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Tinnitus and neuropathic pain share a common neural substrate in the form of specific brain connectivity and microstate profiles

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ABSTRACT

Tinnitus and neuropathic pain share similar pathophysiological, clinical, and treatment characteristics. In this EEG study, a group of tinnitus (n = 100) and neuropathic pain (n = 100) patients are compared to each other and to a healthy control group (n = 100). Spectral analysis demonstrates gamma band activity within the primary auditory and somatosensory cortices in patients with tinnitus and neuropathic pain, respectively. A conjunction analysis further demonstrates an overlap of tinnitus and pain related activity in the anterior and posterior cingulate cortex as well as in the dorsolateral prefrontal cortex in comparison to healthy controls. Further analysis reveals that similar states characterize tinnitus and neuropathic pain patients, two of which differ from the healthy group and two of which are shared. Both pain and tinnitus patients spend half of the time in one specific microstate. Seed-based functional connectivity with the source within the predominant microstate shows delta, alpha1, and gamma lagged phase synchronization overlap with multiple brain areas between pain and tinnitus. These data suggest that auditory and somatosensory phantom perceptions share an overlapping brain network with common activation and connectivity patterns and are differentiated by specific sensory cortex gamma activation.

1. Introduction

Both tinnitus and neuropathic pain are considered phantom perceptions, i.e. the continuous awareness of a percept in the absence of a corresponding external stimulus. The vast majority of phantom percepts are those present in the somatosensory modality, such as neuropathic pain, or in the auditory modality, such as tinnitus (De Ridder et al., 2011a). Both symptoms are subjective perceptions that may change in character and quality and are perceived in the deafferented area. Neuropathic pain can be differentiated from nociceptive pain, since it is not caused by tissue damage, as well as from inflammatory and muscular pain as this pain is a direct result of a lesion or disease affecting the somatosensory system (Treede et al., 2008). Neuropathic pain corresponds to the area that was initially innervated by the injured neural structure (Ramachandran and Hirstein, 1998), while tinnitus corresponds to the individual's hearing loss (Norena et al., 2002) or cochlear damage even when the hearing thresholds are in the normal range (Schaette, 2014; Weisz et al., 2006).

In both pathologies it has been suggested that the spontaneous firing of central neurons in the brain continues to convey perceptual experiences even though the corresponding sensory receptor cells have been destroyed or damaged (Birbaumer et al., 1997; Rauschecker, 1999). Tinnitus is related to hyperactivity (De Ridder et al., 2015a; van der Loo et al., 2009; Weisz et al., 2007) and is often, but not always (Langers et al., 2012), associated with map plasticity of the auditory cortex (Muhlnickel et al., 1998). Subjectively perceived tinnitus loudness correlates to increased gamma band activity in the auditory cortex (De Ridder et al., 2015a; van der Loo et al., 2009) as well as in the anterior cingulate cortex and insula (De Ridder et al., 2015a). Neuropathic pain has also been associated with both hyperactivity and reorganization of the somatosensory cortex (Flor et al., 1995), although this is not always the case (Makin et al., 2013). Subjective pain scores have been associated with gamma band oscillations within the primary somatosensory cortex in a study using brief nociceptive stimuli to investigate pain (Zhang et al., 2012).

It is known that both tinnitus and neuropathic pain are modulated by stress, emotions, and fatigue as originally described by the neurophysiological model for tinnitus (Jastreboff, 1990) and are frequently comorbid with both anxiety and depression (Moller, 1997). These affective dimensions of both phantom percepts involve the subgenual

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anterior cingulate cortex, dorsal anterior cingulate cortex, insula, and amygdala (De Ridder et al., 2011b; Moisset and Bouhassira, 2007; Price, 2000; Vanneste et al., 2010).

The assumption that neuropathic pain and tinnitus share similar pathophysiological, clinical and treatment characteristics (De Ridder et al., 2007; De Ridder et al., 2011a; Moller, 1997; Tonndorf, 1987) is based on analogies in the literature and has recently been confirmed using a purely data-driven approach (Vanneste et al., 2018). The study by Vanneste et al. (2018) used machine learning to analyze resting state electroencephalography (EEG) oscillatory patterns in various patient populations, including tinnitus and neuropathic pain patients, and demonstrated that both disorders have the same temporal dynamics where theta and gamma play an important role. This study further revealed that although resting state electroencephalography oscillatory patterns of both disorder differed spatially, the emotional components of both disorders can be localized in the dorsal anterior cingulate cortex. Hence, to further elucidate the parallels between auditory and somatosensory phantom percepts, the present study uses source localized, resting state EEG comparing recordings between healthy subjects, patients with auditory phantom percepts (i.e. tinnitus), and patients with somatosensory phantom percepts (i.e. pain) using multiple different analyses, including fast Fourier transformations, conjunction analyses, microsegmentation, and seed based functional connectivity via lagged phase synchronization. We calculated the correlations to further establish the specific functional roles of the different microstates. It is important A better understanding of the mechanisms underlying both auditory and somatosensory phantom perception will also lead to a better understanding of the mechanisms of normal human perception. Furthermore, it might be beneficial for the development of new treatments for auditory and somatosensory phantom phenomena by a better understanding of the common pathophysiology.

2. Methods

2.1. Participants

All data were collected at the BRAI^{2}N clinic at the Antwerp University Hospital. The data were analyzed retrospectively. This was approved by the local ethical committee of the Antwerp University Hospital (IRB UZA OGA85). All patients gave their written informed consent and agreed that their data could be used for retrospective analysis. This study included three groups of participants, who were medication free at the time of the study: (1) tinnitus patients, (2) pain patients, and (3) healthy control subjects. Previous research has already linked tinnitus and neuropathic pain to deafferentation of some auditory or somatosensory input channels, respectively. However, to unravel the common underlying mechanisms in both auditory and somatosensory phantom perception, we opted to also include a healthy subject group that could be used as a control for both patient groups, rather than use two different control groups.

2.1.1. Tinnitus patients

One hundred patients (M = 48.21 years; Sd = 10.54; 54 males and 46 females) with continuous tinnitus were included in this study. Tinnitus was considered chronic if its onset dated back one year or more. Individuals with pulsatile tinnitus, Ménière's disease, otosclerosis, chronic headache, neurological disorders such as brain tumors, and individuals being treated for mental disorders were excluded from the study to increase the sample homogeneity. All patients were asked about the perceived location of their tinnitus (the left ear, in both ears, centralized in the middle of the head (bilateral), the right ear) as well its psychoacoustic characteristics (i.e. pure tone-like tinnitus or noise-like tinnitus). Forty-nine patients perceived unilateral tinnitus while 51 patients had bilateral tinnitus. Thirty-eight tinnitus patients perceived pure tone tinnitus and 62 perceived narrow band noise tinnitus.

A numeric rating scale ('How loud is your tinnitus?': 0 = no tinnitus and 10 = as loud as imaginable) was assessed indicating that the mean tinnitus loudness score was 7.14 (Sd = 3.21) as well as a validated Dutch translation of the Tinnitus Questionnaire (TQ) (Meeus et al., 2007). 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, i.e. tinnitus-related distress. The TQ measures emotional and cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbances, and somatic complaints. 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). 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. Twenty-seven tinnitus patients had a grade 1 score, 31 had a grade 2 score, 23 had a grade 3 score, and 19 had a grade 4 score.

2.1.2. Pain patients

One hundred pain patients (M = 51.44 years; Sd = 10.41; 51 males and 49 females) were included in this study. These patients reported neuropathic pain related to deafferentation, i.e. peripheral nerve, root, or central tract lesions, and had had these pain complaints for more than one year. Twenty-one pain patients reported their pain on the right side, while 58 pain patients reported their pain on the left side. For 21 patients pain was presented bilateral. Sixty-nine patients reported to have back and limb pain, while 31 reported full body pain. A numeric rating scale ('How much pain do you have?' 0 = no pain and 10 = as painful as imaginable) assessed the intensity of the general pain. General pain is defined as a global pain score experienced during the past week. The mean pain score on the numeric rating scale was 7.34 (Sd = 3.12). The Pain Vigilance and Awareness Questionnaire (PVAQ) was also assessed. The PVAQ measures the preoccupation with or attention to pain, and is associated with pain-related fear and perceived pain severity (Roelofs et al., 2003). It consists of two separable factors that measure (1) attention to pain and (2) attention to changes in pain (Roelofs et al., 2003). The baseline PVAQ score for attention to pain was 14.92 (Sd = 4.56) and for attention to changes in pain it was 15.57 (Sd = 5.12).

2.1.3. Healthy control group

EEG data from a healthy control group (N = 100; M = 50.36 years; Sd = 10.41; 50 males and 50 females) were included in this study. None of these subjects was known to suffer from tinnitus or pain and were group matched age, gender and education. 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.

2.2. Data processing

2.2.1. Data collection

EEG recordings were obtained in a fully lit room with each participant sitting upright in a small but comfortable chair. The actual recording lasted approximately five minutes. The EEG was sampled using Mitsar-201 amplifiers with 19 electrodes placed according to the standard 10–20 International placement, analogous to what is was done in the normative group. Impedances were checked to remain below 5 kΩ. The subjects were asked to close their eyes during recording. The sampling rate was 500 Hz with a band passed 0.15–200 Hz. Off-line data were resampled to 128 Hz, band-pass filtered in the range 2–44 Hz, plotted, and then carefully visually inspected for manual artifact rejection using Eureka! Software (Congedo, 2002). All episodic artifacts suggestive of eye blinks, eye movements, jaw tension, teeth clenching, or body movement were manually removed from the EEG stream. An artifact was defined as an EEG characteristic that differs from signals generated by activity in the brain. 1) Some artifacts are known to be in

a limited frequency range, e.g. above some frequency. These were removed by frequency filtering. 2) Some artifacts consist of discrete frequencies such as 50 Hz (or 60 Hz for USA) or its harmonics. These were removed by notch filtering. 3) Some artifacts are limited to a certain time range such as in the case of eye blinks. These artifacts were recognized by visual inspection and these time intervals were discarded. 4) Some artifacts originate from one or a few distinct sources or a limited volume of space so that the artifact topography is a superposition of characteristic topographies (equivalently, the artifact is limited to a subspace of the signal space). We removed these artifacts by determining the characteristic topographies (equivalently, the artifact subspace) so that the remaining signals do not contain anything from the artifact subspace. 5) Artifacts and true brain signals that can be assumed to be sufficiently independent can be removed by independent component analysis. 6) Some artifacts are characterized by a particular temporal pattern such as exponential decay. We removed these artifacts by modeling the artifact, fitting its parameters to the data, and then removing the artifact.

After artifact rejection, a comparison was made between the different groups for the average length of the EEG. This analysis showed no significant differences between the different groups.

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).

2.2.2. 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. 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 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 (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 label the neocortical (including hippocampus and anterior cingulate cortex) MNI-152 volume in 6239 voxels, each with a volume of 5 mm^3, based on probabilities returned by the Daemon Atlas (Lancaster et al., 2000). The coregistration makes use of the correct translation from the MNI-152 space into the Talairach and Tournoux space (Brett et al., 2002).We used a standardized head model for source localization.

2.3. Data analysis

2.3.1. Auditory and somatosensory cortex region of interest analysis

The log-transformed electrical current density was averaged across all voxels belonging to the region of interest. Regions of interest were the left and right auditory and somatosensory cortex, i.e. four regions in total. Region of interest analyses were computed for the different frequency bands separately.

A MANOVA was performed with group (healthy control subjects, patients with tinnitus, and patients with neuropathic pain) as independent variables and the log-transformed current density for all frequency bands for the regions of interest as dependent variables. We added the lateralization as a covariate.

2.3.2. Between-group conjunction analysis

To investigate what patients with auditory or somatosensory deafferentation have in common, a conjunction analysis between both groups was performed (Friston et al., 1999; Friston et al., 2005; Nichols et al., 2005; Price and Friston, 1997). Conjunction analysis identifies a so-called “common processing component” for two or more tasks/situations by finding areas activated in independent subtractions (Friston et al., 1999; Friston et al., 2005; Nichols et al., 2005; Price and Friston, 1997). Friston et al. (1999) also indicated that although conjunction analysis is generally used within groups/conditions, it can also be applied between groups; see e.g. some recent papers (Bangert et al., 2006; Heuninckx et al., 2008). For the conjunction analysis, we combine two independent statistical analyses performed in the same cortical space as the sLORETA images. For each voxel and for each frequency, the z-scores are calculated. These probabilities correspond to the Gaussian distribution. We computed for each voxel and frequency the conjunction z-score, which is conveniently interpreted as follows: conjunction z-score = 1.96 corresponds to $p_c = 0.05$, including the FDR correction for multiple comparisons (Benjamini and Hochberg, 1995).

2.3.3. Microsegmentation

Microsegmentation of the EEG data was also performed. The spontaneous fluctuations of EEG recorded activity are classified as belonging to some microstate, thus producing a natural segmentation of resting brain electrical activity. Resting state brain electrical activity can be considered as a series of scalp maps of momentary potential distributions, i.e. the “landscape”, which change their geometric distribution over time (Lehmann et al., 1987). The series of momentary potential distribution maps can then be clustered into successive time epochs (“microstates”) that are defined by quasi-stable landscapes of the brain's electrical field (Lehmann et al., 1987).

Representations of source localized EEG afford temporal resolution at the millisecond level and do not change randomly or continuously over time, remaining stable over periods of 50–120 ms. These stable and unique topographic distributions have been called microstates (Lehmann, 1990; Lehmann et al., 1987). These microstates reflect the summation of concomitant neuronal activity across brain regions rather than traditionally spontaneous EEG analysis on the power variation in different frequency bands (Koenig et al., 2002).

Individual resting state EEG datasets were segmented with a specific module in the sLORETA software package (Pascual-Marqui et al., 2002) in which microstates are characterized as normalized vectors due to the underlying neural generators established by scalp electrodes. The algorithm implemented for estimating the microstates is based on a modified version of the classical k-means clustering method, in which cluster orientations are estimated (Pascual-Marqui et al., 1995). The algorithm searches four classes of microstate topography and assigns each EEG topography to one of these classes. This number of classes has previously been found to be optimal for resting state EEG and was maintained for compatibility with the existing literature (Kikuchi et al., 2011; Koenig et al., 1999).

Microstate class topographies were computed individually and averaged across subjects using a permutation algorithm that maximizes the common variance over subjects (Kikuchi et al., 2011; Koenig et al., 1999).

To display the data, we performed a current density analysis in 3-D Talairach space of the resting EEG microstates using sLORETA. sLORETA images represent the standardized electrical activity at each voxel as amplitude of the computed current source density ($\mu A/cm^2$) (Pascual-Marqui, 2002). Computations were made in a realistic head model (Fuchs et al., 2002) using the MNI-152 template (Mazziotta et al., 2001) with the three-dimensional solution space restricted to cortical gray matter, as determined by the probabilistic Talairach atlas (Lancaster et al., 2000). The intracerebral volume is partitioned into 6239 voxels at 5 mm spatial resolution.

Only voxels significant $p < .05$ level after correction for multiple comparisons were retained, i.e., the significance of changes in activity compared to baseline was assessed using nonparametric analyses adapted to source comparisons (Holmes et al., 1996).

2.3.4. Seed based lagged phase coherence conjunction

To further understand the microstates, we calculated the phase synchronization between time series corresponding to different spatial locations that are interpreted as indicators of functional connectivity. However, any measure of dependence is highly contaminated with an instantaneous, non-physiological contribution due to volume conduction (Pascual-Marqui, 2007b). However, Pascual-Marqui and colleagues (Pascual-Marqui, 2007a; Pascual-Marqui et al., 2011) introduced a new technique, i.e. Hermitian covariance matrices, that remove this confounding factor. As such, this measure of dependence can be applied to any number of brain areas jointly, i.e. distributed cortical networks, whose activity can be estimated with sLORETA. Measures of linear dependence (coherence) between the multivariate time series are expressed as the sum of lagged dependence and instantaneous dependence. These measures are non-negative and take the value zero only when there is independence. Furthermore, they are defined in the frequency domain: 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 (30.5–45 Hz). Based on this principle, lagged linear connectivity or partial coherence was calculated. The auditory seed regions were defined for the inferior anterior middle gyrus. Based on these findings, we applied a conjunction analysis to identify the brain areas involved in both auditory and somatosensory deafferentation after subtraction in both groups of the matched healthy control subjects; in other words, we identified the areas with common activity across both disorders that is also absent in healthy subjects.

2.3.5. Correlation analysis

For the activity in each region of interest at each frequency band, we calculated the Pearson correlations with: (1) the numeric rating scale for tinnitus intensity, (2) the TQ for tinnitus patients, (3) the numeric rating scale for pain intensity, and (4) the PVAQ for pain patients. These correlations help to establish the specific functional roles of our regions of interest in each disorder.

3. Results

3.1. Auditory and somatosensory cortex region of interest analysis

A MANOVA reveals an overall effect for group ($F = 15.17$, $p < .001$). Between-subjects analysis (i.e. comparing across groups) shows a significant effect for the different groups in gamma band activity $F = 12.11$, $p < .001$. A univariate ANOVA shows a significant effect for the left ($F = 32.07$, $p < .001$) and right ($F = 26.21$, $p < .001$) primary auditory cortex as well as for the left ($F = 24.26$, $p < .001$) and right ($F = 20.94$ $p < .001$) primary somatosensory cortex (see Fig. 1). A pairwise comparison revealed that for the left and right primary auditory cortex patients with tinnitus had a higher log-transformed current density in the gamma frequency band in comparison to healthy control subjects and pain patients ($p = .035$). In addition, a pairwise comparison demonstrated that for the left and right somatosensory cortex pain patients had a higher log transformed current density in the gamma frequency band in comparison to healthy control subjects and tinnitus patients ($p = .025$). No significant results were obtained for the delta, theta, alpha1, alpha2, beta1, beta2, or beta3 frequency bands.

3.2. Between-group conjunction analysis

The between-group conjunction analysis showed significance in brain areas activated in auditory deafferentation (versus healthy control subjects) and somatosensory deafferentation (versus healthy control subjects) for both the theta, beta2, and beta3, frequency bands (see Fig. 2). Auditory and somatosensory deafferentation share decreased activity in the posterior cingulate cortex for the theta frequency band and increased activity in the pre-supplementary motor area and dorsal anterior cingulate cortex for the beta2 and beta3 frequency bands. No significant differences were obtained for the delta, alpha1, alpha2, beta1, and gamma frequency bands.

3.3. Microsegmentation

We conducted up to 200 iterative calculations with sLORETA for the EEG dataset which accounts for a mean variance of 82% across the healthy controls, 76% across tinnitus patients, and 74% across pain patients. In each subject, four recurrent quasi–stable scalp electrical topographic distributions were identified analogous to previous research (Koenig et al., 2002) and each EEG dataset was segmented accordingly (see Fig. 3).

In healthy controls, the first microstate includes the sensorimotor system corresponding to pre- and post-central gyri characterized predominantly by theta and beta3 band activity. The second and third microstates include the posterior default network including the posterior cingulate cortex and the precuneus. While the second microstate involves activity at the theta and beta frequency bands, the third microstate involves more delta and gamma band activity. The fourth microstate involves the visual system with mainly alpha and low beta frequency band activity. Further analysis revealed that healthy control subjects remained in the third microstate for 44.49% of the time, in the first for 26.09%, in the second for 14.83%, and in the fourth for 14.59%.

In the tinnitus patients, the first microstate is located at the right dorsolateral prefrontal cortex and is characterized predominantly by delta and gamma band activity. The second microstate is similar to that of the healthy control subjects, namely the posterior default network including the posterior cingulate cortex and the precuneus involving theta and beta band activity. The third microstate involves activity in the left anterior middle temporal gyrus in the delta and gamma bands. The fourth microstate involves the visual system with mainly alpha and low beta band activity, which is also similar to the healthy control subjects. Patients with an auditory phantom percept remained in the third microstate for 50% of the time, in the first for 11.23%, in the second for 19.82%, and in the fourth for 18.95%.

In the neuropathic pain patients, the first three microstates are all similar to those of the auditory deafferentation patients. That is, the first microstate is also located at the right dorsolateral prefrontal cortex in the delta and gamma frequency bands. The second microstate is similar to both the tinnitus patients and the healthy control subjects describing the posterior default network namely the posterior cingulate cortex and the precuneus and is predominantly characterized by beta frequency band activity. The third microstate also involves the left anterior middle temporal gyrus in the delta and gamma frequency bands. The fourth microstate corresponds to the pre and post-central gyri mainly in the alpha and low beta frequency bands. Once again the third microstate is the most important one, occuring 35.96% of the time, followed by the fourth (23.48%), second (21.27%), and first (21.09%).

For the healthy controls, tinnitus patients, and pain patients, there is a high probability that they will switch to the third microstate after being in the first, second and fourth microstate.

3.4. Seed based lagged phase coherence conjunction

A conjunction on the seed based connectivity at the left anterior middle temporal gyrus, which is the most dominant area in the microstate for between the tinnitus and pain patients (controlling for healthy subjects), revealed a significant effect within the delta, alpha1, and gamma frequency bands (see Fig. 4). Our analysis revealed that, for the delta frequency band, tinnitus and pain patients share an increased lagged phase coherence between the left anterior middle temporal gyrus and the left temporal-parietal junction and the left orbitofrontal cortex. For the alpha1 frequency band, increased lagged phase

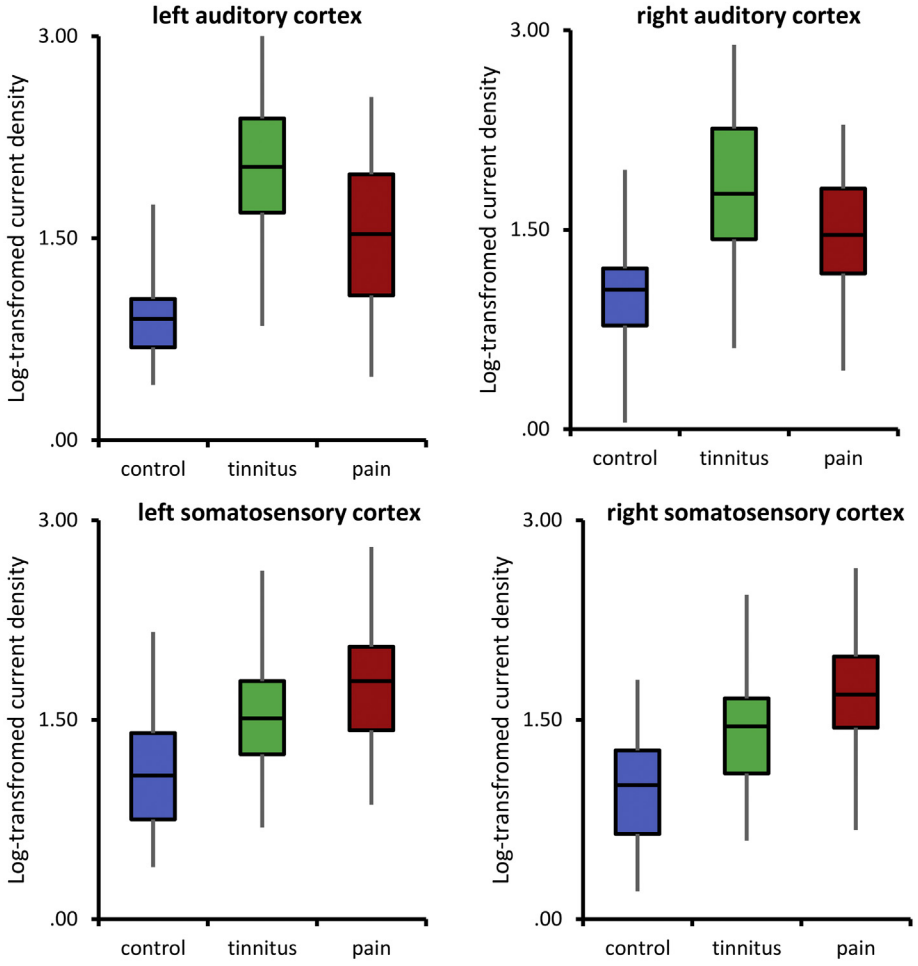

Fig. 1. A comparison for the gamma frequency band between log-transformed current density at the primary auditory and somatosensory cortex for healthy control subjects, and patients with tinnitus or neuropathic pain.

coherence was demonstrated between left anterior middle temporal gyrus and the posterior part of the left insula and the retrosplenial cortex. Tinnitus and pain patients share increased lagged phase coherence in the gamma frequency band between the left anterior middle temporal gyrus and the pregenual and dorsal anterior cingulate cortex as well as the cuneus.

3.5. Correlation analysis

To further explore the data, we calculated the correlations between the areas (dorsolateral prefrontal cortex, dorsal anterior cingulate cortex, posterior cingulate cortex, and the anterior middle temporal gyrus) in the different microstates and the conjunction analysis with the assessment measures (numeric rating scale for tinnitus/pain, TQ, and PVAQ) for the tinnitus and pain patient groups. See Fig. 5 for an

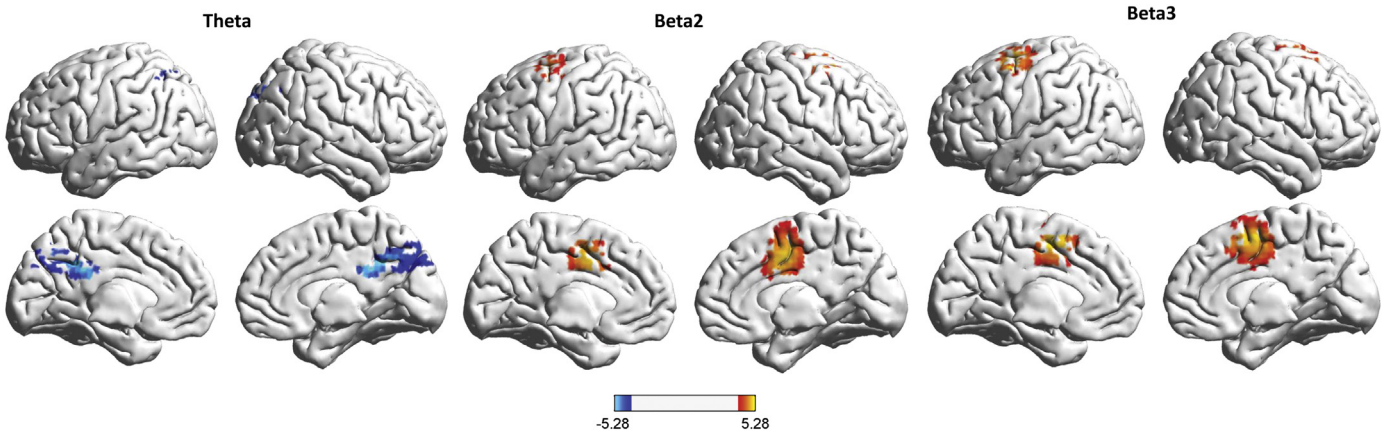

Fig. 2. A conjunction analysis between auditory deafferentation (versus healthy control subjects) and somatosensory deafferentation (versus healthy control subjects). Auditory deafferentation and somatosensory deafferentation share decreased activity in the posterior cingulate cortex for theta frequency band and increased activity the in the dorsolateral prefrontal cortex for the beta 2 and beta 3 frequency band.

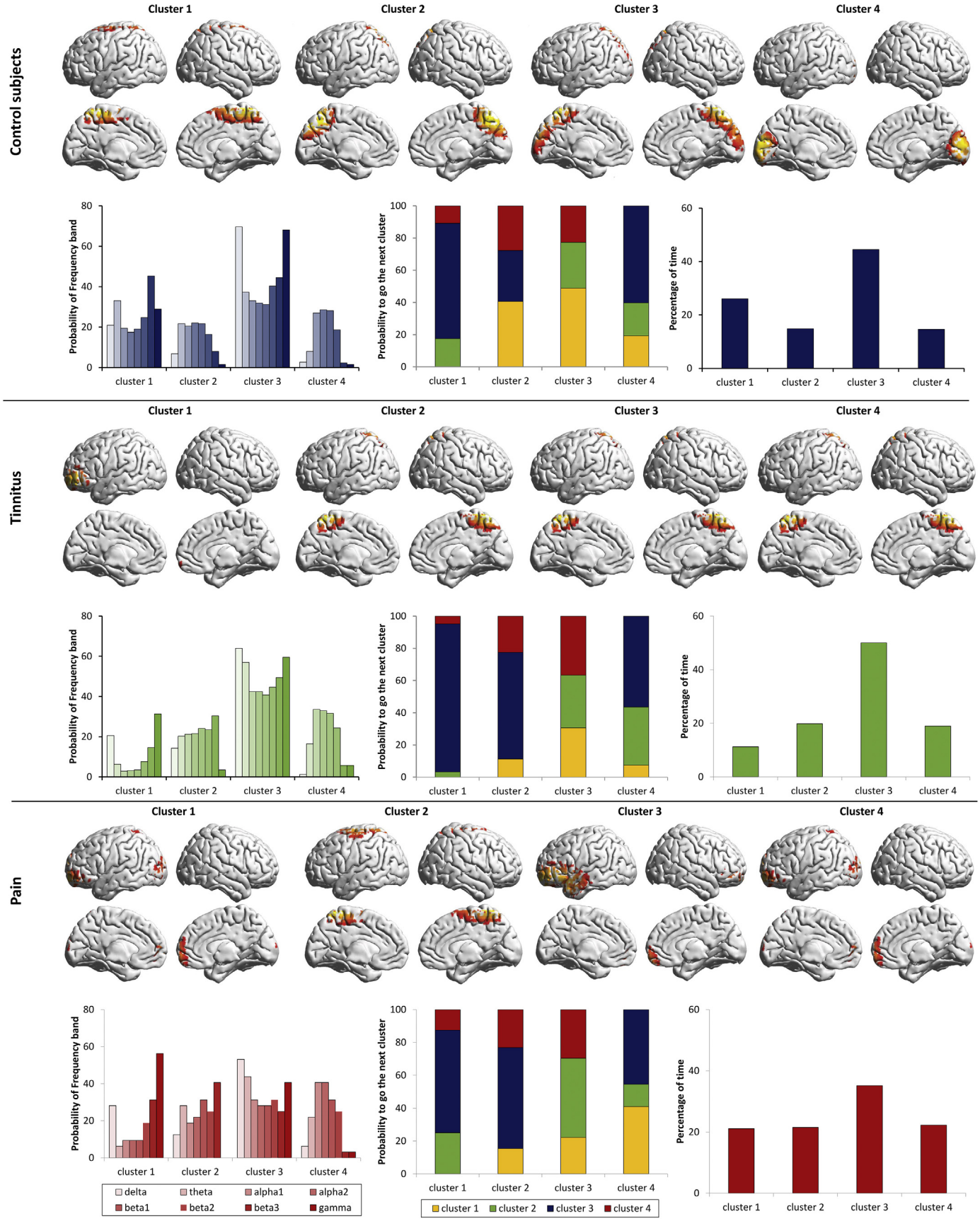

Fig. 3. Microsegmentation for healthy control subjects, and patients with tinnitus and neuropathic pain. (top) Source localized activity for the four microstate or clusters respectively heathly subjects, tinnitus and neurpathic pain patients, (left) For each cluster seperately the percentage of time that within a microstate or cluter a certain frequency is present. (Middle) The probability that depending that you will switch from a certain microstate or cluster to another microstate or cluster. (Right) The percentage of time that a microstate or cluter is present.

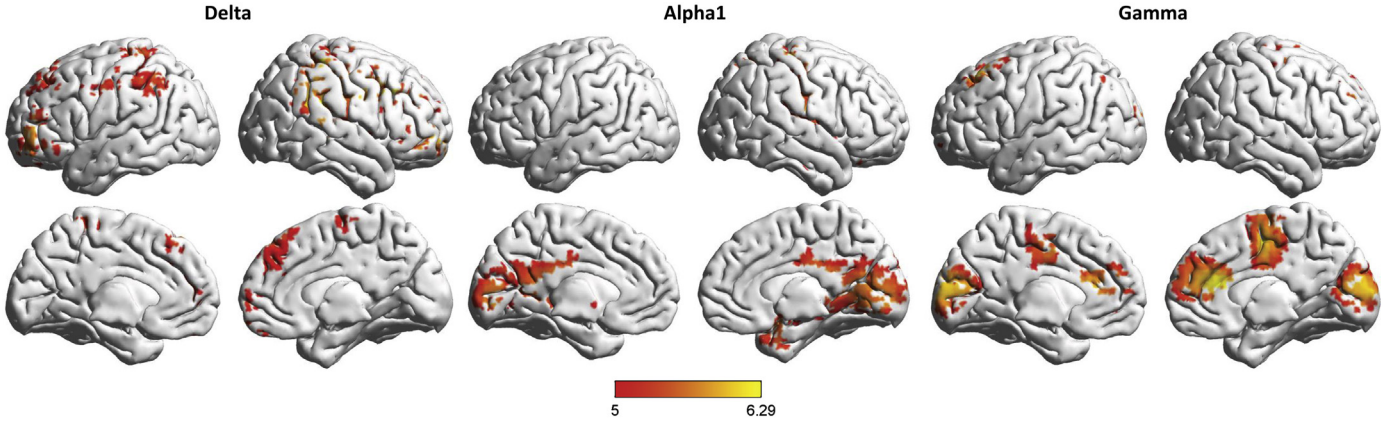

Fig. 4. Conjunction analysis of seed based connectivity at the left anterior middle temporal gyrus, which is the most dominant microstate for both the tinnitus and pain patients (controlling for healthy subjects) revealed a significant effect within the delta, alpha1 and gamma frequency band indicating for the delta frequency band auditory and somatosensory deafferentation patients share an increased lagged phase coherence between the left anterior middle temporal gyrus and the left temporal-parietal junction and the left orbitofrontal cortex. For the alpha1 frequency band increased lagged phase coherence was demonstrated between left anterior middle temporal gyrus and the posterior part of the left insula and the retrosplenial cingulate cortex. Auditory and somatosensory deafferentation patients share increased lagged phase coherence in the gamma frequency band between the left anterior middle temporal gyrus and the pregenual and dorsal anterior cingulate cortex as well as the cuneus.

overview.

For the numeric rating scales for tinnitus or pain, no significant effects were found in any of the regions of interest for any of the frequency bands tested. A significant correlation was obtained with the right dorsolateral prefrontal cortex and TQ ($r = 0.30$, $p < .001$) and PVAQ ($r = 0.26$, $p < .001$) for the gamma frequency in tinnitus and pain patients, respectively. For the beta3 frequency band, a significant correlation was obtained between the right dorsolateral prefrontal cortex and the TQ ($r = 0.21$, $p = .01$), but not for the PVAQ. Only the effects in the gamma band remained after Bonferoni correction for multiple comparisons controlling for frequency bands and disorders (tinnitus, pain), i.e. $p = .05/(8$ freq. Bands x 2 disorders$) = 0.003$. No significant correlations were obtained for delta, theta, alpha1, alpha2, beta1, and beta2 frequency bands.

For the dorsal anterior cingulate cortex, a significant correlation was obtained with the TQ (beta2, $r = 0.25$, $p < .001$; beta3, r = 0.25, $p < .001$; gamma, $r = 0.32$, $p < .001$) and with the PVAQ (beta3, r = 0.25, $p < .001$; gamma, $r = 0.27$, $p < .001$). All of these effects survived the Bonferoni correction mentioned previously. No significant effect was obtained for the delta, theta, alpha1, alpha2, and beta1 frequency for the tinnitus or pain patients. In addition no, significant effect was obtained between the PVAQ and the beta2 frequency band for the pain patients.

For the posterior cingulate corex a significant correlation was obtained with the TQ (beta2, r = 0.27, $p < .001$; beta3, $r = 0.35$, $p < .001$; gamma, $r = 0.22$, $p = .02$) and with the PVAQ (beta2, $r = 0.32$, < 0.001; beta3, $r = 0.28$, $p < .001$; gamma, $r = 0.26$, $p < .001$). The correlation between TQ and the gamma frequency band did not survive after Bonferoni correction for multiple comparison. No significant effect was obtained for the delta, theta, alpha1, alpha2, and beta1 frequency for both the tinnitus and pain patients.

For the left anterior middle temporal gyrus, no significant correlation were obtained between TQ and PVAQ for tinnitus and pain patients, respectively, for the delta, theta, alpha1, alpha2, beta1, beta2, beta3, and gamma frequency bands.

4. Discussion

The aim of this study was to evaluate whether auditory and somatosensory phantom percepts share a common underlying neural substrate, differentiated by respective auditory and somatosensory cortex activation. To this end, we investigated two clinical groups, one with tinnitus and one with neuropathic pain, and performed different analyses on source localized EEG during the resting state, recorded while the patients perceived their phantom percept.

4.1. Involvement of the auditory and somatosensory cortex in tinnitus and neuropathic pain

An initial region of interest comparison between tinnitus and neuropathic pain showed that there was a significant difference between the primary auditory and somatosensory cortex for the gamma frequency band in comparison to healthy controls. This is in line with previous research suggesting that tinnitus (van der Loo et al., 2009; Vanneste et al., 2011b; Weisz et al., 2007) and pain (Ploner and May, 2017; Ploner et al., 2017; Zhang et al., 2012) are related to hyperactivity in the gamma frequency band in the auditory and somatosensory cortex, respectively, as shown both with EEG and MEG. This fits with the thalamocortical dysrhythmia model which has been proposed to explain both deafferentation related tinnitus and neuropathic pain (Llinás et al., 1999; Vanneste et al., 2018). According to this model, tinnitus and neuropathic pain are both caused by abnormal, spontaneous, and constant gamma band activity generated as a consequence of deafferentation-induced hyperpolarization of the thalamus. In the deafferented state, however, oscillatory alpha activity (8–12 Hz) decreases to theta frequencies (4–7 Hz) within the affected thalamic nuclei (Steriade, 2006). As a result, GABAa-mediated lateral inhibition is reduced in the region of cortex targeted by the deafferented thalamic nucleus. This induces gamma band activity in a halo-shaped region surrounding the disinhibited cortex, i.e. the “edge effect” (Llinas et al., 2005). This abnormally persistent dysrhythmia will then be relayed to the primary sensory cortex, selectively for the deafferented thalamocortical columns. Furthermore, it has been shown that both tinnitus (De Ridder et al., 2015a; van der Loo et al., 2009) and pain (De Pascalis and Cacace, 2005) intensity correlate with the amount of gamma band activity.

4.2. Common brain areas in tinnitus and neuropathic pain

The conjunction analysis of tinnitus and neuropathic pain demonstrated decreased activity in the posterior cingulate cortex in the theta frequency band as well as positive correlation for both tinnitus and pain with their associated distress measures for the beta2, beta3, and gamma frequency bands. The posterior cingulate cortex is one of the core hub

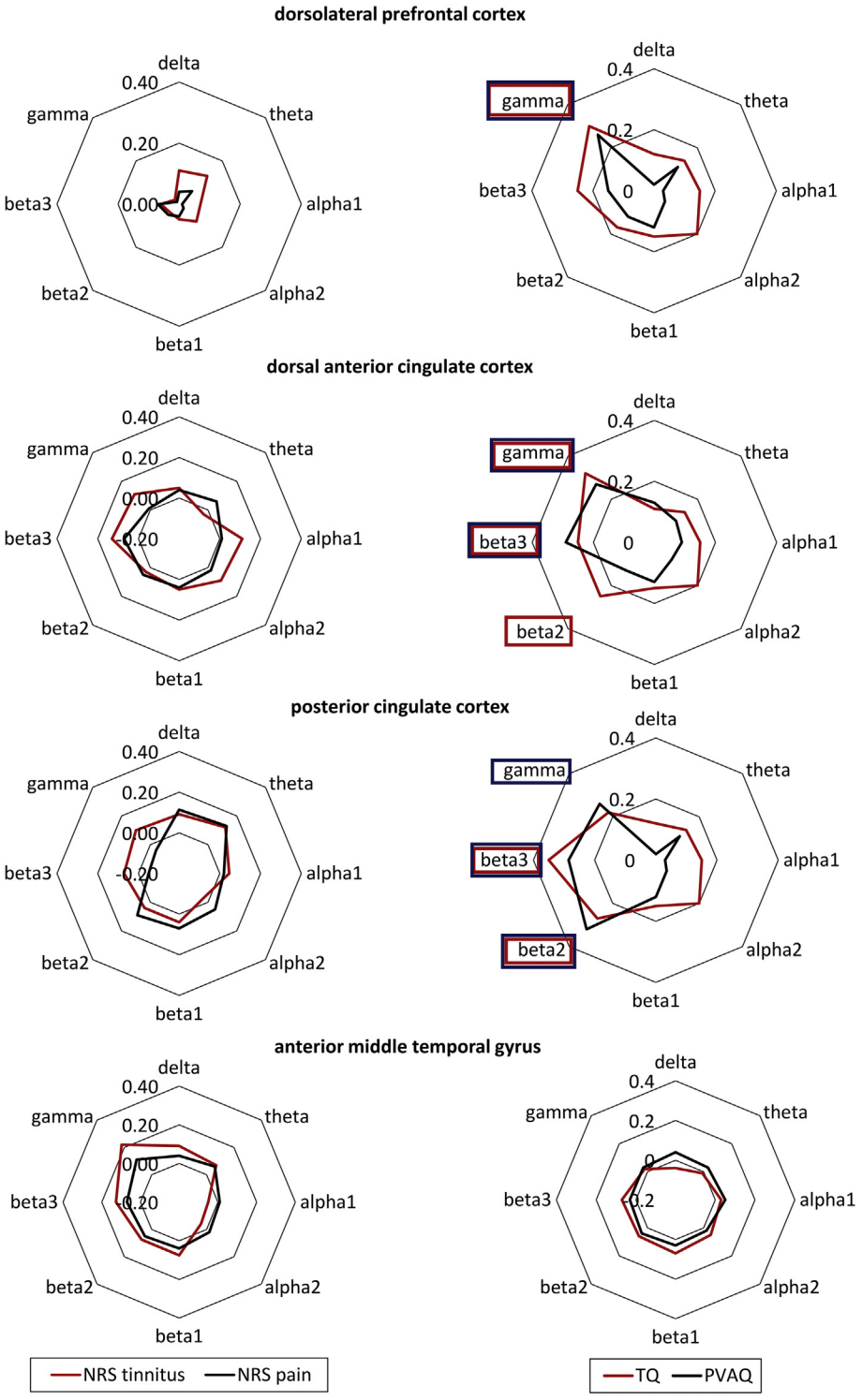

Fig. 5. Correlation analysis between the log-transformed current density for the dorsolateral prefrontal cortex, the anterior cingulate cortex, the posterior cingulate cortex and the left anterior middle temporal cortex and respectively the numeric rating scale for tinnitus patients and TQ for tinnitus and the numeric rating scale for pain, and PVAQ for pain patients. Frequency in a red square show a significant effect for tinnitus; Frequency in a blue square show a significant effect for tinnitus pain. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

regions of the default network (Andrews-Hanna et al., 2010; Christoff et al., 2016) and is anti-correlated with the somatosensory and auditory cortex, which are part of the dorsal attention system (Dixon et al., 2017; Vincent et al., 2008). The dorsal attention system is activated by external stimuli and suppresses the default network, which is involved in internally oriented cognition (Dixon et al., 2017; Vincent et al., 2008). The activation of the somatosensory and auditory cortex associated with deactivation of the posterior cingulate cortex in this study suggests that the phantom percepts are centrally processed as if triggered by external stimuli.

It is of interest that theta activity is considered to be involved in long range connections (von Stein and Sarnthein, 2000) and might function as a carrier wave for high frequency beta and gamma activity (Lisman and Jensen, 2013). This coupling between low- and high-

frequency brain rhythms coordinates activity in distributed cortical areas transiently, providing a mechanism for effective but transient communication during cognitive processing in humans (Canolty et al., 2006). When this coupling is permanent or triggered in the thalamus it becomes pathological as described for pain and tinnitus (De Ridder et al., 2011a; De Ridder et al., 2015c).

We further revealed that both patients with tinnitus and neuropathic pain have increased activity in the dorsal anterior cingulate cortex in the beta2 and beta3 frequency bands and a positive correlation for both tinnitus and pain with distress for the beta3 and gamma frequency bands. The dorsal anterior cingulate together with the anterior insula is involved in a multimodal non-specific salience network (Legrain et al., 2011; Mouraux et al., 2011), thus attaching salience to the phantom percept, resulting in persisting attention to the tinnitus or the pain. Indeed, frontal lobotomies encompassing the anterior cingulate can remove the attention paid to pain (Freeman and Watts, 1950) and tinnitus (Beard, 1965) as can implanted electrodes at the dorsal anterior cingulate cortex, both for pain(Boccard et al., 2014) and tinnitus(De Ridder et al., 2015b) in selected cases. This is consistent with recent studies showing that the dorsal anterior cingulate cortex is involved in the beta frequency band in tinnitus-related distress (De Ridder et al., 2011b; Vanneste et al., 2010) as well as in pain (Stern et al., 2006).

4.3. Temporally-independent functional modes

It has recently been suggested that the human brain is organized into temporally-independent functional networks of spontaneous activity (Smith et al., 2012). Brain networks dynamically and rapidly reorganize and coordinate on subsequent temporal scales to allow the execution of mental processes in a timely fashion (Bressler, 1995; Bressler and Tognoli, 2006) and this has been proposed for tinnitus, as well (De Ridder et al., 2014). Microsegmentation of the EEG signal has been proposed as a potential electrophysiological correlate of spontaneous BOLD activity (Britz et al., 2010; Musso et al., 2010; Yuan et al., 2012) being highly similar to some established fMRI resting state networks (Damoiseaux et al., 2006; Michel and Koenig, 2017). Cognition (Mohr et al., 2005) and perception (Britz et al., 2009; Britz et al., 2011) have been found to vary as a direct function of the pre-stimulus microstate, and microstates can characterize qualitative aspects of spontaneous thoughts (Lehmann et al., 1993; Lehmann et al., 2010). As such, it has been suggested that the dynamics of EEG microstates reflect the time-course of ongoing mental activities (Lehmann and Michel, 2011). Interestingly, our results revealed that within the four microstates demonstrated two differ from the healthy group whereas the two other microstates were comparable. Based on these findings, it can be hypothesized that within the resting state network some temporally-independent functional modes are involved in phantom percepts, while other temporally-independent functional modes are independent of the tinnitus or neuropathic pain.

4.4. Temporally independent functional modes related to tinnitus and neuropathic pain within the resting state network

Our findings are in line with previous findings that demonstrated that some microstates change as a function of the conscious/mental state of the subject, such as in dementia (Strik et al., 1997), depression (Strik et al., 1995), and schizophrenia (Strelets et al., 2003). In our case, it was shown that the first and the third microstate in tinnitus and neuropathic pain are different from that of healthy subjects.

The first microstate involves the right dorsolateral prefrontal cortex and is predominantly characterized by delta and gamma frequency activity in both pain and tinnitus patients, while in healthy subjects this microstate was in the sensorimotor area, more specifically the pre- and post-central gyri, predominantly characterized by theta and beta3 frequency activity. The involvement of the dorsolateral prefrontal cortex has already been described in tinnitus and pain as the result of a dysfunction in the top-down inhibitory processes (Lorenz et al., 2003; Norena et al., 1999). The dorsolateral prefrontal cortex exerts early inhibitory modulation of input to the primary auditory cortex in humans (Knight et al., 1989) and has been found to be associated with auditory attention (Alain et al., 1998; Lewis et al., 2000; Voisin et al., 2006) resulting in top-down modulation of auditory processing (Mitchell et al., 2005) and tinnitus (De Ridder et al., 2012c; Vanneste and De Ridder, 2011). This top-down inhibitory control over the auditory cortex has been used both with transcranial magnetic stimulation (De Ridder et al., 2012b), transcranial direct current stimulation (Faber et al., 2012) and even cortical implants (De Ridder et al., 2012a) to suppress tinnitus. In pain, it was shown that the dorsolateral prefrontal cortex interacts with midbrain, thalamic, striatal, and cingulate structures of the limbic system and reacts to active manipulation of the behavioral dominance of pain dependent upon motivational and emotional context (Lorenz et al., 2003). This is in line with previous research on transcranial direct current stimulation studies showing that the dorsolateral prefrontal cortex can be a good target to successfully modulate experimental pain threshold (Boggio et al., 2009; Boggio et al., 2008; Mylius et al., 2012a; Mylius et al., 2012b). Our findings support the concept that dorsolateral prefrontal cortex activity plays a role in pain and tinnitus perception.

The third microstate is localized in the left anterior middle temporal gyrus for both the patients with tinnitus or neuropathic pain, and predominantly in the delta and gamma frequency band, while for the healthy control subjects activity was more centralized within the posterior cingulate cortex and the precuneus, i.e. another part of the default network. This third microstate seems to be very important as all three groups spent the most time in this microstate. For healthy subjects, it seems relatively straightfoward that they spent a large percentage of the time in this microstate, as the EEG is recorded in a resting state, not performing any explicit task. However in patients with a phantom percept the third microstate is not localized in the main hub (Tomasi and Volkow, 2010; Zuo et al., 2012) of the self-referential (Buckner et al., 2008) default network but the left anterior middle temporal lobe, more specifically the tip of the left anterior middle temporal pole. The fact that they both spend close to 50% of the time in this microstate and that each microstate is followed by resurgence of the third microstate suggests this area is important in tinnitus and pain as well. The left temporal pole has been hypothesized to be functionally connected to multiple brain networks, including connections to auditory, somatosensory, and language networks (Pascual et al., 2015). For tinnitus, research in primates has suggested that the temporal pole is involved in auditory perception and auditory memories (Munez-Lopez et al.,2010; Ng et al., 2014), but the exact role of this area in tinnitus and neuropathic pain remains unclear. Conceptually, this area could link the phantom percept to a memory trace, both for pain and tinnitus (De Ridder et al., 2011a), integrating multi-modal information from visual, somatosensory, and auditory regions (Muller et al., 2012; Pascual et al., 2015). In a pathological state, this left middle temporal area might be functionally connected to another network than the default network. Therefore, a seed based conjunction analysis was performed, which showed that this area has lagged phase synchronicity with the visual, somatosensory, and auditory areas within the delta and alpha frequency bands as well as with the pregenual and dorsal anterior cingulate cortex within the gamma frequency band. On one hand, this area does indeed appear to integrate multimodal sensory information. On the other hand, it is simultaneously connected to the stimulus-inhibiting pregenual anterior cingulate cortex or stimulus-detecting dorsal anterior cingulate cortex (De Ridder et al., 2016). Thus, in summary, the left middle temporal gyrus could exert its effect on tinnitus and pain by changing the balance between pain detection (Boly et al., 2007) and pain suppression (Jensen et al., 2013), or sound detection (Sadaghiani et al., 2009) and sound suppression (Rauschecker et al., 2010).

4.5. Temporally-independent functional modes unrelated to tinnitus and neuropathic pain within the resting state network

Microstates 2 and 4 include the posterior cingulate cortex and the precuneus. The involvement of the posterior cingulate cortex has been discussed above. The precuneus is a highly integrative structure, supposedly involved in visuospatial imagery, episodic memory, self-consciousness, and the shifting of attention (Le et al., 1998). As tinnitus and phantom pain are considered phantom percepts (Jastreboff, 1990; Muhlnickel et al., 1998), they require awareness. PET studies in persistent vegetative and minimally conscious states suggest that a distributed network of activity is needed for conscious auditory perception (Boly et al., 2004; Laureys et al., 2000), a.k.a. consciousness enabling or consciousness supporting networks (Demertzi et al., 2013). Patients in persistent vegetative states, i.e. who demonstrate only a startle reflex and no purposeful response to auditory stimulation, only activate the midbrain, thalamus, and primary auditory cortex in response to sound presentation (Boly et al., 2004; Laureys et al., 2000) but the auditory stimulus is not broadcasted to the rest of the brain. Similar results are obtained for painful stimuli (Boly et al., 2005; Laureys et al., 2002). However, minimally conscious patients who can localize sound and demonstrate auditory command following, albeit inconsistently, revealed stronger functional connectivity between the secondary auditory cortex and temporal and prefrontal association cortices in comparison to vegetative patients (Boly et al., 2004). These studies suggest that, for conscious auditory and pain perception to arise, activation of a distributed network including the precuneus might be an essential precondition. As such, it has been hypothesized that the precuneus, which is strongly interconnected with the posterior cingulate, is engaged in continuous information gathering and representation of the self and external world.

4.6. Limitations

A limitations of this study is that the three groups were not screened for potential hearing loss. Another limitation of this study is the low resolution of the source localization inherently resulting from a limited number of sensors (19 electrodes) and a lack of subject-specific anatomical forward models. This is sufficient for source reconstruction but results in greater uncertainty in source localization and decreased anatomical precision, and thus the spatial precision of the present study is considerably lower than that of functional MRI. Nevertheless, the tomography sLORETA has received however 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 (PET) (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, 2011c; 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; Zumsteg et al., 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. The involvement of the parahippocampus was already illustrated in previous research using low density EEG and was confirmed subsequently by PET and MRI suggesting the reliabilities of our findings. Our data further illustrate that source reconstruction can clearly make a difference between tinnitus and pain. However, further research could improve spatial precision and accuracy could be achieved using high-density EEG (e.g., 128 or 256 electrodes) and subject-specific head models, and MEG recordings.

5. Conclusions

The present study has shown similarities within the primary auditory and somatosensory cortex for patients with tinnitus and neuropathic pain, respectively. It was further shown that the anterior and posterior cingulate cortex together with the dorsolateral prefrontal cortex are involved in both patient groups but not in healthy controls, possibly related to the conscious perception of and/or the attention paid to the phantom percept. It was also shown that multiple functional temporally independent networks characterize tinnitus and pain patients, both of which differ from the healthy control group in two microstates, whereas the other two microstates were like those of the healthy control group. Based on these findings, it was hypothesized that some temporally-independent functional modes within the resting state network are phantom specific and related to the emotional component, while other temporally-independent functional modes are independent of tinnitus or pain. These phantom specific microstates involve the left anterior middle temporal cortex and right dorsolateral prefrontal cortex, both characterized by delta and gamma activity. These findings fit with the hypothesis that pain and tinnitus share similar pathophysiological, clinical, and treatment characteristics (De Ridder et al., 2011a). This study therefore provides insight into the mechanisms underlying both auditory and somatosensory perception, both phantom and normal.

Ethical statement

The collection of the data was approved by the local ethical committee (Antwerp University Hospital; IRB UZA OGA85) and was in accordance with the declaration of Helsinki. All patients gave an informed consent.

No conflict of interest

None.

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