Chronic subthreshold cortical stimulation to treat focal epilepsy

Brian Nils Lundstrom, MD PhD, Mayo Clinic
Jamie Van Gompel, MD, Mayo Clinic
Jeffrey Britton, MD, Mayo Clinic
Katherine Nickels, MD, Mayo Clinic
Nicholas Wetjen, MD, Mayo Clinic
Gregory Worrell, MD PhD, Mayo Clinic
Matt Stead, MD PhD (corresponding author)
Department of Neurology
Mayo Clinic
200 First St. SW
Rochester, MN 55905
stead.squire@mayo.edu
Introduction
Approximately 1-3 in 1000 people have focal drug resistant epilepsy (DRE)\(^1\). Epilepsy surgery is the most effective treatment but is not feasible when seizures originate from critical cortical areas, i.e. 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 suppression of interictal epileptiform discharges (IEDs) and improvement in clinical seizures.

Methods
Thirteen patients with focal DRE were deemed unsuitable for resective surgery following intracranial electroencephalography (iEEG) monitoring with surgically implanted subdural grid and depth electrodes (Figure 1a). Pre-stimulation monitoring was typically several days, as clinically determined to accurately estimate the seizure focus. If not a surgical candidate, they were offered a therapeutic trial of continuous cortical stimulation (biphasic, 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 2x8 surgical leads or DBS electrodes 3387, 3389 or 3391) was implanted when iEEG electrodes were explanted.

Data were analyzed retrospectively with Mayo Clinic approval. IED rates were quantified for patients undergoing stimulation at 2 Hz who had 24 hours of pre- and post-stimulation iEEG data available for analysis (\(n=6\)). Patients stimulated at >2 Hz (\(n=7\)) were excluded from IED rate analysis due to artifact. Six 15-minute blocks from a 24-hour period of 500-Hz sampled data were analyzed before and during stimulation. IEDs were automatically detected using a previously validated method\(^3\) in five electrodes per patient (electrode with the highest IED rate and four background electrodes). To account for stimulation artifact, spike time differences of [2, 1, 0.5] Hz +/- 2 ms were removed for pre- and post-stimulation data. Results from IED rates calculated via manual detection for three patients using 1 hour of data were similar. Assessment of epilepsy severity and life satisfaction (scale 1-10) as well as frequency of disabling seizures was based on retrospective patient report.

Results
Ten (77\%) of the 13 patients reported improvement for both epilepsy severity and life satisfaction following chronic stimulation (Table 1). Mean decrease in disabling seizures was 80\% (range 33-100\%), mean epilepsy severity decreased from 7.2±2.0 to 2.4±2.6 (\(p=0.0002\)), and mean life satisfaction improved from 4.5±2.2 to 7.3±1.6 (\(p=0.003\)). Patients tolerated permanent implantation without serious side effects. IED rates decreased significantly for all analyzed patients, with 3 patients achieving near complete cessation of IEDs (Figure 1c). The reduction in IED rate occurred within minutes of initiating stimulation. The mean IED rate decreased from 0.61 to 0.08 IED/s (\(p=0.002\)) (Figure 1d).

Discussion
These results suggest clinical benefit and quantitative reduction in IED rate following subthreshold cortical stimulation. Prior work, including time-limited cortical stimulation\(^4\), chronic cortical stimulation in two patients\(^5\) and initial case reports from three patients\(^6\), suggested clinical benefit with
this approach. The majority of patients experienced >50% reduction in seizures, 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 correlates with seizure probability. Clinically, IED rate could be a useful biomarker for treatment efficacy.

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

### Table 1: Summary of patient data.

Data from patients in the first six rows were suitable for IED quantification. Assessment of Disabling Seizures, Epilepsy Severity and Life Satisfaction were based on retrospective patient report. Severity and Satisfaction were based on non-validated patient report on a 1-10 scale. FCD = focal cortical dysplasia, FDS = focal dyscognitive seizures, EPC = epilepsia partialis continua, R = right, L = left.
Figure 1: Quantifying interictal discharges. (a) Steps of patient evaluation and treatment. (b) Example traces from two patients (upper and lower rows) before and during stimulation. Red dots mark detected IEDs. (c) Comparison of IED rate before and during cortical stimulation (step 4 in panel a) with each bar representing six 15-minute blocks of data from a single patient. $P = [0.001, 0.003, 0.014, 0.000, 0.008, 0.000]$. These 6 subjects correspond to patients in the first 6 rows of Table 1. (d) Comparison of mean IED rate prior to and during stimulation ($n=6$). $P = 0.002$. Error bars represent standard error.

References:

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