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## Research report

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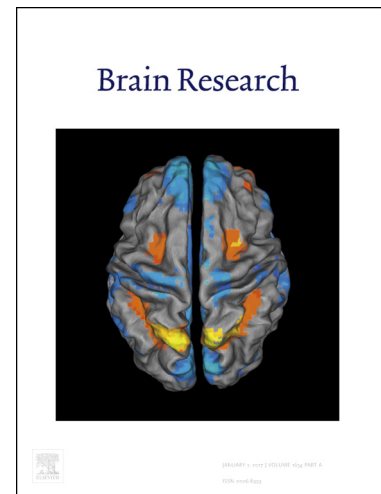
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# EEG oscillatory power dissociates between distress- and depression-related psychopathology in subjective tinnitus

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## Abstract

Recent research has used source estimation approaches to identify spatially distinct neural configurations in individuals with chronic, subjective tinnitus (TI). The results of these studies are often heterogeneous, a fact which may be partly explained by an inherent heterogeneity of/in the TI population and partly by the applied EEG data analysis procedure and EEG hardware.

Hence this study was performed to re-enact a formerly published study (Joos et al., 2012) to better understand the reason for differences and overlap between studies from different labs. We re-investigated the relationship between neural oscillations and behavioral measurements of affective states in TI, namely depression and tinnitus-related distress by recruiting 45 TI who underwent resting-state EEG. Comprehensive psychopathological (depression and tinnitus-related distress scores) and psychometric data (including other tinnitus characteristics) were gathered. A principal component analysis (PCA) was performed to unveil independent factors that predict distinct aspects of tinnitus-related pathology. Furthermore, we correlated EEG power changes in the standard frequency bands with the behavioral scores for both the whole-brain level and, as a post hoc approach, for selected regions of interest (ROI) based on sLORETA. Behavioral data revealed significant relationships between measurements of depression and tinnitus-related distress. Notably, no significant results were observed for the depressive scores and modulations of the EEG signal. However, akin to the former study we evidenced a significant relationship between a power increase in the *beta1*-bands and tinnitus-related distress. In conclusion, it has emerged that depression and tinnitus-related distress, even though they are assumed not to be completely independent, manifest in distinct neural configurations.



## 1 Introduction

Tinnitus is the notion of a subjective, auditory phantom percept of chronic high-pitched noise, sound or ringing, which lacks any objective, external sound source (Eggermont and Roberts, 2004). In the steadily aging populations of Western industrialized countries, the number of individuals who suffer from tinnitus is immense. Cederroth and colleagues (2013) estimate that it affects approximately 50 million people in the US and 70 million people (roughly 10% of the population) in the European Union. At present, it is widely accepted that tinnitus should not be considered as a sole dysfunction of the outer or inner ear, even though tinnitus is normally preceded and accompanied by transient to severe hearing loss (Henry and Meikle, 2000; Roberts et al., 2012). Rather, it has been suggested that subjective tinnitus is engendered by a perplexing network that involves both the cochlea and the auditory pathway, but is primarily generated, maintained and chronically accommodated by the (human) brain (Adjamian et al., 2009; De Ridder et al., 2011a; Elgoyhen et al., 2015; Rauschecker et al., 2015; Jastreboff, 1990; Vanneste and De Ridder, 2012).

No matter which circumstances may account causally for the generation of tinnitus, the reality of it is highly subjective in nature and, for this reason, it is not considered to be a physical disease but rather a heterogeneous diffuse phenomenon that lacks a clearly defined neurological pathogenesis (Sedley et al., 2012). Thus, it is unsurprising that several, partly conflicting, neurobiological models exist, each sketching the complex interplay between multiple cortical and subcortical human brain areas underlying the subjective experience of chronic tinnitus (De Ridder et al., 2014, 2011a; Llinas et al., 1999, 2005; Rauschecker et al., 2010; Sedley et al., 2012). These models are partly based on observations provided by functional imaging studies and partly on evidence gathered from electro- and/or magnetencephalographic (M/EEG) studies. The numerous, specific constraints in data acquisition and analysis inherent to these methods may have worsened the present situation even further (Adjamian et al., 2014). While hemodynamic-based neuroimaging techniques lack a reasonable temporal resolution, neuroelectrical-based M/EEG are less advantageous in the identification of neural sources that reside in widely distributed cortical and deeply encased subcortical areas. To date, no ideal solution has been offered with which to amalgamate the advantages of the two different approaches into one setting. However, we favor neurophysiological M/EEG techniques in the context of tinnitus research because these approaches are not accompanied by bothersome gradient noise and hence are more comfortable for TI, who often show symptoms of hyperacusis. Further, comprehensive leaps have been made to improve the spatial resolution of M/EEG through the development of innovative source estimation approaches (Adjamian, 2014).

In the realm of M/EEG, spectral power analysis of spontaneous oscillations during the resting-state has been identified as an advantageous tool, because TI have demonstrated deviations from the normal EEG pattern in the activity strength of various frequency bands (for an overview see Adjamian 2014; Elgoyhen et al. 2015).

Resting-state neurophysiological measurements seem ideally suited to investigate the neural correlates of tinnitus because, during data acquisition, participants are in a relaxed and quiet setting without the distractions of external stimulation. However, it should be noted that the outcomes of different studies, which have applied the relatively controlled resting-state condition, exhibit substantial differences in EEG activity in the  $\delta$ -,  $\theta$ -,  $\beta$ -, and  $\gamma$ -bands. While it cannot be ruled out that differences in technical and methodological parameters (e.g., recording device, measurement protocol, signal processing, experimental setting) may account for the discrepancies in the results, it is also possible that the psychopathological heterogeneity within the population of TI is the source of these disparities.

At present, it is widely agreed that TI differ considerably in subjective quality and loudness of the perceived tinnitus sound, the presence and degree of hearing-loss, the duration since onset of tinnitus, and age. On the other hand, psychopathological aspects, namely the extent of distress and the presence and influence of clinically relevant comorbidity like depression and anxiety contribute to this heterogeneity. Recent suggestions towards overcoming these challenges include abandoning the established approach, in which TI are compared to healthy controls (CO) (Meyer et al., 2014; Vanneste et al., 2014a). Instead, it has become imperative to search for relationships between psychometric, psychopathological and neural patterns in a sample of TI only. This approach is advisable for several reasons. First, important variables, amongst others the presence of affective disorders and/or hearing loss, have often been ignored in the samples of CO leading to systematic errors being made in the comparison of two groups along only one dimension, that being the presence/absence of chronic tinnitus. Second, the investigation of and concentration on the psychometric, psychopathological and neural profiles of TI only, allows for due attention to be paid to the differences between TI. Along these same lines, Elgoyh et al. (2015, p. 639) emphasize that “studies with better patient stratification, and controlling for hearing loss, hyperacusis, distress, depression and tinnitus perceptual characteristics are needed”. Eventually, this approach will result in a classification of tinnitus subtypes. Third, by using a data-driven PCA approach, the analysis of behavioral data serves as a reliable platform from which to establish relationships between tinnitus-related pathophysiology and changes in EEG frequency bands along the entire power spectrum (Pierzycki et al., 2016; Meyer et al., 2014).

Even supposing that one carefully considers the above mentioned suggestions it is not guaranteed that a simplified study design only including TI will yield replicable results as long as data recording and analysis do not concur with established and standardized procedures. The present study primarily aims at leaping forward into this direction in that it re-enacts former studies while it systematically minimizes conceptual and methodological error sources to enhance comparability between past and present data.

### The present study

The present situation in tinnitus research is unsatisfactory because a number of different studies have used resting-state EEG to identify oscillatory modulations, and have reported either heterogeneous (De Ridder et al., 2011b; Joos et al., 2012; Meyer et al., 2014; Moazami-Goudarzi et al., 2010; Ortmann et al., 2011; Van der Loo

et al., 2009, 2011; Vanneste et al., 2010a, 2014b,a; Zobay et al., 2015) or nil results (Pierzycki et al., 2016). To overcome the unsatisfactory inconsistency between tinnitus-related neurophysiological studies (which provide the bases for many tinnitus network models), we believe that it is of the utmost importance to replicate and to confirm previous results as provided by other labs, rather than continuously producing new studies, data, and models that generate more questions than answers. Hence, we decided to tackle one topic by re-enacting a former neurophysiological study (Joos et al., 2012) that addressed the relationship between tinnitus-related distress and depression. For this purposes we compiled a sample of TI with similar psychopathological profiles. Clinically pertinent prevalences of depressive and anxiety disorders were noted consistently in TI populations (Loprinzi et al., 2013; Zöger et al., 2001; Weidt et al., 2016). However, it should be emphasized that tinnitus-related distress must not be automatically equated with the umbrella term depression. We think it is mandatory to propose that tinnitus-related distress aggregates cognitive, somatic and emotional aspects. Both depression and distress are well operationalized and standardized concepts that can be empirically and behaviorally quantified in subjective, chronic tinnitus. Recent approaches using power spectrum analysis have attempted to correlate measured psychopathology of depression and distress with specific changes of oscillations in either distinct or a selection of frequency-bands (De Ridder et al., 2011b; Joos et al., 2012; Song et al., 2013a; Van der Loo et al., 2011; Vanneste et al., 2010a, 2014a; Weisz et al., 2004, 2005). As these studies suggest, it can be concluded that even high distress may be completely independent from depression (De Ridder et al., 2011b; Joos et al., 2012; Van der Loo et al., 2009; Vanneste et al., 2014a) and may be the most pertinent factor for predicting psychological and somatic disturbance in TI (Vanneste et al., 2010a).



One previous study that explicitly addressed this question observed the recruitment of distinct neural circuits tied to depression and distress in the tinnitus brain (Joos et al., 2012). In this study, a source estimation using sLORETA revealed a correlation between distress and modulations in the  $\alpha$ - and  $\beta$ -bands over the right frontopolar and orbitofrontal regions, and changes in the  $\beta$ 2-band activity originating from the anterior cingulate cortex. According to these results, behavioral measurements of depressive symptoms were more strongly associated with increased activity in the  $\alpha$ 2-band over the left frontopolar and orbitofrontal cortex. Additionally, both distress and depression were linked to activity in the  $\beta$ 3-band originating from the parahippocampal area. To learn more about the relationship between distress and depression in tinnitus we re-enacted this study by investigating a sample of TI who also underwent resting-state EEG. Principal conditions and parameters of the study by Joos et al. (2012) were fairly well matched in psychopathology (distress and depression) and psycho- and audiometrics (tinnitus duration since onset, peripheral hearing loss) and to a lesser degree age and number of participants. Unlike the former study, we applied high-density EEG with 64 channels. Our psychometric toolbox comprised standard questionnaires on tinnitus experience, distress, depression, and other health and psychometric details. Akin to previous studies (Meyer et al., 2014; Pierzycki et al., 2016), we used a principal component analysis (PCA) to identify the independent dimensions underlying our comprehensive, psychometric



data. The advantage of this procedure was that it avoided the need for a priori constraints regarding latent relationships between behavioral variables.

With respect to the heterogeneity of previous results, we formulate our predictions with care. First, we hypothesize that the PCA would identify independent dimensions for distress and affective disorders (mainly depression) based on behavioral data within the TI population. Second, we predict a significant positive relationship between the two aspects and corresponding distinct neural signatures for depression and distress as elicited by a source estimation approach (sLORETA). This reasoning is based on the previous results of Joos et al. (2012), who reported separate activation clusters for the differential psychopathological aspects.

## 2 Results

### 2.1 Behavioral data

We correlated measures of depression (“Beck’s Depression Inventory”, BDI Hautzinger et al. 1995) with measures of tinnitus-related distress as elicited through the “Tinnitus Questionnaire” (TQ Goebel and Hiller 1998b) and a numeric rating scale (NRS).

First, we observed a significant correlation between BDI and TQ ( $r=.422$ ,  $p < .01$ ). Furthermore, a significant correlation was obtained between TQ and distress as measured by the NRS ( $r=.41$ ,  $p < .05$ ). No significant correlations were found between the TQ and age, tinnitus duration, tinnitus laterality or tinnitus type, and neither the BDI nor the NRS produced any significant correlations with these variables.

#### 2.1.1 PCA

To further explore the interplay between the domains of affective disorders and tinnitus-related distress, we performed a PCA on various psychometric scores. For a complete list of the included questionnaires and variables the reader is referred to the “Experimental Procedure” section or Table 1.

The threshold for the loading of the variables on the components was set to  $< 0.32$  according to recommendations and guidelines by Backhaus et al. (2006). Use of the Kaiser-Meyer-Olkin measure (KMO) verified the sampling adequacy for the analysis with  $KMO=.615$ . Bartlett’s test of sphericity indicated that correlations between measures were sufficiently large for a PCA ( $p < .001$ ) (Backhaus et al., 2006). The extracted components were rotated using Promax rotation with Kaiser normalization. Promax rotation was chosen due to the generally high correlations between variables. The exploratory use of the Varimax rotation method, which is better suited for uncorrelated variables, did not produce qualitatively differing results.

The PCA revealed 6 components with eigenvalues  $> 1$ , and the scree plot showed an inflexion which justified the retention of 6 components. In total the 6 components accounted for 76.4 percent of the total variance. Table

1 shows the resulting pattern matrix.

– Please insert Table 1 near here –

Component 2 revealed itself to be of primary interest with respect to distress, and was termed the “Tinnitus Distress” (TD) as all tinnitus questionnaires, TQ subscores (except for sleeping disturbances and auditory perceptual difficulties), and a nonverbal self-evaluation for pictorial representation of illness and self measure (PRISM), Buchi et al. 1998a conglomerated on this component. It is noteworthy that the distress NRS did not load on the TD. Several variables amassed in component 1, including BDI, BAI, SCL, the psychological domain of SF, and the WHOQOL-BREF without its subdomain of social relationships. This component could be termed “Affectional Disorders, Health and Quality of Life” (AHQ). The remaining components are not covered as they are not relevant to the scope of this article. TD and AHQ were then used for correlation analyses with whole-brain and ROI EEG data analogously to the TQ total score.

## 2.2 EEG data

In the sLORETA whole-brain analysis, TQ showed a positive correlation in the  $\beta_1$ -band over the right posterior intra- and peri-Sylvian regions ( $r=.567$ ,  $p < 0.05$ , TAL  $x=54$ ,  $y=-42$ ,  $z=25$ , Talairach and Tournoux 1988). Table 2 indexes the sLORETA-based cluster of significant activity ( $p < .05$ ) comprising of 15 significant, adjacent voxels.

– Please insert Table 2 near here –

The cluster of significant voxels (TQ) covers parts of the inferior parietal lobule, posterior insula, supramarginal gyrus, planum parietale, and superior temporal gyrus (Brodmann areas 13, 40, 41). For other psychopathological measurements, namely NRS, BDI and BAI, we noted no significant correlations.

Tables 3-8 show the results of the correlation analysis with the selected ROIs. More specifically, Tables 3, 5, and 7 list the bivariate correlations between TD, TQ, and BDI with activity in the three selected ROIs. Anatomical labelling was performed by assigning xyz-coordinates to anatomical regions based on application of the stereotactic atlas of Talairach and Tournoux (1988). Accordingly the ROIs were labelled as the posterior insula (pINS, BA 13), the posterior peri-Sylvian region (pPSR, BA 40), and the posterior auditory-related cortex (pARC, BA 41). Tables 4,6 and 8 present the results of the reciprocally corrected partial correlations between TD, TQ and BDI, respectively, within both INS and PSR. In the context of the present ROI analysis, we focused on the partial correlations because we were interested in the pure relations between TD and TQ with EEG activity, respectively. Significant correlations between distress-related measures at the level of  $p < .01$  were only observed for the  $\beta_1$ -band ( $r = .412$ ) over INS (Table 4, TD) and for the  $\beta_1$ - ( $r = .449$ ) and  $\beta_2$ -bands ( $r = .395$ ) over INS (Table 6, TQ).

– Please insert Table 3-8 near here –



### 3 Discussion

Spectral power analysis of resting-state EEG in subjective tinnitus has provided a plethora of data that describe changed patterns in neural oscillations throughout several frequency bands. An excellent overview about studies that have observed EEG oscillations deviating from the normal EEG pattern is provided by Elgoyhen et al. (2015) (supplementary information S1). In short, many authors have observed enhanced or decreased EEG activity in the  $\delta$ -,  $\theta$ -,  $\alpha$ -,  $\beta$ - and  $\gamma$ -bands either in studies comparing TI with CO, contrasting sub-types of tinnitus, or correlating behavioral measures with neurophysiological data. However, it is not yet understood whether changes in distinct frequency bands can be specifically interpreted. At present, a universal model that convincingly determines the functional roles of distinct frequency bands in tinnitus is lacking. Of particular difficulty with respect to tinnitus, findings that contradict and conflict with each other far outnumber those that complement and harmonize. It has become the standard approach to suggest that a multitude of concepts (e.g., heterogeneity between TI and CO; severity of tinnitus; measurement of differential psychopathological aspects), psychometric (age; hearing loss, duration, tinnitus intensity), and methodological differences (number of investigated patients; different software packages for EEG data acquisition/analyses or different handling of the same software package) account for the discrepancies in results between EEG resting-state studies, rendering them not comparable. Unfortunately, the discrepancy between studies will continue to grow steadily as long as labs and groups persist in using their favored experimental setting, software, TI database etc..

A first possible solution for this dilemma would be the mandatory requirement to use approaches aimed at maximum comparability between studies, and seeking to re-enact studies and to replicate data. This should be considered a necessary step before the (hopefully) replicated pattern of results from various studies can be interpreted and in consequence solid models can be developed. Second, we consider it prudent to undertake further steps towards minimizing variability and unwanted noise by controlling as many conceptual, psychometric, and experimental aspects as possible.

The present study sought to take our own recommendations into consideration by performing two principal actions. First, we conceive it imperative to adhere to recently proposed guidelines for experimental resting-state EEG protocols in tinnitus research. For this purpose we refer to a document recently released by an European tinnitus initiative that is meant to establish standardized experimental procedures ([http : //tinnet.tinnitusresearch.net/images/Standardisation\\_Report\\_v5.pdf](http://tinnet.tinnitusresearch.net/images/Standardisation_Report_v5.pdf)). Second, we re-enacted a former study by uptaking the same conceptual research question based on a similar sample of TI and comparable procedures. Accordingly, we identified a recent study that was relatively straightforward to replicate (Joos et al., 2012). In it, tinnitus-related distress and depressive symptoms were disentangled based on behavioral and neurophysiological data. The analysis revealed two different neural networks that appeared to correlate with the two psychological disturbances; a correlation between distress and modulations in the  $\alpha$ - and  $\beta$ -bands over the right frontopolar and orbitofrontal regions, and changes in the  $\beta$ 2-band activity originating from the anterior cingulate cortex was revealed using sLORETA. According to these results, behavioral measurements of depressive symptoms were

more strongly associated with increased activity in the  $\alpha 2$ -band over the left frontopolar and orbitofrontal cortex. Our findings are similar to the findings of Joos et al. (2012) in that the depression scores are moderately correlated with tinnitus-related distress which comes as no surprise. However, the PCA we applied conglomerated several questionnaires and subscales to a tinnitus-related distress factor (TD) that is distinct (but not independent,  $r=0.46$ ,  $p<0.01$ ) from another factor which is mainly attributable to depressive mood, health and quality of life (AHQ). With respect to the neurophysiological data, we noted partial differences in our pattern when compared to that of Joos et al. (2012). The whole-brain analysis laid bare a significant cluster comprised of 15 voxels that correlate with tinnitus-related distress, and covers the right posterior intra- and peri-Sylvian regions. These 15 voxels can be assigned to three ROIs, namely pINS (BA 13), pPSR (BA 40), and pARC (BA 41), which we used in a post hoc test akin to the former study. Separate correlations between TD and TQ, respectively, and neural oscillations exposed a number of significant values in these ROIs, most prominently in the lower  $\beta 1$ -band (13-21 Hz). No voxels that correlate with measurements of depression were found.

These differences notwithstanding, we note that Joos et al. (2012) also observed modulations in the lower  $\beta$ -band and in the adjacent upper  $\alpha$ -band, which might indicate that the studies did indeed tap the same pathological mechanisms. The same observation holds true for a study done by Vanneste et al. (2010a), who reported increased  $\alpha$ - and  $\beta$ -activity as a function of distress, and presumably originating from the dorsal anterior cingulate cortex. Stronger  $\beta$ -activity in TI with high distress scores was also revealed in our previous study, occurring mostly over the frontal electrodes (Meyer et al., 2014). However, it should be mentioned that this study was computed based solely on topographical maps. A source estimation approach did not yield any significant results. The compilation of these studies potentially lends credence to the proposal that the  $\beta$ -band plays a prominent role in TI with high distress, even though the studies differ with respect to the source estimation solutions that they provide. We think that the aforementioned differences in the application of the source estimation and the inherent heterogeneity of the TI population may account for this discrepancy, while the increase of  $\beta$ -oscillations appears to be the lowest common denominator. Even though a widely accepted model that predicts and delineates changes in distinct EEG frequency bands as a function of tinnitus experience has yet to be developed we think that at least there is a consensus that rapidly modulating frequencies (higher *alpha*, *beta*, and lower *gamma*) reflect excitatory neural activity. Whereas De Ridder et al. (2014) suggest that the increase of  $\beta$ -activity in medial frontal brain regions is related to a noise-cancelling mechanism, we prefer not to provide any interpretation as long as reliable replications of frequency-band based source estimation results are not at hand. This reservation notwithstanding we would like to mention that our result of a correlation between tinnitus-related distress and insular *beta*-band activity is to some extent unsurprising, as it has already been suggested that this region is a major hub, which binds together auditory and affective sensations (De Ridder et al., 2014). The insula has frequently been nominated as a key component of the tinnitus network due to the unique anatomical situation of this region, which facilitates integration across multiple domains, including social, emotional, and attentional systems (Chiarello et al., 2013). Backing evidence for a

relationship between tinnitus-related distress and insular morphology comes from a recent study using structural surface-based imaging (Meyer et al., 2016). However, we refrain from a comprehensive discussion of its tinnitus-related role because we strongly think that further studies which will replicate our results are needed. Our reluctance is even more justified as the insula can be functionally and neuroanatomically be divided into an anterior and a posterior part. The standardized ROI we used (BA 13, approximated in sLORETA voxel space) lacks a subdivision to segment the insula into an anterior and a posterior part which makes it impossible to settle upon firm conclusions in this matter. We were unsurprised to find that voxels in the vicinity of the retro-insular cortex cover auditory-related regions in the peri-Sylvian regions. The nature of tinnitus is such that auditory and nociceptive sensations mediated by the insula become amalgamated, eventually resulting in tinnitus-related distress (De Ridder et al., 2015). The reasoning behind this is compelling as the auditory cortex and the insula are not only situated in direct vicinity, they are also densely interconnected (Bamiou et al., 2003; Ardila et al., 2014) and belong to the same network in the tinnitus brain (Husain and Schmidt, 2014). Albeit of our aforementioned reservations towards the interpretability of our sLORETA results we would like to comment our finding. In our study, we observed correlations between distress measurements and  $\beta$ 1-activity over insular and peri-auditory regions, which may imply that the chronic noise generated by the auditory cortex becomes more and more salient and intrudes successively via the insular circuits into the awareness of some TI (De Ridder et al., 2011a), but not of others.

Interestingly, we did not observe significant relationships between depressive scores and neural oscillations. This finding supports previous articles that have proposed a difference of neural circuits underlying tinnitus-related distress and depression. While the former appears to be the specific signature of discomfort in the tinnitus brain, the latter may be a minor aspect too diffuse and multifactorial to be traced to stable and measurable neural underpinnings. An exploration of the differences and similarities between study designs and outcomes between the current study and that done by Joos et al. (2012) provides the context for further interpretation of our data. First, we report a smaller sample size ( $n=45$  vs.  $n=56$ ), a younger cohort (mean age=42.78, SD=11.97 vs. mean age=54.74, SD=14.49), and a skewed female-to-male ratio (11/34 vs. 29/27) (see Table 9). Second, tinnitus characteristics diverged only slightly between the studies as duration (mean=82.71 months, SD=124.03 vs. mean=83.04, SD=114.12) and tinnitus laterality are comparable. A comparison of tinnitus laterality is not straightforward as only the number of cases of uni- and bilateral tinnitus are reported by Joos et al. (2012); nevertheless, both study samples exhibited a distribution considered common in the TI population (Lockwood et al., 2002). We could not obtain a sample of TI with narrow band noise type tinnitus only, however we doubt its involvement in tinnitus-related distress and depression networks in the brain. Differences in neural correlates of tinnitus types have been reported but are deemed irrelevant to the context here as distress networks seem to be unrelated to tinnitus type (Vanneste et al., 2010b). Regarding the main variables of interest, namely TQ and BDI scores, the data is comparable with a mean TQ score of 38 (SD=13.14) in our study, and 40.93 (SD=17.03) in the study by Joos et al. (2012). Both mean scores are in range of ‘moderately’ graded tinnitus

distress as suggested in the TQ (Goebel and Hiller, 1998a). A similar constellation can be seen in the case of depression scores with a BDI mean score of 9.36 (SD=8.13) vs. 10.95 (SD=9.73). Another psychometric aspect, namely peripheral hearing loss, would be really important to consider and discuss. Actually we cannot compare our results of hearing loss to the findings of Joos et al. (2012) because in this study it was assessed but not reported. The reporting of descriptive data regarding hearing loss would be advantageous so as to better explore any influence it may have on brain activity (Humes et al., 2012). At present, however, it appears that distress is not tightly linked to hearing loss and, thus, is probably not directly related to the deafferented and dysfunctional auditory system. Furthermore, it would be applicable to integrate all relevant variables, including hearing loss, in correlational analyses (here, partial correlations) and/or advanced statistical models (e.g., multiple regression), especially when working with neurophysiological data. Despite the numerous small differences indicated between the studies, we remain convinced that our approximation of all possible instruments and analysis steps to those of the former study should enable a comprehensive comparison of the results. As tangible and similar as the results are in the domain of psychometry, they quickly become incongruent with respect to the whole-brain and subsequent ROI correlational analyses. At the very least we could report correlations in similar EEG frequency bands, most prominently in the  $\beta$ - and  $\alpha$ -bands. Regarding source localization in the whole-brain analysis, we noted a single significant positive correlation in the  $\beta_1$ -band for TQ over the right posterior peri- and intra-Sylvian region ( $r=.567$ ,  $p < 0.05$ ), which contrasts with the other study's manifold of significant clusters in the  $\alpha$ - and  $\beta$ -bands in frontopolar, orbitofrontal and pregenual anterior cingulate regions. In addition, significant whole-brain correlations for BDI, or distress NRS do not appear at all in our data, which further relativizes the positive findings for BDI and the confirmational validity of the parallel analysis of TQ and distress NRS in the former study (see Figures 2 and 3 of the original publication of Joos et al. (2012)).

Besides the common inherent heterogeneity of the TI population, the main differences between the studies are most probably to be found in the analysis of the EEG data, and to a lesser degree, in the EEG hardware and setting, including electrode density. Joos et al. (2012) applied a 19-channel MITSAR (Mitsar-201, NovaTech <http://www.novatecheeg.com/>) system whereas we used a 64-channel BrainAmp (Brain Amp DC, <http://www.brainproducts.com>) system. With certainty, the use of higher density electrode arrays is advantageous for producing precise and reliable source estimations (Michel et al., 2004). Nevertheless, we are restricted to speculation on this point as the positions of the clusters in the brain clearly diverge between studies, which certainly cannot be explained by a possible 'blurriness' of the source localization inversely related to the electrode count (Michel et al., 2004). It is our view that details about the EEG preprocessing steps and, more importantly, the exact details of the LORETA calculation options up to the visualization of the results are of utmost importance and should be reported transparently. For instance, details about electrode registration and in particular subsequent possible regularization of the transformation matrix for the inverse solution (i.e., source estimation), constituting the first steps in the LORETA pipeline, are already deemed as useful information. Generally, it is considered necessary to report the exact source estimation algorithm, either sLORETA (Pascual-Marqui, 2002a)

or eLORETA (Pascual-Marqui, 2007), and indicate the exact program version to avoid confusions. Looking at the frequency transformation of the data, we identify two issues: the window function cannot be defined and a boxcar window (i.e. no window) is automatically chosen by the software. Following common M/EEG guidelines (Keil et al., 2014) the window type and parameters, among other signal processing details, should be reported. Second, a “force average reference” option is checked per default so that preprocessed and possibly already average-referenced data may again be referenced to the average of all channels lowering the effective channel count by one. Looking at the built-in statistical toolbox, normalization and transformation of variables should be clearly reported as these parameters may lead to substantial differences in the results. Finally, we are puzzled as to why details of the resulting clusters (e.g., voxel count and distribution over several brain areas) have not been reported in previous studies (see Table 2). Following on from this, we lack information about visualization and color-coding thresholds in the presented LORETA data, and therefore can only guess at the extent, maximum and gradients of the clusters of significant activation. We are well-aware, that not all of these suggestions have the same gravity in regards to source estimation and diverging results across studies, yet are convinced that also minor differences may influence results as in tinnitus research weak effects, nil findings and irreconcilable results are omnipresent. Finally, while not directly addressing the methodological comparison of the two studies but general validity of the applied source estimation, limitations of the method should be considered and properly discussed (Adjamian, 2014). Of central interest here, we identify the fact the standardized boundary element method volume conductor model behind the LORETA algorithm (Fuchs et al., 2002) is based on a standardized MNI brain template derived from a young, healthy cohort in their mid-twenties, which generally contrasts the mean age of the samples used in tinnitus studies (mean=42.78 years, in our study). Beyond that, individual differences in (local) morphology like in the peri-auditory regions (Marie et al., 2015; Rademacher et al., 2001) should also be considered as possibly confounding factors on the quality of source estimation. Alternative source estimation algorithms may also suffer from this limitation yet offer the possibility to apply individual or group templates, as, for example, implemented in the fieldtrip toolbox (Oostenveld et al., 2010). Cross-validation and joint use of the different algorithms within tinnitus research may be fruitful future proceedings towards reconciliation of results.

The strategy sketched above should be standardized and added to the guidelines issued by tinnitus research initiatives such as TINNET (<http://tinnet.tinnitusresearch.net/>) and become consensus to overcome the heterogeneity in findings. Given the wide application of the LORETA approach within tinnitus research but lack of replication studies, our proposal to standardize procedures, as similarly proposed for all aspects of M/EEG data acquisition and analysis in a recent paper (Adjamian et al., 2014), should then ease respective replication efforts, further the understanding of the complex tinnitus symptom, and allow the development of solid models based on findings across different research groups.

### 3.1 Limitations

The sample size of 45 was sufficient for our analysis but, compared to the study of Joos et al. (2012), fewer by 11 participants. Ideally, future studies would profit from the existence of a freely accessible database that accommodates behavioral and neurophysiological data of TI collected, pooled and provided by different centers (e.g. <https://www.tinnitus-database.de>).

BDI and BAI means are within range of the lower grades, or very mild symptoms (BDI: mean=9.36, SD=8.13, range=0-49(of 63); BAI: mean=10.2, SD=9.46, range=0-48(of 63)), which may explain the non-existent or weak significant effects in the correlations of these variables, particularly with the neurophysiological data. This reasoning is relevant to both the study at hand and the former study by Joos et al. (2012) (BDI: mean=10.95, SD=9.73).

ROI sizes are comparatively large and elongated (BA 13, 40, 41) with their current density activity averaged over all their voxels.

Within this study we only applied EEG in combination with the sLORETA approach. Various aspects of the validity and reliability of sLORETA analyses should be explored through the application of different M/EEG source estimation techniques, such as Beamformer (Adjamian et al., 2014), or be complemented by functional and (possibly) structural MRI.

### 3.2 Conclusions

The current study was primarily set out to test the reliability of resting-state EEG in a sample of TI with varying psychopathology. For this purpose we re-enacted a formerly published study that reported relationships between behavioral and neurophysiological data. We consider this approach as an important step towards a better understanding of the heterogeneity of TI and towards the development of solid models. Furthermore, the present study specifically addressed the relation between behaviorally measured distress and depressive disorder in the tinnitus brain. We partly succeeded in replicating the results of the former study. While we discovered comparable correlational patterns between behavioral measures of distress and depression as well as distress and  $\beta$ -band activity, we were not able to observe a correlation between depressive scores and neurophysiology. The overlap in behavioral results and frequency band correlations notwithstanding, our sLORETA-based results considerably differed in source estimation from the former study. A careful comparison of the conceptual, psychometric, and experimental aspects of the two studies indicates a high likelihood that, besides the identified and widely discussed heterogeneity of TI, primarily the applied EEG data analysis procedure and to a lesser degree the EEG hardware account for this difference. This outcome suggests that controlled replication of previous research is a necessary prerequisite to confirm results collected at different labs before comprehensive models of the tinnitus brain can be developed. This conclusion is of particular importance as it fits with the guidelines and adheres to the policy of the TINNET initiative (European Union COST Action BM1306, <http://tinnet.tinnitusresearch.net/>). Irrespective of these methodological and strategical considerations and in

agreement with previous studies, our behavioral and neural data partly add to the existing evidence that distress and depression should be conceived as distinct but not completely independent aspects of the tinnitus brain.

## 4 Experimental Procedure

### 4.1 Participants

We recruited a sample of 45 right-handed TI (11/34, female/male). Table 9 shows their demographics and clinical details. The lateralisation of tinnitus varied across the sample of participants and thus represents a common distribution amongst the TI population (Lockwood et al., 2002): 4 participants indicated a right-lateralized tinnitus, 5 a left-lateralized, 11 a central, 10 with a preference to the right side, 9 with a preference to the left side, 5 diffusely inside the head, and 1 participant in “some other place”. 34 participants indicated tonal tinnitus, 4 a noise-like tinnitus, and 7 participants a undefinable type. Tinnitus distress as assessed by the Tinnitus Questionnaire (TQ) ranged from 10 (slight) to 63 (very severe), ( $M = 38$ ,  $SD = 13.14$ ). No participants reported suffering from any mental and/or neurological disorders. Standard peripheral audiometry was performed by well-trained otolaryngologists starting at 125 Hz with pure tone presentation (in 5 dB steps) up to 8 kHz (i.e., 125, 250, 500, 1000, 2000, 4000, 6000, and 8000 Hz). The participants were comprehensively informed about the aim and rationale of the study. Without exception they all gave their written informed consent. The study was approved by the appropriate Ethics Committee (Kantonale Ethikkommission Project KEK-ZH-Nr. 2012-0324).

– Please insert Table 9 near here –

### 4.2 Questionnaires



A range of questionnaires was used to assess multiple psychopathological variables, namely depression, tinnitus-related distress, and other health and well-being aspects of life, according to the international guidelines of the Tinnitus Research Initiative (TRI, Langguth et al. 2007). To assess tinnitus-related information, a German adaption of the “Tinnitus Case History Questionnaire” (TSCHQ, Langguth et al. 2007) was used. Furthermore, the German adaptation of the “Tinnitus Questionnaire” (TQ, Goebel and Hiller 1998a) was applied to measure the tinnitus-related distress. The latter questionnaire comprises 52 statements which are judged on a three-point Likert scale (‘true’, ‘partially true’, ‘not true’). As well as a total score for tinnitus distress, we also derived six subscores (‘cognitive distress’, ‘emotional distress’, ‘intrusiveness’, ‘auditory perceptual difficulties’, ‘sleep disturbances’, and ‘somatic complaints’). Further, we used a “Numeric Rating Scale” (NRS, 0-10) as an additional validating device to illustrate the individual distress.





Symptoms of depression were measured by means of “Beck’s Depression Inventory” (BDI Hautzinger et al. 1995), which comprises 21 items that protocol the various symptoms of depression. The sum score of all items indicates the degree of depressive mood or clinically relevant depression. In addition, we used the “Beck Anxiety Inventory” (BAI, Beck et al. 1988) to assess for symptoms of anxiety in a similar fashion.

The PCA analysis was applied over a wider selection of tinnitus-related, well-being and quality of life questionnaires, as well as relevant items of the TSCHQ (“age”, “age of tinnitus onset”, “tinnitus awareness”, “tinnitus duration”, and “loudness”). In addition, we used the following sum and subscores from the “Tinnitus Handicap Inventory” (THI, Newman et al. 1996) and a short version of its German adaptation “Tinnitus Belastungs-Fragebogen” (TBF12, Greimel et al. 2000) to complement the tinnitus suffering assessment of TQ. Physical and psychological well-being were assessed with short forms of the “Symptom Check List” (SCL, Derogatis 1977) and “Health Questionnaire” (“Gesundheitsfragebogen”, SF, Bullinger and Kirchberger 1998). The short form of “WHO Quality of Life” (WHOQOL-BREF, WHOQoL Group 1998) covered general well-being and aspects of daily life. Finally, a subjective pictorial measuring tool was used to assess the individual tinnitus-related burden of suffering, or the place and the relation to the self the tinnitus occupies in one’s life “Pictorial Representation of Illness and Self Measure” (PRISM), Buchi et al. 1998b; Meyer et al. 2014; Peter et al. 2016). The parameter of interest is the distance between the “self” and the tinnitus representation in millimeters on the pictorial board.

### 4.3 EEG recordings

The recordings were made using a BrainAmp DC amplifier system in combination with a 64 active channel EasyCap electrode cap (BrainProducts, 2008). The array of electrodes corresponded with the 5/10 electrode position system (Oostenveld and Praamstra, 2001). Online recording was referenced against the FCz electrode. The sampling rate was set to 1000 Hz and impedances were kept below 5k $\Omega$ . Recordings were done in direct current (DC) mode with no online filters applied.

#### 4.3.1 Procedure

After giving their written informed consent, the psychometric data was obtained electronically from the participants at the Department of Otorhinolaryngology (University Hospital of Zurich) during clinical and audiometric evaluation. The participants were then seated upright in a comfortable chair for the EEG data acquisition. We collected EEG data during a standardized, vigilance-controlled, resting-state session in which participants were asked to alternately open (EO) and close (EC) their eyes for 20 and 40 seconds, respectively. An asterisk on the wall in front of the participant served as a fixation point in the EO condition. Participants were instructed to carefully avoid any body movements which may have had negative effects on the data quality. Presentation software (Neurobehavioral Systems, Inc., 2010) was used to control the playback of vocal EO and EC instructions. The total recording duration was 8 minutes, resulting in eight 40 second eyes closed (EC) segments and



eight 20 second EO segments.

## 4.4 Data analysis

### 4.4.1 Behavioral data and questionnaires

Statistics of the behavioral data were calculated using SPSS Version 22 (SPSS Inc., Chicago, IL). Pearson correlations and partial correlations between variables of interest were computed akin to the analysis of Joos et al. (2012). Additionally, all psychometric data were subjected to a PCA in order to identify latent variables in the data set.

### 4.4.2 Preprocessing of EEG data

Preprocessing of the EEG data was performed with BrainVision Analyzer 2 (BrainProducts, 2013). The data was bandpass-filtered with Butterworth zero-phase filters between 0.1 Hz and 100 Hz with a slope at the low cutoff of 24 dB/octave and a slope at the high cutoff of 48 dB/octave. As the alternating current hum had only minimal influence on the EEG signal, a 2nd order band rejection filter with a central frequency of 50 Hz and a bandwidth of 1 Hz was sufficient to eliminate the electrical interference. Bad channels were excluded following the standardized criteria (i.e., noise, drift or low activity). As a next step, an independent component analysis (ICA) was run with the whole data set by applying the restricted Infomax (Gradient) algorithm with classic sphering in 512 iterations. The resulting components (indicative of eye blinks and very few pulse artifact components) were removed from the data with the subsequent inverse ICA procedure. Next, excluded channels were (re-)interpolated using the spline-type topographical interpolation algorithm, through which the signal of a bad channel was estimated based on the activity of neighboring channels. An average reference (channel) was calculated and then applied. This included the implicit reference channel of the actual recording (i.e., Fcz), which was then reused in the subsequent analysis pipeline. After segmenting the data into the EC (sub-)conditions, and always discarding the first 3 seconds due to excessive artifacts caused by the transition from EO to EC, we extracted 8 segments with 37 seconds of EC recordings each, and then further subdivided these into 2-second segments. The last step in the EEG preprocessing pipeline was the semi-automatic rejection of remaining artifacts following the standardized criteria. On average, the artifact rejection procedure yielded 127.37 (SD=16.82) segments per participant.

#### 4.4.3 Source estimation based analysis of EEG

sLORETA Pascual-Marqui (2002b) was used to source-localize electric potentials to possible intracortical generators (LORETA software suite, version 20150303). Besides being an established source-localization algorithm throughout EEG neurophysiology (Yao and Dewald, 2005; Greenblatt et al., 2005), LORETA is also widely used in tinnitus-related EEG studies (e.g., (Song et al., 2013b; Vanneste et al., 2013a,b; Joos et al., 2012; Van der Loo et al., 2011; Vanneste et al., 2011, 2014b; Adamchic et al., 2014)). Technical details of power analysis and source estimation implemented in the LORETA software suite can be found in the respective sources (Pascual-Marqui, 2002b; Pascual-Marqui et al., 2011). The volume conductor model (of the brain) behind the sLORETA algorithm is described in Fuchs et al. (2002) and the integrated proper electrode position system in Jurcak et al. (2007). Standard electrode positions were registered using the integrated tool and no regularization was performed for the transformation matrix. Correlations with psychometric data were calculated using log-transformed sLORETA data in the frequency domain (i.e., FFT current density analysis). Besides the log-transformation of the EEG/sLORETA data, no normalization or any other transformation of variables was performed. Further, correlation analysis was performed between the psychometric variables and EEG on the whole-brain level. The use of statistical non-parametric methods yielded a differential activity map, which was corrected for multiple comparisons using a permutation based approach with 5000 iterations (Nichols and Holmes, 2002). Standard frequency bands were used ( $\delta$  (2-3.5 Hz),  $\theta$  (4-7.5 Hz),  $\alpha 1$  (8-10 Hz),  $\alpha 2$  (10-12 Hz),  $\beta 1$  (13-18 Hz),  $\beta 2$  (18.5-21 Hz),  $\beta 3$  (21.5-30 Hz) and  $\gamma$  (30.5-44 Hz)). For the post hoc ROI analysis, the averaged activity of BA 13, 40 and 41 over the right hemisphere was calculated. Pearson and partial correlations were used for the ROI analyses.

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Table 1: Pattern matrix of PCA

Component	AHQ <sup>a</sup>	TD <sup>b</sup>	3	4	5	6
Summed BDI/BAI score <sup>c</sup>	0.98					
BAI total score	0.976					
SCL Global Severity Index	0.95					
BDI total score	0.863					
SF psychological sum score	-0.818					
WHOQOL-BREF domain 1: physical	-0.705				0.374	
WHOQOL-BREF domain 2: psychological	-0.702					
WHOQOL-BREF global score	-0.455				0.443	
WHOQOL-BREF domain 4: environmental	-0.384					
TQ total score without APD <sup>d</sup>		0.942				
TQ total score		0.887				
TQ emotional distress		0.853				
TQ cognitive distress		0.843				
TQ intrusiveness	-0.367	0.741				
PRISM	-0.356	-0.672			-0.338	
TBF_12 sum score	0.521	0.632				
THI total score	0.476	0.628				
TQ somatic complaints		0.604			-0.451	
Tinnitus duration (months)			0.766	-0.385		
Tinnitus awareness (%)			0.736			
Tinnitus loudness (NRS, 0-100)			0.652			
Age of tinnitus onset				0.988		
Age			0.342	0.741		
SF physical sum score					0.766	
TQ auditory perceptual difficulties	-0.351		0.342		-0.412	
WHOQOL-BREF domain 3: social relationships					0.396	
Tinnitus distress (NRS)						0.837
TQ sleep disturbances						0.621

<sup>a</sup> = Affectional Disorders, Health and Quality of Life. <sup>b</sup> = Tinnitus Distress. <sup>c</sup> = sum score for the affective disorders derived from Leaver et al. (2011). <sup>d</sup> = TQ total score without the items for auditory perceptual difficulties derived from Schecklmann et al. (2013). BAI = Beck's Anxiety Inventory (Beck et al., 1988). BDI = Beck's Depression Inventory (Hautzinger et al., 1995). PRISM = Pictorial Representation of Illness and Self Measure (Buchi et al., 1998a; Peter et al., 2016). SCL = Symptom Check List (Derogatis, 1977). SF = "Gesundheitsfragebogen" (Bullinger and Kirchberger, 1998). TBF\_12 = "Tinnitus Belastungsfragebogen" (Greimel et al., 2000). THI = Tinnitus Handicap Inventory (Newman et al., 1996). TQ = Tinnitus Questionnaire (Goebel and Hiller, 1998a). WHOQOL-BREF = WHO Quality of Life (WHOQoL Group, 1998).

Table 2: sLORETA cluster of significant positive correlations between TQ and  $\beta 1$ -activity in whole brain analysis ( $p < .05$ )

Anatomical Label	BA	x	y	z	r
post. Insula	13	50	-38	20	.562
		45	-38	20	.540
		45	-33	20	.537
post. intra-Sylvian Fissure	13	50	-43	21	.540
Superior Temporal Gyrus	41	45	-33	15	.536
		45	-33	11	.517
Supramarginal Gyrus / Inferior Parietal Lobe	40	59	-47	25	.521
		59	-42	25	.533
		54	-47	25	.517
		54	-42	25	.567
		54	-42	30	.517
		59	-42	30	.546
		64	-42	30	.518
		59	-37	30	.536
	40	-37	39	.515	

Coordinates of the single voxels refer to the Co-Planar Stereotaxic Atlas of Talairach and Tournoux (1988). r = correlation coefficient.



Table 3: Correlations of distress using tinnitus distress (TD) for specific regions and frequency bands of interest

post. insula (BA 13)	$\delta$	$\theta$	$\alpha 1$	$\alpha 2$	$\beta 1$	$\beta 2$	$\beta 3$	$\gamma$
r	.200	.259	.131	.317*	.383**	.330*	.302*	.328*
p	.188	.296	.390	.034	.009	.027	.044	.028
post. PSR (BA 40)	$\delta$	$\theta$	$\alpha 1$	$\alpha 2$	$\beta 1$	$\beta 2$	$\beta 3$	$\gamma$
r	.252	.147	.072	.282	.352*	.306*	.291	.291
p	.095	.334	.636	.060	.018	.041	.052	.052
post. ARC (BA 41)	$\delta$	$\theta$	$\alpha 1$	$\alpha 2$	$\beta 1$	$\beta 2$	$\beta 3$	$\gamma$
r	.142	.083	.061	.327*	.306*	.277	.290	.266
p	.353	.586	.690	.029	.041	.065	.054	.077

r = correlation coefficient (pearson). p = p-value of the correlation. \*\* =  $p < 0.01$ , \* =  $p < 0.05$ .

Table 4: Partial correlations of distress using tinnitus distress (TD) controlling for BDI for specific regions and frequency bands of interest

post. insula (BA 13)	$\delta$	$\theta$	$\alpha 1$	$\alpha 2$	$\beta 1$	$\beta 2$	$\beta 3$	$\gamma$
r	.140	.123	.061	.375*	.412**	.324*	.306*	.270
p	.365	.426	.693	.012	.005	.032	.043	.076
post. PSR (BA 40)	$\delta$	$\theta$	$\alpha 1$	$\alpha 2$	$\beta 1$	$\beta 2$	$\beta 3$	$\gamma$
r	.105	.022	-.047	.296	.249	.207	.226	.149
p	.498	.885	.763	.051	.103	.178	.139	.335
post. ARC (BA 41)	$\delta$	$\theta$	$\alpha 1$	$\alpha 2$	$\beta 1$	$\beta 2$	$\beta 3$	$\gamma$
r	.065	.064	.000	.370*	.300*	.263	.284	.199
p	.677	.682	.998	.013	.048	.085	.062	.196

r = correlation coefficient (pearson). p = p-value of the correlation. \*\* =  $p < 0.01$ , \* =  $p < 0.05$ .

Table 5: Correlations of distress using TQ for specific regions and frequency bands of interest

post. insula (BA 13)	$\delta$	$\theta$	$\alpha 1$	$\alpha 2$	$\beta 1$	$\beta 2$	$\beta 3$	$\gamma$
r	.151	.243	.211	.300*	.424*	.398*	.348*	.335*
p	.322	.107	.164	.045	.004	.007	.019	.024
post. PSR (BA 40)	$\delta$	$\theta$	$\alpha 1$	$\alpha 2$	$\beta 1$	$\beta 2$	$\beta 3$	$\gamma$
r	.255	.253	.201	.308*	.427**	.398**	.322*	.346*
p	.091	.093	.185	.039	.003	.007	.031	.020
post. ARC (BA 41)	$\delta$	$\theta$	$\alpha 1$	$\alpha 2$	$\beta 1$	$\beta 2$	$\beta 3$	$\gamma$
r	.140	.161	.141	.341*	.346*	.315*	.327*	.305*
p	.358	.289	.355	.022	.020	.035	.028	.042

r = correlation coefficient (pearson). p = p-value of the correlation. \*\* =  $p < 0.01$ , \* =  $p < 0.05$ .

Table 6: Partial correlations of distress using TQ controlling for BDI for specific regions and frequency bands of interest

post. insula (BA 13)	$\delta$	$\theta$	$\alpha 1$	$\alpha 2$	$\beta 1$	$\beta 2$	$\beta 3$	$\gamma$
r	.090	.219	.157	.345*	.449**	.395**	.353*	.281
p	.560	.154	.308	.022	.002	.008	.019	.064
post. PSR (BA 40)	$\delta$	$\theta$	$\alpha 1$	$\alpha 2$	$\beta 1$	$\beta 2$	$\beta 3$	$\gamma$
r	.124	.158	.113	.319*	.345*	.322*	.266	.229
p	.421	.307	.465	.035	.022	.033	.081	.135
post. ARC (BA 41)	$\delta$	$\theta$	$\alpha 1$	$\alpha 2$	$\beta 1$	$\beta 2$	$\beta 3$	$\gamma$
r	.071	.151	.095	.376*	.341*	.303*	.322*	.248
p	.648	.328	.538	.012	.023	.046	.033	.105

r = correlation coefficient (pearson). p = p-value of the correlation. \*\* =  $p < 0.01$ , \* =  $p < 0.05$ .

Table 7: Correlations of depression using BDI for specific regions and frequency bands of interest

post. insula (BA 13)	$\delta$	$\theta$	$\alpha 1$	$\alpha 2$	$\beta 1$	$\beta 2$	$\beta 3$	$\gamma$
r	.167	.110	.167	-.030	.041	.098	.068	.202
p	.274	.474	.273	.845	.787	.524	.657	.183
post. PSR (BA 40)	$\delta$	$\theta$	$\alpha 1$	$\alpha 2$	$\beta 1$	$\beta 2$	$\beta 3$	$\gamma$
r	.354*	.274	.241	.045	.306*	.279	.204	.361
p	.017	.068	.111	.771	.041	.064	.179	.154
post. ARC (BA 41)	$\delta$	$\theta$	$\alpha 1$	$\alpha 2$	$\beta 1$	$\beta 2$	$\beta 3$	$\gamma$
r	.183	.059	.131	-.001	.090	.099	.085	.201
p	.228	.702	.389	.994	.556	.520	.580	.185

r = correlation coefficient (pearson). p = p-value of the correlation. \*\* =  $p < 0.01$ , \* =  $p < 0.05$ .

Table 8: Correlations of depression using BDI controlling for TQ for specific regions and frequency bands of interest

post. insula (BA 13)	$\delta$	$\theta$	$\alpha 1$	$\alpha 2$	$\beta 1$	$\beta 2$	$\beta 3$	$\gamma$
r	.115	.008	.088	-.181	-.167	-.085	-.093	.071
p	.458	.960	.569	.240	.277	.585	.549	.646
post. PSR (BA 40)	$\delta$	$\theta$	$\alpha 1$	$\alpha 2$	$\beta 1$	$\beta 2$	$\beta 3$	$\gamma$
r	.281	.191	.175	-.099	.153	.133	.079	.253
p	.065	.215	.255	.523	.321	.388	.610	.098
post. ARC (BA 41)	$\delta$	$\theta$	$\alpha 1$	$\alpha 2$	$\beta 1$	$\beta 2$	$\beta 3$	$\gamma$
r	.138	-.011	.080	-.170	-.066	-.040	-.062	.084
p	.371	.945	.605	.270	.672	.797	.689	.588

r = correlation coefficient (pearson). p = p-value of the correlation. \*\* =  $p < 0.01$ , \* =  $p < 0.05$ .

Table 9: Participant Characteristics

	Mean	SD <sup>a</sup>	Median	Minimum	Maximum
Age (years)	42.78	11.97	43	23	65
Tinnitus duration (months)	82.71	124.03	28	2	708
Age of tinnitus onset (years)	35.58	12.94	34	5	60
TQ total score (0-84)	38.00	13.14	38	10	63
BDI total score (0-63)	9.36	8.13	8.00	0	49
BAI total score (0-63)	10.20	9.46	7.00	0	48
NRS distress	4.8	1.86	6	1	9
Tinnitus loudness (NRS, 0-100)	48.16	28.32	50	5	100
Hearing loss (both ears, dB)	19.75	13.55	15	3.13	56.25

a. SD=Standard Deviation.

Study dissociates tinnitus-related distress and affective disorders with EEG.

Replication attempt of previous study with better spatial resolution.

Proposition of standards for homogenous reporting of LORETA in tinnitus.

Extension and evaluation of psychopathological data with assumption-free methods.