



## Low-frequency electrical stimulation reduces cortical excitability in the human brain

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### ABSTRACT

Effective seizure control remains challenging for about 30% of epilepsy patients who are resistant to present-day pharmacotherapy. Novel approaches that not only reduce the severity and frequency of seizures, but also have limited side effects are therefore desirable. Accordingly, various neuromodulation approaches such as cortical electrical stimulation have been implemented to reduce seizure burden; however, the underlying mechanisms are not completely understood. Given that the initiation and spread of epileptic seizures critically depend on cortical excitability, understanding the neuromodulatory effects of cortical electrical stimulation on cortical excitability levels is paramount. Based on observations that synchronization in the electrocorticogram closely tracks brain excitability level, the effects of low-frequency (1 Hz) intracranial brain stimulation on the levels of cortical phase synchronization before, during, and after 1 Hz electrical stimulation were assessed in twelve patients. Analysis of phase synchronization levels across three broad frequency bands (1–45 Hz, 55–95 Hz, and 105–195 Hz) revealed that in patients with stimulation sites in the neocortex, phase synchronization levels were significantly reduced within the 55–95 Hz and 105–195 Hz bands during post-stimulation intervals compared to baseline; this effect persisted for at least 30 min post-stimulation. Similar effects were observed when phase synchronization levels were examined in the classic frequency bands, whereby a significant reduction was found during the post-stimulation intervals in the alpha, beta, and gamma bands. The anatomical extent of these effects was then assessed. Analysis of the results from six patients with intracranial electrodes in both hemispheres indicated that reductions in phase synchronization in the 1–45 Hz and 55–95 Hz frequency ranges were more prominent in the stimulated hemisphere. Overall, these findings demonstrate that low-frequency electrical stimulation reduces phase synchronization and hence cortical excitability in the human brain. Low-frequency stimulation of the epileptic focus may therefore contribute to the prevention of impending epileptic seizures.

### 1. Introduction

Despite continuing research and the emergence of novel treatment approaches, adequate seizure control remains a major hurdle in the subgroup of epilepsy patients who are resistant to pharmacological treatment (Brodie et al., 2012; Löscher and Schmidt, 2011; Perucca and Tomson, 2011; Ryvlin et al., 2014). In addition, the adverse effects of

antiepileptic drugs remain a leading cause of treatment failure in about 25% of patients (Perucca and Gilliam, 2012). Therefore, the development of novel therapeutic approaches for both drug-responsive and drug-refractory epilepsy patients is highly desirable in order to reduce the severity and frequency of seizures and limit adverse effects (Dalic and Cook, 2016; Moshé et al., 2015). Recent studies have demonstrated that various electrical stimulation techniques, such as vagus nerve

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stimulation (VNS), thalamic stimulation, responsive focus stimulation (Bergey et al., 2015), and chronic subthreshold cortical stimulation (Child et al., 2014; Lundstrom et al., 2016) may offer ways to reduce seizure burden, even in patients who are pharmacoresistant (Fisher and Velasco, 2014; Schulze-Bonhage, 2017). However, the mechanisms by which such neuromodulatory approaches exert their antiepileptic effects are not completely understood and optimal stimulation paradigms have not yet been identified.

Several lines of research suggest that altered levels of cortical excitability in epilepsy patients may arise from a shift in balance between synaptic excitation and inhibition that favours excitation (Galarraga and Hestrin, 1998; Nelson and Turrigiano, 1998; Stafstrom, 2006; Trevelyan and Schevon, 2013). Given that epileptic seizures are complex multiscale phenomena characterized by synchronized hyperexcitation of neurons within networks (Bazhenov et al., 2008), their initiation and spread are presumably sensitive to the overall level of cortical excitability. The critical role of cortical excitability in epilepsy is underscored by antiepileptic drugs (AEDs), which aim to reduce cortical excitability levels via different pharmacological mechanisms (Bialer and White, 2010). Monitoring and controlling cortical excitability is therefore of central importance to epilepsy diagnosis, care, and treatment.

Cortical excitability is usually determined by measuring the transient or steady-state brain response to an electrical or magnetic stimulus (Badawy et al., 2013; Freestone et al., 2011; Matsumoto et al., 2005), such as the size of evoked potentials (Meisel et al., 2015). However, while external brain stimulation measurements such as transcranial magnetic stimulation (TMS) or external electrical stimulation can be applied as a proof of principle and serve as non-invasive, patient-friendly options for identifying or enriching responders, they are not suitable for long-term continuous monitoring of excitability levels. Therefore, tracking excitability levels based on ongoing brain activity using implantable devices could serve as an advantageous, non-stigmatizing means of long-term monitoring and treatment of patients with chronic conditions such as epilepsy.

It was recently shown that synchronization levels of cortical activity may closely track AED action (Meisel et al., 2016; Meisel et al., 2015). More specifically, increased AED levels are associated with reduced levels of phase synchronization in cortical activity in a dose-dependent manner. This suggests that monitoring the level of phase synchronization in cortical activity may provide a means for tracking excitability levels in the human brain based on ongoing activity, without the need for external perturbations.

While electrical brain stimulation may provide an alternative treatment strategy for patients otherwise resistant to treatments, the fundamental mechanisms of action of electrical brain stimulation on cortical excitability are not well understood. Using phase synchronization level changes that arise in response to electrical brain stimulation as an indirect measure of cortical excitability may therefore help to uncover the underlying mechanisms by which electrical brain stimulation affects cortical excitability. In turn, this knowledge may facilitate the development of optimised stimulation protocols and help to determine the most effective target sites for stimulation, the appropriate timing of interventions, and the degree of their efficacy. The present study therefore assessed the effects of low-frequency intracranial brain stimulation at the seizure focus on overall cortical excitability. To this end, phase synchronization as an intrinsic measure of cortical excitability was monitored in several frequency bands before, during, and after 1 Hz cortical stimulation (Meisel et al., 2015).

## 2. Materials and methods

### 2.1. Dataset

Long-term intracranial electroencephalography (iEEG) was recorded in twelve adult epilepsy patients undergoing presurgical evaluation for potential resective treatment (7 males, 5 females). Patients in whom a

single seizure onset zone (SOZ) could be delineated and who only displayed minor disturbances in EEG signal quality introduced by the stimulation setup were consecutively enrolled between August 2018 and November 2020 (Table 1). Written informed consent was obtained from all patients. Board-certified epileptologists visually evaluated the EEG data to verify that it was free from artifacts beyond those induced by the stimulus during the assessment periods. Six patients had electrodes implanted bilaterally. Patients were implanted with strip, grid, and/or depth electrodes based on clinical criteria. Intracerebral electrodes contained 4–12 contiguous contacts consisting of cylinders with an area of 6.53 mm<sup>2</sup> (Epilepsy/LTM Behnke Fried depth electrode, Ad-Tech Medical Instrument Corporation, Oak Creek, USA), or 8.29 mm<sup>2</sup> (Epilepsy/LTM Spencer Probe depth electrodes Ad-Tech Medical Instrument Corporation, Oak Creek, USA). Subdural electrodes contained 4–8 contiguous contacts with an area of 50.26 mm<sup>2</sup> (subdural strip electrodes, Ad-Tech Medical Instrument Corporation, Oak Creek, USA) or 8 × 8 contiguous contacts with an area of 12.57 mm<sup>2</sup> (subdural grid electrodes, Ad-Tech Medical Instrument Corporation, Oak Creek, USA). All of the aforementioned electrode contacts were made from platinum.

The iEEG was typically recorded over a period of 1–2 weeks. Patients were awake and at rest during the measurement period. iEEG data were obtained using a Compumedics digital video-EEG system with Neuro amplifiers containing up to 256 channels at an initial sampling rate of 320 kHz, and a 24-bit analog-to-digital converter. The signal was filtered by the recording system using an analog low-pass filter with a cut-off frequency of 10,610 Hz. For this study, iEEG data was filtered by a digital low-pass 2nd order IIR Butterworth filter with a cut-off frequency of 200 Hz, and downsampled at a sampling frequency of 500 Hz. To minimize noise and artifacts, the electrodes on each hemisphere were re-referenced to an ipsilateral electrode located in white matter, thus enabling electrophysiological activity to be recorded at very low amplitude. This allowed the use of a referential montage with a high signal-to-noise ratio – which is more suitable than a bipolar montage – for the assessment of phase synchronization between channels (Guevara et al., 2005).

Only intracranial recording sites were used for analysis, excluding stimulation channels and channels with artifacts (identified by visual inspection). The trigger channel was used to detect the exact stimulation onsets required to determine the stimulation epochs.

### 2.2. Stimulation

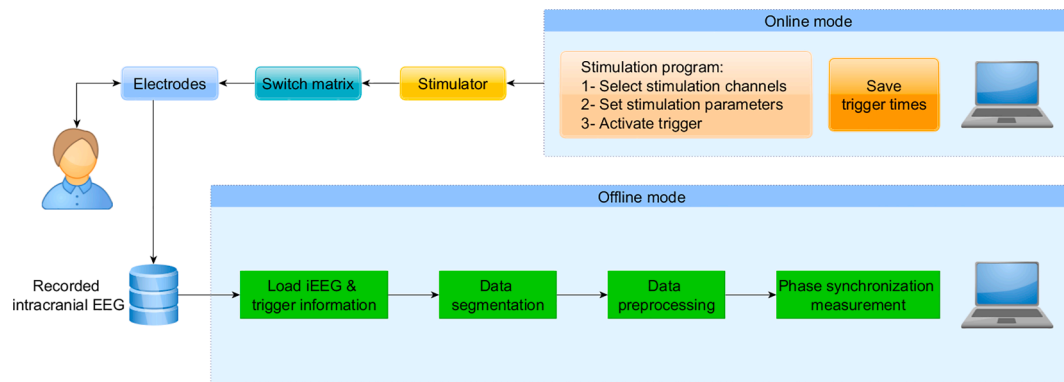
Bipolar stimulation was applied during interictal periods to the SOZ of the epileptic focus, which was visually defined by board-certified epileptologists of the Freiburg Epilepsy Center. The SOZ was defined based on an analysis of recorded seizures independent of this study. Recordings sites varied between patients, since they were determined based on clinical reasons; SOZ sites included the hippocampus, anterior temporal lobe, entorhinal cortex, and cingulate cortex. The stimulation was applied for the purposes of this study only. The recording and stimulation setup is depicted in Fig. 1.

Biphasic rectangular, charge-balanced electric currents (250 μs/phase) were delivered to two adjacent electrodes (with an intercontact distance of 4–5 mm) in the SOZ using a certified constant current stimulator (OSIRIS NeuroStimulator from inomed Medizintechnik GmbH, Emmendingen, Germany) at a stimulation frequency of 1 Hz. Stimulation intensities were below the safety limits for the charge per stimulation phase, and varied between 1.5 mA (hippocampus) and 3 mA (neocortex) (Prime et al., 2018). With electrode contact areas of 6.53 mm<sup>2</sup> and 8.29 mm<sup>2</sup>, the charge density per stimulation phase in all cases was <11.5 μC/cm<sup>2</sup>. This is therefore far below the limit of 57 μC/cm<sup>2</sup>, which has been reported as a biologically safe electrochemical charge injection limit, based on histological findings in humans (Cogan, 2008; Craggs et al., 1986; Gordon et al., 1990; Merrill et al., 2005; Rose and Robblee, 1990; Shannon, 1992; Stieglitz, 2004).

Stimulation was applied in three 10 min blocks (=600 stimulations),

**Table 1**  
Patient-specific information regarding the stimulation and recording procedure.

Patient number	Stimulation region	Stimulation amplitude (mA)	Medication on day of stimulation procedure (mg)	Regions implanted	Number of channels analyzed
1	Hippocampus, right	1.5	Lamotrigine: 100	Left and right temporal lobe and mesiotemporal structures	33
2	Temporopolar cortex, left	3	Eslicarbazepine acetate: 400	Left and right temporal lobe and mesiotemporal structures	70
3	Entorhinal cortex, right	3	Oxcarbazepine: 300	Right temporal and frontal lobes, Hippocampus	29
4	Anterior middle temporal gyrus, left	2	Brivaracetam: 200	Left temporal lobe and mesiotemporal structures	20
5	Anterior cingulate gyrus, left	2.5	Brivaracetam: 300, Zonisamide: 250	Left frontal, parietal and insular lobes	59
6	Temporopolar cortex, left	2.5	Lamotrigine: 150	Left and right temporal lobe (including mesiotemporal structures)	65
7	Temporopolar cortex, right	2.5	No anticonvulsant medication	Left and right temporal lobe and mesiotemporal structures	55
8	Hippocampus, right	2	Oxcarbazepine: 1650, Brivaracetam: 100, Perampnel: 4	Right temporal lobe and mesiotemporal structures	61
9	Temporopolar cortex, right	2.5	Levetiracetam: 2500, Oxcarbazepine: 1800	Left and right temporal lobe	54
10	Anterior middle temporal gyrus, right	2	No anti-convulsant medication	Left and right temporal lobe	63
11	Hippocampus, left	2.5	Levetiracetam: 1000, Lacosamide: 300	Left temporal lobe and mesiotemporal structures	38
12	Temporoanterior cortex, right	2	Eslicarbazepine acetate: 400	Right temporal, frontal, and parietal lobe and mesiotemporal structures	62



**Fig. 1.** Schematic outline of the low-frequency stimulation process and recording setup for phase synchronization measurements. The stimulation program first switches the selected stimulation channels from recording mode to stimulation mode using a multichannel switch matrix. The stimulation program then triggers the stimulator to deliver the stimulation to the selected electrodes. The iEEG data is recorded simultaneously from the remaining electrodes and transferred to the recording computer. Stimulation and interstimulation epochs are determined using the trigger channel. After data preprocessing, mean phase synchronization between all the recording channels is measured.

with 10 min breaks in-between. A 10 min data interval in which no electrical brain stimulation was applied (starting ~ 20 min prior to the first stimulation) served as the baseline for the analysis.

### 2.3. Phase synchronization measurement

iEEG data were analyzed using a moving-window technique. Specifically, the data were first divided into segments of 20 sec each (10,000 sampling points), without overlap. This window length was deemed to be a sound compromise between (i) the required statistical accuracy for calculating the degree of neural synchronization and (ii) the approximation of stationarity within the window's length (Mormann et al., 2000).

Mean phase synchronization was first estimated within three different broad frequency bands (i.e., 1–45 Hz, 55–95 Hz, and 105–195 Hz) (Honey et al., 2012). To avoid interference of power-line noise, data was filtered with a margin of 5 Hz at 50, 100, and 200 Hz. In the second analysis, mean phase synchronization was estimated across the classic EEG frequency bands (delta, 0.1–4 Hz; theta, 4–8 Hz; alpha, 8–13 Hz; beta, 14–30 Hz; and gamma, 30–95 Hz).

Because electrical stimulation leads to the formation of artifacts in the iEEG, the preprocessing steps for baseline and post-stimulation intervals differed from those for the stimulation intervals (which were included as a control). For baseline and post-stimulation intervals, the entire interval was first band-pass filtered with the corresponding low and high cut-off frequencies. This was achieved with a Chebyshev Type II 20th order filter (40 dB stopband attenuation) in the forward and reverse directions to get a zero-phase distortion. The following steps were then performed for each 20-sec segment:

1. Data were tapered with a cosine half-wave (Hanning window) before performing the Hilbert transform.

2. A phase trace  $\theta_i(t)$  of the segment  $E_i(t)$  was calculated by applying a Hilbert transform  $H[E_i(t)]$ :

$$\theta_i(t) = \arctan \frac{H[E_i(t)]}{E_i(t)} \quad (1)$$

3. The calculation of the Hilbert transform requires integration over infinite time, but this is not possible for a window of finite length. Therefore, 5% of the calculated instantaneous phase values were discarded at both ends of every 20-sec segment (10% in total).

4. Phase coherence was used as a time-dependent measure of phase synchronization (Meisel et al., 2015), and calculated by:

$$r(t) = \frac{1}{N} \left| \sum_{j=1}^n e^{i\theta_j(t)} \right| \quad (2)$$

where  $N$  is the number of channels in the data segment.

5. The mean phase synchronization ( $R$ ) in each segment was then quantified by:

$$R = \langle r(t) \rangle = \frac{1}{L} \sum_{t=1}^L r(t) \quad (3)$$

where  $L$  is the length of the data segment in samples.

For the stimulation intervals, the following steps were performed to take the stimulation artifacts into account:

1. To exclude stimulation artifacts, the first and last 20 ms of each stimulation epoch (each lasting 1 s) were removed.
2. Band-pass filtering: data were band-pass filtered in forward and reverse directions using the same filter.
3. The remaining steps were the same as those described in steps 1 to 5 of the phase synchronization measurements of the baseline and post-stimulation intervals.

#### 2.4. Statistical analysis

The effects of cortical stimulation on phase synchronization levels as an indirect measure of cortical excitability were compared between stimulation-free intervals (10 min). Specifically, the baseline interval was compared to both the immediate post-stimulation intervals and the late post-stimulation interval in order to evaluate the persistence of the modulatory effects of the stimulation. The late post-stimulation interval was defined as the last 10 min of the 30-min post-stimulation interval.

In the first analysis, changes in phase synchronization levels were investigated at the patient group level and across all electrodes over the whole brain. For this purpose, the recording channels that were not affected by stimulation artifacts were included. The analysis focused on phase synchronization level changes within three broad frequency bands (1–45 Hz, 55–95 Hz, and 105–195 Hz), because these have been shown to correlate well with AED load and cortical excitability levels, especially those within the higher gamma range (Meisel et al., 2016; Meisel et al., 2015). In addition, to assess the possible differential effects of stimulation sites, patients with stimulation sites in the neocortex ( $n = 8$ ) and archicortex ( $n = 4$ ) were analyzed separately. Changes in phase synchronization levels in the classic, more confined frequency bands (including delta, theta, alpha, beta, and gamma) were then investigated.

To obtain a better understanding of the anatomical extent of the effects of low-frequency stimulation on phase synchronization level changes, a second analysis was performed in which stimulated and non-stimulated hemispheres were compared amongst the six patients with bihemispheric recordings.

To assess the effects of low-frequency stimulation on phase synchronization levels, a one-way repeated measures analysis of variance (ANOVA) with factor period (baseline, post-stimulation interval 1, post-stimulation interval 2, post-stimulation interval 3, and late post-stimulation interval) was conducted. In cases where the ANOVA yielded a significant result ( $p < 0.05$ ), a post-hoc paired  $t$ -test ( $p < 0.01$ ) was performed to compare the baseline period to each post-stimulation interval. In addition, the consecutive post-stimulation intervals were compared with each other. The average phase synchronization levels that were calculated across data segments for each patient were used as

input for the ANOVA.

### 3. Results

#### 3.1. Group analysis of phase synchronization level changes across the whole brain

The mean phase synchronization levels amongst all patients are shown in Fig. 2, separately for the baseline period and each stimulation and post-stimulation interval.

In the 1–45 Hz frequency band, phase synchronization levels were not significantly reduced during the post-stimulation intervals in comparison to the baseline period (ANOVA,  $p = 0.593$ ,  $F = 0.704$ , degrees of freedom (DoF) = 4).

In contrast, phase synchronization levels in the 55–95 Hz and 105–195 Hz frequency bands were significantly reduced during the post-stimulation intervals in comparison to baseline (55–95 Hz frequency band: ANOVA,  $p = 0.030$ ,  $F = 2.800$ , DoF = 4, post-hoc  $t$ -tests, all  $p < 0.001$ ; 105–195 Hz frequency band: ANOVA,  $p = 0.001$ ,  $F = 4.519$ , DoF = 4, post-hoc  $t$ -tests, all  $p < 0.001$ ). Comparison of the consecutive post-stimulation intervals with each other revealed a significant reduction in the 105–195 Hz frequency band between the first and second post-stimulation intervals ( $p = 0.001$ ).

These results show that low-frequency stimulation reduces phase synchronization in the gamma and high-gamma frequency bands. This indicates that electrical brain stimulations leads to a reduction in cortical excitability (Meisel et al., 2016; Meisel et al., 2015).

The average phase synchronization levels across the two groups of patients with stimulation sites in neocortex and archicortex are shown in Fig. 3, separately for the baseline period and each stimulation and post-stimulation interval. For the group of patients with the stimulation site in the neocortex, phase synchronization levels were not significantly reduced in the 1–45 Hz frequency band during the post-stimulation intervals as compared to the baseline period (ANOVA,  $p = 0.075$ ,  $F = 2.384$ , DoF = 4). In the 55–95 Hz and 105–195 Hz frequency bands, phase synchronization levels were significantly reduced during the post-stimulation intervals in comparison to baseline (55–95 Hz frequency band: ANOVA,  $p < 0.001$ ,  $F = 6.748$ , DoF = 4, post-hoc  $t$ -tests, all  $p < 0.001$ ; 105–195 Hz frequency band: ANOVA,  $p < 0.001$ ,  $F = 9.429$ , DoF = 4, post-hoc  $t$ -tests, all  $p < 0.001$ ).

However, for the group of patients with the stimulation site in the archicortex, no statistically significant reduction in phase synchronization levels was observed during the post-stimulation intervals in any of the selected frequency bands (1–45 Hz frequency band: ANOVA,  $p = 0.897$ ,  $F = 0.260$ , DoF = 4; 55–95 Hz frequency band: ANOVA,  $p = 0.984$ ,  $F = 0.091$ , DoF = 4; 105–195 Hz frequency band: repeated measures ANOVA,  $p = 0.934$ ,  $F = 0.204$ , DoF = 4).

#### 3.2. Group analysis of phase synchronization level changes in EEG frequency bands across the whole brain

The mean phase synchronization levels within the classic EEG frequency bands of all patients are plotted in Fig. 4, separately for the baseline period, each stimulation interval, and each post-stimulation interval.

Based on the repeated measures ANOVA test and the post-hoc paired  $t$ -test results, a significant reduction in phase synchronization levels in comparison to baseline was observed during the post-stimulation intervals within the following frequency bands: alpha ( $p = 0.002$ ,  $F = 4.241$ , DoF = 4), beta ( $p < 0.001$ ,  $F = 7.172$ , DoF = 4), and gamma frequency bands ( $p < 0.001$ ,  $F = 10.015$ , DoF = 4). In line with the ANOVA test, the post-hoc  $t$ -test results yielded a  $p < 0.001$  for each of

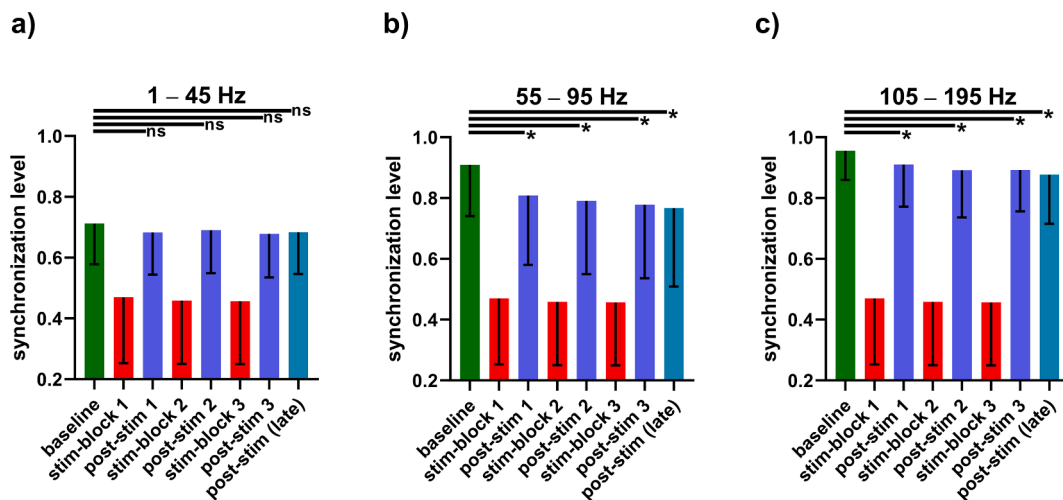


Fig. 2. Mean phase synchronization levels across all patients. a) Bar plot showing mean phase synchronization levels for the 1–45 Hz frequency band during the different periods of measurement. b) Bar plot showing mean phase synchronization levels for the 55–95 Hz frequency band. c) Bar plot showing mean phase synchronization levels for the 105–195 Hz frequency band. \* $p < 0.05$ ; ns, not significant. The black vertical lines in each bar represent the standard deviation. The final 10 min of the 30-min post-stimulation interval was defined as the late post-stimulation interval. A synchronization level of 1 corresponds to 100% mean phase synchronization.

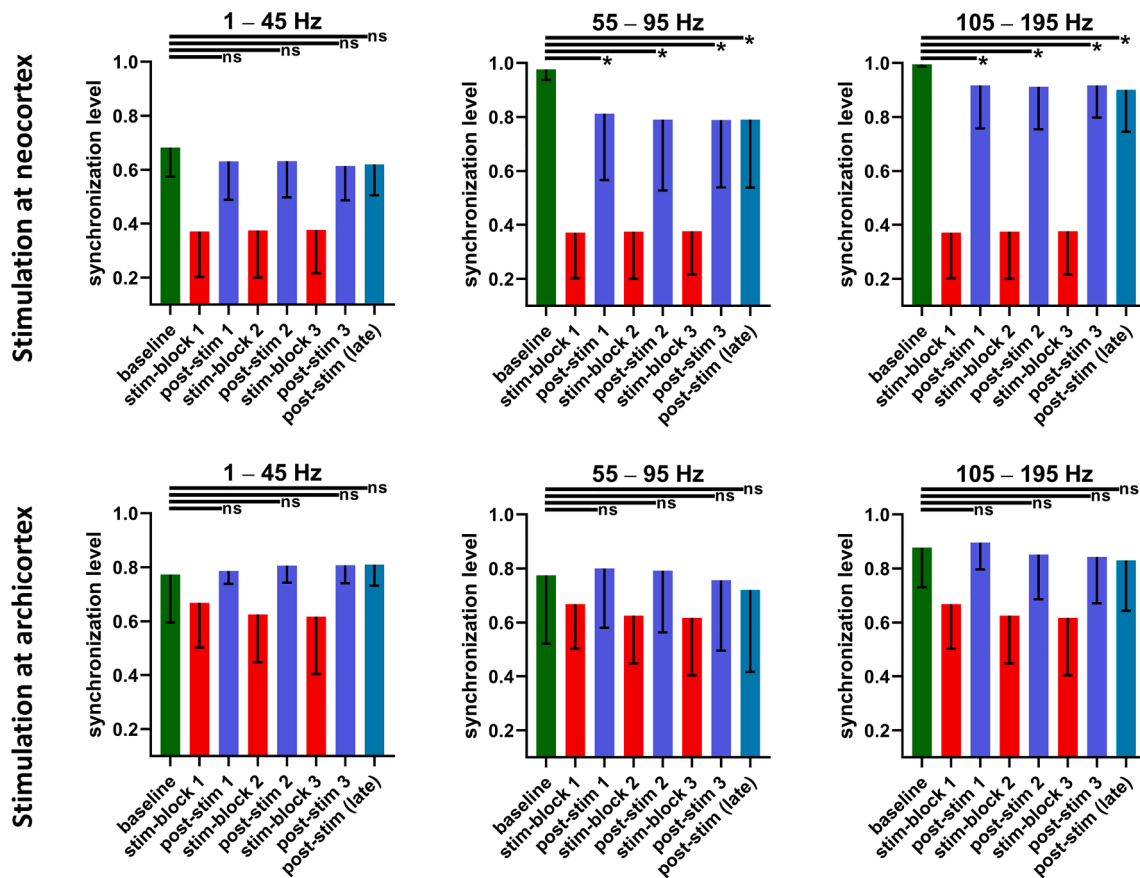
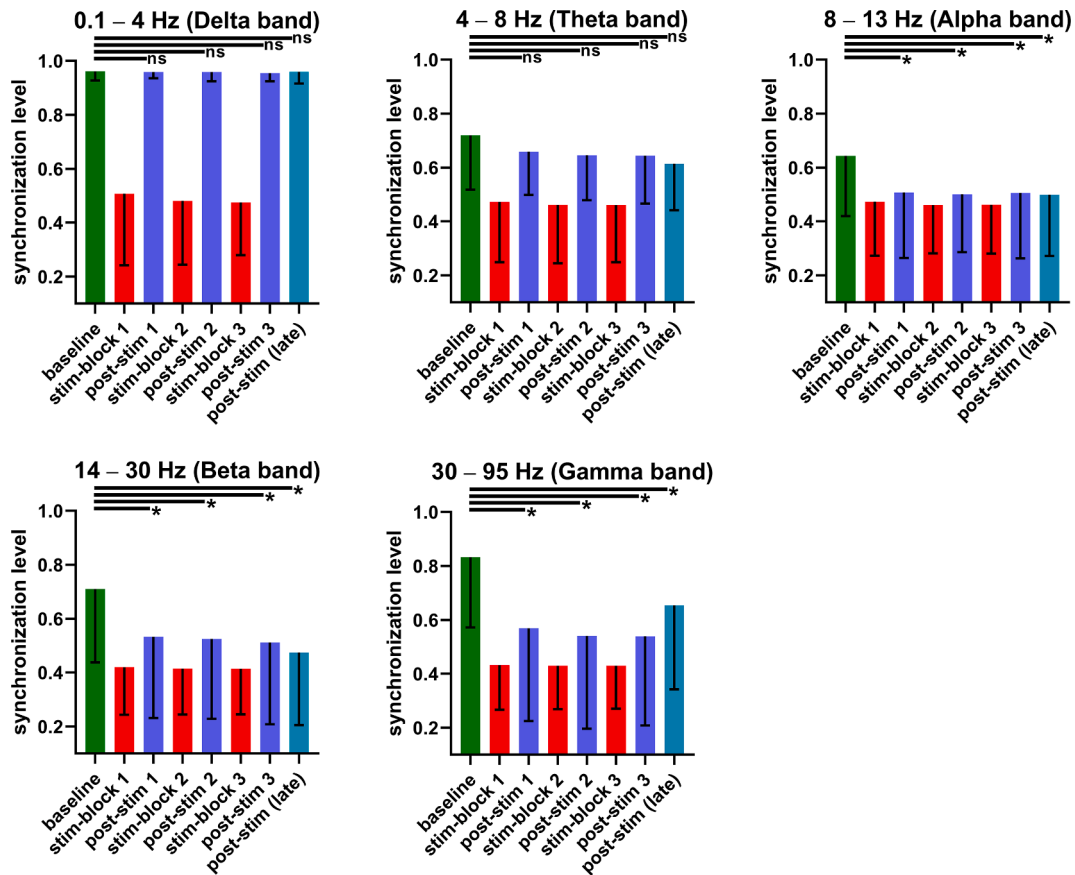


Fig. 3. Comparison of mean phase synchronization levels between patients with neocortical and archicortical stimulation sites. A significant reduction in phase synchronization levels within the 55–95 Hz and 105–195 Hz frequency bands was observed in the group of patients with neocortical stimulation sites, however not in those with archicortical stimulation sites. \* $p < 0.05$ ; ns, not significant. The black vertical lines in each bar represent the standard deviation.

these frequency bands. In contrast, no statistically significant reduction in phase synchronization levels was observed in the delta (ANOVA,  $p = 0.915$ ,  $F = 0.238$ ,  $DoF = 4$ ) and theta (ANOVA,  $p = 0.083$ ,  $F = 2.128$ ,  $DoF = 4$ ) frequency bands. Comparison of the consecutive post-stimulation intervals with each other within the beta frequency band

revealed a significant reduction between the third and fourth post-stimulation intervals ( $p = 0.001$ ). In the gamma frequency band, the phase synchronization level was significantly reduced between the first and second post-stimulation intervals ( $p < 0.001$ ), while it was significantly increased between the third and fourth post-stimulation intervals





**Fig. 4.** Mean phase synchronization levels across all patients in 5 different EEG frequency bands. A significant reduction in phase synchronization levels compared to the baseline period was observed during post-stimulation intervals in the alpha, beta, and gamma frequency bands, whereas no significant changes were measured in delta and theta frequency bands. \* $p < 0.05$ ; ns, not significant. The black vertical lines in each bar represent the standard deviation.

( $p < 0.001$ ).

### 3.3. Comparison of phase synchronization level changes between stimulated and non-stimulated hemispheres

The mean phase synchronization levels across stimulated and non-stimulated hemispheres that were measured during the baseline period, stimulation intervals, and post-stimulation intervals are shown in Fig. 5.

In the 1–45 Hz and 55–95 Hz frequency bands, significant reductions in phase synchronization levels during post-stimulation intervals compared to baseline were observed within the stimulated hemispheres (ANOVA,  $p = 0.016$ ,  $F = 3.899$ , DoF = 4, post-hoc  $t$ -tests, all  $p < 0.005$ ; ANOVA,  $p = 0.004$ ,  $F = 4.423$ , DoF = 4,  $t$ -tests, all  $p < 0.001$ , respectively), whereas no significant reduction was observed in the non-stimulated hemispheres (ANOVA,  $p = 0.071$ ,  $F = 2.545$ , DoF = 4;  $p = 0.065$ ,  $F = 2.384$ , DoF = 4, respectively).

In contrast, within the 105–195 Hz frequency band, a significant reduction in phase synchronization levels was also observed in the contralateral hemispheres (ANOVA,  $p < 0.001$ ,  $F = 8.071$ , DoF = 4, post-hoc  $t$ -tests, all  $p < 0.001$ ; ANOVA,  $p = 0.018$ ,  $F = 3.176$ , DoF = 4, post-hoc  $t$ -tests, all  $p < 0.001$ , respectively).

Comparison of the consecutive post-stimulation intervals with each other revealed that phase synchronization levels were significantly reduced between the first and second post-stimulation intervals not only in the stimulated hemisphere ( $p = 0.003$ ), but also in the non-stimulated hemisphere ( $p = 0.010$ ). Moreover, in the non-stimulated hemisphere, a significant increase in phase synchronization levels was observed between the second and third post-stimulation intervals ( $p < 0.001$ ).

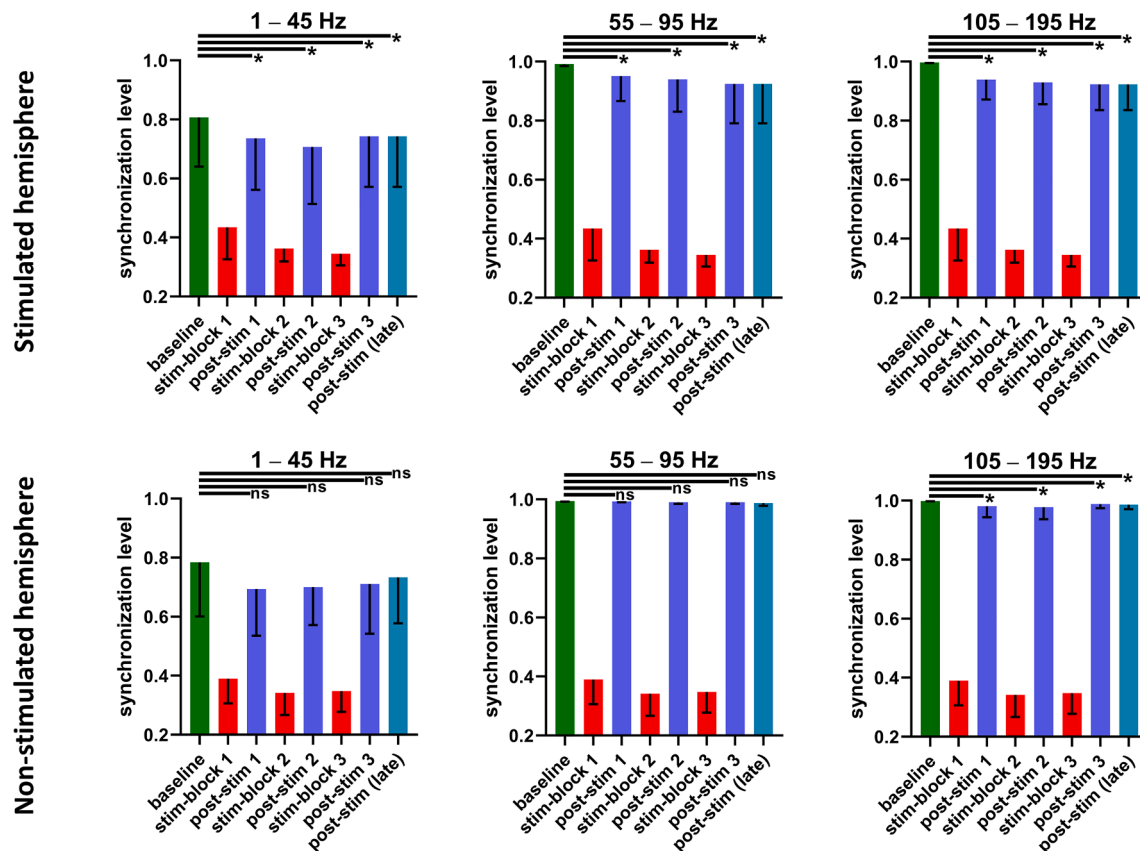
## 4. Discussion

This study investigated the effects of low-frequency (1 Hz) stimulation at the epileptic focus on widespread cortical phase synchronization levels. A significant reduction in phase synchronization levels was observed in patients who received neocortical stimulation. Reductions were observed across alpha, beta, gamma, and high-gamma (105–195 Hz) frequency bands. A comparison between stimulated and non-stimulated hemispheres indicated that the modulatory effects of 1 Hz electrical stimulation were more pronounced in the stimulated hemispheres. Furthermore, an analysis of late post-stimulation intervals indicated that the effects of cortical stimulation persisted for at least 30 min.

A number of studies in animal and brain slices have demonstrated the efficacy of low-frequency stimulation in the suppression of epileptiform activity (Albensi et al., 2004; Mockett et al., 2002). Furthermore, previous studies have shown that low frequency stimulation leads to a reduction in seizure frequency and severity, even in patients with treatment-refractory epilepsy (Lundstrom et al., 2016; Yamamoto et al., 2006). The results of this study now provide a physiological explanation for these effects: Low-frequency brain stimulation reduces cortical excitability, which, in turn prevents the emergence of epileptic seizures.

The application of low-frequency stimulation for the purposes of modulating brain activity is of interest beyond intracranial approaches. For example, a transcranial implantation device (EASEE System, Precisis AG, Heidelberg, Germany) is currently under development, which offers a spectrum of electrical stimulation paradigms for modulation of the epileptogenic area, including low-frequency stimulation.

Low-frequency repetitive TMS (rTMS) is a non-invasive method that



**Fig. 5.** Mean Comparison of mean phase synchronization levels between stimulated vs. non-stimulated hemispheres across 6 patients with bilateral electrode implantations. A significant reduction in phase synchronization levels was observed in the stimulated hemispheres in all frequency bands examined. In contrast, no significant changes were detected in the non-stimulated hemispheres within the 1–45 Hz and 55–95 Hz frequency bands. In the 105–195 Hz frequency band, a significant reduction in phase synchronization levels was additionally observed in the non-stimulated hemisphere. \* $p < 0.05$ ; ns, not significant. The black vertical lines in each bar represent the standard deviation.

has been investigated as a therapy for epilepsy, again with the intention of exerting inhibitory effects (Chen et al., 2016; Kimiskidis, 2010). Lee et al., 2013 applied 1 Hz rTMS to the temporal cortex for 30 min over 5 consecutive days and observed regional hypometabolism in the stimulated areas thereafter (Lee et al., 2013). Likewise, reduced motor-evoked potential amplitudes were reported by Chen et al., 1997 when 0.9 Hz-stimulation was applied to the motor cortex (Chen et al., 1997). This reduction in cortical excitability lasted for at least 15 min after the stimulation period ended (Chen et al., 1997). Low-frequency rTMS has also been reported to reduce the number of epileptic seizures (Fregni et al., 2006; Menkes and Gruenthal, 2000; Sun et al., 2012; Tergau et al., 1999), in part with prolonged effects as well as interictal epileptic discharges (Fregni et al., 2006; Sun et al., 2012), although these observations were not reproduced in other studies (Boon et al., 2018; Theodore et al., 2002).

Low-frequency stimulation may also be of use beyond the scope of epilepsy, and could hold therapeutic potential for a wide spectrum of diseases with altered states of network excitability; these include pain conditions (Di Lazzaro et al., 2008), spasticity (Kuzu et al., 2021), extrapyramidal motor disorders (Vallabhajosula et al., 2015), sleep disorders (Hathaway et al., 2021) and craving (Liu et al., 2017). A better understanding of the underlying neurophysiology as well as the affected aspects of synchronization could further contribute to its targeted application.

One possible explanation for the persistent reduction (at least 30 min) in phase synchronization levels during the post-stimulation interval is the induction of long-term depression (LTD) (Albensi et al., 2004; Keller et al., 2018; Mockett et al., 2002; Schiller and Bankirer, 2007; Yamamoto et al., 2002). A similar study by Schiller and Bankirer (2007),

reported partial recovery of excitatory postsynaptic potentials (EPSPs) in neocortical brain slices after 15 min of 1 Hz stimulation. The authors suggested that this effect was due to the induction of LTD (Schiller and Bankirer, 2007). In the present study, 10 min of low-frequency stimulation was sufficient to demonstrate a depression of cortical excitability, which is well compatible with LTD as a possible underlying physiological mechanism. Understanding the exact mechanism underlying the physiological and functional effects of low-frequency stimulation needs further investigation, including effects on ongoing oscillatory activity.

The observed changes in broadband synchronization levels may help to identify the effects of low-frequency stimulation on cortical network dynamics and seizure propensity in these networks. Previous studies have shown that overall phase synchronization serves as a measure for closely tracking AEDs action (Meisel et al., 2016; Meisel et al., 2015); in particular, the use of cortical phase synchronization as an intrinsic measure of network excitability was particularly robust in the gamma and high-gamma frequency bands.

Understanding the effects of 1 Hz stimulation on different frequency ranges in more detail was possible by analyzing phase synchronization level changes in the classic EEG frequency bands. A significant phase synchronization level reduction was observed during post-stimulation intervals within the alpha, beta, and gamma frequency bands, but not in the delta and theta bands. These results are in line with the notion that synchronous activity in alpha, beta and gamma frequency bands is a robust indicator of cortical excitability level changes. Furthermore, the changes in phase synchronization levels observed in the present study are in line with those reported in the literature (Sobayo and Mogul, 2016).

Brain stimulation has become increasingly used over the last few

years in epilepsy patients who show insufficient therapeutic responses to pharmacological treatment (Schulze-Bonhage, 2017). The first implanted devices were based on VNS, and have been tested in large, heterogeneous patient groups. In the meantime, new devices that enable targeted brain stimulation at the site of seizure generation (cortical stimulation of the epileptic focus) or at network hubs (thalamic stimulation) (Schulze-Bonhage, 2017) have been developed. Such stimulation methods are conducted either in an open-loop or closed-loop fashion. To date, closed-loop stimulation is based either on the detection of tachycardia (in the case of VNS) or on ictal EEG patterns with responsive focus stimulation (Schulze-Bonhage, 2017). Although the therapeutic efficacy of VNS and responsive focus stimulation has already been demonstrated, there is still a considerable proportion of patients in which seizure frequency and severity are not affected by these types of stimulation (Saggio et al., 2020; Schulze-Bonhage, 2017). The results of this study suggest that 1 Hz stimulation reduces cortical phase synchronization levels, particularly in higher frequency bands. Considering phase synchronization levels as an indirect measure of cortical excitability, 1 Hz stimulation can reduce the cortical excitability levels and may therefore exert an antiepileptic effect. Indeed, some studies have indicated the antiepileptic effects of 1 Hz stimulation during the interictal phase, suggesting that this type of stimulation may also be appropriate for open-loop application (Schiller and Bankirer, 2007; Yamamoto et al., 2002). For example, Yamamoto et al., 2006 reported the inhibitory effects of low-frequency (0.9 Hz) stimulation not only during interictal, but also during ictal activities in patients with intractable partial epilepsy (Yamamoto et al., 2006). In addition, phase synchronization has been used as a means of seizure prediction in several studies (Winterhalder et al., 2006; Zheng et al., 2014). Based on these results, another possible stimulation method could be the closed-loop application of low-frequency stimulation: The phase synchronization levels within the cortical tissue could be monitored continuously by intracranial electrodes and, in cases where there is a local significant increase in phase synchronization levels compared to baseline, low-frequency stimulation would be applied to the epileptic focus. This method follows the same principle as that used for application of AEDs, whereby the overall aim is to reduce excitability in cortical tissue. New devices such as the EASEE-System (Precisus AG, Heidelberg, Germany) allow the application of low-frequency stimulation and may therefore offer new approaches to the treatment of focal epilepsy.

Future studies with higher sample sizes should aim to replicate and extend the present findings based on larger datasets, which may then allow the assessment of differential effects based on specific brain regions and their connectivity (Novitskaya et al., 2020). The non-significant phase synchronization level changes from the small patient group who received archicortical stimulation do not exclude changes in excitability, as shown in experimental hippocampal stimulation (Albensi et al., 2004; Mockett et al., 2002). Accordingly, with the use of larger – and preferably more homogeneous – patient groups, it may be possible to address the question of whether the effects of stimulation systematically decrease according to either distance or the anatomical structure (e.g. sublobar or lobar entities).

A limitation of this study was the short duration of the applied low-frequency stimulation; further studies with longer stimulation and recording intervals are thus needed to determine the effects of long-term stimulation, as well as the endurance of these effects. For example, the use of additional stimulation blocks may provide valuable information about the long-term effects of low-frequency stimulation, and aid in assessing the effects of low-frequency stimulation on seizure occurrence and severity. Future studies with long-term designs may further allow to investigate the degree of correlation between phase synchronization level reduction and its anti-seizure treatment effect, i.e., the reduction in seizure burden during and after chronic low-frequency stimulation.

According to the whole brain analysis of the selected broad frequency bands, a significant reduction in phase synchronization levels was observed within the 55–95 Hz and the 105–195 Hz frequency bands.

These observations are in line with those showing that broadband phase synchronization level in the high-gamma ranges are particularly informative about cortical excitability levels (Meisel et al., 2015). They also indicate that the changes in phase synchronization levels are sensitive to the selected frequency band, and band definitions based on physiological processes likely lead to more interpretable results than the equidistant percolations of the available frequency content given by the measurement system.

Further studies with implantable devices allowing for long-term designs are therefore of considerable interest in order to apply the findings of this study for investigating clinical efficacy during inter-ictal and ictal periods.

## 5. Conclusion

In the present study, the effects of 1 Hz cortical stimulation on phase synchronization levels as an indirect measure of cortical excitability were analyzed. A neuromodulatory effect of low-frequency electrical stimulation, at least in the short term, was demonstrated across a broad range of frequencies, from the alpha to the high-gamma frequency bands. Moreover, an analysis of the anatomical extent of these effects on phase synchronization levels revealed that the reduction in phase synchronization levels was widespread, albeit more prominent in the stimulated hemisphere. These findings may serve as a basis for developing novel approaches for focal epilepsy patients whose seizures are insufficiently controlled by AED therapy and who are not eligible for surgical intervention.

## CRedit authorship contribution statement

**Farrokh Manzouri:** Conceptualization, Data curation, Formal analysis, Investigation, Software, Validation, Visualization, Writing - original draft. **Christian Meisel:** Conceptualization, Methodology, Validation, Writing - original draft. **Lukas Kunz:** Investigation, Methodology, Validation, Writing - review & editing. **Matthias Dümpelmann:** Data curation, Investigation, Writing - review & editing. **Thomas Stieglitz:** Supervision, Writing - review & editing. **Andreas Schulze-Bonhage:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing - review & editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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