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Highlights

Intrinsic cortical excitability is hard to approach for association cortices

Spatial phase synchronization as proxy for excitability has been suggested

Application on MEG data of healthy participants during acoustic stimulation

Excitability decreases in frontal and increases in temporal lobe during exposure

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Auditory white noise exposure results in intrinsic cortical excitability changes

Anna-Lisa Schuler,[1,2,6,*] Diandra Brkić,[1] Giulio Ferrazzi,[3] Giorgio Arcara,[1] Daniele Marinazzo,[4] and Giovanni Pellegrino[5]

SUMMARY

Cortical excitability is commonly measured by applying magnetic stimulation in combination with measuring behavioral response. This measure has, however, some shortcomings including spatial limitation to the primary motor cortex and not accounting for intrinsic excitability fluctuations. Here, we use a measure for intrinsic excitability based on phase synchronization previously validated for epilepsy. We apply this measure in 30 healthy participants' magnetoencephalography (MEG) recordings during the exposure of auditory white noise, a stimulus that has been suggested to modify cortical excitability. Using cortical parcellation of the MEG source data, we could find a specific pattern of increased and decreased excitability while participants are exposed to white noise vs. silence. Specifically, excitability during white noise exposure decreases in the frontal lobe and increases in the temporal lobe. This study thus adds to the understanding of cortical excitability changes due to specific environmental stimuli as well as the spatial extent of these effects.

INTRODUCTION

Measuring the excitability level of the cerebral cortex is of major interest for neuroscientific research and in clinical practice.[1,2] A standard way to access excitability levels is to apply transcranial magnetic stimulation (TMS) in the primary motor cortex and measure motor evoked potentials (MEPs) mostly in the hand muscles: it is assumed that the higher the cortical excitability, the larger the MEP.[3,4] Moreover, dual-coil approaches have been applied to investigate the interaction between inhibitory and excitatory processes on a network level, thus probing the excitability levels of the nodes of the network.[5,6] Similarly to M1, the level of excitability of the primary visual cortex can be assessed by applying TMS to the occipital cortex and measuring the occurrence of phosphenes, which is, however, less objective.[7,8] For other cortical areas, including association cortices, the estimation of cortical excitability becomes even more challenging and less reliable.[9,10] TMS is usually combined with other techniques, i.e., with electroencephalography (EEG;[11,12]) in order to evaluate excitability levels beyond M1. TMS-EEG allows for the estimation of cortical excitability by assessing the effects of TMS stimulation on the EEG in any point of the neocortex.[13–19] However, this method is prone to strong artifacts.[20]

In clinical practice the assessment of cortical excitability levels is especially important for neurological patients that suffer from conditions due to aberrant synchronization of neuronal firing and overexcitability of neurons, such as migraine and epilepsy.[21–24] The methods described previously are time-consuming, rely on an expert for application and subsequent data interpretation, do not allow for reliable evaluation of associative cortices, and are no cost-efficient applications in clinical routine, especially for long-term/longitudinal monitoring of patients.

Recently, an alternative measure for excitability has been introduced that is based on the phase synchronization of EEG or electrocorticography (ECoG) recordings in different frequency bands, especially in the higher gamma range (55–95 Hz).[25] This measure has been validated on a whole-brain level investigating fluctuations of cortical excitability due to subdural stimulation, administration of anti-epileptic drugs and during wake/sleep cycle.[26,27] In a recent study, it was shown that 1Hz electrical stimulation using cortical electrodes (invasive EEG) reduces this intrinsic excitability measure, with the effect localized to the stimulated hemisphere in patients that had bilateral recordings.[28]

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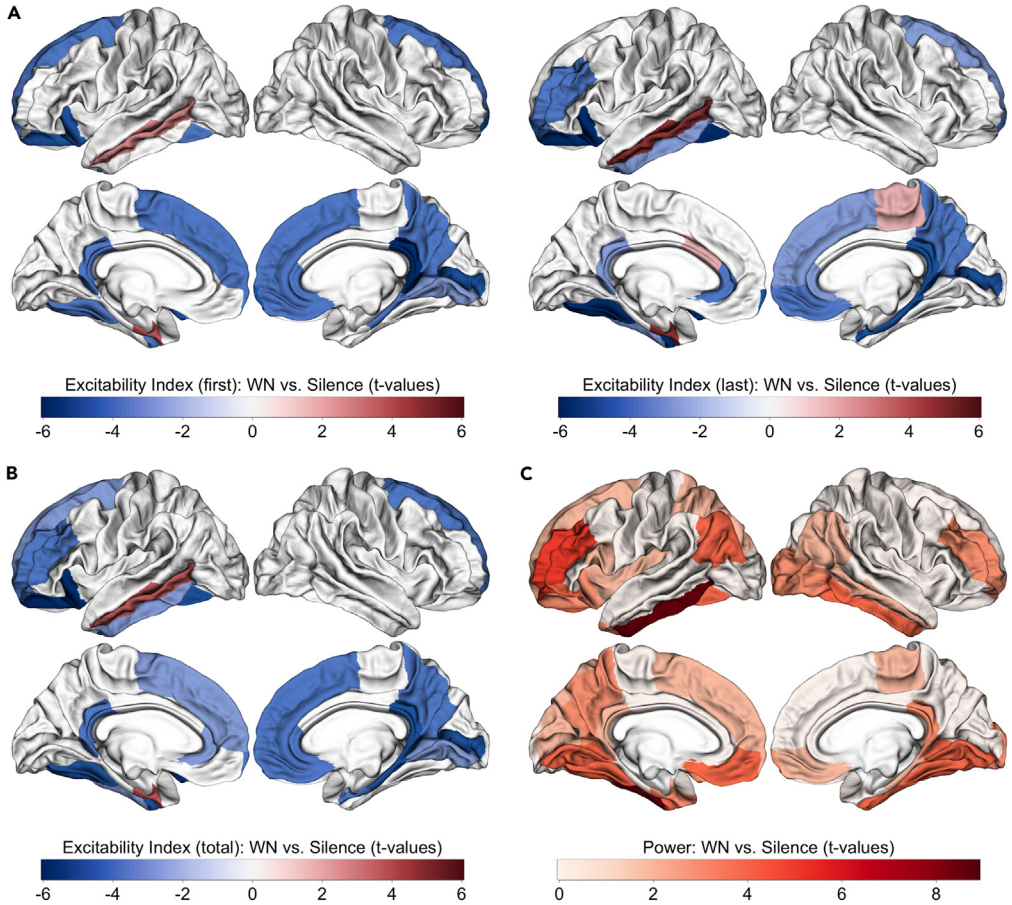

Figure 1. Excitability and Power changes during WN exposure

(A) Comparison WN > Silence excitability for first epochs (left side) and last epochs (right side): Excitability was stronger in the middle temporal gyrus during the last part of the experiment, while excitability decreased in left rostral middle frontal and left inferior temporal cortices.

(B) Comparison WN > Silence excitability for total exposition time: For the whole duration of exposure there were significant excitability decreases along the midline and in left rostral middle frontal and left inferior temporal cortex as well as an increase in left middle temporal gyrus.

(C) Comparison WN > Silence power for total exposition time: Power was higher during WN exposure over various parcels of the cortex, especially in the left hemisphere.

We have recently shown that acoustic white noise stimulation leads to an increase in excitability in the motor cortex and improved sensory-motor integration using TMS and behavioral tasks.[29] We have furthermore shown that this acoustic white noise stimulation decreases cortical connectivity in seven common brain networks in an MEG study.[30]

Following up on these results, we aim at investigating here how excitability changes based on acoustic white noise exposure are reflected in intrinsic excitability measures. For this purpose we calculated phase synchronization as suggested in Meisel et al.[26] on an MEG dataset during acoustic white noise exposure.

RESULTS

Excitability index

In order to investigate, if there is a difference between shorter and longer exposure of white noise (WN) we split the datasets for the 40 first and 40 last sections. Excitability decreased during WN compared with Silence in the left rostral middle frontal and left inferior temporal cortex, while excitability increased in the paracentral cortex during the last epochs of exposure (Figure 1A) as revealed by permutation paired t-tests.

Considering the entire duration of the experiment, there was a significant increase in excitability for the WN condition as compared to Silence in the left middle temporal and left entorhinal parcels (Figure 1B).

Furthermore, there was a significant decrease in excitability within a variety of parcels, especially along the midline, in the (left) frontal, and parietal lobes (Figure 1B, and Table S1).

On a whole-brain level there was a significant decrease in excitability ($t = -8.529$) for WN > Silence over the total time of the experiment.

Power

Beyond excitability, there was a significant increase in gamma power for WN > Silence across several parcels, especially involving the left frontal, temporal, and parietal cortices (Figure 1D, and Table S2). There was no decrease in gamma power during WN exposure.

Relationship between excitability and power

There was no significant correlation between excitability and power after correcting for multiple comparisons as revealed by a Pearson correlation.

Other frequency bands

There was no significant difference for excitability indices between WN and Silence in the theta, alpha, beta, and low gamma bands.

DISCUSSION

In this study, we could show that WN exposure: (1) leads to an excitability enhancement in the middle temporal gyrus that increases over the time of exposure, (2) leads to an excitability decrease in the inferior temporal gyrus and in the rostral middle frontal gyrus as compared to Silence that sets in at least after 4 min of stimulation, and (3) leads to a gamma power increase, unrelated to excitability.

Concerning topographical effects of acoustic white noise stimulation, an early fMRI study,[31] demonstrated that pure white noise stimulation results in an increase in blood-oxygen-level-dependent (BOLD) response in the Heschl's gyrus, superior temporal gyrus, posterior cingulate cortex, cuneus, precuneus, middle temporal gyrus, anterior cingulate cortex, insula, fusiform gyrus, and temporal poles. Our excitability results partly overlap with changes due to stimulation with acoustic white noise in fMRI. It remains, however, an open question, why auditory white noise exposure did not result in a direct change in excitability in the primary auditory cortex or in the primary motor cortex, as recently suggested by our group with a TMS study[29] and by an event-related magnetoencephalography (MEG) study investigating listening within background noise.[32] As we could show here, there might be a temporal component involved in the excitability changes during WN exposure, it might therefore be possible that sustained exposure to WN leads to excitability changes unrelated to primary auditory and motor processing.

In this respect, exposure to acoustic white noise has been shown to have a modulatory effect in a variety of cognitive tasks that are associated with memory and therefore dopaminergic neurotransmission.[33] More specifically, exposure to white noise might influence mnestic processes such as short-term memory, recall and recognition of learned items, and perceptual judgments in the visual and linguistic domain.[33–37]

WN exposure was also shown to increase free verbal recall in inattentive but decrease verbal recall in attentive children.[37] Herweg and Bunzeck (2015) suggested that WN also impaired working memory when exposed during the maintenance phase. Here, we demonstrate that WN exposure decreases cortical excitability in the rostral middle frontal gyrus, a brain area that is involved in memory retrieval and working memory.[38,39]

Furthermore, we found an excitability increase in left middle temporal gyrus excitability, a brain area involved in lexico-semantic retrieval.[40–42] On a behavioral level, in fact, WN exposure has been associated with improved word learning.[34]

In terms of the temporal component of excitability changes there might be a sensitization or habituation effect over time. We observed here an increase in excitability of the temporal lobe but decrease in frontal lobe after 4 min of exposure. This might be explained by a shift between conscious processing of the stimulus toward more primary auditory processing. Moreover, for transcranial random noise stimulation it has been proposed that plasticity effects build up relatively shortly after exposure onset.[43,44] However, more specific research is needed in order to gain more insights into the temporal mechanisms of WN stimulation.

Concerning the relationship between the excitability index used here and power, the validation study by Meisel et al. (2015) has already shown on a group level that there is no relationship between gamma range power and stimulation intensity via cortical electrodes. Conversely, there was a significant relationship between cortical stimulation and the excitability index. We additionally show here that there is no direct group-level correlation between gamma range power and excitability index, underlining the independence of this measure of excitability from simple power. Furthermore, as suggested in Meisel et al. (2015) excitability seems to be specific for the high gamma range.

Taken together, the effects of WN on cortical excitability revealed by an intrinsic excitability measure[26] based on MEG data, show a topographical overlap with fMRI results and are in agreement with behavioral data reported in previous studies.

Limitations of the study

Since the excitability measure applied here was mainly used in the context of epilepsy, it remains to be evaluated how intrinsic cortical excitability in healthy volunteers relates to excitability levels in epilepsy patients. However, the good overlap between behavioral results of previous studies and the localization of our effects suggest that gamma range phase synchronization might be a valid measure to depict excitability changes due to external stimulus exposure.

Future studies remain to be conducted to: (1) Understand the relationship between TMS-based and intrinsically measured excitability and (2) Evaluate the spatial resolution of this measure in patient populations.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2023.107387.

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AUTHOR CONTRIBUTIONS

A.-L.S.: Formal Analysis, Visualization, Writing, Conceptualization.

D.B.: Writing, Conceptualization.

G.F.: Methodology.

G.A.: Resources.

D.M.: Methodology, Conceptualization, Supervision.

G.P.: Conceptualization, Methodology, Formal Analysis, Visualization, Writing, Resources, Data Acquisition, Supervision.

DECLARATION OF INTERESTS

The authors have no conflict of interest to disclose.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Brainstorm Database	Schuler et al., 2023[45]	https://www.openaccessrepository.it/record/77099; https://doi.org/10.15161/oar.it/77099
Software and algorithms		
MATLAB	Matlab[46]	https://it.mathworks.com/products/matlab.html
Brainstorm	Tadel et al., 2011[47]	https://neuroimage.usc.edu/brainstorm/Introduction
RStudio	Allaire, 2012[48]	https://posit.co/downloads/
Excitability Index	Meisel et al., 2015[26]	https://www.pnas.org/doi/abs/10.1073/pnas.1513716112
Code for Calculating Excitability Index	Pellegrino, Ferrazzi & Marinazzo, 2023[49]	https://www.openaccessrepository.it/record/77097; https://doi.org/10.15161/oar.it/77097

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Anna-Lisa Schuler (schuler@cbs.mpg.de).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- Deidentified Brainstorm database is made available under https://www.openaccessrepository.it/record/77099 (https://doi.org/10.15161/oar.it/77099). Due to local restrictions data will be made available upon request to the lead contact. The DOI is listed in the key resources table.
- Code is made available under https://www.openaccessrepository.it/record/77097 (https://doi.org/10.15161/oar.it/77097). Due to local restrictions code will be made available upon request to the lead contact. The DOI is listed in the key resources table.
- Any additional information will be made available by the lead contact upon reasonable request

EXPERIMENTAL MODEL AND PARTICIPANT DETAILS

Experimental models

- human subjects
- caucasian
- mean age: 28.57 $\pm$ 4.18 years
- 24/30 female
- cortical excitability might be in general higher in females and is partly dependent on the menstrual cycle[50]

Participants

Thirty healthy participants aged 20–50 were included (mean age = 28.57 $\pm$ 4.18 years; 24 female) in this study. All participants were right-handed according to the Edinburgh Handedness Inventory (EHI, 88.00 $\pm$ 16.32).[51] Exclusion criteria were: present or past-history of neurological or psychiatric disorders,

hearing deficits, irregular wakefulness-sleep cycle, and use of central nervous system active medications (e.g., antiseizure medications, neuroleptics). In order to check these criteria a trained neurologist interviewed the participants prior to data acquisition. The study was approved by the Research Ethics Board of the Province of Venice, Italy and complied with the 1964 Declaration of Helsinki and its later amendments. Participants signed a written informed consent prior to their participation.

METHOD DETAILS

Materials and procedure

MEG data acquisition and stimulus material

MEG recordings were performed at the MEGLab of the Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) San Camillo Hospital in Venice, Italy. MEG recording consisted of two blocks of 500 s: at rest with no auditory sound (hereafter Silence), and at rest with exposure to white noise (hereafter WN). The order of the blocks within any acquisition was counterbalanced across participants. A schematic representation of the experimental design is provided in Figure S1. Participants additionally underwent an anatomical MRI scan in order to perform source reconstruction.

The position of scalp points including anatomical landmarks (nasion, left and right pre-auricular points) were digitized with a 3D Fastrak Digitizer (Polhemus, Colchester, Vermont, USA) immediately before MEG. MEG scans were performed in a three-layer shielded room with a CTF-MEG (VSM MedTech Systems Inc., Coquitlam, BC, Canada) equipped with 275 axial gradiometers. Head position within the dewar was monitored using three coils attached to anatomical landmarks through the Continuous Head Localization system of the MEG. The sampling rate was set to 1200 Hz.[52] The white noise during WN MEG recordings was digitally engineered in the MATLAB environment (Ver. 2018b, The Mathworks). WN and Silence conditions lasted 500 s each.

Participants lying supine with eyes closed, wearing MEG-compatible earplugs connected to the audio delivery system, were instructed to relax during the recordings. The sound pressure level of WN was set to 85 dB at each earplug. The sound pressure level was checked before each session with a sound meter.[53,54] We opted for this sound level for multiple reasons: (i) this is loud enough to be properly heard by everybody, without the need to adjust for hearing threshold; (ii) this is the sound level to which people are often exposed in daily life (The noise level is roughly 60–65 dB in cities with average street traffic and peaks 90 dB with larger vehicles (trucks and diesel busses).

MRI acquisition and analysis, MEG-MRI co-registration

The brain magnetic resonance imaging (MRI) was performed with a 1.5 T Achieva Philips scanner (Philips Medical Systems, Best, The Netherlands). A 3-dimensional Magnetization Prepared Rapid Gradient Echo (MP-RAGE) T1-weighted scan was acquired using an 8-channel receiver head coil with the following parameters: repetition time [TR] = 8.3 ms, echo time [TE] = 4.1 ms, flip angle = 8°, isotropic spatial resolution = 0.87 mm. MRI data processing was performed with CAT12.[55] Cortical regions were labeled according to the Desikan-Killiany atlas.[56] The mesh of the 'mid' cortical layer, which is equidistant from the white/gray matter and pia mater, was downsampled to 8000 vertices. The co-registration of brain MRI and MEG sensors was performed with Brainstorm applying a surface fitting between the head shape obtained from the MRI, the head points and fiducials digitized with the neuronavigation system at every MEG recording. The procedure relied on a rigid geometrical transformation, with 3 rotations and 3 translations.[57–59]

MEG source imaging

The individual head model was estimated with the OpenMEEG toolbox,[60] applying the Boundary Element Method (BEM), considering one cortical layer and a conductivity of 0.33 S/m. The inverse problem was solved with the whitened and depth-weighted linear L2-minimum norm estimate, also known as weighted minimum norm estimate (wMNE).[61] For further data processing the normal to the cortical mesh between each of the three dipole vectors was considered as dipole orientation. Diagonal noise covariance was estimated from 2 min of empty-room noise acquired for each participant prior to MEG scan. Activity maps were projected onto a cortical template from standard ICBM-MRI.[62]

MEG data processing

A schematic representation of the analysis pipeline is provided in Figure S2. Continuous data was epoched into 100 5-s long epochs. Excitability index (based on specific phase synchronization according to[26]) was then calculated over all epochs within the 68 parcels of the Desikan-Killiany atlas[56] for the WN and Silence conditions. For the calculation of phase synchronization we followed the approach suggested in[26] and focused on synchronization in the gamma band (55–95 Hz). For the exact calculation scheme of the excitability index, please refer to the Materials and Methods section of Meisel et al. (2015). The excitability measure applied here is a spatial measure of phase synchrony in a given frequency band. In contrast, inter-trial phase consistency is a measure of temporal phase synchrony across multiple trials (or resting state chunks of data).[57,58,63,64] As a consequence, whereas it is possible to compute finely spatially resolved inter-trial phase consistency, the computation of the excitability considers multiple time-series across sensors, within a parcel or even across the entire brain.[25–28]

We looked at the total excitability index averaged over all epochs as well as split for the first and last 40 epochs. Additionally, we looked at the whole brain excitability index calculating an average over all parcels. In order to specify the effects were limited to high gamma band, we additionally calculated excitability indices in theta (5–7 Hz), alpha (8–12 Hz), beta (15–29 Hz) and low gamma bands (30–48 Hz).

Furthermore, we calculated power in the same frequency range by means of Mortlet wavelets (central frequency = 1 Hz, temporal resolution = 3 s) within the 68 parcels of the Desikan-Killiany atlas averaged over epochs, time and frequencies.

QUANTIFICATION AND STATISTICAL ANALYSIS

Analytic plan

The primary research question of this study was, if the continuous exposure to WN does modify cortical excitability. To test this hypothesis we applied permutation paired t-tests between WN and Silence, considering the 68 parcels of the Desikan-Killiany atlas (5000 permutations) and setting the significance level to $p < 0.05$, FDR-corrected. In order to evaluate possible changes of the excitability pattern over time, we split the datasets for first and last 40 epochs and calculated paired t-tests for these data samples. Additionally, we compared excitability indices for the whole brain, pooling together (average) all parcels.

Second we were interested if the applied excitability index is distinct from band power. In order to evaluate this we 1. applied permutation paired t-tests analogously to the excitability comparison (see above), and 2. calculated Pearson correlations between WN excitability indices and baseline normalized (WN/Silence) power (significance level set to $p < 0.05$, Bonferroni-corrected).

Finally, we were interested if the effect is only valid for the gamma band. Thus we did additional comparisons (permutation paired t-tests between WN and Silence parcels of the Desikan-Killiany atlas (5000 permutations) with a significance level of $p < 0.05$, FDR-corrected) in the theta, alpha, beta and low gamma bands.

ADDITIONAL RESOURCES

No additional resources were used.