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Effective deep brain stimulation regularizes neuronal activity

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Abstract

Chronic high frequency electrical stimulation of the brain, called deep brain stimulation (DBS), has evolved from a highly experimental technique to an established therapy for the treatment of movement disorders including dystonia, essential tremor (ET), and Parkinsons disease (PD). While the clinical benefits of DBS are well documented, fundamental questions remain about the mechanisms of action. This lack of understanding will limit the full development and optimization of this promising treatment.

Determining the mechanisms of DBS presents a paradox of how high-frequency ($\geq\sim$ 100Hz) stimulation results in therapeutic outcomes similar to those resulting from surgical lesion of target structures in the thalamus (Vim), subthalamic nucleus (STN), or globus pallidus internus (GPi). Based on the "rate model" of basal ganglia function used to describe the mechanisms of movement disorders, the effects of DBS have been attributed to changes in the firing rates of neurons within the basal ganglia and thalamus. However, recent data support that changes in the patterns of neuronal firing also play a significant role in movement disorders. We describe two recent studies, combining computation and clinical measurements, that suggest that the relief of symptoms by DBS may result from changes in the pattern of neuronal activity, and not simply from changes in rate.

We quantified the effects of stimulation frequency and amplitude on neuronal firing patterns in a model of a population of intrinsically bursting thalamocortical (TC) neurons, and compared these effects to the changes in postural tremor with Vim DBS at different frequencies and amplitudes measured in subjects with ET. Neuronal firing patterns were dependent on stimulation frequency and amplitude in a manner remarkably similar to the clinical tremor response. Above a critical frequency, stimulation masked the intrinsic neuronal bursting and increasing the amplitude reduced the coefficient of variation (CV) of the neuronal firing pattern. Conversely, low frequency stimulation exacerbated neuronal bursting, and increasing the amplitude increased the CV of neuronal activity. Similarly, for high frequencies ($\geq$ 90Hz), increasing amplitude suppressed tremor, whereas for low frequencies ($<$ 60Hz), increasing amplitude aggravated tremor. Thus, the frequency- and amplitude-dependent changes in neuronal regularity in the population model paralleled changes in tremor, with increased regularity correlating with tremor suppression and decreased regularity correlating with tremor aggravation.

Using the same model, we quantified the response of a population of intrinsically bursting TC neurons to paired-pulse DBS, and measured the effects of paired-pulse Vim DBS on tremor in subjects with ET. The stimuli were pulse pairs delivered at 65Hz, and we varied the intra-pair interval between the beginning of the first pulse and the beginning of the second pulse in each pair between 0.3 and 7.7 ms, such that all trains had an average frequency of 130Hz. The CV of the interspike interval distribution of model neuron responses across the population was lower for regular 130Hz stimulation than for paired-pulse stimulation with large differences between the inter-pair and intra-pair intervals ($\mathrm{IPI_{diff}}$). Increasing $\mathrm{IPI_{diff}}$ rendered model neurons more likely to fire synchronous bursts, more likely to fire irregularly, and less likely to entrain to the stimulus. The changes in neuronal regularity in the population model paralleled the effects of paired-pulse thalamic DBS on tremor in subjects with ET. $\mathrm{IPI_{diff}}$ had a significant effect on tremor, and tremor increased significantly as a function of $\mathrm{IPI_{diff}}$. Thus, DBS at an average rate of 130Hz was more effective at reducing tremor when pulses were evenly spaced than when there were large differences between intra-pair and inter-pair intervals.

The correlation between the changes in tremor and the changes in neuronal firing supports the hypothesis that regularization of neuronal firing pattern during DBS is one of the mechanisms underlying tremor suppression.

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