Letters

RESEARCH LETTER

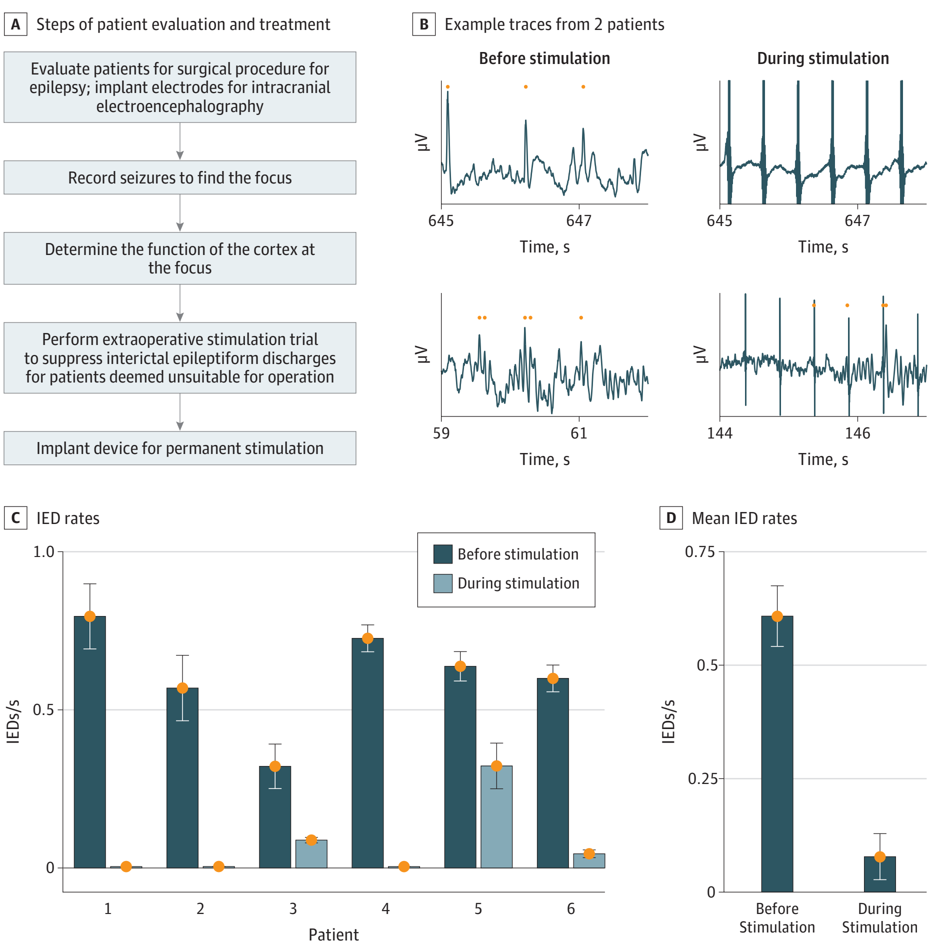
Chronic Subthreshold Cortical Stimulation to Treat Focal Epilepsy

Approximately 1 to 3 in 1000 people have drug-resistant focal epilepsy.[1] Resective surgical procedures are the most effective treatments for patients with epilepsy but are not feasible when seizures originate from critical cortical areas, ie, the eloquent cortex. Despite evidence for efficacy, current approaches to focal brain stimulation rarely yield seizure-free outcomes.[2] We report on 13 patients treated with continuous subthreshold electrical cortical stimulation, which led to the suppression of interictal epileptiform discharges (IEDs) and improvement in clinical seizures (ie, reduced frequency, with some experiencing reduced intensity and duration).

Methods | The Mayo Clinic Institutional Review Board approved this study, and informed consent was waived, as data were obtained through a deidentified database. Thirteen patients with drug-resistant focal epilepsy were deemed unsuitable for resective surgical procedures following intracranial electroencephalography monitoring with surgically implanted subdural grid and depth electrodes (**Figure**, A). To accurately estimate the seizure focus, prestimulation monitoring was typically several days, as clinically determined. If they were not a surgical candidate, patients were offered a therapeutic trial of continuous cortical stimulation (biphasic; frequency, 2-100 Hz; pulse width, 90-450 μs; amplitude, 1-6 V in voltage mode) via adjacent strip and occasional depth electrodes in the region of seizure onset. Permanent stimulation hardware (16-contact Medtronic PrimeAdvanced Neurostimulator with Medtronic 6-mm^2 platinum-iridium 2×8 surgical leads or Medtronic DBS electrodes [model 3387, 3389, or 3391]) was implanted when intracranial electroencephalography electrodes were explanted.

Data were analyzed retrospectively. Rates of IED were quantified for 6 patients who underwent stimulation at 2 Hz

Figure. Quantifying Interictal Discharges



B, The dots indicate detected interictal epileptiform discharges (IEDs). C, Each bar represents six 15-minute blocks of data from a single patient. The patients in the figure correspond to the patients in the first 6 rows of the Table. The comparison of rates was significant for each patient ($P = .001$; $P = .003$; $P = .01$; $P < .001$; $P = .008$; $P < .001$). Error bars indicate standard error. D, The comparison of the mean rates was significant ($P = .002$). The error bars indicate standard error.

Table. Summary of Patient Data[a]

Patient Age, y/Sex	Lesion	Seizure Type	Follow-up, mo	Disabling Seizures/mo, No.		Epilepsy Severity (Worst, 10)		Life Satisfaction (Best, 10)		Comments
				Before	After	Before	After	Before	After	
56/M	Scattered encephalomalacia	Reflex	3.3	NA	NA	8	2	4	9	Unable to walk with right foot for >35 y; now walks with right foot
9/M	Left parietal FCD	FDS	7.6	6	0	9	7	5	5	NA
14/M	Right parietal FCD	Focal motor	7.9	4	1	6	1	2	8	NA
15/F	Left MCA infarct	FDS	6.7	1	0.5	4	7	7	6	Seizure frequency improved but seizures more severe
26/M	Left frontal FCD	FDS	6.7	1.5	1	7	3	7	8	NA
27/F	Right temporal FCD	FDS	9.0	8	0	7	0	4	7	NA
39/F	Left parietal atrophy	EPC motor	7.3	NA	NA	10	4	7	6	Seizures now not noticeable to others; reduced satisfaction from chemotherapy
6/F	Right frontal FCD	FDS	8.4	8	0	8	0	4	9	NA
14/M	Left central FCD	FDS	10.7	12	2	4	2	6	8	NA
27/M	Right mesial parietal FCD	Reflex	16.2	NA	NA	8	0	2	4	Unable to walk for >15 y; now walks
22/M	Nonlesional	Focal sensory motor	20.5	25	7	7	1	7	9	NA
12/M	Left parietal FCD	FDS	61.2	150	0	10	0	2	8	NA
17/M	Right hemispheric infarct	Focal motor	74.6	40	5	7	4	1	8	NA

Abbreviations: EPC, epilepsia partialis continua; FCD, focal cortical dysplasia; FDS, focal dyscognitive seizures; MCA, middle cerebral artery; NA, not applicable.

[a] Data from patients in the first 6 rows were suitable for interictal epileptiform discharge quantification (Figure, C). Assessment of disabling seizures, epilepsy severity, and life satisfaction were based on retrospective patient report. Severity and satisfaction were based on nonvalidated patient report on a scale from 1 to 10.

and had 24 hours of pre- and poststimulation intracranial electroencephalography data available for analysis; the 7 patients who were stimulated at greater than 2 Hz were excluded from IED rate analysis because of stimulation artifact. Six 15-minute blocks from a 24-hour period of 500-Hz sampled data were analyzed before and during stimulation. Interictal epileptiform discharges were automatically detected in 5 electrodes per patient (electrode with the highest IED rate and 4 background electrodes) using a previously validated method[3] (Figure, B). Within a 4 millisecond window, spikes that occurred at a frequency of 2, 1, or 0.5 Hz were excluded to account for stimulation artifact. Results from IED rates calculated via manual detection for 3 patients using 1 hour of data were similar. Assessments of epilepsy severity and life satisfaction (on a scale from 1 to 10) as well as frequency of disabling seizures were based on retrospective patient report. Statistical significance was set at $P < .05$.

Results | Ten of the 13 patients (76.9%) reported improvement for both epilepsy severity and life satisfaction following chronic stimulation (**Table**). According to patient self-report, the mean (range) decrease in disabling seizures was 80% (33-100), mean (SD) epilepsy severity decreased from 7.2 (2.0) to 2.4 (2.6; $P < .001$), and mean (SD) life satisfaction increased from 4.5 (2.2) to 7.3 (1.6; $P = .003$). Patients tolerated permanent implantation without serious adverse effects. Rates of IED decreased significantly for all analyzed patients, with 3 patients achieving near-complete cessation of IEDs (Figure, C). The reduction in IED rate occurred within minutes of initiating stimulation. The mean IED rate decreased from 0.61 to 0.08 IEDs per second ($P = .002$) (Figure, D).

Discussion | These results suggest a clinical benefit and quantitative reduction in IED rates following subthreshold cortical stimulation. Prior work, including time-limited cortical stimulation,[4] long-term cortical stimulation in 2 patients,[5] and initial case reports from 3 patients,[6] has suggested a clinical benefit with this approach. Most patients experienced more than a 50% reduction in seizure frequency, and the reduction in IED rate with cortical stimulation was pronounced. The immediate reduction in IED rate at the time of stimulation in conjunction with clinical improvement suggests that IED rate is associated with seizure probability. Clinically, IED rate could be a useful biomarker for treatment efficacy.

Conclusions | Further investigation is needed to quantify treatment effects and examine the effect mechanism. Limitations in the current retrospective data include suboptimal pre- and poststimulation assessments of seizure frequency, epilepsy severity, and quality of life. In sum, continuous subthreshold cortical stimulation may be a suitable treatment for patients with focal epilepsy with lesions involving critical cortical areas or for whom a potentially reversible procedure is attractive.

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Study concept and design: Lundstrom, Worrell, Stead.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Lundstrom, Stead.
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