16 Epilepsy

Epilepsy is the third most common neurological disorder and has a prevalence of 0.5–1% worldwide. Current antiepileptic regimens are unable to provide adequate seizure control for 20–40% of patients—who are consequently labeled medically refractory. Surgical resection of a specific epileptogenic focus is capable of treating only about 60% of patients with medically refractory epilepsy. Current nonablative applications for the treatment of medically intractable epilepsy include vagus nerve stimulation (VNS), trigeminal nerve stimulation (TNS), deep brain stimulation (DBS), and more recently closed-loop stimulation systems (Rolston et al 2012, Wu and Sharan 2013). Here, I review cortical stimulation for the control of medically refractory epilepsy.

16.1 Open-Loop Cortical Stimulation

The epileptogenic zone is the minimum amount of cortex that must be resected (inactivated or completely disconnected) to achieve seizure freedom. Five “zones” have been described as those most essential to identify during pre-surgical evaluation: 1) irritative zone – the area from which spontaneous interictal spikes originate, 2) seizure onset zone – the area from which spontaneous seizures arise, 3) symptomatogenic zone – the area from which seizure symptoms and/or signs may be elicited via stimulation, 4) epileptogenic lesion – an area which is either grossly damaged (due to cortical dysplasia or tumor, for example) or is secondarily excitable due to nearby lesioned tissue, and 5) function deficit zone – an area of cortex that functions abnormally interictally. The extent of the epileptogenic zone may or may not coincide with the zone of ictal onset; in most cases, the epileptogenic zone is larger than that of the ictal onset. Furthermore, the epileptogenic zone is often dynamic, as it has been observed to migrate over the course of a patient’s disease process, and in other cases remain static. Accordingly, a static epileptogenic zone will be easier to control via focal cortical stimulation. In deciding the goal for therapeutic electrical stimulation of the cortex, the main consideration is to determine what facet of the epileptic network is to be affected by stimulation. In addition, the dynamic nature of epileptogenic zones should be kept in mind as the primary area for seizure control may migrate over the course of the patient’s disease progress. Finally, contacts should be less than 2 cm apart for effective epileptic control (Gwinn et al 2008). In light of these considerations, cortical stimulation (CS) becomes an option in select cases. Noninvasive CS (rTMS, tDCS) has evinced mixed results (Nitsche and Paulus 2009), while there is only one report in the literature of open-loop ICS (i.e. stimulation delivered regardless of neuronal activity) (Elisevich et al 2006). These authors implanted a strip electrode

(Resume quadripolar lead) subdurally along the axis of the dorsolateral convexity of the precentral gyrus (M1) in a man with intractable postencephalitic epilepsy with ictal onset in M1. For the five years of follow-up, cortical stimulation (2.1 mA, PW 450 μ s, 50 Hz, ON 3 min/OFF 10 min), with minimal alterations, successfully eliminated the jacksonian march and secondary generalization and reduced seizure frequency and intensity, with an immediate postictal return of motor function. Over time, the seizure frequency subsided by more than 90%, without adverse effects. Modeling of temporal lobe epileptogenicity suggests that a small redistribution of cerebral blood flow from non-epileptic to epileptic cortex should produce substantial reduction in temporal lobe seizure frequency in association with prolongation of inter-hemispheric prolongation time (Weinand 2000). Blood flow perturbations can be easily achieved with cortical stimulation and as such may put this theory to test.

16.2 Closed-Loop Responsive Cortical Stimulation

A closed-loop system administers stimulation only if triggered by early seizure activity. The lower doses of stimulation provided by such devices not only reduce power consumption, but also minimize the adverse reactions created by continuous stimulation, including the possibility of habituation to long-term stimulation. At the end of 2013, the first closed-loop system for the treatment of medically intractable partial epilepsy (Responsive NeuroStimulator, NeuroPace, Inc, MountainView, CA, USA) received a pre-market approval by the FDA, the target of stimulation depending on each patient's seizure focus or foci. This system is based both on progress in automated seizure detection over the past 40 years, epitomized by the International Workshop On Seizure Prediction (e.g. Jouny et al 2011) – a progress that is still ongoing in search of an ideal system- and Penfield and Jasper (1954)'s observation that in awake patients, in some cases, acute focal electrical stimulation of the exposed cortex resulted in a flattening of the local electrocortico-graphy (both normal rhythms and spontaneous epileptiform discharges) (Box 16.1). Further human trials used electrical stimulation to abort seizures by means of subdural electrodes placed for the purpose of localizing the epileptic focus for surgical excision; the clinical outcome pursued was a decrease in number of after-discharges (AD) or an increase in AD threshold (see detailed review in Mogul et al 2009).

Pulse Generator (IPG). The IPG is a hermetically-sealed neurostimulator containing electronics, battery, telemetry coil, and connector hardware that accommodates one or two 4-contact electrodes. The IPG continuously analyzes the patient's electrocorticogram (ECoG) and triggers electrical stimulation when it detects specific ECoG characteristics programmed by the clinician as indicative of interictal or ictal epileptiform activity. The IPG then stores diagnostic information that details detections and stimulations, including multichannel stored ECoGs. The IPG has the following dimensions: 41 mm wide, 60 mm long and 7 mm thick (weight 19.5 g, volume 10.5 cm³). The IPG is curved in shape to facilitate cranial implantation. It is positioned extradurally in a tailored cranial defect and held in place with a ferrule ([Fig. 16.1](#): craniectomy with the implanted ferrule; [Fig. 16.1b](#): IPG in place).

Electrodes. Depth electrodes are quadripolar and designed for stereotactic implantation. They are available with 3.5mm and 10mm intercontact spacings, with lengths of 30 cm and 44 cm. The individual contacts are 1.1 mm in diameter and 2.3 mm in length. Subdural strip electrodes are quadripolar with 4 mm diameter circular electrodes and intercontact spacings of 10 mm. They are available in 15 cm and 25 cm lengths. All electrodes are composed of platinum (90%) and iridium (10%).

Programmer - The programmer is a laptop computer with specialized software and a telemetry wand that communicates with the IPG. The programmer downloads diagnostic and ECoG data from the IPG. In addition, the programmer has an electrophysiology test stimulation mode, which allows real-time stimulation with simultaneous ECoG viewing.

Box 16.1: NeuroPace™ System Components

The NEUROPACE™ system (Smith et al 2009) is capable of performing real-time seizure detection and delivering responsive electrical stimulation. The implantable components of the system include a cranially implanted neurostimulator and intracranial depth and strip leads. The neurostimulator is a battery-powered, microprocessor-controlled device that continuously monitors electrographic activity from the cortical depth and strip leads and delivers programmable electrical stimulation in response to detected events to two distinct epileptogenic zones independently. Due to technological constraints, the sensed electrographic data are not continuously recorded; however, the neurostimulator can store segments of the electrographic data for review by the physician. The neurostimulator system has a 32-minute ECoG memory buffer. The number of ECoGs stored depends on the number of recording channels and the recording time selected. Typically, 2 bipolar recording channels are selected with a 60-second pretrigger and 30-second posttrigger duration, which allows 9 ECoGs to be stored. Any additional ECoGs overwrite the previous recordings. ECoG storage can be triggered by any of several electrographic events, including seizure onset. An important feature is the use of a personalized 'training period', in which the device is individually tuned to the patient after it has recorded seizures.

The RNS neurostimulator is designed to match typical skull thickness and curvature, and is intended for implant in a ferrule, or socket, placed in a craniectomy ([Box 16.2](#)). Up to two leads, each containing four electrodes, can be connected to the neurostimulator; each may be a depth lead or cortical (subdural) strip lead, and each has four electrode contacts, which are used for sensing and providing stimulation. To provide early seizure detection and delivery of focal electrical stimulation, leads are

positioned as close as possible to the seizure focus or foci. The external components of the system include a physician programmer, a patient data transmitter and a telemetry wand. The programmer is used by the physician to program detection and stimulation settings and retrieve stored information (e.g., electrographic activity) from the neurostimulator. The data transmitter is provided to the patient to allow uploading and remote monitoring of the device between clinic visits. The telemetry wand allows wireless communication between the neurostimulator and the programmer (or data transmitter). The device data and electrographic data are uploaded via the Internet to a central patient data management system and may be reviewed by physicians using a secure Web browser.

Invasive monitoring is used in all cases to determine seizure focus localization and therefore, optimization of the location and type of closed loop electrodes used. For example, patients with a seizure focus in the left lateral temporal neocortex would receive two 1x4 subdural electrodes. If the seizure focus were left hippocampal in a patient in whom Wada memory testing revealed absence of contralateral memory support, a 1x4 hippocampal depth electrode and an ipsilateral anterior subtemporal 1x4 subdural electrode would be implanted. In general, the type and location of electrode implantation will be tailored to the individual patient. Implantation site for the IPG will be determined by the implantation site of the two electrodes. If depth electrodes alone are used, a large skin flap will be needed to expose enough skull to incorporate the IPG and its ferrule as well as the two 14 mm diameter burr holes and their burr hole rings and covers. If there was a previous craniotomy performed for invasive monitoring, this area may be re-exposed for implantation of both the subdural electrodes and the IPG and ferrule (Fig. 16.2). If a hippocampal depth electrode is implanted through an occipital entry in a case requiring repeat temporal craniotomy or repeat burr hole for implantation of a subdural electrode, then the tail of the depth electrode will need to be tunneled into the area of cranial exposure. Passing the tail of the depth electrode through the appropriate length of silastic tubing provided in the depth electrode kit will protect the electrode tail when the old or new craniotomy incision is subsequently made for subdural strip electrode and IPG placement. The patient is appropriately positioned on the operating table by attaching the base-ring to a Mayfield holder. The craniotomy incision is marked off and the surgical area is prepped and draped in a standard sterile fashion. The previously marked-off incision is infiltrated with local anesthetic and a horseshoe-shaped craniotomy flap is turned. A sterile ferrule template is provided than can be overlaid over the exposed skull to find an area where the convex contour of the template best fits that of the skull (diminishing the potential risk of bone erosion). Monopolar cutting current is used to mark off this rectangular area. A single burr hole is placed at either end of the rectangle and a Penfield 3 dissector is used to separate the dura from the skull prior to using the craniotome to cut out the rectangle of bone. A full thickness craniectomy is preferred in order to minimize protrusion of the IPG. Note that one burr hole of the craniectomy should be off center to accommodate the fixation tab that secures the IPG in the ferrule (Fig. 16.1a-b). Depth electrodes are placed using a frame-based stereotaxic system and depth electrode implant planning with a commercially available computer workstation. Frame application is carried out using IV sedation consisting of Alfentanil and Propofol. A field block of the scalp is performed using approximately 40 cc of a 1:1 mixture of 0.25% Marcaine and 0.5% Lidocaine. Carbon fiber posts and aluminum pins are used to limit metal artifacts on the CT scan, which follows the MRI study. A contrast-enhanced, T-1 weighted, volume acquisition MRI is performed consisting of 1.3 mm axial slices with 0 mm slice gap.

Box 16.2: Technique of implantation (From Smith et al 2009)

The MRI is followed with non-contrasted axial CT with 3 mm axial slices and 0 mm slice gap. The images are transferred over the local area network to the computer workstation which is used to perform image fusion of the MRI study to the CT study. After depth electrode trajectories are generated, a probe view algorithm is used to assess (1) the proximity of any cortical vessels to the depth electrode entry and (2) the proximity of the trajectory to the ventricular system or any subependymal veins. Any appropriate adjustments to trajectories are made before actual implantation. The stereotactic arc system is attached to the base ring and a drill guide tube is then advanced through the incision down to the skull and antibiotic irrigation is flushed through the tube. The appropriate burr hole is outlined on the skull and a high-speed air-driven drill is used. The underlying dura is opened in a linear fashion in order to facilitate subsequent passage of the guide block. At this point, a 2.1 mm inner-diameter guide block is introduced and the dura and pia are cauterized with a monopolar electrode. The diameter of the burr hole must exactly match the diameter of the securing device for the implanted depth lead. Next a 14-gauge depth electrode cannula is passed through the same guide block to the target point. Intraoperative fluoroscopy verifies proper placement. The cannula and guide tube are then withdrawn. A cranial base and cap device are then implanted into the burr hole and secured by using the two self-tapping screws provided. The surgeon must align the exit groove on the base in the posterolateral direction, in the same direction that the subcutaneous portion of the lead would later be directed. An insertion tool is then passed through a large diameter guide block and inserted into the slot and the securing device. The insertion tool and guide block are then removed. The depth lead is then carefully inserted into the target point. After fluoroscopy confirmation, the stylet of the lead is removed and the distal shaft of the implanted lead is secured into the securing device. Postimplant intraoperative fluoroscopy is performed after locking the depth electrodes in place in order to assure proper positioning. If the subdural strip lead is to be placed, the dura is opened linearly and the appropriate cortical lead is inserted through the dural opening under fluoroscopy. The distal shaft of the implanted lead is safely attached to the securing device. At this point, the provided ferrule is placed on the exposed bone and the desired bony defect is outlined. The outlined bone is drilled out by high-speed air-driven drill, bony edges are smoothed, irrigated and waxed. The provided ferrule is then implanted and secured to the adjacent bone at four points with the provided self-tapping mini-screws. The IPG is connected to the distal end of the already implanted lead or leads and then is safely secured in the implanted ferrule. *To summarize*, burr holes for depth electrodes are made with a 14 mm diameter bit so that the manufacturer supplied burr hole rings, which are secured with self-tapping screws, will exactly fit. Subdural electrodes are secured with purse string 4-0 silk suture at the dural incision exit site. If the depth electrode implant is bilateral, the entire procedure is done with the patient in the stereotaxic frame using local anesthesia and i.v. Propofol and Alfentanil. If the implant is unilateral, the tail of the depth electrode is tunneled to the planned craniotomy site, the burr hole incision is closed, and the frame removed. The area of the subsequent craniotomy incision will determine the area of skull to be clipped (avoid razors to minimize skin microtrauma and possible infection). The patient is intubated and ventilated, but the procedure may also be carried out under neuroleptoanalgesia along with field blocks of the scalp. Control of blood pressure minimizes potential intraoperative hemorrhage. The operative blood loss is generally minimal (<100 ml). At the end of the procedure, all components of the RNS neurostimulator system are connected, the skin flap is positioned for closure, and a telemetry wand (covered with a sterile camera drape) is placed over the IPG so that recording of electrode contact impedances as well as intraoperative electrocorticography (ECoG) can be performed. If impedances and ECoG recordings are satisfactory, skin closure is completed. The surgical wound is irrigated with an antibiotic solution and then closed in anatomical layers and the wound is covered with a sterile dressing. Perioperative i.v. antibiotic therapy is begun the morning of the procedure and continued 24 hours post-operatively. On the third postoperative day, the first interrogation-detection session is performed.

Fig. 16.1: **a** Rectangular craniectomy with implanted ferrule. Arrow points to the burr hole which will accommodate the fixation tab used to secure the IPG in the ferrule **b.** Ferrule secured in position with self tapping screws in the four tongs at the corners of the ferrule. Note the fixation tab (arrow) which is accommodated by the burr hole. Note single depth electrode (short arrow) inserted in connector port.

Fig. 16.2: Example of RNS with 2 4-contact subdural strip electrodes implanted over the left superior and middle temporal gyri. The three arrows (left to right) point to the connector port, microchip, and battery of the IPG.

Electrographic data storage can be triggered by detection, responsive stimulation, scheduled time of day, magnet (used by the patient to indicate a clinical event), or other events as programmed by the physician. These data allow physicians to assess detection sensitivity and effects of stimulation. The detection algorithms implemented in the RNS system are designed to be computationally efficient and are highly optimized to perform real-time seizure detection within the constraints of currently available implantable technology, such as limited power and processing capabilities. Three detection tools are provided: *area*, *line-length*, and *half-wave*. The detection tools are highly configurable and can be adjusted by the physician to

optimize the sensitivity and specificity trade-off for each individual patient. Up to two independent detectors can be programmed for any two sensing channels.

The neurostimulator delivers current-controlled, charge-balanced biphasic pulses; it can be programmed by the physician to deliver stimulation frequencies ranging from 1 to 333 Hz, current amplitudes from 1 to 12 mA, and pulse-widths from 40 to 1000 μ s. Any of the electrode contacts or the pulse generator housing may be programmed as anode or cathode. The stimulation montage can be configured to deliver current between any combination of electrodes and the neurostimulator case. Up to five individually configured sequential therapies of electrical stimulation may be programmed, where each therapy is composed of two independently configurable bursts. The RNS will attempt to redetect the epileptiform activity after each therapy is delivered. If the epileptiform activity is still detected, the next (sequential) therapy will be delivered. If the epileptiform activity is no longer detected, the remaining therapies will not be delivered and the episode ends. The therapy sequence will refresh with the detection of each new episode. Stimulation parameters are determined empirically, while respecting safety limits for charge density. The parameters of each therapy and each burst may be the same or varied. The RNS system has controls in place at the programmer and neurostimulator, so that current densities remain below a conservative limit of 25 μ C/cm² per phase. Furthermore, intermittent (more acute-like) stimulation may pose fewer risks to neural tissue than does continuous stimulation. The stimulation configuration is also determined empirically. Options include providing bipolar stimulation across electrode pairs or stimulating across all eight electrodes to the case of the neurostimulator. Whether stimulation is delivered to a few or many electrodes depends to some extent on the area of onset. Studies show that, unlike depth electrodes, the mean impedance of subdural strip electrodes increased over time to peak at 16-20 months and returned to baseline by 2 years (Wu et al 2013).

16.2.1 Patient Selection and Outcomes

Closed-loop stimulation is indicated for patients 18 or older with drug-resistant epilepsy who are not candidates for resective surgery. Although resection is preferred, closed-loop stimulation has also been offered to patients who decline traditional surgical options. It may be used to treat patients with bitemporal or multifocal epilepsy, but patients generally should not have more than two distinct epileptogenic foci. Because electrode implantation depends so heavily on accurate localization of seizure foci, closed-loop systems should only be implanted if the exact epileptogenic focus or foci are known, particularly if their seizures are not hippocampal in origin. This form of stimulation can also be more readily applied to eloquent brain without affecting neurologic function.

The RNS System Pivotal Clinical Investigation was a multicentered, randomized, double-blind sham stimulation controlled trial in which 191 patients were implanted across 31 institutions. This study included adult subjects 18–70 years of age with medically refractory epilepsy with an average of three or more seizures per 28 days. During the initial 12-week blinded evaluation period, an initial implantation effect was noted as the mean percentage of seizure reduction was reduced in both stimulation and sham groups: by 34.2% and 25.2%, respectively. It remains unclear if this initial effect can be attributed to the placebo effect, to anesthesia, or to some aspect of the surgical procedure itself. Over the course of the blinded period, this implantation effect was substantiated as the stimulation group continued to demonstrate seizure reduction by a mean of 41.5% at the end of the blinded period, while the sham group failed to maintain its effect, with a mean reduction of 9.4% at the end of this period. After two years, median seizure frequency was reduced by more than 50% with a responder rate of greater than 45% with stimulation. Longer term follow-up has demonstrated the sustainability of RNS, as the responder rate increases to 53% at three years after implantation. Follow-up on these 191 implanted patients presented class I evidence that closed-loop stimulation significantly reduced the frequency of disabling partial-onset seizures that were refractory not only to antiepileptic drugs (AEDs), but also to VNS or resective surgeries (Morrell et al 2011). Also important are the significant improvements in overall quality of life as reported by patients receiving stimulation via the Quality of Life in Epilepsy Inventory (QOLIE-89). There was no deterioration in mood and neuropsychological function. Side effects included (among others, like implant site pain and headache) serious brain hemorrhage (2.1%) due to the implantation (no mortality, no morbidity) and infection (5.2%), but not of the brain or skull. Mortality was due in 4 cases to SUDEP (3 with implant running) and in other 2 to unrelated causes. Some patients implanted with the first generation of the system reported a transient buzzing sensation with the onset of stimulation. Fortunately, the source of this side effect was identified and there have been no such reports in patients implanted with later generations. The administration of stimulation directly to the suspected seizure focus also reduces the potential for adverse effects by sparing normal brain. In order to avoid damage to neurons from chronic stimulation, the conservative limit to the charge density is 25 $\mu\text{C}/\text{cm}^2/\text{phase}$ —while it has been determined that densities of 50–60 $\mu\text{C}/\text{cm}^2/\text{phase}$ can be safely delivered to human cortex for acute intermittent stimulation.

After the fifth post-implant month, all subjects received responsive stimulation in an open label period (OLP) to complete 2 years of post-implant follow-up. The percent change in seizures at the end of the blinded period was -37.9% in the active and -17.3% in the sham stimulation group ($p = 0.012$, Generalized Estimating Equations). The median percent reduction in seizures in the OLP was 44% at 1 year and 53% at 2 years, which represents a progressive and significant improvement with time ($p < 0.0001$). There were no adverse effects on neuropsychological function or mood (Heck et al 2014). Nevertheless, long-term experience beyond five years is currently very limited.

The side effects of intermittent chronic stimulation remain unclear, and it is uncertain whether or not deleterious kindling or other problematic effects will emerge.

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