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Tinnitus and musical hallucinosis: The same but more

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ABSTRACT

While tinnitus can be interpreted as a simple or elementary form of auditory phantom perception, musical hallucinosis is a more complex auditory phantom phenomenon not only limited to sound perception, but also containing semantic and musical content. It most often occurs in association with hearing loss. To elucidate the relation between simple and complex auditory phantom percepts a source localized electroencephalography (EEG) study is performed. The analyses showed in both simple and complex auditory phantoms an increase in theta–gamma activity and coupling within the auditory cortex that could be associated with the thalamocortical dysrhythmia model. Furthermore increased beta activity within the dorsal anterior cingulate cortex and anterior insula is demonstrated, that might be related to auditory awareness, salience and its attribution to an external sound source. The difference between simple and complex auditory phantoms relies on differential alpha band activity within the auditory cortex and on beta activity in the dorsal anterior cingulate cortex and (para) hippocampal area. This could be related to memory based load dependency, while suppression within the primary visual cortex might be due the presence of a continuous auditory cortex activation inducing an inhibitory signal to the visual system. Complex auditory phantoms further activate the right inferior frontal area (right sided Broca homolog) and right superior temporal pole that might be associated with the musical content. In summary, this study showed for the first time that simple and complex auditory phantoms might share a common neural substrate but differ as complex auditory phantoms are associated with activation in brain areas related to music and language processing.

Introduction

Many people perceive an auditory percept in the absence of any objective physical sound source (Jastreboff, 1990). This has been attributed as a mechanism that resolves sensory uncertainty, possibly explaining its high prevalence (De Ridder et al., in press). This phantom sound can be a tone, hissing, or buzzing sound and in some cases the auditory phantom can present as music or voices. The hearing of a simple tone or noise has been referred to as tinnitus, from the Latin word *tinnire* for "to ring", while hearing voices and music are named respectively verbal and musical hallucinations. While tinnitus can be interpreted as a simple or elementary form of auditory phantom perception, musical and verbal hallucinations are more complex auditory phantom phenomena not only limited to sound perception, but also containing semantic content. Whereas verbal hallucinations are a typical feature of a psychiatric condition (i.e. psychosis or schizophrenia), musical hallucinations often result from severe auditory deprivation or deafness due to deafferentation or a lesion situated anywhere along the auditory pathway beside other sometimes unknown factors (Braun et al., 2003; Griffiths, 2000). Musical hallucinations have been reported as arising from lesions of early stages of sound processing (brainstem, pons, thalamus and auditory radiation), and of higher-level auditory association cortices such as the temporal lobe (Cope and Baguley, 2009) and insula (Isolan et al., 2010). The cause of the lesion also appears unimportant, with musical hallucinosis being caused by intracranial aneurysms, ischemic infarction, hemorrhage and tumors (Cope and Baguley, 2009). The commonly used term musical hallucinosis refers to a state characterized by the presence of music perception in the absence of an external sound source, and without impairment of consciousness. In most cases people with musical hallucinosis are initially unaware that these sounds are subjectively generated, but readily become aware that they are internally generated as nobody else hears the music. This is analogous to some forms of tinnitus. This however is in contrast to verbal hallucinations in the setting of psychosis. Musical hallucinosis is also different from vivid auditory imagery as the auditory percepts in musical hallucinosis are

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involuntary. It is thus very similar to tinnitus, which most commonly is also constantly present, in contrast to the intermittent character of verbal hallucinations.

Although many studies investigate the neural correlates of tinnitus (De Ridder et al., 2011a) and verbal hallucinations (Diederen et al., 2010; Sommer et al., 2010), few studies address musical hallucinosis (Griffiths, 2000; Kasai et al., 1999) and none have compared simple versus complex auditory phantom percepts. As both tinnitus and musical hallucinosis are often related to sound deprivation, in contrast to psychotic verbal auditory phantoms, tinnitus and musical hallucinosis as auditory phantom perceptions might share a common neural substrate differing only in its complexity, with musical hallucinosis encompassing areas processing higher-level semantic and melodic sound patterns (Griffiths, 2000).

Thalamocortical dysrhythmia has been proposed to explain the positive and negative symptoms in neurological disorders like movement disorders, epilepsy, neuropathic pain, depression and tinnitus (Llinás et al., 1999). This pathophysiological model is based on deafferentation and might explain both tinnitus and musical hallucinosis, as both clinical entities are related to auditory deafferentation. According to this model tinnitus is caused by an abnormal, spontaneous and constant gamma band activity associated with low frequency theta or delta activity generated as a consequence of hyperpolarization of specific thalamic nuclei; in this case, the medial geniculate body. In normal circumstances auditory stimuli increase thalamocortical alpha oscillations to gamma band activity (Crone et al., 2001; Joliot et al., 1994). In the deafferented tinnitus state however, oscillatory alpha activity decreases (Lorenz et al., 2009) and theta band activity increases (Llinas et al., 1999; Steriade, 2006). As a result, lateral inhibition is reduced inducing a surrounding gamma band activity known as the "edge effect" (Llinás et al., 1999, 2005).

The difference between tinnitus and musical hallucinosis might be related to the right homolog of Broca's area and the right superior temporal pole. Previous research already showed that activation in the right homolog of Broca's area and right superior temporal gyrus is important in verbal hallucinations (Copolov et al., 2003; Sommer et al., 2008; Woodruff et al., 1995). The main difference between cerebral activity during auditory phantoms and activity during normal inner speech appears to be the lateralization in the right inferior frontal gyrus (Sommer et al., 2008). Records of magnetoencephalography (MEG) and single photon emission computed tomography (SPECT) in the presence and absence of musical hallucinosis in a case report showed increase of blood flow in the right superior temporal gyrus and right inferior frontal gyrus during musical hallucination (Kasai et al., 1999). Both areas have not been associated to tinnitus.

To elucidate the relation between simple and complex auditory phantom percepts a source localized electroencephalography (EEG) study is performed comparing resting state EEG recordings between healthy subjects, patients with a simple (i.e. tinnitus) and complex auditory phantoms (i.e. musical hallucinosis). Resting state EEG recordings were performed during a period of auditory phantom perception. In this study we assume that phantom sounds are related to activity within a complex neural network of different brain areas. Based on the thalamocortical dysrhythmia model we hypothesize that simple and complex auditory phantoms might share a common neural substrate characterized by a decrease in oscillatory alpha activity (Lorenz et al., 2009) associated with an increase in theta and gamma band activity, typical for thalamocortical dysrhythmia. Except for these spectral differences, we also hypothesize that simple and complex auditory phantoms differ in extend of involved brain areas as musical hallucinosis should involve music and language processing areas in contrast to tinnitus. In order to define a neural signature of "phantom percept" (simple and complex), the resting state electrical brain activity of both patient groups will be compared to healthy subjects. To delineate the shared network and specify the differences between simple and complex auditory phantom percepts subsequently both pathologies will also be compared electrophysiologically in a source localized way.

Methods

Participants

Ten patients ($M = 65.75$ years; $Sd = 15.92$; 10 females) with continuous chronic musical hallucinosis (i.e. complex auditory phantom percept) were recruited from the TRI multidisciplinary Tinnitus Clinic at the University Hospital Antwerp, Belgium. Ten tinnitus patients, 10 patients with musical hallucinosis and 10 healthy control subjects were selected from a large database in the TRI multidisciplinary Tinnitus Clinic at the University Hospital Antwerp. The patients and controls had the same age and gender. For the healthy subjects, none of these subjects was known to suffer from tinnitus or pain. Exclusion criteria for the healthy subject database were known psychiatric or neurological illness, psychiatric history or drug/alcohol abuse, history of head injury (with loss of consciousness) or seizures, headache, or physical disability and report of having severe hearing loss. The tinnitus patients and musical hallucinosis patients were further selected so that laterality (both tinnitus and musical hallucinosis were bilaterally perceived) loudness (both phantoms are perceived equally loud), distress level and hearing loss were not significantly different. See Table 1 for a demographic comparison among the three different groups.

Simple or complex auditory phantom percepts were considered chronic if its onset dated back one year or more. Simple or complex auditory phantoms were selected with comparable hearing loss: all patients were screened for the extent of hearing loss using a pure tone audiometry using the British Society of Audiology procedures at .125 kHz, .25 kHz, .5 kHz, 1 kHz, 2 kHz, 3 kHz, 4 kHz, 6 kHz and 8 kHz (Audiology, B.S.o, 2008; Meeus et al., 2010, 2011) (see Fig. 1).

A numeric rating scale (NRS) for loudness ("How loud is your tinnitus/musical hallucinosis?": 0 = no tinnitus/musical hallucinosis and 10 = as loud as imaginable) as well as a validated Dutch translation of the Tinnitus Questionnaire (TQ) (Meeus et al., 2007) was assessed. The TQ is comprised of 52 items and is a well-established measure for the assessment of a broad spectrum of tinnitus-related psychological complaints. The TQ measures emotional and cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbances, and somatic complaints. The global TQ score can be computed to measure the general level of psychological and psychosomatic distress. In several studies, this measure has been shown to be a reliable and valid instrument in different countries (Hiller and Goebel, 1992; McCombe et al., 2001). Also for NRS loudness ($M = 6.58$, $Sd = 1.57$ for simple auditory phantoms; $M = 6.28$, $Sd = 1.91$ for complex auditory phantom) and TQ ($M = 54.31$, $Sd = 14.54$ for simple auditory phantoms; $M = 53.51$, $Sd = 15.09$ for complex auditory phantom) the tinnitus patients and patients with musical hallucinosis had a comparable loudness and distress. Patients who had a musical hallucinosis described their hallucinosis as hearing one or different songs that could change in character.

Table 1
Demographics.

	Healthy subjects	Auditory phantom percept		Statistical comparisons
		Simplex	Complex	
Gender	10 females	10 females	10 females	*n.s.*[a]
Age (years)	$M = 67.25$	66.88	$M = 65.75$	*n.s.*[b]
	$Sd = 15.92$	$Sd = 10.77$	$Sd = 15.92$	
NRS loudness	–	$M = 6.58$	$M = 6.28$	*n.s.*[b]
		$Sd = 1.57$	$Sd = 1.91$	
TQ	–	$M = 54.31$	$M = 53.51$	*n.s.*[b]
		$Sd = 14.54$	$Sd = 15.09$	
Lateralization	–	Bilateral	Bilateral	*n.s.*[a]
Sound	–	Narrow band noise	Music	–

n.s. no significant effect.
[a] Comparison between groups using a χ^2-test.
[b] Comparison between groups using one-way ANOVA.

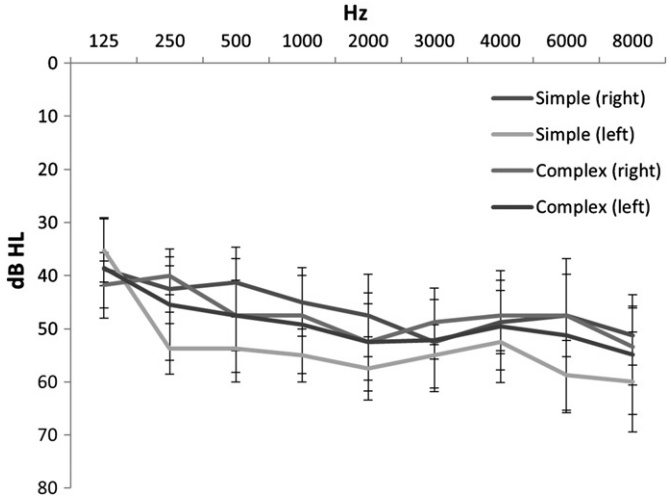

Fig. 1. Mean audiogram and standard errors of the mean for patients with a simple or complex auditory phantom percept for the left and right ears.

The local ethical committee at the University Hospital Antwerp approved the data collection and is in accordance with the declaration of Helsinki.

Data collection

EEG data were obtained as a standard procedure. Recordings were obtained in a fully lighted sound attenuated, electrical artifact-free room with each participant sitting upright on a small but comfortable chair. The actual recording lasted approximately 5 min. Both patients with simple or complex auditory percept confirmed that they perceived a phantom percept during the EEG recording. The EEG was sampled using Mitsar-201 amplifiers (NovaTech http://www.novatecheeg.com/) with 19 electrodes (pure tin electrode electrocap http://www.mitsar-medical.com/eeg-accessories/#aecap) placed according to the standard 10–20 International placement (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, O2) referenced to digitally linked ear. Impedances were checked to remain below 5 kΩ. Data were collected eyes-closed (sampling rate = 500 Hz, band passed 0.15–200 Hz). Off-line data were resampled to 128 Hz, band-pass filtered in the range of 2–44 Hz and subsequently transposed into Eureka! software (Congedo, 2002), plotted and carefully inspected for manual artifact-rejection. All episodic artifacts including eye blinks, eye movements, teeth clenching, body movement, or ECG artifact were removed from the EEG recording. Recordings after artifact rejection were at least 3.5 min. Average Fourier cross-spectral matrices were computed for frequency bands delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma (30.5–44 Hz). These frequency bands are based on previous research in tinnitus (Song et al., 2013a, 2013b; Vanneste and De Ridder, 2012; Vanneste et al., 2010, 2011c).

Source localization

Standardized low-resolution brain electromagnetic tomography (sLORETA) (Pascual-Marqui, 2002) was used to estimate the intracerebral electrical sources. As a standard procedure a common average reference transformation (Pascual-Marqui, 2002) is performed before applying the sLORETA algorithm. The solution space used in this study and associated leadfield matrix are those implemented in the LORETA-Key software (freely available at http://www.uzh.ch/keyinst/loreta.htm). This software implements revisited realistic electrode coordinates (i.e. link between stereotaxic coordinates and relative head-surface-based positioning systems) (Jurcak et al., 2007) and the leadfield (Fuchs et al., 2002) applying the boundary element method on the MNI-152 (Montreal Neurological Institute, Canada) template (Mazziotta et al., 2001). The sLORETA-Key anatomical template divides and labels the neocortical (including hippocampus and anterior cingulated cortex) MNI-152 volume in 6239 voxels of dimension 5 mm^3, based on probabilities returned by the Demon Atlas (Lancaster et al., 2000).

The tomography sLORETA has received considerable validation from studies combining LORETA with other more established localization methods, such as functional Magnetic Resonance Imaging (fMRI) (Mulert et al., 2004; Vitacco et al., 2002), structural MRI (Worrell et al., 2000), Positron Emission Tomography (Dierks et al., 2000; Pizzagalli et al., 2004; Zumsteg et al., 2005) and was used in previous studies to detect for example activity in the auditory cortex (Vanneste et al., 2011a; Zaehle et al., 2007). Further sLORETA validation has been based on accepting as ground truth the localization findings obtained from invasive, implanted depth electrodes, in which case there are several studies in epilepsy (Zumsteg et al., 2006a, 2006c) and cognitive ERPs (Volpe et al., 2007). It is worth emphasizing that deep structures such as the anterior cingulate cortex (Pizzagalli et al., 2001) and mesial temporal lobes (Zumsteg et al., 2006b) can be correctly localized with these methods.

Region of interest

The log-transformed electric current density was averaged across all voxels belonging to the region of interest: left and right auditory cortices (BA21, 40 & 41). The different frequency bands delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma (30.5–44 Hz) were computed as well as discrete frequencies between 2 and 44 Hz.

Statistical analysis

sLORETA was used to perform a voxel-by-voxel analysis (comprising 6239 voxels) for the different frequency bands in the between-condition comparisons of the current density distribution to identify potential differences in brain electrical activity between healthy control subjects and patients with a simple or complex auditory phantoms. Nonparametric statistical analyses of functional sLORETA images (statistical nonparametric mapping: SnPM) were performed for each contrast using sLORETA's built-in voxel wise randomization tests (5000 permutations) and employing a log-*F*-ratio statistic for independent groups with a threshold $p < 0.05$. As explained by Nichols and Holmes, the statistical nonparametric mapping method does not rely on an assumption of a Gaussian distribution for the validity and corrects for all multiple comparisons (i.e. for the collection of test performed for all voxels and for all frequency bands) by employing a locally pooled (smoothed) variance estimate that outperforms the comparable statistical parametric mapping (Holmes et al., 1996; Nichols and Holmes, 2002). A comparison was made between the patients with an auditory phantom sound (including both simple and complex auditory phantoms) and a healthy control group as well as between patients with simple and complex auditory phantoms.

In addition to the group comparison between patients with a simple and complex auditory phantom we conducted a conjunction analysis (Friston et al., 1999, 2005; Nichols et al., 2005; Price and Friston, 1997). A conjunction analysis identifies a 'common processing component' for two or more tasks/situations by finding areas activated in independent subtractions (Friston et al., 1999, 2005; Nichols et al., 2005; Price and Friston, 1997). Friston et al. (1999) also indicated that although general conjunction analysis is used within group condition, this can also be applied between groups and was applied in some recent papers (Bangert et al., 2006; Heuninckx et al., 2008). We applied a conjunction analysis to identify the common brain areas involved both in simple and complex auditory phantoms after subtraction in both groups of the healthy control subjects. We opted to subtract

images of the healthy subjects group from both the simple and complex auditory phantom group so that only pathological activity (activity that deviated from the healthy subjects) remains for both simple and complex auditory phantom group separately. Based on the images of both simple and complex auditory phantom group we conducted a conjunction to see what pathological activity they have in common. This method allows us to look specifically at the brain activity related to the auditory phantom percept.

A Kruskal–Wallis one-way analysis of variance by ranks was used to compare the healthy control group, patients with a simple and complex auditory phantom on their log-transformed electric current density for the left auditory cortex for the different frequency bands separately. This test allows correcting for multiple of comparisons. However, the analysis was uncorrected for the amount of frequency bands. A similar analysis was conducted for the right auditory cortex. When significance was obtained we applied a Mann–Whitney U-test to compare the healthy control group with patients with a simple auditory phantom percept, healthy control group with patients with a complex auditory phantom, and patients with a simple and patients with a complex auditory phantom to verify how they differ.

Spearman autocorrelations are calculated for respectively the left and right auditory cortices for the healthy control subjects, patients with a simple and patients with a complex auditory phantom by calculating the log-transformed current density for each frequency (1 Hz) for each individual. The Spearman correlation was calculated for each frequency with all other frequencies. This method has already been applied (De Ridder et al., 2011b; Vanneste and De Ridder, 2011).

Results

A comparison between an auditory phantom percept and healthy control subjects

A comparison between patients with an auditory phantom percept (including both simple and complex auditory phantoms) and healthy control subjects revealed significant differences in source localized activity for the theta, beta3 and gamma frequency bands (see Fig. 2 & Table 2). For the theta frequency band a significant difference was obtained for the right auditory cortex in patients with an auditory phantom percept in comparison to healthy control subjects. For the beta3 frequency increased activity was found in the dorsal anterior cingulate cortex, the (para)hippocampal area as well as the left and right insula and decreased activity in the primary visual cortex (see Fig. 2 & Table 2). In the gamma frequency band patients with a phantom percept showed increased activity in the left and right auditory cortices (see Fig. 2 & Table 2). No significant differences were obtained within the delta, alpha1, alpha2, beta1, and beta2 frequency bands between both groups with auditory phantoms.

Conjunction analysis

The group conjunction analysis showed significance in brain areas activated in both simple and complex auditory phantoms for both the theta and gamma frequency band activity within the left auditory cortex and in the left orbitofrontal/frontopolar cortex for the gamma frequency band (see Fig. 3 & Table 2). No significant differences were obtained for the delta, alpha1, alpha2, beta1, beta2 and beta3 frequency bands.

A comparison between simple and complex auditory phantoms

A comparison between simple and complex auditory phantoms revealed significant differences in source localized activity for the alpha1, beta1, beta2 and gamma frequency bands (see Fig. 4 & Table 2). It was shown that for alpha1 patients with complex auditory phantoms had increased activity in the left inferior temporal area in comparison to patients with simple auditory phantoms. Furthermore, for the beta1 and beta2 frequency bands it was shown that patients with complex auditory phantoms had increased activity in comparison to patients with simple auditory phantoms in the dorsal anterior cingulate cortex. For the gamma frequency band increased activity in the right inferior frontal gyrus and medial frontal gyrus was noted for the patients with complex auditory phantoms in comparison to

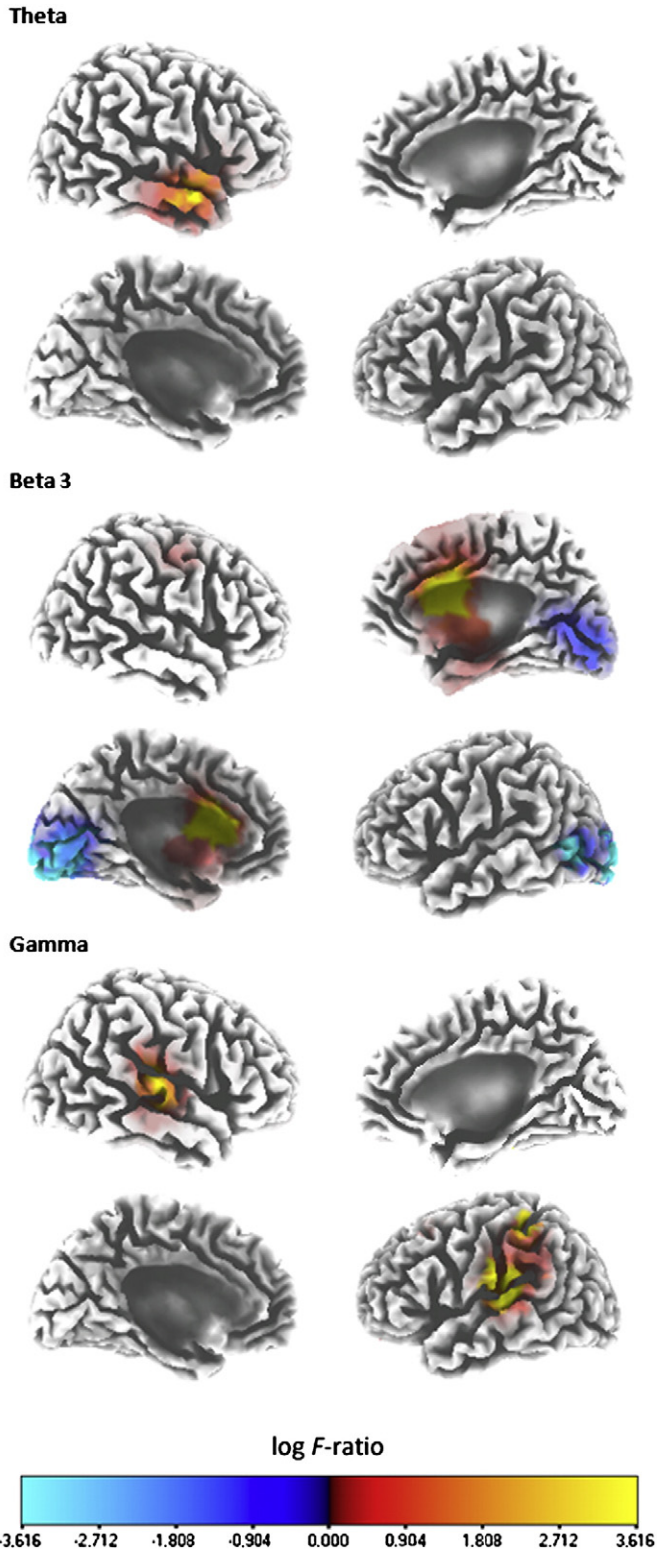

Fig. 2. A comparison of source analyzed resting state brain activity between auditory phantom percepts (tinnitus + musical hallucinosis) and healthy control subjects.

Table 2
MNI coordinates and Brodmann of peak voxels for each cluster.

Analysis	Frequency band	MNI coordinate			Brodmann area	Name	t-Value
		x	y	z			
Auditory phantom percept versus healthy control subjects	Theta	60	3	−15	21	Right auditory cortex	3.46
	Beta3	−4	22	20	33	Dorsal anterior cingulate cortex	3.28
	Beta3	−5	−93	−15	18	Primary visual cortex	3.41
	Gamma	−65	−24	17	42	Left auditory cortex	3.09
	Gamma	66	−24	4	22	Right auditory cortex	3.23
Conjunction analysis[a]	Theta	−65	−25	10	21	Left auditory cortex	2.21
	Gamma	−10	65	−11	11	Orbitofrontal/frontopolar cortex	2.17
	Gamma	−60	−24	−12	21	Left auditory cortex	1.99
Simple auditory phantoms versus complex auditory phantoms	Alpha1	−60	−31	−25	20	Inferior temporal gyrus	2.85
	Beta1	5	10	25	24	Dorsal anterior cingulate cortex	2.38
	Beta2	5	10	15	24	Dorsal anterior cingulate cortex	2.98
	Gamma					Inferior frontal gyrus	

[a] Conjunction analysis is expressed by a z-score.

simple auditory phantoms. No significant differences were obtained within the delta, theta, alpha2 and beta3 frequency bands between both groups with auditory phantoms.

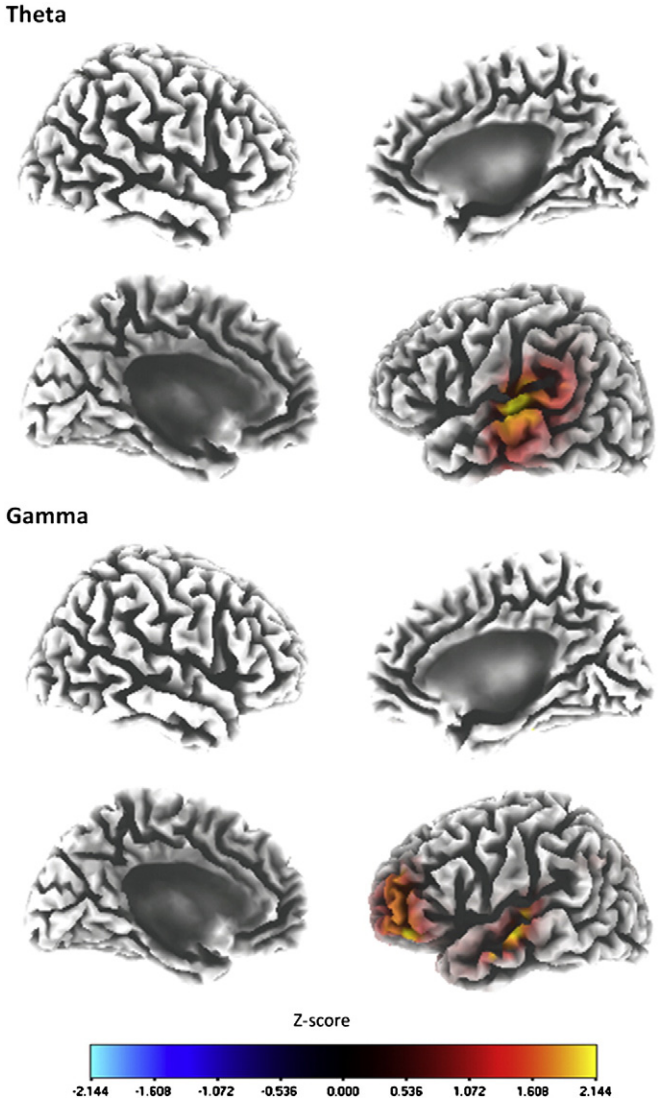

Fig. 3. A conjunction analysis between simple auditory phantoms and complex auditory phantoms (versus healthy control subjects). Simple and complex auditory phantoms share activation of the left auditory areas (theta and gamma) and prefrontal (frontopolar/orbitofrontal) cortices (gamma).

Region of interest analysis: left and right auditory cortices

A comparison between the three groups (the healthy control subjects, patients with a simple and patients with a complex auditory phantom) demonstrated for the theta (left $\chi^2(2) = 5.86$, $p = .05$, right $\chi^2(2) = 5.88$, $p = .05$) and gamma (left $\chi^2(2) = 5.90$, $p = .05$, right $\chi^2(2) = 4.53$, $p = .10$) a significant difference in the left and right auditory cortices. Both patients with a simple (theta: left $U(20) = 13$, $p = .04$, right $U(20) = 13$, $p = .04$; gamma: left $U(20) = 14$, $p = .05$, right $U(20) = 13$, $p = .04$) and patients with a complex (theta: left $U(20) = 12$, $p = .03$, right $U = 11$, $p = .02$; gamma: left $U(20) = 12$, $p = .03$, right $U(20) = 11$, $p = .02$) auditory phantom showed increased activity in comparison to the healthy control group (see Fig. 5). No differences were obtained between patients with a simple and patients with a complex auditory phantom. In addition, for alpha1 (left $\chi^2(2) = 6.97$, $p = .04$, right $\chi^2(2) = 6.42$, $p = .04$) and alpha2 (left $\chi^2(2) = 5.92$, $p = .05$, right $\chi^2(2) = 6.03$, $p = .05$) it was revealed that the complex auditory phantom patients demonstrated increased activity in comparison to the healthy control group (alpha1: left $U(20) = 13$, $p = .04$, right $U(20) = 12$, $p = .03$; alpha2: left $U(20) = 12$, $p = .03$, right $U(20) = 14$, $p = .05$) and patients with a simple auditory phantom (alpha1: left $U(20) = 12$, $p = .03$, right $U(20) = 13$, $p = .04$; alpha2: left $U(20) = 13$, $p = .04$, right $U(20) = 15$, $p = .08$) (see Fig. 5).

Autocorrelations within the left and right auditory cortices

The autocorrelations in the left and right auditory cortices for the healthy control subjects revealed no correlations between low and high frequencies (see Fig. 6). However, for patients with a simple or complex auditory phantom we found significant correlations ($p < .05$) between low and high frequencies. A comparison between these two groups further revealed that high frequencies with the beta and gamma range correlate stronger with theta activity within patients with a complex auditory phantom in comparison to patients with a simple auditory phantom. If was further shown that the alpha frequencies do not correlate over the three groups (see Fig. 6).

Discussion

This study investigated brain activity during an auditory phantom percept that is constantly present. Both the comparison to healthy subjects as well as the conjunction analysis revealed increased activity in the auditory areas for both theta and gamma frequency band activity in patients with an auditory phantom percept. In addition, increased activity was found in the left and right dorsal anterior cingulate cortices, the (para)hippocampal area, the left and right insula, as well as decreased activity in the primary visual cortex for the beta3

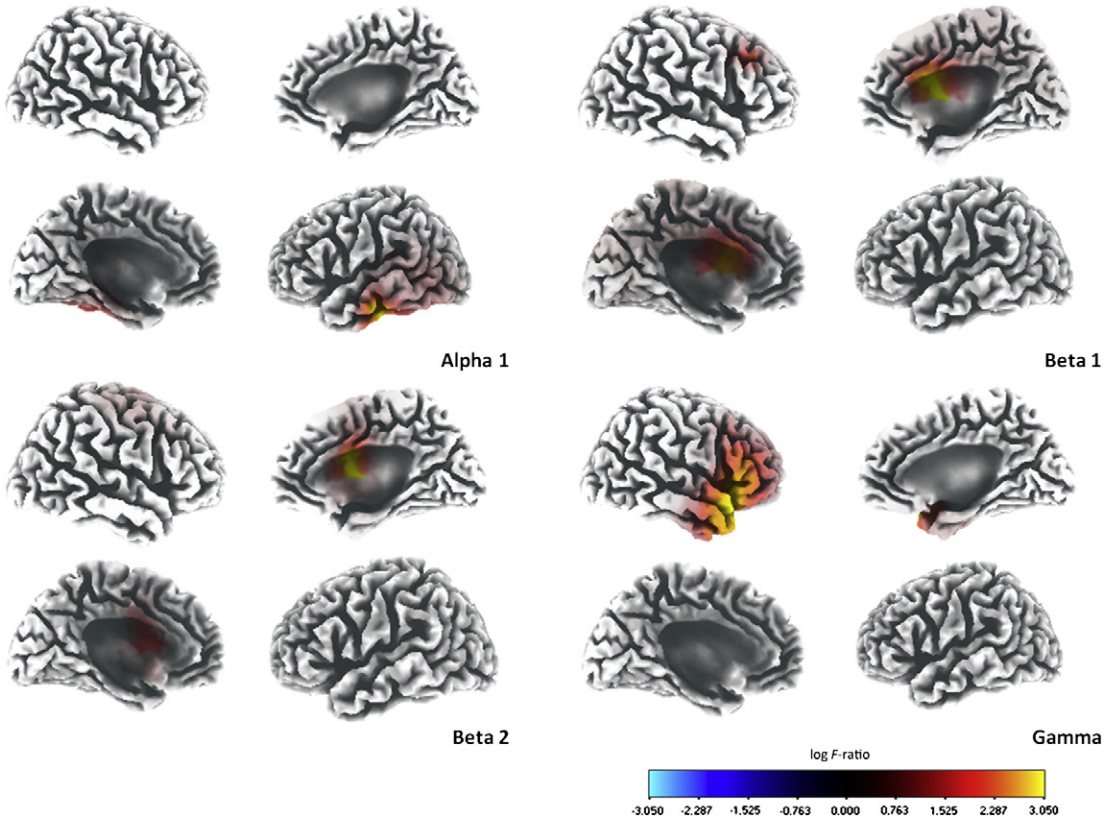

Fig. 4. A comparison between patients with tinnitus (=simple auditory phantom percept) and musical hallucinosis (=complex auditory phantom percept) revealed a significant ($p < .05$) increase in activity in alpha1 in the left inferior temporal cortex, beta1 and beta2 in the dorsal ACC and gamma frequency band in the right inferior frontal and right superior temporal poles for complex in comparison to simple auditory phantoms.

frequency band. Simple (i.e. tinnitus) versus complex (musical hallucinosis) auditory phantom percepts demonstrated differences in the left inferior temporal area for alpha1 and the dorsal anterior cingulate cortex for the beta1 and beta2 frequency bands. For the gamma frequency band increased activity was revealed within the right inferior frontal gyrus (right sided Broca's homolog) and medial frontal gyrus for the patients with complex auditory phantoms in comparison to simple auditory phantoms.

Based on the similarities and differences in brain activation profiles, we propose that these simple (i.e. tinnitus) and complex (musical hallucinosis) auditory phantom percepts share a common neural substrate that might be related to a thalamocortical dysrhythmia, but differ as complex auditory phantoms are associated with activation of brain areas related to music and language processing.

Thalamocortical dysrhythmia

Our results showed increased theta–gamma activity in patients with an auditory phantom percept within the auditory cortex. Region of interest analysis further confirmed that theta and gamma activity increased both in patients with simple and complex auditory phantoms. Changes of oscillatory activity within the auditory cortex have previously been revealed in radiologically or surgically objectified lesion studies in the presence of phantom sounds (i.e. auditory hallucinations) (see Braun et al., 2003 for overview).

In simple and complex auditory phantoms theta and gamma activity at the auditory cortex is strongly coupled as shown by the autocorrelations, suggesting that thalamocortical dysrhythmia might underlie both simple and complex auditory phantom phenomena. The idea of Llinas et al. is that this abnormally persistent coupled theta–gamma band dysrhythmia is relayed to the cortex, selectively in the deafferented thalamocortical columns (Llinás et al., 1999). Synchronized gamma band activity in the auditory cortex is proposed to bind auditory events into one coherent conscious auditory percept (Crone et al., 2001; Llinas et al., 1998; Ribary et al., 1991). It has been suggested that theta activity synchronizes large spatial domains (von Stein and Sarnthein, 2000) and binds together specific assemblies by the appropriate timing of spatially restricted higher frequency localized oscillations (Buzsaki and Chrobak, 1995; Canolty et al., 2006; Engel et al., 2001; Varela et al., 2001) and that higher frequency gamma oscillations are confined to a small neuronal space, whereas very large networks are recruited by means of slow oscillations (Csicsvari et al., 2003; von Stein and Sarnthein, 2000). A recent study indeed confirmed transient theta–gamma coupling, synchronizing geographically distributed gamma band activity in auditory attention (Doesburg et al., 2012). In tinnitus it has been suggested that the normally waxing and waning theta gamma coupling remains permanently present (De Ridder et al., 2011a), and intracranial recordings in a patient with simple auditory phantom, which disappears when tinnitus is suppressed by electrical stimulation of the auditory cortex (De Ridder et al., 2011b). The results of this study are in line with the thalamocortical dysrhythmia model that predicts increased theta–gamma in patients with an auditory phantom percept within the auditory cortex, and extends it to musical hallucinosis.

Auditory versus visual processing

A decrease in the primary visual cortex for the beta3 frequency band for both patient groups with auditory phantom percepts was demonstrated in comparison to healthy control subjects. This is in line with recent research that sound-induced activation of the primary auditory cortex in animals drives an inhibitory signal to the primary visual system (Iurilli et al., 2012). As for both patients with a simple

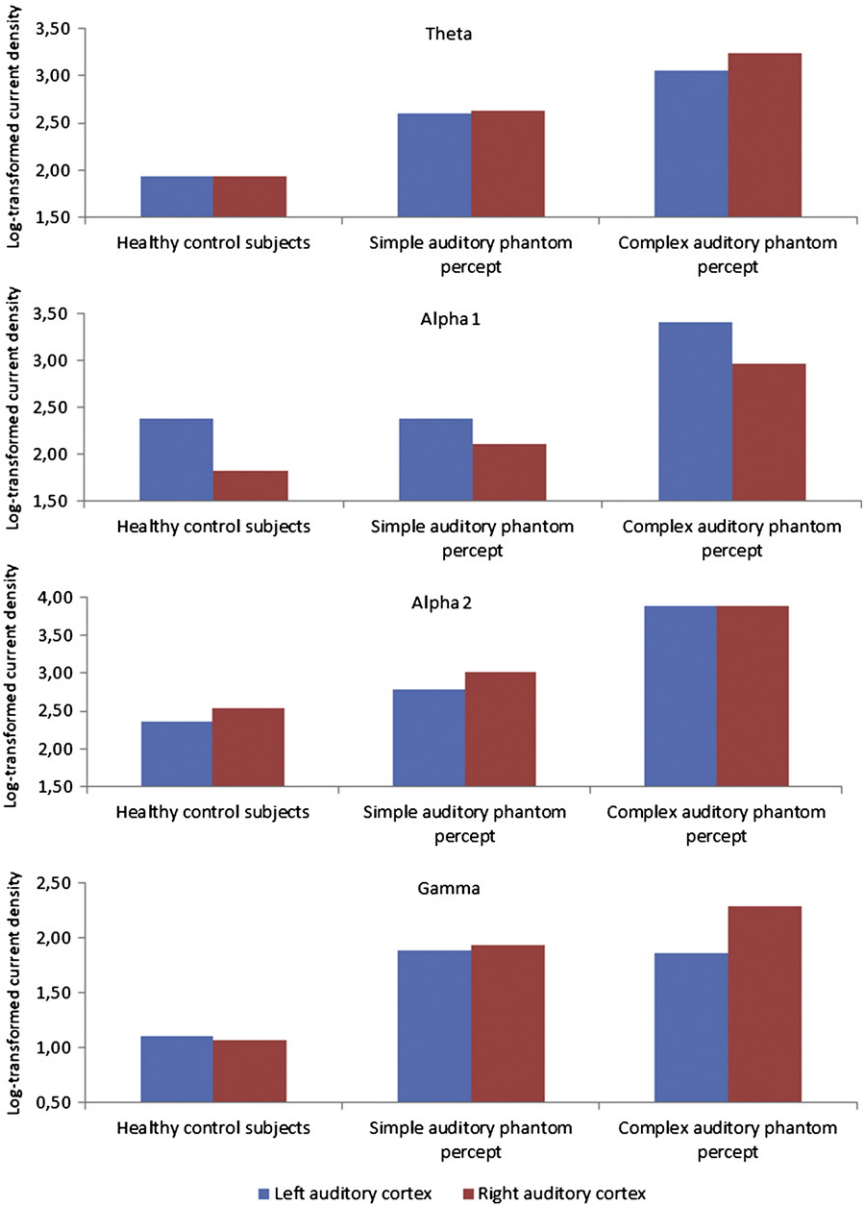

Fig. 5. A comparison of brain activity in the left and right auditory cortices between healthy control subjects, patients with a simple and complex auditory phantom perception revealed significant differences ($p < .05$) in theta, alpha 1, alpha2 and gamma frequency bands. Y-axis represents the log-transformed current density in the left (blue) and right (red) auditory cortices.

and complex auditory phantom percept, the phantom is constantly present and a similar effect might be at the core of this decrease in the visual system. This is in agreement with recent research that indicated reciprocal negative correlations in connectivity between the auditory and visual network that reflects dissociation between both areas in bothersome tinnitus (Burton et al., 2012).

Auditory awareness

Whether an auditory stimulus is perceived consciously or not depends on fluctuations in activity in the dorsal anterior cingulate cortex and anterior insula (Sadaghiani et al., 2009), analogous to what has been described for pain (Boly et al., 2007). The dorsal anterior cingulate cortex plus the insula have been implicated as salience network (Seeley et al., 2007), encoding behaviorally important or functionally relevant external input. Furthermore, they are involved in filling in missing auditory information (Shahin et al., 2009). Thus it is plausible that dorsal anterior cingulate cortex and insula signify a lack of habituation to the constant phantom, analogous to what has been described for pain (Mobascher et al., 2010). This is in agreement with studies demonstrating that unsuccessful auditory memory retrieval and unsuccessful auditory imagery are associated with deactivations in the anterior cingulate, and that successful auditory memory retrieval is associated with activation in the dorsal anterior cingulate (Huijbers et al., 2011). Moreover, the dorsal anterior cingulate cortex and insula have been proposed as interaction areas of auditory attention and comprehension (Giraud et al., 2004). Based on these previous findings it can be suggested that increased activity within the dorsal anterior cingulate cortex and anterior insula during simple as well as complex auditory phantoms might be related to filling in the missing auditory information and bringing this auditory percept to awareness. Musical hallucinations have been described after the resection of an insular glioma (Isolan et al., 2010), suggesting that this area might indeed be involved in the generation

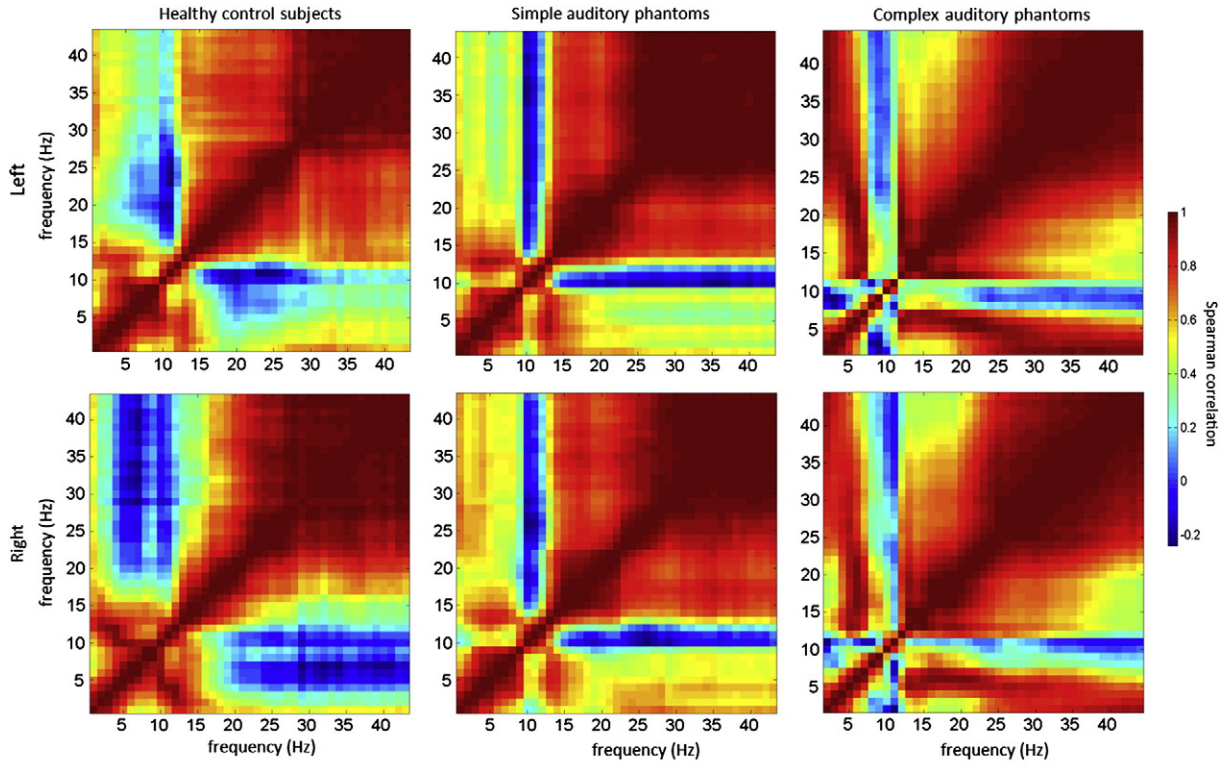

Fig. 6. Autocorrelations within the auditory cortex between discrete frequencies (2–44 Hz) for healthy control subjects, patients with a simple and complex auditory phantom. X-axis and Y-axis represent discrete frequencies in Hz. Frequency bands delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma (30.5–44 Hz).

of the musical hallucinosis, in line with the insula's function in auditory processing (Bamiou et al., 2003).

Simple versus complex auditory phantoms

In patients with a complex auditory phantom increased current density was demonstrated in the alpha frequency band for the left and right auditory cortices in comparison to patients with a simple auditory phantoms and healthy control subjects. This is in line with previous research on auditory phantoms that demonstrated increase of alpha band frequency-specific synchrony maximum values (Angelopoulos et al., 2011). Above that, alpha power increased linearly with memory load and load-dependent enhancement (Jensen et al., 2002).

That parahippocampus is involved as phantom perception, both in tinnitus and musical hallucinosis, is not new and already suggested in previous research (De Ridder et al., 2011a; Diederen et al., 2010; Vanneste et al., 2010, 2011b). It is known that the auditory cortex is anatomically densely connected to the (para)hippocampal area (Rouiller et al., 1990; Vogt and Pandya, 1987). The (para)hippocampal area is the main node of entry for auditory information to the medial temporal lobe memory system, where salient information is encoded into long-term memory (Engelien et al., 2000). It has therefore been associated with learning and memory processing (Aguirre et al., 1996; Bunsey and Eichenbaum, 1993; Zola-Morgan et al., 1989). Activation of association cortices originally involved in the encoded fragment has consistently been shown during memory retrieval (Wheeler et al., 2000).

Our results further showed increased activity within the left inferior temporal gyrus for patients with complex auditory phantoms in comparison to patients with a simple auditory phantom. The inferior temporal gyrus activation correlated with the severity of auditory hallucinations in an fMRI study (Raij et al., 2009), and bilateral inferior temporal gyrus volume reduction in chronic schizophrenia patients has been identified in a voxel-based morphometry study of structural MRI (Onitsuka et al., 2004).

Furthermore, we found increased activity for the patients with a complex auditory phantom within the right inferior frontal area and right superior temporal pole in contrast to patients with a simple auditory phantom. This is in line with previous records of MEG and SPECT that showed increase of blood flow in the right superior temporal gyrus and right inferior frontal gyrus during musical hallucination (Kasai et al., 1999). In addition, Halpern and Zatorre observed activation in the right inferior frontal area during a musical imagery task and assumed that it reflected the involvement of these regions in the retrieval of familiar musical information (Halpern and Zatorre, 1999). However, activity in the right inferior frontal area may reflect also retrieval from musical episodic memory (Platel et al., 2003).

The role of oscillations in different frequency bands

All significant spectral changes were found in the theta, alpha, beta and gamma frequency bands. Interestingly these frequency bands have previously been recognized as important in schizophrenia (Uhlhaas et al., 2008).

Recently the presence of both verbal hallucinations (Fletcher and Frith, 2009) and tinnitus (De Ridder et al., in press) has been explained based on the predictive coding theory with Bayesian updating. In essence, the auditory prediction tries to reduce environmental uncertainty relating both to 'when' and 'what' auditory stimulus is likely going to arrive and has been related to specific oscillatory activity. Whereas predicting 'when' predominantly involves low-frequency delta and theta oscillations, predicting 'what' points to a combined role of beta and gamma oscillations (Arnal and Giraud, 2012). Beta and gamma oscillations could underlie the flow of information in opposite directions, that

is, forward versus backward. Along the lines of predictive coding, this suggests that prediction errors could be propagated in a feed-forward manner, mainly using the gamma frequency band. Predictions could be transmitted 'backward' using mainly the beta band (Arnal and Giraud, 2012). Thus, beta oscillations may synchronize neuronal populations that encode expected sensory inputs. In other words, beta activity reflects the status quo (Engel and Fries, 2010), the reference to which the prediction error is compared. Conversely, if the neuronal population recruited by sensory stimulation differs from the pre-activated one, gamma activity would be proportional to the prediction error (Arnal and Giraud, 2012).

In this model, beta changes within the dorsal anterior cingulate cortex, the insula and parahippocampus might be related to expected top–down predictions in the absence of auditory input. Previous findings already demonstrated that beta oscillations are involved in highlighting a stimulus as salient (Kisley and Cornwell, 2006; Uhlhaas et al., 2008).

Limitations

A limitation of this study is that both tinnitus and musical hallucinosis are self-reported entirely subjective experiences, as currently there are no recognized methods to objectively measure these percepts. Furthermore, it cannot be excluded that healthy control subjects are engaged in mental auditory imagery during the resting state measure. However, it is important to unravel the underlying mechanisms in both simple and complex auditory phantom phenomena, as this might help to understand the basic fundamentals of how humans come to an auditory conscious percept. Furthermore it might be beneficial for the development of new treatments for simple and complex phantom phenomena.

Although none of the healthy subjects report severe hearing loss, some hearing loss cannot be excluded, and this may have influenced the results. Yet, the data obtained when comparing both pathologies with a healthy control fit with previously obtained studies. Future studies should try to include a healthy control group with similar hearing loss as the phantom percept group.

Conclusion

In summary, our analyses showed in both simple and complex auditory phantoms an increase in theta–gamma activity and coupling within the auditory cortex that could be associated with the thalamocortical dysrhythmia model. Furthermore, an increased beta activity within the dorsal anterior cingulate cortex and anterior insula is demonstrated, that might be related to auditory awareness and its attribution to an external sound source. The difference between simple and complex auditory phantoms relies on differential alpha band activity in the auditory cortex and for beta activity in the dorsal anterior cingulate cortex and (para)hippocampal area. This could be related to memory based load dependency, while suppression of the primary visual cortex might be due to the presence of continuous auditory cortex activation inducing an inhibitory signal to the visual system. Complex auditory phantoms further activate that right inferior frontal area and right superior temporal pole that might be associated with the musical content. In summary, this study showed for the first time that simple and complex auditory phantoms might share a common neural substrate but differ as complex auditory phantoms are associated with activation of brain areas related to music and language processing.

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Conflict of interest

No conflict of interest.

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