



## Brain Stimulation for Epilepsy: Of Mice and Man

### Closed-Loop Control of Epilepsy by Transcranial Electrical Stimulation.

Berényi A, Belluscio M, Mao D, Buzsáki G. *Science* 2012;337(6095):735–737.

Many neurological and psychiatric diseases are associated with clinically detectable, altered brain dynamics. The aberrant brain activity, in principle, can be restored through electrical stimulation. In epilepsies, abnormal patterns emerge intermittently, and therefore, a closed-loop feedback brain control that leaves other aspects of brain functions unaffected is desirable. Here, we demonstrate that seizure-triggered, feedback transcranial electrical stimulation (TES) can dramatically reduce spike-and-wave episodes in a rodent model of generalized epilepsy. Closed-loop TES can be an effective clinical tool to reduce pathological brain patterns in drug-resistant patients.

### Commentary

Berényi et al. describe an experiment in which transcranial stimulation is applied in a rodent model with spontaneously occurring generalized spike-wave (SW) discharges. Stimulation electrodes were placed over thinned skull bitemporally. Multi-unit and field potentials were recorded via tripolar electrodes in the frontal and parietal cortex. Initially, sinusoidal stimulation was delivered independent of spontaneous spike-wave activity in an ON–OFF mode at 1 Hz. Multi-unit neuronal activity was modulated with stimulation regardless of whether SW discharges occurred or not. With this stimulation paradigm, the amplitude of the spikes was altered but not the duration of the SW discharges. The stimulation configuration with the highest modulation index of multi-unit activity was chosen for closed-loop (responsive) stimulation. Responsive stimulation was triggered by the spike component of the discharge as detected by a combined measure of current source density. A Gaussian 50-millisecond stimulus was applied after every detected spike. This stimulation paradigm resulted in significant reduction in the duration of SW discharges and the overall percentage of time spent in SW activity. The therapeutic effect on SW activity was dependent on the size of the voltage gradient applied.

What can we learn or deduct from this experiment and translate to human epilepsy? Electrical brain stimulation has evolved into a new treatment venue for intractable epilepsy (1–3). There are systems that stimulate in an ON–OFF mode in the anterior nucleus of the thalamus or hippocampus (2, 4) and systems that deliver responsive stimulation triggered by seizures or epileptiform activity occurring in the seizure onset zone (3, 5). Both systems have already proven to be effective in human focal epilepsy (2, 3).

The above study provides evidence that electrical stimulation in some form modulates multi-unit activity. This is reassuring and confirms that neuromodulation is achieved with stimulation. However, in the rodent, SW activity was only reduced with closed-loop stimulation. The authors conclude that the stimulation has to be timed to the underlying rhythm. They hypothesize that the reverberation of the thalamo-cortical loop can be suppressed by cortical excitation during the wave period of the SW activity. Cortical excitation “quenches” more or less the reverberating loop. The authors try to confirm this with another experiment embedded into the study utilizing optogenetic suppression of cortical circuits in mice (Figure S6). One could conclude that the use of responsive systems is of greater advantage than mere ON–OFF stimulation independent of the underlying rhythm. However, this conclusion is not valid if directly translated into human use. Human systems with ON–OFF stimulation are not delivering stimuli at the cortex but in the deeper structures of the brain and may affect the thalamo-cortical circuits in a different way. Another significant difference to the animal study is that ON–OFF stimulation was delivered at 1 Hz, while in humans, higher frequency stimulation is applied.

All systems for brain stimulation in humans have been studied in focal epilepsy, not for generalized epilepsy with spike-wave discharges. Focal seizures frequently do not have an SW pattern. Stimulating non–spike-wave seizure patterns may not be as effective if approached in the same way as the study by Berényi et al. Stimulation in the animal persisted as long as SW persisted. Systems in humans are limited to a certain number of stimuli if used in a responsive mode (3).

Furthermore, SW discharges in the rodent are well defined and easier to detect by composite measures than epileptiform activity in humans. Epileptiform activity in humans is frequently heterogeneous, variable, and specific to the patient (6). Reliable detection requires intracranial recordings (3, 7). Automated systems that reliably detect scalp epileptiform activity have not been overly successful and are still not considered reliable by clinicians (7).



What is the ideal electrical stimulus that would abort seizure activity? From the human studies, we know that high-frequency ON-OFF stimulation in the anterior nucleus and responsive high-frequency stimulation in the seizure onset zone decrease seizure frequency. This animal study shows that responsive Gaussian cortical stimulation of a generalized spike-wave discharge decreases epileptiform activity. However, we do not know whether stimulation would be even more effective at other frequencies, at a different intensity, or at other epileptic network sites. Studies such as this one by Berényi et al. are very valuable, as these questions can be more easily examined in animal models. Human studies for brain stimulation are expensive, difficult to control, and require safe and sophisticated technology. Another altogether different approach to test the most effective stimulation could be computational modeling (8).

After the conclusion that electrical stimulation is effective, where should the stimulator be placed? Possibilities include subcortical, at or in the cortex, or extracerebral. The stimulation by Berényi et al. was applied transcranially, outside the skull, but under the skin. Would this be something feasible in humans? The authors state that continuous brain stimulation has “detrimental” side effects. Brain stimulation in humans is well-established therapy, and although not risk free, it carries a very low risk of long-term morbidity (2, 3). The thickness of the human skull may prohibit extracranial stimulation. Skin irritation and paresthesias with external systems are a significant consideration. Implanted systems always carry a risk of infection, even if they are not intracerebral, but certainly ensure absolute compliance.

Human stimulation studies have frequently been criticized for the lack of animal data. This study certainly provides animal evidence that responsive stimulation is effective and under certain circumstances seems more effective than ON-OFF stimulation. As there are many leaps to make from the animal to the human, going right to the problem based on clinical observations can be a defensible approach (9). The never-ending discussion of which animal model truly reflects which type of epilepsy demonstrates that conundrum clearly (10).

In conclusion, more such studies are needed to examine the effects of electrical stimulation on seizures. We need to learn more about which stimulation paradigm is most effective from animal and computational models, as well as from humans. Devices need to be available to the clinician to gain experience. This will promote further research and technologic

development. The goal being that one day we may be able to treat medical-refractory epilepsy with a less-invasive intervention than removing valuable brain tissue.

by Barbara C. Jobst, MD

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