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Pinpointing a Highly Specific Pathological Functional Connection That Turns Phantom Sound into Distress

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It has been suggested that an auditory phantom percept is the result of multiple, parallel but overlapping networks. One of those networks encodes tinnitus loudness and is electrophysiologically separable from a nonspecific distress network. The present study investigates how these networks anatomically overlap, what networks are involved, and how and when these networks interact. Electroencephalography data of 317 tinnitus patients and 256 healthy subjects were analyzed, using independent component analysis. Results demonstrate that tinnitus is characterized by at least 2 major brain networks, each consisting of multiple independent components. One network reflects tinnitus distress, while another network reflects the loudness of the tinnitus. The component coherence analysis shows that the independent components that make up the distress and loudness networks communicate within their respective network at several discrete frequencies in parallel. The distress and loudness networks do not intercommunicate for patients without distress, but do when patients are distressed by their tinnitus. The obtained data demonstrate that the components that build up these 2 separable networks communicate at discrete frequencies within the network, and only between the distress and loudness networks in those patients in whom the symptoms are also clinically linked.

Keywords: auditory phantom percept, distress, independent component analysis, loudness, tinnitus

Introduction

Tinnitus is an auditory phantom percept with a tone or hissing in the absence of any objective physical sound source that is experienced by 5–15% in the population (Eggermont and Roberts 2004). Up to 25% of the affected people report interference with their lives as tinnitus causes a considerable amount of distress (Heller 2003). Distress can play an important role in the development of tinnitus; however, it is not a necessity as not everyone who experiences tinnitus becomes chronically distressed (Andersson and Westin 2008).

It is known that the cerebral cortex is organized into parallel, segregated systems of brain areas that are specialized for processing distinct forms of information (Buckner et al. 2009). Based on previous findings, it has been proposed that the unified percept of tinnitus could be considered as an emergent property of multiple parallel networks (De Ridder, Elgoyhen et al. 2011). That is, since there is not always a relationship between measures of loudness and distress, 2 separate networks in the brain might underpin these 2 aspects of tinnitus.

Research has shown that tinnitus is related to the reorganization (Muhlnickel et al. 1998) and hyperactivity (Weisz et al. 2007) of the auditory cortex. The loudness of auditory verbal hallucinations, a complex phantom sound, has further been associated with the anterior cingulate cortex and frontal gyrus, insula, and with strong activation of the inner speech processing networks (Vercammen et al. 2011), which could be considered to be a "loudness network."

On the other hand, it was revealed that, in tinnitus, a "distress network" of functionally interconnected nonauditory brain areas, including amygdala, anterior cingulate cortex, parahippocampus, and insula, are important (Vanneste, Plazier, der Loo et al. 2010). Using standardized low-resolution brain electromagnetic tomography (sLORETA), source analysis of Fourier-transformed data demonstrated that the distress was related to anterior cingulate beta activity, and the amount of distress was correlated to the amount of alpha activity in the medial temporal lobe (amygdala, hippocampus, and parahippocampus) as well as the subgenual anterior cingulate cortex, and insula (Vanneste, Plazier, der Loo et al. 2010). By using a blind source separation (BSS) technique, namely independent component analysis (ICA), in a different group of patients with low and high distress, it was shown that tinnitus distress results from alpha and beta abnormal activities in the subgenual anterior cingulate cortex, extending to the pregenual and dorsal anterior cingulate cortex and the ventromedial and ventrolateral prefrontal cortex, insula, and parahippocampal area (De Ridder, Vanneste et al. 2011). This network overlaps partially with brain areas implicated in distress in patients suffering from pain (Price 2000; Moisset and Bouhassira 2007), dyspnea (von Leupoldt et al. 2009), functional somatic syndromes, and post-traumatic stress disorder (Vermetten et al. 2007) and might therefore represent an aspecific distress network.

A study of resting-state electroencephalography (EEG) in large databases of healthy subjects has pointed to the existence of multiple distributed independent components with partially overlapping brain areas, each with a specific spontaneous oscillatory pattern (Congedo, John, De Ridder, Prichep et al. 2010). The analyses of the lagged phase coherence between these components have suggested that these components at rest are organized in a small number of networks. That is, ensembles of components communicate within networks, but do not communicate between networks (Congedo, John, De Ridder, Prichep et al. 2010). The interaction between the components occurs at multiple discrete frequencies in parallel (Congedo, John, De Ridder, Prichep et al. 2010). Such narrowband communication is analogous to what has been described for animals (Fujisawa and Buzsaki 2011). The identification of specific oscillatory patterns and

connectivity signatures within parallel networks for tinnitus might further explain the underlying neurophysiological mechanism and as a result helps in the identification of a treatment as to date no treatment exists for this auditory phantom phenomenon (Langguth et al. 2009).

The present study used a group BSS of resting-state EEG to map the involvement of different brain networks in auditory phantom perception. Resting-state networks can be identified using completely data-driven approaches, using EEG, magnetoencephalography, and also functional magnetic resonance imaging (fMRI) techniques. The resting-state networks are evident in the human brain during the awake resting state, as well as during task performance, sleep, and anesthesia (Fox and Raichle 2007), or at different vigilance levels (Olbrich et al. 2009). Meanwhile, emerging evidence shows that neurological or psychiatric diseases are associated with alterations in resting-state activity (Fornito and Bullmore 2010). Thus, the spontaneous activity of resting-state network reflects a fundamental aspect of cerebral physiology and pathophysiology.

The BSS approach, such as ICA, is currently enjoying increasing popularity thanks to its complete data-driven nature (Scheeringa et al. 2008). While the BSS analysis shows the relationship between different brain areas within a component (i.e. network), we also verify the lagged phase coherence (i.e. out of phase) between the different independent components (i.e. sources) by verifying the intercomponent coherence (Congedo, John, De Ridder, Prichep et al. 2010). This latter method helps to understand how different networks can communicate with each other in an out of phase matter. We hypothesized that patients with an auditory phantom percept would be discernible from a healthy control group during resting activity, and that different independent components might form 2 separable networks involved in the distress and loudness of the auditory phantom percept. We furthermore hypothesized that tinnitus-related distress would be electrophysiologically characterized by the presence of internetwork functional connectivity.

Materials and Methods

Patients With an Auditory Phantom Percept

Three hundred and seventeen patients (M = 50.24 years; SD = 14.32; 184 males and 133 females) with continuous tinnitus were included in this study. Tinnitus was considered chronic if its onset dated back 1 year or more. Individuals with pulsatile tinnitus, Ménière disease, otosclerosis, chronic headache, neurological disorders such as brain tumors, and individuals being treated for mental disorders, were excluded from the study in order to increase the sample homogeneity. All patients were interviewed as to their perceived location of the tinnitus [the left ear, in both ears, and centralized in the middle of the head (bilateral), the right ear] as well the tinnitus tone (pure tone-like tinnitus or noise-like tinnitus). In addition, all patients were screened for the extent of hearing loss using a pure tone audiometry using the British Society of Audiology procedures at 0.125, 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz (Audiology BSo 2008). Tinnitus patients were tested for the tinnitus frequency doing a tinnitus analysis. In unilateral tinnitus patients, the tinnitus analysis was performed contralateral to the tinnitus ear. In bilateral tinnitus patients, tinnitus analysis was performed contralateral to the worst tinnitus ear. The tinnitus analysis consisted of the assessment of the tinnitus pitch and loudness. First, a 1-kHz pure tone was presented contralateral to the (worst) tinnitus ear at 10 dB above the patient's hearing threshold in that ear. The pitch was adjusted until the patient judged the sound to resemble most to his/her tinnitus. The loudness of this tone was then adjusted in a similar way until it corresponded to the patient's specific tinnitus as well. The tinnitus loudness [dB sensation level (SL)] was computed by subtracting the absolute tinnitus loudness [dB hearing level (HL)] with the auditory threshold at that frequency (Meeus et al. 2009, 2011). See Table 1 for an overview of the tinnitus characteristics.

A visual analog scale for loudness ("How loud is your tinnitus?": 0 = no tinnitus and 10 = as loud as imaginable) was assessed as well as the Dutch translation of the Tinnitus Questionnaire (TQ; Meeus et al. 2007). This scale 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. As previously mentioned, the global TQ score can be computed to measure the general level of psychological and psychosomatic distresses. 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). A 3-point scale is given for all items, ranging from "true" (2 points) to "partly true" (1 point) and "not true" (0 points). The total score (from 0-84) was computed according to standard criteria published in previous work (Hiller and Goebel 1992; Hiller et al. 1994; Meeus et al. 2007). Based on the total score on the TQ, patients can be assigned to a distress category: Slight (0–30 points; grade 1), moderate (31–46; grade 2), severe (47–59; grade 3), and very severe (60–84; grade 4) distress. Goebel and Hiller stated that grade 4 tinnitus patients are psychologically decompensated, indicating that patients categorized into this group cannot cope with their tinnitus (Goebel and Hiller 1994). In contrast, patients that have a score <60 on the TQ can cope with their tinnitus.

This study was approved by the local ethical committee (Antwerp University Hospital) and was in accordance with the declaration of Helsinki.

Healthy Control Group

EEG data of a healthy control group ($N = 256$; M = 49.514 years; SD = 14.82; 154 males and 102 females) were collected. None of these subjects was known to suffer from tinnitus. Exclusion criteria were known psychiatric or neurological illness, psychiatric history or drug/alcohol abuse, history of head injury (with loss of consciousness) or seizures, headache, or physical disability. For these healthy controls, hearing assessment was not performed.

Data Collection

EEG data were obtained as a standard procedure. Recordings were obtained in a fully lighted room with each participant sitting upright on a small but comfortable chair. The actual recording lasted approximately 5 min. The EEG was sampled using Mitsar-201 amplifiers (NovaTech, http://www.novatecheeg.com/) with 19 electrodes 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, and O2) referenced to digitally linked ears, analogous to what is was done in the normative group. Impedances were checked to remain <5 kΩ. Data were collected eyes-closed (sampling rate = 500 Hz, band passed

Table 1
Tinnitus characteristics

Ear	
Left	61
Right	49
Bilateral	207
Tone	
Pure tone	138
Noise like	179
Tinnitus frequency (Hz)	
Mean	4905.51
SD	3257.72
Hearing loss at the tinnitus frequency (dB SL)	
Mean	7.60
SD	8.58

0.15–200 Hz). Off-line data were resampled to 128 Hz, band-pass filtered in the range 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 stream of the EEG.

Group Blind Source Separation

In the fMRI literature, BSS approaches such as ICA are currently enjoying increasing popularity thanks to their complete data-driven nature (Greicius et al. 2004; Bluhm et al. 2008; Scheeringa et al. 2008). In EEG also, BSS has recently been extended to the group analyses of the resting state (Congedo, John, De Ridder, Prichep 2010). As any other source separation method of this family, the BSS approach we use decomposes the whole EEG in a number of elementary statistically independent components. Each component is characterized by its time course and spatial pattern, therein used as input to tomographic source localization by the sLORETA inverse solution (Pascual-Marqui 2002).

We employed the group BSS approach consisting in the approximate joint diagonalization of grand-average Fourier cospectral matrices on the tinnitus group (Congedo, John, De Ridder, Prichep et al. 2010). Such method can separate uncorrelated sources with non-proportional power spectra (Congedo et al. 2008) and is analogous to the averaging group ICA approach described for fMRI (Schmithorst and Holland 2004). The BSS method we employ measures the intra-component relationship between different brain areas. Only cospectra in the range 2–44 Hz were diagonalized, because in this band-pass region continuous EEG features the highest signal-to-noise ratio. This method finds a "group" mixing and demixing matrix. The demixing matrix was then used to extract the power of the components on both the tinnitus and healthy group, as described in detail in Congedo, John, De Ridder, Prichep et al. (2010). To estimate the number of components in the tinnitus group that can be found reliably, we apply a bootstrap resampling test–retest strategy; each resample is obtained selecting 100 patients at random. For each resample, the group BSS analysis is performed limiting the number of components to 2, 3, 4, 5, 6, 7, and 8 components. This process was conducted 50 times. Based on these analyses, we conducted the group BSS on the total group estimating the 6 most energetic components, as these generated the most reliable and reproducible findings over the different resamplings.

Source Localization

sLORETA (Pascual-Marqui 2002) was used to estimate the intracerebral electrical sources that generated the 7 group BSS components. As a standard procedure, a common average reference transformation (Pascual-Marqui 2002) is performed before applying the sLORETA algorithm. sLORETA computes electric neuronal activity as current density (A/m^2) without assuming a predefined number of active sources. The solution space used in this study and associated lead-field 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 (Jurcak et al. 2007), and the lead field produced by Fuchs et al. (2002) applying the boundary element method on the MNI-152 (Montreal Neurological Institute, Canada) template. The sLORETA-key anatomical template divides and labels the neocortical (including hippocampus and anterior cingulate 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 coregistration makes use of the correct translation from the MNI-152 space into the Talairach and Tournoux (1988) space (Brett et al. 2002).

Comparison Between BSS Component Power of Patients With Auditory Phantom Percept Group With a Healthy Control Group

For each group, BSS components relative power was computed with 1-Hz resolution with respect to the total energy across all components, on both the tinnitus and healthy group. Then, the relative power for each frequency and each component was compared between the 2 groups. Multiple comparison Student *t*-tests were performed separately for each component. The significance threshold was based on a permutation *t*-max test with 5000 permutations. The methodology used is nonparametric. It is based on estimating, via randomization, the empirical probability distribution for the max-statistic, under the null hypothesis (Nichols and Holmes 2002). This methodology corrects for multiple testing across frequencies and guarantees that the probability of falsely rejecting even only one hypothesis is less than the chosen alpha level. To correct for multiple testing across components, the type II error rate for significance of the *t*-max tests was set to 0.05 components.

Correlation Analysis

A correlation analysis was conducted between the relative power of the 6 tinnitus components and the scores of tinnitus distress as measured with the TQ and tinnitus loudness as measured with the visual analogue scale. The correlation analysis was performed in all 4-Hz spaced discrete Fourier frequencies in the range 2–44 Hz (2–4, 4–8, … , 42–44 Hz). Corrections were performed for multiple comparisons across the 10 frequency bands using a Bonferroni method. Each component was tested separately without correction.

Lagged Phase Coherence (Out of Phase Coherence)

The BSS method we employed cancels the in-phase correlation at all frequencies between all sources taken pair-wise; however, it does not interfere with their out of phase correlation. The residual out-of-phase correlation among sources can then be studied, for instance, in the frequency domain (coherence). Such "lagged phase coherence" between 2 sources can be interpreted as the amount of cross-talk between the regions contributing to the source activity (Congedo, John, De Ridder, Prichep et al. 2010). Since the 2 components oscillate coherently with a phase lag, the cross-talk can be interpreted as information sharing by axonal transmission. More precisely, the discrete Fourier transform decomposes the signal in a finite series of cosine and sine waves (in-phase and out-of-phase carrier waves, forming the real and imaginary part of the Fourier decomposition) at the Fourier frequencies. The lag of the cosine waves with respect to their sine counterparts is inversely proportional to their frequency and amounts to a quarter of the period; for example, the period of a sinusoidal wave at 10 Hz is 100 ms. The sine is shifted a quarter of a cycle (25 ms) with the respect to the cosine. Then the lagged phase coherence at 10 Hz indicates coherent oscillations with a 25-ms delay, while at 20 Hz the delay is 12.5 ms, etc. The threshold of significance for a given lagged phase coherence value according to asymptotic results can be found as described by Pascual-Marqui (2007), where the definition of lagged phase coherence can be found as well. This analysis was corrected for the amount of pair-wise comparisons using a Bonferroni correction.

In addition, time-series of current density were extracted from the different region of interests using sLORETA. Power in all 6239 voxels was normalized to a power of 1 and log transformed at each time point. The region of interest values thus reflect the log-transformed fraction of total power across all voxels, separately for specific frequencies. Regions of interest were defined based on all brain areas

Table 2

The means and standard deviations of TQ (distress) and VAS (loudness) for the total patient group and patients with grade 1 (slight distress), grade 2 (moderate distress), grade 3 (severe distress), or grade 4 (very severe distress) separately as well as the Pearson correlations (*r*) between the TQ and VAS for the different groups

	TQ (distress) M (SD)	VAS (loudness) M (SD)	*r*	*N*
Total	35.88 (16.28)	5.11 (2.44)	0.45	317
Grade 1	20.12 (6.79)	3.74 (2.29)	0.05	53
Grade 2	37.75 (4.93)	5.58 (1.98)	0.01	104
Grade 3	52.03 (4.29)	6.12 (1.82)	0.18	84
Grade 4	66.07 (4.63)	7.51 (2.05)	0.12	76

*$P < 0.01$.

involved in components III and IV (Fig. 3) at specific frequencies (Fig. 7). We calculated the log-transformed power for each brain area with the 2 different networks separately. A comparison was made between each tinnitus group (grade 1, grade 2, grade 3, and grade 4) and control subjects for the lagged phase coherence for the frequencies 10 and 11.5 Hz, respectively. We conducted this additional analysis to verify how exactly the 2 networks, that is, the loudness network and the distress network, communicate with each other.

Results

Behavioral Measurements

A significant positive correlation between the TQ and the tinnitus loudness was obtained, indicating that the higher the TQ the louder patients perceive their tinnitus (Table 2). When dividing the tinnitus patients into different grades, going from slight to very severe distress, based on their TQ score, no significant correlations could be obtained between the TQ and the tinnitus loudness for each group separately (Table 2).

Group Blind Source Separation on the Control Sample

Similar to Congedo, John, De Ridder, Prichep et al. (2010), we applied a BSS analysis extracting 7 components explaining 82.35% of the total variance. Components I, II, III, and VII are located more posteriorly, while components IV, V, and VI are located more anteriorly (Fig. 1). Component I shows activity in the dorsal anterior cingulate [Brodmann area (BA)24]

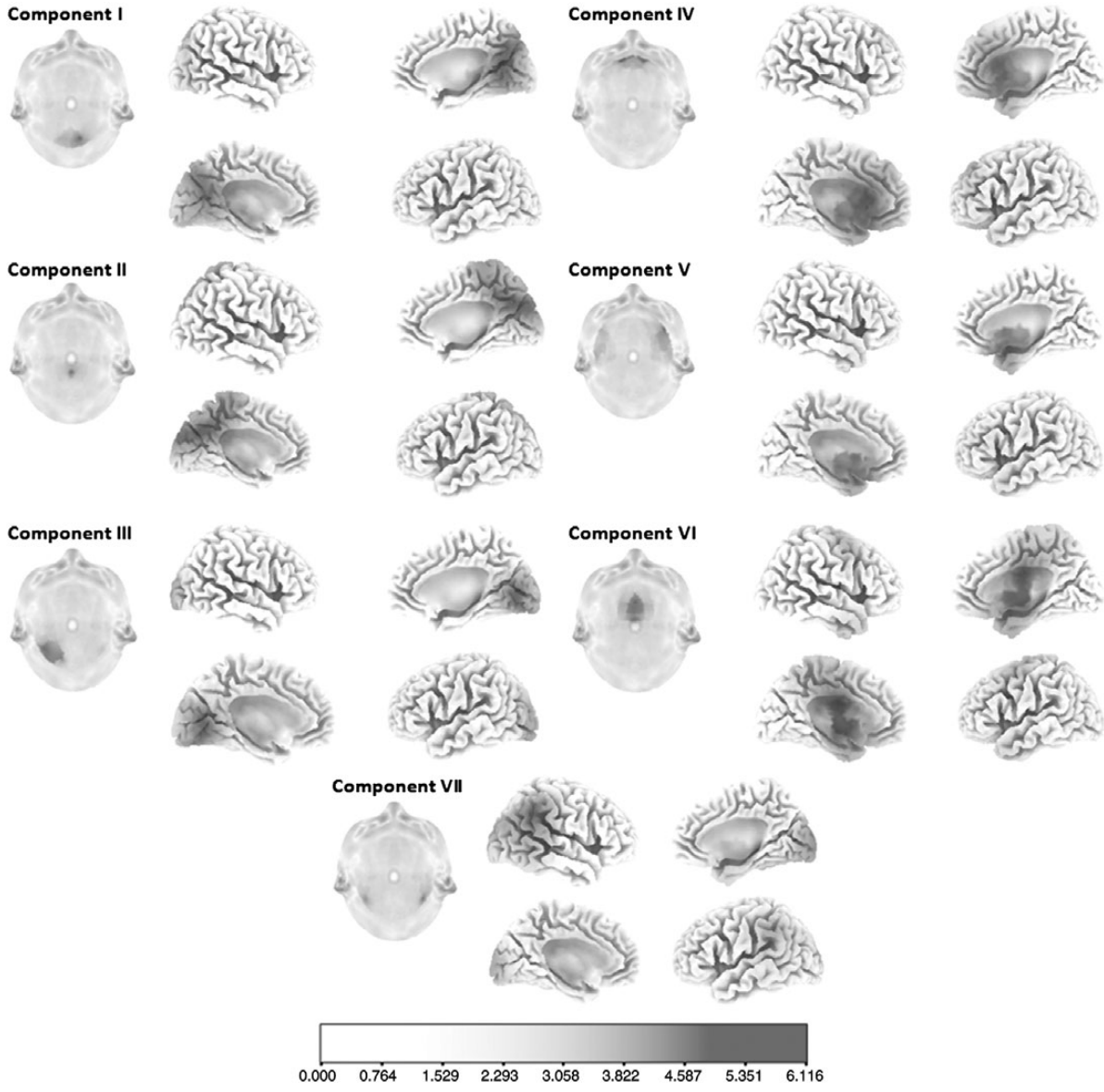

Figure 1. Overview of the obtained BSS components for the healthy control group. Component I: dorsal anterior cingulate (BA24) extending to the subgenual anterior cingulate cortex/ventromedial prefrontal cortex (BA25), insula (BA13), and parahippocampal area (BA28). Component II: cuneus/precuneus (BA7 and BA31) extending to the posterior cingulate gyrus (BA23 and BA31) and right superior parietal lobule (BA7). Component III: cuneus/precuneus (BA31 and BA7), retrosplenial posterior cingulate (BA30), parahippocampal gyrus (BA18 and BA19). Component IV: lingual gyrus, fusiform gyrus, middle and inferior occipital gyrus (occipital pole) (BA17, BA18, and BA19). Component V: dorsal anterior cingulate (BA24), subgenual anterior cingulate cortex/ventromedial prefrontal cortex (BA25), inferior frontal gyrus (BA47), parahippocampal gyrus (BA28 and BA34). Component VI: subgenual anterior cingulate/ventromedial prefrontal cortex (BA25), inferior frontal gyrus (BA47), parahippocampal gyrus (BA28 and BA34), insula (BA13). Component VII: postcentral gyrus (BA1, BA2, and BA3), middle occipital gyrus (BA18), superior and middle temporal gyrus (BA39 and BA41), angular gyrus (BA39).

extending to the subgenual anterior cingulate cortex/ventromedial prefrontal cortex (BA25), the insula (BA13), and the parahippocampal area (BA28). Component II demonstrates activity within the cuneus/precuneus (BA7 and BA31) extending to the posterior cingulate gyrus (BA23 and BA31) and the right superior parietal lobule (BA7), while component III shows activity in the cuneus/precuneus (BA31 and BA7), retrosplenial posterior cingulate (BA30), and visual areas (BA18 and BA19). Component IV revealed activity in the lingual gyrus, fusiform gyrus, and middle and inferior occipital gyrus (occipital pole) (BA17, BA18, and BA19). Component V shows activity in the dorsal anterior cingulate (BA24), the subgenual anterior cingulate cortex/ventromedial prefrontal cortex (BA25), the inferior frontal gyrus (BA47), and the parahippocampal gyrus (BA28 and BA34). Component VI demonstrated activity within the subgenual anterior cingulate/ventromedial prefrontal cortex (BA25), the inferior frontal gyrus (BA47), the parahippocampal gyrus (BA28 and BA34), and the insula (BA13). Component VII shows activity in the postcentral gyrus (BA1, BA2, and BA3), the middle occipital gyrus (BA18), the superior and middle temporal gyrus (BA39 and BA41), and the angular gyrus (BA39).

Group Blind Source Separation on the Tinnitus Sample

Based on the bootstrap analysis, 6 components could repeatedly be obtained. Analysis on the total group reveals that these 6 components explain 62.07% of the total variance. Components I, II, and III are located posteriorly in the brain, while components IV, V, and VI are positioned anteriorly in the brain (Fig. 2). Component I reveals activity within the posterior cingulate cortex (BA23, BA30, and BA31) and the precuneus (BA7), and component II demonstrates activity within the posterior cingulate cortex (BA30, BA30, and BA31) extending to the precuneus (BA7) and the inferior parietal cortex (BA40) as well as in the parahippocampal area (BA19, BA30, BA35, and BA36). The third component shows activity in the retrospenial posterior cingulate cortex (BA29, BA30, and BA31), the anterior end of lingual gyrus (BA7 and BA18), and the parahippocampal area (BA19 and BA30). Component IV yielded activity within the pregenual anterior cingulate cortex (BA24 and BA32), subgenual anterior cingulate cortex/ventromedial prefrontal cortex (BA25), and left and right insula (B13). Component V demonstrates activity in the subgenual anterior cingulate cortex/ventromedial prefrontal cortex (BA25), hippocampal area (BA34), amygdala, and medial frontal gyrus (BA11), while component VI shows activity in the dorsal anterior cingulate cortex (BA24), supplementary motor area (BA6), subgenual anterior cingulate cortex/ventromedial prefrontal cortex (BA25), and medial frontal gyrus (BA11).

Component I is characterized by prominent alpha activity, while components II and III by beta activity (Fig. 3*A*). Component II can be categorized by low beta and component III low and medium beta activity. Component IV is characterized

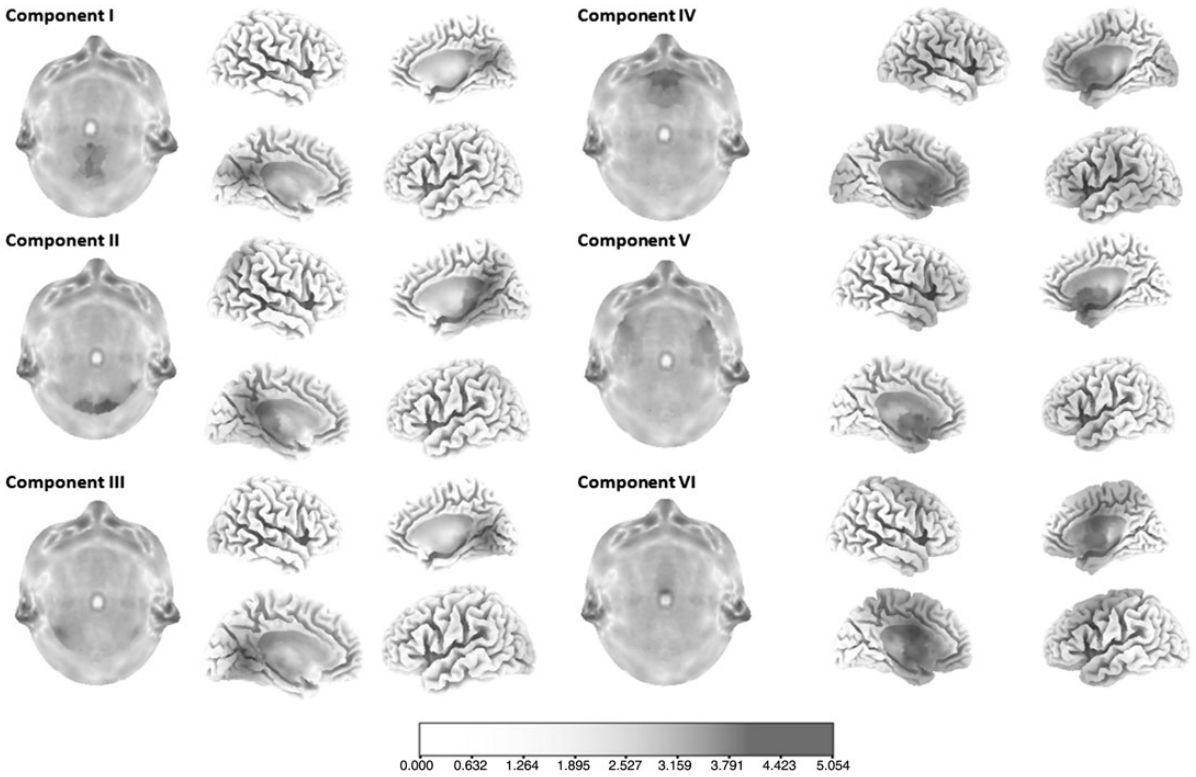

Figure 2. Overview of the obtained BSS components for the patients with an auditory phantom percept. Component I: posterior cingulate cortex (BA23, BA30, and BA31) extending to the precuneus (BA7). Component II: posterior cingulate cortex (BA30, BA30 and BA31) extending to the precuneus (BA7), inferior parietal cortex (BA40), and parahippocampal area (BA19, BA30, BA35 and BA36). Component III: posterior cingulate cortex (BA29, BA30, and BA31), extending to the anterior end of the lingual gyrus (BA7 and BA18) and parahippocampal area (BA19 and BA30). Component IV: subgenual anterior cingulate cortex and dorsal anterior cingulate cortex (BA25, BA24, and BA32) extending to the left and right insula (B13). Component V: subgenual anterior cingulate cortex (BA25), hippocampal area (BA34), amygdala, and orbitofrontal gyrus (BA11). Component VI: subgenual anterior cingulate cortex and dorsal anterior cingulate cortex (BA25 and BA24) supplementary motor area (BA6), and orbitofrontal gyrus (BA11).

by high-beta and gamma activities, while component V and VI are characterized by delta, theta, and gamma activities (Fig. 3*A*).

A comparison between the power produced by the 6 independent components in the tinnitus group and the healthy control group revealed several significant results. For component I, the tinnitus group had less delta, theta, alpha, and beta activities, and more gamma activity (Fig. 3*B*). Component II revealed less beta activity and more gamma activity, while component III revealed less beta activity (Fig. 3*B*). Component IV and V yielded more delta, theta, alpha, and beta activities for the tinnitus group in comparison with a healthy control group. Furthermore, component IV showed additional increased gamma activity, while component V showed decreased gamma activity for the tinnitus group in comparison with the healthy control group (Fig. 3*B*). For the tinnitus group, component VI showed more beta and gamma activities in comparison with the control group (Fig. 3*B*).

Auditory Cortex

Further analyses were conducted to verify the involvement of the auditory cortex. As no group BSS component involved the auditory cortex, a separate group BSS analysis was conducted for the 3 separate subgroups: A group that presents right-sided tinnitus, left-sided tinnitus, and bilateral tinnitus. The reason for this latter analysis is that previous research indicated that the activity in the auditory cortex can differ depending on the tinnitus lateralization.

Extracting 7 components instead of 6 revealed that component VII was indeed an auditory component for both left and right-sided tinnitus patients (Fig. 4). For the bilateral tinnitus, patients only after extracting 8 components such an auditory component could be found (Fig. 4). The explained variance of the auditory component for the different groups was very low, 4.75% for left-sided tinnitus patients, 4.59% for the right-sided tinnitus patients, and 4.75% for the bilateral tinnitus patients.

Lagged Phase Coherence on the Healthy Sample

The estimated lagged phase coherence was computed between all components in the healthy control subjects (Fig. 5). This analysis revealed no significant results, indicating that all components are uncorrelated in an out-of-phase manner.

Lagged Phase Coherence on the Tinnitus Sample

The estimated lagged phase coherence was obtained between all components (Fig. 6*A*,*B*). The profile appears clearly non-random and seems to concentrate in discrete frequency regions of high-communication rate, interleaved with by regions of low communication rate. Our data show communication among component pairs interplaying at multiple frequencies (multiple time-lags) simultaneously, although most of the pairs demonstrate a narrow band communication window. Significant coherences are reported in Figure 6*C* in the form of a connectivity graph. By definition (of ICA BSS),

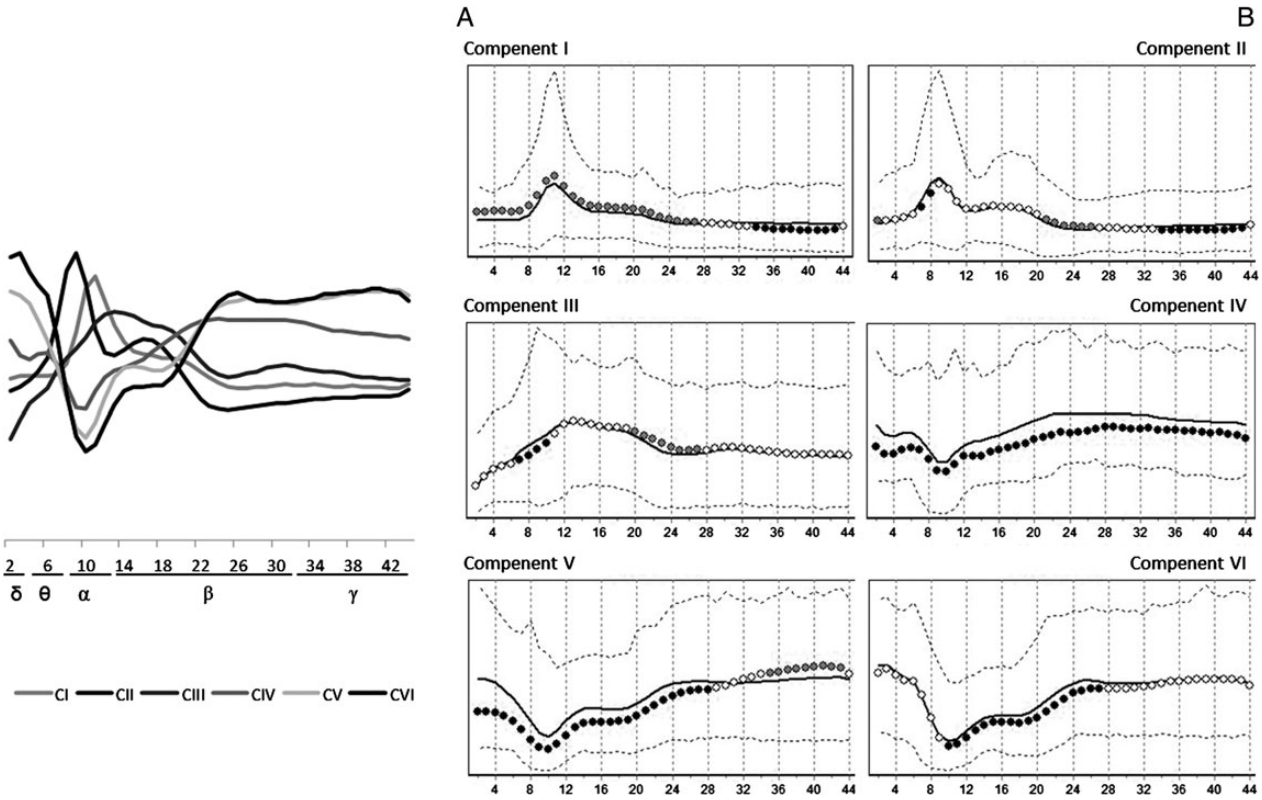

Figure 3. (*A*) Relative spectral power (*Y*-axis) for patients with an auditory phantom percept in the 2–44 Hz (*X*-axis) range. CI: component I; CII: component II; CIII: component III; CIV: component IV; CV: component V; CVI: component VI. (*B*) The differences between patients with an auditory phantom percept and the healthy control subjects. Grey disks flag a statistically higher power ($P < 0.05$, uncorrected) in the normal power of the healthy subjects when compared with the patients with an auditory phantom percept. Black disks flag a statistically lower power ($P < 0.05$, uncorrected) in the normal power of the healthy subjects when compared with the patients with an auditory phantom percept.

all components are uncorrelated in-phase; however, here we look at the lagged "out-of-phase" coherence. Since the different components oscillate coherently with a phase lag, the cross-talk can be interpreted as information sharing by cortico-cortical transmission. We see that the 6 components are organized in 2 independent networks (neither in-phase nor out of phase communication exists between networks), whereas significant out-of-phase cross-talk exists within each network. Within the 2 independent networks, it seems that the first network, including components I, II, IV, and VI, is functionally connected at slow frequencies (i.e. 2.5–9 Hz), while the second network, which including components III and V, is functionally connected at fast frequencies (i.e. 30.5 Hz).

Correlation Analysis Between Brain Activity and Distress and Loudness

Separate correlation analyses were conducted between tinnitus distress as measured by the TQ and the log power of 4 Hz spaced discrete Fourier frequencies in the range 2–44 Hz (2–4, 4–8, … , 42–44 Hz) for the different components (components I, II, III, IV, V, and VI). These correlation analyses demonstrated significant negative correlations between tinnitus distress and the log power for component I at frequency range 8–12 and 12–16 Hz and for component II at frequency range 8–12, 24–28, 29–32, and 32–38 Hz (Table 3). In addition, a positive correlation was obtained between tinnitus distress and the log power of component IV at the frequency range 8–12 Hz and the log power of component VI at frequency range 24–28 and 28–32 Hz (Table 3). No significant results were obtained between tinnitus distress and the log power of components III and IV at the specific frequency ranges. Based on these findings, we could claim that the combination of components I, II, IV, and VI represents a distress network.

Separate correlation analyses were conducted between the tinnitus loudness as measured by a visual analog scale and the log power of 4 Hz spaced discrete Fourier frequencies in the range 2–44 Hz (2–4, 4–8, … , 42–44 Hz) for the different components (components I, II, III, IV, V, and VI). This correlation analysis revealed a significant negative correlation between tinnitus loudness and the log power of component III at frequency range 20–24, 24–28, and 28–32 Hz (Table 3). For component V, a positive correlation was obtained between tinnitus loudness and the log power at the frequency range 12–16 Hz (Table 3). No significant results were obtained between tinnitus loudness and the log power of components I, II, IV, and VI at the specific frequency ranges. As such we could name this III–V network a loudness network.

Correlation analyses between the log power of discrete frequencies in the range 2–44 Hz (2–4, 4–8, … , 42–44 Hz) of the different components (components I, II, III, IV, V, and VI) and, respectively, hearing loss measured as the loss in decibels (dB SL) at the tinnitus frequency, tinnitus frequency (Hz) and age showed no significant results.

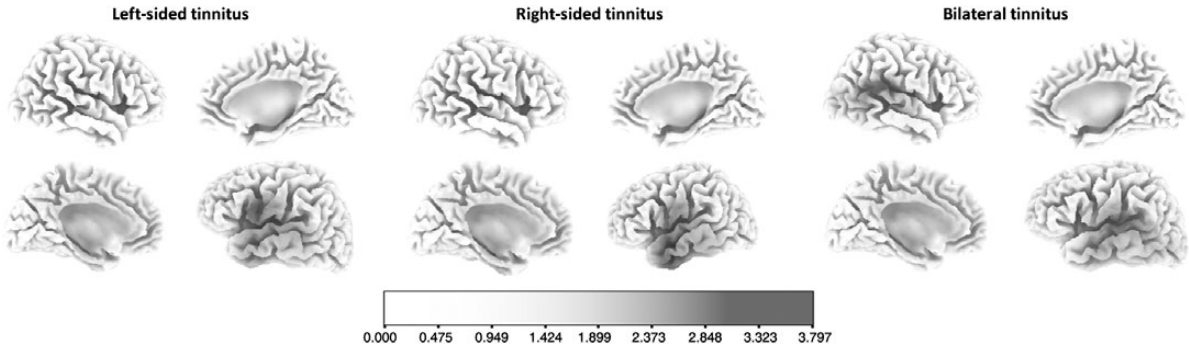

Figure 4. Overview of the obtained auditory BSS components for the patients with an auditory phantom percept in, respectively, left-sided, right-sided, and bilateral tinnitus.

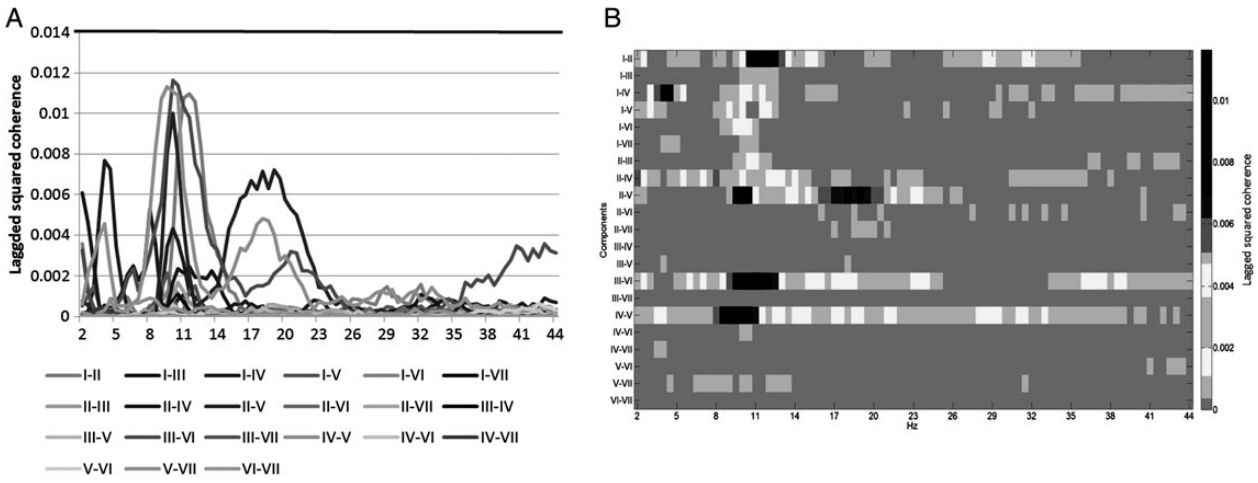

Figure 5. (*A* and *B*) Lagged phase coherence (*Y*-axis) in the 2–44 Hz (*X*-axis) range for all pair-wise couples of the 7 components for healthy control subjects (i.e. 1–2: is coupling between component I and component II). No significant results could be obtained.

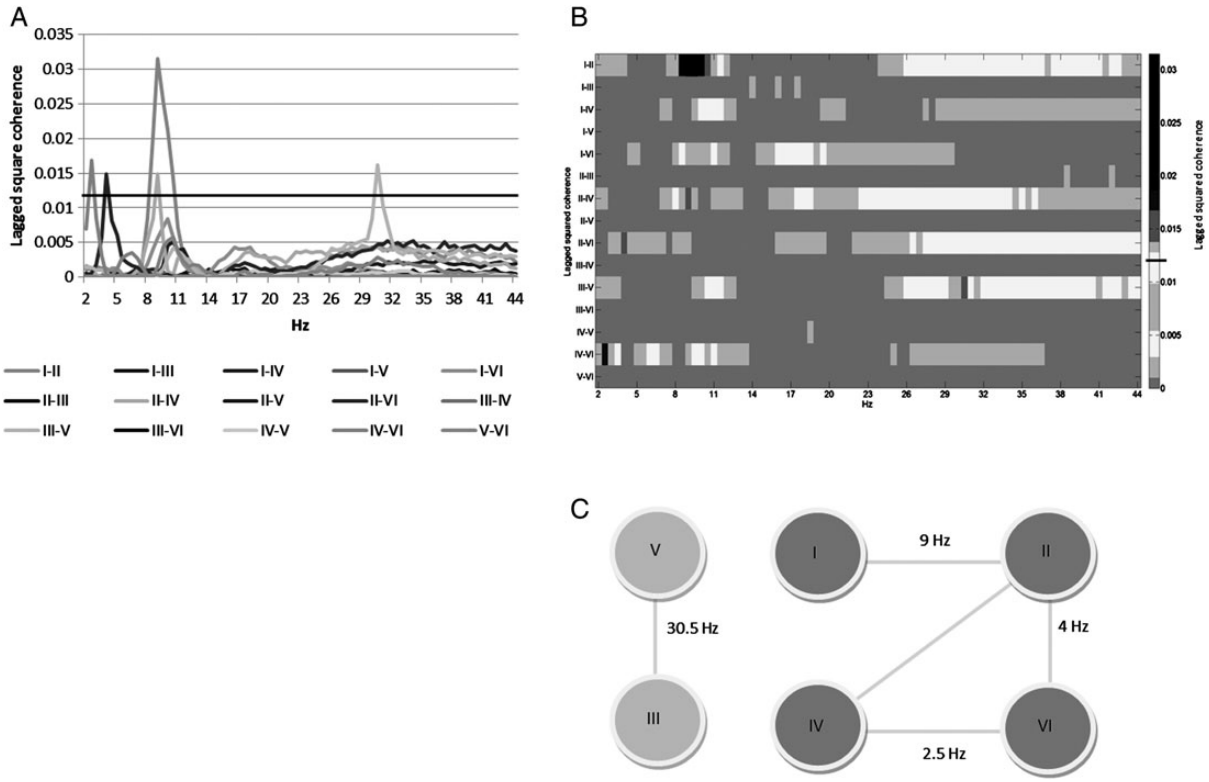

Figure 6. (*A* and *B*) Lagged phase coherence (*Y*-axis) in the 2–44 Hz (*X*-axis) range for all pair-wise couples of the 6 components for patients with an auditory phantom percept (i.e. 1–2: is coupling between component I and component II). The horizontal black line indicates the threshold of significance ($P < 0.05$). In (*A*), the coherence profiles of component pairs exceeding the threshold for at least one frequency are drawn using a thick line. (*C*) Significant lagged phase coherence as a connectivity graph. Light grey: loudness network, Dark grey: distress network. Significant connections are represented by lines connecting the components. The 6 components organize in 2 fully independent modules. CI: component I; CII: component II; CIII: component III; CIV: component IV; CV: component V; CVI: component VI. This analysis was corrected for the amount of pairwise comparisons.

In addition, a correlation analysis was conducted on the auditory component (components VII or VIII depending on the tinnitus lateralization) to verify whether tinnitus loudness correlated with this component for the respective tinnitus groups. No significant results could be obtained. A correlation analysis between tinnitus distress (TQ) and the auditory component for the respective tinnitus groups showed no significant effects.

Inter-relationship Between the Distress and Loudness Network

Our results suggest that 2 independent networks exist, one related to distress and another related to tinnitus loudness. Based on the behavioral measurements, a positive correlation was obtained between distress and loudness. Previous research also suggested that there might be a link between the distress and loudness network for specific groups of tinnitus patients (De Ridder, Elgoyhen et al. 2011). Hence, we conducted a secondary lagged phase coherence analysis for, respectively, tinnitus patients with grade 1 (slight distress), grade 2 (moderate distress), grade 3 (severe distress), or grade 4 (very severe distress) distress scores.

We applied a BSS analysis on the different tinnitus groups separately to verify whether similar components could be obtained. This BSS analysis revealed similar 6 components for all 4 grades going from slight to very severe distress (Supplementary Fig. 2*A–D*). A second step was to calculate the lagged phase coherence for the 4 grades (Supplementary Fig. 2). Figure 7*A–D* shows the estimated lagged phase coherence obtained between all pair-wise components for, respectively, grade 1, grade 2, grade 3, and grade 4. For grade 1, no significant communication was found between the different components (Fig. 7). However for grade 2, grade 3, and grade 4, a specific communication was obtained within the loudness and distress networks (Fig. 7*A–D* and Supplementary Fig. 2). In addition, the profile appears clearly nonrandom and seems to concentrate in discrete frequency regions of high-communication rate, interleaved with by regions of low communication rate. In addition, we found significant coherences between the loudness and distress network (trough communication between component III and component IV) for grade 3 and grade 4 tinnitus patients, but not for grade 1 and grade 2 (Fig. 7*C–F*). No other significant lagged phase coherence could be obtained between the distress and loudness network. Our data show a lagged phase coherence between component III and IV at 10 Hz for grade 3 (Fig. 7*A*,*B*,*D*), and at 11.5 Hz for grade 4 (Fig. 7*A*,*B*,*E*).

Brain-Specific Connectivity Between the Distress and Loudness Network

To further explore the lagged phase coherence between the different tinnitus groups [i.e. grade 1 (slight distress), grade 2 (moderate distress), grade 3 (severe distress), or grade 4 (very severe distress)] and an age- and gender-matched healthy control group, the current density was extracted on the raw EEG data including all the regions of component III (i.e. the

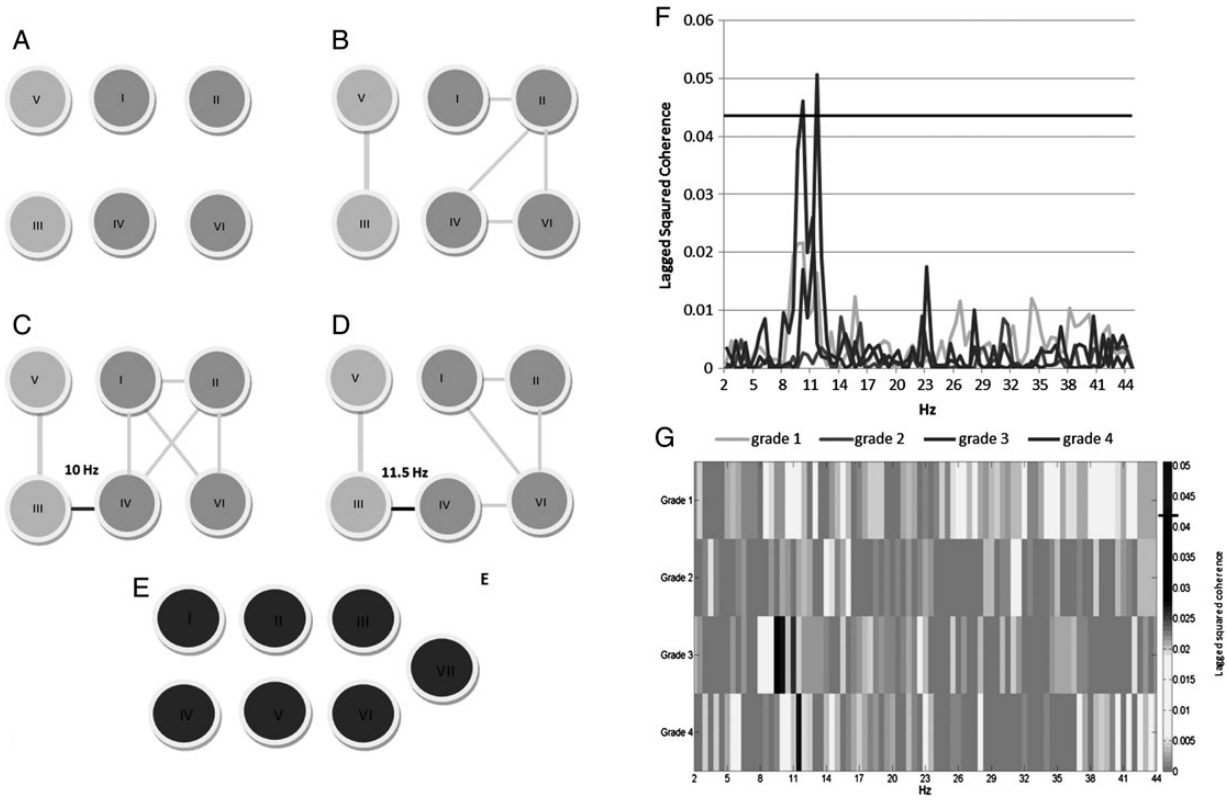

Figure 7. (*A–D*) Lagged phase coherence connectivity graph for grade 1 (slight distress) (*A*), grade 2 (moderate distress) (*B*), grade 3 (severe distress) (*C*), and grade 4 (very severe distress) (*D*). Light grey: loudness network, Dark grey: distress network. (*E*) Healthy control subjects show no significant connections. Significant connections are represented by lines connecting the components. (*F* and *G*) Lagged phase coherence (*Y*-axis) in the 2–44 Hz (*X*-axis) range for coupling between component III and component IV for patients with an auditory phantom percept. This analysis was corrected for the amount of pairwise comparisons.

Table 3
Significant Pearson correlations (*r*) between TQ (distress) and the VAS (loudness) with the log power of the 6 BSS components

	Frequencies	*r*
Component I		
Distress	8–12	−0.24**
	12–16	−0.28**
	16–20	−0.29**
Loudness	–	–
Component II		
Distress	8–12	−0.23**
	24–28	−0.18*
	28–32	−0.18*
	32–38	−0.17*
Loudness	–	–
Component III		
Distress	–	–
Loudness	20–24	−0.23**
	24–28	−0.18*
	28–32	−0.25**
Component IV		
Distress	8–12	0.18*
Loudness	–	–
Component V		
Distress	–	–
Loudness	12–16	0.21**
Component VI		
Distress	24–28	0.21**
	28–32	0.18*
Loudness	–	–

Note: Corrections were performed for multiple comparisons across the 10 frequency bands using a Bonferroni method. Each component was tested separately without correction.
*$P < 0.05$; **$P < 0.01$.

posterior cingulate cortex, the anterior lingual gyrus, and the parahippocampal area) and component V (i.e. the subgenual anterior cingulate cortex/ventromedial prefrontal cortex, dorsal anterior cingulate, left and right insula) specifically for 10 and 11.5 Hz, respectively. We opt for these latter frequencies as the above-mentioned analyses clearly revealed that both frequencies are important in, respectively, grade 3 and grade 4 tinnitus patients.

A sLORETA connectivity comparison between the control group and the respective tinnitus groups (i.e. healthy control, grade 1, grade 2, grade 3, and grade 4) demonstrated a significant difference at 10 Hz in lagged phase coherence between healthy subjects and, respectively, grade 3 and 4 patients (Fig. 8). A significant connection at 10 Hz between the parahippocampal area that was included in component III and the subgenual anterior cingulate cortex/ventromedial prefrontal cortex that was included in component IV between the grade 3 tinnitus patients and the healthy control subjects was obtained, revealing that grade 3 tinnitus patients had an increased lagged phase coherence. For grade 4 tinnitus patients, a similar result was obtained between the parahippocampal area and the subgenual anterior cingulate cortex/ventromedial prefrontal cortex at 10 and 11.5 Hz, respectively, in comparison with the healthy subjects group. No significant effects were obtained between both grade 1 and grade 2 tinnitus patients and the healthy control group for the 10 Hz, as well as for grade 1 tinnitus patients at 11.5 Hz in comparison with the healthy control group. A significant decrease in lagged phase coherence was, however, obtained in grade 2

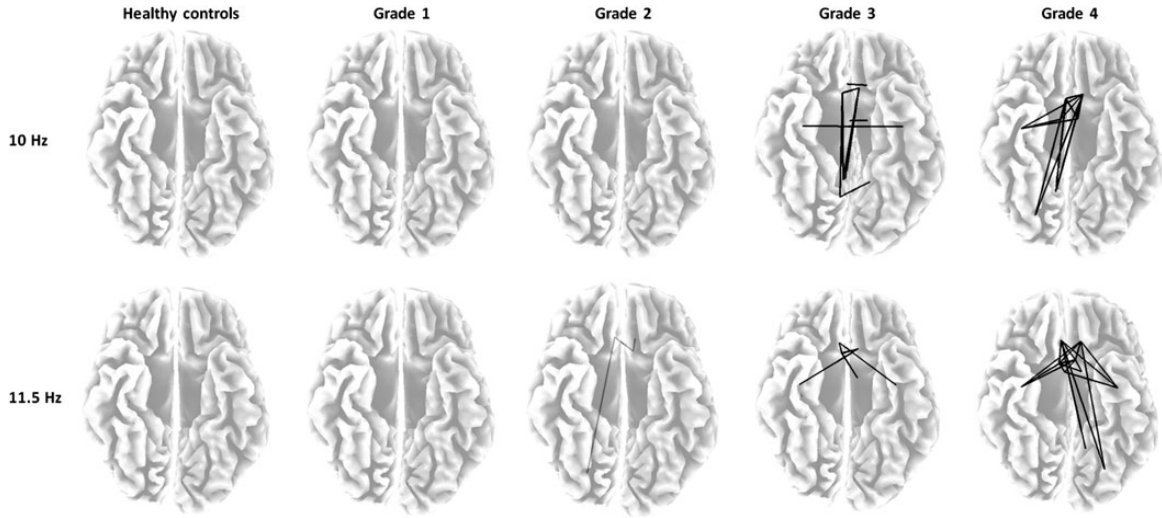

Figure 8. A comparison for the lagged phase coherence between healthy controls and grade 1 (slight distress), grade 2 (moderate distress), grade 3 (severe distress), grade 4 (very severe distress) tinnitus patients and matched healthy control groups at 10 and 11.5 Hz. Light grey lines show significantly decreased lagged phase coherence in the specific tinnitus group in comparison with the healthy control subjects, while dark grey lines show significantly increased lagged phase coherence in the specific tinnitus group in comparison with the control group. This analysis was corrected for the frequency bands, but not for the amount of comparisons.

tinnitus patients in comparison with the healthy control group at 11.5 Hz between the parahippocampal area included in component III and the subgenual anterior cingulate cortex/ventromedial prefrontal cortex included in component IV.

Discussion

Recently, it was shown that spontaneous, temporally fast, electrophysiological activity as reflected in EEG is correlated with the slower hemodynamic fluctuations of the blood oxygenation-level dependent (BOLD) signal in resting-state fMRI (Britz et al. 2010; Musso et al. 2010). Results revealed that each of the BOLD resting-state networks identified in the resting-state fMRI data was characterized by a relatively specific electrophysiological signature involving a combination of several microstates (Yuan et al. 2012). The concurrently acquired fMRI and EEG data thus reveal that complex spatial and temporal dynamics of neuronal activity are reflected by the inter-relationships between neuroimaging measures obtained using modalities that vastly differ in their spatial and temporal properties (Yuan et al. 2012). These findings support the potential of multimodal fMRI and EEG approaches to elucidate normal and pathological interactions between cerebral function and behavior, cognition, or emotion (Britz et al. 2010; Musso et al. 2010; Yuan et al. 2012).

The main goal of the study was to characterize the loudness and distress networks in patients with an auditory phantom percept to verify whether the loudness and distress are generated by 2 separable networks and to analyze how the components of these 2 networks communicate within the networks and between the networks by using a BSS method on electrophysiological data. Understanding how and when the loudness and distress interact at an electrophysiological level might lead in the future to a neurophysiologically based, frequency-selective and anatomically restricted neuromodulation approach to functionally separate these networks, clinically leading to the continued perception of the phantom sound without the associated distress. The study reveals 2 separate networks, one reflecting the loudness and the other distress, with partially overlapping brain areas, each with a specific spontaneous oscillatory pattern and functional connectivity signature.

The Independent Components

An ICA in the healthy control subjects revealed similar networks as obtained previously by Congedo, John, De Ridder, Prichep et al. (2010). A comparison between the components obtained for the healthy control subjects and the tinnitus patients showed similar components. However, component VII is different between the healthy control subjects and tinnitus patients. In healthy controls, this component is more localized within the postcentral gyrus, the middle occipital gyrus, the superior and middle temporal gyrus, and the angular gyrus (BA39).

Only after a further analysis, an additional auditory component (i.e. component VII/VIII) was obtained for patients with an auditory phantom percept. These results depended on the lateralization of the tinnitus. This component is specifically associated with the auditory cortex. Previous research already demonstrated that this brain area might be important in tinnitus. That is, previous research has demonstrated a reorganization (Muhlnickel et al. 1998) and hyperactivity (Weisz et al. 2007) of the auditory cortex in tinnitus patients in comparison with the healthy control subjects, and tinnitus loudness might be related to the amount of hyperactivity within the auditory cortex (van der Loo et al. 2009). Our results showed that, for the healthy controls, no auditory component could be demonstrated, which is likely due to the fact that resting-state electrical brain activity recording was performed in a sound attenuating room, precluding a constant auditory percept during recording.

The Distress Network

The distress network is characterized by increased alpha activity in the subgenual anterior/ventromedial prefrontal

cortex and beta activity in the dorsal anterior cingulate cortex, correlating positively with distress, while for the posterior cingulate cortex distress correlates negatively with alpha and high-beta activities. These findings are in agreement with previous research conducted on a separate group of tinnitus patients, revealing that highly distressed tinnitus patients have increased alpha activity within the subgenual anterior cingulate cortex/ventromedial prefrontal cortex extending to the ventromedial prefrontal cortex, insula, and parahippocampal area and decreased activity in the posterior cingulate cortex extending to the precuneus in comparison with tinnitus patients with low distress (Vanneste, Plazier, der Loo et al. 2010). In comparison with the healthy control group, highly distressed tinnitus patients show more alpha and beta activities within the dorsal anterior cingulate cortex (Vanneste, Plazier, der Loo et al. 2010; De Ridder, Vanneste et al. 2011). This network overlaps partially with brain areas implicated in distress in patients suffering from pain, dyspnea, functional somatic syndromes and post-traumatic stress disorder and might therefore represent a nonspecific distress network (Peyron et al. 2000; Phan et al. 2002; Craig 2003; Critchley 2005). This suggests that the distress associated with tinnitus perception might be related to activation of a general distress network.

The Loudness Network

The loudness network is built up by 2 components, one located anteriorly and one posteriorly. This is different than the results obtained by an auditory cortex-centered approach used in previous research, demonstrating that tinnitus loudness is correlated to decreased alpha (Lorenz et al. 2009) and increased gamma band activities in the auditory cortex (Llinas et al. 1999; Weisz et al. 2007). An independent component, source localized to the auditory areas could only be retrieved in subgroups selected on perceived lateralization of the phantom sound. Based on this analysis, it appears that the auditory cortex is less important in tinnitus than previously expected, considering that the auditory component could only explain a small amount (4–5%) of the total variance. Furthermore, no correlation was found between the auditory component and tinnitus loudness. This finding seems in contrast with previous findings that showed that the auditory cortex is correlated to gamma activity (van der Loo et al. 2009). However, the auditory components are spectrally constructed of multiple frequency bands, and the gamma band on continuously recorded EEG features a very low signal-to-noise ratio. Moreover, the electrical dipolar activity of the primary auditory cortex is mainly tangential to the cortical surface, resulting in little visibility by EEG. Similar investigations using magnetoencephalography, which is sensitive to tangential dipole orientation, may confirm this hypothesis. The poor sensitivity of EEG to electrical activity produced in the auditory cortex, especially in the gamma band, can explain the lack of correlation between the auditory component and subjectively perceived loudness.

Communication Between the Independent Components Within Each Network

Our results indicate that the independent components within the 2 networks communicate at different frequency bands. While the distress network (C1–C2–C4–C6) seems to communicate or is functionally connected at slow frequencies (i.e. 2.5–9 Hz), the loudness network (C3–C5) communicates or is functionally connected at fast frequencies (i.e. 30.5 Hz).

It has already been argued that both slow and fast rhythms have a different role in perception (Varela et al. 2001). More precisely, slow waves would constitute the "context" and fast waves the "content" of neuronal representations (Poppel 1994; Llinas et al. 1998). Applied to our findings, it can be suggested that the distress network would function as context, while the tinnitus loudness is important for the content of the auditory phantom percept. It has indeed been shown that highly distressed patients perceive the tinnitus louder (Henry and Wilson 1995), demonstrating the contextual modulation of the phantom auditory content.

Decreased Posterior and Increased Anterior Brain Activity

The group BSS analysis resulted in 6 components of which 3 components are located more posteriorly, including the retrosplenial posterior cingulate cortex, the posterior cingulate cortex, the precuneus, the parahippocampal area, and 3 components located more anteriorly, including the subgenual anterior cingulate cortex/ventromedial prefrontal cortex, the pregenual anterior cingulate cortex, the left and right insula, the hippocampal area, the amygdala, the medial frontal gyrus, and the dorsal anterior cingulate cortex. These 6 non-auditory components obtained in our study are in line with previous research on source localized ICA on resting-state EEG conducted in healthy subjects (Congedo, John, De Ridder, Prichep 2010) and in tinnitus distress (De Ridder, Vanneste et al. 2011). Spectrally, the tinnitus group was characterized by decreased activity in the delta, theta, alpha, and beta bands for the first 3 posterior components (i.e. I, II, and III), and increased activity was demonstrated within delta, theta, alpha, and beta bands for the last 3 anterior components (i.e. IV, V, and VI) in comparison with the control subjects. Tinnitus patients are thus characterized by decreased activity posteriorly and increased activity anteriorly in comparison with the healthy control group. These finding are in line with previous research using transcranial magnetic stimulation (TMS), suggesting that targeting the anterior cingulate with low-frequency TMS (supposedly decreasing the activity of the underlying cortex) can reduce the tinnitus perception, while targeting the posterior cingulate cortex with high-frequency TMS (supposedly increasing the activity of the underlying cortex) can decrease the tinnitus perception (Vanneste, Plazier, Van de Heyning et al. 2011; Vanneste and De Ridder 2013).

While the anterior cingulate has been implicated in emotional (Sinha et al. 2004), attentional (Cohen et al. 1999), reward (Bush et al. 2002), and executive (Vogt et al. 1992) processing, the posterior cingulate seems to be related more to cognitive and memory aspects of information processing (Vogt et al. 1992). The posteriorly based components found in the group BSS analysis might be related to cognitive and memory aspects of the tinnitus percept, as the posterior cingulate cortex is implicated in auditory memory (Grasby et al. 1993; Fletcher et al. 1995) and in cognitive aspects of auditory processing (Laufer et al. 2009). Activity in the precuneus and adjacent retrosplenial posterior cingulate cortex and posterior cingulate cortex has indeed been linked to successful retrieval from auditory (and visual) memory (Shannon and Buckner 2004; Sadaghiani et al. 2009). The posterior cingulate cortex, precuneus component, has been proposed to exert a salience-based cognitive auditory comparator function (Laufer et al. 2009).

Multiple Networks With Partially Overlapping Brain Areas

Our results demonstrate that components I, II, IV, and VI, composing the first network, a distress network, as well as components III and V, composing the second network, a loudness network, communicate with each other at specific frequency bands in parallel. However, these 2 brain networks do not communicate between each other in the total tinnitus population. In addition, it was shown that the first brain network (components I–II–IV–VI) correlates with the distress, while the second brain network (components III–V) correlates with loudness. These latter findings could maybe explain why previous clinical research could not find a clear relationship between loudness, as measured by psychophysical tinnitus matching testing, and distress in tinnitus (Goodwin and Johnson 1980; Andersson 2003), and it confirms our hypothesis that tinnitus distress is the result of a distress network separable from a tinnitus loudness network (De Ridder, Elgoyhen et al. 2011).

That is, the distress network and the loudness network both include the subgenual anterior cingulate cortex and the posterior cingulate cortex. However, the activity of these structures correlates with distress and loudness scores at different frequencies; the subgenual cingulate cortex/ventromedial prefrontal cortex correlates with distress in the alpha band (as part of component IV), whereas with loudness in the beta band (as part of component V); the posterior cingulate cortex correlates with distress in the alpha band and low beta band (as part of component I) and with loudness in high-beta activity (as part of component III). The results within the subgenual anterior cingulate cortex, however, need to be interpreted with care, as tinnitus distress and loudness may be related to separate midline frontal structures (Leaver et al. 2012). Using spatial location of sources in EEG is relatively limited, especially in deeper midline frontal cortex and cingulate cortex areas due to the inherent low resolution of the used methodology. Hence, it is difficult to claim that the distress and loudness in the subgenual anterior cingulate cortex really overlap or are generated very closely but adjacently to each other.

The Lagged Phase Coherence Between the Distress and Loudness Network

It has also been shown that, in highly distressed patients, the tinnitus is perceived louder (Henry and Wilson 1995). And indeed in highly distressed patients (grades 3 and 4), a functional connection exists between independent components III and IV, thus between a component of the distress network and the loudness network, that is, not present in patients with low distress, that is, in patients in whom the tinnitus, whatever its loudness is not distressing. This functional connection occurs in the alpha range, that is, at 10 and 11.5 Hz in the distressed patients.

To find out which brain areas are critically involved in determining whether a patient is distressed by the phantom sound or not, the brain areas that are part of the independent components III and IV are used as regions of interest and the lagged phase synchronization between the regions of interest are computed specifically for 10 and 11.5 Hz both for tinnitus without distress (grades 1 and 2) and tinnitus patients with distress (grades 3 and 4) and statistically compared with a nontinnitus control group. This demonstrates that, in patients with tinnitus but without distress, there is no functional connection between any of the regions of interest, that is, different from nontinnitus patients, as is expected, but that, in distressed patients, there exists a pathological functional connection between the parahippocampal area and the subgenual anterior cingulate cortex/ventromedial prefrontal cortex at 10 and 11.5 Hz, respectively. The subgenual anterior cingulate cortex/ventromedial prefrontal cortex are also functionally connected to the insula in these patients at the same discrete frequencies.

Thus, whether a patient is distressed or not by his/her phantom sound might be critically dependent on a very specific subgenual anterior cingulate cortex/ventromedial prefrontal cortex–parahippocampal connection at a very narrow frequency band. Being able to pinpoint that this highly selective pathological connection opens up the way for very selective modulation of this connection, for example, by implanting an electrode that is capable of disrupting the 10 and 11.5 Hz communication between the parahippocampus and subgenual anterior cingulate cortex/ventromedial prefrontal cortex.

This pathological 10–11.5 Hz connection is not surprising in view of the known tinnitus pathophysiology. It has been proposed that the subgenual anterior cingulate cortex extending to the ventromedial prefontal cortex is involved in tinnitus loudness perception (Muhlau et al. 2006; Rauschecker et al. 2010; Leaver et al. 2011). Structural deficits have been observed in the subgenual cingulate cortex/nucleus accumbens area. Based on these findings, it has been postulated that tinnitus is the result of a deficient sensory attentional gating mechanism, originating in the subgenual cingulate cortex/nucleus accumbens area and acting on the reticular thalamic nucleus (Rauschecker et al. 2010). Not only is the loudness modulated by the subgenual anterior cingulate cortex. The amount of distress perceived by tinnitus patients is related to alpha activity in a network encompassing the subgenual anterior cingulate cortex and insula, extending to the amygdala–hippocampus and parahippocampus (Vanneste, Plazier, der Loo et al. 2010; De Ridder, Vanneste et al. 2011). The 10 and 11.5 Hz functional connectivity between the subgenual anterior cingulate cortex and insula, coupling loudness to increased distress, also fits with the fact that the insula is associated with tinnitus-related distress (van der Loo et al. 2011) and interoceptive perception (Craig 2002). The parahippocampal area is involved in different tinnitus characteristics, such as lateralization and tinnitus type (Vanneste, Plazier, van der Loo et al. 2010; Vanneste, de Heyning et al. 2011; Vanneste, Plazier, van der Loo et al. 2011). Furthermore, in chronification, its functional connectivity (lagged phase synchronization) to the auditory cortex is increased (Vanneste, van de Heyning et al. 2011). The parahippocampal area is also associated with tinnitus distress (Vanneste, Plazier, der Loo et al. 2010; De Ridder, Vanneste et al. 2011). Thus, it is not surprising that the parahippocampal area, which has a sensory gating function for irrelevant or redundant auditory input (Boutros et al. 2008) and subgenual anterior cingulate cortex, which has an attentional gating function, when functionally coupled, link phantom sound to distress.

Is This a Universal Mechanism?

It has been suggested before that the tinnitus distress network is actually a nonspecific distress network, in view of the fact

that the areas involved in tinnitus distress are similar to those in pain (Moisset and Bouhassira 2007), social rejection (Masten et al. 2009), somatoform disorder (Landgrebe et al. 2008), and asthmatic apnea (von Leupoldt et al. 2009).

The connectivity between the parahippocampal area and subgenual anterior cingulate cortex/ventromedial prefrontal cortex is proposed to be part of a general aversive network, involving the cerebellum, parahippocampal area, and hypothalamus, as it is activated both by pain and unpleasant visual images (Moulton et al. 2011). Unfortunately, EEG cannot pick-up electrical activity from neither the cerebellum nor the hypothalamus.

Our results also showed that communication between the different components as well as between the distress and loudness network are within narrowband frequencies. Narrowband frequency communication has already been described for animals (Fujisawa and Buzsaki 2011). In humans, interactions between the independent components also appear to occur at multiple narrowband frequencies (Congedo, John, De Ridder, Prichep et al. 2010). The findings of this study add to these previous findings and suggest that pathological functional connectivity between specific networks at specific frequencies can lead to a problematic auditory phantom percept.

Whether or not the described mechanism in this paper is universal is impossible to say, but in view of the above arguments it is definitely worthwhile to further explore this possibility.

Limitations

One limitation of the current study is related to the fact that we did not control between the tinnitus group and healthy control group for hearing loss. Previous research on structural differences in tinnitus patients has shown that hearing loss can have an important impact on the results (Husain et al. 2011; Melcher et al. 2012). As our research showed that similar components were obtained in both the healthy control subjects and the tinnitus group, this suggested that hearing loss might have only a minor influence on the component analysis. In addition, it was shown that correlations with the different components did not correlate with the hearing loss in the tinnitus group. Nevertheless, this might be a factor to take into account in further research.

Conclusion

In summary, this study suggests that tinnitus is the result of disproportionate activity between anteriorly and posteriorly based components in comparison with healthy control subjects. Based on these results, it can be proposed that auditory phantom percept can be separated in at least 2 independent brain networks with overlapping brain areas characterized by a specific spontaneous oscillatory pattern. One network is involved in the distress, while another network is involved in the loudness of the phantom percept. Within the distress and loudness network, the different independent components that make up the network communicate at narrowband frequencies, but the distress and loudness network do not seem to directly intercommunicate in the total group of patients. However, in those patients who are severely distressed, the sound and distress are linked both clinically and electrophysiologically. A specific functional connection exists in the distressed patients between components III (loudness) and IV (distress) at 10 and 11.5 Hz, respectively. More specifically, it can be pinpointed between the parahippocampal area and the subgenual anterior cingulate cortex/ventromedial prefrontal cortex. This is in accordance with a recently proposed model that states that tinnitus is generated by multiple dynamically active separable but overlapping networks, each characterizing a specific aspect of the unified tinnitus percept (De Ridder, Elgoyhen et al. 2011), but adds to this concept empirical findings characterizing the communication protocol within and between these 2 of multiple separable networks.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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Notes

Conflict of Interest: None declared.

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