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### Title

Neuromodulation: The Search Is On for the Most Effective Parameters

### Permalink

<https://escholarship.org/uc/item/2jn683xs>

### Journal

Epilepsy Currents, 20(6)

### ISSN

1535-7597

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### Publication Date

2020-11-01

### DOI

10.1177/1535759720954227

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Peer reviewed



# Neuromodulation: The Search Is On for the Most Effective Parameters

Epilepsy Currents  
2020, Vol. 20(6) 359-361  
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DOI: 10.1177/1535759720954227  
journals.sagepub.com/home/epi



## The Effects of Direct Brain Stimulation in Humans Depend on Frequency, Amplitude, and White-Matter Proximity

Mohan U, Watrous A, Miller J, et al. *Brain Stimul.* 2020;13(5):1183-1195. doi:10.1016/j.brs.2020.05.009

**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 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.

## Commentary

Responsive neurostimulation (RNS), a type of closed-loop electrical stimulation, is an alternative treatment for drug-resistant epilepsy patients who are not candidates for respective or ablative surgery. The goal of the therapy is to modulate a pathological network that generates seizure activity. The mechanisms of action described for this type of neuromodulation include direct suppression of neuronal firing, depolarization blockade, neuronal desynchronization, and hyperpolarization. For example, *in vitro* effects of electrical stimulation involve disruption of synchronous activity and modulation of short-term activity distant to the site of stimulation,<sup>1</sup> while electrical stimulation of CA3 mossy fibers has been reported to increase intracellular chloride, leading to local inhibitory effects.<sup>2</sup>

The acute effects of stimulation depend on whether low- or high-frequency stimulation is used. Low-frequency stimulation of white matter fibers connecting the hippocampi induces long-lasting hyperpolarization that is mediated by GABAB inhibitory postsynaptic potentials and by slow afterhyperpolarization.<sup>3</sup> In contrast, high-frequency stimulation ( $\geq 100$  Hz)

produces a local axonal block of both afferent and efferent fibers that creates a functional disconnection.<sup>4</sup>

Understanding the network-wide effects of focal stimulation can direct the development of protocols that could maximize the therapeutic benefit. These effects depend on the location of the stimulating electrode (thalamic vs cortical structures), the positioning of the implanted electrode and its specific orientation relative to white matter tracks or cortical layers,<sup>5</sup> and the frequency and amplitude of the stimulation parameters.

Until the report by Mohan et al,<sup>6</sup> there has not been a systematic study of the various parameters that can affect the neuronal response to closed-loop neuromodulation. The authors evaluated the effects of stimulation in a group of 109 patients with refractory epilepsy evaluated with depth and subdural cortical electrodes who were participating in a multicenter stimulation study aimed at determining which parameters could enhance episodic and spatial memory. Electrode location was evaluated by coregistration of a postimplant computed tomography scan to preimplant magnetic resonance imaging, correcting for postoperative brain shift. Each stimulation site



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was categorized as being localized to either white or gray matter.

After determining the maximum current that could be applied to individual contacts without resulting in after-discharges, bipolar stimulation was then applied at frequencies between 10 and 200 Hz, with incremental amplitudes up to the site's determined maximum. Each targeted stimulation site received 24 stimulation trials for each combination of frequency and amplitude. On average, 2.8 sites were studied per patient. To measure the effects of stimulation on mean neuronal firing rates, the high-frequency activity (HFA) signal, a reliable measure of mean neuronal activity,<sup>7</sup> was extracted from each recording site. A linear mixed-effects model, a type of regression model that relates the variation of a dependent variable as a function of fixed and random effects, was used to analyze the effects of stimulation on neuronal activity and identify how these effects vary with different stimulation parameters.

The results demonstrate that the neuronal effects of direct brain stimulation are frequency-dependent. Population analysis showed that overall HFA decreases were most prevalent than increases, regardless of stimulation frequency and electrode type. Furthermore, stimulation on depth electrodes at high and low frequencies, respectively, was associated with HFA increases and decreases. High-frequency surface stimulation rarely caused HFA increases, whereas high-frequency depth stimulation reliably caused HFA power increases. While these trends were statistically robust, there was moderate variability across individual stimulation sites in HFA power changes, with an average of 20% to 35% of the recording electrodes showing these changes.


In terms of spatial spread of neuronal activity, the prevalence of HFA decreases fell off more drastically with distance to stimulation when compared to HFA increases. The HFA increases from depth stimulation were more prevalent and showed a greater distance effect than increases from surface stimulation. Additionally, larger stimulation amplitudes increased the spatial spread of stimulation-induced HFA decreases; this type of distance dependence was not evident for sites that showed HFA increases.

An interesting observation was the adjustment to a fixed level, or resetting, of the HFA power following stimulation, a phenomenon that occurred in and outside of epileptogenic areas. This significant decrease in the variance of HFA power from pre- to poststimulation without a significant change in the mean power was more commonly seen in electrodes near the stimulation site and in white compared to gray matter sites.


This observation begets the question, could the benefits of closed-loop stimulation relate to stimulation-induced modulation of seizure network activity rather than by direct effects on individual seizure activity? In other words, is neuromodulation a disease-modifying therapy that can induce neuroplasticity and have a true antiepileptic effect? Animal studies suggest that the sustained therapeutic effects of repeated cortical stimulation might be related to changes in synaptic plasticity, neurogenesis, and cortical reorganization.<sup>8</sup> Recently, Kokkinos et al<sup>9</sup> evaluated the modulation effects of RNS in a group of

11 patients implanted with the NeuroPace device. Modulation effects were categorized as either direct, in which the recorded events manifested systematic time/or frequency changes in the immediate poststimulation interval (<5 seconds), or indirect, in which the recorded events manifested changes in time, frequency, or both before or long after the stimulation volley (>10 seconds), that is, not time locked to the stimulation. Their results suggest that direct effects of stimulation (ictal inhibition and early frequency modulation) were not associated with clinical efficacy, while indirect effects did correlate with improved clinical outcomes. The timing of the appearance of indirect frequency modulation effects at a mean (SD) of 20 (20.8) weeks after activation of responsive stimulation is suggestive of the emergence of neuroplastic effects.

While the report by Mohan et al is informative, additional studies are needed to determine the most effective patient-specific stimulation parameters that result in improved clinical outcomes. Clinical experience supports the notion that effective stimulation parameters differ between medial temporal and neocortical sites. Applying the results of these findings with the use of other techniques, such as functional magnetic resonance imaging or tractography,<sup>10</sup> might help guide the location of electrode placement that generates a desired electrical field and impact on targeted neuronal populations.

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