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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).

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). Llinas' 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 deafferentiated thalamocortical 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), clinicaltrails.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 ($\geq$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.