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Brain stimulation for the treatment of epilepsy

Barbara C. Jobst, Terrance M. Darcey, Vijay M. Thadani, and David W. Roberts

Dartmouth Medical School, Hanover, New Hampshire, U.S.A.

Summary

Direct brain stimulation is an emerging treatment of epilepsy. Scheduled or responsive stimulation has been applied. The most explored targets for scheduled stimulation are the anterior nucleus of the thalamus and the hippocampus. The anterior nucleus of the thalamus was studied in a large multicenter trial. There was a significant seizure reduction with the stimulator "on" versus "off" during several months after stimulator implantation. The hippocampus as stimulation target has not yet been studied in a large randomized trial. Responsive stimulation applies a stimulus whenever epileptiform activity occurs. It requires on-line detection of epileptiform activity. This concept is based on the observation that epileptiform activity during functional mapping can be aborted by brief pulses of cortical stimulation. Current technology is able to detect seizure activity intracranially on-line and delivers a high frequency stimulus if epileptiform activity is detected. A large randomized multicenter trial has been conducted testing this system for focal epilepsy.

KEY WORDS: Deep brain stimulation, Responsive neurostimulation, Afterdischarges, Anterior nucleus of the thalamus, Hippocampal stimulation, Focal seizures.

Resective surgery and vagus nerve stimulation are currently the mainstay of treatment for intractable, medication-resistant focal epilepsy (Jobst, 2009). Resective epilepsy surgery remains the most successful. However, associated functional deficits such as language or motor impairment often limit resection. Bilateral or multiple seizure foci are not amendable to surgery. Direct brain stimulation has a potential to overcome those limitations (Morrell, 2006; Theodore & Fisher, 2007).

Brain Stimulation Paradigms for Epilepsy

Scheduled stimulation has been applied to specific cortical or subcortical targets. An electrical pulse is delivered at scheduled, timed intervals. Scheduled stimulation is hypothesized to alter the intrinsic neurophysiologic properties of epileptic networks (Theodore & Fisher, 2007; Saillet et al., 2009). Therefore, it increases seizure threshold. Stimulation has been targeted to the anterior and ventromedian nucleus of the thalamus, the subthalamic nucleus, the caudate nucleus, the mamillary bodies, the cerebellum and the hippocampus with variable success in small human series (Theodore & Fisher, 2007; Jobst, 2010; Saillet et al., 2009). Responsive stimulation directs an electrical pulse to the seizure onset zone in the cortex or hippocampus. Stimulation occurs at the time of epileptiform activity and ideally prevents propagation to more involved seizures (Morrell, 2006). Seizure prediction or early detection is a prerequisite.

Scheduled Stimulation

Scheduled stimulation is delivered via commercially available stimulators (Medtronic, Minneapolis, MN, U.S.A.), identical to stimulators used in movement disorders. The pulse generator is implanted into the chest and connected to the intracranial target via four contact leads. Stimulation can be continuous or intermittent, with a frequency between 130 and 200 Hz, a pulse width of 450 μs, and constant voltage (0.1–5 V).

Stimulation of the anterior nucleus of the thalamus

Lately, the focus has been on stimulation of the anterior nucleus of the thalamus. Its close connection to the mesial temporal structures via the fornix, mamillothalamic tracts, and thalamocortical radiations make it an attractive target. Several uncontrolled trials yielded varying results (Fig. 1).

Address correspondence to Barbara C. Jobst, Dartmouth-Hitchcock Medical Center, 1 Medical Center Drive, Lebanon, NH, U.S.A. E-mail: Barbara.c.jobst@hitchcock.org

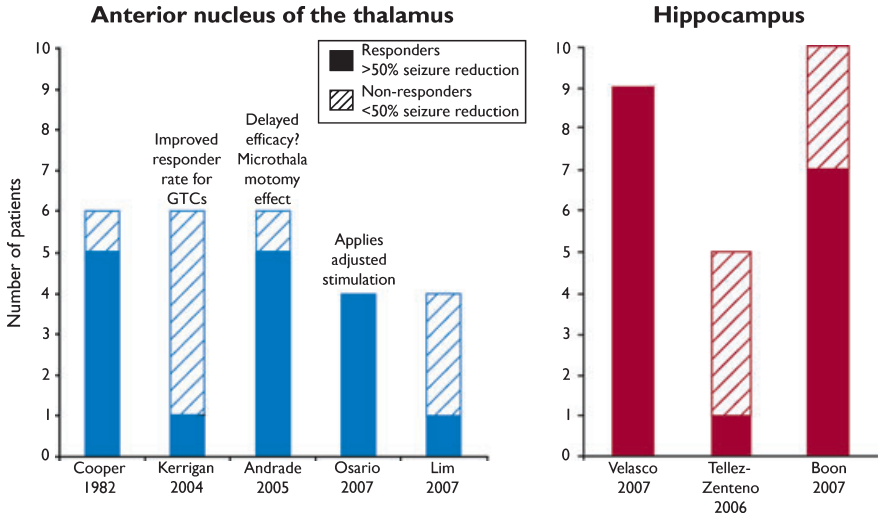

Figure 1.
Uncontrolled trials of scheduled stimulation of the anterior nucleus of the thalamus and hippocampus. The *x*-axis represents number of patients. Kerrigan et al. (2004) reported increased efficacy in generalized tonic–clonic convulsions (GTCs). Andrade et al. (2006) found delayed efficacy and suggested a microthalamotomy effect, as patients were responders even if the stimulators were off. Osorio et al. (2005)applied seizure specific adjusted stimulation.

A microthalamotomy effect on seizure expression by implantation of the electrodes alone without stimulation was suggested (Andrade et al., 2006).

A large industry-sponsored controlled study of 110 patients with focal epilepsy (SANTE [Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy]; Medtronic) was conducted. Patients were blinded during the study period with the stimulators either ON or OFF. Results were presented at the American Epilepsy Society Meeting in 2008 and otherwise reported only in a press release (Fisher, 2008). Patients with the stimulator ON had a 38% seizure reduction as compared to patient with the stimulator OFF. This excludes a microthalamotomy effect. Long-term follow-up was available in 86 patients, and 60% had a seizure reduction of >50%. Nine percent of patients were seizure free (Fisher, 2008).

Stimulation of the anterior nucleus of the thalamus (AN) and related network nodes has been studied in the animal model. (Mirski et al., 1997). In pentylenetetrazole (PTZ) –induced seizures in rats, 100 Hz stimulation of the AN did not alter the expression of seizure but did raise the clonic seizure threshold. Low frequency stimulation was proconvulsive (Mirski et al., 1997). Pilocarpine-induced seizures in rats treated with AN stimulation developed with the same latency as in nonstimulated rats, but latency to develop status epilepticus was prolonged (Hamani et al., 2004). A follow-up study demonstrated that most likely stimulation current, not frequency, was determining effective stimulation. Application of stimulation after status epilepticus developed was ineffective (Hamani et al., 2008). Seizure threshold in flurothyl-induced seizures increased with stimulation at 130 Hz, but was not affected by stimulation at 260 Hz. Stimulation at 800 Hz was proconvulsive (Lado, 2006). Lado performed AN stimulation in the kainic model of epilepsy in rats (Lado 2006). Stimulation of the AN produced a 2.5-fold increase in seizure frequency as compared to baseline. Stimulation outside the AN did not increase seizure frequency.

Hippocampal stimulation

Scheduled stimulation of the seizure onset zone is another attempt to control seizures by brain stimulation. Uncontrolled studies with good responder rates have been conducted as a proof of principle (Fig. 1) (Tellez-Zenteno, et al. 2006; Boon, et al. 2007; Velasco, et al. 2007. Treating temporal lobe epilepsy with stimulation could potentially avoid memory deficits associated with surgery. Both hippocampi can be stimulated. Currently larger, systematic, controlled studies of scheduled stimulation of the mesial temporal structures are under way (CoRaStir [Prospective Randomized Controlled Study of Neurostimulation in the Medial Temporal Lobe for Patient with Medial Temporal Lobe Epilepsy] and MET-TLE [Randomized Controlled Trial of Hippocampal Stimulation for Temporal Lobe Epilepsy]) (Jobst, 2010).

Responsive Stimulation

Afterdischarges (ADs) as a model of seizures

Patients evaluated for epilepsy surgery are frequently implanted with intracranial subdural electrodes for seizure onset zone localization. To map eloquent areas, functional mapping is routinely performed. An electrical stimulus is delivered to the cortex to either inhibit language or elicit motor responses. Traditionally 2–5 s long, 50-Hz pulses with a pulse width of 300 μs and a current between 0.5 and 15 mA are applied. The traditional 50 Hz, 5-s–long pulse frequently may induce ADs, which can evolve into clinical seizures. Those limit the validity of functional mapping. However, the mode and intensity of current delivered significantly influence whether ADs or seizures occur. Alternative methods of motor mapping were studied in the epilepsy setting. Pulse trains of seven pulses at 500 Hz and a pulse width of 300 μs with a constant current up to 20 mA result in reliable motor mapping under electromyography (EMG) control (Darcey et al., 2004). ADs were not noted in this small study (Darcey et al., 2004). This demonstrates that intensity and frequency of stimulation at the cortical surface has impact on the generation of ADs and seizures.

Termination of afterdischarges (ADs)

Lesser et al., (1999) reported that brief bursts of 50-Hz stimulation inhibit ADs in humans. Induced ADs (5-s stimulus) are terminated by the identical stimulus applied for a shorter period. Continuous rhythmic activity is more likely to terminate than ADs consisting of rhythmic spiking (Motamedi et al., 2002). A stimulus at a latency of less than 4.5 s was more likely to terminate ADs. Stimulation at the primary site was more likely to be successful (Motamedi et al., 2002).

In two patients with stimulation in the primary motor and supplementary motor area cortex during functional mapping, termination of AD was studied (Jobst et al., 2009). Latency of stimulation did not determine successful termination, but the number of channels involved at the time of the terminating stimulus was inversely associated with termination (Jobst et al., 2009).

It remains unanswered whether ADs are a model of spontaneous seizures, but ADs can certainly evolve into habitual seizures.

Responsive neurostimulation for epilepsy

The above-described concept of terminating ADs via brief bursts of stimulation initiated development of responsive stimulation. The ideal treatment scenario includes detection of an electrographic seizure is before the onset of clinical symptoms. An electrical stimulus aborts the electrographic seizure and, therefore, prevents clinical symptoms from occurring.

Prerequisites for this treatment paradigm are the exact knowledge of the seizure onset zone and seizure detection algorithms that are specific for the patient's electrographic seizures. Subsequent technology was developed that would apply brief electrical stimuli specific to the patients unique seizure onset pattern (Responsive Neurostimulator, Neuropace, Mountain View, CA, U.S.A.).

In an initial proof of principle, an external stimulator was developed that detects electrographic seizures and applies responsive stimulation. Patients evaluated for epilepsy surgery with grid and strip electrodes were connected to the device, and responsive stimulation was applied through conventional electrodes (Kossoff, et al. 2004). After proof of principle, a safety and feasibility study followed testing an implantable device (Morrell et al., 2008).

Depth electrodes or cortical strip electrodes are implanted into the seizure onset zone (Fig. 2). The intracranial leads are connected to the device placed into the skull. The device is not cosmetically visible. The device detects electrographic seizures as recorded with electrocorticography. Patient specific algorithms detect early epileptiform activity. If an electrographically abnormal activity is detected, a short pulse of high frequency stimulation is applied for termination. Due to limited memory capacity, the patient is required to download saved electrocorticography on a regular basis. This allows for optimal stimulation and detection parameters. The device is independently interrogated via a wand and computer by the patient. Data are transmitted over the Internet to the treatment team.

With current technology two different seizure-onset zones can be targeted, which can be spacially separated. This enables treatment of multifocal or bilateral epilepsy. In addition, the technology is intended to treat epilepsy with seizure onset in eloquent areas. The brief, high frequency stimuli do not interfere with cortical function.

The feasibility and safety of this device was demonstrated by implantation in 65 patients (Morrell et al., 2008). There were no unanticipated serious adverse events. Anticipated device-related events in six patients included infection, skin erosion, cranial reconstruction, increased seizures, and falling. All of the anticipated events resolved. Anticipated uncertain device-related events in seven patients included hemorrhage, increased seizures, depression, headaches, and SUDEP (sudden unexplained death in epilepsy). In this study not designed specifically for seizure reduction, the median responder rate increased with the length of time that patients were followed. This could reflect either a long-term effect of stimulation of the seizure onset zone or better familiarity and expertise programming of the device. Responsive stimulation was more effective in hippocampal structures in the feasibility trial; however, hippocampal seizure onset is easier to identify than

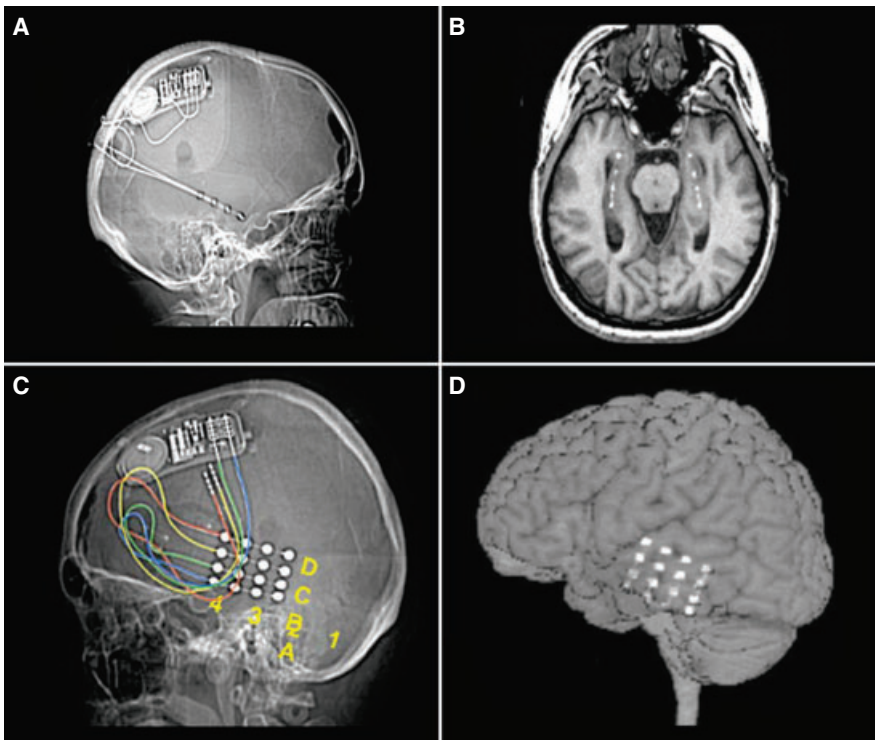

Figure 2.
Responsive stimulation of the bilateral hippocampus (**A**, **B**) and the left temporal language area (**C**, **D**). (**A**, **C**) Conventional x-ray. (**B**, **D**) Coregistration with preoperative magnetic resonance imaging (MRI). (**C**, **D**) Only eight contacts at one time can be connected to the neurostimulator. RNS (NeuroPace, Mountain View, CA, U.S.A.) is not an US Food and Drug Administration (FDA)–approved treatment for epilepsy and is purely investigational.

neocortical onset. In addition, the study was not powered for efficacy (Morrell et al., 2008).

A pivotal double-blind, controlled trial for responsive neurostimulation was conducted with stimulation ON or OFF for 3 months. One hundred ninety-one patients were implanted (at the time of the WONOEP meeting). Results are pending.

Overall the total experience with responsive stimulation is 431 patient-years and a total of 256 patients implanted (Data from Neuropace, Inc. June 2009). As this technology is emerging, further development will certainly improve treatment success.

Conclusions

Direct brain stimulation is an emerging treatment of epilepsy, which in the future could avoid functional deficits associated with epilepsy surgery and minimize sedative side effects of antiepileptic medications. Trials for scheduled and responsive brain stimulation have been conducted; however, the best target and mode of stimulation are still under investigation. Only large double-blind placebo-controlled trials are reliably able to evaluate efficacy. Brain stimulation trials are difficult to conduct due to difficulties with blinding and associated costs. Nevertheless, only the pursuit of such large human trials can advance this venue of treatment further.

Disclosure

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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