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Is STN Neuromodulation of Focal Motor Seizures Ready for Prime Time?

Subthalamic Nucleus Stimulation Modulates Motor Epileptic Activity in Humans.

Ren SL, Yu T, Wang D, et al. *Ann Neurol*. 2020;88(2):283-296. doi:10.1002/ana.25776.

Objective: Pharmacorefractory focal motor epileptic seizures pose a significant challenge. Deep brain stimulation is a recently recognized therapeutic option for the treatment of refractory epilepsy. To identify the specific target for focal motor seizures, we evaluate the modulatory effects of the subthalamic nucleus (STN) stimulation because of the critical role of STN in cortico–subcortical motor processing. Methods: Seven patients with epilepsy with refractory seizures who underwent chronic stereoelectroencephalography monitoring were studied in presurgical evaluation. Seizure onset zone was hypothesized to be partially involved in the motor areas in 6 patients. For each patient, 1 electrode was temporally implanted into the STN that was ipsilateral to the seizure onset zone. The cortical–subcortical seizure propagation was systemically evaluated. The simultaneously electrophysiological responses over distributed cortical areas to STN stimulation at varied frequencies were quantitatively assessed. Results: We observed the consistent downstream propagation of seizures from the motor cortex toward the ipsilateral STN and remarkable cortical responses on motor cortex to single-pulse STN stimulation. Furthermore, we showed frequency-dependent upstream modulatory effect of STN stimulation on motor cortex specifically. In contrast to the enhanced effects of low-frequency stimulation, high-frequency stimulation of the STN can significantly reduce interictal spikes, high-frequency oscillations over motor cortex disclosing effective connections to the STN. Interpretation: This result showed that the STN is not only engaged in as a propagation network of focal motor seizures but STN stimulation can profoundly modulate the epileptic activity of motor cortex in humans, suggesting a mechanism-based alternative for patients suffering from refractory focal motor seizures.

Commentary

Although not the most frequent seizure type, focal motor seizures (FMS) arising from primary motor cortex can induce considerable disability. These seizures can be tonic or involve clonic jerks of any part of the contralateral hemibody, restricting motor activity and sometimes resulting in falls or accidents. Unacceptable risks of permanent motor deficits are possible if surgical resection of the epileptogenic focus is attempted. Fortunately, responsive brain stimulation[1] and deep brain stimulation (DBS) of the anterior nucleus of the thalamus[2] have been shown to be effective in the treatment of drug-resistant FMS. Unfortunately, the response is not always absolute. Are there other targets for neuromodulation that might be beneficial for the treatment of this seizure type?

Experimental data support the contribution of the motor part of the basal ganglia in the expression of FMS. The subthalamic nucleus (STN) is part of the cortico–subcortical network that integrates sensory motor activity and modulates the excitatory function of the motor cortex via direct and indirect pathways. Connectivity between the STN and motor cortex has been demonstrated in animal studies by several methods, including deoxyglucose autoradiography,[3] micro-recording and local field potentials of the STN,[4] and cortical potentials evoked by STN stimulation, which suggests the presence of antidromic activation of the cortico–subthalamic pathway.[5] Additionally, pharmacological inhibition of STN excitability by GABA agonists can suppress seizure activity.[6]

Is there evidence for the participation of the STN in FMS from human studies? The answer is yes. There have been small case series reporting the benefit of electrical stimulation of the STN in the treatment of FMS. In an open pilot study of 3 patients, Chabardes et al[7] reported that high-frequency stimulation of STN reduced seizure frequency by up to 80% and that bilateral STN stimulation was more effective than unilateral stimulation. Likewise, Loddenkemper et al[8] reported that 2 of the 5 patients who underwent STN stimulation had a reduction in seizure frequency of 60% and 80% after 16 and 10 months of follow-up, respectively.

Now, Ren et al[9] present data on the short-term use of STN-DBS in a mixed group of patients with FMS. The cohort

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included 7 patients who were evaluated with stereoelectroencephalography (sEEG), with 1 electrode implanted into the dorsolateral part of the STN that was ipsilateral to the presumed epileptogenic focus. This location was different than the location used in previous case series, where the target was the inferior part of the STN. Placement of the STN electrode was verified with a postimplant computed tomography coregistered with a preimplant magnetic resonance imaging. Five patients had unilateral tonic–clonic seizures, with cortical dysplasia identified in 3; 1 patient had clusters of unilateral fasciobrachial myoclonic jerks associated with heterotopia over the contralateral primary and premotor cortex; and 1 patient had focal with impaired awareness seizures, without a motor component, associated with atrophy of the insula and putamen.

The authors report that regardless of the motor seizure semiology, ictal activity from the cortical surface propagated almost simultaneously to the ipsilateral STN in all spontaneous and stimulated FMS. To probe the connectivity between STN and cortex, cortical-evoked potentials were analyzed while recording sEEG from unstimulated contacts after single-pulse STN stimulation at 1 Hz. Cortical potentials were mainly detected within the seizure-onset zone, with the maximum amplitude detected in the ipsilateral motor cortex.

To evaluate the modulatory effects of STN stimulation, the impact on interictal spikes (IIS) and high-frequency oscillations (HFOs) at ripple band of 100 to 250 Hz was quantitatively evaluated during incremental stimulation frequencies (10-130 Hz) at 2 mA for 60 seconds. Both IIS and HFOs were assessed by automatic detection, comparing 30-second pre- to 60-second poststimulation intervals. The contact within the STN which showed the most robust propagated ictal pattern was selected for the cathodal referential simulation, with the adjacent contact as the anode, and concurrent unstimulated cortical contacts were continuously monitored during the procedure. The data showed that an increase in IIS occurred within the motor areas, compared to nonmotor cortex, when 20 Hz stimulation was applied. The HFO rate *increased* during 20 Hz stimulation compared to baseline but *decreased* with 100 Hz stimulation. In a patient with frequent subclinical seizures, stimulation at 130 Hz attenuated the rhythmic discharges occurring during the ictal period, with the effect lasting through the period of stimulation.

By performing an analysis of spontaneous seizure propagation and time-locked cortical-evoked potentials to single-pulse STN stimulation, the study redemonstrates the results of animal studies showing involvement of a corticothalamic loop in the expression of FMS. Additionally, data illustrate that the STN is not only engaged in the propagation of FMS but that high-frequency stimulation can modulate the epileptic activity of cortical regions, with frequency-dependent upstream effects on motor cortex. Taken together, these findings confirmed previous observations of the potential therapeutic value of STN stimulation for FMS.

Additional work is needed to define the optimal target, stimulation parameters, and whether closed loop is more efficacious than continuous open-loop stimulation if chronic stimulation of the STN is to be used for the treatment of drug-resistant FMS. But given the data provided by Ren et al,[9] it seems that the time is right to conduct a controlled clinical trial. Because patients are unaware of the electrical stimulus,[8] designing a blinded protocol is possible. Furthermore, chronic STN stimulation for the treatment of tremor or Parkinson disease is associated with a low frequency of side effects and with almost no impairment of cognitive functions.[10] Whether the optimal STN target is the inferior or dorsolateral region, it is reasonable to expect similar tolerability when treating epilepsy patients.

By David King-Stephens

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