On the Standardisation of M/EEG procedures in tinnitus research

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Objective and Action

In recent years there has been a surge of interest in using Electroencephalography (EEG) and Magnetoencephalography (MEG) to study tinnitus. A main objective of the Neuroimaging Working group is to investigate the feasibility of devising standardised guidelines in recording of electrophysiology data from human participants in order to improve neuroimaging methods to further enhance our understanding of tinnitus heterogeneity.

Currently there is already a number of existing publications on standardised practices on data collection, analysis and communication of results for M/EEG research in general. We have selected a number of publications, which we think are excellent, and can be recommended as a guideline for M/EEG studies in tinnitus research.

Additionally, we identified several important issues in M/EEG that are specific for tinnitus research. They are highlighted and discussed here. The key consideration is to provide an initial guideline towards more focused methodologies to investigating the tinnitus abnormality across research centres.

Background

MEG and EEG (M/EEG) are important techniques for understanding neural changes in tinnitus. This is because the data derived from these techniques provide direct information regarding the activity of underlying neurons with millisecond time resolution. This allows researchers to investigate the dynamics of brain activity and their interaction across brain regions of interest. Furthermore, as M/EEG data is collected in quiet environments (unlike functional MRI), it is possible to investigate spontaneous brain activity during the brain at rest, as well as the responses of neurons to specific stimuli of interest. Additionally, a fraction of tinnitus patients suffers from hyperacusis which make the application of fMRI almost impossible as this technique is accompanied by considerable noise produced by switching gradients.

The precise mechanism of tinnitus remains unknown and despite the increasing number of studies using M/EEG to study the pathophysiology of the condition, the results remain contradictory to a large extent (Adjamian et al., 2009; Adjamian, 2014). Changes in M/EEG activity in tinnitus could be due to the following (among others):

1- the quality and the loudness of the perceived tinnitus sound;

2- the attention, or lack thereof, to the tinnitus percept during data collection;

3- the emotional state of the tinnitus patient;

4- the severity of tinnitus;

5- the moment-to-moment variability of the underlying brain activity;

6- the presence of comorbidities such as depression or anxiety;

7- the presence and degree of hearing loss;

8- the cognitive status of (elderly) individuals with tinnitus

9- present age of patients, duration since onset of tinnitus,

10- the environmental situation during the M/EEG recording (e.g. surrounding noise)

Any one, or combination, of the above factors in a single patient with tinnitus can alter the observed M/EEG activity in as yet unknown ways.

To understand the neural mechanism of tinnitus, it is first necessary to understand the potential reasons behind the discrepant results within the existing literature. The heterogeneity of the condition is undoubtedly an important contributory factor, where better subtyping of the condition based on clinical characteristics can help significantly. However, there may also be factors external to the patient that adversely affect the outcome of studies, namely the way data is collected, pre-processed, and analysed at various research centres. Therefore, at the very least there is a need to ensure that certain guidelines for data collection and treatment are followed as far as possible in an attempt to minimise the number of confounding factors.

The lack of standards specifically for tinnitus studies means that meaningful comparison between different studies from different research centres is difficult. Numerous general guidelines exist on both EEG and MEG data collection, including detailed description of performing each stage of the process, from participant preparation through to data collection and analysis (Pivik et al., 1993; Picton et al., 2010; Light et al., 2010; Gross et al., 2013; Keil et al., 2014). While these guidelines are not specifically for M/EEG studies of tinnitus, the majority of recommendations are forthwith applicable to tinnitus studies and constitute the minimum requirement for all research with M/EEG. For this reason, producing a comprehensive set of guidelines exclusively for tinnitus research cannot avoid repetition of a large snippets of what has already been recommended in the above publications.

It must also be stated that the provision of guidelines does not mean adherence to the recommended standards by the research community. Irrespective of the latter, there are minimum requirements that should be practiced across the research centres as far as possible, which would greatly help to understand the discrepant findings. At the very least, adhering to certain standard practices will help the research community to concentrate on other possible causes for the discordant results.

Types of M/EEG data

Tinnitus M/EEG data can be recorded in two ways: either as ongoing spontaneous brain activity in which no external (auditory or otherwise) stimulus is presented, or as measuring neural responses to variety of external stimuli, usually auditory. The aim of spontaneous recordings is to observe spatiotemporal patterns of oscillatory activity which appear to occur randomly, and compare these between a group of tinnitus patients and non-tinnitus controls. It is also possible to compare different states within tinnitus participants, for example, before and after intake of medication, or before and after masking of tinnitus. Furthermore, tinnitus may be examined based on specific grouping subtypes that can ideally be determined by factorial analysis of psychometric and psychopathological data. The compelling advantage of this approach is that it is devoid of any a priori assumptions. Conversely, stimulus-driven M/EEG activity reflects specific aspects of auditory and extra-auditory brain in tinnitus when modulated by specific input.

General recommendations for EEG and MEG research

Below is a list of recommendable literature with general guidelines for the EEG and MEG research.

Literature suggestions

Topic	Reference	Open access link to publication
EEG: recording and analysis.	Pivik, R. T., Broughton, R. J., Coppola, R., Davidson, R. J., Fox, N., & Nuwer, M. R. (1993). Guidelines for the recording and quantitative analysis of electroencephalographic activity in research contexts. *Psychophysiology*, *30*(6), 547-558.	http://onlinelibrary.wiley.com/doi/10.1111/j.1469-8986.1993.tb02081.x/epdf
EEG: recording and analysis. Focus on ERPs.	Light, G. A., Williams, L. E., Minow, F., Sprock, J., Rissling, A., Sharp, R., ... & Braff, D. L. (2010). Electroencephalography (EEG) and event-related potentials (ERPs) with human participants. *Current Protocols in Neuroscience*, 6-25.	https://www.researchgate.net/profile/Lisa_Williams12/publication/44800031_Electroencephalography_(EEG)_and_event-related_potentials_(ERPs)_with_human_participants/links/0fcfd4faa937d86e70000000.pdf
EEG: recording and analysis. Focus on how to report the study in a peer-reviewed publication.	Picton, T. W., Bentin, S., Berg, P., Donchin, E., Hillyard, S. A., Johnson, R., ... & Taylor, M. J. (2000). Guidelines for using human event-related potentials to study cognition: recording standards and publication criteria. *Psychophysiology*, *37*(02), 127-152.	http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.327.386&rep=rep1&type=pdf
MEG: recording, analysis and statistics. Focus on how to report the study in a peer-reviewed publication.	Gross, J., Baillet, S., Barnes, G. R., Henson, R. N., Hillebrand, A., Jensen, O., ... & Parkkonen, L. (2013). Good practice for conducting and reporting MEG research. *Neuroimage*, *65*, 349-363.	http://www.fil.ion.ucl.ac.uk/spm/doc/papers/M/EEG_good_practice.pdf
M/EEG: data recording and analysis. Focus on how to report the study in a peer-reviewed publication.	Keil, A., Debener, S., Gratton, G., Junghöfer, M., Kappenman, E. S., Luck, S. J., ... & Yee, C. M. (2014). Committee report: publication guidelines and recommendations for studies using electroencephalography and magnetoencephalography. *Psychophysiology*, *51*(1), 1-21.	http://lucklab.ucdavis.edu/uploads/5/8/4/6/58469631/keil_2013_psychophysiology_publication_guidelines.pdf

Recommendations specific for tinnitus research

While it was decided that an extended list of recommendations is not necessary, the subgroup identified and discussed two issues, particularly relevant to the recording of spontaneous brain activity. These issues and questions are: should spontaneous M/EEG data be collected with eyes open or with the eyes closed; what instruction should be given to participant, and the assessment of comorbidities. These will now be expanded below:

1) Eyes open or closed?

When no specific task or stimulus is involved and participant engagement is not required, resting state M/EEG data can be recorded with either the eyes kept open or the eyes kept closed. The consensus was a preference for eyes open. First, eye closure is known to generate widespread alpha activity, which although has occipital origin, it will interfere with signals of interest and present difficulties in separating this from potentially tinnitus-related changes in alpha activity. Moreover, with eyes closed there is a significant risk of drowsiness which will cause even more unrelated signals. Any differences observed between groups could potentially be related to levels of drowsiness rather than tinnitus. While eyes open has its own problems, such as eye-movement and blinking, the effects are not as severe and in these perturbations can be identified and excluded from the data offline. It is also possible to ask the participants to stare at a specific location in order to minimise eye movement-related artefacts.

Recommendation: Both eyes-open and eyes-closed data should be collected in alternate trials of arbitrary length and repeated. Typically 5 minutes of resting state data is sufficient. We suggest that at a minimum, 10 minutes of resting-state M/EEG should be collected with 1-minute of eyes open (n=5) and 1-minute of eyes-closed (n=5) interleaved with one another. For subsequent analysis of this data, the first and last 2 seconds of each trial should be excluded as these contain the ocular artefacts. During eyes-open trials, a fixation spot should be used to minimise possibility of eye movements.

2) Participant instructions

The question here is what instruction should participants be given prior to recording of spontaneous resting state brain activity? Until now, most studies (tinnitus or otherwise) that assess resting state brain M/EEG activity tend to simply ask their participants to “do nothing” for the duration of data recording. While the instruction is used to imply that no task performance is required, it is inevitable that the structure which produces the signals of interest, namely the human brain, is active and processing information related to the internal state of the participant, such as attention to tinnitus, spontaneous thoughts and mind wandering cannot be controlled appropriately. In a PET study by Andersson et al., (2006), it was found that brain activity during resting state changes depending on the instruction participants were given, for example, whether they were asked to concentrate on their tinnitus or engage in other thoughts.

The oscillatory activity recorded with M/EEG is highly variable spatially and temporally, and is highly sensitive to small changes in conditions and internal states, such as arousal or discomfort. For example, although delta activity has been observed as a marker of various abnormal neurological conditions, it is also correlated with conditions such as fatigue or feeling of hunger (Knyazev, 2012). Non-verbalised thoughts and cognitive processes, such as implicit motion, for example, are also known to change oscillatory brain activity in different ways (Fawcette et al., 2007). For examination of clinical conditions such as tinnitus, changes in oscillatory activity could be misinterpreted for condition-related brain activity. Furthermore, changes in oscillatory activity due to internal states, cognitive and random thought processes could underlie the variability in resting state M/EEG data. It is also not known whether tinnitus patients and controls experience the M/EEG recording sessions differently, given that in the former group the perception of tinnitus is likely to alter the experience.

All this makes it expedient to obtain as much information as possible about the state of the participant, their experience, feelings, and random thoughts, during the resting-state data collection.

Recommendation: A resting state questionnaire should be administered to all participants undergoing resting-state M/EEG following the completion of data recording. Specifically, a variation of the self-report Amsterdam Resting-State Questionnaire (ARSQ) (Diaz et al., 2013) that is relevant to tinnitus is being developed by members of the working group.

The ARSQ is a validated tool that quantifies resting-state experiences and is particularly designed for the use of neuroimaging community. ARSQ can be used to quantify the resting-state brain activity and shed further light on the variability between participants and studies. With regard to tinnitus studies specifically, this data when gathered, has the potential to indicate reasons for heterogeneity between participants and studies.

One impending problem is the analysis of the resting state M/EEG data alongside the information from ARSQ, and how to relate the participant feedback on individual elements of the latter to specific changes in oscillatory activity. In order to make meaningful and robust connections between individual elements of ARSQ and oscillatory phenomena, a large dataset of both resting state M/EEG and ARSQ are required in order to identify reliable patterns. However, these data do not currently exist. To this end, the specific suggestion of this committee is that all future resting state M/EEG studies should administer the ARSQ. Effort will be undertaken to find ways to translate the ARSQ in languages for which no translation exists so far. It is envisaged that this collective effort will deliver a large reserve of valuable data, for which the members of the committee can consider appropriate analytical approaches in due course. Overall, it is hoped that this action will pave the way for better understanding the heterogeneity of tinnitus resting state data as well as shed light on the inconsistent findings between research centres.

3) Assessment of Comorbidities

It was shown repeatedly, that severely distressing tinnitus tends to be comorbid with increased indications of depression, anxiety, sleep disorders and somatic symptoms, with depression showing the closest association with tinnitus severity. These conditions are known to have an influence on their own on spontaneous and evoked M/EEG activity. Therefore their contribution needs to be estimated when comparing brain activity of tinnitus patients differing with regard to tinnitus severity and for the comparison with controls without tinnitus. Other working groups within the TINNET programme are considering these issues but for now we recommend that participant groups are matched as far as possible for the existence of comorbidities.

Recommendation: Indications of depression and anxiety should be assessed with self-report questionnaires. There exist several short and well-established inventories that have been repeatedly employed in tinnitus research, and which are available in a variety of languages. A well accepted screener for depression and anxiety is the Hospital Anxiety and Depression Scale (HADS: https://en.wikipedia.org/wiki/Hospital_Anxiety_and_Depression_Scale). A further instrument is the Patient Health Questionnaire (PHQ), a self-report version of the Primary Care Evaluation of Mental Disorders (PRIME-MD) designed for use in primary care. It consists of several short scales that can be used independently. The PHQ9 assesses depression (http://impact-uw.org/tools/phq9.html) and the GAD7 addresses general anxiety (https://en.wikipedia.org/wiki/Generalized_Anxiety_Disorder_7). An advantage of the PHQ over the HADS is that it is free of royalties. A potential limitation of HADS in clinical settings, namely that they do not address suicidal ideation, does not represent a major obstruction for scientific purposes.

Medication: In every experiment, information regarding medication taken by participants and a list of comorbid conditions should be collected from tinnitus and non-tinnitus controls.

Checklist for decisions and considerations that should be made before study start:

Data Collection

- Spontaneous eyes-open Data [ ]
  A total of 5 min recordings each of eyes open and eyes closed divided into 1 min intervals per condition
- Resting-state questionnaire [ ]
- If stimuli are presented, indicate intensity in (dB SPL/SH/HL) [ ]
- If stimuli are presented, include pre-event baseline data [ ]
- Equal treatment across groups (stimuli, conditions etc) [ ]
- Reference electrode (for EEG) (mastoid/earlobes/nose or average of all channels)

  - EEG-recording: Report position of ground electrode, position of reference electrode(s), choose high sampling rate (results in larger files, but later down-sampling is possible), determine filter settings following the Nyquist-Shannon sampling theorem.

  - Reference electrodes

  The position of the reference electrode(s) has been and still is a matter of controversy (e.g. Kayser and Tenke, 2010, Clinical Neurophysiology 121). The following reference electrode positions have shown to yield interpretable results in auditory and tinnitus research and are therefore recommended:

  o Linked ear lobes for recording resting state activity

  o Mastoid (or linked mastoids) for recording auditory evoked potentials

Study Design

- Eyes open/closed [ ]
- Instruction for the participants [ ]
- Fixation cross [ ]
- Resting state questionnaire [ ]
- In ERP studies: Loudness of the stimuli? Consider hearing loss [ ]

Data Pre-processing

- Visual inspection of data [ ]
- Artefact rejection/correction [ ]
- Offline filtering [ ]
- Isolating components (ICA or PCA) [ ]

Data Analysis

- Consideration of measurement time-windows [ ]
- Distributed Source analysis [ ]
- Spectral analysis (include baseline, ideally at source level) [ ]
- Time-frequency analysis [ ]
- Frequency domain analysis (amplitude and phase) [ ]
- Assess amplitude/latency (for evoked response paradigms) [ ]
- Statistical analysis (including effect size) [ ]
- Connectivity analysis (ideally at source level) [ ]

Comorbidities Assessment

- Depression/Anxiety screening HADS or PHQ9 [ ]
- Hyperacusis Assessment [ ]
- Group-matched comorbidities [ ]

Tinnitus Patient Characteristics

- Tinnitus questionnaire (THI/TFI or equivalent) [ ]
- Age-matched groups [ ]
- Hearing loss and audiometric evaluation [ ]
- Matched Hearing loss [ ]

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