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Two cases of beneficial side effects from chronic electrical stimulation for treatment of focal epilepsy

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Letter to the Editor

Brain stimulation can reduce seizure frequency in epilepsy patients. However, side effects that may result from continuous cortical stimulation remain less well-described. When the epileptogenic focus is not well-localized or involves eloquent cortex, invasive neurostimulation is an alternative to resection. Current stimulation approaches significantly improve seizure frequency and quality of life [1,2]. Stimulation can target the seizure onset zone (SOZ) using closed loop stimulation, such as with Responsive NeuroStimulation (RNS) [3], or open loop stimulation, such as the less common method Chronic Subthreshold Cortical Stimulation (CSCS) [4]. One concern with continuous stimulation is the potential for tissue damage. Velasco and colleagues reported on 10 patients who received 2–3 weeks of continuous hippocampal stimulation prior to temporal lobectomy without evidence of histopathologic damage [5]. Another concern is that continuous stimulation of eloquent cortex may lead to deleterious side effects [6]. We have previously reported promising retrospective clinical results from CSCS in 13 patients showing an 80% reduction in seizure frequency and an approximate 40% seizure freedom rate [4]. Here, we describe two patients who were treated with CSCS and reported beneficial side effects from stimulation.

Case descriptions

Patient A is 41-year-old right-handed man with a history of depression with onset of focal epilepsy at age 18. Prior to stimulation, his seizures occurred 1–3 times per week despite treatment with two antiseizure medications and previous treatment with four others. His longest seizure-free period was 3 weeks. Presurgical work-up included MRI, interictal PET, and subtraction ictal SPECT, which were not localizing. Prolonged scalp EEG recorded independent bitemporal interictal epileptiform discharges and nine clinical seizures with left frontotemporal onset. Invasive stereotactic EEG monitoring captured six seizures with left insular onset (Fig. 1). Cortical mapping showed difficulty with swallowing, speech, and reading with intermittent stimulation to the SOZ. He was deemed a poor surgical resection candidate. Continuous trial stimulation targeting two left anterior and two posterior insular contacts for approximately 24 hours (contact surface area 5 mm^2, pulse width 450 μs, 2 Hz, 2 V) showed decreased frequency of interictal epileptiform discharges. Two months later he was implanted with two permanent electrodes (Medtronic DBS 3391) targeting the anterior and posterior insula. At last follow-up of seven months post-implant, he reported being seizure-free since implantation. He reported improvements in life satisfaction from 4 prior to implant to 8.5 at 5-month follow-up (10 is best) and similar improvement in epilepsy severity from 6.5 prior to implant to 1 at 5-month follow-up (10 is worst). He and his family reported a significant change in his demeanor, with notable improvements in motivation and markedly decreased feelings of irritability and depression. He reported feeling like a “new person,” and his wife noted that he is now more engaged with daily housework.

Patient B is a 36-year-old left-handed woman with focal seizures since age 5 that remained refractory despite treatment with four antiseizure medications and previous treatment with six others. Her seizures included left leg and arm paresthesias followed by flexion movements without loss of awareness. Prior to stimulation, these were occurring 25–50 times daily typically involving left leg and arm tightening and significantly impairing function as a grade school teacher. She noticed loss of fine motor dexterity of her left hand as well as intermittent weakness secondary to postictal paresis. MRI and PET imaging were not localizing. Prolonged scalp video EEG monitoring revealed four seizures with midline and right frontocentral onset. Subtraction ictal SPECT and MEG demonstrated abnormal findings in the right peri-rolandic region. Invasive stereotactic EEG monitoring showed abundant interictal epileptiform discharges and very frequent (>20/day) clinical seizures emanating from the right peri-rolandic area (Fig. 1). Cortical mapping demonstrated motor function overlapping with areas of seizure onset. Continuous trial stimulation (contact surface area 5 mm^2, pulse width 200 μs, 2 Hz, 0.5 V) over a three-day period targeted an area spanning the supplementary motor area to the postcentral gyrus. A marked reduction in interictal activity and clinical seizures to fewer than 5 per day was observed. She reported improvement of strength and dexterity of her dominant left hand when continuous stimulation was delivered. This improvement was apparent on physical exam and dissipated within seconds of stimulation cessation. Six months later, she underwent permanent implantation of electrodes (three Medtronic DBS 3391s and one 3387) to the right peri-rolandic region. At last follow-up of ten months, she reported a maximum of ten daily sensory seizures, an approximate 70%

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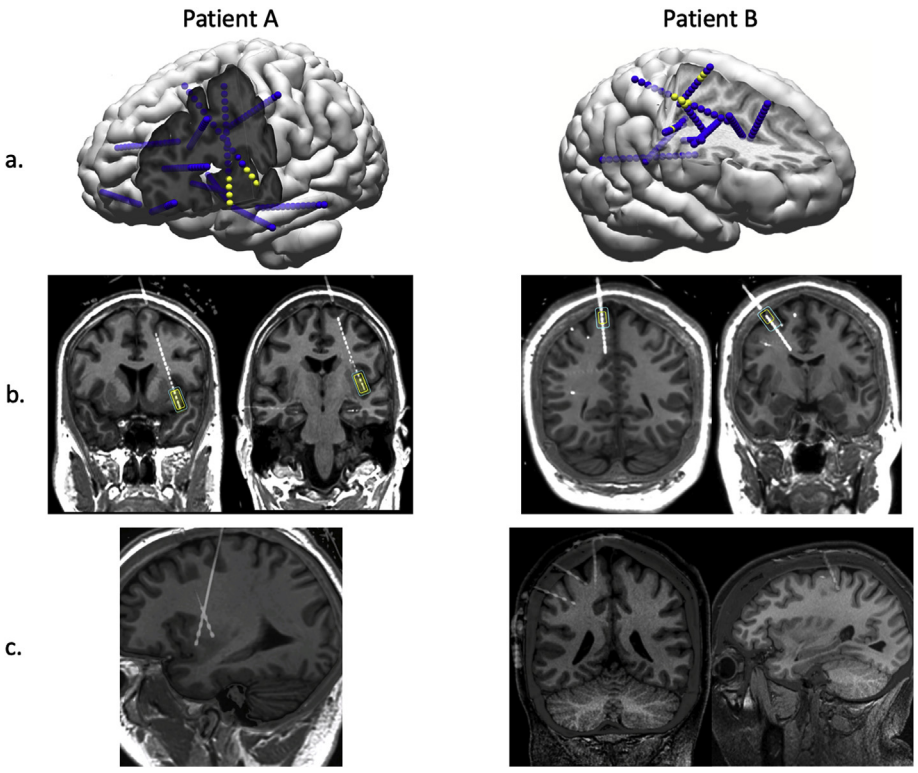

Fig. 1. 3D reconstructions and CT-MRI co-registered images. a: Pre-implant 3D-reconstructed image showing stereotactic EEG electrode trajectories. b: Coronal views of stereotactic EEG electrodes. Seizure onset contacts are highlighted in yellow rectangles, and trial stimulation contacts are in the blue rectangles. c. Sagittal and coronal views of permanent stimulation electrodes. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

decrease in seizure frequency, and 1 definite motor seizure in the past six months. She resumed driving five months prior and discontinued one of her antiseizure medications. She reported an 80–90% reduction in missed activities because of seizures. She continued to experience an estimated 50–75% improvement in dexterity of her left hand with continuous stimulation.

Discussion

Although characterized by paroxysmal events, epilepsy is a chronic disease and neuropsychological comorbidities are common [7]. Neurons involved in seizure generation may contribute to normal function. Continuous stimulation of eloquent cortex could potentially improve or worsen function. We present two patients who had meaningful reduction of disabling seizures with treatment with CSCS. In addition, they experienced improved neurological function that may not be directly related to ongoing seizure activity or postictal phenomena. A third patient without seizures treated with CSCS to the right perirolandic region for phantom limb pain experienced restoration of volitional movement of his left fifth digit for the first time in decades [8]. Elsewhere, Valentin et al. reported a patient with 40–50 right-sided motor seizures per day who was treated with CSCS over the left lateral frontal cortex. With stimulation he had a 90% seizure reduction as well as a significant improvement in right arm fine motor control, becoming able to draw and write for the first time in years [9]. For patients in the open-label arm of the RNS trial, two years of RNS to neocortical temporal structures led to improvements in naming that were not attributable to changes in seizure frequency [10].

Conclusions

Continuous electrical stimulation may offer the potential to restore neurological function. Further studies to elucidate relevant mechanisms will be important to guide patient selection.

Conflicts of interest

Mayo Clinic is co-owner of Cadence Neuroscience Inc, the development of which has been assisted by Drs. Brinkmann, Stead, Van Gompel, and Lundstrom. Drs. Brinkmann, Stead, and Van Gompel have rights to receive future royalties from the licensing of technology related to this research.

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