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SPECIAL REPORT

Chronic subthreshold cortical stimulation: a therapeutic and potentially restorative therapy for focal epilepsy

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ABSTRACT

Introduction: Approximately one third of patients with focal epilepsy continue to have ongoing seizures despite adequate trials of anti-seizure medications. Surgery to remove the epileptogenic zone remains the most efficacious treatment option for focal drug-resistant epilepsy. However, when cortical areas are eloquent or there are multiple epileptogenic zones, surgical resection is not an ideal approach. Cortical stimulation provides an attractive alternative.

Area covered: Here, the authors describe Chronic Subthreshold Cortical Stimulation (CSCS), which uses continuous intracranial electrical stimulation applied near the epileptogenic zone to lower seizure probability. The authors review literature related to CSCS. One challenge is finding the most efficacious set of stimulation parameters for each patient.

Expert commentary: Data supporting CSCS are limited but promising for the treatment of patients with focal drug resistant epilepsy who are not surgical candidates. Additional electrophysiological biomarkers to estimate cortical excitability are needed.

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Cortical stimulation; focal seizures; drug-resistant epilepsy; chronic electrical stimulation

1. Introduction: rationale behind invasive brain stimulation for epilepsy

Neurons are the foundational computing unit of the brain, using electricity to communicate and process information. In many neurological diseases, the assumption is that a chronic reduction or loss of neuronal function underlies the disorder. However, epileptic seizures appear to result from sudden, brief, and transitory neuronal dysfunction. Seizures are paroxysmal events involving dysfunctional electrical currents. First-line treatments for those with a tendency towards recurrent seizures, or epilepsy, involve anti-seizure medications (ASMs), which are taken daily and chronically alter the excitability of many or most cerebral neurons. When seizures have a focal onset and are refractory to medications, the gold standard treatment is surgical resection. The critical portion of dysfunctional brain is removed, so that further seizures will not be triggered. This simplified explanation of the treatment approach to epilepsy relies on two key points: (1) taking ASMs systemically and chronically is advisable because they are effective and have tolerable side effects and (2) when ASMs are ineffective hopefully there is a piece of brain not necessary for function that can be removed and lead to seizure cessation.

In general, brain stimulation techniques have been introduced to provide treatment alternatives when at least one of these two points is untrue. Multiple recent review articles describe brain stimulation for epilepsy [1–3]. Here, we focus on describing a lesser known alternative form of intracranial brain stimulation termed chronic subthreshold cortical stimulation (CSCS).

Invasive stimulation can be categorized by the method of stimulation and the intended goal (Figure 1). The most common form of invasive stimulation is vagus nerve stimulation (VNS). Stimulation is typically provided via a duty cycle during which stimulation is provided during a relatively shorter period and a lack of stimulation for a relatively longer period of time. Aside from practical benefits such as improved battery life, the supposition is that the beneficial effect of stimulation is either enhanced by or longer lasting than the silent period. This is in the context of the intent of VNS, which is to globally lower seizure probability by altering autonomic afferent inputs to the brain. Deep brain stimulation (DBS) is similar: typically duty cycle stimulation has been provided with the intent of globally altering seizure probability or by increasing cortical inhibition [4]; however, treatment with closed-loop stimulation and open-loop continuous stimulation has also been used.

Responsive neuro stimulation (RNS) is fundamentally different. When a focal region of cortex is found to be the source of seizure onset through invasive monitoring but also performs critical so-called eloquent brain function such as speech and movements, resection without functional deficit is not feasible. RNS targets the epileptogenic zone. RNS is not intended to reduce seizure probability. Rather, it uses a closed-loop or feedback system to detect initial seizure activity. This individualized detection algorithm triggers pre-programmed responses aimed at aborting nascent seizures.

CSCS combines aspects of the above approaches. Like VNS and DBS, the goal of stimulation is to lower the seizure probability such that seizures never start. To this end, stimulation is provided in a continuous fashion. Like RNS, the goal is to

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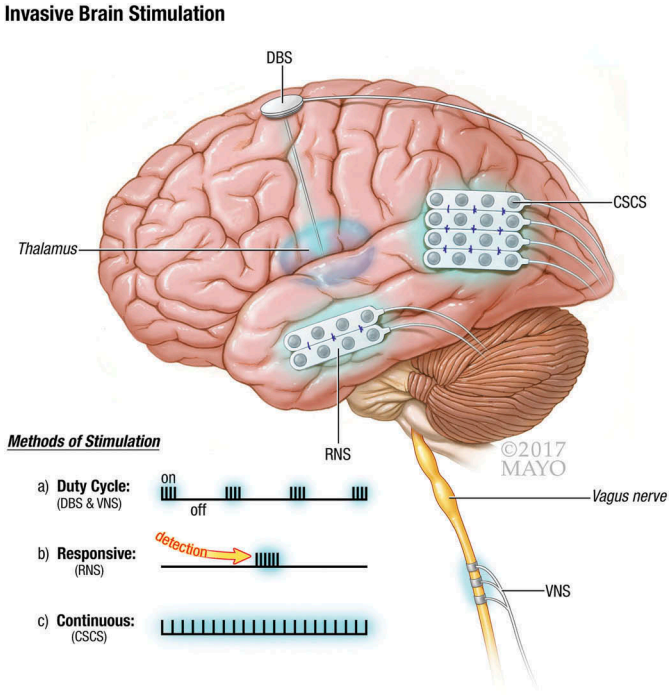

Figure 1. Methods of invasive brain stimulation use different stimulation protocols for reducing seizure burden. (a) DBS and VNS typically use duty cycle stimulation during which stimulation is off the majority of time. (b) RNS only stimulates in response to the detection of putative seizure activity. (c) CSCS stimulates continuously with one set of parameters until altered by a provider.

apply stimulation locally to the area of dysfunctional cortex containing the epileptogenic zone. With CSCS, the intent is to chronically alter local neuronal function such that seizure probability is reduced while preserving, or perhaps even enhancing, existing cortical function.

2. Cortical stimulation for treatment of epilepsy

The history of cortical stimulation is relatively limited. Some of the earliest stimulation studies for seizures used the cerebellar cortex as the target with the hypothesis that inhibitory efferent cerebellar tracts could be augmented, for example, showing improvement in six of seven patients [5]. Many of these patients had cerebral palsy and spasticity, with spasticity as an indication for implantation. A larger study found that chronic cerebellar stimulation led to seizure control in 18 of 32 patients [6]. Interestingly, electrodes were placed over the cerebellar hemispheres and stimulated the cortex continuously, similar to CSCS.

Regarding cerebral cortical stimulation, patients with chronic facial pain have been permanently implanted for motor cortex stimulation since the 1990s [7]. Nonetheless, there has been concern that chronic stimulation would damage the cortex when delivered at effective levels. Thus, patients with hippocampal disease were implanted and chronically stimulated for 2–3 weeks prior to temporal lobectomy [8]. Stimulation (130 Hz, 0.45 ms duration, 0.2–0.4 mA amplitude) led to cessation of seizures and a dramatic decrease of interictal discharges in 7 of 10 patients after approximately 1 week of continuous stimulation. Hippocampal pathology did not show any signs of stimulation-related damage. To treat foci in motor eloquent cortex, the same group chronically stimulated with similar parameters (charge density <3.0 microcoulombs/phase) and found greater than 90% seizure reduction in two patients who received stimulation for about 1 year [9]. Furthermore, a case report noted that direct current stimulation at the seizure onset zone in primary motor cortex was safely tolerated for 5 years, reduced seizure frequency by 90%, and eliminated seizure generalization [10].

Beginning in 2010, approximately 20 patients have been permanently implanted at Mayo Clinic in Rochester for cases in which eloquent cortex in the epileptogenic zone precluded resection. Patients received treatment based on compassionate, off-label use of commercially available devices that were US FDA approved for treating spinal pain. Patient ages ranged from 6 to 56. Stimulation parameters (1–6V, 0.06–0.45 ms, 2–100 Hz) led to typical charge densities of approximately 5–10 microcoulombs/cm^2. After it was determined patients were not candidates for surgical resection, CSCS was trialed. Efficacy was determined not only by seizure frequency but also by the extent to which interictal discharges could be decreased with appropriate parameter choices, such as location of stimulating electrodes and frequency of stimulation. It had been previously noted that the rate of intracranial interictal discharges decreases with cortical stimulation [8,10]. With early patients, stimulation frequencies were started at 100 Hz, but empirically lower frequencies were deemed more effective. An initial case series of three patients suggested CSCS is effective [11], and a more recent analysis of 13 patients showed that both seizure severity and life satisfaction were improved for 77% of patients [12]. Interictal epileptiform discharges were shown to be significantly reduced following stimulation initiation, an effect that appeared to occur within minutes. Further, despite utilizing hardware inherently designed for spinal cord stimulation and DBS, no major complications have been seen following permanent implantation after subdural grid monitoring. Figure 2 illustrates a typical implant for CSCS.

3. Efficacy of invasive brain stimulation

Used for focal onset seizures, long-term use of RNS leads to an approximately two-thirds reduction in median seizure frequency with responder rates (=50% reduction in seizure frequency) of about 60% [13]. Thirteen percent of participants in the 7-year study were seizure-free for 1 year or longer; no one was seizure-free for the entire period. Long-term use of DBS for focal onset seizures, which has yet to be approved for clinical use in epilepsy, shows similar results. Median seizure reduction is 69% with a responder rate of 68% at 5 years [14]. For focal seizures, the efficacy of VNS is less, with around a 25% responder rate and reduction in median seizure frequency [15]. However, outcomes can be significantly improved for generalized seizures, with reduction of median seizure frequency of up to 80% [16].

Results regarding efficacy for CSCS are limited and based on a single retrospective analysis of 13 patients [12]. Follow-up time ranged from 3.3 months to 6.2 years (mean 1.6 years).

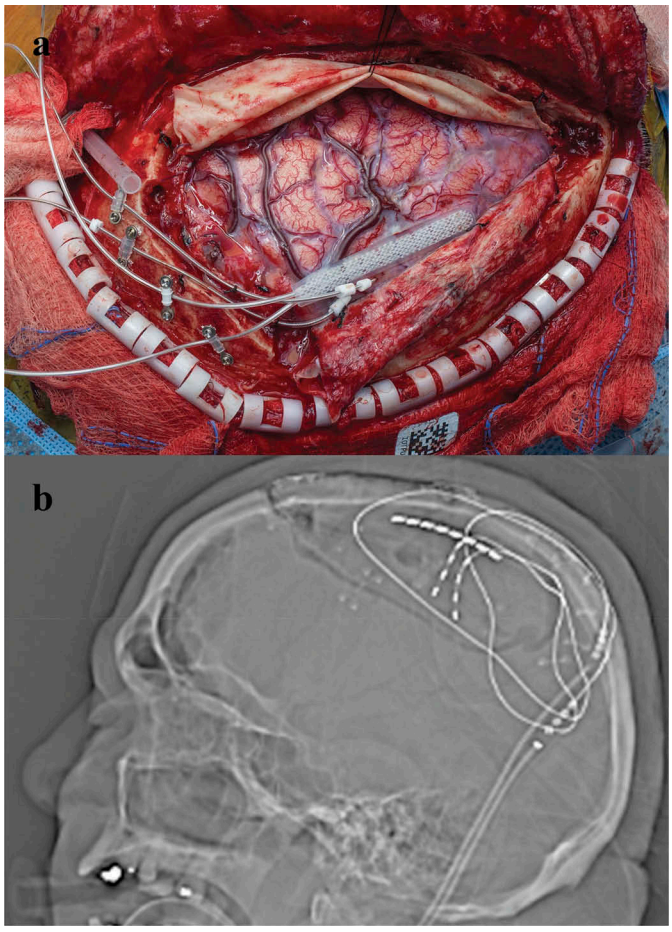

Figure 2. Intraoperative (a) photo and postoperative scout film (b) showing a typical CSCS implant.

Patients reported an 85% reduction in median seizure frequency and greater than a 90% responder rate. No major complications were encountered with CSCS.

4. Choosing brain stimulation parameters

One of the key components to successful seizure management is appropriate titration of therapy, for example, balancing benefits with adverse effects. With ASMs, in principle this is somewhat more straightforward insofar as there are a limited number of parameters to adjust, such as medication dosage. However, with brain stimulation techniques, appropriate titration is a vastly more complex problem with an essentially infinite parameter space to explore. There are spatial parameters, such as where to stimulate, and stimulation-related parameters, such as pulse width, amplitude, duration, waveform, etc. Although seizure frequency is helpful and remains the gold standard for evaluating efficacy, counting seizures is inefficient and typically inaccurate. For example, despite years of experience with VNS, it remains unclear what percentage of patients are optimized – perhaps responder rates could be markedly higher? Regarding CSCS, there remains no clear way of optimizing parameters, such as the precise location of cathodal and anodal contacts and choice of stimulation frequency. In part, parameters are altered so that the rate of interictal epileptiform discharges is minimized [12]. Overall, this process remains more art than science. Improved ways to estimate cortical excitability and electrophysiological biomarkers of epilepsy are clearly needed to guide treatment [17].

Cortical excitability has most often been assessed following perturbations to cortical function, using both invasive and noninvasive methods. Single-pulse electrical stimulation delivered via subdural or depth electrodes has been used to identify epileptogenic cortex [18,19]. Noninvasively, transcranial magnetic stimulation (TMS) generates intracranial electrical currents and provides a means to measure cortical excitability in normal as well as epilepsy patients [20]. For example, frontal cortex excitability has been found to increase with time spent awake [21]. Regarding epilepsy, TMS-related cortical excitability measures were increased for both epilepsy patients and their asymptomatic siblings, in comparison to controls, suggesting a genetic predisposition towards seizures even in focal epilepsy patients [22]. Similar measures suggest that focal seizures can lead to global changes in excitability [23].

Less commonly, cortical excitability has been assessed via intrinsic measures that do not rely on any external perturbations. Measures of synchrony have been found to globally increase with ASM reduction or prolonged wakefulness [24]. Although in many cases the rate of interictal discharges is not thought to be helpful, in the case of CSCS it appears that the rate of intracranial discharges correlates with seizure probability [8,10,12]. In a somewhat similar fashion, high rates of scalp EEG discharges (more than 60 per hour) have been correlated with poor outcomes after temporal lobe resections [25]. Electrophysiological biomarkers that assess cortical excitability, whether via provoked excitability measures or intrinsic excitability measures, allow treatment to be delivered efficiently and efficaciously.

5. Conclusion

CSCS is a novel brain stimulation technique for the treatment of focal drug-resistant epilepsy. Although there is limited clinical data relating to the efficacy of CSCS, initial studies are promising and comparable with other stimulation techniques. One of the primary challenges with CSCS, and brain stimulation in general, is that of choosing appropriate stimulation parameters. For these, improved methods of estimating seizure probability are needed.

6. Expert commentary

The intent with CSCS is to target areas of cortical dysfunction and focally lower seizure probability. Prior work has suggested that apparent epileptiform activity is more prevalent and widespread than can be appreciated by macroelectrodes [26]. This sparsely distributed small-scale epileptiform activity was termed microseizures and postulated to be related to epileptogenesis. Thus, the hypothesis is that highly epileptogenic cortex requires continuous stimulation to prevent very frequent microseizures from developing into seizures. The hope is that targeted continuous stimulation will not only prove to be more effective in lowering seizure probability, but may allow for the restoration of dysfunctional cortex. The potential benefits of CSCS include the potential for

continuously stimulating a wider area of cortex with greater flexibility.

Although CSCS is indeed a surgical therapy for focal epilepsy, to hold it to the same expectations as ablative therapies such as temporal lobectomy may be a mistake. Rather than remove brain tissue, the goal is to modulate excitability, similar to medical therapies. In general, ASMs do not target particular focal cortical areas but rather act diffusely, which can lead to nonspecific adverse effects, such as cognitive clouding, tremor, etc. In many cases, the effectiveness of ASMs is reduced due to their adverse effects, which often appear to be related to their widespread cortical action. On the other hand, while maintaining the similar goal of cortical modulation, CSCS acts locally without the same potential as ASMs for systemic side effects. Given the goal for modulation of excitability, it may be more appropriate to apply standards set for medical responsiveness to evaluate the efficacy of therapies such as CSCS. Regardless, as a brain stimulation technique the present data supporting CSCS is very limited and accompanied by suboptimal clinical outcome measures. Prospective clinical data, ideally in the form of a randomized controlled trial, are needed.

In addition to clarified standards defining efficacy for CSCS and other stimulation techniques, perhaps the most critical need at this juncture is improved methods for assessing seizure probability. The state of the art includes seizure logs or, in the case of RNS, brief recordings of triggered intracranial electrographic events. The inherent difficulty is that the parameter space for any stimulation technique, and especially cortical stimulation, is immense. There simply is not time enough to efficiently sample even a small subset of potentially effective stimulation protocols. Furthermore, it is likely that a significant portion of patients could experience improved seizure control if parameter settings could be appropriately optimized.

Thus, what is needed is a means to assess seizure probability without relying on estimating seizure frequency. Ideally, these measures would be noninvasive such that a patient's seizure threshold could be assessed prior to and following parameter adjustments of their brain stimulation device. This would significantly increase titration efficiency. In addition, an improved understanding of underlying mechanisms is also needed such that parameters can be chosen in a rational individualized manner. At present, mechanisms underlying the efficacy of stimulation are largely unknown. Finally, the relationships between treatment with brain stimulation, epilepsy, and co-morbidities of epilepsy such as depression and anxiety are unclear.

7. Five-year view

In coming years, how we conceive of optimal treatment for focal epilepsy may change. At present, the primary undertaking in medically refractory epilepsy is that of determining which pieces of brain can be safely removed and lead to seizure cessation. This approach implicitly relies on making a binary decision about whether cortex is necessary or unnecessary. Future approaches may be more nuanced if progress can be made towards focally modulating neuronal function.

Regarding cortical stimulation, there remains a significant unknown question: is it more effective to abort early seizures or to focally lower the probability of seizures? Advances in RNS would assume the former while a primary motivation for CSCS is an assumption of the latter. Clearly, an improved understanding of underlying pathophysiological mechanisms may help push the field towards the more effective alternative. Or, it may be that for particular locations or types of seizures, aborting seizures may be preferable to altering the steady-state balance.

We envision progress in the hardware utilized to perform CSCS. Currently, devices designed for other purposes are used, and as we learn more about the three-dimensional space of the epileptogenic zone, we will need more sophisticated electrode implants to provide effective local modulation. This is currently a significant limitation with this technology. Progress would likely improve CSCS outcomes as well as further our understanding about the pathophysiology of the epileptogenic zone. In addition, improvements in the ability to record and store ongoing cortical electrical activity would be extremely valuable.

Beyond technology, brain stimulation has the potential to be restorative. For example, it may be that stimulating an injured part of the brain for several years leads to local changes that permanently lower seizure probability. Although direct evidence for a restorative effect is lacking, long-term studies of VNS [27], DBS [14], and RNS [13] have shown increasing efficacy over years of continuous treatment. In addition, treatment with TMS can lead to a reduction in seizure frequency that lasts for weeks following treatment cessation [28,29]. Thus, it appears that prolonged stimulation can lead to focal or network changes that persist following stimulation cessation. To some extent stimulation might then be viewed as disease-altering and could be applied to non-eloquent brain areas. Furthermore, stimulation techniques with the appropriate flexibility such as CSCS may allow for the long-term testing of putative epileptogenic zones. This would reduce the incidence of ineffective resections and potentially provide increased confidence regarding long-term prognosis following resection.

Finally, we expect that further work will further characterize the relationships between the many comorbidities of epilepsy and epileptogenic cortex. One of the attractions of CSCS is the theoretical potential to alter dysfunctional cortex and improve function, not simply prevent catastrophic paroxysmal dysfunction. In this way, stimulation could not only prevent seizures but also treat at least in part epilepsy comorbidities, such as anxiety, depression, and cognitive deficits. In short, the future may bring a paradigm shift such that goal of epilepsy treatment becomes the restoration of dysfunction cortex rather than its removal.

Key issues

- Chronic Subthreshold Cortical Stimulation (CSCS) is an alternative treatment for refractory focal seizures when resective surgery is not feasible.
- CSCS provides chronic intracranial electrical stimulation to areas of cortex.
- Stimulation is open loop and does not depend on direct feedback.

- The intent of CSCS is to continuously reduce the probability of seizures from a particular cortical location.
- CSCS reduces the rate of intracranial interictal epileptiform discharges.
- Chronic stimulation does not typically lead to appreciable symptoms.
- Preliminary studies suggest CSCS is a safe long-term approach and has comparable efficacy to other stimulation approaches.
- Developing electrophysiological biomarkers to assess cortical excitability is a critical need for efficient and effective cortical stimulation.

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Declaration of interest

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