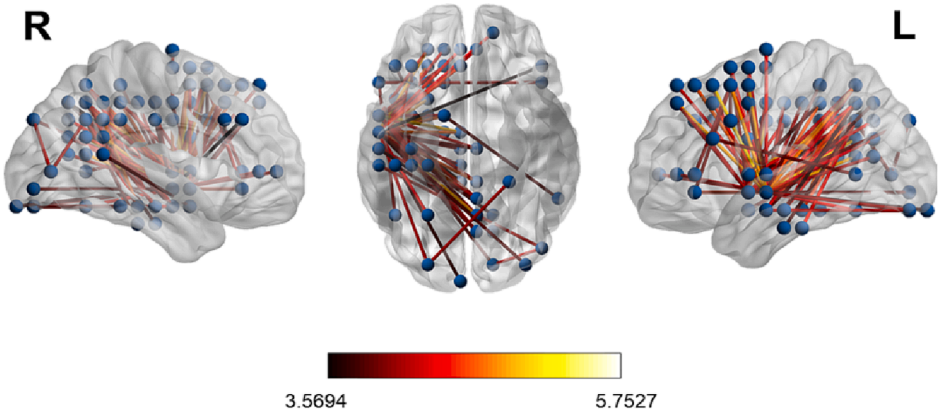

Fig. 6. Statistically significant differential brain network of the TT > CT contrast. The statistically significant regions are represented as nodes in the network in blue color. The edges that represent the interconnection of the nodes are colored based on the t-value range given on the color bar at the bottom of the figure. The edges are significant at p <.001 significance level, FDR corrected. The left and the right image depict the left and right view of the brain, respectively and the middle image depicts the top view of the brain (with parietal lobe pointing up).

4. Discussion

Magnetoencephalographic measurements were used to investigate brain alterations in 54 chronic tonal tinnitus patients using event-related source space analysis and functional brain connectivity analysis of cortical networks. The purpose of the current study was instead of examining general cortical differences between tinnitus patients and healthy controls, to investigate, in more detail, auditory processing within patients by comparing the processing of the tinnitus frequency with the processing of control sounds. More specific, we aimed at identifying frequency-specific activity patterns attributable to the auditory stimulation. Using Statistical Parametric Mapping, we found cortical differences between the TT and the CT in three different time-windows after stimulus onset, i.e. 20–60 ms, 80–120 ms and 140–220 ms corresponding to the P1, N1, and P2 auditory evoked component-latencies, respectively (Alho et al., 1994; Crowley & Colrain, 2004). We further included a control group in our analysis to ensure that current differences did not derive due to frequency-specific activation differences. A differential brain network was also revealed by the functional connectivity analysis indicating frequency-specific brain alterations in tinnitus patients, comprised of temporal, frontal and parietal connectomes.

4.1. Source space analysis

The TT condition demonstrated brain activation in dorsal brain areas involving the prefrontal and the parietal lobe, whereas the CT involved mainly temporal regions being evident during all time windows (c.f. Fig. 4). The fact that reduced brain activation of auditory sensory regions was demonstrated in the TT condition might reflect the dysfunctional sensory processing specifically of the tinnitus frequency but not of the control tone (note, that this cannot be due to hearing loss per se, because intensity of stimuli was individually adapted for each stimulus). Interestingly, the earliest activation difference (i.e. 20–60 ms after the tone onset) was located in putamen, showing a decreased amplitude in the processing of TT compared to the CT. This region is acknowledged as an important hub in several thalamocortical loops (Ghandili & Munakomi, 2022; Haber, 2003; Parent & Hazrati, 1995); also the P1 wave is presumed to represent the gating of auditory input to the auditory cortex (Alho et al., 1994). Given that the putamen has an inhibitory effect on the thalamus (Gonzales et al., 2013), our results might suggest that the putamen has a reduced inhibitory effect on the thalamus in tinnitus network. This assumption is in agreement with a previously reported case of a 40-year-chronic-tinnitus patient whose tinnitus was eliminated after a stroke in the putamen and caudate nucleus (Lowry et al., 2004). Nevertheless, we are aware that 20–60 ms after stimulus presentation is a very fast response and, thus, this results should be taken with caution and await further replication.

Increased activation in parietal and frontal regions was found in the 80–120 ms during TT stimulation. According to the literature, dorsofrontal regions are related to higher-level cognitive functions of attention and emotion in the context of tinnitus processing (Henry et al., 2005; Husain & Schmidt, 2014; Pattyn et al., 2016). Increased activation of these regions might reflect the constant distress and focus of attention on the tinnitus sound since it is often an alarming and disturbing stimulus for patients. Numerous studies employing evoked fields or potentials demonstrated that negative emotional stimuli lead to enhanced processing during early time intervals (Bröckelmann et al., 2011; Steinberg et al., 2013). These effects become expressed in frontal regions which are also involved in the attentional processing of painful stimuli (Bornhövd et al., 2002; Lorenz et al., 2003). This lends support to previous findings in the literature, which showed a reduction of neuronal activity in combination with reduced tinnitus distress after tinnitus treatment (Stein et al., 2015a, Stein et al., 2015b).

In a similar vein, during the 140–220 ms time-interval that corresponds to the P2-wave, our findings yielded increased activation in frontal areas. Previous studies have shown that the P2 component is increased in response to emotional auditory information relative to neutral sounds (Liu et al., 2012; Spreckelmeyer et al., 2006; Steinberg et al., 2013). The tinnitus perception is highly related to distress and emotional processing (Henry et al., 2005; Pattyn et al., 2016), and given the fact that we found increased brain activation in TT > CT contrast, it is likely that the TT is appraised as an emotional sound stimulus, whereas the CT might be perceived as neutral. However, we did not provide any relevant questionnaire to assess the emotional aspects of the sounds, and thus we cannot make a conclusive interpretation of this view. It would be interesting, though, in a future study to consider this aspect.

Furthermore, our results demonstrated decreased amplitude in response to the TT in the temporal cortex and parahippocampal gyrus. The latter is well acknowledged to be involved in the tinnitus network (Besteher et al., 2019) and has been related to the evaluation of salient auditory information (Shahsavarani et al., 2019). Previous studies suggested that the parahippocampal gyrus is involved in the maintenance of tinnitus by avoiding habituation (De Ridder et al., 2006, De Ridder et al., 2011). It is likely that decreased amplitude of this region reflects the reduced efficacy to habituate due to misperceptual judgment of the tinnitus sounds as a salient stimulus. Interestingly, our second analysis with the healthy-hearing group confirmed the significant role of the current region. In this analysis we showed that the processing of the tones differs for the two groups involving two main regions, the right parahippocampal gyrus and the left primary somatosensory regions. These regions have been strongly related to the tinnitus brain network (Maudoux et al., 2012; Paraskevopoulos et al., 2019). For instance, our previous findings showed that the parahippocampal gyrus is highly interconnecting with temporal and frontal regions in tinnitus patients

compared to healthy controls (Paraskevopoulos et al., 2019). Nevertheless, source space analysis can offer some insights concerning the regions contributing to the processing of the tinnitus tone, however without explaining how the involved sources interact. For this reason, we also included a functional connectivity analysis to investigate brain connectomes differences between the tones. Current analysis however was not performed for the group study, since the control group was included mainly as a benchmark to ensure that the differences we find is due to tinnitus perception and due to low and high frequency.

4.2. Functional connectivity

Our findings, as derived from the functional connectivity analysis, suggest that the processing of the TT involves a widespread cortical network differing significantly from the processing of a control frequency. Our results are consistent with previous findings employing resting state designs, confirming that fronto-temporal, parieto-frontal, tempo-parietal junctions are crucially involved in the tinnitus network. The fact that a similar network is replicated by many studies and by different means (MEG, PET, fMRI) of measurement, is striking and it stresses the robustness of these findings. These results emphasize again that tinnitus should be regarded as a "network disorder" rather than stemming from one dysfunctional source.

In consistence with our findings, previous ones have demonstrated increased connectivity between left parahippocampal regions and auditory cortices (Maudoux et al., 2012; Schmidt et al., 2013). Left lateralized junctions were also replicated in our recent study (Paraskevopoulos et al., 2019). The left parahippocampal gyrus in connection to the temporal cortex might serve as bottom-up processing of auditory information associated with auditory recognition and discrimination of meaningful from meaningless sounds (Engelien et al., 2000). Accordingly, the constant perception of tinnitus might be a result of the reduced efficacy to evaluate the TT as 'meaningless sound'. It should be noted here that the gradiometers used in our analysis are less sensitive to deeper sources. However, there exists support for our results demonstrating that equivalent signals can be obtained with both magnetometers and gradiometers in typical MEG experiments (Garcés et al., 2017) and that sophisticated MEG techniques can localize deeper sources such as the amygdala, hippocampus and thalamus (Coffey et al., 2016; Dumas et al., 2013; Hillebrand et al., 2016). Nevertheless, the current results should be treated with caution, although there exist many fMRI studies in the literature that demonstrate the same regions.

We could also replicate fronto-parietal connectomes, which have been related to the integration of sensory and emotional features of tinnitus (Jastreboff, 1990; Weisz et al., 2005a; Weisz et al., 2007) and in fact they seem to play a key role in the preservation of tinnitus perception (Schlee et al., 2009; Weisz et al., 2005a). Moreover, our results demonstrated the involvement of the anterior cingulate cortex and insula, which have been associated with a top-down attentional amplification, in the tinnitus network (Maudoux et al., 2012). Taken together, it seems that enhanced top-down attentional and emotional response to the tinnitus frequencies has a direct impact on the auditory cortices, which in turn might increase tinnitus awareness and distress. Such an assumption was also supported by our recent resting state study (Paraskevopoulos et al., 2019). We showed there that the dorso-medial prefrontal cortex (dmPFC) was the main modulator in the tinnitus network affecting the left temporal cortex and the left parahippocampal region. The dmPFC is involved in the dorsal attention, as well as, in the emotional appraisal network (Bermpohl et al., 2006; Eden et al., 2015; Morawetz et al., 2017). Although we did not provide a paradigm to manipulate attention and emotion, the current connectomes have been replicated in most of the previous studies and were there associated with attentional and emotional processes (Husain & Schmidt, 2014; Maudoux et al., 2012; Shahsavarani et al., 2019). This assumption concurs well with numerous studies showing a decrease in the tinnitus perception after stimulating frontal regions to alter the tinnitus network by means of tDCS and TMS (De Ridder et al., 2013; Faber et al., 2012; Vanneste et al., 2010; Vanneste & De Ridder, 2011). That is, if higher order regions are targeted, either by psychotherapy or other means of treatment, then the overall activity of the network can be decreased and might reduce the subjective perception of the tinnitus sound.

In comparison to our previous mentioned study (Paraskevopoulos et al., 2019), in the current one by providing an auditory stimulus paradigm, we were able to further show that the brain alterations found in tinnitus patients, seem to be attributed specifically to the tinnitus-frequency, a finding that cannot be demonstrated by resting state studies and which is not seen in control participants. A likely explanation is that patients even at rest perceive a similar percept, as in response to the tone of their tinnitus frequency. The left unilateral activation in tinnitus network has been demonstrated in numerous previous studies (for review see Shahsavarani et al., 2019), yet no adequate interpretation has been suggested. In addition, the causal role of the left hemisphere in tinnitus network is emphasized by transcranial magnetic/electric stimulation studies revealing statistically significant tinnitus loudness reduction after treatment (Burger et al., 2011; Piccirillo et al., 2011, Piccirillo et al., 2013). Previous findings also indicate grey matter differences in left auditory cortices of tinnitus patients compared to both hearing loss patients and controls (Boyen et al., 2013; Boyen et al., 2013) and it seems that the left lateralization is independent of tinnitus laterality, severity and duration (Langguth et al., 2006).

Nevertheless, it is important to be mentioned that the interpretation given on the current findings are mainly based on previous studies and should be taken with caution. In order to relate the tinnitus network with attentional and emotional mechanisms and thus replicate current interpretation, a relevant paradigm or subjective measurements manipulating these factors should be involved in a future study. This fact can count as a limitation of our study. Although it was not the main focus of the study, it would have given additional important information to our findings. Another point to take into consideration is the lack of individuals head model. We found very early response already 20 ms after stimulus onset, as well as, brain activation in deeper regions, for which MEG is less sensitive. To ensure that these findings are attributable to tinnitus and not an artefact as the result of the lack of individual MRIs, we suggest the individuals head models to be included in future studies. It should also be mentioned here, that we did not acquire MRIs as, according to patients' reports, it is a very disturbing procedure owing to the loud scanner noise, according to their reports. With this regard, we applied the LORETA source reconstruction with a 10 mm resolution, since it has been shown that with at least 7 mm resolution and a spherical head model, LORETA provides 14 mm localization accuracy at worst (Domingo Pascual-Marqui, 1999).

4.3. Conclusion

Tinnitus patients show differential neurophysiological processing of control and tinnitus frequencies. By comparing tinnitus with normal-hearing subjects, we further showed that this differential processing derives from the perceptual differences between the two groups in processing the tones and not due to frequency differences (e.g. low versus high pitch). Generally, the results showed activation of a typical auditory network in response to the CT, while the processing of the TT involved an enhanced network comprising fronto-temporal, fronto-parietal and tempo-parietal junctions. Although a consensus exist that points the generation of the tinnitus sound on re-organizational processes initiated by peripheral damage, the transition from acute to chronic tinnitus seems to involve higher cognitive functions. Our results demonstrated differential processing specifically attributable to the TT, already in early responses in the putamen; an area that exerts an inhibitory influence on the thalamus, which in turn gives output to and receives feedback from various cortical regions. This feedback transmission of the affected frequency within the thalamo-cortical loop could provide some explanation for the plastic reorganization that is

frequency-specific and seems to alter the processing of the TT specifically while not affecting the processing of other frequencies. An important aspect of the study was the fact that the analysis of functional connectivity was data-driven. That is, we did not set the regions of interest a-priori but rather we investigated whole-head cortical activation. To our knowledge, this is the first MEG study examining whole-head functional connectivity of auditory evoked fields in response to individual TT and a CT. Although, the experimental design was different from previous studies, mainly using resting states, the results are remarkably in consistence. However, with the current analysis we were able to further suggest that the tinnitus network seem to be attributable to the individual tinnitus tone specifically, and not to other frequencies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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