Direct Electrical Stimulation of the Human Brain Has Inverse Effects on the Theta and Gamma Neural Activities

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Abstract*—*Objective: **Our goal was to analyze the electrophysiological response to direct electrical stimulation (DES) systematically applied at a wide range of parameters and anatomical sites, with particular focus on neural activities associated with memory and cognition.** ***Methods:*** **We used a large set of intracranial EEG (iEEG) recordings with DES from 45 subjects with electrodes implanted both subdurally on the cortical surface and subcortically into the brain parenchyma. Subjects were stimulated in blocks of alternating frequency and amplitude parameters during quiet wakefulness.** ***Results:*** **Stimulating at different frequencies and amplitudes of electric current revealed a persistent pattern of response in the slow and the fast neural activities. In particular, amplification of the theta (4–7 Hz) and attenuation of the gamma (29–52 Hz) power-in-band was observed with increasing the stimulation parameters. This opposite effect on the low and high frequency bands was found across a network of selected local and distal sites proportionally to the proximity and magnitude of the electric current. Power increase in the theta and decrease in the gamma band was driven by the total electric charge delivered with either increasing the frequency or amplitude of the stimulation current. This inverse effect on the theta and gamma activities was consistently observed in response to different stimulation frequencies and amplitudes.** ***Conclusion:*** **Our results suggest a uniform DES effect of amplifying theta and suppressing gamma neural activities in the human brain.** ***Significance:*** **These findings reveal the utility of simple power-in-band features for understanding and optimizing the effects of electrical stimulation on brain functions.**

***Index Terms*—Direct electrical stimulation (DES), intracranial EEG (iEEG), electrocorticogram (ECoG), Theta, Gamma, neural activities, memory enhancement, cognition.**

Manuscript received December 30, 2020; revised April 15, 2021; accepted May 11, 2021. Date of publication May 20, 2021; date of current version November 22, 2021. The work of Michał Lech, Çağdaş Topçu and Michal T. Kucewicz was supported by the First Team Programme of the Foundation for Polish Science co-financed by the European Regional Development Fund POIR.04.04.00-00-4379/17-00 / First TEAM/2017-4/35. Data collection was supported by the DARPA Restoring Active Memory (RAM) program under Grant N66001-14-2-4032. Dr. Gross serves as a consultant to Medtronic, which is a subcontractor on this research. Dr. Gross receives compensation for these services. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict of interest policies. *(Corresponding author: Michał Lech.)*

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This article has supplementary downloadable material available at https://doi.org/10.1109/TBME.2021.3082320, provided by the authors.

Digital Object Identifier 10.1109/TBME.2021.3082320

I. Introduction

DIRECT electrical stimulation (DES) in the human brain has been successfully applied as a therapy in a spectrum of brain disorders. Ranging from movement deficits in motor tremor, muscle dystonias, Parkinson's or Huntington's disease, through to dysfunctional limbic symptoms in the Obsessive Compulsive Disorder, Tourette syndrome, or severe depression, therapies like Deep Brain Stimulation (DBS) have become a standard of clinical care [1]–[7]. More recently, memory deficits as observed in Alzheimer's disease and other dementias are new targets for DES therapies [8]–[11]. Despite the rapid progress in implementing this targeted brain modulation approach, the fundamental neural mechanisms underlying the effects of DES

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remain elusive even in cases of mapping language areas or in other cases such as modulating basic motor functions such as bradykinesia and rigidity as in Parkinson's disease [12], [13].

Memory and cognitive functions have been probed using DES since the classical experiments by Wilder Penfield and others. In these experiments, subjects relayed subjective experience of re-living past events during the application of electric current in discrete regions of the cortex [14], [15]. These pioneering studies searched for a set of parameters for eliciting this effect, proposing that specific patterns of neural activities were evoked by electrical stimulation at a particular frequency and amplitude. Subsequent studies reported changes in memory performance [16]–[18] and other subjective mental phenomena [19] elicited at different electric current frequency and amplitude, which were presumed to modulate specific neural activities. One hypothesis inspired by these studies proposes that patterns of neural oscillatory activity can be entrained by specific parameters of the stimulation current [18], [20] to enhance memory processing. For instance, theta frequency stimulation would entrain local theta rhythm and the associated memory processes. Alternatively, electrical stimulation can affect multiple neural activities locally and across a network of brain regions, which could explain inconsistent effects of DES on memory performance reported in various studies [12], [17]–[21].

Given that stimulating with the same parameters in one brain region can result in various behavioral outcomes depending on the exact location of the electrode, arrangement in relation to the cortical layers and proximity to the white matter tracts [12], several methodological improvements have been proposed for DES studies [17], [20], [21]. Two reports of opposite outcomes in memory performance with using similar DES paradigms [22], [23] prompted a need for careful localization of stimulation sites relative to white matter tracts [24], for larger multi-center studies with reproducible results [23], [25], [26], and for neurophysiological correlates of the behavioral effects [27]. Finally, there is a growing need for basic research into the effects of brain stimulation on specific neural activities. These can be systematically studied by analyzing electrophysiological responses to DES applied at a defined set of current amplitudes, frequencies and other parameters analyzed outside of any task, e.g., during quiet wakefulness. Previous studies were focused on specific network activities and on other measures of cortical network synchrony and connectivity [28], [29]. Here we investigated the effect of DES on basic oscillatory activities (as represented by power-in-band) during quiet wakefulness, ranging from theta to gamma rhythms, in epilepsy patients with intracranial EEG (iEEG) recordings and stimulation from electrodes implanted in various cortical regions. Both theta and gamma rhythms were implicated in processes supporting memory and cognitive functions [30], [31] with known neuronal networks generating these slow and fast oscillations. By quantifying basic oscillatory power responses to DES that was repeatedly applied at systematically changing current amplitude and frequency, our goal was to test whether specific stimulation parameters induced corresponding patterns of neural activities. We first summarized how many electrodes showed any significant power response to changing DES parameters. Then we compared the magnitude and polarity of the significant responses in the frequency bands studied. Finally, power responses in the theta and the gamma bands, where the greatest effect of DES was observed, were correlated with the frequency and amplitude of the stimulating current and the distance from the stimulation site. All of these responses were studied on the group level and also in individual subjects who reported memory enhancement as a result of DES at particular sites [26].

II. Material and Methods

A. Participants and Data Acquisition

Forty five subjects (22 females) undergoing intracranial seizure monitoring for surgical treatment of epilepsy participated in the study. Brain regions selected for monitoring with electrode implantation were determined solely by the clinical requirements of each case. The electrodes were implanted both subdurally on the cortical surface (grid and strip electrodes) and subcortically into the brain parenchyma (depth electrodes) as summarized in Fig. 1d. Bipolar montage was employed with stimulation applied across a pair of neighboring electrodes, where one was an anode and the second one was a cathode. A midpoint between the physical electrodes was adopted for a simplified point localization. One should bear in mind, however, that during stimulation the charge density is the greatest at the electrodes and decreases with distance to the midpoint. The midpoint localization was assumed both for the stimulating and the recording electrodes. All electrodes were used to derive the bipolar montage signals. The coordinates of electrode sites were provided in Talairach space. The electrode sites were plotted onto 3D brain surface using FreeSurfer [32] and Iso2mesh packages [33]. Euclidean distances of all electrode sites showing a significant power change to the site of stimulation were calculated using Matlab *vecnorm* function (MathWorks Inc.). Bipolar differential signals were derived by subtracting all possible pairs of adjacent electrodes to locally remove confounding artifacts from the reference channel recordings. Data were acquired at a sampling rate of at least 500 Hz at multiple clinical locations of this collaborative study: Mayo Clinic, Thomas Jefferson University Hospital, University of Texas Southwestern Medical Center, Emory University Hospital, Dartmouth–Hitchcock Medical Center, Hospital of the University of Pennsylvania, National Institutes of Health, and Columbia University Hospital. The iEEG data signals acquired with higher sampling rate were down sampled to the common frequency of 500 Hz. Written informed consent for participation was obtained from every subject according to the institutional review board approval granted at each of the clinical sites.

B. Stimulation

All experiments were performed as part of a multi-center collaborative project with custom-designed system for brain stimulation (CereStim 96, Blackrock Microsystems Inc., Salt Lake City, Utah). Stimulation was delivered using charge-balanced biphasic rectangular pulses of a width equal to 300 μs at particular amplitudes (0.25–1.50 mA, 0.25 mA steps) and frequencies (10, 25, 50, 100, or 200 Hz) of the electric current for 500 ms, with a minimum of 3 s between subsequent stimulation

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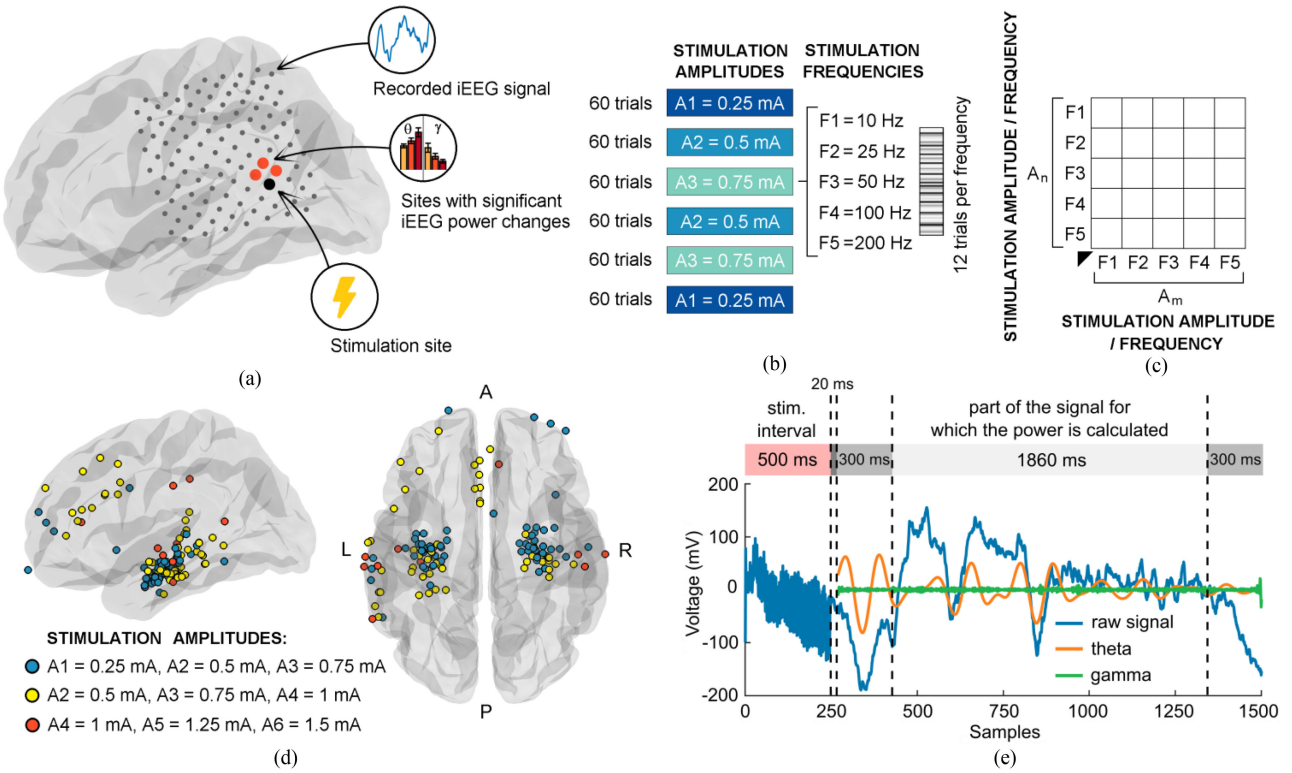

Fig. 1. Direct electrical stimulation of large scale activities in the human brain. (a) Distribution of all bipolar sites (each dot corresponds to midpoint between two neighboring contacts) derived from an example case of 8 × 8 grid of implanted electrodes, recording power changes from intracranial EEG (iEEG) in response to stimulation. (b) Summary of the study design with blocked sets of example three out of six current amplitudes that were tested with each of the five current frequencies. Notice that each amplitude-frequency combination was applied for 24 trials (12 trials in two blocks) to detect instances of significant effect on iEEG signal power. (c) Each two possible amplitude-frequency combinations are compared pairwise with regard to the direction of a parameter change (arrow), each cell showing the number of significant instances. (d) Localization of all stimulation sites from 45 subjects is shown on a unified brain surface color-coded with respect to the set of amplitudes used. (e) Diagram of a single trial delineates boundaries of the post-stimulation interval that was used to estimate the signal power from bandpass filtered signals of low and high frequency activities. Notice that 20 samples after the stimulation pulse were excluded due to possible contamination with noise from stimulus artifact, as well as 150 samples (300 ms) at both ends of the interval to remove filtering artifacts[34].

events. Each subject was stimulated at a set of three amplitude values, which were grouped in this study into the following three groups: A1–A3 (0.25–0.75 mA), A2–A4 (0.5–1.0 mA), and A4–A6 (1.0–1.5 mA). For each of the three amplitude values 120 trials were performed in two separate blocks of 60 trials, ordered pseudo-randomly, as presented in Fig. 1b. Within each block 12 randomly spaced trials with each of the five frequencies were performed. Thus, stimulation at each amplitude-frequency combination was delivered 24 times in the two blocks. During stimulation, subjects were instructed to rest quietly in the bed and neither sleep nor perform any other task. This experimental procedure was applied for 1–8 stimulation sites in the brain, independently as separate sessions spaced across multiple days of the patient stay in the hospital for seizure monitoring. Each experimental session was assisted by a trained epileptologist in case of a seizure.

C. iEEG Power Analysis

An interval of 1230 samples (2460 ms) was separated from the stimulation interval by 20 samples (40 ms) to minimize influence of any propagated noise immediately following electrical stimulation (Fig. 1e) and processed in order to estimate absolute signal power. This fixed, 20-sample separating interval was considered sufficient based on visual analysis of 5000 randomly chosen signals. No inter-trial interval was applied in this study due to a large number of parameter combinations tested. Five frequency bands were selected for the power analysis – theta (4–7 Hz), alpha (8–13 Hz), beta (14–28 Hz), low gamma (29–52 Hz), and high gamma (68–115 Hz). The band between 52 and 68 Hz was excluded to eliminate confounds from the electrical line noise on the power estimates. To calculate power of the theta, alpha and beta oscillations, the signal was first filtered for the corresponding bands using minimum-order IIR elliptical filters. For the low and high gamma frequencies Kaiser window minimum-order FIR filters were applied. Filters were automatically assigned and designed using Matlab R2018a *bandpass* function (Mathworks Inc.), based on the provided frequency band ranges and signal characteristics that were derived by the function.

Both in case of the IIR and FIR filters a stopband attenuation was equal to 60 dB and a passband ripple was equal to 0.1 dB. Filter orders were equal to 12, 12, 14, 410, and 176, respectively to the five frequency bands. The *bandpass* function compensated for the delay introduced by the filters. Prior to filtering, linear trend was removed from the signal using Matlab *detrend* function. The average power was calculated in the time

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domain by summing squared sample values and dividing the result by the total number of samples. In each frequency band the average power was normalized by dividing it by the total average power being a sum of average power in 4–52 Hz and 68–115 Hz frequency bands for the corresponding low or high frequency bands studied.

To calculate power in the 4–52 Hz band the signal was filtered using minimum-order IIR elliptical filter, designed using the Matlab *bandpass* function (stopband attenuation = 60 dB, passband ripple = 0.1 dB, order = 16). In order to remove filtering smoothing artifacts occurring occasionally on the edges of the signal [34], first and last 150 samples (300 ms) of the bandpass filtered signals were excluded from further analysis. The 150-sample period was chosen based on signals exhibiting the largest filtering artifact.

D. Deriving sites with Significant iEEG Power Changes

In each of the five frequency bands studied, relative power response to amplitude and frequency of the stimulation current was compared using two-way ANOVA. Hence, we determined electrode sites showing a significant power change in response to changing both current amplitude and frequency. Each combination of the current amplitude and frequency response was represented by 24 values given that there were 24 trials of stimulation with the same parameters at any one stimulation site. A post-hoc procedure with Dunn-Sidak correction for multiple comparisons was applied to identify individual instances of significant power change in response to changing parameters of the stimulation current from one amplitude-frequency combination to another. Given that there were $n = 15$ amplitude-frequency combinations of the stimulation current (3 amplitude values x 5 frequency values), the number c of all possible post-hoc comparisons (the maximum number of instances with a significant power response) was equal to 105, according to the following equation:

$$c = n(n-1)/2$$

The power responses were separated into either increases or decreases of magnitude with increased amplitude and frequency of the stimulation current.

E. Noise Filtering and Removal of Artifacts

Signals highly affected by an electrical line noise or containing sharp-wave transitions like the inter-ictal epileptiform spikes, resulting in the Gibbs phenomenon after filtering [35], [36], were excluded from the analysis. To quantify the ratio between the line noise and iEEG signal the interval of interest (1230 samples after the stimulation) was filtered for the full gamma band (29–115 Hz) using a 4-th order Butterworth bandpass filter. First and last 150 samples (300 ms) of the filtered signal were excluded from further analysis to remove filtering artifacts. The obtained signal was z-scored and short-time Fourier transformed to create a spectrogram with dimension of 101 x 87 (time domain range x frequency domain range). A Hamming window of 128 samples and an overlap of 100 samples were applied. For each time point n of the spectrogram a median value $m(F_n)$ of all the frequency values F_n was calculated using Matlab medfreq function. A median value M of all the median values $m(F_n)$ was calculated. A signal was determined to be contaminated with the line noise if the following condition was met:

$$\underset{n}{V} |m(F_n) - M| < thr$$

where *thr* is a threshold frequency range equal to 6 Hz.

Exclusion of the signals containing the epileptiform spikes or another sharp transitions resulting in the Gibbs phenomenon was performed according to the following procedure. A spectrogram of each z-scored signal, after bandpass filtering in each frequency band, was obtained. For each time point n of the spectrogram a sum $s(F_n)$ of all the frequency values F_n was calculated. It was assumed that the signal contained the sharp transitions if the following criterion was met:

$$\hat{s}/M > thr$$

where $\hat{s}$ and M are a mean and a median value of all the $s(F_n)$ values, respectively, and *thr* is a threshold value representing phenomenon critical level of the Gibb's artifact. As signals were relatively short (2460 ms), power was assumed to be uniformly spread across time. It was confirmed manually in individual spectrograms that were not affected by either this artifact or the line noise. Thus, the applied method results in the ratio values centered around 1 in case of artifact-free signals. Values in the range of 2–5 correspond to signals containing sharp transitions expected for physiological processes, including sharp-wave ripple complexes [37]–[39] and other high frequency oscillations [40], [41]. Ratio values equal to or greater than 5 meant that the signal contained sharp transitions of pathological or non-physiological origins, which were excluded from further analysis.

F. Statistical Testing

To assess the effect of changing DES parameters on the iEEG power response in the entire population of 45 subjects and in individual subjects, we used non-parametric Kruskal-Wallis analysis of variance with post-hoc Dunn-Sidak approach adjusting for multiple comparisons. These tests were used to compare the following relationships: proportions of all sites that showed significant power changes in the theta and gamma band in response to the three sets of stimulation amplitude (Fig. 2b); proportions of instances with either higher or lower power within those sites (Fig. 2c); mean estimates of the iEEG power for 15 amplitude-frequency combinations, which were assessed both for the entire population (Fig. 4) and for individual subjects with respect to the memory effect (Fig. 5). The significance level α in each case was equal to 0.05.

A relationship between the number of instances of a significant power response, taken from all 45 subjects, and the distance from the stimulation site was assessed using Spearman's rank correlation coefficient r_s (Fig. 3). P-values for the correlation coefficients were computed using the exact permutation distributions. Given that the power values were correlated across discrete ordinal variables, Pearson correlation was not appropriate for this test. The Spearman's rank correlation with exact permutation distributions was also applied in assessing a relationship

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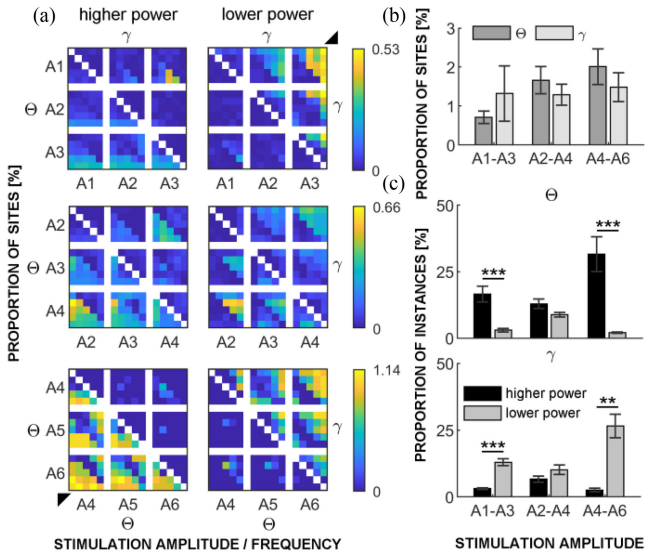

Fig. 2. Stimulation at increasing amplitude and frequency induces gradually more higher power responses in the theta and more lower power responses in the gamma band. (a) Matrices summarize the total proportion of electrode sites that showed significantly higher (left) or lower (right) power in the theta (left diagonal half of each matrix) and in the gamma (right diagonal half of each matrix) bands in response to all possible combinations of amplitude and frequency of the stimulation current (each pixel is one combination of the F1–F5 frequencies and three of the A1–A6 amplitudes – both ordered from top to bottom and from left to right). Notice that the bottom left and the upper right of the matrices reveal consistently more sites with significantly higher power in the theta and lower power in the gamma bands, in response to increasing amplitude and frequency of the stimulation current. (b) Total proportions of all sites, which showed significant power changes in the theta and gamma band in response to the three sets of stimulation amplitude. Note: these mean values correspond to 0–8 sites on average in any one subject experiment. (Kruskal-Wallis test, $p = 0.150$) (c) Within the set of electrode sites that showed significant power responses in the theta (top) and gamma (bottom) band there were increasingly more responses to particular amplitude-frequency combinations of the stimulating current (instances). A1 = 0.25 mA, A2 = 0.5 mA, A3 = 0.75 mA, A4 = 1 mA, A5 = 1.25 mA, A6 = 1.5 mA.

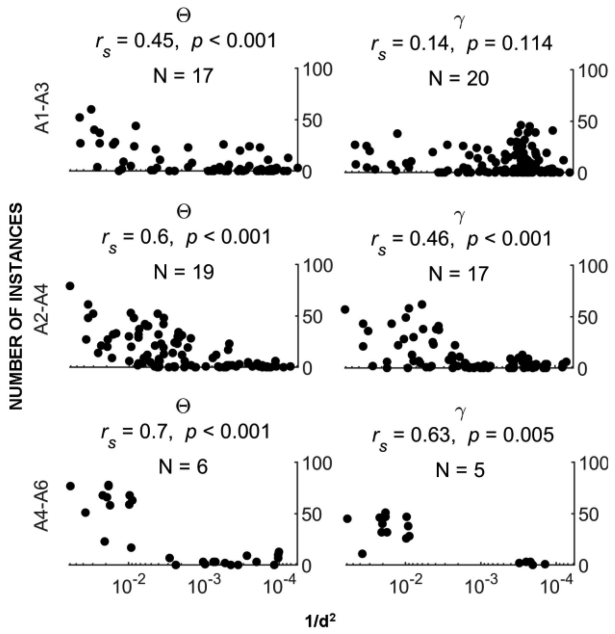

Fig. 3. The number of instances of significant power changes is correlated with distance from the stimulation site. Scatterplots summarize the number of all instances of a significant power response in the theta (left) and gamma (right) bands as a function of $1/d^2$, where d is the Euclidean distance from the stimulation site (each dot corresponds to an electrode site from one of N subjects). Notice that there were increasingly more responses to particular amplitude-frequency combinations of the stimulating current (instances) close to the stimulation site (left side of each figure) (Spearman correlation, $p < 0.01$) for all three amplitude groups, except for the gamma responses to the lowest amplitudes group (upper right). A1 = 0.25 mA, A2 = 0.5 mA, A3 = 0.75 mA, A4 = 1 mA, A5 = 1.25 mA, A6 = 1.5 mA.

between the parameters of the stimulation current and power estimated for each site that showed a significant response to stimulation (Fig. 4b). The significance level α in each case was equal to 0.05.

G. Memory Enhancement Effect

The patterns in iEEG power responses that were obtained for the whole population of subjects were also investigated in selected individuals who had been reported with stimulation-induced memory enhancement during a free-recall memory tasks in our previous studies [26], [27]. The tasks were based on classic paradigms for probing verbal short-term memory, in which subjects learned lists of words for subsequent recall. Two sessions were performed separated by at least three hours. Each session consisted of 25 lists of an encoding-distractor-recall procedure with electrical stimulation applied during the encoding of words on 20 out of 25 randomly assigned word lists. Memory performance was quantified as the count of words recalled per list (with or without stimulation). To normalize the effect of stimulation on the performance, the raw counts from all sessions in a given subject were transformed into z-scores. Difference between means of the scores on the stimulated and the non-stimulated lists was defined as a measure of the effect of stimulation on memory performance [27], defined here as the memory effect (ME). Positive or negative ME values corresponded to an enhancement or an impairment of recall, respectively.

G. Data Availability

All de-identified raw data used in this study may be requested at: http://memory.psych.upenn.edu/Electrophysiological_Data

III. Results

Our study focused on bipolar electrode 'sites' that showed a significant change of the iEEG signal power in response to changing amplitude and frequency of the stimulating current. Herein, a statistically significant power change in response to a particular amplitude-frequency combination of the stimulation current is defined as an 'instance' (Fig. 1a–c). DES was applied from depth or subdural electrodes localized mainly but not exclusively in the mesial and lateral temporal cortex (Fig. 1d). Effect of DES on the instances of significant iEEG power response were quantified in a selected post-stimulation period (Fig. 1e)

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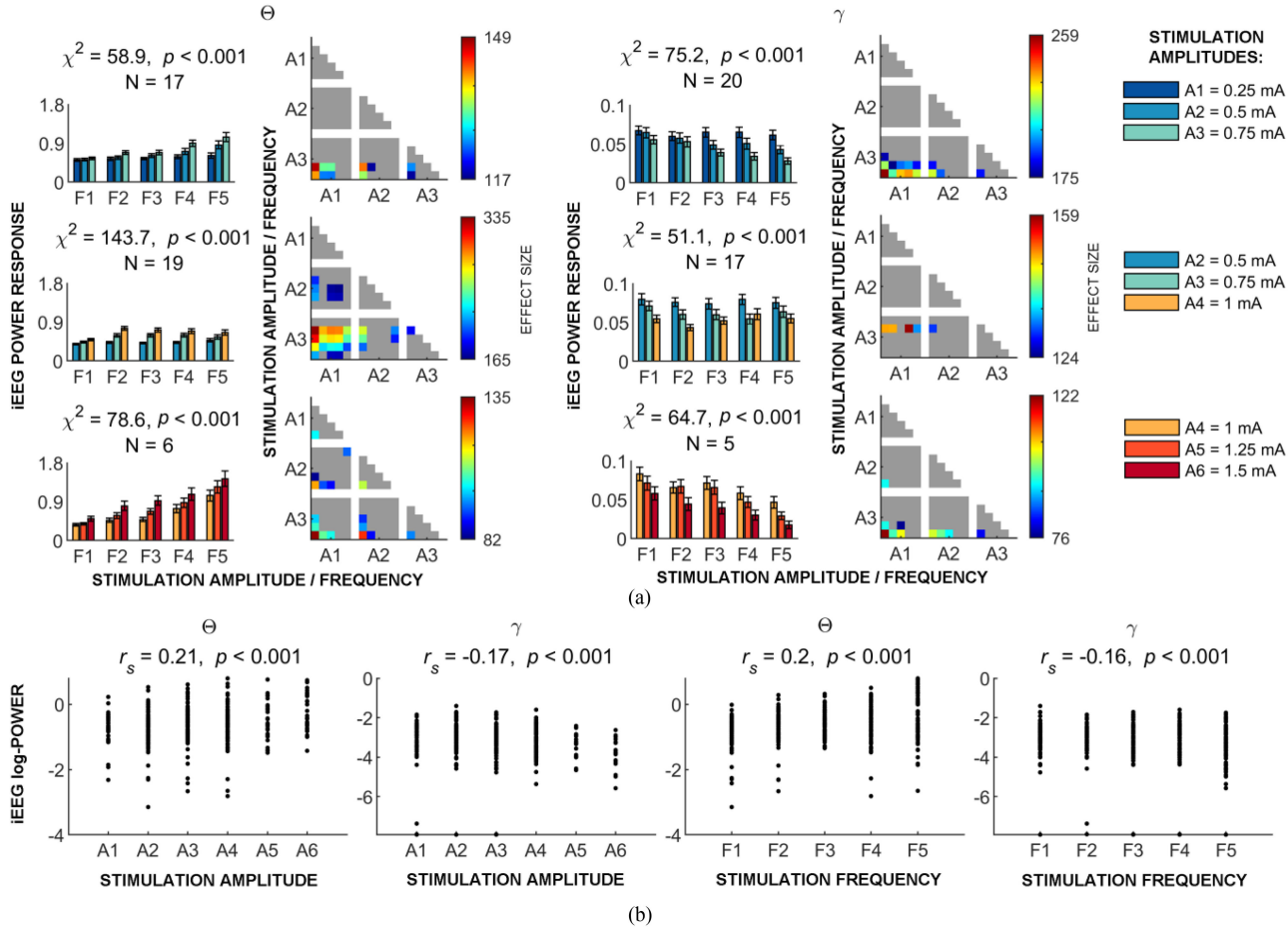

Fig. 4. Theta power is increasing whereas gamma power is decreasing relative to the amplitude and frequency of electrical current stimulation. (a) Mean estimates of the theta (left panel) and the gamma (right panel) power are compared according to the amplitude (color-coded) and frequency of the stimulation current with statistical comparison between all possible groups presented as significance matrices on the right (Dunn-Sidak approach, $p < 0.05$; gray means non-significant). Notice the clustering in the corners of the matrices, confirming significantly increasing and decreasing power of the theta and gamma activities in response to gradually higher stimulation amplitude and frequency across all electrode sites and subjects (N). (b) Scatterplots reveal significant correlations of the current amplitude (left panel) and frequency (right panel) with the power estimated for each site with a significant response to stimulation (dot) taken from all 45 subjects (Spearman correlation, $p < 0.001$). Notice consistent positive correlations for the theta power and opposite negative correlation between the stimulation amplitude and the gamma power. F1 = 10 Hz, F2 = 25 Hz, F3 = 50 Hz, F4 = 100 Hz, F5 = 200 Hz.

with minimum influence of electric current from the stimulation interval.

The effect of DES can be quantified with the total number of sites (brain regions) that showed a significant response (instance) or with the total number of instances that occurred on selected sites. We first quantified total number of sites that showed either a significant increase or decrease of the theta (4–7 Hz) and gamma (29–52 Hz) iEEG power in response to all pairwise combinations of the electric current amplitude (0.25–1.5 mA) and frequency (10–200 Hz) parameters investigated in this study. Increasing both the amplitude and the frequency of the stimulation current resulted in more sites showing higher theta power and lower gamma power (Fig. 2a, each pixel represents a percentage of sites that showed a significant change of iEEG power as in Fig. 1c; two-way ANOVA, significance level $\alpha = 0.05$). This effect was observed across the three stimulation amplitude groups with the strongest effect in the highest A4–A6 group. A similar trend was observed in the overall proportion of sites showing the theta response (Fig. 2b). That proportion increased from approx. 0.7 to 2%, as compared between the lowest and the highest stimulation amplitudes. The signals were recorded on average from 112, 100, and 115 electrode sites per subject for each amplitude group, respectively (see Supplementary Table T1). The number of sites showing a significant response in any one subject ranged between 0 and 8.

In some subjects no instances of the power response either in the theta or in the gamma band were recorded. In the 26 subjects stimulated with the lowest amplitudes, stimulation in 52 out of 67 sites resulted in a significant power change either in the theta or in the gamma frequency band. Likewise, in the 22 subjects stimulated with the intermediate amplitudes (A2–A4), a power response to changing the stimulation parameters was observed in sites surrounding 43 out of 54 stimulation sites. All 7 subjects stimulated with the highest amplitudes (A4–A6), for all 10 stimulation sites, showed a theta (9 stimulation sites) or a gamma (7 stimulation sites) response. Disregarding the subjects with no significant power response (in the low and intermediate amplitude groups), increased the average proportion of all

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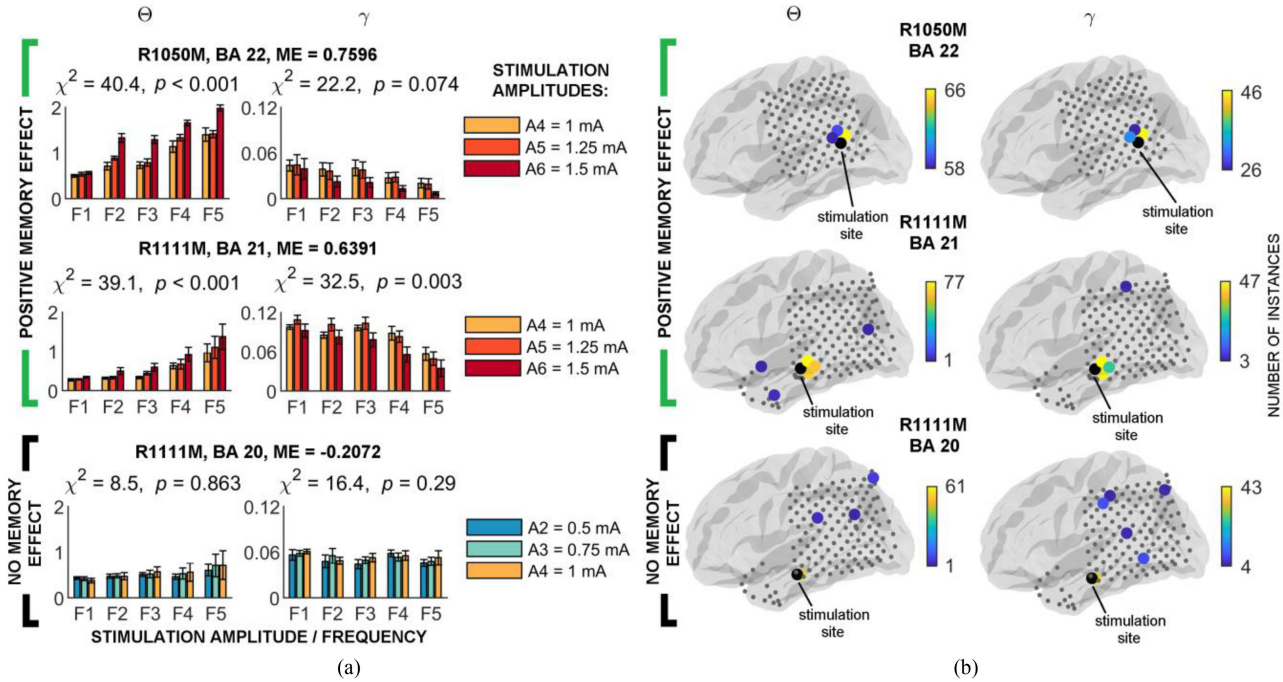

Fig. 5. The theta and gamma power responses are associated with behavioral effects of stimulation on memory performance. (a) Mean estimates of the theta (left) and gamma (right) power confirm the same trends as in Fig. 4 for two stimulation sites (upper and middle row) in two subjects with significant verbal memory enhancement (ME – memory effect) reported previously [26] but not for the same subject stimulated at a different site and a negative memory effect (bottom row). (b) Anatomical localization and the number of instances with significant theta (left) and gamma (right) power response to electrical stimulation are provided on the average brain surface plots. Notice clustering of the significant response sites in close proximity to the stimulation points (midpoint between two neighboring contacts), where the memory effect was reported when stimulating the lateral temporal cortex (Brodmann areas 22 and 21), but not in case of the inferior temporal cortex (Brodmann area 20) with no memory effect. F1 = 10 Hz, F2 = 25 Hz, F3 = 50 Hz, F4 = 100 Hz, F5 = 200 Hz.

sites that showed a significant response by approximately 0.5 percentage points.

In those 0.7–2% of sites with significant power responses to DES, there were consistent differences between the theta and gamma iEEG activities when the instances of power increase and decrease were separated. Similar to the trends in the proportion of sites (Fig. 2a), there were more instances of a higher power response in the theta band with increasing stimulation amplitude (Fig. 2c). Inversely, there were more instances of a lower power response in the gamma band with approximately twice as much response instances to the highest stimulation amplitudes compared to the intermediate and the lowest amplitude groups (Fig. 2c). In general, DES amplitude had a significant effect on the instances of higher or lower power responses (Kruskal-Wallis test, $p < 0.001$ both for theta and gamma), which had opposite direction for the theta (positive) and the gamma (negative) activities. For stimulation amplitude groups A1–A3 and A4–A6, there were significantly more instances of increasing (higher) theta power and of decreasing (lower) gamma power (post-hoc test, Dunn-Sidak approach, $\alpha = 0.05$). The disparity was the largest for the highest amplitude values (Fig. 2c; A4–A6) where proportions of the higher and lower power responses ranged approx. between 30% and 2% (Dunn-Sidak, $p < 0.001$ both for theta and gamma). Hence, changing the parameters of stimulation increased not only the general proportion of responsive electrode sites (Fig. 2a) but also the proportion of the theta and the gamma higher and lower power instances within those responses (Fig. 2c). The overlap between the sites that showed the increased theta power and the decreased gamma power was equal to 59% (expressed as the Szymkiewicz–Simpson coefficient). 47% and 52% of the theta and the gamma sites, respectively, overlapped with the other band.

Are these instances more likely to occur close to the site of electrical stimulation? The number of instances was correlated with the distance from the stimulation site (Spearman correlation, $r_s < -0.45$, $p < 0.001$) for all amplitude groups, except for the smallest ones in case of the gamma responses (Fig. 3). The highest values were observed within a local perimeter of the stimulation site (< 20 Talairach space units) with fewer instances observed at greater distances. These results show that the neural activities were modulated both locally and at a distance in proportion to proximity of the stimulation site.

Herein, we define a response as either a change in the number of instances or sites that show a significant change of the power-in-band, or a change in the magnitude of the power-in-band. Mean power of the theta and gamma response estimated for each responsive site revealed a robust pattern of changes to increasing amplitude and frequency of the stimulation current (Fig. 4a).

Theta power on trials with high stimulation amplitude or frequency was significantly greater (Dunn-Sidak approach, $p < 0.05$) than when the electric current was applied at lower parameters. An opposite pattern was confirmed for the gamma power, which was significantly lower on trials with increasing

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amplitude and frequency of stimulation (Dunn-Sidak approach, $p < 0.05$). This progressive ascending and descending 'stairway' pattern was most evident for the largest stimulation amplitudes (A4–A6). We confirmed a significant correlation between the mean power-in-band and the increasing parameters of electric current in all cases (Spearman correlation, $p < 0.001$). This gradual response to either amplitude or frequency of the stimulating current suggests that it is the total amount of electric charge that drives these changes in the theta and gamma activities. The amount of electric charge can either be increased by elevating the current amplitude or the number of current pulses during the stimulation burst (i.e., frequency). Increasing pulse width would be another way of increasing the total amount of charge but this parameter was kept constant in this study. We did not observe any particular amplitude or frequency of the stimulating current to exert a selective effect on the power of oscillations in these or other frequency bands (see Supplementary Figure F2 for all the studied bands).

Although in this manuscript we focused on the theta and gamma frequency bands, consistent trends were observed in the alpha and the beta frequency bands. The alpha power was gradually greater and the beta power gradually smaller with increasing electric current amplitude or frequency (see Suppl. figure F2). The pattern of the alpha response, even though visible for the smallest and middle stimulation amplitudes (range A1–A4), was not statistically significant (Kruskal-Wallis test, $\chi^2 = 12.5$,$p = 0.566$ and $\chi^2 = 13.2$, $p = 0.515$, respectively). The decreasing pattern of the beta response was statistically correlated with the electric current parameters in every amplitude group ($\chi^2 = 113.5$, $p < 0.001$; $\chi^2 = 26.6$, $p = 0.022$; and $\chi^2 = 60.4$, $p < 0.001$, respectively for the three amplitude groups) (see Supplementary Figure F2).

In our previous study of the effect of DES on verbal memory in the same subjects [26], we reported that electrical stimulation in specific brain regions of the lateral temporal cortex and applied at a defined set of parameters during word encoding led to enhanced recall performance of the stimulated word lists. The same memory enhancing effect was subsequently confirmed in this brain region even with a different stimulation approach and parameters [25]. We wanted to check whether our general effect of DES on the theta and gamma activities was also observed in the previously reported cases of memory enhancement. Indeed, the same pattern of the theta and gamma response to DES (Kruskal Wallis test and Dunn-Sidak post-hoc approach, $\alpha = 0.05$) was induced with lateral temporal cortex stimulation (Fig. 5a) in the two subjects who were found to show stimulation-induced memory effect (ME) in the previous study [26]. Interestingly, DES in another brain region in the same subject, which did not result in a memory enhancement, showed no significant effect of the DES parameters on the theta (Kruskal-Wallis test, $\chi^2 = 7.1$, $p = 0.93$) or the gamma (Kruskal-Wallis test, $\chi^2 = 14$, $p = 0.45$) response. In analogy to the memory effect that was reported significant both on the group level and in individual subjects [26], the DES effect on the theta and gamma rhythms was not only significant for electrodes pooled from all the subjects (Figs. 2–4) but also in the individual cases. In these cases, most of the responsive electrodes were distributed locally close to the stimulation site (Fig. 5b) in congruence with the population-level analysis (see Fig. 3). Memory enhancement was not tested for all patients in this study, hence a potential relationship between the theta/gamma response and the memory effect to DES requires further investigation.

IV. Discussion

In a fraction of electrode sites (1.4% on average), we found a general effect of DES in the human brain, which persistently amplified low and attenuated high frequency activities, particularly in the theta and gamma bands. This effect was not selectively driven by any particular set of optimal DES parameters as would be expected in case of an entrainment response, in which, e.g., theta frequency stimulation selectively enhances theta oscillations. Our results suggest that the stimulation current modulated the rhythmic theta and gamma neural activities that were respectively amplified and attenuated. Changing parameters of stimulation drove this general response in proportion to the amount of electric charge delivered – magnitude of the theta amplification and the gamma attenuation was correlated with gradually increasing amplitude and frequency of the stimulating current. We observed more of this response at local than at distal locations from the stimulation site, especially in individuals who reported stimulation-induced memory enhancement. Systematic analysis of DES parameters and the basic electrophysiological responses in the human brain provides unique advantages for understanding and optimizing DES to invoke iEEG responses in the low and high frequency activities that, like the theta and gamma oscillations, are important for memory and other cognitive functions.

On average, only 1.4% of sites showed a significant response to DES. Given that the Dunn-Sidak correction was applied in every multiple comparison post-hoc test, however, it is highly unlikely that these 1.4% of responses occurred by chance. Moreover, only noise-free signals without any interictal epileptiform spikes were analyzed to further strengthen our conservative approach to detecting significant power responses to DES. Signals from sites adjacent to the stimulation site, exhibiting a slowly decaying voltage offset that overpowered the electrophysiological signal were also excluded from the analysis. Nonetheless, spectral analysis revealed that 37% of the signals with some voltage offset still showed physiological signals that were included in the analysis. Therefore, the small proportion of sites with a significant response (1.4%) detected after the stimulation period and without the nearest channels affected by the artifacts of DES would most likely be considerably greater if all the channels and times during and after stimulation were included. The significant sites identified in our study mostly near the stimulation site are probably a tip of an iceberg of the actual responses to DES buried underneath the stimulation artifacts. All in all, the proportion is small but identified with careful and conservative measures.

We checked that the same opposite effect on the low and high frequency bands occurred both for grid / strip and depth electrodes. Therefore, we combined both types of electrodes in the analysis to increase robustness of our results. We also checked that the obtained effect of increasing low and decreasing high neural activities was not associated solely with a particular brain region.

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Two recent studies investigated DES in the same patient population [28], [29]. Although they confirm part of the results observed in specific low or high frequency bands, the general effect of changing stimulation parameters across the large scale of brain activities has not been reported. In the first study by Solomon et al. [28], the authors confirmed a general trend to increase slow and decrease fast activities but no significant effects of changing the stimulation current frequency or amplitude within 0.25–1.5 mA range were detected. One explanation is that a substantial proportion of electrode channels were excluded from that analysis based on a slowly decaying voltage offset immediately following the last stimulation pulse, occurring on some of the electrodes close to the stimulation site. On average, 28% of channels in that study showed this response and were excluded in any one subject. As mentioned above, we found in spectral analysis that 37% of the signals exhibiting this phenomenon were electrophysiological, contained no DES artifacts, and showed statistically significant response to DES, congruent with the general effect. Ignoring these signals recorded close to the stimulation site could be one reason for not detecting a significant DES response in the two previous studies. The remaining 63% of the signals with a slowly decaying voltage offset accompanied by DES artifacts were identified and excluded from the analysis by either one of the two methods used in this study (see Section II. E).

Both of those studies took a different approach to analyze power responses to DES. They used a pre-stimulus baseline epoch from the previous stimulation trial with different parameters for comparison with the post-stimulus epoch. Given that each trial with a particular combination of the DES frequency and amplitude contained only up to 2400 ms of the artifact-free signal, the baseline epoch could be contaminated by the preceding stimulation that used different parameters. Hence, the general effect of changing stimulation parameters that we observed would be diluted by the baseline variance. Therefore, we decided to compare only the post-stimulus epochs to assess the relative power responses induced by different stimulation parameters. In the second study by Mohan et al. [29], another pattern of DES responses relative to the pre-stimulus baseline was reported. Increasing DES amplitude decreased high frequency (30–100 Hz) activities, quantified as power magnitude and number of sites showing a significant response. These results are consistent with our results obtained in the gamma band. Frequency bands below 30 Hz were not analyzed in the study by Mohan and colleagues. On the other hand, increasing the stimulation frequency showed a modest effect of increasing high frequency activities. This discrepancy with our results remains to be further investigated, taking into account the differences in the analytical approach. Apart from the issue related to the pre-stimulus baseline, other factors related to selection of the post-stimulus period could also be critical, e.g., the rebound phenomenon. A short excitatory response occurs immediately after a stimulation pulse and is followed by a long-lasting (>100 ms) inhibition before a rebound [42], [43]. Duration and magnitude of the rebound effect can itself be differentially modulated by the frequency of the stimulating current and thus affect the power estimates in various time windows from the last stimulation pulse. Hence, DES effects should be quantified across time including the stimulation period to draw further conclusions

Immediate effects of DES during or shortly after the stimulation period could not be analyzed in this or the recent studies. As described above, those studies were challenged by the same issues related to noise contamination. Within the post-stimulation interval, 12% of the signals were contaminated by electrical noise that overpowered the physiological signal. These issues are pertinent not only to the DES but also to the classic DBS studies [13]. Analyzing the effects of DES during and shortly after stimulation will now be possible with the most recent technological solutions for concurrent recordings and stimulation even from the same electrode channels. In this study, we decided to take a conservative approach and limit the possible sources of contamination described above.

One limitation of our approach was that only the iEEG signals during the post-stimulus epochs were used to estimate relative power changes between different stimulation parameters. Hence, the absolute power change induced by any specific set of parameters was not estimated with reference to a control baseline epoch outside of any stimulation task. In other words, our approach can be applied to test whether a particular set of stimulation parameters results in a relative increase or a decrease in power compared to another set of parameters, but not whether this set induces the increase or decrease in power compared to absolute power in the state when no stimulation is applied in the immediate temporal vicinity. Furthermore, any 'baseline' power estimate would inevitably be highly variable depending on the on-going state that is affected by momentary physiological processes related to cognition or the pathophysiology of epilepsy, in case of this subject population. Our approach, on the other hand, is refractory to these momentary state fluctuations.

Still, DES effects are known to be state-dependent [20], [44]. Thus, the power response in a particular frequency band to DES applied during quiet wakefulness might be different from the power response in a more active state of cognitive performance with induced theta or gamma power. Any results thus need to be carefully interpreted with respect to the general background state or any conditions.

Due to the large set of stimulation current parameters and their combinations tested, no extended inter-trial interval could be applied. Applying even a short duration of the interval would substantially prolong the experiment making it difficult to perform in that challenging patient population. To control for any continued effect from the previous stimulation, the order of the parameter combinations was pseudo-randomized. The significant differences between the stimulation parameters show that the continued effect of the preceding stimulation, if any, was negligible. The same approach was applied in similar recent studies [28], [29].

Comparing relative power responses in specific frequency bands to systematically changing parameters of stimulation is robust and potentially also congruent with other applications including DBS in Parkinson's disease. In this case, the effect on pathological beta oscillations in the subthalamic nucleus, which are associated with bradykinesia and rigidity [45]–[49], could be compared between different stimulation parameters. Beta oscillations have already been used as a biomarker feedback

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to control adaptive instead of a continuously delivered DBS to alleviate the motor symptoms [2], [50]–[52]. Stimulation parameters that caused the greatest attenuation of the beta oscillations would be predicted to be most effective for this DBS application. Our results from cortical DES showed that the highest stimulation amplitudes and frequencies caused the largest decrease in the beta band power (Supplementary Figure F2), in agreement with the therapeutically used parameters that correspond to the highest frequencies and amplitudes used in our study. This explains the results of other studies [53]–[55] which showed that DBS at frequencies over 90 Hz in PD patients alleviated tremor. The theta and gamma band power could therefore be analogous biomarkers for the effect of DES for memory enhancement, given their role in cognitive functions and the greatest effect observed in these compared to the other frequency bands (Supplementary Figure F2). Still, the DES and the DBS present significant differences, including a global effect of the latter on beta power in the basal ganglia and the neocortex compared to mostly local effect of the former on theta and gamma power. The beta activities in case of DBS are also considered pathological, making the comparison with DES even more complicated. Nevertheless, the uniform effect of increasing the frequency or amplitude of the stimulation current on physiological or pathological activities may generalize beyond the DES cortical studies.

Finally, we studied the DES responses to both frequency and amplitude of the stimulation current. Analyzing the responses to either stimulation frequency or amplitude alone was not possible here or in the previous studies due to the small number of repeated trials with changing frequency and constant amplitude or, vice versa, changing amplitude and maintaining constant frequency. Nevertheless, our results confirm the same effect for increasing the frequency and the amplitude. It was the total amount of electric charge delivered during stimulation by increasing DES frequency and amplitude that resulted in proportionally enhanced and attenuated power respectively in the theta and gamma bands. Another study design would be needed to compare the effect of the two parameters independently.

Despite the different analysis approaches used in the DES studies, there is an important common theme of a network effect of stimulation. In the study by Solomon et al. [28], DES in the Mesial Temporal Lobe (MTL) was shown to induce robust power changes across a distributed network of regions, particularly if stimulation occurred in or near white matter. Results of the other study by Mohan et al. [29] show that stimulation near white-matter tracts caused increase of neuronal activities, whereas stimulation near gray matter was more likely to be inhibitory. Theta-burst stimulation of the perforant path, a major white matter tract of the MTL, was found to be the most effective for memory enhancement [24]. Activating a distributed network of brain regions was proposed to be the key to successful modulation of memory functions [17], [25], [56]. In our study significant power responses were observed not only in locations proximal to the stimulation site but also, in agreement with a small-world network model, in distal ones. The number of responses was proportional to the distance from the stimulation site. This effect was confirmed also in other studies [43], [57], showing increased firing rate in about 80% of neocortical neurons close to the stimulation, while those at three time greater distance were observed in about 30% of the cases. New metrics of network synchrony provide another biomarker to assess and compare efficiency of the different stimulation parameters for memory enhancement.

In our study, the stimulation current amplitude was within 0.25–1.5 mA range. These amplitude values, however, do not correspond to the ones used in the cortical mapping for epilepsy surgery, which typically use higher amplitude values. Hence, the results may not apply directly to that procedure.

Robust biomarkers and consistent study designs are critical to obtain reproducible results and draw conclusions from the DES studies of memory and other cognitive functions. Studying the effect of DES on the local and distal physiological responses is challenging as it has to control for multiple spatio-temporal factors. Previous studies showed that the size of the modulated cortical area and its receptive fields for a given function [58], neuroanatomical architecture of the modulated neuronal networks [19], proximity and propagation through the white matter tracts [24] or even state of the brain during stimulation [20], [44] can all affect DES outcomes. The effect of DES has been shown to be dependent on relative frequencies of endogenous oscillations and exogenous stimuli [59]. In our previous work we showed that DES in the lateral temporal cortex enhanced high gamma responses to word presentations during a verbal memory task [27]. DES in the cingulate cortex also enhanced high gamma power in the hippocampus during word encoding in the same task [60]. Gamma oscillations studied during quiet wakefulness may thus be modulated differently than those induced in tasks during high attention states. This complex picture explains disparate behavioral outcomes obtained with DES applied at the same parameters and cortical locations, even when mapping basic brain functions [12]. Future studies, therefore, should rely on more mechanistic approaches and models utilizing objective biomarkers of local and distal brain responses before any conclusions about the behavioral or cognitive effects can be drawn.

V. Conclusion

Classic reports of invoking experiences of re-living past events [14] proposed a hypothetical mechanism of DES in specific cortical locations. In this hypothesis, brain activities that were engaged during memory formation would be reactivated by optimal parameters of DES. This explanation was based on the observation that particular set of frequency and amplitude parameters were found to be more effective in invoking this memory recall. We are now in position to investigate the mechanisms of DES using patterns of brain activities induced in specific frequency bands [61]. Entrainment of the activities in specific bands with stimulating current delivered at the corresponding frequency [18] offers one possible mechanism. Another possibility is that activities in multiple bands are induced by the stimulating current delivered at frequencies that are not necessarily corresponding to the specific oscillations. In the case of our results, it was the total charge delivered with the stimulation at increasing frequencies and amplitudes that drove a uniform pattern of enhanced theta and suppressed gamma power. These results speak against the entrainment hypothesis, although

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an immediate effect of DES during the stimulation period cannot be ruled out. There are other measures of a possible entrainment in addition to the power-in-band, including phase coherence with the stimulating current or across the modulated area, which remain to be explored. Future studies require a careful examination of these and other measures of brain activities assessed together with the behavioral effects of DES on memory and cognition [62]. Determining the basic physiological responses to stimulating the brain electrically at different parameters is fundamental for improving the existing therapies and developing new brain-machine interface approaches to modulate brain functions.

Acknowledgment

The authors would like to thank Blackrock Microsystems for providing neural recording and stimulation equipment.

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