Published in final edited form as:

Neurosurg Clin N Am. 2011 October ; 22(4): 425–442. doi:10.1016/j.nec.2011.07.010.

Electrical Stimulation for Epilepsy: Experimental Approaches

John D. Rolston^{1,2}, Sharanya Arcot Desai^{1,2}, Nealen G. Laxpati^{1,3}, and Robert E. Gross^{1,3,4}

¹Department of Neurosurgery, Emory University School of Medicine, Atlanta, Georgia, U.S.A.

²Laboratory for Neuroengineering, Georgia Institute of Technology, Atlanta, Georgia, U.S.A.

³Coulter Department of Biomedical Engineering, Georgia Institute of Technology, Atlanta, Georgia, U.S.A.

⁴Department of Neurology, Emory University School of Medicine, Atlanta, Georgia, U.S.A.

1. Introduction

Direct electrical stimulation of the brain is an increasingly popular means of treating refractory epilepsy [1]. While there has been moderate success in human trials, the rate of seizure freedom does not yet compare favorably to resective surgery [1]. It therefore remains critical to advance experimental investigations aimed toward understanding brain stimulation and its utility. The following article introduces the concepts necessary for understanding these experimental studies, describing recording and stimulation technology, animal models of epilepsy, and the various subcortical targets of stimulation that have been investigated. Due to the continued interest in bidirectional and closed-loop devices, these technologies are also highlighted, along with the challenges presented by their experimental use [2].

2. Electrode Recording

2.1. Types of Signals

Depending on the properties of the recording electronics (electrode material, size, position, sampling rate of the analog-to-digital converters, etc.), signals ranging from individual action potentials to the electrocorticogram can be recorded, with each type of signal providing a different scale of information about brain physiology.

2.1.1. Single units—When a neuron generates an action potential (AP), the current across its cell membrane generates a complex electric field. An electrode placed in this external electric field will detect this activity, referred to as a *spike*. Recording such spiking activity from individual neurons is known as *single unit* recording. Unlike intracellularly recorded APs, which are commonly recorded using patch-clamp techniques, extracellular spikes vary markedly in morphology and even polarity, and are dependent upon the geometry of the cell and the location of the recording electrode. While these variations may be of interest, in that they may indicate location of the recording electrode in well-defined neural tissue [3], most investigations instead examine evoked spikes or characteristics of spike trains.

© 2011 Elsevier Inc. All rights reserved.

rgross@emory.edu .

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Microelectrodes with a tip diameter on the order of micrometers and geometric surface area $<2000\text{--}4000\text{ }\mu\text{m}^2$ are commonly used for recording the extracellular activity of single neurons [4]. The extracellularly recorded action potential is typically $<100\text{ }\mu\text{V}$, about two orders of magnitude lower than that of a corresponding intracellular recording.

During single unit recordings, the largest component of signal noise arises from the multitude of undifferentiated background action potentials and synaptic potentials (neural noise). However, electrode impedance also contributes and is known as thermal noise, with higher impedance electrodes consequently demonstrating more noise and a lower signal-to-noise ratio. In addition, high electrode impedance in combination with the distributed capacitance between the electrode and the recording amplifier will reduce the electrodes' high-frequency response [4]. One method of improving the signal-to-noise ratio is to reduce electrode impedance without increasing the surface extent of the electrodes. This can be achieved either through sputtering or electroplating the tip with a biocompatible material that reduces the impedance without increasing the surface extent of the electrodes [5].

2.1.2. Multiunit Activity (MUA)—If activity from more than one single neuron is detected by a microelectrode, the resulting polyneuronal activity is often referred to as multiunit activity (MUA). Spike sorting methods can then be used to putatively identify each recorded waveform as originating from a particular cell [6]. However, another definition of MUA relies on isolating the “neural noise” described above. If the electrical activity above a certain frequency is isolated (e.g., $>300\text{ Hz}$), the power of those high frequencies can be used as a surrogate for large-scale spiking activity from multiple neurons. This high-pass signal is then typically rectified and low-pass filtered to generate a time-varying estimate of MUA [7].

2.1.3. Local Field Potentials (LFPs)—The local field potential (LFP) is the low frequency (arbitrarily $<300\text{ Hz}$) summed synaptic activity recorded extracellularly from a population of neurons. It can be isolated from micro- or macroelectrodes. Recent studies suggest that the LFP signal originates within a range of $250\text{ }\mu\text{m}$ from the recording electrode [8], smaller than the previously reported range of $400\text{ }\mu\text{m}$ to a few mm [9, 10].

LFP recordings enable the visualization of prominent brain oscillations (e.g., alpha, beta, theta, gamma, delta) when electrodes are placed in appropriate regions. There is some debate about whether the various frequency components of the LFP have unique corresponding spatial footprints. For example, it has been proposed that the higher frequencies (in the gamma range, around $25\text{--}90\text{ Hz}$) may carry information that is more local than the lower frequencies, perhaps as a result of the capacitive properties of neural tissue [8, 11].

2.1.4. Electrocorticography (ECoG)—Electrocorticography utilizes macroelectrodes ($\sim 5\text{ mm}$ in diameter) to record directly from the brain, either superficially or at depth. Although, as compared to electroencephalography (EEG), ECoG is invasive, it enables higher spatial resolution (i.e., tenths of millimeters versus centimeters), broader bandwidth (i.e., $0\text{--}200\text{ Hz}$ versus $0\text{--}40\text{ Hz}$), and higher amplitude (i.e., $50\text{--}100\text{ }\mu\text{V}$ maximum versus $10\text{--}20\text{ }\mu\text{V}$). Surface ECoG does not require electrodes to penetrate the cortex, and thus may have greater long-term stability and safety compared to single-unit penetrating microelectrodes [12]. However, it lacks the spatial resolution of implanted micro- and macroelectrode recordings.

2.1.5. Electroencephalography (EEG)—EEG refers to electrical recordings made with macro electrodes positioned non-invasively on the subject's scalp (but could include other approaches, e.g., epidural peg electrodes). Standard montages are used (e.g., the

international 10–20 system), but are often supplanted by extra electrodes. EEG is most commonly used in the diagnosis and classification of epilepsy, with its main advantages being that it is non-invasive and inexpensive. However, EEG does have a number of limitations. Large areas of the cortex need to be activated synchronously to generate enough potential to be recorded extracranially. Propagation of electrical activity along physiological pathways in extracellular spaces may give a misleading impression as to the source of the electrical activity. Furthermore, EEG suffers from poor spatial resolution, confounding seizure foci localization. Nevertheless, EEG continues to play a central role in the diagnosis of epilepsy and other neurological disorders, and has been used extensively in conjunction with other diagnostic techniques [13].

2.2. Types of electrodes

According to Merrill et al. [14], the ideal material for building electrodes should satisfy six requirements. It should (1) be biologically compatible, (2) maintain its mechanical integrity during the surgical procedure, (3) have sufficient charge storage capacity, (4) not undergo electrochemical reactions that produce toxic products, (5) not undergo Faradaic corrosion reactions, and (6) be stable for the duration of the implant. Criterion (5) depends highly on the duration of implantation—electrodes used in acute studies are unlikely to fail due to corrosion. Based on their size, electrodes can be broadly classified into two categories: microelectrodes and macroelectrodes.

2.2.1. Microelectrodes—Microelectrodes are small diameter ($<50\text{ }\mu\text{m}$) electrodes, typically used in the recording of single-unit activity. Depending on the material and diameter, their impedances range from tens of $\text{k}\Omega$ to more than tens of $\text{M}\Omega$. In addition to recording, microelectrodes can be used to deliver stimulation. In a direct application of Ohm's law, the higher the impedance of the microelectrode, the higher the required voltage to deliver the same amount of current. Thus, microelectrode impedance plays a major role in determining the maximum stimulation potential that may be applied to the electrode without causing undesirable breakdown of water molecules into hydrogen and oxygen gas. This potential limit is known as the “water window,” and with high impedance electrodes care should be taken to ensure the stimulation potential does not exceed an acceptable range [14]. One way of circumventing this problem is to reduce the impedance of microelectrodes while maintaining their small surface extent, for example by electroplating their tips with a biocompatible material. The material deposited with electroplating, however, can sometimes be shed during long recordings, limiting the use of electroplating in chronic recordings. More recently it has been shown by our group that sonicoating—electroplating under ultrasonic agitation—can significantly improve the durability of plating [5]. Lowering microelectrode impedance will produce additional advantages, such as reduced thermal noise, which increases as a function of the electrode impedance, and smaller stimulation artifacts. Reduction of stimulation artifact is particularly important for closed-loop applications, which are discussed later in this review.

(A) Metal microelectrodes: The performance of metal microelectrodes for neural recording and stimulation depends on their geometrical, electrical and mechanical properties [15]. The most frequently used metals for manufacturing microelectrodes include stainless steel, platinum, iridium, tungsten, titanium, nickel-chromium, and their alloys. Copper and silver are known to cause tissue necrosis and hence are not often utilized [4]. Electrodes are often covered in an insulating material—such as varnish, epoxy, parylene, glass, Teflon, or polyimide—to within a few micrometers of their tip, which is left exposed in order to record the highly localized extracellular potentials induced by currents in one or a few of the closest neurons. They may also be used to deliver highly localized stimulation.

Tetodes can be made by twisting four microwires around each other and applying sufficient heat to bind them together by melting the insulation. The four microelectrode tips are then within a micrometers from each other, and consequently have a high probability of picking up APs simultaneously from the same neurons. The shape of the APs picked up by the four electrodes, while different (dependent upon their location with respect to the firing neuron) is also very reproducible (they record the same shape of activity whenever that particular neuron fires), making spike sorting simple and reliable, using a process akin to triangulation to identify particular cells. The tetrode configuration additionally provides stability to the microwires during implantation [16]. Another common practice is to arrange multiple microwires onto a single shaft (microwire arrays) for recording and/or stimulating multiple single units at the same time. TDT (Achua, FL), Neuronexus Technologies Inc. (Ann Arbor, MI) and Plexon (Dallas, TX) are among the vendors who sell such microwire arrays for use in animal studies. More recently, Bartels et al. [17], have designed neurotrophic electrodes for increasing the longevity and stability of recorded signals. Their design induces neurite growth into a glass cone that covers the tip of gold microelectrodes insulated with Teflon, anchoring the glass tip to the neuropil.

(B) Other types of microelectrodes: Silicone based microelectrode arrays are gaining popularity as an alternative to microwire arrays. The most significant advantage of the silicon-based microelectrode technology is that it enables the monolithic integration of electronics, such as amplifiers, filters, and multiplexers, into the probe structure. These active microelectrodes improve the quality of recorded signals over passive microelectrode arrays (without integration of electronics) [18, 19].

PDMS (polydimethylsiloxane) based microelectrodes are deformable, enabling conformation to the structure from which they are recording and/or stimulating. Such flexible designs hold great promise for recording from structures that are otherwise inaccessible to the rigid metal/silicone-based microelectrodes, although they are not yet available for use in human subjects [20, 21]. (Figure 1)

2.2.2. Macro electrode—Macroelectrodes have dimensions on the order of a few millimeters (typically 1–5 mm), with a corresponding surface area around 1–25 mm², and impedance in the range of 500–1000 Ω . Consequently, they are primarily used to record LFP, ECoG and EEG signals.

(A) Depth Macroelectrodes: Depth electrodes are widely used in epileptic patients to delineate seizure foci [22]. Typical depth electrodes consist of four or more 1 mm contacts arranged linearly on a single shaft, separated by a distance of ~10 mm. In addition to recording, similar electrodes are also used for stimulation (e.g., deep brain stimulation in Parkinson's disease and epilepsy) [23–25]. Several groups have investigated the impact of electrode geometry on recorded and stimulated volumes of brain tissue, topography, etc. [26, 27]. Recently, hybrid depth electrodes, consisting of both macroelectrodes and microwires arranged on the same shaft, have been used for simultaneous recording of LFPs and single unit activity [28]. Image guidance techniques are used to ensure proper placement of depth electrodes [29].

(B) Surface Macroelectrodes: ECoG recordings often make use of grid and strip subdural surface electrodes [30]. In many cases subdural electrodes are used in combination with depth electrodes for the purpose of delineating seizure foci. Like hybrid depth electrodes, hybrid surface electrodes—with microelectrodes interspersed between macroelectrodes—are becoming popular due to their increased spatial resolution, and for research purposes [31].

3. Stimulation

3.1. Mechanisms of Stimulation

Little has changed in the 35 years since Ranck observed that “despite the extensive use of electrical stimulation of the central nervous system, both clinically and experimentally, there has been little concern with what cells or parts of cells are stimulated” [32]. To this day, the mechanism of action of electrical stimulation on the nervous system remains poorly understood. What has become clear, however, is that many parameters of stimulation (electrode configuration, pulse width, frequency, etc.) as well as the architectural organization of the stimulated tissue are critical in determining its impact.

Ranck noted thresholds were lowest in myelinated axons, and progressively increased in unmyelinated axons, dendrites, and cell bodies. This point was further substantiated in a series of elegant experiments by Histed et al. [33]. Utilizing simultaneous low-current 250 Hz electrical microstimulation and two-photon calcium imaging in mouse and cat visual cortex, the investigators were able to examine a large population of cells, free of confounding stimulus artifacts, to identify the population and location of neurons activated by cortical microstimulation. Their work revealed a sparse and distributed population of activated neurons that possessed several additional intriguing qualities. Rather than activating neurons whose cell bodies were closest to the electrode tip, cells were sparsely activated in a region surrounding the electrode, in some cases up to 4 mm away. Increasing the stimulating current amplitude increased the number of cells activated within this area, but did not activate those further away. In fact, a large percentage of the neurons identified failed to be activated, even as their immediate neighbors were. These experiments suggest microstimulation is primarily acting on neural elements (hypothesized to be axons) as opposed to cell bodies. If axons are indeed the primary target, it is further unclear what regions are most susceptible to electrical stimulation, with the neuron initial segment [34] and nodes of Ranvier [32] being variably implicated.

Little more is known as to whether electrical stimulation primarily acts in an inhibitory or excitatory manner. One of the more accepted theories suggests that neurons adjacent to stimulating electrodes undergo long-term inactivation as a result of stimulation [35, 36]. This may be based on the similarities in clinical outcome between surgical ablation and deep brain stimulation [37]. However, activation of efferent neurons, even in the context of inhibited cell bodies, has been demonstrated in several reports [33, 38, 39]. Indeed, even Ranck noted that at high currents, elements nearby the electrode would fail to respond, whereas those in a surrounding sphere were activated [32]. Consequently, a single stimulus could produce variable regions of activation and inhibition. The local suppression of APs and bursting activity has been noted by other groups as well [40]: Lian et al. found that 50 Hz sinusoidal current injected locally through a monopolar electrode could effectively block activity in a region close to the stimulation site, but was unable to completely suppress activity remotely. The mechanism underlying this suppression was posited to be through a local depolarization block from a large increase in extracellular potassium, a well-established phenomenon associated with high frequency AC stimulation [40]. Indeed, while electrical stimulation itself may be activating neural elements, the network effects may actually be inhibitory due to changes in electrochemical gradients, neurotransmitter depletion, or signal obfuscation [37].

These observations have served to reinforce early indications that stimulation parameters are crucial for determining clinical outcomes. Despite this, human trials are largely based on empirical evidence and case reports [37, 41, 42]. Ideally, clinicians would tune treatment based on knowledge of the various interdependent properties of electrical stimulation, so as to maximize effectiveness and reduce side effects. While there is much work to be done

before the latter can become standard, current understanding should prove useful in improving clinical efficacy and research methods.

3.2. Targeting

While gross targeting of stimuli to anatomically relevant tissue plays an important role in therapeutic outcome, local cellular cytoarchitecture has been implicated as well [33]. High frequency DBS for Parkinsonian tremor has primarily been targeted to neurons of the subthalamic nucleus, but it is unclear whether or not the effect is primarily mediated through the local neuron bodies, or through fibers of passage [43]. Voges et al. found the best improvements involved electrodes projecting onto fiber tracts located close to the STN [44], and recent optogenetic investigations have implicated fibers of passage to the nuclei itself [45].

Anatomical targets may be better reflected in orthodromic and antidromic projections as opposed to their local soma. Furthermore, orientation within these regions has the potential to be highly influential. Ranck determined that more current was necessary to generate the same results if monopolar electrodes were positioned in such a way that current flow was across the axon (transverse) rather than parallel to it (longitudinal). Indeed, it was only when anodic fields were applied across the dendritic-somatic axis in slice preparations of epileptic hippocampus that seizures could be effectively suppressed [46]. Applying the field perpendicularly to this axis, however, was unable to affect activity even at high field values. Interestingly, Lian et al. found that orientation of a monopolar electrode along the dendritic-somatic axis during AC stimulation (sinusoidal, 50 Hz, 0 DC offset) had no effect on suppression, while DC stimulation was highly orientation-dependent [40]. Higher frequency stimulation (>50 Hz) may indeed be orientation independent [47], despite the initial findings of Ranck. This may be consequent to blockade of voltage-gated currents [48] or accumulation of extracellular potassium [42] or other biochemicals (e.g. adenosine [49]), which could result independently from the direction of current flow.

3.3. Frequency

Frequency of stimulation, as implicated above, can have an important influence as well. Aside from matters of orientation, different network-wide impacts have been implicated for high-frequency (roughly >50 Hz), low-frequency (<50 Hz), and DC stimulation. High frequency stimulation can induce peripheral nerve blocks [50], and in the subthalamic nucleus was seen to inhibit somatic neuronal activity [48], as well as axonal conduction in hippocampal preparations *in vitro* and *in vivo* [51]. High frequency stimulation may thus act, in part, through a conduction blockade of pathologic activity, hence preventing spread and/or synchronization, but effects on efferent axons independent of effects on the cell soma must be considered as well.

Low-frequency stimulation (LFS) is presumed to be excitatory in nature [52], and was seen to reduce seizure frequency in human patients with epilepsy [53, 54], as well as in several animal models of epilepsy [55]. LFS could be inhibiting, however, as it may induce long term depression through the alteration of synaptic weights [54, 55]. It is possible that LFS activates axons, and that this activation, being asynchronous with synaptic input, generates LTD and reduces the activity of the overexcited cell. Further research is necessary to determine the exact mechanisms underlying LFS and its impact on synaptic weighting. Preliminary evidence suggests that LFS may restore normal network responses [56].

DC electric fields can also be applied to brain tissue to suppress spontaneous epileptiform activity [40, 42, 46, 57]. These fields are often created *in vitro* using parallel wires or plates. Anodic fields generate higher potentials at the cell soma vis-à-vis dendrites, resulting in

positive current flow into the soma and out through the dendrites. This hyperpolarizes the soma, preventing excitation to threshold and conduction of epileptiform activity [46]. Even with the obvious difficulties with *in vivo* applications, there are additional drawbacks to the technique. Unbalanced charge deposition results in erosion and electrochemical tissue damage [40]. Further, suppression produces rebound excitation upon removal [46]. These limitations make the application of such fields a challenge in human patients.

3.4. Polarity

Electrode configurations tend to be divided into monopolar and multipolar varieties, the most common of which is bipolar. All configurations (even so-called monopolar) consist of an anode and a cathode, with current flowing from the cathode towards the anode. In monopolar electrodes, the cathode is distant from the anode. For example, DBS stimulators will often use the pulse generator case as the anode [41]. Multipolar configurations have the anode and cathode in relative proximity, such as between neighboring contacts. Monopolar configurations thus create broader extracellular current spread than multipolar arrangements [43], and consequently, bipolar configurations are less likely to generate unwanted side effects. Multipolar configurations allow for greater control of current distribution, enabling more precise targeting.

3.5. Waveform

Most current clinical neural stimulators make use of rectangular, charge-balanced waveforms [58]. Much of this adherence may be based on historical precedent, although charge-balancing helps reduce electrode erosion and electrochemical tissue damage [40]. Aside from potential energy savings and prolongation of stimulator battery lifetime [58], alternative stimulus waveforms have the potential to target different regions in nervous tissue, and may be the difference between an inhibitory or an excitatory response [51]. More research must be performed to support the implications of modeling studies [59].

3.6. Amplitude

It has long been assumed that increasing current amplitude results in a larger sphere of activated neuron bodies around the electrode contact [32, 34]. However, as described above, stimulation results in an activation of cells in a distinct region determined by the local neuroanatomy. Higher amplitudes activate a greater number of fibers, thus increasing the number of cell bodies activated. This does *not* significantly increase the distance at which activation occurs, as it is determined by the *anatomically-defined axonal projections* of the neurons, rather than the soma's distance from the electrode tip [60]. Consequently, while higher amplitude stimulation recruits a larger proportion of neurons, *which* neurons are influenced, and at what distance from the tip, seems to be determined by the local cytoarchitecture.

3.7. Current- vs. Voltage-controlled stimulation

In current-controlled stimulation, which is more commonly used experimentally [14], current is kept constant throughout the pulse period, while voltage varies as a function of impedance. Lempka et al. have shown that current-controlled stimulation may be more effective in maintaining constant voltage distribution, as the impedance of the electrode-electrolyte interface changes drastically with time [61]. In the voltage-controlled stimulation, the voltage is kept constant while the current is allowed to vary. This method is easier to implement technically despite its lack of popularity. It is noted that some studies have shown greater efficacy of voltage-over current-controlled pulses in eliciting neural responses [62].

4. Animal models of epilepsy

Epilepsy is not one disorder, but many. Absence seizures, complex partial seizures, myotonic seizures, etc. have varying degrees of phenomenological and electrophysiological similarities, but stem from disparate etiologies. Even within one class of seizures, generalized tonic-clonic, for instance, a single pathogenic mechanism is unlikely; rather, multiple pathogenic mechanisms beget similar seizure phenotypes.

This diversity of pathogenic mechanisms is easily illustrated by surveying the variety of animal models which generate seizures. For example, both the tetanus toxin and kainate models of epilepsy produce spontaneous generalized tonic-clonic seizures, but do so differently. Kainate, for instance, causes pathological tissue changes in the hippocampus, similar to those found in mesial temporal sclerosis in humans [63], and leads to frequent tonic-clonic seizures within several weeks. Tetanus toxin, after injection, likewise produces tonic-clonic seizures, but does so without a defined histological correlate [64–66]. So, despite clear pathogenic differences, a common seizure phenotype is produced. Similar phenomenology clearly pertains to the human condition as well. This diversity of mechanisms should be kept in mind when using models to investigate the pathogenesis of epilepsy and its treatment. It is likely that seizures are the final common manifestation of several underlying pathologies. Consequently, emphasis should be placed on choosing an experimental model that closest fits each etiology, or as elegantly stated: “[T]he best material model for a cat is another, or preferably the same cat” [67].

4.1 Kindling

One of the more extensively used models of chronic temporal lobe epilepsy (TLE) is the kindling model, wherein subjects undergo daily electrical stimulation (60 Hz sine- or biphasic square-pulse waves at or greater than the after-discharge threshold [68]) to seizure-prone brain regions. Kindling is a progressive phenomenon in which electrical stimulation, initially generating brief, low-frequency electrographic after-discharges without behavioral response, develop with repeated electrical stimulation over several days into long, high-frequency after-discharges with a strong convulsive response [69–71]. After many days of kindling, the subject begins to experience complex seizures with secondary generalizations. While the progression from simple partial seizures to complex seizures is evident through stimulation in all limbic and most forebrain regions, it is most dramatic in the temporal lobe brain structure surrounding and including the amygdala.

4.2 Status epilepticus

Status epilepticus (SE) occurs when the brain remains in a protracted state of persistent seizure, and the state can be generated electrically or chemically. The SE-induced epilepsy models have at least three distinct stages of development: (1) The initial status epilepticus stage lasting 6–12 hours (2) The seizure-free latent period lasting a few days to several weeks and the (3) the final and permanent stage where the animal starts having spontaneous seizures and can be considered to be epileptic [72].

In the kainate and pilocarpine models of SE, the drug can be administered through intraperitoneal, intravenous, subcutaneous, intracerebroventricular, or intrahippocampal injections. These injections can be given either as a single large dose or as repeated smaller doses, with the latter method shown to have a lower mortality in rats [73]. The mortality rates associated with both these models are generally very high. While the mortality rate can be reduced by decreasing the dose of the administered drug, the chances of developing SE also decreases with reducing the drug dose. Alternatively, doses of benzodiazepine (an anticonvulsant) can be given to increase the survival rate of the animals, but this approach

may also lead to lowering the chance of developing SE and subsequently of having recurrent spontaneous seizures [74].

Mazarati et al. [75] have shown that SE can also be induced through electrically stimulating the perforant pathway in free-running rats. This method of inducing SE had a high survival rate (90% to 100%) if the stimulation durations are below 60 minutes. Additionally, it has been shown the SE-induced epilepsy can be developed on already kindled animals either through performing 60 minutes of high frequency stimulation of the basolateral amygdala [76, 77] or through pilocarpine injections [78].

4.3 Tetanus toxin

Tetanus toxin is one of the oldest methods of inducing chronic experimental epilepsies [79]. The model involves the stereotactic injection of a minute dose of the toxin (secreted by the bacterium *Clostridium tetani*) into the brain. Tetanus toxin is highly toxic and hence this method needs several stringent safety controls, including vaccination of the personnel involved in the procedure and proper disposal of contaminated items. The fragile nature of the toxin also requires gentle handling, as vigorous agitations can cause the chains of the toxin to separate.

The model is highly reliable with a very low mortality rate. The rate of spontaneous seizures is very high with up to 30 seizures occurring per day for a period of 2 weeks following seizure [80, 81]. About 90% of the rats gain remission after 6 to 8 weeks of the toxin injection. The model has also been associated with impairments in learning and memory, with these effects enduring indefinitely [82–84].

4.4 Genetic models

Genetic Absence Epilepsy Rats from Strasbourg (GAERS) is a genetic model of absence seizures developed by inbreeding Wistar colonies that displayed spontaneous spike-and-wave discharges. The Wistar Albino Glaxo (WAG/Rij) strain was similarly inbred in the UK and was discovered to have absence seizures [3, 85, 86]. The frequency of seizures in the GAERS strain is more than in the WAG/Rij rats, with the former displaying absence seizures every minute on average and the latter about 15 to 20 per hour. Both these models have seizure characteristics that are highly reminiscent of human absence epilepsy, thus making them valuable for studying the disease in humans. Both genetic models also offer high predictability for studying the anti-absence and adverse effects of antiepileptic drugs. Studies on these models have indicated the thalamocortical circuits to be the critical generator of absence seizures [87].

4.5. Heating/Cooling Models

The neocortical freeze lesion model in the newborn rat has been used to study the pathology of various neuronal migration disorders. This model is achieved by placing a liquid-nitrogen cooled copper cylinder (~1 mm diameter) on the exposed calvarium of newborn rats for about 8 seconds, inducing death of immature cortical neurons and a necrotic center [88]. During the first postnatal week, newly migrating cells destined for the more superficial cortical layers invade the lesion, thus mimicking neuronal migration disorders in humans. The model has high reproducibility and low mortality rate (<5%). It is mostly used *in vitro* for drug screening purposes. *In vivo* studies are less favorable since the model does not produce spontaneous seizures.

Experimental prolonged febrile seizures in immature rats are used to study human febrile seizures. Avishai Elinor et al. [89] have shown that the first year of development of the hippocampal formation in humans compares well with postnatal days 7–14 days in rodents,

making this the ideal time for eliciting febrile seizures in rats. Febrile seizures of ~24 minutes duration can be elicited by maintaining hyperthermia (40–42 °C) for about 30 minutes in rat pups. Like the neocortical freeze lesion model, this model too has high reproducibility and low mortality.

4.6. Alumina Gel Model

In rhesus monkeys, depending on where alumina gel is injected into the brain, two different types of epilepsy can be modeled. Injections into the sensorimotor cortical regions are used to model posttraumatic epilepsy, whereas injections into the temporal lobe cause complex partial seizures and neuropathological changes that mimic temporal lobe epilepsy in humans [90]. Similar to focal motor seizures in humans, the alumina gel sensorimotor model produces spontaneous focal seizures that often become generalized. Injections made into the sensorimotor cortex are well localized providing a good topographic focus for seizure initiation. Further, seizures begin about 4–8 weeks following the application of alumina gel at the sensorimotor cortex, thus giving time to analyze the neuropathological changes underlying the development of seizures.

The alumina gel model for temporal lobe epilepsy includes injections made into the hippocampus, entorhinal and perirhinal cortices, and the amygdala. Complex partial and secondary generalized seizures are observed in all cases, having marked similarities with the ictal symptoms of human temporal lobe epilepsy.

Both the sensorimotor and the temporal lobe alumina gel models suffer from high seizure variability with the subject occasionally developing status epilepticus. Further, the model is expensive causing the number of subjects involved in any project to be low. The obvious advantage of this model is the similarity between nonhuman primates and humans [90].

4.7. Penicillin

Penicillin has long been used as a model of simple partial seizures, as topical application to the brain's surface results in interictal spikes and epileptiform discharges. Initial use in the cat neocortex led to great insight into the neuronal basis of epilepsy, including initial observations about the paroxysmal depolarizing shift [91]. This method has been applied to a number of animal models, including recently the *Macaca fascicularis* [92]. Investigation into the mechanism underlying this effect led to the understanding that at low doses penicillin selectively blocks GABA-mediated inhibitory postsynaptic potentials. As penicillin diffuses into a volume of only a few square millimeters, the surrounding neurons generate increased inhibitory activity in an attempt to control seizure spread. More recently, the penicillin epilepsy model has also been developed in sheep [93].

5. Bidirectional interfaces

Electrical stimulation is a powerful and well-studied means of influencing neural tissue, and electrical recording is one of the most prominent methods for interrogating the brain's ongoing activity. Combining these two modalities offers several benefits, but also presents novel challenges.

Advantages of combining stimulation and recording include the ability to better understand the effects of stimulation by monitoring the evoked activity. This information is critical to improving stimulation paradigms, as knowledge of stimulation effects are needed to rationally direct changes in stimulation parameters. This information (the neurophysiological effects of stimulation) can also be used to better understand the basic neurophysiology of epilepsy (e.g., if stimulation alters the activity of a particular pathway, this information provides knowledge of how these pathways might be organized).

Another advantage of bidirectional interfaces is the direct improvement of treatment paradigms. This is best characterized by closed-loop systems, in which stimulation (the device's output) is altered by recorded neural activity (the device's input). Open-loop systems, like those conventionally employed in DBS for movement disorders, use a fixed stimulation schedule that is unchanged by the brain's state. That is, whether the patient is sleeping, postprandial, exercising, etc., the stimulation paradigm is identical. But because of the brain's dynamism, it is easy to envision that a stimulation protocol that adapts to these changes might be more effective.

The primary challenges of bidirectional systems derive from both the physical limitations of such systems and, paradoxically, their capabilities. The main physical limitation is the problem of stimulus artifacts, described further below. Briefly, trying to record an electrical signal, while simultaneously providing an extrinsic electrical signal, requires disentangling the extrinsic signal (stimulation) from the intrinsic signal (the neural activity). The other primary problem is the sheer number of possibilities unleashed by closed-loop stimulation. There are theoretically an infinite number of stimulation parameters such devices can use, and again an infinite number of control algorithms that transform recorded activity into changes in these stimulation parameters. Searching this space for the optimal parameters and algorithms remains, therefore, incredibly difficult. Guidance usually comes from existing empirical data and systems-level theorizing.

5.1. Stimulus Artifact

Recorded extracellular electrical signals are on the order of microvolts, whether single unit APs or LFPs. Electrical stimuli, on the other hand, are typically in the range of volts, a million-fold difference in amplitude. Therefore, recording equipment designed to operate at one range seldom works well at the other. Thus, when stimulation is amplified by the recording electronics, say at 1000 $\times$, a 5 V pulse becomes a 5000 V input. Since this exceeds the range of the electronics, they saturate at their maximal input value, often for a duration far exceeding the stimulus pulse itself. Depending on hardware filters and the amplifier's construction, this resetting can take from milliseconds to whole seconds. During this time, the amplifier's output is not indicative of any neural signal, and therefore no useful information about the brain can be extracted.

Beyond saturation of the electronics, an additional problem is the electrical waveform produced by stimuli that are non-saturating. This waveform is often treated as a deterministic response to stimulation (though it usually is not), and is superimposed upon the intrinsic neural signals.

There are three primary ways experimenters are dealing with these artifacts: different hardware, specialized software, and by changing experimental design to avoid the issue entirely.

5.1.1. Hardware workarounds—There are many methods described for isolating and preventing stimulus artifacts from corrupting neural recordings. One of the simplest is to rely on high-resolution A/D cards and low amplification to avoid saturation. This was the approach taken by the NeuroRighter closed-loop system described by Rolston et al. [2, 94]. Using 16-bit A/D cards and low amplification (160 $\times$) reduced the amount of time amplifiers remained saturated post-stimulus as compared to more complicated commercially available systems, which typically use higher gains and lower resolution A/D cards. A further advance was attained by conducting most filtering digitally, within software. Hardware filters tend to induce ringing and store saturating charges, leading to longer stimulus artifacts. Because computers are powerful enough to conduct real-time digital filtering, analog filters are unnecessary beyond anti-aliasing filters. Moreover, digital filters are rapidly customizable,

generally in real-time using the recording software. Additionally, storing unfiltered data allows the digital filters to be changed after the experiment, so that different analytical techniques can be employed.

Because of these changes, the NeuroRighter system had artifacts lasting <1 ms, compared to 5 ms to 1.5 seconds for a commercial system (with the range dictated by the analog filters employed) [94]. Moreover, because the NeuroRighter system attained these advances by reducing the required hardware, the custom system cost 1/10th the price of an equivalent commercial system [94].

Another method to prevent artifacts is to physically disconnect the recording electrodes from the amplifiers during the stimulus pulse, preventing the signal from reaching the amplifiers and saturating them. This disconnection usually involves a reconnection to either ground or a sample-and-hold circuit. Using high-speed switches (with switching times on the order of microseconds, far faster than the physiological signals recorded by extracellular electrodes), the circuit will disconnect the input to the recording amplifier from the electrode and connect it to a source which stores the most recently recorded voltage (say, a few mV). When the stimulus pulse is complete, the electrode is reconnected to the recording amplifier. Using a sample-and-hold circuit rather than connecting to ground prevents an artifact induced by reconnecting the amplifier to an electrode with some DC offset, which is effectively seen by the amplifier's analog filters as another stimulus.

5.1.2. Software workarounds—After the data is acquired, some artifacts can be minimized digitally. These algorithms run from the simple, like template subtraction, to the complex, e.g., recursive methods like SALPA[95].

Template subtraction works on the basis of recording multiple responses to a stimulation pulse [96]. These responses are then averaged to create a template for the stimulation artifact, which is then subtracted from the recorded waveform at the time of each stimulus onset. This method assumes that the stimulation artifact's waveform is static. However, hysteresis in the recording electronics and at the electrode-tissue interface can lead to changes in artifact shape over time. These changes are most acute, in our experience, at the onset of stimulation trains or when stimulating with multiple electrodes in an interlaced pattern (e.g., electrode 1, then 2, then back to 1).

The dynamics of the stimulus artifact can be compensated somewhat by scaling the template to maximize its fit to the artifact to be cancelled. This approach was employed by Wichmann et al. [97]. The limitation, however, is if the waveform changes shape in addition to amplitude, during experiments. In this case, scaling will be unable to adapt to artifact changes.

More complicated methods rely on curve fitting, which entails fitting an exponential or polynomial function to each detected stimulus artifact [98]. This method has the advantage of being adaptable to changes in the artifact, and is limited enough in its possible curvature that it will not cancel high frequency components like APs. On the other hand, using a particular function (e.g., exponential) assumes the artifact's shape can be completely captured by such a function. This is not always true, and poor fits lead to residual artifact.

5.1.3. Experimental workarounds—Experiments can also be designed so as to avoid stimulation artifacts. For instance, instead of recording activity during stimulation epochs, when artifacts interfere with the recorded signal, one could stimulate, stop stimulation, then record the stimulation's after-effects [99]. In certain clinical situations, in fact, these after-effects might actually be the most relevant data to analyze. Vagus nerve stimulation [100],

for example, features stimulation-free “off” times lasting several minutes, following brief “on” phases of active stimulation lasting less than a minute.

5.2. Control Algorithms

When integrating stimulation and recording into a closed-loop system, an algorithm must be chosen to translate recorded signals into the stimulator's output. In order for a closed-loop system to be truly closed-loop, it is necessary that stimulation affect the recorded signals. If there is no effect of stimulation, then the system is actually open-loop. Finding signals for control typically requires extracting features from the raw recorded data.

5.2.1. Signal features—A wide range of signal features have been used to extract seizure-related information from extracellular neural recordings. All features fall into one of two categories: discrete and continuous. Discrete features are events, like APs, interictal spikes, seizures, and other time-limited features of the signal that are either present or not (i.e., binary). Continuous features are time-varying signals that can be computed for any time-point of the recorded signal. Examples are signal power [101], accumulated energy [102], nonlinear energy [103], entropy [101], correlation dimension [104], coherence [81], and others.

Importantly, these two categories are not always clearly separated. On one hand, most event detection requires some sort of filtering or extraction of a time-varying signal before ultimately searching for particular events. AP detection, for example, uses high-pass filtering of the data prior to finding spikes [94], and often some sort of digital referencing to reduce common-mode noise [105]. On the other hand, continuous signals can sometimes be computed from discrete events. As an example, Wagenaar et al. [106] used tuning based on AP firing rate to suppress epileptiform events in neural cell cultures. This firing rate is a continuous-time signal, computed by first extracting APs from the raw data [107].

5.2.2. Responsive stimulation—Just as the features used for closed-loop stimulation can be of two kinds, discrete or continuous, so can the stimulation sequences. Responsive stimulation is the analog of the discrete, event-based features found in recordings. In responsive stimulation, stimulation sequences are triggered by the detection of a particular event. This event can be a detected seizure, as done in the NeuroPace Responsive Neurostimulation (RNS) trial, or something more abstract—the crossing of an amplitude threshold in the power spectrum, the detection of interictal spiking, changes in activity coherence, etc.

5.2.3. State control—The counterpart to responsive stimulation is state control [108]. In this method, stimulation is continuous, but altered by ongoing activity. This is in the realm of the more traditional PID-type control systems [109], where output (stimulation, in this case) is a continuous function determined by the input (electrical recordings). Some examples of this are using firing rate to control stimulation amplitude when suppressing epileptiform bursts in culture [106] and using an adapting low-frequency electric field to suppress seizures in hippocampal slices [57].

6. Stimulation pathways and examples

While optimal neural targets for electrical stimulation remain unknown, the diversity of anatomical and functional connections for separate brain structures has led to a growing array of theoretically motivated stimulation sites, ranging from subcortical nuclei to direct cortical stimulation. Subcortical nuclei are particularly attractive due to their widespread projections, offering a potential means for affecting large areas of the brain.

6.1. Limbic

The prevalence of mesial temporal lobe epilepsy is one of the prime arguments for stimulating the limbic cortex to suppress seizures. Various targets within the circuit of Papez have been tried.

6.1.1. Hippocampus—Several groups have conducted trials of direct stimulation of the hippocampus. Velasco et al. [110] studied two groups of patients: one with subacute (2–3 weeks) electrical stimulation of the hippocampus at 130 Hz (8 patients) and the other with chronic (3 months) stimulation (3 patients). In the subacute group, the average number of seizures declined from the time of implantation to the end of the experiment. Velasco et al. [110] also noted a decrease in the average number of interictal spikes. However, the authors did not report baseline seizure and interictal spike rates, so true efficacy is unknown. Furthermore, the data is a population average, rather than examined by patient. The chronic group (3 months of hippocampal stimulation) displayed a trend toward reduced seizure counts and interictal spike rates, but without statistical significance. Overall, this small, uncontrolled trial offers provocative evidence for an effect of hippocampal stimulation, but is an insufficient basis upon which to make a recommendation.

Boon et al. [111] also conducted an open label trial for hippocampal stimulation at 130 Hz in 10 patients. With a follow-up of 12–52 months, 1 patient was seizure-free, 6 patients had a reduction of >50% in seizure frequency, 2 had a reduction of 30–49%, and 1 had no response. This was an encouraging result, which drove the case for randomized clinical trials.

Unfortunately, in the one double-blinded trial to date, using only 4 patients, there was no statistically significant effect of hippocampal DBS [112]. However, this small study did show a 15% reduction in seizure frequency. Furthermore, the stimulation frequency of 190 Hz was decidedly different from that used by Velasco et al. [110] and Boon et al. [111], which may have led to the differential results.

6.1.2. Amygdala—The amygdala has major importance in models of epilepsy, as it is one of the prime targets for kindling. Kindling is the phenomenon where repeated electrical stimulation ultimately produces seizures in animal models [68]. But perhaps because of its role in kindling, direct stimulation of the amygdala has not been studied well in humans. There is a large body of evidence in animal studies, however, which suggests that low frequency or DC (direct current) stimulation might in fact suppress seizures. Weiss et al. [113] showed that 15 minute daily sessions of 10 μ A DC stimulation of the amygdala “quenched” a rat kindling model. That is, the seizure threshold in these kindled animals increased, with the effects lasting more than 30 days after DC stimulation ended. Similar observations have been made by Goodman [114] and Velisek [115].

6.1.3. Mammillothalamic tract and mammillary bodies—In 1984, Mirski showed that sectioning of the mammillothalamic tract guinea pigs prevented pentylentetrazol-induced seizures from spreading [116]. Later, he showed in the rat that electrical stimulation of the mammillary bodies at 100 Hz increased seizure thresholds [117], i.e. mammillary body stimulation made it more difficult to induce seizures in rodents. No human trials of mammillary body or mammillothalamic tract stimulation have been reported in peer-reviewed journals as of this time.

6.1.4. Anterior nucleus of the thalamus—The anterior nucleus of the thalamus, the target of the mammillothalamic tract and one of the inputs to the cingulate cortex, is another

well-studied component of the circuit of Papez, undergoing intense investigation as a stimulation target for refractory epilepsy. It is reviewed elsewhere in this issue.

6.2. Basal ganglia

Several groups have attempted stimulating various structures within the basal ganglia to suppress seizures, including the subthalamic nucleus (STN), substantia nigra pars reticulata (SNr), and caudate nucleus.

6.2.1. Subthalamic nucleus (STN)—Stimulation of the STN bilaterally at 130 Hz was shown to suppress the spontaneous seizures of GAERS rats (a genetic model of absence seizures) by Vercueil et al. in the 1990s [118]. Since then, several uncontrolled clinical trials have attempted stimulating the STN to prevent seizures in humans with modest results [119–121]. No randomized or large clinical trials have yet been reported.

6.2.2. Substantia nigra pars reticulata (SNr)—The SNr has been a target of research for decades. Part of this attraction may stem from work by Karen Gale and her colleagues in the early 1980s [122]. In her studies, she showed that local injections of the GABA agonist muscimol into the substantia nigra prevented seizures evoked by pentylenetetrazol or bicuculline. However, these conclusions were refuted in later work by Mirski et al. [123] and Ono et al [124].

Nevertheless, experiments show a potential role for SNr stimulation. Velisek et al. [125], in particular, showed that bilateral stimulation of the SNr in young rats (postnatal day 15) suppressed flurothyl-induced clonic and tonic-clonic seizures. In adult rats, only stimulation of the anterior portion of the SNr suppressed seizures, and then only clonic, not tonic-clonic.

6.2.3. Caudate nucleus—Chkhenkeli began experimenting with caudate stimulation in humans as early as the 1970s in Eastern Europe [126]. In more recent work, Chkhenkeli et al. showed that low frequency (4–6 Hz) stimulation of the caudate reliably suppressed epileptiform activity in human subjects [127]. Studies in the alumina gel non-human primate model of epilepsy also showed ameliorative effects of stimulation, though at the higher frequency of 100 Hz rather than Chkhenkeli's 4–6 Hz.

6.3. Cerebellum

Stimulation of the cerebellum to suppress seizures has been attempted in humans since the 1970s, when Irving S. Cooper reported his experience [128–131]. However, his data and conclusions were frequently called into question with by other researchers, particularly in double-blind trials [132–134]. Cooper recounts these refutations with chagrin in his memoirs [135]. Most recently, a small double-blind trial was conducted in Mexico by Velasco et al. [136]. In this study, 10 Hz stimulation of the cerebellum reduced seizures by 33% in 3 patients with generalized tonic-clonic seizures.

6.4. Locus coeruleus (LC)

Stimulation of the locus coeruleus (LC), the principle site of production of norepinephrine in the brainstem, was attempted in the 1970s by Libet and colleagues [137]. They implanted two patients with epilepsy and one with cerebral palsy and measured levels of 3-methoxy-4-hydroxyphenylethyleneglycol to verify that the activation of the LC. While a notable reduction in spasticity was achieved, the reduction in seizures was not robust enough to be supported statistically [137].

7. Conclusion

A common set of issues surrounds every attempt to use electrical stimulation to treat epilepsy. What type of electrodes should be used? Where should they be located? What stimulation parameters will be most effective? Which groups of patients will most likely benefit?

Currently, these questions have no definitive answers. But it is our hope that continued research will ultimately provide us the tools to offer rational therapy to our patients. Extracellular recordings will continue to provide insight into the mechanism of stimulation, bidirectional interfaces will offer new means of interacting with nervous tissue in complex and nuanced ways, and animal models will continue illuminating which modes of manipulating the brain are most promising for future experiments in humans.

Acknowledgments

This work was funded by the Wallace H. Coulter Foundation, the Epilepsy Research Foundation, a Neurology/Biomedical Engineering seed grant from Emory University and Georgia Tech, a University Research Council grant from Emory University, the National Institute of General Medical Sciences (NIGMS) for JDR and NGL (GM08169), and, from the National Institute of Neurological Disorders and Stroke (NINDS), a Ruth L. Kirschstein National Research Service Award to JDR (NS060392), a translational research fellowship to JDR (NS007480), a career development award to REG (NS046322), and a research grant to REG (NS054809). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

1. Lockman J, Fisher RS. Therapeutic brain stimulation for epilepsy. *Neurol Clin.* 2009; 27(4):1031–40. [PubMed: 19853222]
2. Rolston JD, Gross RE, Potter SM. Closed-loop, open-source electrophysiology. *Front Neurosci.* 2010; 4
3. Amirmovin R, et al. Experience with microelectrode guided subthalamic nucleus deep brain stimulation. *Neurosurgery.* 2006; 58(1 Suppl):ONS96–102. discussion ONS96–102. [PubMed: 16543878]
4. Cogan SF. Neural stimulation and recording electrodes. *Annu Rev Biomed Eng.* 2008; 10:275–309. [PubMed: 18429704]
5. Desai SA, et al. Improving impedance of implantable microwire multi-electrode arrays by ultrasonic electroplating of durable platinum black. *Front Neuroengineering.* 2010; 3:5.
6. Lewicki MS. A review of methods for spike sorting: the detection and classification of neural action potentials. *Network.* 1998; 9(4):R53–78. [PubMed: 10221571]
7. Stark E, Abeles M. Predicting movement from multiunit activity. *J Neurosci.* 2007; 27(31):8387–94. [PubMed: 17670985]
8. Katzner S, et al. Local origin of field potentials in visual cortex. *Neuron.* 2009; 61(1):35–41. [PubMed: 19146811]
9. Berens P, et al. Comparing the feature selectivity of the gamma-band of the local field potential and the underlying spiking activity in primate visual cortex. *Front Syst Neurosci.* 2008; 2:2. [PubMed: 18958246]
10. Kreiman G, et al. Object selectivity of local field potentials and spikes in the macaque inferior temporal cortex. *Neuron.* 2006; 49(3):433–45. [PubMed: 16446146]
11. Liu J, Newsome WT. Local field potential in cortical area MT: stimulus tuning and behavioral correlations. *J Neurosci.* 2006; 26(30):7779–90. [PubMed: 16870724]
12. Leuthardt EC, et al. A brain-computer interface using electrocorticographic signals in humans. *J Neural Eng.* 2004; 1(2):63–71. [PubMed: 15876624]
13. Smith SJ. EEG in the diagnosis, classification, and management of patients with epilepsy. *J Neurol Neurosurg Psychiatry.* 2005; 76(Suppl 2):ii2–7. [PubMed: 15961864]

14. Merrill DR, Bikson M, Jefferys JGR. Electrical stimulation of excitable tissue: design of efficacious and safe protocols. *Journal of Neuroscience Methods*. 2005; 141(2):171–198. [PubMed: 15661300]
15. Loeb GE, Peck RA, Martyniuk J. Toward the ultimate metal microelectrode. *J Neurosci Methods*. 1995; 63(1–2):175–83. [PubMed: 8788062]
16. Gray CM, et al. Tetrodes markedly improve the reliability and yield of multiple single-unit isolation from multi-unit recordings in cat striate cortex. *J Neurosci Methods*. 1995; 63(1–2):43–54. [PubMed: 8788047]
17. Bartels J, et al. Neurotrophic electrode: method of assembly and implantation into human motor speech cortex. *J Neurosci Methods*. 2008; 174(2):168–76. [PubMed: 18672003]
18. Hoogerwerf AC, Wise KD. A three-dimensional microelectrode array for chronic neural recording. *IEEE Trans Biomed Eng*. 1994; 41(12):1136–46. [PubMed: 7851915]
19. Patterson Wr Fau - Song, Y-K., et al. A microelectrode/microelectronic hybrid device for brain implantable neuroprosthesis applications. p. 0018-9294.Print
20. Guo L Fau - DeWeerth, SP.; DeWeerth, SP. High-density stretchable electronics: toward an integrated multilayer composite. p. 1521-4095.Electronic
21. Guo L Fau - Deweerth, SP.; Deweerth, SP. PDMS-based conformable microelectrode arrays with selectable novel 3-D microelectrode geometries for surface stimulation and recording. p. 1557-170X.Print
22. Behrens E Fau - Zentner, J., et al. Subdural and depth electrodes in the presurgical evaluation of epilepsy. p. 0001-6268.Print
23. Bronstein Jm Fau - Tagliati, M., et al. Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. p. 1538-3687.Electronic
24. Fisher R Fau - Salanova, V., et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. p. 1528-1167.Electronic
25. Sun Ft Fau - Morrell, MJ.; Morrell Mj Fau - Wharen, RE., Jr.; Wharen, RE, Jr.. Responsive cortical stimulation for the treatment of epilepsy. p. 1933-7213.Print
26. Butson Cr Fau - Cooper, SE., et al. Patient-specific analysis of the volume of tissue activated during deep brain stimulation. p. 1053-8119.Print
27. Grill WM, Wei XF. High efficiency electrodes for deep brain stimulation. *Conf Proc IEEE Eng Med Biol Soc*. 2009; 2009:3298–301. [PubMed: 19964297]
28. Worrell GA, et al. High-frequency oscillations in human temporal lobe: simultaneous microwire and clinical macroelectrode recordings. *Brain*. 2008; 131(Pt 4):928–37. [PubMed: 18263625]
29. Yeh HS, Taha JM, Tobler WD. Implantation of intracerebral depth electrodes for monitoring seizures using the Pelorus stereotactic system guided by magnetic resonance imaging. Technical note. *J Neurosurg*. 1993; 78(1):138–41. [PubMed: 8416232]
30. Wyler AR, et al. Subdural strip electrodes for localizing epileptogenic foci. *J Neurosurg*. 1984; 60(6):1195–200. [PubMed: 6726363]
31. Van Gompel JJ, et al. Phase I trial: safety and feasibility of intracranial electroencephalography using hybrid subdural electrodes containing macro- and microelectrode arrays. *Neurosurg Focus*. 2008; 25(3):E23. [PubMed: 18759625]
32. Ranck JB Jr. Which elements are excited in electrical stimulation of mammalian central nervous system: a review. *Brain Res*. 1975; 98(3):417–40. [PubMed: 1102064]
33. Histed MH, Bonin V, Reid RC. Direct Activation of Sparse, Distributed Populations of Cortical Neurons by Electrical Microstimulation. *Neuron*. 2009; 63(4):508–522. [PubMed: 19709632]
34. Tehovnik EJ. Electrical stimulation of neural tissue to evoke behavioral responses. *J Neurosci Methods*. 1996; 65(1):1–17. [PubMed: 8815302]
35. Boon P, et al. Electrical Stimulation for the Treatment of Epilepsy. *Neurotherapeutics*. 2009; 6(2): 218–227. [PubMed: 19332313]
36. Skarpaas TL, Morrell MJ. Intracranial Stimulation Therapy for Epilepsy. *Neurotherapeutics*. 2009; 6(2):238–243. [PubMed: 19332315]
37. Benabid AL. What the future holds for deep brain stimulation. *Expert Review of Medical Devices*. 2007; 4(6):895–903. [PubMed: 18035954]

38. Miocinovic S, et al. Computational Analysis of Subthalamic Nucleus and Lenticular Fasciculus Activation During Therapeutic Deep Brain Stimulation. *J Neurophysiol.* 2006; 96(3):1569–1580. [PubMed: 16738214]
39. Lafreniere-Roula M, et al. Microstimulation-induced inhibition as a tool to aid targeting the ventral border of the subthalamic nucleus. *Journal of Neurosurgery.* 2009; 111(4):724–728. [PubMed: 19408978]
40. Lian J, et al. Local Suppression of Epileptiform Activity by Electrical Stimulation in Rat Hippocampus In Vitro. *The Journal of Physiology.* 2003; 547(2):427–434. [PubMed: 12562909]
41. Fisher R, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia.* 2010; 51(5):899–908. [PubMed: 20331461]
42. Sunderam S, et al. Toward rational design of electrical stimulation strategies for epilepsy control. *Epilepsy & Behavior.* 2010; 17(1):6–22. [PubMed: 19926525]
43. Kuncel AM, Grill WM. Selection of stimulus parameters for deep brain stimulation. *Clin Neurophysiol.* 2004; 115(11):2431–41. [PubMed: 15465430]
44. Voges J, et al. Bilateral high-frequency stimulation in the subthalamic nucleus for the treatment of Parkinson disease: correlation of therapeutic effect with anatomical electrode position. *Journal of Neurosurgery.* 2002; 96(2):269–279. [PubMed: 11838801]
45. Gradinaru V, et al. Optical Deconstruction of Parkinsonian Neural Circuitry. *Science.* 2009; 324(5925):354–359. [PubMed: 19299587]
46. Ghai RS, Bikson M, Durand DM. Effects of Applied Electric Fields on Low-Calcium Epileptiform Activity in the CA1 Region of Rat Hippocampal Slices. *Journal of Neurophysiology.* 2000; 84(1): 274–280. [PubMed: 10899202]
47. Bikson M, et al. Suppression of epileptiform activity by high frequency sinusoidal fields in rat hippocampal slices. *The Journal of Physiology.* 2001; 531(1):181–191. [PubMed: 11179402]
48. Beurrier C, et al. High-Frequency Stimulation Produces a Transient Blockade of Voltage-Gated Currents in Subthalamic Neurons. *Journal of Neurophysiology.* 2001; 85(4):1351–1356. [PubMed: 11287459]
49. Zhong X-L, et al. Deep brain stimulation for epilepsy in clinical practice and in animal models. *Brain Research Bulletin.* In Press, Uncorrected Proof.
50. Gerges M, et al. Frequency- and amplitude-transitioned waveforms mitigate the onset response in high-frequency nerve block. *Journal of Neural Engineering.* 2010; 7(6):066003. [PubMed: 20966536]
51. Jensen AL, Durand DM. High frequency stimulation can block axonal conduction. *Experimental Neurology.* 2009; 220(1):57–70. [PubMed: 19660453]
52. Theodore WH, Fisher RS. Brain stimulation for epilepsy. *The Lancet Neurology.* 2004; 3(2):111–118.
53. Durand, DM. Control of seizure activity by electrical stimulation: Effect of frequency. *Engineering in Medicine and Biology Society, 2009. EMBC 2009. Annual International Conference of the IEEE;* 2009.
54. Schrader LM, et al. Low frequency electrical stimulation through subdural electrodes in a case of refractory status epilepticus. *Clinical Neurophysiology.* 2006; 117(4):781–788. [PubMed: 16458067]
55. Kile KB, Tian N, Durand DM. Low frequency stimulation decreases seizure activity in a mutation model of epilepsy. *Epilepsia.* 2010; 51(9):1745–1753. [PubMed: 20659150]
56. Andrews RJ. Neuromodulation. *Annals of the New York Academy of Sciences.* 2010; 1199(1): 204–211. [PubMed: 20633126]
57. Gluckman BJ, et al. Adaptive electric field control of epileptic seizures. *J Neurosci.* 2001; 21(2): 590–600. [PubMed: 11160438]
58. Foutz TJ, McIntyre CC. Evaluation of novel stimulus waveforms for deep brain stimulation. *Journal of Neural Engineering.* 2010; 7(6):066008. [PubMed: 21084732]
59. McIntyre CC, Grill WM. Extracellular Stimulation of Central Neurons: Influence of Stimulus Waveform and Frequency on Neuronal Output. *Journal of Neurophysiology.* 2002; 88(4):1592–1604. [PubMed: 12364490]

60. Histed MH, Bonin V, Reid RC. Direct activation of sparse, distributed populations of cortical neurons by electrical microstimulation. *Neuron*. 2009; 63(4):508–22. [PubMed: 19709632]
61. Lempka SF, et al. In vivo impedance spectroscopy of deep brain stimulation electrodes. *J Neural Eng*. 2009; 6(4):46001.
62. Wagenaar DA, Pine J, Potter SM. Effective parameters for stimulation of dissociated cultures using multi-electrode arrays. *J Neurosci Methods*. 2004; 138(1–2):27–37. [PubMed: 15325108]
63. Ben-Ari Y. Limbic seizure and brain damage produced by kainic acid: mechanisms and relevance to human temporal lobe epilepsy. *Neuroscience*. 1985; 14(2):375–403. [PubMed: 2859548]
64. Mellanby J, et al. Epileptiform syndrome in rats produced by injecting tetanus toxin into the hippocampus. *J Neurol Neurosurg Psychiatry*. 1977; 40(4):404–14. [PubMed: 874516]
65. Jefferys JG, et al. Neuropathology of the chronic epileptic syndrome induced by intrahippocampal tetanus toxin in rat: preservation of pyramidal cells and incidence of dark cells. *Neuropathol Appl Neurobiol*. 1992; 18(1):53–70. [PubMed: 1579200]
66. Benke TA, Swann J. The tetanus toxin model of chronic epilepsy. *Adv Exp Med Biol*. 2004; 548:226–38. [PubMed: 15250597]
67. Rosenbluth A, Weiner N. The Role of Models in Science. *Philosophy of Science*. 1945; 12:316–321.
68. Pitkanen, A.; Schwartzkroin, PA.; Moshé, SL. *Models of Seizures and Epilepsy*. Elsevier Academic Press; Burlington, MA: 2006.
69. Goddard GV, McIntyre DC, Leech CK. A permanent change in brain function resulting from daily electrical stimulation. *Exp Neurol*. 1969; 25(3):295–330. [PubMed: 4981856]
70. McIntyre DC. Differential amnesic effect of cortical vs. amygdaloid elicited convulsions in rats. *Physiol Behav*. 1970; 5(7):747–53. [PubMed: 5535478]
71. McIntyre DC, Saari M, Pappas BA. Potentiation of amygdala kindling in adult or infants rats by injections of 6-hydroxydopamine. *Exp Neurol*. 1979; 63(3):527–44. [PubMed: 428481]
72. Dudek Fe Fau - Hellier, JL., et al. The course of cellular alterations associated with the development of spontaneous seizures after status epilepticus. p. 0079-6123.Print
73. Hellier JI Fau - Patrylo, PR., et al. Recurrent spontaneous motor seizures after repeated low-dose systemic treatment with kainate: assessment of a rat model of temporal lobe epilepsy. p. 0920-1211.Print
74. Lemos T, Cavaleiro EA. Suppression of pilocarpine-induced status epilepticus and the late development of epilepsy in rats. *Experimental Brain Research*. 1995; 102(3):423–428.
75. Mazarati AM, et al. Self-sustaining status epilepticus after brief electrical stimulation of the perforant path. *Brain Res*. 1998; 801(1–2):251–3. [PubMed: 9729413]
76. McIntyre DC, Nathanson D, Edson N. A new model of partial status epilepticus based on kindling. *Brain Res*. 1982; 250(1):53–63. [PubMed: 7139321]
77. McIntyre DC, Stokes KA, Edson N. Status epilepticus following stimulation of a kindled hippocampal focus in intact and commissurotomy rats. *Exp Neurol*. 1986; 94(3):554–70. [PubMed: 3780907]
78. Buterbaugh GG, Michelson HB, Keyser DO. Status epilepticus facilitated by pilocarpine in amygdala-kindled rats. *Exp Neurol*. 1986; 94(1):91–102. [PubMed: 3758290]
79. Roux E, Borrel A. Tétanos cérébral et immunité contre le tétanos. *Ann Inst Pasteur*. 1898; 4:225–239.
80. Jefferys JG, Borck C, Mellanby J. Chronic focal epilepsy induced by intracerebral tetanus toxin. *Ital J Neurol Sci*. 1995; 16(1–2):27–32. [PubMed: 7642348]
81. Rolston JD, et al. Spontaneous and evoked high-frequency oscillations in the tetanus toxin model of epilepsy. *Epilepsia*. 2010; 51(11):2289–96. [PubMed: 20946126]
82. George G, Mellanby J. Memory deficits in an experimental hippocampal epileptiform syndrome in rats. *Exp Neurol*. 1982; 75(3):678–89. [PubMed: 7060696]
83. Jefferys JG, Williams SF. Physiological and behavioural consequences of seizures induced in the rat by intrahippocampal tetanus toxin. *Brain*. 1987; 110(Pt 2):517–32. [PubMed: 3567534]

84. Mellanby J, et al. The effect of experimental epilepsy induced by injection of tetanus toxin into the amygdala of the rat on eating behaviour and response to novelty. *Behav Brain Res.* 1999; 100(1–2):113–22. [PubMed: 10212058]
85. van Luijckelaar ELJM, Coenen AML. Two types of electrocortical paroxysms in an inbred strain of rats. *Neuroscience Letters.* 1986; 70(3):393–397. [PubMed: 3095713]
86. Vergnes M, et al. Spontaneous paroxysmal electroclinical patterns in rat: A model of generalized non-convulsive epilepsy. *Neuroscience Letters.* 1982; 33(1):97–101. [PubMed: 6818498]
87. Danober L, et al. Pathophysiological mechanisms of genetic absence epilepsy in the rat. *Progress in Neurobiology.* 1998; 55(1):27–57. [PubMed: 9602499]
88. Dvořák K, Feit J, Juránková Z. Experimentally induced focal microgyria and status verrucosus deformis in rats — Pathogenesis and interrelation histological and autoradiographical study. *Acta Neuropathologica.* 1978; 44(2):121–129. [PubMed: 716839]
89. Avishai-Eliner S, Fau - Brunson, KL., et al. Stressed-out, or in (utero)?. p. 0166-2236. Print
90. Ribak CE, et al. Alumina gel injections into the temporal lobe of rhesus monkeys cause complex partial seizures and morphological changes found in human temporal lobe epilepsy. *J Comp Neurol.* 1998; 401(2):266–90. [PubMed: 9822153]
91. Fisher RS. Animal models of the epilepsies. *Brain Research Reviews.* 14(3):245–278.
92. Blauwblomme T, et al. Cortical Stimulation of the Epileptogenic Zone for the Treatment of Focal Motor Seizures: An Experimental Study in the Non Human Primate. *Neurosurgery.* 2010
93. Stypulkowski PH, Giftakis JE, Billstrom TM. Development of a large animal model for investigation of deep brain stimulation for epilepsy. *Stereotact Funct Neurosurg.* 2011; 89(2):111–22. [PubMed: 21336007]
94. Rolston JD, Gross RE, Potter SM. A low-cost multielectrode system for data acquisition enabling real-time closed-loop processing with rapid recovery from stimulation artifacts. *Frontiers in Neuroengineering.* 2009; 2:12. [PubMed: 19668698]
95. Wagenaar DA, Potter SM. Real-time multi-channel stimulus artifact suppression by local curve fitting. *J Neurosci Methods.* 2002; 120(2):113–20. [PubMed: 12385761]
96. Hashimoto T, Elder CM, Vitek JL. A template subtraction method for stimulus artifact removal in high-frequency deep brain stimulation. *J Neurosci Methods.* 2002; 113(2):181–6. [PubMed: 11772439]
97. Wichmann T. A digital averaging method for removal of stimulus artifacts in neurophysiologic experiments. *J Neurosci Methods.* 2000; 98(1):57–62. [PubMed: 10837871]
98. Erez Y, et al. Generalized framework for stimulus artifact removal. *J Neurosci Methods.* 2010; 191(1):45–59. [PubMed: 20542059]
99. Benazzouz A, et al. Responses of substantia nigra pars reticulata and globus pallidus complex to high frequency stimulation of the subthalamic nucleus in rats: electrophysiological data. *Neurosci Lett.* 1995; 189(2):77–80. [PubMed: 7609923]
100. Navas M, et al. Treatment of refractory epilepsy in adult patients with right-sided vagus nerve stimulation. *Epilepsy Res.* 2010; 90(1–2):1–7. [PubMed: 20488666]
101. Greene BR, et al. A comparison of quantitative EEG features for neonatal seizure detection. *Clin Neurophysiol.* 2008; 119(6):1248–61. [PubMed: 18381249]
102. Guo L, et al. Automatic epileptic seizure detection in EEGs based on line length feature and artificial neural networks. *Neurosci Methods.* 2010; 191(1):101–9.
103. D'Alessandro M, et al. Epileptic seizure prediction using hybrid feature selection over multiple intracranial EEG electrode contacts: a report of four patients. *IEEE Trans Biomed Eng.* 2003; 50(5):603–15. [PubMed: 12769436]
104. Elger CE, Lehnertz K. Seizure prediction by non-linear time series analysis of brain electrical activity. *Eur J Neurosci.* 1998; 10(2):786–9. [PubMed: 9749744]
105. Rolston, JD.; Gross, RE.; Potter, SM. Common Median Referencing for Improved Action Potential Detection with Multielectrode Arrays. 31st Annual International Conference of the IEEE Engineering in Medicine and Biology Society; Minneapolis, MN. 2009.
106. Wagenaar DA, et al. Controlling bursting in cortical cultures with closed-loop multi-electrode stimulation. *J Neurosci.* 2005; 25(3):680–8. [PubMed: 15659605]

107. Dayan, P.; Abbott, LF. Computational neuroscience. Massachusetts Institute of Technology Press; Cambridge, Mass.: 2001. Theoretical neuroscience: computational and mathematical modeling of neural systems; p. xvp. 460
108. Schachter SC, et al. Advances in the application of technology to epilepsy: the CIMIT/NIO Epilepsy Innovation Summit. *Epilepsy Behav.* 2009; 16(1):3–46. [PubMed: 19780225]
109. Åström, KJ.; Murray, RM. Feedback systems : an introduction for scientists and engineers. Princeton University Press; Princeton: 2008. p. xii-396.
110. Velasco AL, et al. Subacute and chronic electrical stimulation of the hippocampus on intractable temporal lobe seizures: preliminary report. *Arch Med Res.* 2000; 31(3):316–28. [PubMed: 11036183]
111. Boon P, et al. Deep brain stimulation in patients with refractory temporal lobe epilepsy. *Epilepsia.* 2007; 48(8):1551–60. [PubMed: 17726798]
112. Tellez-Zenteno JF, et al. Hippocampal electrical stimulation in mesial temporal lobe epilepsy. *Neurology.* 2006; 66(10):1490–4. [PubMed: 16554495]
113. Weiss SR, et al. Quenching revisited: low level direct current inhibits amygdala-kindled seizures. *Exp Neurol.* 1998; 154(1):185–92. [PubMed: 9875279]
114. Goodman JH, Berger RE, Tcheng TK. Preemptive low-frequency stimulation decreases the incidence of amygdala-kindled seizures. *Epilepsia.* 2005; 46(1):1–7. [PubMed: 15660762]
115. Velisek L, Veliskova J, Stanton PK. Low-frequency stimulation of the kindling focus delays basolateral amygdala kindling in immature rats. *Neurosci Lett.* 2002; 326(1):61–3. [PubMed: 12052538]
116. Mirski MA, Ferrendelli JA. Interruption of the mammillothalamic tract prevents seizures in guinea pigs. *Science.* 1984; 226(4670):72–4. [PubMed: 6433485]
117. Mirski MA, Fisher RS. Electrical stimulation of the mammillary nuclei increases seizure threshold to pentylenetetrazol in rats. *Epilepsia.* 1994; 35(6):1309–16. [PubMed: 7988525]
118. Vercueil L, et al. High-frequency stimulation of the sub-thalamic nucleus suppresses absence seizures in the rat: comparison with neurotoxic lesions. *Epilepsy Research.* 1998; 31(1):39–46. [PubMed: 9696299]
119. Lee KJ, Jang KS, Shon YM. Chronic deep brain stimulation of subthalamic and anterior thalamic nuclei for controlling refractory partial epilepsy. *Acta Neurochir Suppl.* 2006; 99:87–91. [PubMed: 17370771]
120. Handforth A, DeSalles AAF, Krah SE. Deep Brain Stimulation of the Subthalamic Nucleus as Adjunct Treatment for Refractory Epilepsy. 2006:1239–1241.
121. Benabid AL, et al. Antiepileptic effect of high-frequency stimulation of the subthalamic nucleus (corpus luyi) in a case of medically intractable epilepsy caused by focal dysplasia: a 30-month follow-up: technical case report. *Neurosurgery.* 2002; 50(6):1385–91. discussion 1391–2. [PubMed: 12015863]
122. Iadarola MJ, Gale K. Substantia nigra: site of anticonvulsant activity mediated by gamma-aminobutyric acid. *Science.* 1982; 218(4578):1237–40. [PubMed: 7146907]
123. Mirski MA, McKeon AC, Ferrendelli JA. Anterior thalamus and substantia nigra: two distinct structures mediating experimental generalized seizures. *Brain Res.* 1986; 397(2):377–80. [PubMed: 3801876]
124. Ono K, Wada JA. Facilitation of premotor cortical seizure development by intranigral muscimol. *Brain Res.* 1987; 405(1):183–6. [PubMed: 3032348]
125. Velisek L, Veliskova J, Moshe SL. Electrical stimulation of substantia nigra pars reticulata is anticonvulsant in adult and young male rats. *Exp Neurol.* 2002; 173(1):145–52. [PubMed: 11771947]
126. Chkhenkeli SA. The inhibitory influence of the nucleus caudatus electrostimulation on the human's amygdalar and hippocampal activity at temporal lobe epilepsy. *Bulletin of the Georgia Academy of Sciences.* 1978; 4/6:406–11.
127. Chkhenkeli SA, Chkhenkeli IS. Effects of therapeutic stimulation of nucleus caudatus on epileptic electrical activity of brain in patients with intractable epilepsy. *Stereotact Funct Neurosurg.* 1997; 69(1–4 Pt 2):221–4. [PubMed: 9711758]

128. Cooper IS, Amin I, Gilman S. The effect of chronic cerebellar stimulation upon epilepsy in man. *Trans Am Neurol Assoc.* 1973; 98:192–6. [PubMed: 4206369]
129. Cooper IS, et al. Chronic cerebellar stimulation in epilepsy. Clinical and anatomical studies. *Arch Neurol.* 1976; 33(8):559–70. [PubMed: 821458]
130. Cooper IS, et al. Safety and efficacy of chronic stimulation. *Neurosurgery.* 1977; 1(2):203–5. [PubMed: 308193]
131. Cooper IS, Upton AR. Effects of cerebellar stimulation on epilepsy, the EEG and cerebral palsy in man. *Electroencephalogr Clin Neurophysiol Suppl.* 1978; 34:349–54. [PubMed: 312191]
132. Van Buren JM, et al. Preliminary evaluation of cerebellar stimulation by double-blind stimulation and biological criteria in the treatment of epilepsy. *J Neurosurg.* 1978; 48(3):407–16. [PubMed: 344840]
133. Wright GD, McLellan DL, Brice JG. A double-blind trial of chronic cerebellar stimulation in twelve patients with severe epilepsy. *J Neurol Neurosurg Psychiatry.* 1984; 47(8):769–74. [PubMed: 6381652]
134. Krauss GL, Fisher RS. Cerebellar and thalamic stimulation for epilepsy. *Adv Neurol.* 1993; 63:231–45. [PubMed: 8279308]
135. Cooper, IS. *The vital probe : my life as a brain surgeon.* 1st ed.. Norton; New York: 1981. p. 346
136. Velasco F, et al. Double-blind, randomized controlled pilot study of bilateral cerebellar stimulation for treatment of intractable motor seizures. *Epilepsia.* 2005; 46(7):1071–81. [PubMed: 16026559]
137. Feinstein B, Gleason CA, Libet B. Stimulation of locus coeruleus in man. Preliminary trials for spasticity and epilepsy. *Stereotact Funct Neurosurg.* 1989; 52(1):26–41. [PubMed: 2784007]

Figure 1.

(A) Tetrode: Made by twisting 4 microwires around each other. Mainly used in single unit recording for spike sorting purposes. (A) & (B) Figures courtesy of Dr. Joseph Manns, Emory University

(B) An example of a recording headstage: This particular setup allows multiple tetrodes to be driven into the brain tissue. The individual screws in the headstage allow the experimenter to drive the tetrodes to any depth throughout the span of the experiment. Using this type of headstage gives the flexibility of optimizing the position of tetrodes for picking up the best quality signals.

(C) Microwire electrode array: Many microwires are arranged on a single shaft. Used for recording from many single units at the same time.

(D) Silicone based microelectrodes: The advantage of using this type of microelectrode is the ability to integrate electronics such as multiplexers and amplifying circuits on the electrode system itself. Figure taken, with permission from reference [19]

(E) PDMS based flexible microelectrodes: Flexible PDMS based microelectrodes are being researched as an alternative for recording from brain areas that are otherwise inaccessible to rigid microelectrode designs. Figure courtesy of Dr. Liang Guo, Georgia Institute of Technology

(F) Strip macroelectrodes: These types of macroelectrodes are placed on the cortex most frequently in epileptic patients for the purposes of delineating the seizure onset zone. Electrical stimulations is also commonly performed with them for correlating physiological function with brain area for ensuring safe resection of brain tissue in epileptic subjects. Microelectrode wires can be incorporated into these (and grid) electrodes (e.g. between macro contacts). (G–I) Figures courtesy of AD-Tech, WI

(H) Grid macroelectrodes: They have functions similar to the strip macroelectrodes but have many rows of electrodes instead of one single row.

(I) Depth macroelectrodes: These are used for recording from deeper brain structures like the hippocampus or the amygdala. Hybrid macro/micro depth electrodes of various designs are also available.