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Research paper

Whole scalp resting state EEG of oscillatory brain activity shows no parametric relationship with psychoacoustic and psychosocial assessment of tinnitus: A repeated measures study



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ABSTRACT

Tinnitus is a perception of sound that can occur in the absence of an external stimulus. A brief review of electroencephalography (EEG) and magnetoencephalography (MEG) literature demonstrates that there is no clear relationship between tinnitus presence and frequency band power in whole scalp or source oscillatory activity. Yet a preconception persists that such a relationship exists and that resting state EEG could be utilised as an outcome measure for clinical trials of tinnitus interventions, e.g. as a neurophysiological marker of therapeutic benefit. To address this issue, we first examined the test-retest correlation of EEG band power measures in tinnitus patients ($n = 42$). Second we examined the evidence for a parametric relationship between numerous commonly used tinnitus variables (psychoacoustic and psychosocial) and whole scalp EEG power spectra, directly and after applying factor reduction techniques. Test-retest correlation for both EEG band power measures and tinnitus variables were high. Yet we found no relationship between whole scalp EEG band powers and psychoacoustic or psychosocial variables. We conclude from these data that resting state whole scalp EEG should not be used as a biomarker for tinnitus and that greater caution should be exercised in regard to reporting of findings to avoid confirmation bias. The data was collected during a randomised controlled trial registered at ClinicalTrials.gov (Identifier: NCT01541969).

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1. Introduction

Many studies are published based upon the premise that the phantom percept of tinnitus can be evaluated by measuring brain derived electromagnetic oscillations (Eggermont and Tass, 2015). Linas' et al. (Llinas et al., 1999) proposition that thalamo-cortical

dysrhythmia (TCD) is a general theory for a host of neurophysiological symptoms, has often been invoked by those studying tinnitus. TCD provides a clear prediction of increased power in low frequency (theta, 5–10 Hz) and high frequency (gamma, 25–50 Hz) oscillations. Changes in band power are proposed to be a consequence of reduced incoming signal to the thalamus or due to an overall increase of inhibitory signals to the thalamus. The theta band is proposed to be mediated by Ca^{2+} low threshold spike bursts. With no other input, neighbouring deafferented thalamo-cortical loops become self-entrained with one another and emanate low frequency, theta-band waves of neural activity independent of external input. The postulated impact of thalamic theta-band entrainment on connected cortical regions is that there is a reduction of lateral inhibition and an unopposed increase in neural activity at the edges of the affected area. This *edge effect* generates an increased gamma-band oscillation which is the second prediction of TCD.

Abbreviations: BAI, Beck's Anxiety Inventory; BDI, Becks Depression Inventory; CI, Confidence Interval; EEG, electroencephalography; EMG, Electromyography; ICC, Intraclass correlation; MEG, Magnetoencephalography; NHS, National Health Service; PCA, Principle Component Analysis; TCD, thalamo-cortical dysrhythmia; TFI, Tinnitus Functional Index; THI, Tinnitus Handicap Inventory; THQ, Tinnitus Handicap Questionnaire; WHOQOL-BREF, World Health Organization Quality of Life

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1.1. Tinnitus-related low-frequency oscillations: delta and theta

Increases in theta-band (4–8 Hz)² power are sometimes reported in the tinnitus literature (De Ridder et al., 2011; Moazami-Goudarzi et al., 2010). Slower oscillations, in the delta band (1–4 Hz)² are often considered theoretically equivalent to the original theta-band postulation. Indeed, tinnitus associated increases in delta band power have been reported (Adamchic et al., 2012, 2014; Adjamian et al., 2012; De Ridder et al., 2011; Moazami-Goudarzi et al., 2010; Weisz et al., 2007) since the original work of Weisz et al. (Weisz et al., 2005). Nevertheless, these findings are not corroborated by a roughly equal number of studies examining EEG/MEG band-power related to tinnitus (Ashton et al., 2007; De Ridder et al., 2011; Hebert et al., 2011; Lorenz et al., 2009; Meyer et al., 2014; Ortmann et al., 2011; Pawlak-Osinska et al., 2013; Schlee et al., 2014; Vanneste et al., 2010). At least two studies have reported significantly reduced delta-band power related to tinnitus both during sleep (Hebert et al., 2011) and awake (Pawlak-Osinska et al., 2013). The key reference for increases in tinnitus related delta-band power is that of Weisz et al. (2005) and the study reveals group level, whole scalp differences in power spectra between a heterogenous group of people with tinnitus and hearing loss and a matched normal hearing control group. Subsequent studies rarely show such clear differences but implicitly support the dominant view that low-frequency oscillations relate to tinnitus. Vanneste et al. (2011) for example emphasize that those experiencing unilateral tinnitus show increased delta power compared to those experiencing bilateral tinnitus. Yet there is no comment on either the counter-intuitive direction of the finding, nor comment on the lack of significant difference of either sub-group with the normative data. Although no difference to normative data is found, Tass et al. (2012) describe the findings of Vanneste et al. (2011) as “EEG abnormalities” and select only bilateral tinnitus patients for analysis of delta power in auditory cortex. Moreover, the rationale for invoking the Vanneste et al. (2011) study to exclude the sub-group with the largest supposed pathological delta power is not described. Several large-scale studies using EEG data collection have omitted to report whole scalp power spectra (Vanneste et al., 2014, 2015). Our own group has reported increased delta-band power related to tinnitus but only after controlling for confounding factors such as hearing loss (Adjamian et al., 2012). However, prior to utilizing such biomarkers in clinical research, an objective examination of their relationship to tinnitus should be employed so that findings can inform interpretations about causality.

1.2. Tinnitus-related intermediate-frequency oscillations: alpha

Although the TCD model focuses on high and low frequency oscillatory changes, reduced intermediate-frequency alpha (8–12 Hz)² oscillations have also been observed in TCD (Llinas et al., 1999). Several studies reported reduced alpha frequencies in tinnitus populations compared to control (Adamchic et al., 2014; Schlee et al., 2014; Weisz et al., 2005, 2007). Numerous studies have failed to replicate this finding (Adjamian et al., 2012; Ashton et al., 2007; Hebert et al., 2011; Lorenz et al., 2009; Meyer et al., 2014; Moazami-Goudarzi et al., 2010; Ortmann et al., 2011; Tass et al., 2012; Vanneste et al., 2011, 2010). Null findings are rarely highlighted and additional analysis often undertaken enabling authors to report positive findings. For example Lorenz et al. (2009) reported only differences in the ratio of gamma to alpha power between groups but no differences in alpha power between groups.

However this observation may be due to mathematical artefacts (Zobay et al., 2015), and recent studies reporting reduced alpha band have not sought to replicate the ratio effect.

1.3. Tinnitus-related high-frequency oscillations: beta and gamma

The mixed findings described for low-frequency oscillations are also observed in relation to high-frequency oscillations. Numerous studies report null effects in both beta (12–30 Hz)² and gamma (30–100 Hz)² bands (Adjamian et al., 2012; Hebert et al., 2011; Lorenz et al., 2009; Meyer et al., 2014; Schlee et al., 2014; Weisz et al., 2005). Some studies report tinnitus-related effects in both bands (Adamchic et al., 2014; De Ridder et al., 2011), others in only beta band (Moazami-Goudarzi et al., 2010; Pawlak-Osinska et al., 2013) and others in only gamma band (Ashton et al., 2007; Ortmann et al., 2011; Weisz et al., 2007).

1.4. Summary and present study

Overall there is a contradiction between the theoretical assumptions and empirical data. Alpha bands are relatively rare in showing tinnitus-related effects. However, where the model suggests tinnitus-related changes in high and low frequency bands, there are approximately equal numbers of studies reporting both positive and null effects, with null results rarely highlighted. In spite of this uncertainty, clinical trials of tinnitus are utilising EEG power spectra as outcome measures, e.g. (Adamchic et al., 2012), clinicaltrials.gov identifiers: NCT02383147, NCT00926237 and NCT01541969.

We conducted whole-brain EEG sensor-based analysis on 42 participants with chronic tinnitus before and after a 12-week intervention (intervention $n = 20$; placebo $n = 22$). We measured the test-retest correlation of EEG power spectra within individuals. Additionally, we examined and report the relationship between power spectra and a wide range of tinnitus variables both individually and after Principle Component Analysis (PCA). This paper does not refer to the effects of the intervention *per se*. Our aim is to examine the validity of whole scalp power spectra as a marker of tinnitus severity and hence as a physiological outcome measure in clinical trials.

2. Materials and methods

2.1. Trial design

The research protocol has been published (Hoare et al., 2013). The trial was conducted in accordance with the Declaration of Helsinki and according to the permissions granted by the Nottingham NHS Research Ethics Committee. Data presented here are within subject for two repeated measures. Data from both placebo and intervention groups are included but not compared directly since that is not the focus of this paper.

2.2. Participants

Participants were recruited from the general public actively seeking an intervention to alleviate tinnitus. EEG data were successfully collected for 42 participants, (intervention $n = 20$; placebo $n = 22$). A further eight participants underwent baseline EEG assessment but not at follow-up. Inclusion criteria at screening were as follows: adults (≥ 18 years) experiencing chronic subjective tinnitus (i.e. constant and experienced for >3 months prior to the study); pure tone audiometric average < 60 dB (0.5, 1, 2, 4 kHz) in the ear where tinnitus is perceived and the ability to hear all stimulation tones presented by the sound therapy device; the

² Bandwidths provided are inclusive of various bandwidths used in subsequent referenced studies.

dominant tinnitus frequency measured between 0.2 and 10 kHz; at least ‘mild’ tinnitus defined by a score of ≥ 18 on the Tinnitus Handicap Inventory (THI, Newman et al., 1996). Participants also had to be willing to wear the device 4–6 h daily during the trial and have sufficient command of English language to read, understand and complete the questionnaires as well as be able and willing to give informed consent. Exclusion criteria were as follows: ‘catastrophic tinnitus’ baseline scores ≥ 78 on THI, presentation of comorbid Ménière’s disease, acoustic neuroma, temporomandibular joint disorder; or presenting with pulsatile, intermittent or somatosensory modulated tinnitus. Additional exclusions were severe anxiety (score >25) or depression (score >29) as assessed by the Beck’s Anxiety (BAI) and Depression (BDI-II) Inventories, respectively (Beck et al., 1997). Additionally we excluded participants that had been wearing hearing aids for less than 9 months, long-term hearing-aid wearers with audiological adjustment within the last 3 months or those who had been involved in another trial during the last 30 days.

2.3. Psychoacoustic and psychosocial assessments

Nineteen psychoacoustic and psychosocial variables were collected and analysed (see Table 1). The global score for the THI was utilized to assess overall handicap from tinnitus rather than the separate domain scores as at least one study has demonstrated the THI scale as uni-factorial (Baguley and Andersson, 2003). The severity distribution within our sample was measured by the THI using the five scale (slight, mild, moderate, severe, catastrophic) grading system suggested by (McCombe et al., 2001) and is shown in Table 2. All participants were in the mid-range categories (mild, moderate, severe) at screening.

2.4. Interventions

All participants were fitted at Session 1 with the same device (T30 neurostimulator) according to training given by the manufacturer and funder. The intervention group was prescribed a four-tone stimulation algorithm centered around the estimated dominant tinnitus pitch (Adamchic et al., 2012). The four-tone stimulation for the placebo group was centered on the frequency shifted down from the dominant tinnitus frequency region. The four-tone

Table 2

The number of participants in each categorical outcome derived from the THI assessment at screening, EEG Session 1 and EEG Session 2 for both placebo (P) and intervention (I) groups.

THI Category	Screening		Session 1		Session 2	
	P	I	P	I	P	I
Grade 1 (slight 0–16)	0	0	2	4	5	5
Grade 2 (mild 18–36)	11	9	10	8	5	11
Grade 3 (moderate 38–56)	6	7	4	4	8	1
Grade 4 (severe 58–76)	5	4	6	4	3	2
Grade 5 (catastrophic 78–100)	0	0	0	0	1	1

cycle presentation rate was 0.3 Hz in the placebo, thus five times slower than the 1.5 Hz rate used in the treatment algorithm to shift the cycle rate outside the target delta frequency band. The cycle rate for the placebo group was recommended by the inventor of the intervention algorithm since it was outside the targeted delta-band range. Participants were instructed to use the device between 4 and 6 h per day for 12 weeks.

2.5. EEG recordings

Two EEG recordings were made. Session 1 occurred prior to device fitting and Session 2 was 12 weeks later. The EEG was recorded using the Neuroscan system (SynAmps2 model 8050, Compumedics Neuroscan, Charlotte, NC, USA) with 66 equidistant scalp electrodes (Easycap, GmbH, Germany). A central frontal electrode was used as ground and a nose-tip electrode as reference. Two electrodes were placed below the eyes to record eye movements. Electrode impedances were maintained at 5 k Ω prior to the start of the recordings. The recording was done over a continuous 10-min period with 0.5–200 Hz pass-band and 1000 Hz sampling rate. The participants were seated in a quiet, darkened soundproof booth, and were instructed to relax, keep their eyes open and fix gaze on a marker point in front of them.

2.6. EEG data processing

The EEG recordings were analyzed using EEGLAB (Delorme and Makeig, 2004) run under MATLAB (The Mathworks, Natick, MA,

Table 1
Nineteen psychosocial and psychoacoustic variables examined for relationship with EEG bands power.

Variable type	Domain/Factor	Assessment	Reference		
Psycho-social	1) Intrusiveness	Tinnitus functional index	(Meikle et al., 2012)		
	2) Sense of control				
	3) Cognition				
	4) Sleep				
	5) Auditory				
	6) Relaxation				
	7) Quality of life				
	8) Emotional				
	9) Environmental			World Health Organization Quality of Life (BREF)	The WHOQOL Group (1998)
	10) Social				
	11) Psychological				
	12) Physical			Tinnitus handicap questionnaire	(Kuk et al., 1990)
	13) Social, Environmental and Behavioural				
	14) Tinnitus & hearing				
	Psycho-acoustic			15) Outlook	Tinnitus handicap inventory
16) Global score					
17) Duration of tinnitus		Self-report, given in months.	na		
18) Loudness of tinnitus		Self-report using Visual Analogue Scale (0–100)	(Roberts et al., 2006; Roberts et al., 2008)		
19) Hearing ability		4-point pure tone audiometry average across both ears (0.5, 1, 1.4 KHz).	na		

USA). The pre-processed data (Butterworth filter with 0.8–130 Hz pass-band, down-sampling to 500 Hz, re-referencing to average of scalp electrodes) were divided into 5 s-long epochs and visually inspected. Epochs containing improbable data (± 3.5 SD joint probability criterion; Delorme et al., 2007), electrode artefacts and strong muscle activity across channels were removed. The resulting data (average duration = 8.89 min [min–max = 5.25–10 min]) were further corrected for eye, heart, channel and muscle (EMG) activity using Independent Component Analysis in EEGLAB (Onton et al., 2006). The EMG components were identified using similar criteria as defined by Adamchic et al. (2014): (i) spectra with high broad peaks around 30–40 Hz and higher, (ii) moderately small and clustered distribution on the topographic maps, (iii) periods of high frequency activation in the time domain.

The Power Spectral Density (PSD) was computed on artefact-free sliding 5 s-long windows (Hanning taper, 50% overlap) within 1–90 Hz range. The individual spectra were derived by averaging PSDs across all windows and scalp channels, giving a whole scalp power across scalp. The individual whole scalp power spectra were normalized by dividing power at each frequency by the integral of the power within the 1–90 Hz (Adamchic et al., 2014).

2.7. Statistical methods

The whole scalp power spectra were divided into normalized EEG frequency bands equivalent to previous studies using the T30 neurostimulator, (Adamchic et al., 2014; Tass et al., 2012): delta (1–4 Hz), theta (4.2–7.8 Hz), alpha (8–12 Hz), beta (12.2–29.8 Hz), gamma low (30–48 Hz) and gamma high (52–90 Hz). The 48–52 Hz gap accounted for the power line artifact in the power spectra. The averaged power of the theta, alpha, gamma low and gamma high bands did not show a normal distribution across participants. They were therefore log-transformed prior to analysis. Agreement of band power between sessions was determined using intraclass correlation coefficients (ICC) to avoid an effect of order (Hoare et al., 2014). ICCs are reported with confidence intervals (CI) of 95%. Band spectra were additionally analyzed for correlations with the 19 variables given in Table 1. Those without normal distributions had correlation estimated with Spearman's rank correlation coefficient and are indicated in Fig. 1B with an asterisk.

As psychological variables were often highly correlated (Fig. 1B, Area A & B), we implemented an exploration of the psychoacoustic and psychosocial data with Principle Component Analysis (PCA). Analysis was run once for all subjects for each EEG session. As communalities were high, the number of identified components small ($n = 3$) and model error low, we considered the PCA appropriate (Costello and Osborne, 2005; Preacher and MacCallum, 2002). However, to assess the stability of the components that were identified by the PCA, the identical analysis was undertaken in a jackknife resampling method (Tukey, 1958). A random selection of 90% of data points ($n = 38$) over 500 iterations. In all analyses, extracted components were rotated using Varimax rotation with Kaiser normalization. Agreement of factor loadings between sessions was also calculated using ICC to remove session effects.

The nineteen psychoacoustic and psychosocial variables and the six EEG band power scores were examined for correlation using either Pearson's r value or Spearman's ρ , variables for normally distributed and non-normally distributed data respectively.

3. Results

3.1. EEG power test–retest correlation

In a test-retest paradigm examining between-session

agreement of whole-brain EEG power in delta, theta, alpha, beta, gamma low and gamma high bands we found high intra-class correlation (Fig. 1A). ICC values > 0.7 were taken as acceptable agreement to interpret group level data (Nunnally and Bernstein, 1994) and all power bands passed this threshold (Table 3). ICC values > 0.9 were taken as acceptable agreement values between test to interpret individual participant data at clinical level (Kottner et al., 2011). This threshold was surpassed across all participants in the delta, alpha and gamma bands indicating EEG whole scalp power spectra averages are very stable across sessions and thereby very sensitive to individual change. Crucially the test-retest measures were acceptable for the placebo group for whom we would expect no underlying neural changes over the 12-week period. In addition, our data do not reliably change over time for the intervention group. Discussion of this is beyond the scope of the current article, but the interested reader is directed to a summary of the study results (clinicaltrials.gov identifier: NCT01541969). Correlations between bands were similar between sessions as can be seen in Fig. 1B, sectors I and J.

3.2. EEG power correlations with psychoacoustic and psychological variables

Correlations between 19 tinnitus variables and the six band power spectra were limited in Session 1 (Fig. 1B, sector E). Nineteen variables tested against six bands showed significant correlation on only seven occasions ($p < 0.05$; uncorrected). There was no clear pattern to the findings, none of them passing even a liberal correction for multiple comparisons. Session 2 (Fig. 1B, sector F) showed even fewer associations. The only result replicated between sessions was a significant correlation between EEG power in the low and high gamma range and the Tinnitus Handicap Questionnaire (THQ) – *Social, Emotional and Behavioural effects* subscale (Kuk et al., 1990). Otherwise we identified no significant associations between whole scalp EEG power and the psychoacoustic and psychosocial variables.

3.3. Principle component analysis

The analysis method was identical and the factor structure very similar for both sessions. Initially, the 19 variables were examined in regard to their suitability for PCA. Firstly, all 19 variables were significantly correlated with at least one other item (Fig. 1B, sector A/B), suggesting variables are amenable to PCA. Secondly, the Kaiser-Meyer-Olkin measure of sampling adequacy was above the recommended value of 0.6 (Session 1: 0.78; Session 2: 0.80) and Bartlett's test of sphericity was significant (Session 1: $\chi^2(171) = 617.19, p < 0.001$; Session 2: $\chi^2(171) = 737.82, p < 0.001$). Finally, the communalities were all high (Session 1: > 0.3 ; Session 2: > 0.4), further confirming that each item shared some common variance with other items. Given these overall indicators, PCA was conducted with all 19 variables.

Initial eigenvalues indicated a three-factor solution for both sessions (Session 1: 69%; Session 2: 74% of variance explained). Subsequent components had eigenvalues of < 1 and $< 6\%$ variance explained. The three-factor solution was selected due to the 'levelling off' of eigenvalues on the scree-plot after three components, an insufficient number of primary loadings and difficulty of interpreting the fourth factor and subsequent factors.

Rotated factor loadings from the main PCA analyses ($n = 42$) are shown as the red outline in the constellation plots of Fig. 2. The first factor ('tinnitus severity') includes the Tinnitus Functional Index (TFI) subscales apart from the TFI-Auditory subscale which is consistent with previous findings (Meikle et al., 2012). In the 500

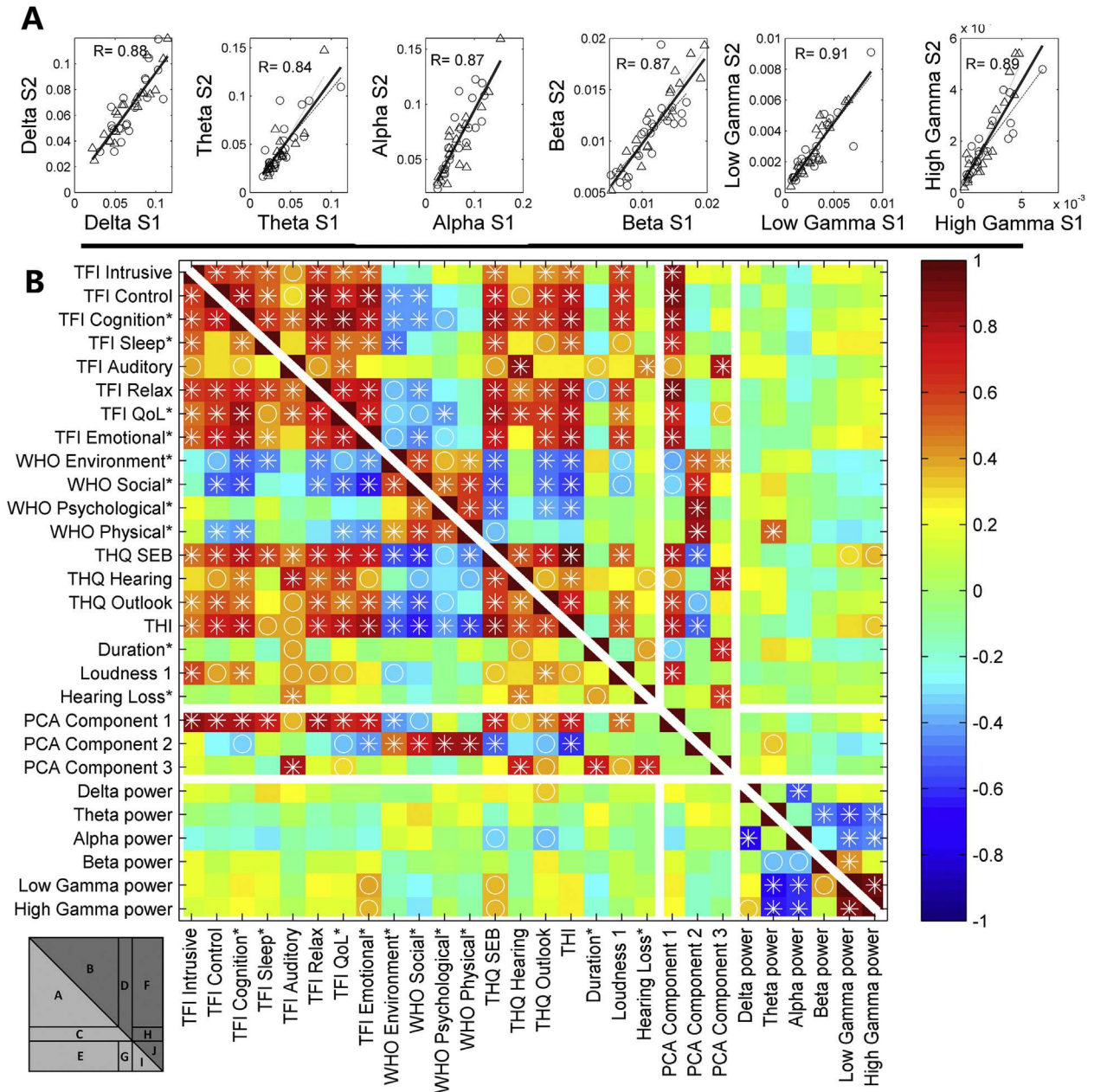


Fig. 1. Panel A: Scatter plots session 1 (S1) against session 2 (S2) EEG power (raw data) in each band showing high degree of stability. r indicates Pearson's correlation coefficient. Δ = intervention; \circ = placebo; thick line shows best fit across all participants. **Panel B:** Correlation matrix showing session 1 & session 2 relationships between variables and EEG measures. The patch colour indicates the correlation between the horizontal and vertical variables (Pearson's r value or Spearman's ρ , variables with non-normal distributions are marked with *). A star or circle in the coloured patch indicates $p < 0.01$ (uncorrected) or $p < 0.05$ (uncorrected), respectively. The bottom left panel indicates the areas of the matrix referred to in the text which are separated by bold white lines in the main image. Sectors A,C,E,G and I show correlations between variables from session 1. Sectors B,D,F,H and J show the same tests from session 2. Sectors A and B show correlations between the psychoacoustic and psychosocial variables. Sectors C and D indicate correlation of PCA components with input variables. Sectors E and F indicate correlations between psychoacoustic/psychosocial variables and the whole scalp EEG power bands. Sectors G and H show correlations between extracted PCA components and the average power in bands of whole scalp EEG. Sectors I and J show correlations between the average power in bands of whole scalp EEG. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

iterations of each analysis with a random selection of 38 participants, this factor was identified 345 times in Session 1 and 500 (all) times in Session 2. Each one of these 500 constellations is overlaid in light green, the intensity of green in Fig. 2 indicates the number of occasions this component was identified. Factor two ('quality of life') included the four domains of the WHOQOL-BREF questionnaire (The WHOQOL group, 1998) plus the TFI-Auditory subscale. This factor was identified 476 times of 500 in Session 1 (Session 2: 469 of 500). Finally the third factor ('hearing') incorporated the THQ - Tinnitus and Hearing subscale, self-reported duration of tinnitus,

audiometric measure of hearing ability and the TFI-Auditory subscale and was represented in 490 iterations in Session 1 (Session 2: 303 of 500).

The correlation of the PCA component scores with Session 1 EEG band power is shown in Fig. 1B, sectors G and H. There were no correlations in Session 1. A single correlation was found between theta band power and factor 2 ('quality of life') in Session 2 ($R = 0.34$, $p < 0.05$ uncorrected). Given the number of comparisons made, we are unable to consider this a true effect. The PCA components extracted did not relate to the whole scalp power band

Table 3
Test-retest agreement of both EEG band power and factor loadings derived from the Principle Component Analysis. Intraclass correlation coefficients (ICC) were used to avoid an effect of order and provide a statistical assessment of agreement between the same measures taken twelve weeks apart (Hoare et al., 2014).

		Placebo group $n = 22$		Intervention group $n = 20$		All Participants $n = 42$	
		ICC	CI	ICC	CI	ICC	CI
EEG power spectra	Delta	0.84	0.68–0.92	0.93	0.86–0.97	0.95	0.91–0.97
	Theta	0.84	0.68–0.92	0.88	0.75–0.94	0.84	0.75–0.91
	Alpha	0.97	0.94–0.99	0.97	0.93–0.98	0.96	0.93–0.97
	Beta	0.84	0.68–0.92	0.93	0.86–0.97	0.88	0.81–0.93
	Gamma low	0.91	0.82–0.96	0.93	0.86–0.97	0.92	0.86–0.95
	Gamma high	0.9	0.8–0.95	0.91	0.81–0.96	0.9	0.83–0.94
Factors	Tinnitus severity	0.76	0.56–0.88	0.58	0.26–0.78	0.66	0.48–0.78
	Quality of life	0.85	0.72–0.93	0.79	0.59–0.90	0.82	0.72–0.89
	Hearing	0.95	0.90–0.98	0.96	0.91–0.98	0.95	0.91–0.97

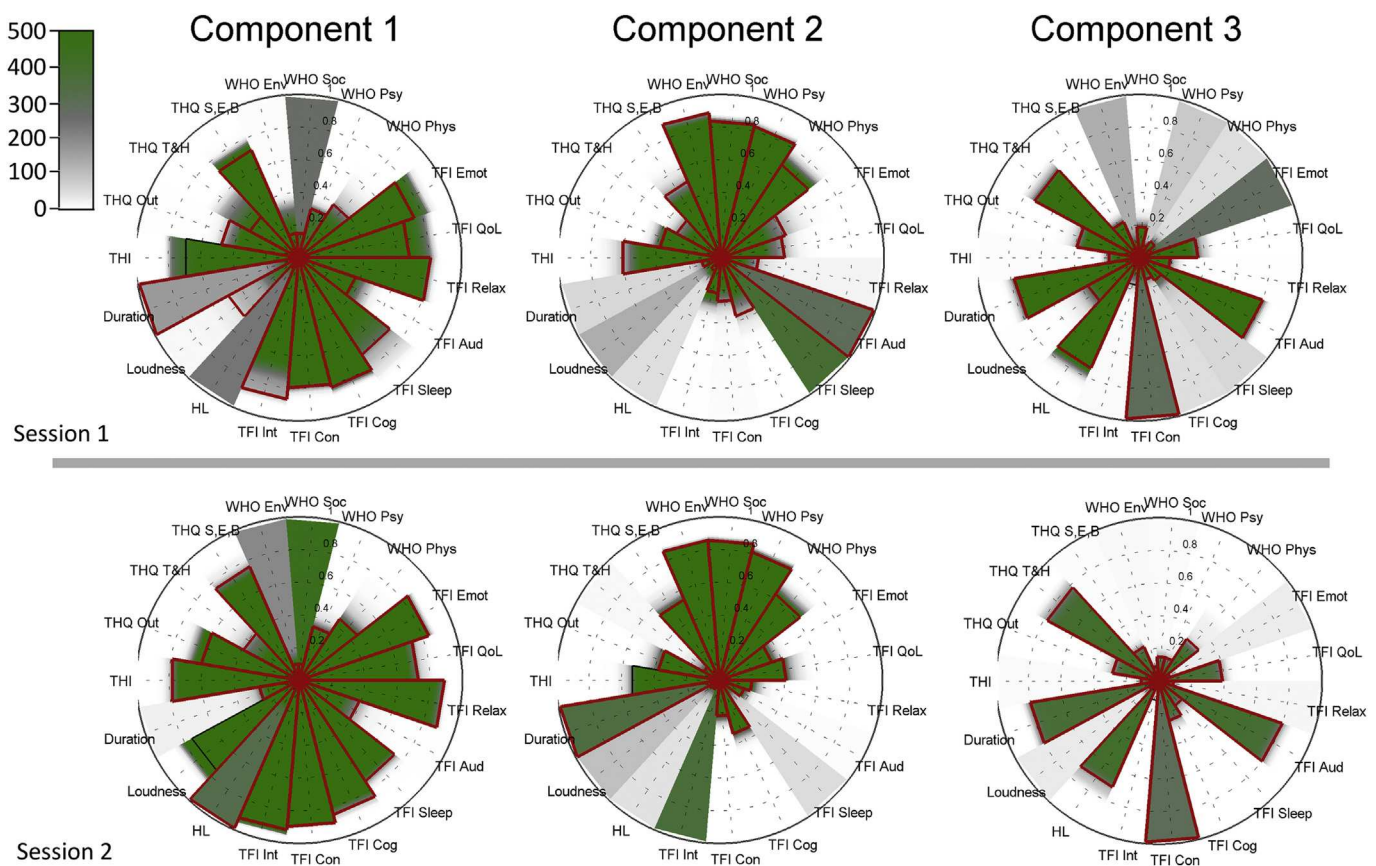


Fig. 2. Results of principle component analyses, top and bottom rows show rotated component matrix loadings for sessions 1 & 2 respectively. The outer red line indicates loading for analysis with all 42 participants. The intensity of green indicates the frequency with which a factor loaded at a given strength upon a component. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

spectra. In other words, in this dataset we found no association between the scores on various psychoacoustic and psychosocial variables, including those related to tinnitus, and whole-brain oscillatory activity.

The extracted factors from the Session 2 dataset are very similar to those from Session 1. On the whole results show that the 19 variables included can be successfully and repeatedly reduced down to three very similar factors. Between-session Pearson's correlation of the three factors across all participants was highly significant at $p < 0.001$ ('tinnitus severity': ICC = 0.66, CI = 0.48–0.78; 'quality of life': ICC = 0.82, CI = 0.72–0.89; 'hearing': ICC = 0.95, CI = 0.91–0.97) indicating good replication of psychoacoustic and psychosocial data across sessions.

4. Discussion

We showed that the test-retest agreement for all selected, whole scalp, EEG power spectra bands are highly significant when tested across a 12-week period. Similarly the PCA components derived from analysis of 19 variables show high degrees of agreement across the same test-retest period. Agreement always crossed threshold for group inference and often crossed thresholds required to interpret individual data for clinical assessment. However we find no substantial evidence that EEG power spectra correlate with any of these variables. EEG power spectra were not linked to any domain of tinnitus symptomology, quality of life nor degree of hearing loss. We conclude that whole scalp EEG

oscillatory brain activity should not be considered as a viable biomarker or outcome measure in clinical trials of tinnitus.

4.1. Potential reasons for the lack of relationship between EEG and behavioural variables

This trial was controlled in terms of participant inclusion and exclusion criteria. Our study includes broad selection of those experiencing, and actively seeking help for tinnitus but extremes were excluded. It cannot be excluded that participant selection schemes in different labs may have led to some of the diversity of reports. The main limitation in the present report is that we do not have a non-tinnitus control group. This is because the primary aim of the trial was to compare between intervention and placebo. Here we explore the reliability of the EEG and behavioural data acquisition methods. We found no relationship between whole scalp EEG with any single tinnitus variable or principle component, even though the measures are reliable over time. We stress that this study does not show that there is no difference between those who experience tinnitus and those that do not experience tinnitus. However, we note considerable evidence in the literature demonstrating that negative and oppositional findings are as equally frequent as positive findings but the former are not addressed. This is to say, we assert that reports concerning tinnitus and oscillatory measures of brain activity are subject to considerable confirmation bias (Dwan et al., 2013). In consequence we suggest the null effect is likely due to the relationship between tinnitus and whole scalp EEG signal lacking substance.

4.2. Spatial and source based analysis

Literature in the tinnitus field frequently uses whole scalp power measures without spatial analysis and the conclusion of this report highlights the likely inappropriate use of this method for clinical trials. We did use spatial analysis to attenuate artefacts (see Section 2.6) but not a spatial analysis with a source model. Our reason for not doing so was that there were no trends in our results to suggest that spatial analysis would be effective and so post-hoc data exploration cannot be justified. Only if general effects are found at the whole scalp level would it be appropriate to undertake further refined spatial analysis (c.f., (Weisz et al., 2005). Additionally, as noted in the introduction, across studies there is near equal amount of positive and negative findings with regard to each frequency band. This strengthens the need to accept and report null findings. Given the multidirectional findings in the literature, the number of potential analysis methods and the number of potential comparisons, it is highly likely that an unplanned exploratory analysis will risk inflating type I error. This may explain positive findings in some reports. We feel that reports focusing on small 'positive' results while neglecting to remark on null effects which directly contradict major theories of tinnitus simply add further confirmation bias to the field.

4.3. Future directions

Whole scalp EEG is a reliable measure but does not appear to be an informative measure for tinnitus and at present should not be used as an outcome measure in clinical trials of tinnitus. Further basic research is required to identify a reliable biomarker for tinnitus and source-based analysis would be more appropriate to achieve this. We argue that efforts for finding such a biomarker would be strengthened by aiming for a robust effect that can be easily identified using standardized participant selection criteria, and a standardized EEG data acquisition and data analysis protocol. Deposition of EEG data for meta-analysis and a standard acquisition

and analysis protocol of resting state EEG will advance research in this important area. Working groups two and three of the TINNET-COST international network (<http://tinnet.tinnitusresearch.net/>), focus upon these two aims.

Conflicts of interest

Data was collected during a clinical trial that was part funded by The Tinnitus Clinic (Brook Henderson Group, Reading, UK) with Adaptive Neuromodulation GmbH (Köln, Germany) who manufactured the device at that time. DAH and DJH were the grant holders and RHP was employed on this funding. DAH has also received payments from Merz Pharmaceuticals GmbH and Oticon A/S for research on tinnitus. The views expressed are those of the authors and not necessarily those of the National Health Service (NHS), the NIHR, or the Department of Health (DH).

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References

- Adamchic, I., Hauptmann, C., Tass, P.A., 2012. Changes of oscillatory activity in pitch processing network and related tinnitus relief induced by acoustic CR neuromodulation. *Front. Syst. Neurosci.* 6, 18.
- Adamchic, I., Toth, T., Hauptmann, C., Tass, P.A., 2014. Reversing pathologically increased EEG power by acoustic coordinated reset neuromodulation. *Hum. Brain Mapp.* 35, 2099–2118.
- Adjajian, P., Sereda, M., Zobay, O., Hall, D.A., Palmer, A.R., 2012. Neuromagnetic indicators of tinnitus and tinnitus masking in patients with and without hearing loss. *J. Assoc. Res. Otolaryngol. JARO* 13, 715–731.
- Ashton, H., Reid, K., Marsh, R., Johnson, I., Alter, K., Griffiths, T., 2007. High frequency localised "hot spots" in temporal lobes of patients with intractable tinnitus: a quantitative electroencephalographic (QEEG) study. *Neurosci. Lett.* 426, 23–28.
- Baguley, D.M., Andersson, G., 2003. Factor analysis of the tinnitus handicap inventory. *Am. J. Audiol.* 12, 31–34.
- Beck, A.T., Steer, R.A., Ball, R., Ciervo, C.A., Kabat, M., 1997. Use of the Beck Anxiety and Depression Inventories for Primary Care with medical outpatients. *Assessment* 4, 211–219.
- Costello, A.B., Osborne, J.W., 2005. Best Practices in exploratory factor analysis: four Recommendations for Getting the Most from Your analysis. *Pract. Assess. Res. Eval.* 10, 1–9.
- De Ridder, D., Vanneste, S., Congedo, M., 2011. The distressed brain: a group blind source separation analysis on tinnitus. *PLoS One* 6, e24273.
- Delorme, A., Makeig, S., 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. methods* 134, 9–21.
- Delorme, A., Sejnowski, T., Makeig, S., 2007. Enhanced detection of artifacts in EEG data using higher-order statistics and independent component analysis. *NeuroImage* 34, 1443–1449.
- Dwan, K., Gamble, C., Williamson, P.R., Kirkham, J.J., Reporting Bias, G., 2013. Systematic review of the empirical evidence of study publication bias and outcome reporting bias – an updated review. *PLoS One* 8, e66844.
- Eggermont, J.J., Tass, P.A., 2015. Maladaptive neural synchrony in tinnitus: origin and restoration. *Front. Neurol.* 6, 29.
- Hebert, S., Fullum, S., Carrier, J., 2011. Polysomnographic and quantitative electroencephalographic correlates of subjective sleep complaints in chronic tinnitus. *J. Sleep. Res.* 20, 38–44.
- Hoare, D.J., Pierzycki, R.H., Thomas, H., McAlpine, D., Hall, D.A., 2013. Evaluation of the acoustic coordinated reset (CR^B) neuromodulation therapy for tinnitus: study protocol for a double-blind randomized placebo-controlled trial. *Trials* 14.
- Hoare, D.J., Edmondson-Jones, M., Gander, P.E., Hall, D.A., 2014. Agreement and reliability of tinnitus loudness matching and pitch likeness rating. *PLoS One* 9, e114553.
- Kottner, J., Audige, L., Brorson, S., Donner, A., Gajewski, B.J., Hrobjartsson, A., Roberts, C., Shoukri, M., Streiner, D.L., 2011. Guidelines for reporting reliability and agreement studies (GRRAS) were proposed. *Int. J. Nurs. Stud.* 48, 661–671.
- Kuk, F.K., Tyler, R.S., Russell, D., Jordan, H., 1990. The psychometric properties of a tinnitus handicap questionnaire. *Ear Hear* 11, 434–445.
- Llinas, R.R., Ribary, U., Jeanmonod, D., Kronberg, E., Mitra, P.P., 1999. Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proc. Natl. Acad. Sci. U. S. A.* 96, 15222–15227.
- Lorenz, I., Müller, N., Schlee, W., Hartmann, T., Weisz, N., 2009. Loss of alpha power

- is related to increased gamma synchronization – a marker of reduced inhibition in tinnitus? *Neurosci. Lett.* 453, 225–228.
- McCombe, A., Baguley, D., Coles, R., McKenna, L., McKinney, C., Windle-Taylor, P., 2001. Guidelines for the grading of tinnitus severity: the results of a working group commissioned by the British Association of Otolaryngologists, Head and Neck Surgeons, 1999. *Clin. Otolaryngol.* 26, 388–393.
- Meikle, M.B., Henry, J.A., Griest, S.E., Stewart, B.J., Abrams, H.B., McArdle, R., Myers, P.J., Newman, C.W., Sandridge, S., Turk, D.C., Folmer, R.L., Frederick, E.J., House, J.W., Jacobson, G.P., Kinney, S.E., Martin, W.H., Nagler, S.M., Reich, G.E., Searchfield, G., Sweetow, R., Vernon, J.A., 2012. The tinnitus functional index: development of a new clinical measure for chronic, intrusive tinnitus. *Ear Hear* 33, 153–176.
- Meyer, M., Luethi, M.S., Neff, P., Langer, N., Buchi, S., 2014. Disentangling tinnitus distress and tinnitus presence by means of EEG power analysis. *Neural plast.* 2014, 468546.
- Moazami-Goudarzi, M., Michels, L., Weisz, N., Jeanmonod, D., 2010. Temporoincubation enhancement of EEG low and high frequencies in patients with chronic tinnitus. QEEG study of chronic tinnitus patients. *BMC Neurosci.* 11, 40.
- Newman, C.W., Jacobson, G.P., Spitzer, J.B., 1996. Development of the tinnitus handicap inventory. *Arch. Otolaryngol.* 122, 143–148.
- Nunnally, J.C., Bernstein, I.H., 1994. *Psychometric Theory*, third ed. McGraw Hill Inc, New York.
- Onton, J., Westerfield, M., Townsend, J., Makeig, S., 2006. Imaging human EEG dynamics using independent component analysis. *Neurosci. Biobehav. Rev.* 30, 808–822.
- Ortmann, M., Muller, N., Schlee, W., Weisz, N., 2011. Rapid increases of gamma power in the auditory cortex following noise trauma in humans. *Eur. J. Neurosci.* 33, 568–575.
- Pawlak-Osinska, K., Kazmierczak, W., Kazmierczak, H., Wierzchowska, M., Matuszewska, I., 2013. Cortical activity in tinnitus patients and its modification by phonostimulation. *Clin. (Sao Paulo)* 68, 511–515.
- Preacher, K.J., MacCallum, R.C., 2002. Exploratory factor analysis in behavior genetics research: factor recovery with small sample sizes. *Behav. Genet.* 32, 153–161.
- Roberts, L.E., Moffat, G., Bosnyak, D.J., 2006. Residual inhibition functions in relation to tinnitus spectra and auditory threshold shift. *Acta Oto-Laryngol* 126, 27–33.
- Roberts, L.E., Moffat, G., Baumann, M., Ward, L.M., Bosnyak, D.J., 2008. Residual inhibition functions overlap tinnitus spectra and the region of auditory threshold shift. *Jaro-J Assoc. Res. Oto* 9, 417–435.
- Schlee, W., Scheckmann, M., Lehner, A., Kreuzer, P.M., Vielsmeier, V., Poepl, T.B., Langguth, B., 2014. Reduced variability of auditory alpha activity in chronic tinnitus. *Neural Plast.* 2014, 436146.
- Tass, P.A., Adamchic, I., Freund, H.J., von Stackelberg, T., Hauptmann, C., 2012. Counteracting tinnitus by acoustic coordinated reset neuromodulation. *Restor. Neurol. Neurosci.* 30, 137–159.
- Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. *Psychol. Med.* 28, 1998, 551–558.
- Tukey, J.W., 1958. Bias and confidence in not-quite large samples. *Ann. Math. Statistics* 29, 614.
- Vanneste, S., Plazier, M., der Loo, E., de Heyning, P.V., Congedo, M., De Ridder, D., 2010. The neural correlates of tinnitus-related distress. *Neuroimage* 52, 470–480.
- Vanneste, S., Plazier, M., van der Loo, E., Van de Heyning, P., De Ridder, D., 2011. The difference between uni- and bilateral auditory phantom percept. *Clin. Neurophysiol.* 122, 578–587.
- Vanneste, S., Congedo, M., De Ridder, D., 2014. Pinpointing a highly specific pathological functional connection that turns phantom sound into distress. *Cereb. Cortex* 24, 2268–2282.
- Vanneste, S., Van De Heyning, P., De Ridder, D., 2015. Tinnitus: a large VBM-EEG correlational study. *PLoS One* 10, e0115122.
- Weisz, N., Moratti, S., Meinzer, M., Dohrmann, K., Elbert, T., 2005. Tinnitus perception and distress is related to abnormal spontaneous brain activity as measured by magnetoencephalography. *PLoS Med.* 2, e153.
- Weisz, N., Muller, S., Schlee, W., Dohrmann, K., Hartmann, T., Elbert, T., 2007. The neural code of auditory phantom perception. *J. Neurosci. off. J. Soc. Neurosci.* 27, 1479–1484.
- Zobay, O., Palmer, A.R., Hall, D., Sereda, M., Adjamian, P., 2015. Source Space Estimation of oscillatory power and brain Connectivity in tinnitus. *PLoS one* 10, e0120123.