Brain Stimulation 13 (2020) 1183–1195

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

The effects of direct brain stimulation in humans depend on frequency, amplitude, and white-matter proximity

Uma R. Mohan [a], Andrew J. Watrous [b], Jonathan F. Miller [a], Bradley C. Lega [c], Michael R. Sperling [d], Gregory A. Worrell [e], Robert E. Gross [f], Kareem A. Zaghloul [g], Barbara C. Jobst [h], Kathryn A. Davis [i], Sameer A. Sheth [j], Joel M. Stein [k], Sandhitsu R. Das [k], Richard Gorniak [l], Paul A. Wanda [m], Daniel S. Rizzuto [m, n], Michael J. Kahana [m], Joshua Jacobs [a, *]

[a] Department of Biomedical Engineering, Columbia University, New York, 10027, USA
[b] Department of Neurology, University of Texas at Austin, Austin, TX, 78712, USA
[c] Department of Neurosurgery, University of Texas-Southwestern, Dallas, TX, 75390, USA
[d] Department of Neurology, Thomas Jefferson University, Philadelphia, PA, 19107, USA
[e] Department of Neurology, Mayo Clinic, Rochester, MN, 55905, USA
[f] Department of Neurosurgery, Emory University, Atlanta, GA, 30322, USA
[g] Surgical Neurology Branch, National Institutes of Health, Bethesda, MD, 20814, USA
[h] Department of Neurology, Dartmouth College, Lebanon, NH, 03756, USA
[i] Department of Neurology, Hospital of the University of Pennsylvania, Philadelphia, PA, 19104, USA
[j] Department of Neurological Surgery, Baylor College of Medicine, Houston, TX, 77030, USA
[k] Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, PA, 19104, USA
[l] Department of Radiology, Thomas Jefferson University Hospital, Philadelphia, PA, 19107, USA
[m] Department of Psychology, University of Pennsylvania, Philadelphia, PA, 19146, USA
[n] Nia Therapeutics, Inc, Radnor, PA, 19087, USA

ARTICLE INFO

Article history:
Received 2 December 2019
Received in revised form
5 May 2020
Accepted 7 May 2020
Available online 21 May 2020

Keywords:
Stimulation frequency
Stimulation current
White-matter
Stimulation protocol design
Stimulation parameter space
Intracranial EEG
Direct brain stimulation

ABSTRACT

Background: Researchers have used direct electrical brain stimulation to treat a range of neurological and psychiatric disorders. However, for brain stimulation to be maximally effective, clinicians and researchers should optimize stimulation parameters according to desired outcomes.
Objective: The goal of our large-scale study was to comprehensively evaluate the effects of stimulation at different parameters and locations on neuronal activity across the human brain.
Methods: To examine how different kinds of stimulation affect human brain activity, we compared the changes in neuronal activity that resulted from stimulation at a range of frequencies, amplitudes, and locations with direct human brain recordings. We recorded human brain activity directly with electrodes that were implanted in widespread regions across 106 neurosurgical epilepsy patients while systematically stimulating across a range of parameters and locations.
Results: Overall, stimulation most often had an inhibitory effect on neuronal activity, consistent with earlier work. When stimulation excited neuronal activity, it most often occurred from high-frequency stimulation. These effects were modulated by the location of the stimulating electrode, with stimulation sites near white matter more likely to cause excitation and sites near gray matter more likely to inhibit neuronal activity.
Conclusion: By characterizing how different stimulation parameters produced specific neuronal activity patterns on a large scale, our results provide an electrophysiological framework that clinicians and researchers may consider when designing stimulation protocols to cause precisely targeted changes in human brain activity.

* Corresponding author. 351 Engineering Terrace, Mail Code 8904, 1210 Amsterdam Avenue, New York, NY, 10027, USA.
E-mail address: joshua.jacobs@columbia.edu (J. Jacobs).

https://doi.org/10.1016/j.brs.2020.05.009

Abbreviations

HFA	High Frequency Activity
LME	Linear Mixed Effects
DBS	Deep Brain Stimulation
iEEG	Intracranial Electroencephalography
MTL	Medial Temporal Lobe
LTL	Lateral Temporal Lobe

Introduction

Direct electrical stimulation shows potential as a treatment for a variety of neurological conditions and as a tool for studying neuropsychiatric disorders and cognition. However, we do not yet have a detailed understanding of the widespread neuronal effects that result from different types of stimulation. The goal of our study was to examine this issue by characterizing at a large scale how different types of brain stimulation modulate directly recorded human neuronal activity.

For years, direct electrical stimulation has been used to effectively treat motor disorders, such as Parkinson's Disease, essential tremor, dystonia, and epileptic seizures [7,14,25,26,46,51,54,55,106]. In the past two decades, researchers have extended stimulation protocols from motor disorders to better understand and modulate brain circuits of neuropsychiatric and cognitive disorders, such as major depression [68], obsessive compulsive disorder [80], addiction [48,57], anorexia nervosa [59], schizophrenia [4,49], and Alzheimer's disease [50,63]. While direct electrical stimulation holds potential to treat patients with neurological disorders who cannot be treated pharmacologically, understanding how different stimulation parameters differentially affect neuronal activity is important for optimizing such therapies.

Researchers and clinicians have found that stimulation produces a wide range of behavioral effects. Cortical stimulation was first linked to human memory in Wilder Penfield's pioneering studies where stimulating an awake patient's temporal lobe caused them to spontaneously recall old memories [82]. Penfield's subsequent work showed that the particular location that was stimulated greatly affected how patients re-experienced old memories. Following this, many studies applied direct electrical stimulation to the temporal lobe using a variety of stimulation parameters. The results from these studies were wide-ranging, emphasizing the complexity of precisely modulating human neuronal activity with stimulation [10,20,88,94]. Early applications of stimulation in non-human primates showed impairment in working memory when stimulating specific frontal cortex locations [100,101]. Subsequent studies in humans showed that stimulation impaired recall of complex scenes [31], subsequent item recognition [13], spatial, and verbal memory recall [40,53]. However, a number of studies have also shown improvements to verbal, visual, and spatial memory [21,23,73,95]. Studies using brain stimulation to treat other neurological diseases also found inconsistent cognitive effects [30,54,55,68]. The stimulation protocols used in these studies varied substantially in terms of locations, frequencies, durations, amplitudes, pulse patterns (continuous or intermittent), and times at which stimulation was delivered. To explain why these studies found such diverse behavioral and cognitive effects from stimulation, it is helpful to understand the physiology of how different kinds of stimulation alter underlying neuronal activity.

Earlier studies showed that stimulation can cause both excitatory and inhibitory effects on local and connected regions. Yet, within the realm of treating Parkinson's Disease with deep brain stimulation (DBS) where clinical outcomes are well established, the electrophysiology of stimulation is unclear. While some studies demonstrate that stimulation causes inhibition [9,18,58,102], other studies show excitation after stimulating at different frequencies and locations [1,34,42,67,105]. There is evidence that the location of a stimulation electrode has an important role in dictating the outcome of stimulation, with white- and gray-matter stimulation sites causing different effects [36,37,78,79]. Further, an early study in non-human primates describes motor and autonomic responses to stimulation that depend on both stimulation frequency and duration [72]. Logothetis et al. [61] build upon this showing evidence of specific microstimulation frequencies and locations simultaneously inducing both inhibitory and excitatory effects in different regions. These findings, which illustrate the diverse range of electrophysiological effects of brain stimulation, demonstrate the challenge in designing brain stimulation protocols to modulate brain activity in targeted ways that achieve desired behavioral outcomes.

The goal of our study was to comprehensively evaluate the effects of different types of stimulation on neuronal activity across the human brain. To examine changes in neuronal activity due to stimulation, we collected and analyzed direct brain recordings from 106 neurosurgical patients who underwent an extensive stimulation "parameter search" paradigm involving a range of stimulation frequencies and amplitudes at different cortical surface and depth locations. We then measured how different stimulation parameters correlated with the directional changes in neuronal activity that resulted from stimulation. Because we sought to understand the effects of stimulation on the mean activity across neuronal populations, we measured high-frequency broadband power (30–100 Hz), which provides an estimate of the mean rate of local neuronal spiking activity [66,99]. Our results provide a more comprehensive examination of the direct electrical stimulation parameter space than any prior human study. We find that the neuronal effects of stimulation are highly parameter dependent. Specifically, the prevalence of excitation and inhibition are modulated by the frequency and amplitude of stimulation and by region and the distance of the stimulation site to white-matter tracts. These results provide a starting point for clinicians and researchers to more optimally design stimulation protocols according to the desired types of changes to ongoing brain activity.

Methods

Participants

The 106 patients in our study were surgically implanted with depth, surface grid, and/or surface strips of electrodes for the purpose of identifying epileptic regions. The patients' clinical teams determined electrode placement to best monitor each patient's epilepsy. We conducted these procedures at eight hospitals: Thomas Jefferson University Hospital (Philadelphia, PA); University of Texas Southwestern Medical Center (Dallas, TX); Emory University Hospital (Atlanta, GA); Dartmouth–Hitchcock Medical Center (Lebanon, NH); Hospital of the University of Pennsylvania (Philadelphia, PA); Mayo Clinic (Rochester, MN); National Institutes of Health (Bethesda, MD); and Columbia University Hospital (New York, NY). Following institutional review board protocols at each hospital, all participating patients provided informed consent.

Stimulation paradigm

This stimulation "parameter search" paradigm was part of a larger project aimed to enhance episodic and spatial memory

using direct electrical stimulation [21,22,40]. Blackrock Microsystems provided neural stimulation equipment for these protocols. As part of this larger project, subjects participated in this paradigm to characterize the brain-wide effects of applying electrical stimulation at different sites with varying frequencies and amplitudes. During each session of this stimulation procedure, we instructed subjects to sit quietly and rest with eyes open as we applied various types of stimulation and measured neuronal activity. The main goal in applying stimulation across frequencies, amplitudes, and sites was to identify specific stimulation locations and parameters that would enhance performance in subsequent memory tasks [21]. Therefore, we often applied stimulation in medial temporal lobe (MTL) and lateral temporal lobe (LTL) locations based on their functional relevance for memory [19,81] (Table S2).

A clinical neurologist oversaw all stimulation sessions. We performed a separate amplitude screening procedure for each target site before stimulation. In the screening procedure, each site was progressively stimulated for 500 ms at each tested frequency, beginning at 0.5 mA, in steps of 0.5 mA, up to a maximum of 1.5 mA for depth electrodes or 3 mA for surface electrodes. A neurologist monitored visually for afterdischarges throughout this process. We then logged for each site the maximum current that could be applied without causing afterdischarges.

In the main stimulation protocol, we applied bipolar stimulation across neighboring anode and cathode electrodes using 300 μs charge-balanced biphasic rectangular pulses. For each site, we stimulated at frequencies of 10, 25, 50, 100, or 200 Hz, with amplitudes from 0.25 mA up to the site's determined maximum in steps of 0.25 mA, as well as 0.125 mA. Each stimulation trial was applied for 500 ms, with a random delay of 2750–3500 ms (uniformly distributed) between the offset and onset of consecutive stimulation trials. Within each ~25-min session that stimulated one location, we randomly ordered stimulation trials with different frequencies and amplitudes to prevent confounds arising from trial order. Each targeted stimulation site received 24 stimulation trials for each combination of frequency and amplitude. Some subjects participated in a version of this procedure that also included sham trials without stimulation. Individual subjects participated in this stimulation protocol for between 1 and 9 individual sites (mean = 2.8 sites). Overall, we collected a total of 354 sessions, stimulating at 319 distinct sites from 106 subjects with between 54 and 173 bipolar recording pairs (mean = 108, total 10,266 electrodes). Following artifact rejection (see below), we included in our data analyses 292 sessions over 264 stimulation sites from 94 subjects while recording simultaneous neuronal activity from 9,775 bipolar electrode pairs, where each subject had between 22 and 170 bipolar recording pairs (mean = 102 electrodes).

Electrocorticographic recordings and referencing

To measure the electrophysiological effects of stimulation, throughout a stimulation session we recorded neuronal activity at 500, 1000, or 1600 Hz using a clinical intracranial electroencephalographic (iEEG) recording system at each hospital (Nihon Kohden EEG-1200, Natus XLTek EMU 128, Natus Quantum EEG, or Grass Aura-LTM64 systems). We referenced each electrode's signal to a common contact placed intracranially, on the scalp, or mastoid process. To reduce non-physiological artifacts, we used bipolar referencing, computed as the voltage difference between pairs of adjacent electrodes. The location of each bipolar pair was taken as the midpoint between the two physical electrodes. We further filtered electrical line noise using a 57–63-Hz Butterworth notch filter.

Anatomical localization

We determined the location of each electrode by co-registering a post-surgical CT scan to T1 and T2 weighted structural MRIs taken prior to implantation. We determined electrode localization in cortical regions by co-registration of the post-implantation CT, corrected for post-operative brain shift, with Freesurfer's automated cortical parcellation based on the Desikan-Killiany brain atlas [17]. We based localization to medial temporal lobe structures on MTL segmentation using Automatic Segmentation of Hippocampal Subfields (ASHS) [108].

Artifact rejection

Applying electrical stimulation can cause the appearance of non-physiological signals in iEEG recordings that manifest as complete amplifier saturation or overall shifts in signal amplitude, such as rise, decay, or deflection following stimulation before returning to baseline (Fig. S2). These non-physiological changes could impair our ability to accurately measure true physiological signals related to stimulation.

Therefore, to minimize the impact of artifacts on our results, we excluded from our analyses any recording electrodes and trials that showed post-stimulation artifacts. We implemented a detection algorithm to identify channels that are prone to complete signal saturation as well as gradual post-stimulation artifact. Following earlier methods [91], we compared the average voltage of the signal from −500 to −100 ms prior to stimulation onset and from 100 to 500 ms after stimulation offset. To include data from as many recording electrodes as possible, we took a two-phase approach to exclude artifacts on the single-trial level as well as on an electrode level. To identify artifacts, we employed Grubb's outlier test to classify the trials that exhibited large non-physiological changes in voltage. Specifically, we excluded the data of any trials that showed a change in voltage between the pre- and post-stimulation intervals that was greater than 2 standard deviations of the corresponding mean voltage changes for matching sham trials for the same electrode (Fig. S2). We excluded any electrodes that showed artifacts on over half of all trials for a particular combination of parameters. Some stimulation sites were especially conducive to spreading artifacts across recording electrodes, and thus we excluded stimulation sites that caused artifacts on over half of all recording electrodes. Overall, we excluded 56 stimulation sites, an average of 10% of bipolar recording electrodes, and 12% of stimulation trials on remaining contacts (see Table S3). In addition to excluding trials, recording electrodes, and stimulation sites affected by amplifier artifact following stimulation, we excluded trials with epileptiform activity if the kurtosis of the voltage signal exceeded a threshold of 3 [16]. Using this method, we excluded an average of 3.2% ±3.8% of stimulation trials.

Spectral power analysis

To measure the effect of stimulation on mean neuronal firing rates, we extracted the high-frequency activity (HFA) signal from each iEEG recording, as prior studies found this signal to be a reliable measure of mean neuronal activity [66,74,99]. We measured HFA power in our data by calculating power spectra post- (100 to 600 ms after stimulation offset, defined as the last pulse of the stimulation trial) and pre- (−600 to −100 ms before stimulation onset) stimulation at 12 log-spaced frequencies between 30 and 100 Hz using multitapers, which provide better resolution at high frequencies [76]. Consistent with prior iEEG studies, we used log-spaced frequencies to better represent broadband electrophysiological properties [66,85,87,90]. We allowed a buffer of 100 ms

before and after stimulation and limited the cycles used to calculate each frequency for finer temporal resolution and prevent any impact of stimulation artifacts on our measurements of pre- or post-stimulation power (see Fig. S4).

Linear mixed-effects model

We used a linear mixed-effects (LME) model to analyze the effects of stimulation on neuronal activity and identify how the prevalence of these effects vary with parameters. An LME model is a type of regression model that models the variation of a dependent variable as a function of both fixed and random effects. An LME model may be implemented in a group-based way that can account for repeated measurements from one sample [3]. This feature is important for our study because our dataset included possibly correlated measurements, as we tested the effects of different parameters at the same stimulation site. Additionally, the LME model is useful for this dataset because it can account for uneven sampling across groups and conditions, which also occurred when separate sites were stimulated with different sets of frequencies and amplitudes.

To apply the LME model to our data, we used fixed factors for variables of frequency (up to 5 possible values per site), amplitude (typically 3 per site), and binned distance between recording electrodes and the stimulation site. We also defined categorical variables of stimulation electrode type and stimulation in white or gray matter as fixed factors.

We defined the dependent variable as the prevalence of HFA changes measured by the percent of recording electrodes showing significant increases or decreases in HFA power. The equation below describes this model in which the outcome variable y indicates the prevalence of HFA changes, X_1 and X_2 represent stimulation frequency and amplitude, β_1 and β_2 are the fitted regression coefficients, and ε is a vector of residuals.

$$y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \varepsilon$$

We then combined across subjects to provide summary coefficients for each factor that indicate its mean effect across the population [6]. We calculated "z"-values as the parameter estimates divided by their standard errors and p-values with respect to 95% confidence intervals of standard normal distributions. Following LME syntax for our main frequency and amplitude results, the model has the following form (Fig. 2) where the interaction of fixed factors was computed separately: ΔHFA ~ frequency + amplitude + (frequency + amplitude | stimulation site). The last term indicates that for each stimulation site, the model fits correlated random intercepts and slopes for frequency and amplitude factors. To compare the effects of stimulating different regions and tissue in Fig. 3, where there were no repeated measures between categories, we used a two-way ANOVA.

Seizure-onset zones

Clinical teams at each hospital provided information about electrodes identified in seizure onset zones (SOZ). To verify that our results were not directly related to abnormal brain tissue, we performed the population analyses of the effects of stimulation frequency and amplitude separately for the sets of stimulation sites and corresponding recording electrodes that were located in healthy tissue and SOZs (Fig. S7). All main frequency- and amplitude-related effects continued to be significant for the separated analyses, confirming our main results (Fig. S4C).

White matter categorization

We categorized each stimulation site as either being in or near white matter or in gray matter to determine the impact of white matter on the effects of stimulation. We estimated the amount of white matter near each stimulation site by counting the number of white matter vertices within a spherical volume around the midpoint of the stimulation anode and cathode. This volume has a radius of 4 mm, which also includes the anode and cathode. We used Freesurfer white matter segmentation of patients' T1 MRI scan to determine white-matter vertex locations [91]. We then categorized stimulation sites as near white matter or in gray matter by splitting the number of white-matter vertices surrounding stimulation sites along the median of the distribution.

Data availability

Raw electrophysiogical data used in this study are available at http://memory.psych.upenn.edu/ElectrophysiologicalData.

Results

The goal of our study was to characterize the effects of different types of direct electrical brain stimulation on ongoing neuronal activity in humans. Here, we recorded iEEG activity from widespread electrodes while delivering electrical stimulation at different locations, frequencies, and amplitudes as patients rested quietly. To assess the effect of stimulation on neuronal activity, we measured the amplitude of signals in the high-frequency-activity (HFA) range (30–100 Hz), which correlates with mean level of spiking activity of a local neuronal population [29,66,74,99].

Effects of stimulation at low and high frequencies

To illustrate the neuronal effects from stimulation at different frequencies, we first show data from an example subject who received electrical stimulation at one location at four frequencies: 10, 50, 100, and 200 Hz. Each frequency was tested 96 times at each amplitude. To measure the effect of stimulation at each frequency, we computed the mean spectral power in the HFA band on each recording electrode in a 500-ms interval before and after each stimulation trial (Fig. 1A). On many recording electrodes, we found statistically reliable HFA changes following stimulation at a particular frequency (Fig. 1B and C; $z = 5.47$, $p < 10^{-6}$, signed-rank test, uncorrected). The extent of these HFA changes across multiple recording sites is illustrated in Fig. 1D, which shows that this subject had widespread electrodes that showed significantly decreased HFA power when 10-Hz, 1-mA stimulation was applied at a site in the left LTL.

To quantify the brain-wide changes in HFA power that resulted from each type of stimulation, we computed the mean power change across stimulation trials for each recording electrode (Fig. 1E), excluding sites showing artifacts (see Methods). For this site, 10-Hz stimulation at 1 mA caused a significant decrease in mean HFA power across electrodes ($z = -7.59$, $p < 10^{-10}$, signed-rank test, uncorrected; Fig. 1E). Notably, the recording electrodes that showed significant changes in HFA power included locations both proximal and distal to the stimulation site, even in contralateral areas (Fig. 1D), which might be considered surprising in light of previous studies that focused on local effects of stimulation [18,58,61].

We next examined HFA changes due to stimulation at other frequencies in this subject. Fig. 1B shows the pattern of HFA power changes that resulted from 200-Hz, 1-mA stimulation at the same site. In contrast to 10-Hz stimulation, we instead found HFA power

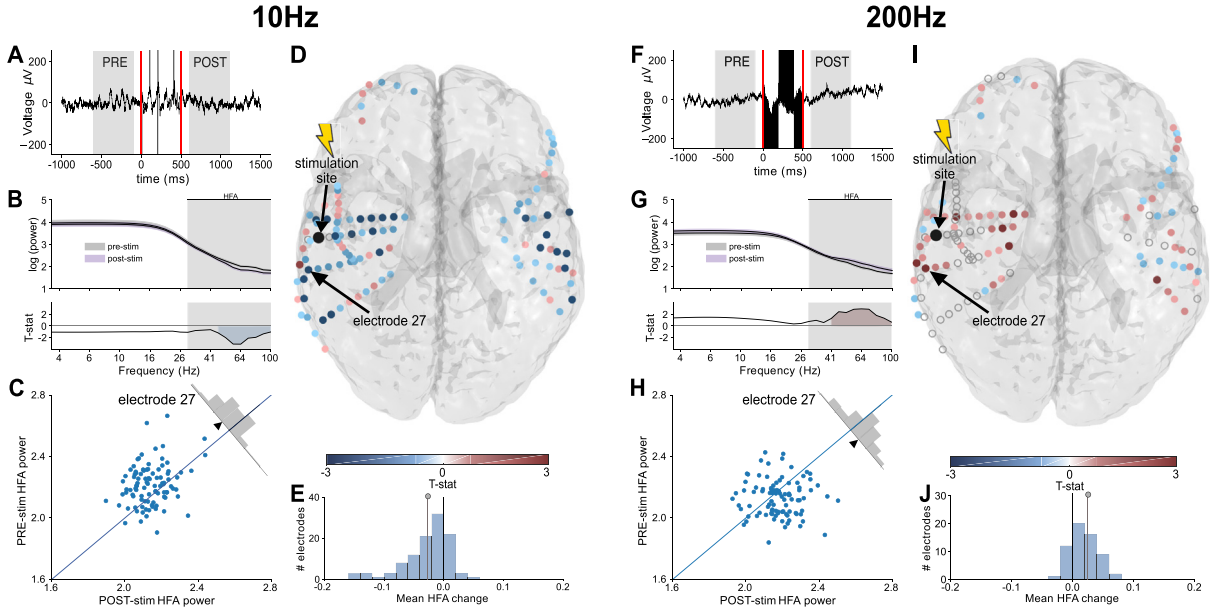

Fig. 1. Effects of low- and high-frequency stimulation on HFA power. Left panels (A–E) indicate effects of 10-Hz stimulation and right panels (F–J) indicate 200-Hz stimulation, all in Patient 195. Stimulation was applied at the same site and amplitude (1 mA) for all panels. **(A)** Raw voltage signal recorded on example electrode 27 on one trial. Shading indicates the 500-ms time periods before and after each stimulation trial during which we measured HFA power. Red lines denote stimulation onset and offset. **(B)** Top panel shows log-transformed mean power spectra from recording electrode 27 for the pre- and post-stimulation intervals across the 96 stimulation trials at 10 Hz and 1 mA. Gray shading indicates the HFA band (30–100 Hz). Bottom panel show t statistic of the difference between pre- and post-stimulation (POST-PRE) power at each frequency. Blue shading indicates significant differences at $p < 0.05$. **(C)** The distribution of pre- and post-stimulation HFA power across individual trials for electrode 27. **(D)** Brain map showing the mean HFA responses to 10-Hz stimulation across all recording electrodes, where each circle is a bipolar pair's midpoint. The stimulation site is indicated in black and color indicates the t statistic of the change in HFA power at each recording electrode. Recording electrodes excluded due to artifact indicated by an open gray circle. Bold colored electrodes are those that are significant following Benjamini-Hochberg correction. **(E)** The distribution across electrodes, of the mean HFA power change in response to 10-Hz stimulation. Each value represents one electrode's mean HFA power change from stimulation (POST-PRE). **(F–J)** Plots follow format from panels A–E except for 200-Hz stimulation. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

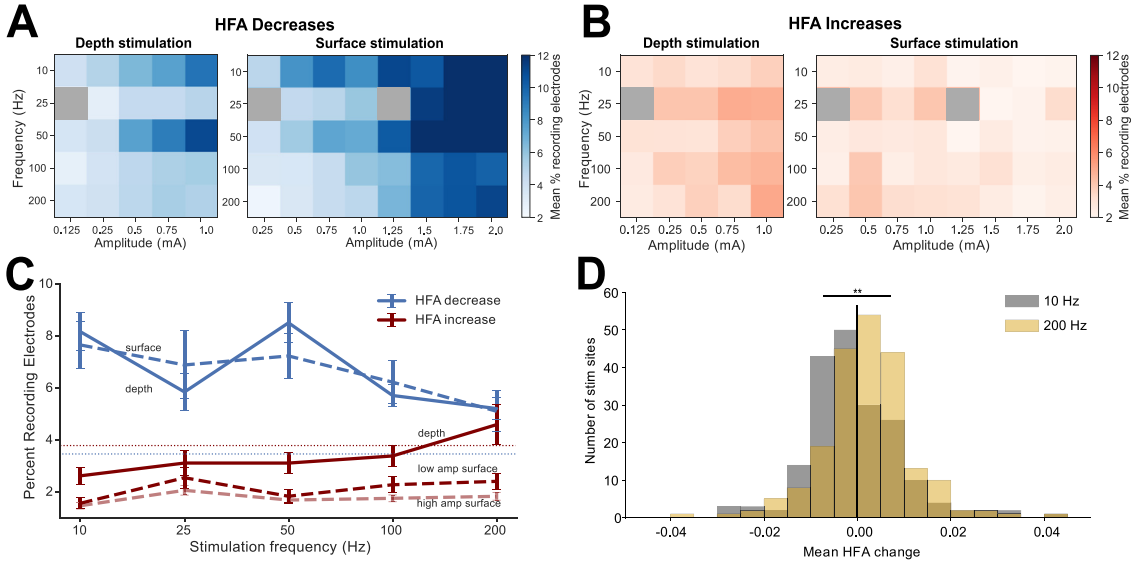

Fig. 2. Population analysis of the frequency- and amplitude-dependence of HFA changes from stimulation. (A) Percent of recording electrodes showing significant HFA decreases for each combination of stimulation frequency and amplitude, separately computed for depth (left) and surface (right) stimulation. Gray blocks indicate an insufficient number of stimulation sites for the parameter combination. **(B)** Percent of recording electrodes showing significant HFA increases for each combination of stimulation parameters. **(C)** Percent of recording electrodes showing significant HFA increases and decreases for each stimulation frequency. Calculations were performed separately across depth and surface stimulation sites. Data in this plot included 1 mA stimulation for both effects of depth stimulation and surface HFA decreases; surface HFA increases calculations separately measured for currents $\geq$0.75 mA and <0.75 mA. Error bars: ±1 SEM. Blue and red dotted lines indicate corrected type 1 error rate of the percent of electrodes increasing or decreasing estimated from a permutation test by randomly circularly shifting stimulation sessions for 100 iterations and calculating the 95% confidence interval of the resulting distribution of numbers of significant electrodes. **(D)** Histogram of the mean HFA change for each stimulation site, separately computed for high and low-frequency stimulation; ** denotes a significant difference ($z = -3.81$, $p = 0.0001$, rank-sum test). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

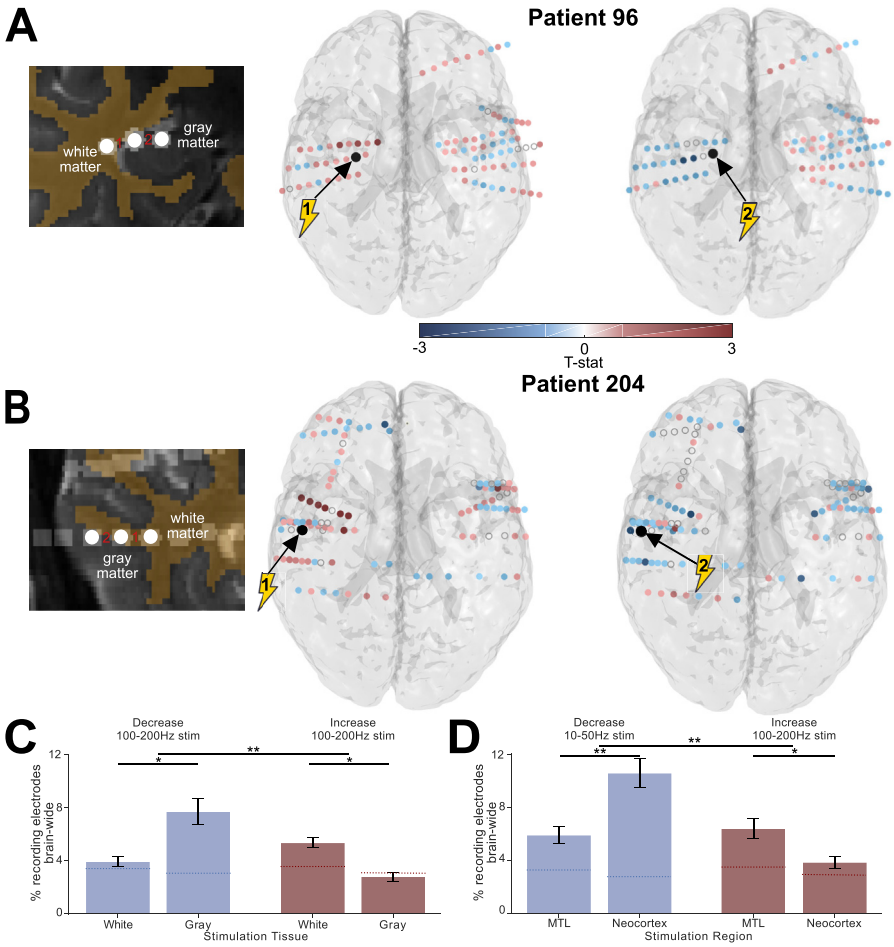

Fig. 3. Role of stimulation location in modulating the effects of stimulation. (A) Brain maps of HFA responses to stimulation near white and in gray matter in example Patient 96. Stimulation site is indicated in black and color indicates t statistic of HFA change for bipolar recording electrodes. Both sites were stimulated at 200 Hz and 0.75 mA. Left brain map indicates data for a stimulation site near white matter, which generally caused HFA power increases. The right brain map shows data from stimulation at a site in gray matter, which generally caused decreases in HFA power. Bold colored electrodes are those that are significant following Benjamini-Hochberg correction. Far left panel, coronal MRI image showing the precise location of these two stimulation sites. The white circles are monopolar electrodes and red labels 1 and 2 correspond with left (white) and right (gray) stimulation site midpoints, respectively. The orange overlay indicates white matter. **(B)** Brain map of HFA responses to stimulation near white and in gray matter in example Patient 204. Both sites were stimulated at 200 Hz and 1 mA. Plot format follows panel A. **(C)** Group-level analysis, illustrating the percent of recording electrodes across the entire dataset that showed significant HFA power increases and decreases for white- and gray-matter stimulation. All blue and red dotted lines indicate corrected type 1 error rates of the percent of electrodes increasing or decreasing. All error bars: ±1 SEM. (*$p < 0.05$, **$p < 0.01$). **(D)** Group-level analysis of percent of recording electrodes grouped by stimulation regions showing decreases for low (10–50 Hz) frequency stimulation and increases for high (100–200 Hz) frequency stimulation. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

increases across many recording electrodes (Fig. 1I). This HFA power increase was robust at the level of individual electrodes (Fig. 1H; $z = 5.03$, $p < 10^{-5}$, signed-rank test, uncorrected) as well as at the group level across this subject's brain (Fig. 1J; $z = 4.64$, $p < 10^{-5}$, signed-rank test, uncorrected). Thus, the data from this subject illustrate that the effect of stimulation can be frequency dependent, with 10- and 200-Hz stimulation at the same site and amplitude having opposite effects on HFA power. Because we also found similar response patterns in other subjects (Fig. S1), we next characterized this effect at the group level.

Population analysis of the effects of stimulation frequency and amplitude

To characterize the effects of stimulation with different parameters across our dataset, we computed the proportion of all recording electrodes that showed significant HFA decreases or increases for each unique combination of stimulation site, frequency, and amplitude. Fig. 2A illustrates, for each stimulation parameter, the percentage of recording electrodes that showed significant HFA power decreases averaged across stimulation sites. HFA decreases were most prevalent for stimulation at low frequencies and high amplitudes. This pattern was present for both depth and surface stimulation sites. When stimulating surface electrodes at high amplitudes, HFA decreases were prevalent for all frequencies.

To assess the reliability of these effects statistically, we used a linear mixed-effects (LME) model to analyze how the prevalence HFA changes depends on stimulation parameters (see Methods). Due to our clinical data collection environments, our dataset is heterogeneous, with individual subjects having variable numbers of stimulation sites and individual sites being stimulated at different frequencies and amplitudes. LME modeling is well-suited for analyzing this type of heterogeneous dataset because it can

identify linear trends (including interactions) across multiple factors and can accommodate both repeated and missing measurements [3]. We used the LME model to analyze the distributions of HFA power changes across the dataset (Fig. 2A). The results confirmed that the frequency and amplitude dependence of HFA power decreases mentioned above were statistically reliable for both depth electrodes (magnitude of all z's = 3.38–5.09; all p's < 10^{-3} for effects of frequency, amplitude, and their interaction) and surface electrodes (magnitude of z's = 2.34–2.5, all p's < 0.05, see Table S4A).

We also used the LME model to examine the parameter dependence of stimulation-induced HFA power increases. Because we found HFA changes to be diverse across recording electrodes, we modeled HFA decreases and increases separately to capture simultaneous positive and negative HFA changes on different recording electrodes that may otherwise be lost when averaging effects. Fig. 2B shows the mean percentages of recording electrodes that showed significant HFA power increases following stimulation at various parameters. Stimulation on depth electrodes at high frequencies and high amplitudes was most closely linked to increases in HFA power. The LME model confirmed that this effect was robust for depth electrodes, by showing significant effects of stimulation frequency and amplitude on HFA power (both p's < 0.05, see Table S4A). This finding that higher stimulation currents are associated with broader HFA power increases is consistent with the earlier findings that higher currents are associated with more widespread phosphenes in the visual cortex [104] and findings that the magnitude of cortical responses to stimulation depend on stimulation amplitude [15]. In contrast, for surface electrodes, HFA increases were most prevalent for high-frequency stimulation at low amplitudes (Frequency × Amplitude interaction: z = 2.01, p = 0.04, see Table S4A).

Fig. 2C summarizes these results. Overall, HFA decreases were more prevalent than increases, regardless of stimulation frequency and electrode type. Further, stimulation on depth electrodes at high and low frequencies, respectively, was associated with HFA increases and decreases (LME model for HFA change direction and Frequency factors: magnitude of all z's = 3.77–4.06, all p's < 10^{-3}, see Table S4C). Notably, high-frequency surface stimulation rarely caused HFA increases, whereas high-frequency depth stimulation reliably caused HFA power increases (see above LME model results).

While these trends were robust statistically, we observed that the HFA power changes showed variability across individual stimulation sites (Fig. 2D). To measure this variability, we quantitatively compared HFA response patterns across different stimulation sites in the same subject. On average, only 16% of subjects showed similar (positively correlated) patterns of HFA power changes in response to stimulation at different sites (Fig. S3A), which supports our approach of separately analyzing individual stimulation sites. Nonetheless, to confirm that our results were not affected by treating stimulation sites independently, we also performed the above analyses at the level of each subject, by averaging response patterns across the stimulation sites within each subject prior to population-level statistical analysis. This subject-level analysis confirmed our primary results of frequency-dependent HFA power changes (Fig. S3B-E). More broadly, the variability between HFA changes caused by different stimulation sites in a subject emphasizes the importance of understanding the role of location in modulating neuronal activity. Additionally, to confirm that HFA changes for each trial do not depend on the effects from prior trials, we performed an analysis of the percent of recording electrodes showing significant changes for each stimulation frequency as a function of the frequency of the trials immediately preceding each trial. This confirmed that HFA power changes depend on the current trial's stimulation frequency and not on the prior trial's frequency for both HFA increases and decreases (Fig. S8, see Table S4F).

Distance to white matter and region mediate the effects of stimulation

Previous studies showed different neurobehavioral changes from applying stimulation in white versus gray matter [68,96]. Modeling and animal studies demonstrated that bipolar stimulation creates an electrical potential field between and around the anode and cathode of the stimulation site that activates elements within a volume of tissue [12,36,65,71]. Based on these models, we hypothesized that stimulation applied in proximity to white-matter tracts would have different neuronal effects compared to stimulation in gray matter.

To compare the physiology of white- versus gray-matter stimulation on a large scale, we investigated how the proximity of stimulation sites to white matter correlates with the resulting change in HFA power. We first classified each depth stimulation site according to whether it was in white or gray matter, based on its mean proximity to white matter tracts (see Methods), and separately compared the HFA changes for each group. The midpoint of white-matter stimulation sites were on average 1.4 mm ± 0.8 mm away from the closest white matter while gray-matter stimulation sites were on average 10.5 mm ± 22.6 mm away from the closest white matter. Fig. 3A and B show data from two patients who were each stimulated at two nearby sites, one near white matter (labeled #1) and near gray matter (#2). Both subjects showed HFA decreases when stimulation was applied at the gray-matter site and, inversely, HFA increases for stimulation at the white-matter site.

We next performed a group-level analysis of the relation of stimulated tissue on HFA changes. We focused this analysis on stimulation parameters in the range of 100–200 Hz and 0.5–1 mA on depth electrodes, which were chosen as the parameters most likely to cause HFA increases. We compared the prevalence of HFA power changes across sites in white (n = 70) and gray matter (n = 61). Stimulation at white-matter sites caused a greater rate of HFA increases compared to sites in gray matter (Fig. 3C). Inversely, gray-matter stimulation caused more HFA power decreases compared to white-matter stimulation. Analyzing the prevalence of each type of HFA change with a two-way ANOVA, we confirmed that there was a statistically significant interaction between stimulating near white- or gray-matter and the prevalence of HFA increases and decreases (Tissue × HFA change: F(1, 1) = 6.55, p = 0.01).

To compare the effects of stimulating different brain regions, we measured the percentages of recording electrodes that showed HFA decreases and increases following stimulation. We focused on stimulation at 0.5–1 mA on depth electrodes to compare MTL (MTL, hippocampus, and limbic areas) and neocortex (temporal, frontal, parietal, and occipital lobes) stimulation. Consistent with our findings in Fig. 2, the prevalence of HFA increases and decreases depended on frequency in all regions (LME Model: Frequency: magnitude of all z's = 2.2–3.94, all p's < 0.05). We then specifically analyzed HFA decreases following 10–50 Hz stimulation and HFA increases following 100–200 Hz stimulation because these stimulation frequencies are most likely to cause each effect. We found 10–50 Hz stimulation in the neocortex caused a greater rate of HFA decreases than it did in the MTL (Fig. 3D). Inversely, we found 100–200 Hz stimulation in the MTL caused a greater rate of HFA increases than it did in the neocortex. This regional difference in the effect of stimulation on HFA power was statistically significant (Region × HFA change: F(1, 1) = 18.42, p < 10^{-4}).

Spatial spread of neuronal activity changes from stimulation

We next examined the spatial spread of stimulation-induced changes in HFA. To do this, we measured the prevalence of HFA increases and decreases as a function of recording electrodes' distance from the stimulation site. Overall, the prevalence of HFA power decreases and increases were greater for recording electrodes near the stimulation site compared to distal electrodes (Fig. 4A–D; Fig. S1). Although HFA increases were generally less prevalent than decreases, the prevalence of HFA decreases fell off more drastically with distance to the stimulation site as compared to HFA increases (LME model: Distance × HFA change direction interaction: $z = 4.43$, $p < 10^{-5}$, see Table S4D).

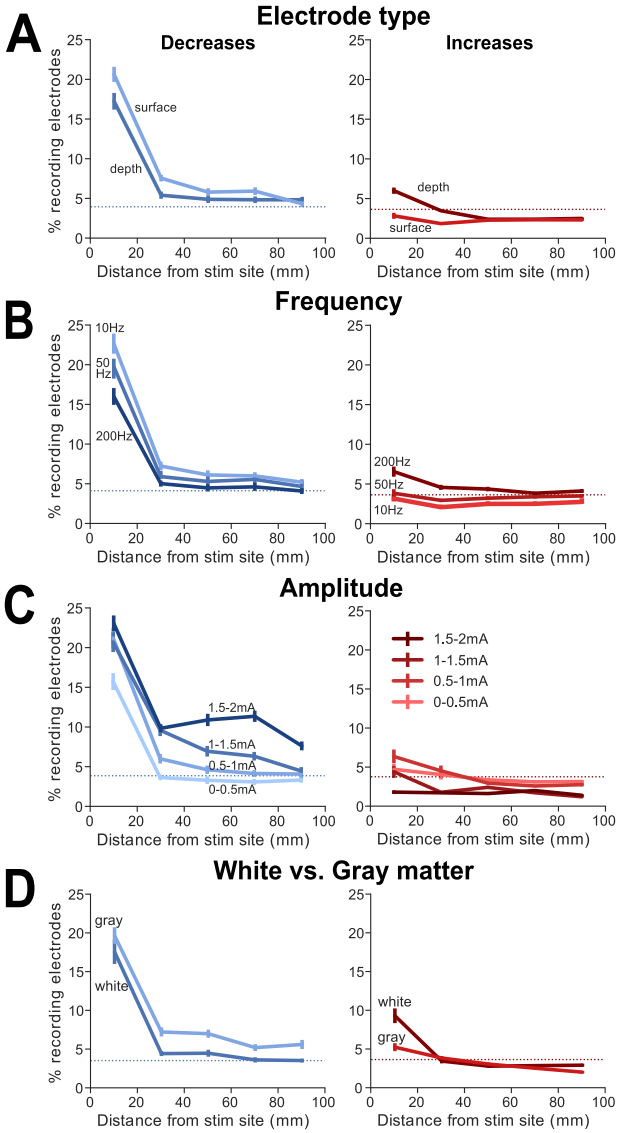

Fig. 4. Spatial spread of neuronal activity changes. All plots show the mean percent of recording electrodes that showed significant HFA power decreases (left) and increases (right) binned by their distance from the stimulation site. **(A)** Comparison of effects between depth and surface stimulation sites. Blue and red dotted lines indicate corrected type 1 error rates of the percent of electrodes increasing or decreasing. All error bars denote: ±1 SEM. **(B)** Analysis for effects of stimulation frequency (10, 50, and 200 Hz) **(C)** Analysis for effects of stimulation amplitude (0–0.5, 0.5–1, 1–1.5, & 1.5–2 mA). **(D)** Analysis for effects of stimulation near white versus gray matter (see Methods). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

We compared the spatial spread of HFA increases and decreases separately for depth and surface stimulation (Fig. 4A). Stimulation at both depth and surface sites showed that the prevalence of HFA decreases diminished with distance at approximately the same rate, but HFA decreases from surface stimulation were more prevalent across the brain (LME Model: magnitude of all z's = 2.47–9.28, all p's < 0.05, see Table S4D). Inversely, HFA power increases from depth stimulation were more prevalent and showed a greater distance effect than increases from surface stimulation (Depth vs. Surface: $z = 2.03$, $p = 0.04$; Distance × Depth vs. Surface interaction: $z = 2.56$, $p = 0.01$, LME model).

Next we examined the role of stimulation frequency on the distance dependence of HFA power changes (Fig. 4B). For all frequencies, HFA power decreases were most prevalent at recording electrodes near the stimulation site. This effect was significantly larger for stimulation at low frequencies (LME model: Distance × Frequency: $z = -3.11$, $p = 0.002$). A related drop-off with distance was also present for the sites that showed HFA power increases (right panel); however, this effect was most prevalent for 200-Hz stimulation (Distance × Frequency: $z = -2.42$, $p = 0.02$, LME model).

We also examined the role of stimulation amplitude in the distance dependence of HFA changes (Fig. 4C). As in the above analyses, the prevalence of HFA changes decreased with distance from the stimulation site. However, the rate of this fall-off inversely correlated with stimulation amplitude. For low stimulation amplitudes, HFA decreases were present at ~5% electrodes with distances ≥30 mm from the stimulation site, but for amplitudes at ≥1 mA, ~10% of electrodes spaced at ≥30 mm showed HFA decreases. Both distance and amplitude had a statistically significant effects on the prevalence of HFA decreases (Distance: $z = -9.38$, $p < 10^{-19}$; Amplitude: $z = 3.06$, $p = 0.002$, LME model). This indicates that larger stimulation amplitudes increase the spatial spread of stimulation-induced HFA decreases. This type of distance dependence was not evident in the sites that showed HFA increases from stimulation (all p's ≥ 0.05, Fig. 4C, right panel).

Finally, we analyzed the spatial spread of HFA power changes from white- versus gray-matter stimulation (Fig. 4D). This analysis showed that the spatial spread of HFA decreases was more prevalent across the brain when stimulation was applied near gray matter (left panel LME Model: magnitude of all z's = 2.39–8.30, all p's < 0.05), and an opposite effect was present for HFA increases, which were more prevalent when stimulating near white matter (right panel LME model: Distance × White vs. Gray Matter interaction: $z = 2.43$, $p = 0.02$). Our results show HFA increases are greater for stimulation on depth electrodes near white matter than other areas, which supports approaches where clinicians select stimulation sites based on tract location to bring about desired changes in neuronal activity.

Stimulation-induced resetting of neuronal activity

In addition to identifying HFA power increases or decreases from stimulation, we also observed a different phenomenon, in which stimulation caused HFA power to adjust to a fixed level. In contrast to the above-described sites that showed increases or decreases in mean HFA power after stimulation, an electrode that exhibited "HFA resetting" would show variable HFA power prior to stimulation across trials that became tightly clustered after stimulation. Therefore, to identify this phenomenon we compared the variances of HFA power at each electrode between pre- and post-stimulation intervals (rather than comparing the means as in earlier analyses). Fig. 5A shows two example left temporal-lobe recording electrodes that exhibited resets in HFA power from stimulation. Each of these electrodes showed substantial variation

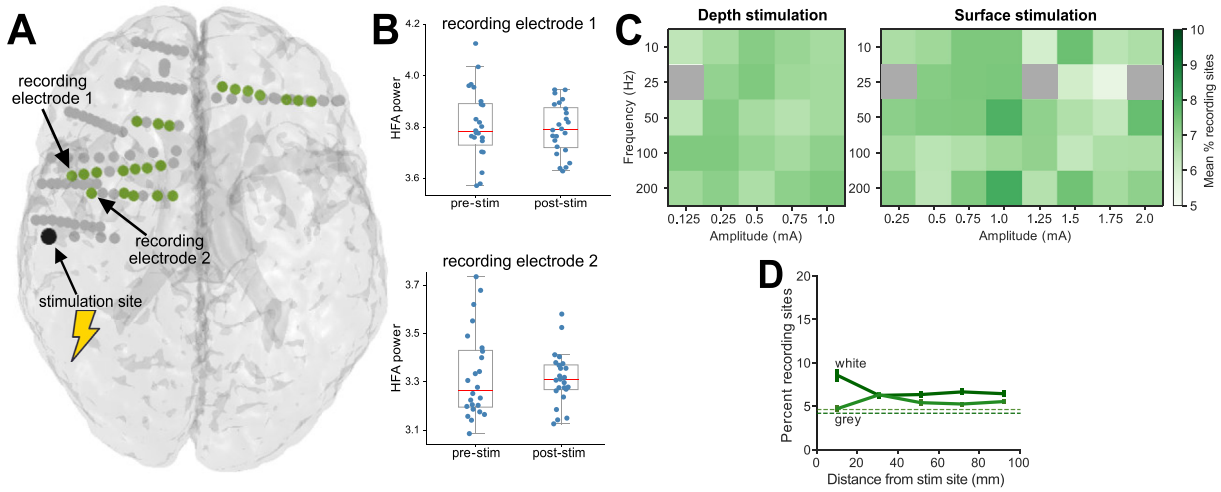

Fig. 5. Stimulation induced HFA power resetting. (A) Brain map from Patient 200 illustrating the recording electrodes that showed significant power resetting (green) following stimulation at the labeled site (black). **(B)** HFA power measured from two example recording electrodes in this patient before and after stimulation. Both sites show significant resetting, in which the variance of HFA power significantly decreases from pre-to post-stimulation without a significant change in the mean power (contact 1: $p < 10^{-6}$; contact 2: $p < 10^{-8}$, uncorrected F-test). **(C)** Group-level analysis showing the overall mean percent of recording electrodes that showed significant HFA resetting for each combination of parameters. **(D)** Mean percent of recording electrodes that showed significant power resetting as a function of distance from white- and gray-matter stimulation sites. Green dotted lines indicate corrected type 1 error rates of the percent of electrodes resetting. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

in HFA power before stimulation, with this variation decreasing significantly afterward (both p's $< 10^{-6}$, F-test, Fig. 5B). The data in this figure illustrate two characteristics of resetting: First, that the recording electrodes that show HFA power resets are often spatially clustered. Second, that HFA resetting does not immediately surround the stimulation site, which could have been driven by artifact.

To statistically characterize HFA resetting, we identified the recording electrodes that showed a significant decrease in the variance of HFA power from pre-to post-stimulation (F-test, $p < 0.05$) with no change in mean (*t*-test, $p > 0.05$). Analogous to the above analyses, we computed the proportions of electrodes that showed significant resetting for each combination of stimulation frequency and amplitude (Fig. 5C). This analysis suggested that HFA resetting from depth stimulation site is slightly dependent on the interaction of frequency and amplitude (Frequency × Amplitude interaction: $z = -1.98$, $p < 0.05$, see Table S4A). The LME model did not show a significant dependence for the prevalence of HFA resetting according to the stimulation amplitude or frequency alone (Depth and Surface: z's = 0.07−1.81, all p's > 0.05).

We also examined the prevalence of HFA resetting as a function of distance to depth stimulation sites. HFA resetting was greater at recording electrodes near the stimulation site. For electrodes near the stimulation site, the prevalence of HFA resetting was significantly less than that of HFA decreases and greater than that of HFA increases (Distance × Resetting vs. Increase vs. Decrease: $z = 2.4$, $p = 0.007$, LME model; Fig. 5D). Additionally, we found that the prevalence of HFA resetting was greater for stimulation in white rather than gray matter (White vs. Gray Matter: $z = 2.66$, $p = 0.008$, see Table S4D). In light of its distinctive characteristics, these results indicate that stimulation-induced HFA resetting reflects a distinctive neuronal phenomenon compared to stimulation-induced HFA power increases and decreases. To assess whether stimulation in epileptic regions affects HFA resetting, we compared the rate of HFA resetting between stimulation in healthy and epileptic regions and found no significant difference ($z = 0.86$, $p = 0.39$, rank-sum test).

Control analyses of stimulation artifact effects

While one cannot completely separate artifact from physiological signals in clinical iEEG recordings, we took a two-stage approach to identify and mitigate their potential impact on our results. As described in the Methods, we ensured that electrical artifacts from the activation of the stimulator did not impact our HFA power calculations by measuring HFA choosing temporally precise multitaper parameters to measure spectral power at an interval that was separated in time from when the stimulator was active. As shown in Figure S4, this approach successfully identified reliable patterns of HFA power increases that had different time-courses compared to stimulation artifacts.

We also examined whether our results were affected by artifacts related to amplifier saturation. After stimulation concludes, many recording electrodes show transient low-frequency deflections, which could disrupt accurate power measurement. To minimize the influence of voltage deflections on our results, as described in the Methods, we removed both individual trials and recording electrodes that exhibited large post-stimulation voltage changes (Fig. S2). To further validate that our results were not correlated with this kind of artifact, we performed the above population analysis (Fig. 2A and B) using three different artifact-rejection thresholds (Fig. S6). The relationship between HFA changes and stimulation parameters remained present for all thresholds (Table S4E), indicating that parameter-dependent HFA changes are not a result of post-stimulation artifacts. We also measured the prevalence of artifacts for each combination of stimulation amplitude and frequency (Table. S3). Because artifact rates, did not substantially vary across stimulation parameters, it supports our view that the frequency dependence of HFA changes we observed was not a result of stimulation artifacts. We also have confidence that our results reflect neural signals because our characterization of HFA changes matches the frequency dependence seen in animals [61]. Additionally, the stimulation-induced HFA changes we found interact with neuroanatomy—HFA increases were more prevalent

when stimulating white rather than gray matter—which is a pattern that is unlikely to appear as the result of electrical artifacts.

Discussion

Clinicians and researchers are increasingly interested in brain stimulation because it provides a way to directly modulate ongoing brain activity which could be used in the treatment of neurological disorders. However, for brain stimulation to be used optimally, stimulation should be targeted precisely according to the desired outcome. One goal of our project was to guide selection of stimulation parameters by characterizing—across space, frequency, and amplitude—the neuronal effects of direct cortical stimulation in humans. Our work indicates that effects of stimulation significantly differ depending on the parameters used for stimulation despite substantial variations in the effects of stimulation across subjects. Together, our results indicate that we may achieve more effective outcomes of stimulation by choosing parameters according to the desired neuronal pattern.

A key result from our work is demonstrating that the neuronal effects of direct brain stimulation in humans are frequency dependent. While the general effect of stimulation on HFA was a decrease in power, we demonstrated that high- and low-frequency stimulation inversely impact neuronal activity, preferentially causing HFA power increases and decreases, respectively (Fig. 2C). In this way, our work helps explain prior studies that demonstrated that the frequency of stimulation was an important factor in driving specific clinical outcomes from stimulation. For example, when using DBS for Parkinson's disease, stimulation at frequencies over 90 Hz alleviated tremor while frequencies below 60 Hz aggravated tremor [27,52,98]. Further, the use of stimulation to treat epilepsy depends on frequency, such that stimulating at frequencies below 2 Hz and above 70 Hz reduced epileptic activity, whereas intermediate frequencies had no effect [75,107]. Of particular relevance to our work is the study by Logothetis et al. [61] who measured the resultant changes in neuronal activity in various brain regions of monkeys following microstimulation at a range of frequencies. This study found that low-frequency stimulation caused decreases in neuronal activity whereas high-frequency stimulation caused mixed increases and decreases in different downstream regions, which is consistent with our findings despite substantial methodological differences. Whereas we applied stimulation at macroelectrodes in human epilepsy patients and measured HFA power, Logothetis et al. [61] used microstimulation in the visual cortex of normal monkeys and measured fMRI and single-neuron spiking. Although the majority of stimulation sites in our study were in the temporal lobe, we found that frequency-dependent patterns were consistent across stimulation of different brain regions (See Fig. 3D). Similarly, our amplitude-dependent HFA changes build upon work from Crowther et al. [15], who measured gamma responses to single pulse cortical stimulation in humans and found that the magnitude of positive responses depended on stimulation amplitude.

A question that arises from these results is why stimulation at low frequencies suppresses and stimulation at high frequencies is more likely to activate. Quantitative models suggest that high-frequency stimulation selectively activates fibers of passage and axon terminals with low thresholds that would not normally be activated by low-frequency stimulation [69]. This may occur because high-frequency stimulation delivers a higher rate of charge with shorter time between pulses, which increases mean spiking rates because neurons have less time to hyperpolarize [8,41,70,84]. Inversely, low-frequency stimulation has been shown to induce long-lasting hyperpolarization, which reduces overall firing [97].

By incorporating neuroanatomy, models may also explain our finding of prevalent HFA decreases near the stimulation site, while HFA increases were relatively more widespread (Fig. 4A–C). These spatial variations may be explained by the anatomical organization of the stimulated neurons. When stimulation activates axons, which is more likely with high frequencies [69], models suggest that excitatory effects can spread more broadly, following axonal projections to other regions. Inversely, when stimulation impacts cell bodies, the effects are likely to be inhibitory and spatially limited [35,69,70].

It is notable that we found variability in HFA power changes between stimulation sites even within an individual. This result is consistent with the idea that local and distal effects of stimulation depend on the neuronal morphology surrounding the stimulation site [10,56,83], specifically, the precise positioning of the implanted electrode and its specific orientation relative to cortical layers or fibers of passage. At the broadest level, our findings support the idea that the effective use of brain stimulation should consider neuron organization, thresholds, and neurotransmitters of an area to better predict the downstream effects of stimulation [84]. This variation that we found in the responses to stimulation at different sites might help explain prior studies that showed diverse perceptual and behavioral responses to stimulation between subjects and stimulation locations [10,83,88]. Additionally, glial responses to implanted electrodes, structural abnormalities associated with patients' neurological conditions, and anti-seizure medications may also contribute to variability to between patients and stimulation sites [86]. Despite this variability, in 16% subjects, we found significantly correlated patterns of HFA power changes across different stimulation sites. This suggests that some individuals have distinctive neuroanatomical patterns, perhaps involving connectivity or genetic differences [28], that cause them to show consistent HFA changes even across widespread stimulation targets.

We found that inhibitory and excitatory effects were relatively more likely from stimulation in gray and white matter, respectively. This result adds to a growing body of literature emphasizing that behavioral and electrophysiological outcomes depend on the proximity of stimulation to structural connections. In particular, studies showed that positive behavioral outcomes result from stimulation in white rather than gray matter. In particular, studies reported improvement of memory specificity and depression symptoms when applying stimulation specifically in white matter [30,68,95,96]. Similarly, one recent study showed that white-matter stimulation amplifies oscillatory theta coherence across memory networks [91]. Additionally, studies in rodents show similar results, demonstrating that microstimulation in white matter was more effective for exciting distal neuronal populations [78,79]. Our findings add to this body of work, by suggesting a mechanism for white-matter stimulation to improve behavior, by preferentially causing neuronal excitation. Recent modeling studies determined patient-specific stimulation locations from predictions of electrical-field generation based on patient tractography [65]. Going forward, it may be beneficial for clinicians to integrate parameter selection procedures with patient-specific models to guide stimulation locations relative to structural connections.

Our findings also help extend closed-loop, or responsive, neurostimulation therapies currently used to treat intractable epilepsy and Parkinson's Disease to the treatment of cognitive disorders [45,60,77,93]. Prior closed-loop stimulation studies aimed to improve memory continuously monitored brain state and delivered stimulation to increase or decrease a particular measure of neuronal activity when it crossed a critical threshold [21,22,38]. Our results inform which stimulation parameters are most likely to change a specific biomarker in a desired direction. Besides using stimulation to excite and inhibit, we observed the novel

phenomenon of stimulation-induced HFA resetting. In contrast to using stimulation to shift neuronal activity in one direction, the stimulation-induced resetting indicates that targeted stimulation can induce a specific state regardless of the level of neuronal activity prior to stimulation. By leveraging stimulation-induced resetting, we hypothesize that targeted white-matter stimulation protocols can transition brain activity into particular states [92], supplementing existing closed-loop methods that focus on shifting ongoing neuronal patterns in one direction.

Although we conducted our work with electrodes implanted in surgical patients, our results also have implications for non-invasive brain stimulation. Much like direct electrical stimulation, transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (TES) have been shown to produce mixed excitatory and inhibitory responses. The direction of the changes in neuronal activity caused by TMS and TES have been shown to depend on parameters that were analogous to those we tested, such as the location, frequency, and amplitude of stimulation [2,5,24,32,33]. In fact, Sokhadze et al. [89] show the effects of TMS on gamma oscillations depend on stimulation frequency such that 10–15 Hz stimulation often excites while 0.5–2 Hz frequencies inhibit. These frequency-dependent responses suggest that TMS may produce analogous excitatory and inhibitory responses to different stimulation frequency ranges when compared to our results. Furthermore, non-invasive brain stimulation studies also found substantial inter-subject variability [62,103], which is also consistent with our results. Given these similarities, our results support the approach of customizing non-invasive stimulation parameters for each individual.

A focus of many brain stimulation therapies is to recapitulate a target neuronal pattern [21,43,44]. Because we show the stimulation parameters that cause different types electrophysiological signals, our work offers guidelines for clinicians to select stimulation frequencies and amplitudes that recreate particular target patterns. In this regard, the most important features of our results are (1) that high- and low-frequency stimulation are associated with HFA power increases and decreases, respectively, and (2) that high stimulation currents cause HFA power decreases across broader cortical regions. These patterns help explain key features of previous neuromodulation work. For example, in one study we found that stimulation at a particular site caused a patient to spontaneously recall an old autobiographical memory, and, notably, this site showed HFA decreases when the patient remembered the memory normally [39]. Our findings help explain why this occurred, because they link the 50-Hz stimulation that was used to HFA power decreases that matched the neuronal pattern associated with that memory. Further, our results help explain the recent finding that high-frequency stimulation in the LTL can help improve episodic memory encoding [21,47]. Normally, successful learning of episodic memories is associated with elevated HFA power [11]. Therefore, our results help explain that high-frequency stimulation improved memory encoding because it recreated the elevated HFA power that was normally associated with successful encoding.

Conclusions

We systematically characterized brain-wide responses to stimulation on a large scale and found changes in neuronal activity depend on stimulation frequency, amplitude, region, and proximity to white matter. Current standard functional stimulation mapping protocols do not select parameters based on specific responses in line with the desired clinical outcome [10]. In many cases, the stimulation parameters chosen for a given task are modeled after the ones used in other protocols or in other subjects [64]. Our findings do not eliminate the current clinical procedure of iteratively testing parameters to select patient-specific optimal stimulation parameters. They do, however, contributed the first general guidelines from a large-scale dataset in humans for the types of electrophysiological effects that might be expected from stimulating at different parameters. Additionally, this analysis framework provides a systematic method of evaluating brain-wide neuronal responses to stimulation at different parameters on an individual level as well as across subjects with variable stimulation protocols. A future avenue building upon this work may combine our observations of electrophysiological effects of stimulation with modeling and knowledge of behaviorally linked neuronal patterns so that clinicians and researchers can design more targeted therapeutic stimulation protocols to more effectively treat neurological and psychiatric disorders.

Funding

This work was supported by the DARPA Restoring Active Memory (RAM) program (Cooperative Agreement N66001-14-2-4032). The views, opinions and/or findings expressed are those of the author and should not be interpreted as representing the official views or policies of the Department of Defense or the U.S. Government. The work also received support from National Institutes of Health Grant R21-MH117682. K.Z. was supported by the Intramural Research Program of the National Institute of Neurological Disorders and Stroke.

Author contributions statement

U.M. and J.J. designed and implemented the data analyses and wrote the manuscript. A.W. and J.M advised analysis framework. M.K., and D.R. designed the stimulation-mapping protocol, B.L., M.R.S., G.W., R.E.G, K.Z., B.J., K.D., S.S. recruited subjects, collected data, and performed clinical duties associated with data collection including neurosurgical procedures or patient monitoring. J.S., R.G., and S.D. performed anatomical localization of electrodes. All authors participated in editing.

Declaration of competing interest

M.K. and D.R. have started a company, Nia Therapeutics, Inc., intended to develop and commercialize brain stimulation therapies for memory restoration. Each of them holds >5% equity interest in Nia. R.E.G. serves as a consultant to Medtronic, which was a subcontractor on the RAM project. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict of interest policies. B.J. receives research funding from NeuroPace and Medtronic not relating to this research. G.W. has rights to receive future royalties from the licensing of brain stimulation technology. Mayo Clinic has a financial interest related to brain stimulation technology, and is co-owner of Cadence Neuroscience Inc, the development of which has been assisted by G.W. The remaining authors declare no competing interests.

Acknowledgements

We are indebted to all patients who volunteered their time to participate in our study. We thank Shachar Maidenbaum and Salman Qasim for providing helpful feedback on the manuscript. We thank Blackrock Microsystems for providing neural recording and stimulation equipment.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2020.05.009.

References

[1] Anderson ME, Postupna N, Ruffo M. Effects of high-frequency stimulation in the internal globus pallidus on the activity of thalamic neurons in the awake monkey. J Neurophysiol 2003;89(2):1150–60.
[2] Antal A, Paulus W. Transcranial alternating current stimulation (tacs). Front Hum Neurosci 2013;7:317.
[3] Baayen RH, Davidson DJ, Bates DM. Mixed-effects modeling with crossed random effects for subjects and items. J Mem Lang 2008;59(4):390–412.
[4] Bakay RA. Deep brain stimulation for schizophrenia. Stereotact Funct Neurosurg 2009;87(4). 266–266.
[5] Barker AT, Shields K. Transcranial magnetic stimulation: basic principles and clinical applications in migraine. Headache J Head Face Pain 2017;57(3): 517–24.
[6] Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. 2014. arXiv preprint arXiv:1406.5823.
[7] Benabid A, Pollack P, Loveau A, Henry S, de Rougemont J. Combined (thalamototmy and stimulation) stereotactic surgery of the vm thalamic nucleus for bilateral Parkinson disease. Stereotact Funct Neurosurg 1987;50(1–6).
[8] Benazzouz A, Hallett M. Mechanism of action of deep brain stimulation. Neurology 2000;55(12 Suppl 6):S13–6.
[9] Boraud T, Bezard E, Bioulac B, Gross C. High frequency stimulation of the internal globus pallidus (gpi) simultaneously improves parkinsonian symptoms and reduces the firing frequency of gpi neurons in the mptp-treated monkey. Neurosci Lett 1996;215(1):17–20.
[10] Borchers S, Himmelback M, Logothetis NK, Karanath H. Direct electrical stimula- tion of the human cortex - the gold standard for mapping brain functions? Nat Rev Neurosci 2012;13(1):63–70.
[11] Burke JF, Zaghloul KA, Jacobs J, Williams RB, Sperling MR, Sharan AD, Kahana MJ. Synchronous and asynchronous theta and gamma activity during episodic memory formation. J Neurosci 2013;33(1):292–304.
[12] Butson CR, Cooper SE, Henderson JM, McIntyre CC. Patient-specific analysis of the volume of tissue activated during deep brain stimulation. Neuroimage 2007;34(2):661–70.
[13] Coleshill SG, Binnie CD, Morris RG, Alarcon G, van Emde Boas W, Velis DN, Sim- mons A, Polkey CE, van Veelen CWM, van Rijen PC. Material-specific recognition memory deficits elicited by unilateral hippocampal electrical stimulation. J Neurosci 2004;24(7):1612–6.
[14] Coubes P, Roubertie A, Vayssiere N, Hemm S, Echenne B. Treatment of dyt1-generalised dystonia by stimulation of the internal globus pallidus. Lancet 2000;355(9222):2220–1.
[15] Crowther LJ, Brunner P, Kapeller C, Guger C, Kamada K, Bunch ME, Frawley BK, Lynch TM, Ritaccio AL, Schalk G. A quantitative method for evaluating cortical responses to electrical stimulation. J Neurosci Methods 2019;311:67–75.
[16] Delorme A, Makeig S, Sejnowski T. Automatic artifact rejection for EEG data using high- order statistics and independent component analysis. In: Proceedings of the third international ICA conference, san Diego; December 2001.
[17] Desikan R, Segonne B, Fischl B, Quinn B, Dickerson B, Blacker D, Buckner RL, Dale A, Maguire A, Hyman B, Albert M, Killiany N. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 2006;31(3):968–80.
[18] Dostrovsky J, Levy R, Wu J, Hutchison W, Tasker R, Lozano A. Microstimulation- induced inhibition of neuronal firing in human globus pallidus. J Neurophysiol 2000;84(1):570.
[19] Eichenbaum H. A cortical-hippocampal system for declarative memory. Nat Rev Neurosci Oct 2000;1(1):41–50.
[20] Ezzyat Y, Rizzuto DS. Direct brain stimulation during episodic memory. Curr Opin Biomed Eng 2018;8:78–83.
[21] Ezzyat Y, Kragel JE, Burke JF, Levy DF, Lyalenko A, Wanda P, O'Sullivan L, Hurley K, Busygin S, Pedisich I, Sperling MR, Worrell GA, Kucewicz MT, Davis KA, Lucas TH, Inman CS, Lega BC, Jobst BC, Sheth S, Zaghloul K, Jutras M, Stein JM, Das S, Gorniak R, Rizzuto DS, Kahana MJ. Direct brain stimulation modulates encoding states and memory performance in humans. Curr Biol 2017;27(9):1251–8.
[22] Ezzyat Y, Wanda P, Levy DF, Kadel A, Aka A, Pedisich I, Sperling MR, Sharan AD, Lega BC, Burks A, Gross R, Inman CS, Jobst BC, Gorenstein M, Davis KA, A WG, Kucewicz MT, Stein JM, Gorniak RJ, Das SR, Rizzuto DS, Kahana MJ. Closed-loop stimulation of temporal cortex rescues functional networks and improves memory. Nat Commun 2018;9(1):365. https://doi.org/10.1038/s41467-017-02753-0.
[23] Fell J, Staresina BP, Do Lam AT, Widman G, Helmstaedter C, Elger CE, Axmacher N. Memory modulation by weak synchronous deep brain stimulation: a pilot study. Brain Stimul 2013;6(3):270–3.
[24] Fertonani A, Miniussi C. Transcranial electrical stimulation: what we know and do not know about mechanisms. Neuroscientist 2017;23(2):109–23.
[25] Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, Oommen K, Osorio I, Nazzaro J, Labar D, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 2010;51(5): 899–908.
[26] Fisher RS, Velasco AL. Electrical brain stimulation for epilepsy. Nat Rev Neurol 2014;10(5):261.
[27] Fogelson N, Kühn AA, Silberstein P, Limousin PD, Hariz M, Trottenberg T, Kupsch A, Brown P. Frequency dependent effects of subthalamic nucleus stimulation in Parkinson's disease. Neurosci Lett 2005;382(1–2):5–9.
[28] Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci Unit States Am 2005;102(27):9673–8.
[29] Fries P, Nikolić D, Singer W. The gamma cycle. Trends Neurosci 2007;30(7): 309–16.
[30] Gutman DA, Holtzheimer PE, Behrens TE, Johansen-Berg H, Mayberg HS. A tractography analysis of two deep brain stimulation white matter targets for depression. Biol Psychiatr 2009;65(4):276–82.
[31] Halgren E, Wilson CL, Stapleton JM. Human medial temporal-lobe stimulation disrupts both formation and retrieval of recent memories. Brain Cognit July 1985;4(3):287–95.
[32] Hallett M. Transcranial magnetic stimulation and the human brain. Nature 2000;406(6792):147.
[33] Hallett M. Transcranial magnetic stimulation: a primer. Neuron 2007;55(2): 187–99.
[34] Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL. Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. J Neurosci 2003;23(5):1916–23.
[35] Herrington TM, Cheng JJ, Eskandar EN. Mechanisms of deep brain stimulation. J Neurophysiol 2015;115(1):19–38.
[36] Histed M, Bonin V, Reid C. Direct activation of sparse, distributed populations of cortical neurons by electrical microstimulation. Neuron 2009;63:508–22.
[37] Histed MH, Ni AM, Maunsell JH. Insights into cortical mechanisms of behavior from microstimulation experiments. Progr Neurobiol 2013;103: 115–30.
[38] Iturrate I, Pereira M, Millán JdR. Closed-loop electrical neurostimulation: challenges and opportunities. Curr Opin Biomed Eng 2018;8:28–37.
[39] Jacobs J, Lega B, Anderson C. Explaining how brain stimulation can evoke memories. J Cognit Neurosci 2012;24(3):553–63.
[40] Jacobs J, Miller J, Lee SA, Coffey T, Watrous AJ, Sperling MR, Sharan A, Worrell G, Berry B, Lega B, Jobst B, Davis K, Gross RE, Sheth SA, Ezzyat Y, Das SR, Stein J, Gorniak R, Kahana MJ, Rizzuto DS. Direct electrical stimulation of the human entorhinal region and hippocampus impairs memory. Neuron December 2016;92(5):1–8.
[41] Jensen M, De Meyts P. Molecular mechanisms of differential intracellular signaling from the insulin receptor. Vitam Horm 2009;80:51–75.
[42] Johnson MD, Miocinovic S, McIntyre CC, Vitek JL. Mechanisms and targets of deep brain stimulation in movement disorders. Neurotherapeutics 2008;5(2):294–308.
[43] Jun S, Lee SA, Kim JS, Jeong W, Chung CK. Task-dependent effects of intracranial hippocampal stimulation on human memory and hippocampal theta power. Brain Stimul 2020;13(3):603–13.
[44] Kim K, Ekstrom AD, Tandon N. A network approach for modulating memory processes via direct and indirect brain stimulation: toward a causal approach for the neural basis of memory. Neurobiol Learn Mem 2016;134(Pt A): 162–77.
[45] Kokkinos V, Sisterson ND, Wozny TA, Richardson RM. Association of closed-loop brain stimulation neurophysiological features with seizure control among patients with focal epilepsy. JAMA Neurol 2019;76(7):800–8.
[46] Koller W, Pahwa R, Busenbark K, Hubble J, Wilkinson S, Lang A, Tuite P, Sime E, Lazano A, Hauser R, Malapira T, Smith D, Tarsy D, Miyawaki E, Norregaard T, Ko- rmos T, Olanow CW. High-frequency unilateral thalamic stimulation in the treatment of essential and parkinsonian tremor. Ann Neurol 1997;42(3):292–9.
[47] Kucewicz MT, Berry BM, Kremen V, Brinkmann BH, Sperling MR, Sharan A, Jobst BC, Gross RE, Lega B, Sheth S, Stein JM, Das SR, Stead SM, Rizzuto DS, Kahana MJ, Worrell GA. Dissecting gamma frequency activity during human memory processing. Brain 2017;140(5):1337–50.
[48] Kuhn J, Lenartz D, Huff W, Lee S, Koulousakis A, Klosterkoetter J, Sturm V. Remis- sion of alcohol dependency following deep brain stimulation of the nucleus accumbens: valuable therapeutic implications? J Neurol Neurosurg Psychiatr 2007;78(10):1152–3.
[49] Kuhn J, Bodatsch M, Sturm V, Lenartz D, Klosterkotter J, Uhlhaas P, Winter C, Gründler T. Deep brain stimulation in schizophrenia. Fortschr Neurol Psychiatr 2011;79(11):632–41.
[50] Kuhn J, Hardenacke K, Lenartz D, Gruendler T, Ullsperger M, Bartsch C, Mai J, Zilles K, Bauer A, Matusch A, et al. Deep brain stimulation of the nucleus basalis of meynert in alzheimer?s dementia. Mol Psychiatr 2015;20(3):353.
[51] Kumar R, Dagher A, Hutchison W, Lang A, Lozano A. Globus pallidus deep brain stimulation for generalized dystonia: clinical and pet investigation. Neurology 1999;53(4). https://doi.org/10.1212/WNL.53.4.871. 871–871.
[52] Kuncel AM, Cooper SE, Wolgamuth BR, Clyde MA, Snyder SA, Montgomery Jr EB, Rezai AR, Grill WM. Clinical response to varying the stimulus parameters in deep brain stimulation for essential tremor. Mov Disord 2006;21(11):1920–8. official journal of the Movement Disorder Society.
[53] Lacruz ME, Valentín A, Seoane JJG, Morris RG, Selway RP, Alarcon G. Single pulse electrical stimulation of the hippocampus is sufficient to impair human episodic memory. Neuroscience Oct. 2010;170(2):623–32.
[54] Lang AE, Lozano AM. Parkinson's disease. N Engl J Med 1998;339(15): 1044–53.

[55] Lang AE, Lozano AM. Parkinson's disease. N Engl J Med 1998;339(16):1130–43.
[56] Lesser RP, Lee HW, Webber W, Prince B, Crone NE, Miglioretti DL. Short-term variations in response distribution to cortical stimulation. Brain 2008;131(6):1528–39.
[57] Levy D, Shabat-Simon M, Shalev U, Barnea-Ygael N, Cooper A, Zangen A. Repeated electrical stimulation of reward-related brain regions affects cocaine but not natural reinforcement. J Neurosci 2007;27(51):14179–89.
[58] Limousin P, Pollack P, Benazzouz A, Hoffman D, Broussolle E, Perret E, Benabid A. Bilateraly subthalamic nucleus stimulation for sever Parkinson's disease. Mov Disord 1995;10:672–4.
[59] Lipsman N, Lam E, Volpini M, Sutandar K, Twose R, Giacobbe P, Sodums DJ, Smith GS, Woodside DB, Lozano AM. Deep brain stimulation of the subcallosal cingulate for treatment-refractory anorexia nervosa: 1 year follow-up of an open-label trial. Lancet Psychiatr 2017;4(4):285–94.
[60] Little S, Pogosyan A, Neal S, Zavala B, Zrinzo L, Hariz M, Foltynie T, Limousin P, Ashkan K, FitzGerald J, et al. Adaptive deep brain stimulation in advanced Parkinson disease. Ann Neurol 2013;74(3):449–57.
[61] Logothetis N, Augath M, Murayama Y, Rauch A, Sultan F, Goense J, Oeltermann A, Merkle H. The effects of electrical microstimulation on cortical signal propagation. Nat Neurosci 2010;13(10):1283–91. ISSN 1097-6256.
[62] Lopez-Alonso V, Cheeran B, Río-Rodríguez D, Fernández-del-Olmo M. Inter-individual variability in response to non-invasive brain stimulation paradigms. Brain Stimul 2014;7(3):372–80.
[63] Lozano AM, Fosdick L, Chakravarty MM, Leoutsakos J-M, Munro C, Oh E, Drake KE, Lyman CH, Rosenberg PB, Anderson WS, et al. A phase ii study of fornix deep brain stimulation in mild alzheimer?s disease. J Alzheim Dis 2016;54(2):777–87.
[64] Lozano AM, Lipsman N, Bergman H, Brown P, Chabardes S, Chang JW, Matthews K, McIntyre CC, Schlaepfer TE, Schulder M, et al. Deep brain stimulation: current challenges and future directions. Nat Rev Neurol 2019:1.
[65] Lujan JL, Chaturvedi A, Choi KS, Holtzheimer PE, Gross RE, Mayberg HS, McIntyre CC. Tractography-activation models applied to subcallosal cingulate deep brain stimulation. Brain Stimul 2013;6(5):737–9.
[66] Manning JR, Jacobs J, Fried I, Kahana MJ. Broadband shifts in local field potential power spectra are correlated with single-neuron spiking in humans. J Neurosci 2009;29(43):13613–20.
[67] Maurice N, Thierry A-M, Glowinski J, Deniau J-M. Spontaneous and evoked activity of substantia nigra pars reticulata neurons during high-frequency stimulation of the subthalamic nucleus. J Neurosci 2003;23(30):9929–36.
[68] Mayberg H, Lozano A, Voon V, McNeely H, Seminowicz D, Hamani C, Schwalb J, Kennedy S. Deep brain stimulation surgery for treatment resistant depression. Neuron 2005;45:651–60.
[69] McIntyre CC, Grill WM. Extracellular stimulation of central neurons: influence of stimulus waveform and frequency on neuronal output. J Neurophysiol 2002;88(4):1592–604.
[70] McIntyre CC, Grill WM, Sherman DL, Thakor NV. Cellular effects of deep brain stimulation: model-based analysis of activation and inhibition. J Neurophysiol 2004;91(4):1457–69.
[71] McIntyre CC, Savasta M, Kerkerian-Le Goff L, Vitek JL. Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. Clin Neurophysiol 2004;115(6):1239–48.
[72] Mihailovic L, Delgado JM. Electrical stimulation of monkey brain with various frequencies and pulse durations. J Neurophysiol 1956;19(1):21–36.
[73] Miller JP, Sweet JA, Bailey CM, Munyon CN, Luders HO, Fastenau PS. Visual-spatial memory may be enhanced with theta burst deep brain stimulation of the fornix: a preliminary investigation with four cases. Brain 2015;138(7):1833–42.
[74] Miller KJ, Sorensen LB, Ojemann JG, den Nijs M, Sporns O. Power-law scaling in the brain surface electric potential. PLoS Comput Biol 2009;5(12).
[75] Mina F, Benquet P, Pasnicu A, Biraben A, Wendling F. Modulation of epileptic activity by deep brain stimulation: a model-based study of frequency-dependent effects. Front Comput Neurosci 2013;7:94.
[76] Mitra PP, Pesaran B. Analysis of dynamic brain imaging data. Biophys J 1999;76:691–708.
[77] Morrell MJ. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology 2011;77(13):1295–304.
[78] Nowak L, Bullier J. Axons, but not cell bodies, are activated by electrical stimulation in cortical gray matter i. evidence from chronaxie measurements. Exp Brain Res 1998;118(4):477–88.
[79] Nowak L, Bullier J. Axons, but not cell bodies, are activated by electrical stimulation in cortical gray matter ii. evidence from selective inactivation of cell bodies and axon initial segments. Exp Brain Res 1998;118(4):489–500.
[80] Nuttin BJ, Gabrïels LA, Cosyns PR, Meyerson BA, Andréewitch S, Sunaert SG, Maes AF, Dupont PJ, Gybels JM, Gielen F, et al. Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. Neurosurgery 2003;52(6):1263–74.
[81] Ojemann G, Ojemann J, L E, Berger M. Cortical language localization in left, dominant hemisphere: an electrical stimulation mapping investigation in 117 patients. J Neurosurg 1989;71:316–26.
[82] Penfield W, Perot P. The brain's record of auditory and visual experience. Brain 1963;86(4):595–696.
[83] Pouratian N, Cannestra AF, Bookheimer SY, Martin NA, Toga AW. Variability of intraoperative electrocortical stimulation mapping parameters across and within individuals. J Neurosurg 2004;101(3):458–66.
[84] Ranck Jr JB. Which elements are excited in electrical stimulation of mammalian central nervous system: a review. Brain Res 1975;98(3):417–40.
[85] Salahuddin S, Porter E, Meaney PM, Halloran MO. Effect of logarithmic and linear frequency scales on parametric modelling of tissue dielectric data. Biomed Phys Eng Expr 2017;3(1):015020.
[86] Salatino JW, Ludwig KA, Kozai TD, Purcell EK. Glial responses to implanted electrodes in the brain. Nat Biomed Eng 2017;1(11):862–77.
[87] Sederberg PB, Schulze-Bonhage A, Madsen JR, Bromfield EB, McCarthy DC, Brandt A, Tully MS, Kahana MJ. Hippocampal and neocortical gamma oscillations predict memory formation in humans. Cerebr Cortex 2007;17(5):1190–6.
[88] Selimbeyoglu A, Parvizi J. Electrical stimulation of the human brain: perceptual and behavioral phenomena reported in the old and new literature. Front Hum Neurosci 2010;4(46).
[89] Sokhadze EM, El-Baz A, Baruth J, Mathai G, Sears L, Casanova MF. Effects of low frequency repetitive transcranial magnetic stimulation (rtms) on gamma frequency oscillations and event-related potentials during processing of illusory figures in autism. J Autism Dev Disord 2009;39(4):619–34.
[90] Solomon E, Kragel J, Sperling M, Sharan A, Worrell G, Kucewicz M, Inman C, Lega B, Davis K, Stein J, Jobst B, Zaghloul K, Sheth S, Rizzuto D, Kahana M. Widespread theta synchrony and high-frequency desynchronization underlies enhanced cognition. Nat Commun 2017;8(1):1704.
[91] Solomon EA, Kragel JE, Gross RE, Lega B, Sperling MR, Worrell G, Sheth SA, Zaghloul KA, Jobst BC, Stein JM, Das S, Gorniak R, Inman CS, Seger S, Rizzuto DS, Kahana MJ. Medial temporal lobe functional connectivity predicts stimulation-induced theta power. Nat Commun 2018;9(1):4437.
[92] Stiso J, Khambhati AN, Menara T, Kahn AE, Stein JM, Das SR, Gorniak R, Tracy J, Litt B, Davis KA, et al. White matter network architecture guides direct electrical stimulation through optimal state transitions. 2018. arXiv preprint arXiv:1805.01260.
[93] Sun FT, Morrell MJ. Closed-loop neurostimulation: the clinical experience. Neurotherapeutics 2014;11(3):553–63.
[94] Suthana N, Fried I. Deep brain stimulation for enhancement of learning and memory. Neuroimage 2014;85:996–1002.
[95] Suthana N, Haneef Z, Stern J, Mukamel R, Behnke E, Knowlton B, Fried I. Memory enhancement and deep-brain stimulation of the entorhinal area. N Engl J Med 2012;366:502–10.
[96] Titiz AS, Hill MR, Mankin EA, Aghajan ZM, Eliashiv D, Tchemodanov N, Maoz U, Stern J, Tran ME, Schuette P, et al. Theta-burst microstimulation in the human entorhinal area improves memory specificity. eLife 2017;6.
[97] Toprani S, Durand DM. Long-lasting hyperpolarization underlies seizure reduction by low frequency deep brain electrical stimulation. J Physiol 2013;591(22):5765–90.
[98] Ushe M, Mink JW, Revilla FJ, Wernle A, Schneider Gibson P, McGee-Minnich L, Hong M, Rich KM, Lyons KE, Pahwa R, et al. Effect of stimulation frequency on tremor suppression in essential tremor. Mov Disord 2004;19(10):1163–8. official journal of the Movement Disorder Society.
[99] Watson BO, Ding M, Buzsáki G. Temporal coupling of field potentials and action potentials in the neocortex. Eur J Neurosci 2018;48(7):2482–97.
[100] Weiskrantz L, Mihailović L, Gross CG. Stimulation of frontal cortex and delayed alter- nation performance in the monkey. Science 1960;131(3411):1443–4.
[101] Weiskrantz L, Mihailovic L, Gross C. Effects of stimulation of frontal cortex and hip- pocampus on behaviour in the monkey. Brain 1962;85(3):487–504.
[102] Welter M-L, Houeto J-L, Bonnet A-M, Bejjani P-B, Mesnage V, Dormont D, Navarro S, Cornu P, Agid Y, Pidoux B. Effects of high-frequency stimulation on subthalamic neuronal activity in parkinsonian patients. Arch Neurol 2004;61(1):89–96.
[103] Wiethoff S, Hamada M, Rothwell JC. Variability in response to transcranial direct current stimulation of the motor cortex. Brain Stimul 2014;7(3):468–75.
[104] Winawer J, Parvizi J. Linking electrical stimulation of human primary visual cortex, size of affected cortical area, neuronal responses, and subjective experience. Neuron 2016;92(6):1213–9.
[105] Windels F, Bruet N, Poupard A, Urbain N, Chouvet G, Feuerstein C, Savasta M. Effects of high frequency stimulation of subthalamic nucleus on extracellular glutamate and gaba in substantia nigra and globus pallidus in the normal rat. Eur J Neurosci 2000;12(11):4141–6.
[106] Yianni J, Bain P, Giladi N, Auca M, Gregory R, Joint C, Nandi D, Stein J, Scott R, Aziz T. Globus pallidus internus deep brain stimulation for dystonic conditions: a prospective audit. Mov Disord 2003;18(4):436–42. official journal of the Movement Disorder Society.
[107] Yu T, Wang X, Li Y, Zhang G, Worrell G, Chauvel P, Ni D, Qiao L, Liu C, Li L, et al. High-frequency stimulation of anterior nucleus of thalamus desynchronizes epileptic network in humans. Brain 2018;141(9):2631–43.
[108] Yushkevich PA, Pluta JB, Wang H, Xie L, Ding S-L, Gertje EC, Mancuso L, Kliot D, Das SR, Wolk DA. Automated volumetry and regional thickness analysis of hippocampal subfields and medial temporal cortical structures in mild cognitive impairment. Hum Brain Mapp 2015;36(1):258–87.