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# Stress-Related Functional Connectivity Changes Between Auditory Cortex and Cingulate in Tinnitus

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**Abstract**

The question arises whether functional connectivity (FC) changes between the distress and tinnitus loudness network during resting state depends on the amount of distress tinnitus patients' experience. Fifty-five patients with constant chronic tinnitus were included in this study. Electroencephalography (EEG) recordings were performed and seed-based (at the auditory cortex) source localized FC (lagged phase synchronization) was computed for the different EEG frequency bands. Results initially demonstrate that the correlation between loudness and distress is nonlinear. Loudness correlates with beta3 and gamma band activity in the auditory cortices, and distress with alpha1 and beta3 changes in the subgenual, dorsal anterior, and posterior cingulate cortex. In comparison to non-tinnitus controls, seed-based FC differed between the left auditory cortices for the alpha1 and beta3 bands in a network encompassing the posterior cingulate cortex extending into the parahippocampal area, the anterior cingulate, and insula. Furthermore, distress changes the FC between the auditory cortex, encoding loudness, and different parts of the cingulate, encoding distress: the subgenual anterior, the dorsal anterior, and the posterior cingulate. These changes are specific for the alpha1 and beta3 frequency bands. These results fit 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, but adds to this concept that the interaction between these networks is a complex interplay of correlations and anti-correlations between areas involved in distress and loudness depending on the distress state of the tinnitus patient.

**Key words:** distress; seed-based connectivity; state dependent; tinnitus

## Introduction

Tinnitus is a symptom characterized by the perception of a sound in the absence of an external sound source. Most causes of tinnitus are related to transient or permanent deprivation of auditory input, associated to listening to loud music (Axelsson and Prasher, 2000), sudden sensorineural hearing loss (Schreiber et al., 2010), noise trauma (Folmer and Griest, 2003), or other causes. The development of tinnitus has been explained as a compensation mechanism to reduce deafferentation-related sensory uncertainty (i.e., lack of information) by filling in the missing auditory input (De Ridder et al., 2014a), which possibly explains its high prevalence in hearing loss (Axelsson and Ringdahl, 1989). Tinnitus can lead to or is associated with distress, an aversive state in which a patient with tinnitus is unable to adapt completely to stressors (i.e., tinnitus) resulting in distress and maladaptive behaviors in about 20% of tinnitus patients (Axelsson and Ringdahl, 1989). This can lead to psychological complications such as annoyance, concentration problems, depression, anxiety, irritability, sleep disturbances, and intense worrying (Erlandsson and Holgers, 2001; Scott and Lindberg, 2000). Functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) research has shown that tinnitus is often but not always (Langers et al., 2012) related to tonotopic map reorganization (Muhlnickel et al., 1998) and hyperactivity (Weisz et al., 2007) of the auditory cortex and that the subjectively perceived tinnitus loudness is correlated to increased gamma band activity in the auditory cortex as determined through electroencephalography (EEG) (van der Loo et al., 2009). The tinnitus-related distress, on the other hand, is related to activity in nonauditory brain systems (i.e., distress network), including the subgenual and dorsal anterior cingulate cortex, insula, as

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well as the posterior cingulate cortex as shown by structural and resting-state fMRI, EEG, and positron emission tomography (PET) research (De Ridder et al., 2011; Golm et al., 2013; Leaver et al., 2011; Schecklmann et al., 2013a; Vanneste et al., 2010a; Vanneste and De Ridder, 2012b).

Functional connectivity (FC) reflects temporal associations between separate brain areas and can be measured using lagged phase synchronization. Lagged phase synchronization can be interpreted as the amount of cross-talk synchronization between anatomically different brain regions (Congedo et al., 2010). FC is highly dynamic and stress dependent (van Marle et al., 2010). Tinnitus loudness can be associated with stress and negative mood (Dobie, 2003; Sullivan et al., 1988). Some theories of tinnitus pathophysiology even argue that negative emotional reactions to tinnitus are necessary for the disorder to become chronic (De Ridder et al., 2011; Jastreboff, 1990). If aversive reactions to tinnitus are necessary components of tinnitus pathophysiology, one might expect a relationship between the perceived loudness and amount of distress (De Ridder et al., 2011; Jastreboff, 1990). If tinnitus loudness is related to the amount of distress in tinnitus patients, it can be hypothesized that loudness related areas such as the auditory cortex (van der Loo et al., 2009) are functionally connected to the distress network (De Ridder et al., 2011; Golm et al., 2013; van der Loo et al., 2011; Vanneste et al., 2010a) in distressing tinnitus. A highly specific 10 and 11.5 Hz lagged phase synchronization has been shown between the parahippocampal area, and the subgenual anterior cingulate cortex in severely distressed patients (TQ grade 3 and 4 respectively) using EEG (Vanneste et al., 2014). However, recently, it has been suggested that the auditory cortex is also involved in tinnitus-related distress (Schecklmann et al., 2013b). How this auditory cortex involvement is governed is yet unknown.

In this article, we investigate whether the FC between the loudness and distress networks during resting-state EEG recordings is dependent on the amount of distress in tinnitus patients. Resting-state functional networks in the brain can be disentangled using lagged phase synchronization by applying seed-based FC. Seed-based FC allows mapping the resting state correlations of a single-seed region with every other voxel in the brain (Fox et al., 2006). We hypothesized that patients with distressing tinnitus show different FC patterns between the auditory cortex and the distress network system (De Ridder et al., 2011; Leaver et al., 2012; Maudoux et al., 2012a, 2012b; Vanneste et al., 2010a) depending on the amount of distress. As tinnitus loudness is related to gamma band activity in the auditory cortex, we take the auditory cortex as the seed for analyzing the FC differences related to the distress state.

## Methods and Materials

### *Participants*

Fifty-five patients (M = 48.31 years; SD = 13.99; 33 males and 22 females) with chronic constant 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 (i.e., brain tumors), and individuals being treated for mental disorders were excluded from the study to increase the sample homogeneity. This study was approved by the local ethical committee (Antwerp University Hospital, Belgium) and was in accordance with the declaration of Helsinki.

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 as for information related to the tinnitus sound (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 according to the British Society of Audiology (2008) procedures at 0.125, 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz. Tinnitus patients were tested for the tinnitus frequency through performance of a tinnitus matching procedure (Audiology, 2008). See Table 1 for an overview of the tinnitus characteristics.

Patients were also given the validated Dutch version of the Tinnitus Questionnaire (TQ) (Meeus et al., 2007) originally published by Goebel and Hiller (1994). Goebel and Hiller described the TQ as a global index of distress, and the Dutch version was further confirmed as a reliable measure for tinnitus-related distress (Meeus et al., 2007; Vanneste et al., 2011a). Based on the total score on the TQ, participants were 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, 1994; Meeus et al., 2007; Vanneste et al., 2011a). In addition, a numeric rating scale (NRS) for loudness (''How loud is your tinnitus?'': 0 = no tinnitus and 10 = as loud as imaginable') was assessed.

### *Healthy control group*

EEG data of a healthy control group ($N = 55$; M = 48.33 years; SD = 13.99; 33 males and 22 females) was collected out of a large EEG database recorded with the same EEG equipment and matched for age and gender. 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.

### *EEG data collection*

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.

Table 1. Tinnitus Characteristics

| | |
|---|---|
| Ear | |
| Left | 14 |
| Right | 11 |
| Bilateral | 30 |
| Tone | |
| Pure tone | 25 |
| Noise like | 30 |
| Tinnitus frequency (Hz) | |
| Arithmetic mean | 5154.55 (SD = 3144.47) |
| Hearing loss at the tinnitus frequency (dB HL) | |
| Arithmetic mean | 28.24 (SD = 15.11) |
| Hearing loss at the tinnitus frequency (dB SL) | |
| Arithmetic mean | 6.69 (SD = 8.93) |

The EEG was sampled using Mitsar-201 amplifiers (NovaTech 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, O2) referenced to digitally linked ears analogous to what was done in the normative group. Impedances were checked to remain below 5 kΩ. Data were collected with the patients' eyes closed (sampling rate = 500 Hz, band passed 0.15–200 Hz). Off-line data were, resampled to 128 Hz, re-referenced to average reference, band-pass filtered in the range 2–44 Hz, 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. 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 (10.5–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz), and gamma (30.5–44 Hz). These frequency bands are based on previous research with tinnitus (Vanneste et al., 2010b, 2011c; Vanneste and De Ridder, 2012a).

### *Source localization*

Standardized low-resolution brain electromagnetic tomography was used (sLORETA; Pascual-Marqui, 2002). 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/m2) 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 www.uzh.ch/keyinst/loreta.htm). This software implements revisited realistic electrode coordinates (Jurcak et al., 2007) and the lead field produced by Fuchs and colleagues (2002) applying the boundary element method on the MNI-152 (Montreal neurological institute, Canada) template of Mazziotta and colleagues (2001). The sLORETA-key anatomical template divides and labels the neocortical (including hippocampus and anterior cingulated cortex) MNI-152 volume in 6,239 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 space (Brett et al., 2002).

The tomography sLORETA has received considerable validation from studies combining LORETA with other more established localization methods such as fMRI (Mulert et al., 2004; Vitacco et al., 2002), structural MRI (Worrell et al., 2000), and PET (Dierks et al., 2000; Pizzagalli et al., 2004; Zumsteg et al., 2005). It was used in previous studies to detect activity in the auditory cortex (Vanneste et al., 2011b, 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, 2006c) and cognitive event-related potentials (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.

### *Seed-based phase synchronization*

Phase synchronization between time series corresponding to different spatial locations are usually interpreted as indicators of the ''functional connectivity.'' Such ''lagged phase coherence'' between two sources can be interpreted as the amount of cross-talk between the regions contributing to the source activity (Congedo et al., 2010). Since the two brain areas oscillate coherently with a phase lag, the cross-talk can be interpreted as information sharing by axonal transmission. Any measure of dependence is highly contaminated with an instantaneous, nonphysiological contribution due to volume conduction (i.e., the transmission of electric or magnetic fields from an electric primary current source through biological tissue toward measurement sensors) (Pascual-Marqui, 2007b). However, Pascual-Marqui, (Pascual-Marqui, 2007a; Pascual-Marqui et al., 2011) introduced a new technique that removes this confounding factor. As such, this measure of dependence can be applied to any number of brain areas jointly, that is, distributed cortical networks, whose activity can be estimated with sLORETA. Measures of linear dependence (coherence) between the multivariate time series are defined. The measures are expressed as the sum of lagged dependence and instantaneous dependence. The measures are non-negative, take the value zero only when there is independence, and are defined in the frequency domain: delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10.5–12 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 was calculated. The auditory seeds were placed at the left and right auditory cortex (Table 2 for overview).

### *Regions of interest analyses*

The log-transformed electrical current density was averaged across all voxels belonging to the regions of interest. Regions of interest were the left and right auditory cortex, the subgenual anterior cingulate cortex, the dorsal anterior cingulate cortex, and the posterior cingulate cortex. In addition, we opted for the seed-based FC to put the seed in the auditory cortex. These brain areas were predefined based on the MNI-coordinate, and based on the fact that they belonged to a specific Brodmann area on a standard brain. Regions of interest analyses were computed for the different frequency bands separately.

### *Statistics*

Behavioral measures. To compare the TQ scores as well as the NRS for loudness for the different distress grades, we applied an ANOVA with as independent variable the grade (1, 2, 3, or 4) and as dependent variable, respectively, the TQ and the NRS for loudness. A simple contrast analysis

TABLE 2. SEEDS

| | *Seeds* | | |
|---|---|---|---|
| | *x* | *y* | *z* |
| Left auditory cortex | −46.1 | −29.0 | 9.81 |
| Right auditory cortex | 46.7 | −28.6 | 10.0 |

was used to compare the different grades from each other. This latter test includes a correction for multiple comparisons using a Bonferroni correction.

To verify the association between the loudness, as measured with the NRS, and the score on the TQ, we applied a Pearson linear correlation as well as a nonlinear (logarithmic) regression. For the comparison of variations between these two correlation outcomes (linear vs. nonlinear), we applied an *F*-test for equality of variances.

We applied a Chow test to determine whether the loudness has different impacts on different subgroups (i.e., distress grades) of the population. The Chow test is a statistical test evaluating whether the coefficients in two linear regressions on different data sets are equal and can be used to determine whether the variable (i.e., loudness) has a different impact on different subgroups (i.e., distress state) of the population. This Chow test follows an *F*-distribution. The Chow test was used to verify whether the association between loudness (NRS) and distress (TQ) was different between different tinnitus grades.

Functional measurements. A MANOVA was performed, including loudness (NRS) and distress (TQ) as independent variables and the log-transformed current density for different frequency bands, namely delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10.5–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz), and gamma (30.5–44 Hz), as dependent variables for the subgenual anterior cingulate cortex, the dorsal anterior cingulate cortex, the posterior cingulate cortex, and the auditory cortex. In addition, a logistic regression was used with TQ grade (low distress vs. high distress) as dependent variables and the different frequency bands, namely delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10.5–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz), and gamma (30.5–44 Hz) as independent variables for the posterior cingulate cortex.

To identify potential differences in brain electrical activity, voxel-by-voxel analysis using sLORETA was performed for each frequency band. Nonparametric statistical analyses of sLORETA images (statistical nonparametric mapping; SnPM) were performed for each contrast using sLORETA built-in voxelwise randomization tests (5000 permutations) and *t*-statistics for independent groups ($p < 0.05$). The SnPM methodology does not rely on any Gaussian assumptions by employing a locally pooled (smoothed) variance estimate that can outperform the Statistical Parametric Mapping approach (Segrave et al., 2011). SnPM's permutation method for correction for multiple comparisons (5000 permutations in the current study) has been proved similar to those obtained using a standard GLM approach with multiple comparisons corrections derived from random field theory (Holmes et al., 1996; Nichols and Holmes, 2002).

To determine differences in seed-based connectivity between the tinnitus groups and healthy controls, we performed *t*-statistics for independent groups with a corrected threshold $p < 0.05$, which were also corrected for multiple comparisons by conducting sLORETA-built-in voxelwise randomization tests (5000 permutations).

In addition, to correlate electrical brain activity, voxel by voxel, with distress as measured with TQ, and loudness as measured with NRS, a permutation test was used that corrects for multiple comparisons by conducting sLORETA-built-in voxelwise randomization tests (5000 permutations).

## Results

### *Behavioral measurements*

Mean scores on distress and loudness. Table 3 shows the mean scores and standard deviations for distress as measured with the TQ (Goebel and Hiller, 1994; Meeus et al., 2007) and loudness as measured with an NRS. A significant difference was obtained for the distress when divided into distress states (i.e., grades), $F = 157.39$, $p < 0.001$. More importantly a significant effect was obtained for loudness when divided into distress states, $F = 5.55$, $p < 0.01$.

The relationship between loudness and distress. The linear correlation between NRS loudness and TQ revealed a significant positive correlation ($r = 0.47$, $p < 0.001$). In addition, a nonlinear correlation (logarithmic) between NRS loudness and TQ also revealed a significant positive correlation ($r = 0.51$, $p < 0.001$) (Fig. 1A). This nonlinear method explained 26% of the variance, whereas the linear method revealed 22% of the variance. An *F*-test between the difference of the $R^2$'s between two models in a single sample revealed a marginally significant effect ($F = 2.89$, $p = 0.09$).

We compared low distress (grade 1 and 2) tinnitus patients with high distress (grade 3 and 4) tinnitus patients and showed that a linear analysis of both groups separately is statistically relevant, $F = 3.03$, $p < 0.05$ using a Chow test. A linear correlation of two groups separately revealed a significant positive correlation for the patients with a low tinnitus-related distress ($r = 0.50$, $p < 0.001$) (Fig. 1B) and no significant correlation for grade 3 and 4 (Fig. 1E).

In addition, a Chow test was applied for the comparison between grade 1 and 2 tinnitus patients. This test revealed a significant effect, $F = 3.59$, $p < 0.05$. A linear correlation of two groups separately revealed a significant positive correlation for the patients with a low tinnitus-related distress ($r = 0.44$, $p < 0.001$) (Fig. 1C) and no significant correlation for grade 2 (Fig. 1D). Using a similar Chow test, it was also shown that a comparison between grade 1 and grade 3 and 4 tinnitus patients as well as a comparison between grade 2 and grade 3 and 4 tinnitus patients revealed a

Table 3. The Means and Standard Deviations of TQ (Distress) and NRS (Loudness) for the Total Patient Group and Patients with a Grade 1, Grade 2, Grade 3, or Grade 4 Separately

| | | *Grade* | | | | |
|---|---|---|---|---|---|---|
| | | *1* | *2* | *3* | *4* | *Total* |
| Distress | M | 20.72[a] | 38.23[b] | 52.00[c] | 72.75[d] | 40.53 |
| | SD | 7.65 | 5.50 | 3.57 | 5.60 | 18.70 |
| Loudness | M | 4.67[a] | 6.32[a,b] | 7.17[b] | 6.63[b] | 6.01 |
| | SD | 1.64 | 2.08 | 1.40 | 1.92 | 2.00 |
| Patients | | 18 | 17 | 12 | 8 | |

Mean scores with a different superscript significantly differ from each other.

NRS, numeric rating scale; TQ, tinnitus questionnaire.

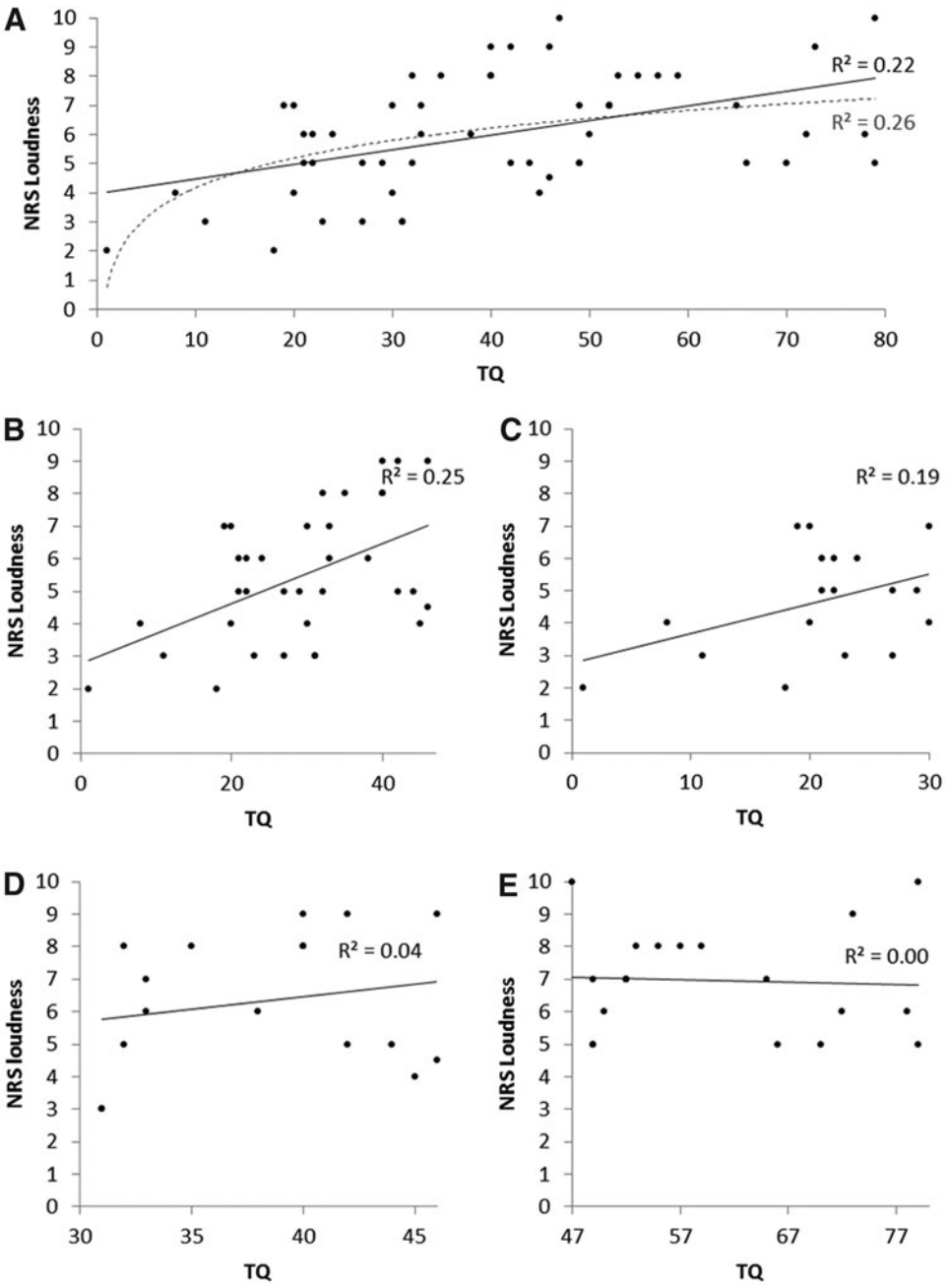



**FIG. 1.** Linear and nonlinear correlation between tinnitus-related distress as measured with the tinnitus questionnaire (TQ) and numeric rating scale (NRS) measuring loudness on the whole group of tinnitus patients **(A)**; Correlation between distress and loudness for low distress (grade 1 and 2) tinnitus patients **(B)**; Correlation between distress and loudness for very low distressed (grade 1) tinnitus patients **(C)**; Correlation between distress and loudness for moderately distressed (grade 2) tinnitus patients **(D)**; Correlation between distress and loudness for highly distressed (grade 3 and 4) tinnitus patients **(E)**.

(marginally) significant effect, respectively $F = 3.72$, $p < 0.05$ and $F = 2.70$, $p = 0.06$.

### *Functional measurements*

The relationship between specific brain areas and loudness and distress. Separate MANOVA's, including loudness (NRS) and distress (TQ) as independent variables and the log-transformed current density for different frequency bands as dependent variables for subgenual anterior cingulate cortex, the dorsal anterior cingulate cortex, the posterior cingulate cortex, and the secondary auditory cortex, were applied.

The subgenual anterior cingulate cortex revealed a significant effect for alpha1 ($F = 4.08$, $p < 0.05$) and beta 3 ($F = 3.20$, $p < 0.05$), but not for delta, theta, alpha 2, beta1, beta2, and gamma ($p > 0.17$). More specifically, between-subjects effects revealed for alpha1 ($F = 6.72$, $p < 0.01$, $\beta = 14.31$) and beta3 ($F = 6.43$, $p < 0.02$, $\beta = 10.52$) a significant effect for TQ, but not for loudness. Figure 2 gives an overview of the obtained results.

For the dorsal anterior cingulate cortex, the analysis revealed only a significant effect for beta3 (left: $F = 3.58$, $p < 0.05$ and right: $F = 3.39$, $p < 0.05$), but not for delta, theta, alpha1, alpha 2, beta1, beta2, and gamma ($p > 0.26$). Between-subjects effects demonstrated that this was for TQ (left: $F = 7.02$, $p < 0.05$, $\beta = 172.75$ and right: $F = 6.82$, $p < 0.05$, $\beta = 167.70$), but not for loudness. See Figure 2 for overview.

For the posterior cingulate cortex, no significant effect was found. However, when applying a logistic regression with TQ grade (low distress vs. high distress) as dependent

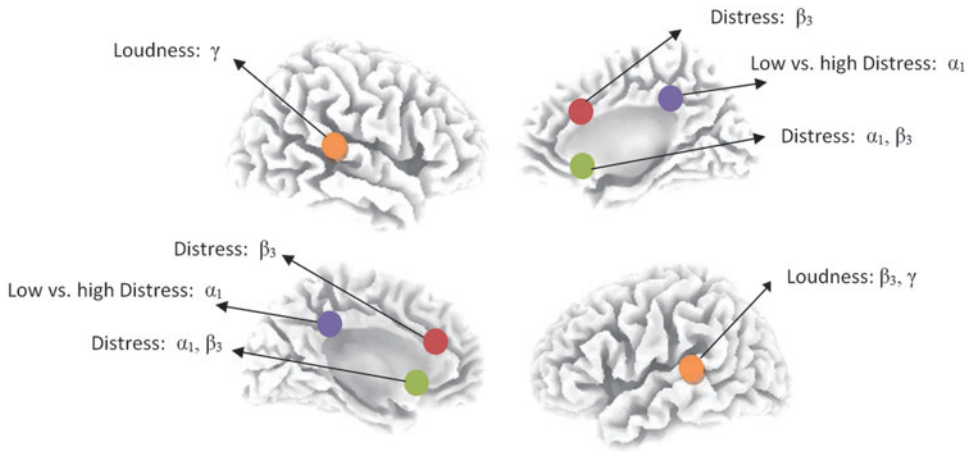



**FIG. 2.** The significant effects of the log-transformed current density at the specific regions of interest (i.e., dorsal anterior cingulate cortex (red), subgenual anterior cingulate cortex (green), posterior cingulate cortex (purple), auditory cortex (yellow)) for the specific frequency bands on loudness and distress. Color images available online at www.liebertpub.com/brain

variables and the different frequency bands as independent variables, a significant effect ($\chi^2 = 15.79$, $p < 0.05$, Nagelkerke $R^2 = 0.40$) was revealed. A closer look at the data showed that this effect was obtained for, respectively, alpha 1 (W = 5.74, $p < 0.05$, $\beta = -2.56$) and alpha2 (W = 4.15, $p < 0.05$, $\beta = -1.76$), demonstrating that the lower the log-transformed current density is in both frequency bands, the higher chance a patient has for high distress (grade 3 or 4) (Fig. 2). No significant effects were obtained for delta, theta, beta1, beta2, beta3, and gamma.

For the left auditory cortex, a similar analysis was conducted that yielded a significant effect for beta3 ($F = 5.25$, $p < 0.01$) and gamma ($F = 5.37$, $p < 0.01$), but not for delta, theta, alpha1, alpha 2, beta1, and beta2 ($p > 0.12$). Between-subjects effects showed for beta3 ($F = 5.25$, $p < 0.01$ $\beta = 3.67$) and gamma ($F = 10.49$, $p < 0.01$, $\beta = 11.91$) a significant effect for loudness, but not for TQ as indicated in Figure 2.

Similar analysis for the right auditory cortex revealed a significant effect for beta3 ($F = 3.60$, $p < 0.0$) and gamma ($F = 5.64$, $p < 0.01$), but not for delta, theta, alpha1, alpha 2, beta1, and beta2 ($p > 0.12$). Between-subjects effects showed for beta3 $F = 7.39$, $p < 0.01$, $\beta = 15.52$) and gamma ($F = 10.72$, $p < 0.01$, $\beta = 7.13$) a significant effect for loudness, but not for TQ. Figure 2 gives an overview of the obtained results.

Seed-based connectivity: Patients with tinnitus versus healthy control subjects. A comparison with the seed at the auditory cortex demonstrated increased lagged phase synchronization for the alpha1 and beta3 frequency bands for patients with tinnitus in comparison to healthy control subjects (Fig. 3). For the alpha1 frequency, band-increased lagged phase synchronization was demonstrated with the posterior cingulate cortex (BA23) extending into the parahippocampal area. For the beta3 frequency band, increased lagged phase synchronization was shown with the right insula (BA13), the posterior cingulate cortex (BA23), and the left (BA35) and right (BA28) parahippocampal area. No significant effect could be obtained in the delta, theta, alpha 2, beta1, beta2, and gamma frequency bands.

No significant results were obtained when placing the seed in, respectively, the right auditory cortex for delta, theta, alpha1, alpha 2, beta1, beta2, beta3, and gamma frequency bands.

The relationship between seed-based connectivity and distress. Seed-based lagged phase synchronization with the seed at, respectively, the left auditory cortex correlating with tinnitus-related distress as measured by the TQ revealed a significant effect for the alpha1 and beta3 frequency bands. For alpha1 also, a decrease in lagged phase synchronization was found between the seed, the left secondary auditory cortex, and both the left inferior frontal gyrus (BA44) and the premotor cortex (BA6) in association with an increase in TQ (Fig. 4). For beta3, it was shown that that there was a

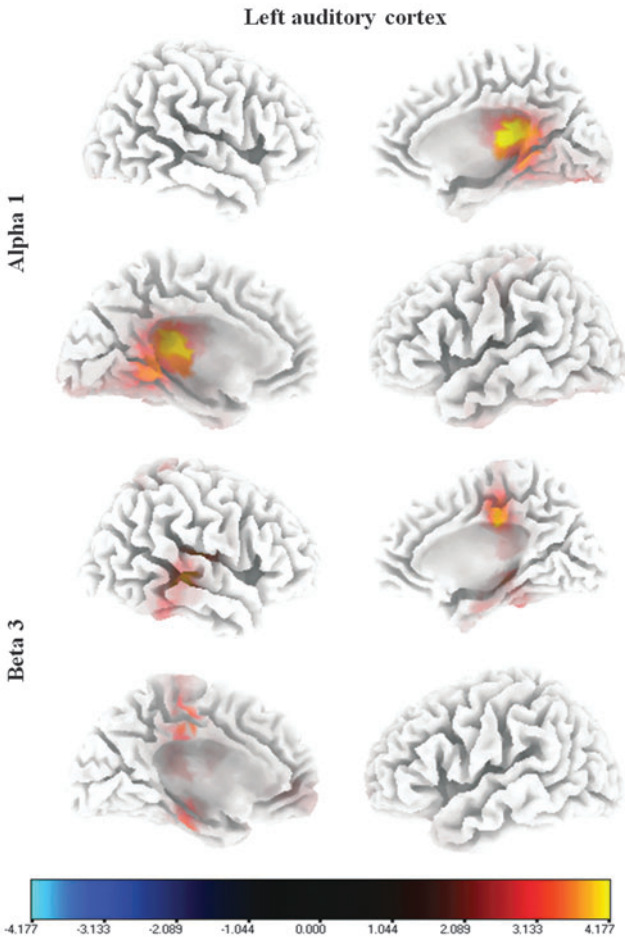



**FIG. 3.** A comparison between tinnitus patients and a healthy control group for the seed-based lagged phase synchronization with the seed at, respectively, the left auditory cortex. Color images available online at www.liebertpub.com/brain

decrease in lagged phase synchronization between the seed, respectively, in the left auditory cortex or secondary cortex auditory cortex and the dorsal anterior cingulate cortex (BA24) in association with an increase in TQ (Fig. 4). No significant results were obtained for delta, theta, alpha 2, beta1, beta2, and gamma frequency bands.

No significant results were obtained when placing the seed in, respectively, the right auditory cortex and correlating with tinnitus-related distress as measured with the TQ for delta, theta, alpha1, alpha 2, beta1, beta2, beta3, and gamma frequency bands.

The relationship between seed-based connectivity and loudness. Seed-based lagged phase synchronization with the seed at, respectively, the left auditory cortex, the right auditory cortex correlating with tinnitus loudness revealed no significant effects for delta, theta, alpha1, alpha 2, beta1, beta2, beta3, and gamma frequency bands.

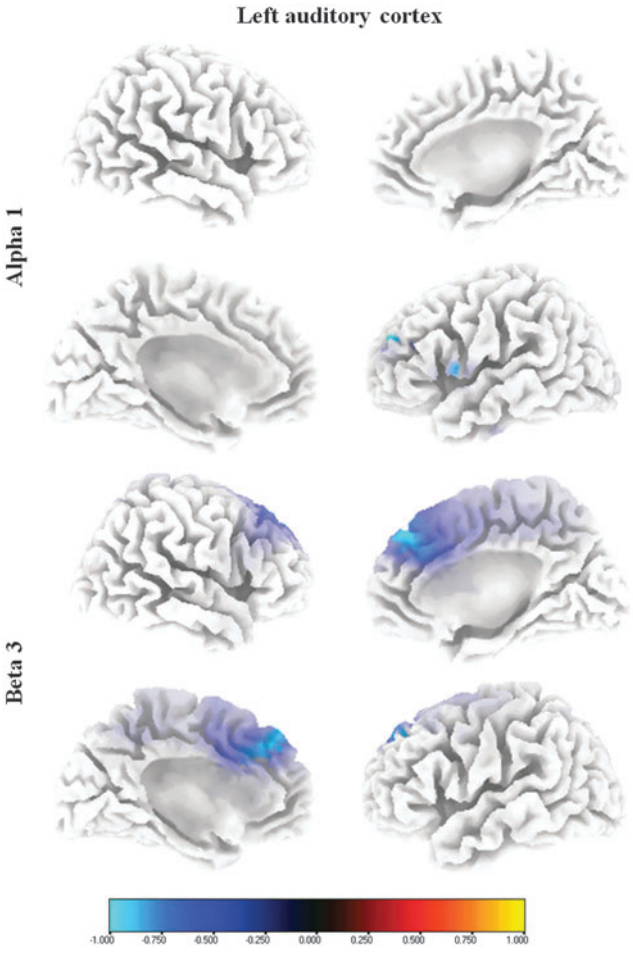



**FIG. 4.** Correlation for seed-based lagged phase synchronization with the seed at, respectively, left auditory cortex and distress as measured with the TQ. For alpha1 also, a decrease in lagged phase synchronization was found between the seed, the left secondary auditory cortex, and both the left inferior frontal gyrus (BA44) and the premotor cortex (BA6) in association with an increase in TQ. For beta3, it was shown that that there was a decrease in lagged phase synchronization between the seed, respectively, in the left auditory cortex and the dorsal anterior cingulate cortex (BA24) in association with an increase in TQ. No significant results were obtained for delta, theta, alpha 2, beta1, beta2, and gamma frequency band. Color images available online at www.liebertpub.com/brain

The relationship between seed-based connectivity and, respectively, grade 1, grade 2, and grade 3–4 tinnitus-related distress. Based on the finding that there is a difference in the relationship between the loudness and distress for, respectively, grade 1, grade 2, and grade 3–4, an analysis is performed to evaluate seed-based connectivity for, respectively, grade 1, grade 2, and grade 3–4 separately.

### *The relationship between seed-based connectivity and grade 1 tinnitus-related distress*

When we apply seed-based lagged phase synchronization with the seed at the left auditory cortex, a significant effect could be obtained for the alpha2 frequency band, revealing an increased synchronization between the seed and the dorsal anterior cingulate cortex (BA24), but a decrease in the pregenual anterior cingulate cortex (BA32) in association with an increase on the TQ for grade 1 tinnitus patients (Fig. 5A). No significant effects could be demonstrated for delta, theta, alpha1, beta1, beta2, beta3, and gamma frequency bands.

No significant results were obtained when placing the seed in, respectively, the right auditory cortex and correlating with tinnitus-related distress for grade 1 tinnitus patients as measured with the TQ revealed for delta, theta, alpha1, alpha 2, beta1, beta2, beta3, and gamma frequency bands.

### *The relationship between seed-based connectivity and grade 2 tinnitus-related distress*

Seed-based lagged phase synchronization with the seed at, respectively, the left auditory cortex, the right auditory cortex correlating with grade 2 tinnitus-related distress revealed no significant effects for delta, theta, alpha1, alpha 2, beta1, beta2, beta3, and gamma frequency bands.

### *The relationship between seed-based connectivity and grade 3 and 4 tinnitus-related distress*

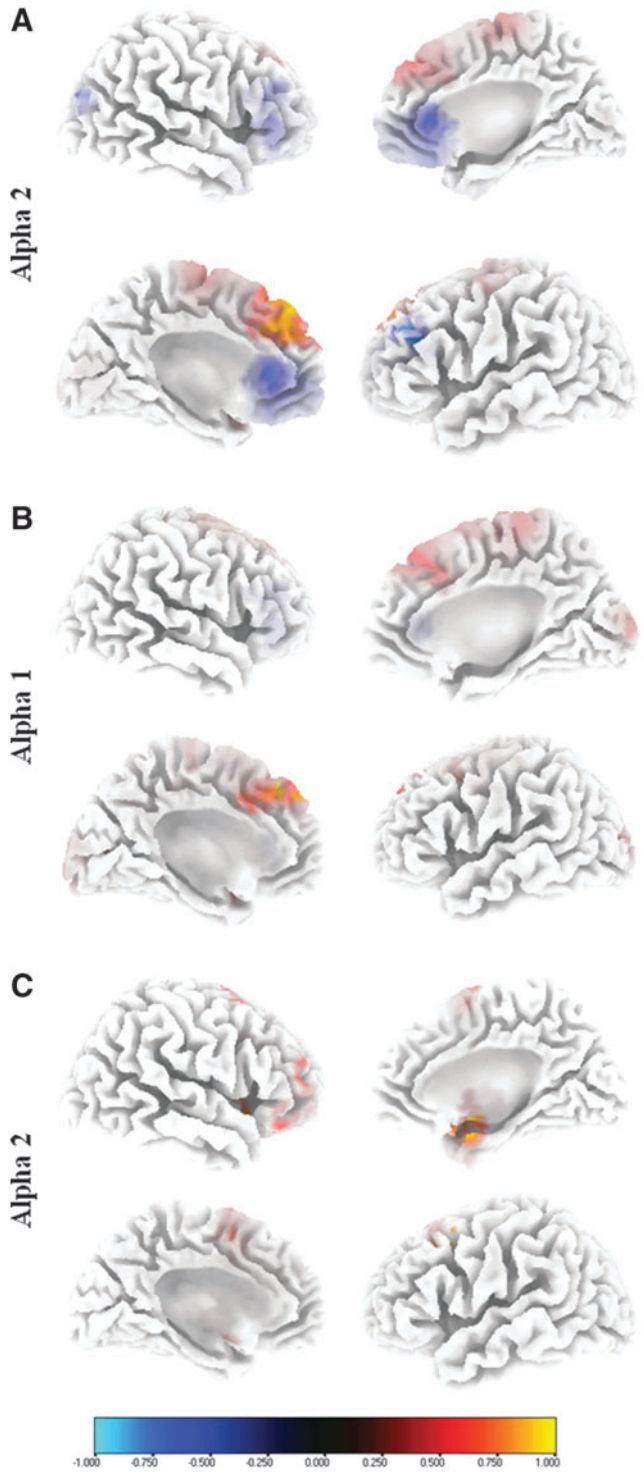
When we apply a similar analysis with the seed at the left auditory cortex, a significant effect could be obtained for the alpha2 frequency band, revealing an increased synchronization between the seed and the subgenual anterior cingulate cortex (BA25), in association with an increase on the TQ for grade 3 and 4 tinnitus patients (Fig. 5C). No significant effects could be demonstrated for delta, theta, alpha1, beta1, beta2, beta3, and gamma frequency bands.

No significant results were obtained when placing the seed in, respectively, the right auditory cortex and correlating with tinnitus-related distress for grade 3 and 4 patients for delta, theta, alpha1, alpha 2, beta1, beta2, beta3, and gamma frequency bands.

## Discussion

The brain can be considered a highly dynamically complex adaptive system, adjusting its activity and FC constantly to accommodate for changes in the environment. Its primary aim is to reduce inherent uncertainty in the environment (De

Ridder et al., 2014a). Tinnitus can be regarded as a mechanism that resolves sensory uncertainty by filling in missing auditory information arising as a consequence of auditory deprivation (De Ridder et al., 2014a). In 1 out of 5 patients, this solution leads to or is associated with distress (Axelsson and Ringdahl, 1989; De Ridder et al., 2011). Distress is associated with changing FC between a loudness and distress network within the brain. The results provide new insights in how different brain networks interact in a complex way depending on the distress state of the tinnitus patient (see Figure 6).




*The relationship between distress and loudness*

Our data suggest that the subjectively perceived loudness (NRS) and distress (TQ) interact logarithmically, revealing a difference between the relationship of distress and loudness for, respectively, grade 1, 2, 3, and 4. That is, a strong relationship exists between loudness and distress for grade 1, while no significant relationship could be obtained for grades 2, 3, and 4. Based on these data, it can be hypothesized that patients with low distress can be stressed by variations of the loudness of the tinnitus; while in patients with higher distress, modulation of distress by loudness is very limited, that is, they are already distressed.

*The frequency bands*

Our main electrophysiological findings are related to the alpha and the beta frequency band. Using MEG, it has been demonstrated that long-range coupling between brain areas in ''alpha and gamma networks'' are related to tinnitus distress (Schlee et al., 2008) as are activity changes (Schlee et al., 2009; Weisz et al., 2005, 2007), whereas EEG studies have shown predominant changes in alpha and beta activity related to tinnitus distress (De Ridder et al., 2011; Vanneste et al., 2010a). Therefore, distress changes in FC are found in the same frequency bands as the activity changes.

*The relationship between the distress and loudness dependent on the brain state*

A correlation between the behavioral measure of distress and loudness revealed that a nonlinear correlation could better explain the results than a linear correlation ($r^2 = 0.26$ vs. 0.22). By splitting up the groups based on their distress state (respectively grade 1, 2, 3, and 4), a more detailed analysis revealed that there was a significant difference between loudness and distress between grade 1 and 2 distress states. Only grade 1 tinnitus patients, that is, those without distress, experience an increase in perceived loudness in correlation with increased distress or vice versa. It is of interest that this is not unique for tinnitus. When evaluating pain, which has pathophysiological (De Ridder et al., 2011), clinical (Moller, 1997, 2000, 2007), and treatment (De Ridder et al., 2007) analogies with tinnitus, a similar nonlinear

**FIG. 5.** **(A)** Correlation for seed-based lagged phase synchronization with the seed at, respectively, left auditory cortex and distress as measured with the TQ. An increased synchronization between the seed and the dorsal anterior cingulate cortex (BA24), but a decrease in the pregenual anterior cingulate cortex (BA32) in association with an increase on the TQ for grade 1 tinnitus patients for alpha2 frequency band. **(B)** Correlation for seed-based lagged phase synchronization with the seed at, respectively, left auditory cortex and distress as measured with the TQ for grade 1 tinnitus patients. An increased synchronization between the seed and the dorsal anterior cingulate cortex (BA24); **(C)** Correlation for seed-based lagged phase synchronization with the seed at, respectively, left auditory cortex and distress as measured with the TQ for grade 3 and 4 tinnitus patients. Increased synchronization between the seed and the subgenual anterior cingulate cortex (BA25) was obtained. Color images available online at www.liebertpub.com/brain

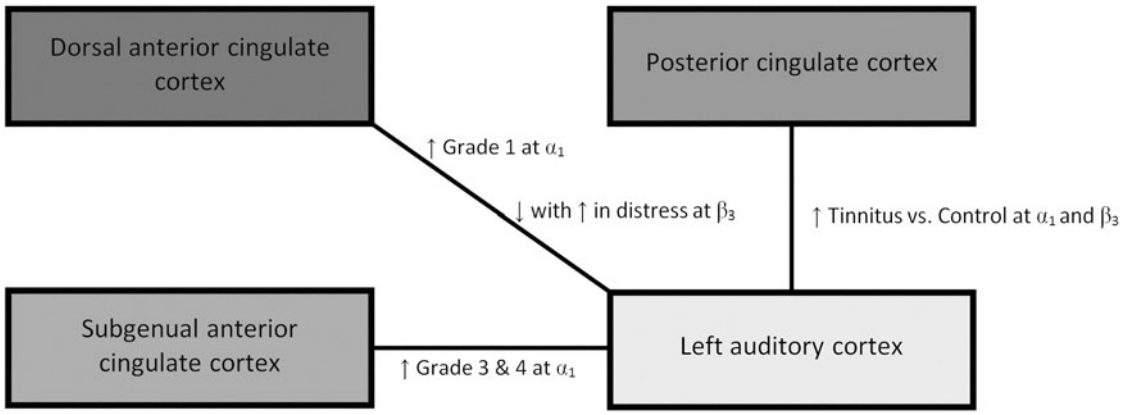



**FIG. 6.** An overview of the obtained results. Lower right box: brain area correlates with loudness at beta3 and gamma; lower left box: brain area correlates with distress at alpha1 and beta 3: upper left box: brain area correlates with distress at alpha1 and beta 3; upper right box: brain activity is different between low and high distress correlates of alpha1 and alpha2.

correlation is found between pain intensity and the affective components of pain (Litcher-Kelly et al., 2004). This could be related to the fact that scales are inherently nonlinear (Svensson, 2000), even though this seems not to be the case for low to moderate pain (Myles et al., 1999), or because the pain or tinnitus has to cross a threshold for it to become a salient stressor (Alpini and Cesarani, 2006; Hummel et al., 2010).

We confirm that subjectively perceived loudness is correlated with brain activity within the auditory cortex within the beta3 and gamma frequency band (van der Loo et al., 2009). These findings fit with the thalamocortical dysrhythmia that might underlie in tinnitus. The idea of Llinas and colleagues is that this abnormally persistent coupled theta-gamma band dysrhythmia is relayed to the cortex, selectively in the deafferented thalamocortical columns (Llinás et al., 1999). Synchronized gamma band activity in the auditory cortex is proposed to bind auditory events into one coherent conscious auditory percept (Crone et al., 2001; Llinas et al., 1998; Ribary et al., 1991). It has been suggested that theta activity synchronizes large spatial domains (von Stein and Sarnthein, 2000) and binds together specific assemblies by the appropriate timing of spatially restricted higher-frequency localized oscillations (Buzsaki and Chrobak, 1995; Canolty et al., 2006; Engel et al., 2001; Varela et al., 2001) and that higher-frequency oscillations are confined to a small neuronal space, whereas very large networks are recruited by means of slow oscillations (Csicsvari et al., 2003; von Stein and Sarnthein, 2000). A recent study confirmed transient theta–gamma coupling and synchronizing geographically distributed gamma band activity in auditory attention (Doesburg et al., 2012). In tinnitus, it has been suggested that the normally waxing and waning theta gamma coupling remains permanently present (De Ridder et al., 2011) and intracranial recordings in a patient with simple auditory phantom. This disappears when tinnitus is suppressed by electrical stimulation of the auditory cortex (De Ridder et al., 2011).

However, when we correlated this loudness measurement with seed-based lagged phase synchronization with the seed at the auditory cortex, no FC differences were shown in contrast to the distress. Our data revealed that distress is positively correlated to activity in dorsal anterior cingulate cortex within the beta3 frequency band (De Ridder et al., 2011).

*Brain state-dependent connectivity*

For patients with tinnitus who have a relatively low amount of distress (i.e., grade 1), a strong correlation was shown between loudness and distress in the behavioral data. These findings are in accordance with the functional data. Grade 1 tinnitus patients demonstrated increased seed-based lagged phase synchronization between the auditory cortex seed and the dorsal anterior cingulate cortex in the alpha frequency band. Furthermore, there is decreased FC with the pregenual anterior cingulate cortex. This area is known to be involved in antinociception (Kong et al., 2010) as well as noise cancelling (De Ridder et al., 2012). This is in line with the hypothesis that dorsal anterior cingulate cortex is involved in persisting attention to the tinnitus but independent of loudness, as grade 1 tinnitus patients are usually only aware of the tinnitus when they are really focusing on the tone or noise, causing the loudness to increase due to a decreasing in the noise-cancelling mechanism (Leaver et al., 2011; Rauschecker et al., 2010). For grade 2 and grade 3–4 patients, there is no more change in loudness with increasing distress, possibly due to the fact that the FC has already decreased to zero, that is, no more modulation of the loudness is possible, in agreement with the clinical data. However, in grade 2 distress, the persisting FC between the auditory cortex and dorsal anterior cingulate cortex remains, suggesting too much attention is being paid to the tinnitus.

For tinnitus patients with a high distress (grade 3 and 4), increased alpha lagged phase synchronization is seen between the auditory seed and the subgenual anterior cingulate cortex associated with an increase in distress on the behavioral measurement. This goes together with this positive correlation between the distress on the behavioral measurement and the subgenual anterior cingulate cortex in both the alpha and the beta frequency band. Structural deficits have been observed in the subgenual cingulate cortex/nucleus accumbens (Leaver et al., 2011) and the subgenual anterior cingulate cortex. Alpha activity reflects the amount of tinnitus-related distress perceived by patients (Vanneste et al., 2010a). Previous research has demonstrated that subgenual cingulate cortex FC increases with increasing length of a depressive episode, suggesting that the resting-state

signal in the subgenual cingulate cortex region may be a marker for refractoriness to treatment (Greicius et al., 2007). In tinnitus, it has been shown that for grade 3 and 4 distress acts as a functional connection between the sgACC and the parahippocampal area exists at 10 Hz and 11.5 Hz, respectively, determining the amount of tinnitus-related distress. The sgACC is involved in autonomic control in tinnitus (Vanneste and De Ridder, 2013), mediated via theta activity. It is therefore possible that the alpha activity in high distress actually speeds up theta activity, analogous to the increasing speed seen in FC between the sgACC and parahippocampal area in increasing distress (Vanneste and De Ridder, 2013).

It is of interest that the anterior cingulate cortex is also involved in distress related to pain (Moisset and Bouhassira, 2007), somatoform disorders (Landgrebe et al., 2008), asthmatic dyspnea (von Leupoldt et al., 2009), and social rejection (Masten et al., 2009). As such, it is possible that when this nonspecific distress network is already active and linked to the sound intensity encoding network (Schlee et al., 2008), it can result in the tinnitus sound being perceived as distressing.

### *The role of the auditory cortex*

Although the right auditory cortex seems to be involved in the tinnitus loudness, these brain areas are not involved in the distress network. Confirmation for this hypothesis was further shown on the seed-based connectivity analyses, as there was no difference between healthy control subjects and tinnitus patients with the seed at, respectively, the right auditory cortex. An ongoing debate discusses whether tinnitus is always generated in the left or the contralateral auditory cortex (De Ridder, 2010). This debate arose because of dissimilar functional imaging results. Functional MRI (Melcher et al., 2000; Smits et al., 2007), MEG (Llinas et al., 2005; Muhlnickel et al., 1998; Weisz et al., 2007), and EEG (van der Loo et al., 2009) suggest the neural generator of the tinnitus is located in the contralateral auditory cortex, whereas most PET studies suggest tinnitus is always generated in the left auditory cortex (Arnold et al., 1996; Eichhammer et al., 2007). Other PET studies, however, report that left-sided auditory cortex activation is predominantly in left-sided tinnitus (Andersson et al., 2000) or irrespective of the tinnitus side (Arnold et al., 1996). Similar findings are demonstrated from modulating the auditory cortex. Several studies have demonstrated that using transcranial magnetic stimulation (TMS) targeting the left auditory cortex irrespective of the lateralization of tinnitus can suppress tinnitus (Kleinjung et al., 2008; Langguth et al., 2006). However, other studies using TMS or implanted extradural cortex stimulation reveal that modulating the contralateral auditory cortex to the tinnitus can also suppress tinnitus (De Ridder et al., 2007, 2010). Although our findings suggest that both the left and right auditory cortex are important in this respect, it is possible that, depending on the distress level, the left is more involved as it could indirectly influence distal areas connected to the auditory cortex. Previous research, indeed, already demonstrated that different neuoromodulation techniques in general (Hallett, 2000; Kimbrell et al., 2002) or specific for tinnitus (Vanneste and De Ridder, 2011) influence distal brain areas functionally connected to the targeted area. Another possibility is that the right auditory cortex could be more involved in tinnitus-related depression, as it has been shown that a similar network involving the parahippocampal area, sgACC, and orbitofrontal cortex is involved in both tinnitus-related distress and tinnitus-related depression but that these are lateralized, with distress lateralized to right parahippocampal area, right sgACC, and right orbitofrontal cortex and depression to the left homologue areas. Further research will have to verify this possibility.

### *Limitations*

Due to the fact that sLORETA has a lower spatial resolution in comparison to fMRI and PET, we did not make a differentiation between the primary and secondary auditory cortex. This could be considered a potential weakness, as previous research has shown that there might be a difference between the primary and secondary auditory cortex.

### *Conclusion*

These results suggest how the different brain areas interact in tinnitus is state dependent and related to the amount of distress the patients perceived. This corroborates with a recently proposed model that states that tinnitus is generated by multiple dynamically active separable but overlapping networks. Each network characterizes a specific aspect of the unified tinnitus percept (De Ridder et al., 2011, 2014b) but adds to this concept that the interaction between these networks is a complex interplay between specific brain areas involved in distress and loudness depending on the distress state of the tinnitus patient. This augments recent findings that during resting state, spontaneously distinct networks not only interact on the basis of their temporal nonstationary dependency (Smith et al., 2012) but also are dependent on the distress state in pathologies such as tinnitus.

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## Author Disclosure Statement

No competing financial interests exist.

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