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REVIEW

Deep Brain Stimulation for the Treatment of Epilepsy: Circuits, Targets, and Trials

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Abstract Deep brain stimulation (DBS) has proven remarkably safe and effective in the treatment of movement disorders. As a result, it is being increasingly applied to a range of neurologic and psychiatric disorders, including medically refractory epilepsy. This review will examine the use of DBS in epilepsy, including known targets, mechanisms of neuromodulation and seizure control, published clinical evidence, and novel technologies. Cortical and deep neuromodulation for epilepsy has a long experimental history, but only recently have better understanding of epileptogenic networks, precise stereotactic techniques, and rigorous trial design combined to improve the quality of available evidence and make DBS a viable treatment option. Nonetheless, underlying mechanisms, anatomical targets, and stimulation parameters remain areas of active investigation.

Key Words Epilepsy · deep brain stimulation · neuromodulation · centromedian nucleus · anterior nucleus · SANTE

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Introduction

Epilepsy afflicts 1 % of the world's population, and is medically refractory in 30–40 % of cases [1–4]. A substantial portion (10–50 %) of medically refractory patients are candidates for resective surgery [5], with postoperative seizure freedom rates of 40–90 % depending, in part, on underlying pathology. Nonetheless, there remain millions of patients who either cannot undergo resective surgery or who have recurrent seizures despite surgery [3, 5–8]. Very few of these will respond to additional medication trials [9], and <10 % will achieve seizure freedom with vagal nerve stimulation after failed resection [10]. Thus, there is a pressing need for alternative therapies in medically refractory epilepsy.

Deep brain stimulation (DBS) has proven remarkably effective, safe, and practical in the treatment of movement disorders—primarily Parkinson's disease, dystonia, and essential tremor [11, 12]. These successes have inspired the application of DBS to an ever-broadening range of neurologic and psychiatric disorders, including depression [13], obsessive–compulsive disorder [14], and Gilles de la Tourette syndrome [15], as well as epilepsy. This review will examine the use of DBS in epilepsy, including potential targets, mechanisms of neuromodulation and seizure control, clinical evidence and recent clinical trials, as well as future directions and novel therapies.

Rationale: Cortical–Subcortical Networks in Epilepsy

Although partial-onset seizures—the most common seizure type in medically refractory epilepsy—are heterogeneous in

onset zone and clinical manifestations, they often propagate along well-defined neural pathways. The networks incorporating these pathways—such as the cortical–striatal–thalamic network [16–18] and the limbic circuit of Papez (Fig. 1) [19, 20]—provide nodes at which neuromodulatory tools such as electrical stimulation have the potential to regulate the flow of neural information, including pathological signals mediating seizure propagation.

One of the most well-studied of these networks is the circuit of Papez [20]. Originally characterized for its role in mediating emotions, more recently this circuit has been associated with memory, as well as the generation and propagation of limbic (e.g., mesial temporal lobe) seizures [19, 21]. The circuit originates from the hippocampus and subiculum, projects via the fornix to the mammillary body, then via the mammilothalamic tract to the anterior nucleus of the thalamus (ANT) (Fig. 1). The ANT projects to the cingulate gyrus, then to the parahippocampal gyrus, followed by the entorhinal cortex, which finally projects via the perforant pathway back to the hippocampus [19, 20]. Supporting the notion that neural networks provide multiple points for potential therapeutic interactions, lesions and high-frequency electrical stimulation at several locations along this pathway—including the hippocampus, mammillary bodies, subiculum, and ANT—have demonstrated effective modulation of seizure propagation [22–27].

Cortico–thalamo–cortical excitatory loops appear to be involved in absence epilepsy [28] and motor cortex seizures [18]. In a nonhuman primate model of chronic focal motor seizures, thalamotomy restricted to the anterior part of the ventro–postero–lateral nucleus was able to produce long-lasting benefit and in most cases led to nearly complete seizure suppression [29]. Thalamic relays are also thought to mediate the benefits from lesions and electrical stimulation of the cerebellum for epilepsy, but this circuit and its influence is less clearly defined [30–32]. More precise work identifying

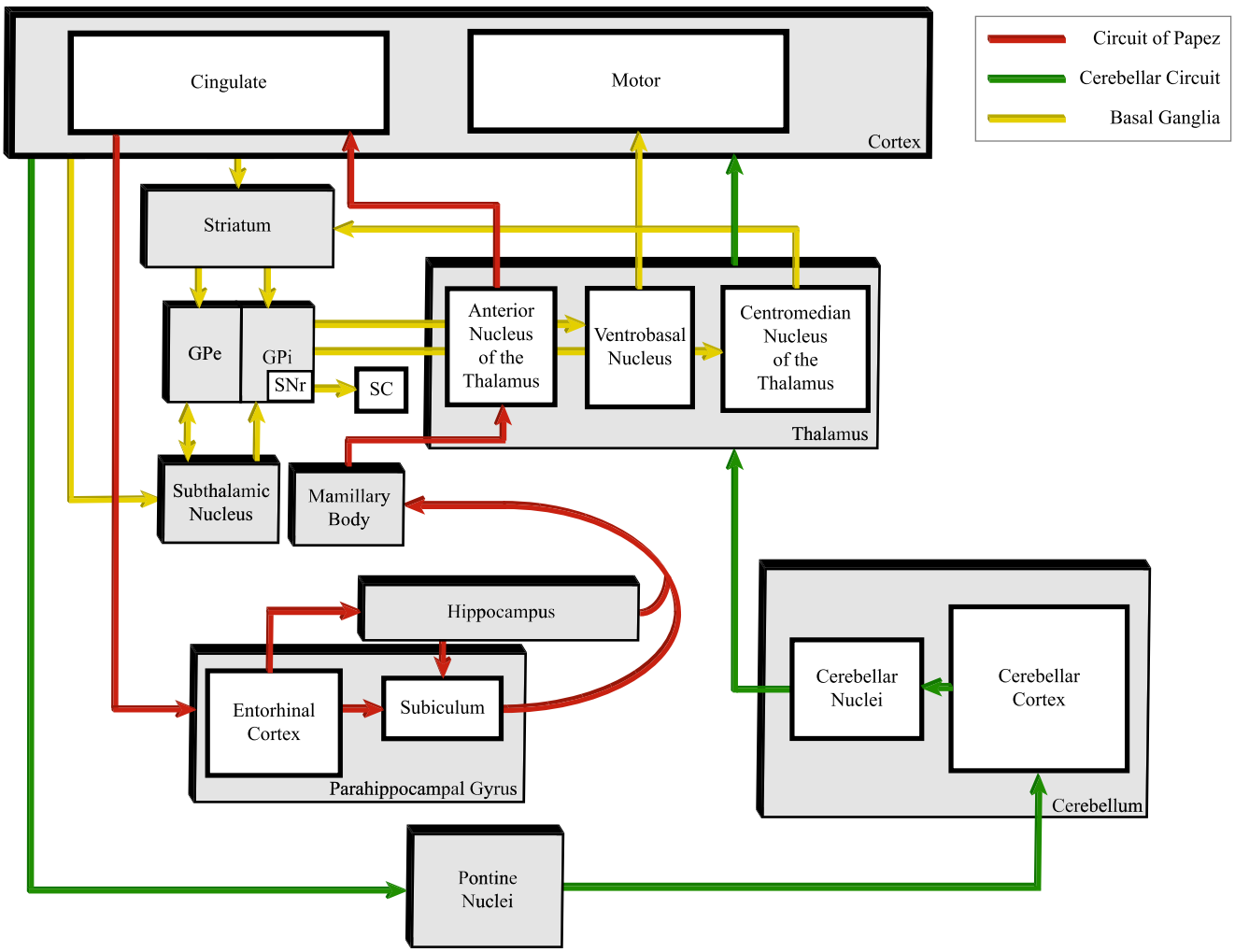

Fig. 1 Neural circuits and anatomical targets for stimulation. Several major neural circuits have been identified and targeted for neuromodulation of epileptic seizures, including the Circuit of Papez (red), the Cerebello-cortico circuit (green), and the basal ganglia (yellow). GPe = external globus pallidus; GPi = internal globus pallidus; SNr = substantia nigra; SC = superior colliculus

and manipulating neural signaling within the thalamocortical network is currently being performed [33].

These networks, in conjunction with lesional studies and investigations in animal models, have implicated several potential neuromodulatory targets for the treatment of epileptic seizures. However, to achieve the greatest therapeutic effects and to identify the optimum targets and parameters for deep brain stimulation requires a greater understanding of the mechanisms underlying the effects of electrical stimulation.

Mechanism: Neuromodulation Via Electrical Stimulation

The stimulation parameters utilized in clinical trials have remained largely empirical in nature—oftentimes unchanged from the arbitrary patterns that were initially explored for each particular anatomical target (Table 1). Only recently have more complex deep brain stimulation parameters begun to be entertained in experiments with human patients [34]. A more reasoned approach would be to understand the underlying mechanisms guiding the effects of electrical stimulation on the nervous system, and to implement the most efficacious parameters in clinical trials and practice.

Despite the extensive use of DBS in neuromodulation, its mechanism of action remains poorly understood. The initial observation that high-frequency (>50 Hz) stimulation mimicked the effects of ablative procedures [35] suggested that DBS was inhibitory in nature [36], inducing a reversible, functional lesion. Increasingly, however, the functional action of DBS on neural circuits has been recognized as complex and multifaceted. Stimulation amplitude, frequency, and pulse width play a major role in determining the effects of stimulation, and manipulating other parameters such as waveform and polarity can also have significant effects [37, 38].

Early work by Ranck [39] indicated that electrical fields have differential effects on different neuronal structures. Activation thresholds were lowest in myelinated axons, increasing in unmyelinated axons, dendrites, and cell bodies, respectively. Further work by Histed et al. [40], utilizing low-current 250-Hz electrical microstimulation with concurrent 2-photon calcium imaging to identify the location of electrically activated neurons, has supported these hypotheses.

Using multicompartment cable models of neurons coupled to a finite element model of extracellular electric fields, McIntyre et al. [41] suggest that the majority of cells within ~2 mm of the electrode will generate efferent (axonal) output at the stimulus frequency, whereas those stimulated at subthreshold levels will be suppressed [41]. Consequently, electrical stimulation may be "hijacking" the neural circuit [42]—blocking the extant neural activity and replacing the efferent output with its own. Our own work demonstrates "entrainment" of downstream (both orthodromic and antidromic) neuronal firing by deep brain stimulation in a Parkinson's patient (R. Gross, K. Mewes, M. DeLong, unpublished data). The consequences of this new efferent output on downstream circuits will depend on their neural connections.

Other mechanisms may also be important, including neurochemical mechanisms, gene, and protein expression. The anticonvulsant effects of low-frequency stimulation have been correlated with changes in adenosine receptor expression [43], and vagal nerve stimulation has been associated with alterations in a variety of neurotransmitters and hormones in cerebrospinal fluid [44]. Furthermore, the progressive improvement in outcome associated with electrical stimulation for movement disorders [45] and epilepsy (see below) [23, 46], suggest that synaptic, neurochemical, and/or expression changes are occurring in response to electrical stimulation of the pathologic neural network.

Targets for Electrical Stimulation in Epilepsy

The history of electrical stimulation for epilepsy has been one of extreme heterogeneity (Table 1), with a great variety of anatomical targets, stimulation parameters, and outcome measures being evaluated. These have primarily been investigated in small case series, and the varying nature of these studies has often made synthesizing conclusions—particularly statistical conclusions—quite difficult. To this end, we attempt here to highlight and summarize the results of these investigations—where possible using the original authors own phrasing with regards to outcome—categorized by anatomical target. In general, the results are described in terms of complete freedom from seizures (seizure-free), a clinically significant reduction in seizure frequency (reduction, response, improvement), or no response (unresponsive, no benefit).

Cerebellum

The earliest subcortical target of stimulation for epilepsy was the cerebellum, which was found as early as the 1950s to modify or halt seizures in animal models of both cortically induced [47, 48] and hippocampal [49] seizures. The mechanism of action was originally thought to be thalamic inhibition via stimulation-induced Purkinje cell output, but this remains somewhat unclear [32]. In the 1970s, Cooper and colleagues were the first to report human cerebellar stimulation for epilepsy. A heterogeneous patient population underwent subdural stimulation of the superior surface of the cerebellar cortex via an inductively driven system using variable stimulation parameters [50]. Of 15 patients, 10 showed significant seizure improvement for up to 3 years [51]. However, when Van Buren et al. [52] used a similar technique to perform a

Table 1 Published reports of deep brain stimulation for epilepsy

Study	Target	Design	*n*	Seizure type	Stimulation parameters	Follow-up*	Results	Adverse events
Cooper et al. [50, 51]	Cerebellum	Open-label	15	Variable (6 CPSz, 6 GTC, 3 myoclonic)	Variable (most 10 Hz, 10 V; 1-min epochs alternating hemispheres)	11–38	4/15 SF at ≥30 mo (2 CPSz, 1 GTC, 1 myo) 6/15 improved (2 CPSz, 2 GTC, 2 myo) 5/15 no change	1 broken lead
Van Buren et al. [52]	Cerebellum	Double-blind crossover	5	Variable	10 Hz, 10–14 V; 8 min ON R/OFF L, 8 min ON L/OFF R	24–29	0/5 SF 0/5 improved	3 CSF leaks 1 increased CSF pressure
Levy et al. [53]	Cerebellum	Open-label	6	Variable	10 Hz, 2–4 V; 8 min ON R/OFF L, 8 min ON L/OFF R	7–20	0/6 SF 2/6 improved	1 infection resulting in explantation All had headaches
Wright et al. [54]	Cerebellum	Double-blind crossover	12	Variable	10Hz, 5–7 mA; 1 min ON R/OFF L, 1 min ON L/OFF R	6	0/11 SF 0/11 improved	6 patients >1 operation 2 postoperative wound infections, 1 resulting in explantation 4 reoperations 1 lead repositioning 1 device failure
Velasco et al. [55]	Cerebellum	Double-blind crossover	5	Variable	10 Hz, 3.8 mA, PW 450 μs, 2.0 μC/cm^2 4 min ON B/l, 4 min OFF B/l	24	3 months: mean seizure reduction of 33 % 6 months: mean seizure reduction of 41 %	3 reoperations for migration 1 wound infection resulting in removal 1 ataxia and dysmetria 4 electrode migrations
Velasco et al. [27]	HC	Open-label	16	TLE	130 Hz, 0.2–0.4 mA, PW 450 μs	2 weeks	7/10 SF after 6 d 3/3 chronic stimulation improved Interictal spikes decreased	N/A
Tellez-Zenteno et al. [65]	HC	Double-blind crossover	4	MTLE	190 Hz, 1.8–4.5 V, PW 90 μs	6	0/4 SF 3 months: median seizure reduction of 15 %	None reported
Velasco et al. [60]	HC	Open-label	9	MTLE	130 Hz, 0.3 mA, PW 450 μs 1 min ON B/l, 4 min OFF B/l	18	4/9 SF 5/9 improved	3 skin erosion and local infection, 1 requiring hospitalization 2 explantations
Boon et al. [62]	HC	Open-label	12	TLE	130 Hz, 2–3 V, PW 450 μs	15–52	1 patient exited trial before stimulation 1/11 SF 9/11 improved (6/11>50 %) 3/11 SF after additional leads	1 asymptomatic hemorrhage
McLachlan et al. [71]	HC	Double-blind crossover	2	MTLE	185 Hz, "subthreshold", PW 90 μs	9	0/2 SF 3 months: mean seizure reduction of 33 %	None reported
Cukiert et al. [68]	HC	Open-label	6	Variable	130 Hz, 4 V, PW 300 μs		Clinical outcomes pending	None reported

Table 1 (continued)

Study	Target	Design	*n*	Seizure type	Stimulation parameters	Follow-up*	Results	Adverse events
				(5 TLE)		Acute stimulation only	4/6 with interictal spikes suppressed	
Boëx et al. [66]; Bondallaz et al. [26]	HC	Open-label	8	MTLE (2 HS)	130 Hz, 0.5–2.0 V, PW 450 μs	10–74	2/8 SF 4/8 improved (50–90 %)	1 electrode displacement resulting in reimplantation 1 electrode fracture 2 reversible memory deficits with stimulation
Tyrand et al. [67]	HC	Open-label	12	TLE (6 HS)	130 Hz 1 V peak-to-peak, PW 210 or 450 μs	Acute stimulation only	No seizure outcomes reported Patients with HS demonstrated 51.8 % decrease in epileptiform discharges with biphasic stimulation	N/A
Benabid et al. [87]; Chabardès et al. [88]	STN	Open-label	5	Variable	130 Hz, 0.8–5.2 V, PW 90 μs	30	0/5 SF 3/5 improved (67–80 %)	1 infection 1 postimplantation subdural hematoma
Handforth et al. [83]	STN	Open-label	2	CPSz	185 Hz, < 3.5 V, PW 90 μs	27	2/2 improved (33–50 %)	1 repeated surgery 1 hardware failure
Vesper et al. [84]; Wille et al. [89]	STN	Open-label	5	Myoclonic	130 Hz, 3.0 V, PW 90 μs	12–42	1/5 SF 4/5 improved (>30 %)	
Capecci et al. [85]	STN	Open-label	2	Variable	130 Hz, 2–3 V, PW 60 μs	12–48	1/2 improved (65 %)	1 patient demonstrated mild balance impairment, dysarthria, severe aboulia, apathy, and mood changes under chronic stimulation
Sramka et al. [90]; Chkhenkeli et al. [91]; Chkhenkeli et al. [92];	Caudate	Open-label	57	Variable	Variable	Variable	Unclear	N/A
Velasco et al. [97]; Velasco et al. [98]; Velasco et al. [99];	CMT	Open-label	18	Variable	60 Hz, 0.5–0.6 mA 1 min ON R/OFF L, 4 min OFF B/l, 1 min ON L/OFF R, 4 min OFF	18	Lennox–Gastaut: 2/13 SF, 8/13 improved (50–80 %) Partial seizures: 2/5 improved (>80 %)	2 patients explanted owing to repeated skin erosions
Fisher et al. [102]	CMT	Double-blind crossover	6	Variable	65 Hz, 0.5–10.0 V, PW 90 μs 1 min ON, 4 min OFF × 2 h/day	9	30 % mean seizure reduction With stimulation 24 h/day, 3/6 improved (>50 %)	1 connection repair 1 minor hemorrhage with no symptoms or complications
Andrade et al. [103]	CMT	Open-label	2	Variable	100–185 Hz, 1–10 V, PW 90–120 μs,	20–80	1/2 improved (>50 %)	1 intermittent nystagmus with stimulation 1 possible auditory hallucinations and anorexia during stimulation

Table 1 (continued)

Study	Target	Design	*n*	Seizure type	Stimulation parameters	Follow-up*	Results	Adverse events
Valentin et al. [104]	CMT	Single-blind	11	Variable (6 PGE, 5 FLE)	130 Hz, < 5 V, PW 90 μs	6–72	PGE: 5/6 improved (>50 %) FLE: 1/5 improved (>50 %)	1 infection resulting in explantation 1 transient agraphia
Hodaie et al. [108]; Andrade et al. [103]	ANT	Single blind	6	Variable	100–185 Hz, 1–10 V, PW 90–120 μs	50–70	Difficult to interpret; 6/6 improved (>50 %) by implantation; no further improvement with stimulation	1 skin erosion requiring wound revision 1 lethargy with continuous stimulation
Kerrigan et al. [109]	ANT	Open-label	5	Variable	100 Hz, 1–10 V, PW 90–330 μs	6–36	Difficult to interpret; nonsignificant improvement in 4/5	1 reimplantation for incorrect positioning
Lim et al. [110]	ANT	Open-label	4	Variable	90–110 Hz, 4–5 V, PW 60–90 μs	33–48	4/4 improved (37–75 %)	1 resolved mild left-hand weakness associated with hemorrhage 1 scalp erosion resulting in explantation
Osorio et al. [111]	ANT	Single-blind	4	Variable	145 Hz, 4.1 V, PW 90 μs, 1 min ON b/l, 5 min OFF b/l	36	4/4 improved (53–92 %)	None reported
Fisher et al. (SANTE) [23]	ANT	Double-blind parallel group	110	Partial-onset	145 Hz, 5 V, PW 90 μs	4 (blinded) 13–37 (open)	4 months: median seizure reduction 40.4 % with active stimulation, 14.5 % with sham stimulation 13 months: 2/110 SF; 43 % with >50 % response 25 months: 6/81 SF; 54 % with >50 % response	808 reported in 109 participants, 55 in 40 categorized as serious, 238 of 808 events considered device-related 18.2 % paresthesias 14.8 % depression during blinded phase 13.0 % memory impairment during blinded phase 12.7 % implant site infection 10.9 % implant site pain 8.2 % replaced leads for poor placement 4.5 % nonsymptomatic hemorrhages 5 deaths 5 status epilepticus

SANTE = Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy; HC = hippocampus; STN = subthalamic nucleus; CMT = centromedian nucleus of the thalamus; ANT = anterior nucleus of the thalamus; CPSz = complex partial seizure; GTC = generalized tonic-clonic seizure; TLE = temporal lobe epilepsy; MTLE = mesial temporal lobe epilepsy; HS = hippocampal sclerosis; FLE = frontal lobe epilepsy; R = right; L = left; PW = pulse width; b/l = bilateral; SF = seizure-free; myo = myoclonic; PGE = primary generalized epilepsy; CSF = cerebrospinal fluid; N/A = not available

*Follow-up in months unless otherwise specified

double-blind crossover study of 5 patients with intractable epilepsy, no significant differences in seizure frequency were detected. Contemporary results were also published by Levy and Auchterlonie [53], showing a modest response rate of 33 % (2/6 patients). Following these results, Wright et al. [54] published a prospective, double-blind, crossover study of 12 patients with stable, long-term epilepsy (10–32 years) using bilateral 8-contact electrodes inserted over the superior cerebellar surface via occipital burr holes. Patients received 2 months of continuous 5–7 mA 10 Hz stimulation of alternating polarity that alternated hemispheres every other minute (some patient parameters were uniquely adjusted based on their individual responses), 2 months of self-controlled stimulation, and 2 months of no stimulation. There was no observed decrease in the frequency of seizures in the 11 patients available for follow-up. There was a 25 % rate of lead migration, a 16.6 % rate of wound infection, and an 8.3 % rate of mechanical failure. Interestingly, although there was no objective effect on either seizures or neuropsychological testing, the majority of patients reported that stimulation was beneficial [54].

The failure of these two trials, despite the previous apparent clinical successes, led to the cerebellum falling out of favor as a target for epilepsy until it was revisited by Velasco et al. in 2005 [55]. In this double-blind crossover study of 5 patients with medically intractable epilepsy, participants were implanted bilaterally with 4-contact electrodes on the superomedial surface of the cerebellum. Stimulation parameters were adjusted to deliver a charge density of 2.0 μC/cm^2/phase, with a fixed pulse width of 0.45 ms and current amplitude of 3.8 mA. Stimulation frequency was set at 10 Hz, akin to that explored by Cooper et al. [51], Van Buren et al. [52] and Wright et al. [54]. At the end of the 3-month blinded evaluation, seizure frequency had decreased by 33 % in the group receiving stimulation versus no reduction in the unstimulated group. At the end of the 6-month unblinded stimulation period, the mean seizure reduction rate was 41 % (range 14–75 %). Statistical analysis demonstrated a significant reduction in tonic-clonic seizures ($p<0.001$) and tonic seizures ($p<0.05$). As with previous trials, there was a high incidence of lead migration (60 %).

The small sample sizes, conflicting results, and high complication rate of cerebellar stimulation make its role in the treatment of epilepsy unclear without further investigation [52, 54, 55]. A pooled analysis of prior small series has recently been published by Krauss and Koubeissi [56], demonstrating a seizure freedom rate of 27 % (31/115 patients) and at minimum a reduction of seizures in 76 % (87/115 patients) in the prior, heterogeneous case series. More rigorously controlled studies across 17 patients found none seizure free and 5/17 with reduced seizures. A detailed review on the patient has also recently been published [32].

Hippocampal Formation

Mesial temporal lobe epilepsy (MTLE) is the most common form of medically refractory epilepsy and enjoys a high rate of seizure freedom following amygdalohippocampal resection [3, 5, 8, 57]. However, hippocampal resection or ablation may be contraindicated in cases of dominant-onset MTLE with preserved verbal memory, cases with bilateral mesial temporal onsets, or recurrent MTLE contralateral to a prior resection. Thus, the ability to prevent or abort seizures arising from the mesial temporal structures without resection or ablation—potentially preserving interictal function—would represent a major advance in the surgical treatment of epilepsy.

The hippocampus is an appealing target for neuromodulation. Although larger than most other DBS targets, and therefore potentially more prone to targeting error and variability, the hippocampus is often stereotactically accessed with recording electrodes and consequently is a relatively familiar target for epilepsy surgeons. Several studies of hippocampal slices and rodent models provided preclinical support for hippocampal DBS [22, 36, 58, 59]. The first systematic human studies of hippocampal stimulation came from Velasco and colleagues, initially in a pilot study of stimulation prior to temporal lobectomy in 10 patients [27]. More recently, the same group reported 18-month follow-up of 9 patients with MTLE, 4 with classic radiological signs of hippocampal sclerosis (HS), and 5 with normal magnetic resonance (MR) images, who experienced 15–70 seizures per month (average of 28 seizures) [60]. All patients initially underwent invasive monitoring with bilateral 8-contact hippocampal depth electrodes in preparation for amygdalohippocampectomy, but did not undergo resection owing to bilateral independent onsets (4 patients) or onsets on the dominant side associated with preserved verbal memory (3 patients). One patient with right-sided onset did not undergo resection owing to occasional left-sided epileptiform discharges and another because of bilateral MR imaging (MRI) evidence for HS. After the completion of the diagnostic phase, the depth electrodes were removed and quadripolar DBS leads (1.5 mm contacts, 0.5 mm spacing) were placed within the long axis of the hippocampus, targeted so that at least 2 contacts were within the identified area (or bilateral areas) of maximal seizure onset. As per their diagnostic findings, 4 patients were implanted bilaterally, 3 unilaterally on the left and 2 unilaterally on the right. Bipolar stimulation within the seizure focus (usually the pes hippocampus or amygdala–pes junction) was performed with 1-min trains of square wave pulses at 130 Hz, a duration of 450 μs, and an amplitude of 300 μA, followed by 4-min stimulation-free intervals (alternating side-to-side in bilateral cases). Five patients were randomized to an initial 1-month, double-blinded period without stimulation in order to investigate possible implantation effects.

Of the 9 patients, 4 (44 %) were seizure-free at the 18-month follow-up. Interestingly, these 4 were all in the normal MRI group, and all showed early and dramatic responses

within the first 2 months of stimulation. The fifth patient with a normal MRI also had an immediate, sharp decrease in seizure frequency and, although not seizure-free, continued with only brief, occasional complex partial seizures throughout the study. In contrast, the 4 patients with evidence of HS on MRI showed more delayed and partial responses to stimulation, with seizure reduction becoming statistically significant by 8 months and leveling off (with a reduction of between 50 % and 70 %) by 10 months. Seizure freedom and levels of seizure reduction were maintained through 18 months of follow-up in all patients.

Important features of this series include the use of 8-contact diagnostic depth electrodes followed, in a separate procedure, by DBS placement targeted to the ictal onset zone, which in one case resulted in more posterior DBS placement than would have occurred with standardized placement in the pes hippocampus. As the authors state, a substantial minority (20 % in some studies [61]) of patients with MTLE demonstrate onset in the posterior hippocampus, and standardized anterior placement of quadripolar electrodes might leave these patients' ictal onset zone outside the area of stimulation. Second, the stimulation paradigm used a constant current design, which may be more physiologically appropriate in compensating for changes in electrode and/or tissue impedance. Third, in contrast to the study of Boon et al. [62] discussed below, better responses were seen in patients with normal MR images than in those with MRI evidence for HS. The authors suggest the decreased cell counts and, presumably, lesser network connectivity of a sclerotic hippocampus as an explanation for the delayed effectiveness in these patients. The authors also considered the possibility that tissue impedances may be substantially different in sclerotic versus normal tissue, but felt this was unlikely, as stimulation artifacts were seen on scalp electrodes at similar threshold voltages in all patients. Finally, a few pieces of evidence support a true effect of stimulation in this trial. The 5 patients who experienced 1 double-blind month absent stimulation onset did not show a change in seizure frequency compared with baseline during the first postoperative month, whereas the 4 patients who underwent stimulation during that month showed immediate decreases in seizure frequency. In addition, 3 patients in whom stimulation was later interrupted (1 from battery depletion, 2 from skin erosion and device removal) showed a partial return to baseline seizure frequency.

Boon et al. [62] published their experience with acute and long-term hippocampal DBS in patients with refractory TLE. In 12 patients, 2 quadripolar DBS electrodes were implanted bilaterally through parieto-occipital burr holes, with one electrode terminating in the amygdala and one terminating in the anterior hippocampus. During the same surgery, recording grid and/or strip electrodes were implanted, and monitoring was performed to ascertain seizure onset zone(s). One patient with unilateral mesial temporal onsets exited the trial in favor of resective surgery prior to the stimulation phase. Of the patients that went on to stimulation, 10 had unilateral and 1 had bilateral onsets. All 8 contacts across the amygdala and hippocampal quadripolar electrodes on the side of onset were used for stimulation in each unilateral patient; the bilateral patient was stimulated through the bilateral hippocampal electrodes only. Bipolar stimulation was delivered through 2 pairs of contacts on each electrode, with a mean output voltage of 2.3 V (range 2–3 V), a frequency of 130 Hz (1 patient at 200 Hz), and a pulse width of 450 μs. Initial acute stimulation was performed using a temporary external pulse generator, followed by long-term stimulation with an implanted pulse generator if >50 % reduction of interictal spike frequency was achieved with temporary stimulation, which occurred in 10/11 patients. Outcome was assessed by comparing each patient's mean monthly seizure frequency during the last 6 months of follow-up (mean total follow-up 33 months; range 15–52 months) to the preintervention baseline. One patient (10 %) became seizure free, 1 had >90 % seizure frequency reduction, 5 had seizure reduction >50 %, 2 had 30–49 % seizure reduction, and 1 had <30 % reduction. Long-term follow-up of the same group plus 1 additional patient was recently reported, with stimulation adjustments including implementation of bilateral stimulation in 6 patients with <90 % response to unilateral stimulation [63]. Going from unilateral to bilateral stimulation improved 3/5 patients, with 1 becoming seizure-free, despite onset regions being unilateral. The previous 1 patient who was seizure-free continued as such, despite stimulation being discontinued at battery end-of-life, and 1 other patient became seizure-free when stimulation was stopped. Thus, while a total of 6 (55 %) patients achieved >90 % seizure reduction, the overall 27 % rate of seizure freedom (3/11) in this long-term follow-up group must be interpreted with caution. In contrast to the results of Velasco et al. [60], discussed previously, 2/3 patients in this study with HS became seizure-free (vs 1/11 without), although 1 of them was the patient that became seizure-free when stimulation was turned off, and the other maintained seizure freedom despite stimulation discontinuation.

The low rate of seizure freedom in this study may have been attributable, in part, to the proportion of patients (50 %) with regional onset in the temporal lobe, rather than a well-defined mesial temporal onset. Another issue may be that stimulation was delivered to only a small region of the hippocampus: the electrodes spanned, at most, 21 mm (10.5 mm×2 electrodes) and, as the anterior one was in the amygdala, the posterior electrode did not extend much beyond the hippocampal head. Moreover, bipolar stimulation only delivers cathodic pulses to one of the pair owing to the Lilly pulse waveform (charge-balanced biphasic pulses designed to prevent charge deposition and resultant tissue damage [64]). It

would be interesting to know the effects of using all 8 contacts as cathodes with the case as the anode ("monopolar" stimulation), to affect a larger volume of hippocampal tissue.

Two small series of hippocampal stimulation have been reported by the University of Western Ontario group [65, 66]. In the first, 4 patients with left mesial temporal seizure onset who were unable to undergo resection (1 owing to prior right temporal resection, 3 owing to failed intracarotid amobarbital testing) underwent placement of unilateral quadripolar electrodes (3 mm contacts, 6 mm spacing; total span 30 mm) with the first contact in the pes hippocampus and 3 contacts in the hippocampal body. All 4 had imaging evidence of HS (2 left, 2 bilateral, including the patient with prior right-sided resection). Monopolar stimulation using all 4 contacts (190 Hz, pulse width 90 μs, voltage adjusted below the patients' conscious thresholds, ranging from 1.8 to 4.5 V) was delivered in a double-blinded, randomized, crossover design for 6 months (3 consecutive 2-month periods randomized to on–off vs off–on). Median seizure frequency reduction between the 3 on months and 3 off months was 15 %, although the results did not reach statistical significance. No patient was rendered seizure-free, and the results were somewhat variable among the 4 patients. This investigation went so far as to explore multiple neuropsychological measures, which, importantly, did not show any difference between the stimulation-on and stimulation-off states. In their second series, the same group reported their results in 2 patients with independent, bilateral mesial temporal seizure onset, 1 of whom had a normal MRI and 1 of whom had bilateral MRI evidence for HS. Electrode placement and stimulation parameters were similar (with the only difference being stimulation at 185 Hz instead of 190 Hz). The 2 patients were randomized to undergo 3 months on and 3 months off (in this series, as 3-month blocks) in random order, with a 3-month washout period. Results with bilateral stimulation were slightly more robust than in the earlier, unilateral series, with a mean seizure frequency reduction of 33 % in on periods compared to off. Again, no patient was rendered seizure-free. One patient showed declines in verbal and visuospatial learning scores during stimulation. Of note, the volume of tissue stimulated in these 6 patients is likely larger than in the Belgian group, as electrodes spanning 3 cm of hippocampal length were used in a "monopolar" configuration.

More recently, the Swiss group of Boëx et al. [66] presented a series of 8 TLE patients (2 with HS, 6 nonlesional) who were unable to undergo amygdalohippocampectomy owing to bilateral onset (5 patients) or onset ipsilateral to preserved verbal memory (3 patients). All patients received unilateral DBS placement on the side of more frequent seizure onset as determined noninvasively (3 patients) or with intracranial recording (5 patients). A single DBS lead was placed along the long axis of the hippocampus at its junction with the parahippocampal gyrus, with the anterior-most contact at the amygdalo–hippocampal junction. The first 5 patients received quadripolar electrodes (3 mm contacts with 6 mm spacing; total length 30 mm) and the last 3 received octrodes (3 mm contacts with 1.5 mm spacing; total length 34.5 mm). Stimulation was tested in both monopolar configuration, with 4 contacts as the cathode (130 Hz, pulse width 450 μs, 1–2 V), and in bipolar configuration (130 Hz, pulse width 450 μs, 0.5–1.5 V), using the 2 contacts with the highest frequency of interictal discharges as cathode and anode.

Of the 8 patients reported, 2 (25 %) became seizure-free (1 without stimulation, as with Vonck et al. [63], discussed above). Four patients, including the 2 with HS, had a 50–90 % reduction in seizure frequency, and 2 patients did not show statistically significant seizure reduction. In the 2 patients with presumed HS, monopolar stimulation appeared to be more effective than bipolar, but there did not appear to be significant differences between monopolar and bipolar stimulation in nonlesional patients. Interestingly, a subsequent reanalysis of this cohort demonstrated that all 6 patients with >50 % seizure frequency reduction had active contacts located within 3 mm of the subiculum [26], whereas the 2 nonresponders had electrodes >3 mm from the subiculum. In contrast, proximity to the presumed seizure onset zone was not associated with outcome, with responders' and nonresponders' active contacts located 11±4.3 mm and 9.1±2.3 mm from the ictal onset zone, respectively.

Although this study demonstrated significant overall seizure reduction, several inconsistencies make it difficult to interpret. First, the lack of intracranial evaluation in 3/8 patients introduces some degree of diagnostic uncertainty, although 2 of these 3 had MRI evidence for HS concordant with the side of seizure onset, and would have thus proceeded directly to resection were it not for the results of their intracarotid amobarbital testing. Second, the use of 2 different types of DBS leads and multiple stimulation parameters introduces additional variables; however, this may more accurately reflect real practice, which will likely require patient-by-patient stimulation adjustments. Third, by the authors' own admission, the use of unilateral stimulation even in cases with documented bilateral seizure onset may have limited the effectiveness of DBS therapy in comparison to the series of Velasco et al. [60]. Fourth, stimulation voltages were generally low in comparison with other studies, with a maximum amplitude of 2 V, potentially limiting the volume of tissue modulated. Finally, the use of battery depletion as a method of "off" testing raises an additional degree of heterogeneity, as the exact timing of "off" periods may not be precisely known and will not be consistent, and as variable degrees of neuromodulation may have occurred prior to battery depletion in individual patients.

This group recently published a comparison of biphasic and pseudomonophasic stimulation using hippocampal depth electrodes in 12 patients undergoing intracranial monitoring

[67]. Stimulation (1 V peak-to-peak, 130 Hz, pulse width 210 and 450 μs) via perpendicular depth electrodes (and, in 3 cases, also via longitudinal DBS leads prior to internalization) was performed in 4-h epochs during an acute hospital stay. The effect on the interictal epileptiform discharge rate (IEDR) was measured using an automated detection algorithm. In patients with MRI evidence for HS, there was a reduction in IEDR of 51.8±10.3 % using biphasic stimulation, but no significant reduction using pseudomonophasic stimulation. In nonlesional patients, neither waveform produced a decrease in IEDR. Thus, waveform characteristics, which may select differently oriented fibers for activation by more heavily weighting cathodic or anodic pulses at each electrode, may play a role along with other DBS parameters in determining the effectiveness of stimulation.

Cukiert et al. [68] recently reported suppression of interictal spiking with intraoperative test stimulation (130 Hz, 300 μs, 4 V) in 4/6 patients undergoing bilateral hippocampal DBS placement, but associated clinical outcomes have not yet been reported for this cohort.

The above open-label studies laid the groundwork for 2 clinical trials to further evaluate the effectiveness of hippocampal stimulation in epilepsy therapy: the Controlled Randomized Stimulation Versus Resection (CoRaStiR) trial, based in Belgium and Germany (NCT00431457) [69], and the Medical vs. Electrical Therapy for Temporal Lobe Epilepsy (METTLE) study, based at the University of Calgary (NCT00717431) [70], the latter of which has been terminated owing to insufficient enrollment. The CoRaStiR trial will randomize patients with TLE into 3 arms: immediate amygdalohippocampectomy, immediate hippocampal stimulation, and implantation of hippocampal electrodes with delayed initiation of stimulation by 6 months. Treatment will be unblinded and results compared at 12 months postsurgery using measures of seizure frequency, neuropsychological outcome, mood, and quality of life. Also at this period, patients undergoing neurostimulation will have the option to either continue neurostimulation or undergo resective surgery.

Despite promising small series and open-label data, the value of hippocampal DBS remains difficult to assess in the absence of larger, prospective data sets. The procedure appears to be safe and does not appear to carry significant neuropsychological risks [60, 71, 72]. However, as seizure freedom rates have been low in open-label trials performed thus far, the prospect for hippocampal DBS achieving a high rate of seizure freedom in blinded controlled trials is similarly low. This is substantiated by the randomized, double-blind, sham-stimulation controlled trial of responsive neurostimulation (RNS; Neuropace, Mountainview, CA, USA), in which 50 % of the 191 patients with medically refractory seizures had mesial temporal onsets and were implanted with 4-contact leads in the amygdala/hippocampus [46]. Overall, 7.1 % of patients were seizure-free over the last 3 months of follow-up available (≥1 year). In the long-term continuation trial, combining all implanted RNS patients (feasibility plus pivotal trials), this number increased to 13 % (31/247); 20.3 % had at least 1 seizure-free period of 6+months during the trial, albeit not necessarily at last follow-up (Bergey et al., submitted). It should be noted that in this combined group, only 43.4 % had seizures arising solely from the mesial temporal lobe. While detailed outcome analysis of the mesial temporal patients was not provided in either report of this trial, seizure localization to the mesial temporal lobe (vs other locations) was not a significant factor in determining the treatment response, suggesting that there was not a high rate of seizure freedom in patients with MTLE in this trial (see Morrell et al., in this issue [46]). Thus, neurocognitive factors notwithstanding, it is likely that hippocampal DBS will emerge as a tool to reduce the frequency of—but not eliminate—seizures in patients who are not candidates for surgical resection or ablation, which remains the gold standard for achieving seizure freedom in MTLE.

Subthalamic Nucleus/Substantia Nigra

Control of limbic seizures in rats by bilateral pharmacological inhibition of the substantia nigra (SNr) was first demonstrated in the early 1980s [73–76]. Although the mechanisms of such control in animal models is unclear [76–79], it has been suggested that the release of nigral inhibition of a dorsal midbrain (i.e., superior colliculus) anticonvulsant zone is involved (Fig. 1) [80]. Thus far, rather than directly modulating SNr with DBS, animal studies have attempted to achieve SNr inhibition via modulation of the subthalamic nucleus (STN) [76], with the idea that high-frequency stimulation of the STN would reduce excitatory input from the STN to SNr. Although STN DBS was found to be effective in rodent models of epilepsy, more recent evidence that high-frequency stimulation actually *drives* STN activity rather than inhibits it, in addition to supportive neurotransmitter evidence [79], suggests the possibility that inhibitory effects of STN stimulation on SNr were mediated indirectly via activation of external globus pallidus [77]. Resulting elevated gamma-aminobutyric acid levels in SNr from overdriving its external globus pallidus afferents would be predicted to dominate any increased glutamate release in SNr from STN driving owing to the more proximal location of gamma-aminobutyric acid versus glutamate receptors on SNr cell bodies [77]. Additional mechanistic explanations for the use of STN DBS include antidromic neuromodulation of the motor cortex [77, 78], or other frontal neocortex [81], from STN [82].

Several small case series of STN stimulation have been reported [83–89]. In 2002, the Grenoble group reported 5 patients who underwent bilateral STN DBS (some with multiple leads) for inoperable seizures of various types [88, 89]. Three patients (all with paracentral neocortical seizures) experienced a seizure reduction of 67–80 %, while 2 patients (1

with Dravet syndrome and 1 with fronto-insular seizures) did not show significant improvement. In 2006, Handforth et al. [84] reported 2 patients with refractory partial-onset seizures in whom bilateral STN stimulation (<3.5 V, 90 μs ,185-Hz pulses) was performed. The first, with partial complex seizures and bitemporal electroencephalogram onset, had a 50 % reduction in seizure frequency. The second, with postencephalitic hemiatrophy and left-sided seizure onset, experienced a 33 % reduction in seizure frequency, and a reduction in seizure severity, including arrest of generalized convulsions, fewer seizure-related injuries, and an improved quality of life. In 2007, Vesper et al. [85] described a single patient with myoclonic epilepsy who received monopolar stimulation (3.0 V, 90 μs, 130 Hz) via 2 contacts spanning the inferior STN and SNr bilaterally. At 1-year follow-up, a 50 % reduction in the severity and frequency of myoclonic seizures was achieved, and the patient's vagal nerve stimulator (VNS) was turned off without recurrence of generalized seizures, which previously had been controlled only with VNS. In 2012, Capecci et al. [86] presented 2 cases of bilateral STN DBS after failed disconnective surgery. With STN stimulation (2.0 V, 60 μs, 130 Hz; stimulator off at night), the first case, a patient with widespread cortical atrophy, multiple seizure types, and prior anterior callosotomy, demonstrated a 70 % reduction of partial seizures and 85 % reduction of secondarily generalized seizures at 1 year. The second case, a patient with bilateral temporal and occipital cortical and white matter abnormalities, had previously undergone anterior commissurotomy. Continuous stimulation (3.0 V, 130 Hz, 60 μs) was associated with a decrease in tonic-clonic seizures, but a sharp rise in absence seizure frequency, leading to discontinuation of stimulation.

Following their successful 2007 case report [85], Wille et al. [90] reported a series of 5 adults with progressive myoclonic epilepsy who were implanted with STN DBS and followed in an unblinded fashion for 12–42 months. All 5 experienced improvement, with reduction of myoclonic seizure frequency between 30 % and 100 % and accompanying improvement in quality of life. Of note, 4 patients were implanted with bilateral Vim thalamus leads in addition to STN, but no benefit was seen with Vim stimulation.

Based on the above case series, STN DBS may be a palliative option, particularly in cases of myoclonic epilepsy. Unfortunately, with the termination of the Grenoble-based STIMEP trial (NCT00228371) owing to insufficient enrollment, no larger-scale or randomized trials of STN stimulation appear to be forthcoming.

Caudate Nucleus

With the rationale of modulating the cortico–striato–thalamic network and inducing cortical hyperpolarization, Chkhenkeli and colleagues [91–93] tested DBS of the ventral caudate in a large number of patients undergoing stereoelectroencephalography for seizure disorders. Low-frequency (4–8 Hz) stimulation decreased cortical and hippocampal interictal spiking and epileptiform activity in a subset of these patients, several dozen of whom subsequently underwent placement of internalized DBS systems. Twelve of 21 patients underwent chronic stimulation of the head of the caudate nucleus (HCN) after resection of the epileptic focus did not provide benefit received a Class 1C [94] (seizure-free) outcome, with the remaining 9 achieving worthwhile improvement (class IIIA) [93]. Amongst unlesioned patients, 9/17 experienced a 1C with chronic therapeutic HCN stimulation, with 5 experiencing worthwhile reduction and 3 no improvement. The authors speculated on a suppressive effect due to inhibitory processes from HCN activation, although they noted variability in the excitatory and inhibitory effects of stimulation. However, a heterogeneous patient population, varying targets and stimulation paradigms, uncontrolled observations, and insufficient follow-up render this large, single institution series difficult to interpret.

Centromedian Nucleus of the Thalamus

The centromedian nucleus of the thalamus (CMT) has widespread projections to the cortex and plays a central role in wakefulness and cortical excitability (Fig. 1) [95]. As these circuits seem to play a role in seizure generation and propagation [18, 28, 29, 96], CMT has been explored as a potential target for DBS therapy. However, it is important to note that CMT also has strong projections to the striatum, and some of its effects, at least in part, may be mediated via the cortico–striato–thalamic circuit [97].

Velasco et al. reported their first 5 cases of CMT DBS in 1987 [98], and larger series in 2000 [99] and 2006 [100], using an alternating left–right stimulation paradigm (60 Hz, 500–600 μA, 1 min on/4 min off, 24 h/day). Seizure frequency was measured during a 1-month baseline period and monthly for 18 months postoperatively during open-label stimulation. Of the 18 patients reported, the most clearly positive results were seen in the 13 patients with Lennox–Gastaut syndrome, 2 of whom became seizure-free, 8 demonstrating 50–80 % seizure reduction, and 3 having no response to therapy. Consistent with other observations of progressively decreasing seizure frequency during DBS [23], VNS and RNS [46], seizure frequency decreased immediately after implantation, and continued to decline thereafter, reaching its minimum after 6 months of stimulation. Double-blinded 3-month periods of stimulation cessation (between 6 and 12 months after surgery) did not show a return to baseline frequency, whereas open-label interruption of stimulation and explantation in 2 patients with skin erosion and battery depletion after 20 and 39 months on-stimulation, respectively, was associated with increases in seizure frequency to reach or surpass the baseline period. These results indicate a residual antiepileptic effect,

possibly due to neural plasticity; however, patient bias cannot be excluded. In contrast to the patients with generalized tonic-clonic seizures and consistent with previous results [101, 102], 5 patients with partial epilepsy syndromes fared less well, with only 2/5 achieving >80 % seizure reduction.

Fisher et al. [103] attempted to subject CMT DBS to objective evaluation using a randomized, double-blind, sham-stimulation controlled design. Six patients were enrolled in a crossover design with 3-month blinded periods; 3-month washout periods were interposed between stimulation periods [103]. Although there was a 30 % decrease in seizures during stimulation, as compared with an 8 % decrease during sham periods, the results were not statistically significant. Several critical factors mitigate interpretation of these findings to support the ineffectiveness of CMT DBS. First, the amplitude for active stimulation was set at 50 % of the sensory threshold in order to maintain effective blinding. Although details of the actual stimulation amplitude (range 0.5–10.0 V) were not provided, it was likely somewhat below that used in the series in which amplitudes 90 % of sensory threshold were used. Thresholds were allowed to increase to this level during the open-label extension in the study by Fisher et al. [103]; 3/6 patients experienced a >50 % reduction of generalized tonic-clonic seizures during this phase. Moreover, as sensory threshold arises from current spread to the ventrobasal sensory nucleus, it is subject to proximity of the electrode to that structure; low thresholds would lead to correspondingly low stimulation dosages with respect to CMT and would undermine effectiveness. Second, the small number of patients studied place findings at risk of being nonrepresentative (this is true of both studies). Third, the controlled study design may well have affected outcomes. On one hand, the presence of a sham stimulation period may have limited biasing "placebo" responses (actually contributed to by both patient and experimenter bias), making the Fisher study more accurate by controlling type 1 error. On the other hand, 1 patient who was initially randomized to active stimulation had a marked reduction in seizures and refused to undergo sham stimulation, eliminating 1 of the responders from the data analysis. In the latter context, the controlled study design may have introduced type 2 error. This early controlled trial of DBS was—if nothing else—highly illustrative that even the ability to perform sham (or "placebo") stimulation does not render DBS trials free of methodological challenges. A crossover design with a washout period is methodologically rigorous, but is still fraught with difficulties and assumptions, and has rarely been used since publication of this trial.

Additional studies of CMT DBS have been reported. Andrade et al. [104] reported 2 patients in an uncontrolled design, 1 of whom had a seizure reduction of >50 %. Most recently, Valentín et al. [105] reported 11 patients (5 with frontal lobe epilepsy, 6 with primary generalized epilepsy) treated with CMT DBS at 2 centers (London and Madrid). After bilateral implantation, patients underwent single-blinded treatment with 3 months of sham stimulation followed by 3 months of therapeutic stimulation (up to 5 V at 130 Hz with a pulse width of 90 μs), followed by 6 months of open-label therapeutic stimulation. Open-label stimulation was maintained after 12 months for patients in whom stimulation was thought to be effective. Two patients with generalized epilepsy became seizure-free immediately after implantation, 1 of whom was maintained off stimulation throughout 50 months of follow-up; another was seizure-free for 12 months, and recurrence of seizures after that was eliminated with 60-Hz stimulation. All 6 patients with generalized epilepsy had >50 % seizure reduction during the blinded phase, and 5/6 maintained >50 % seizure reduction during the long-term extension phase. The 5 frontal lobe epilepsy patients did not fare as well, with only 1 patient with >50 % improvement in seizure frequency during the blinded phase. During the open-label, long-term extension, the frontal lobe patients had a heterogeneous response, with 3 demonstrating 50–90 % reductions in seizure frequency and 2 showing no clear signs of improvement.

Taken together, these data suggest that CMT DBS may be effective for a subset of patients with generalized epilepsy, namely those with Lennox–Gastaut syndrome, or with a predominance of tonic-clonic or other generalized seizures. CMT DBS appears to show strong implantation and carryover neuromodulatory effects, even without active stimulation.

Anterior Nucleus of the Thalamus

The ANT consists of several distinct subnuclei, some of which have extensive frontal and temporal cortical projections, and others of which are key stations in the limbic circuit of Papez [20]. Thus, the ANT is an attractive target for both modulation of overall thalamocortical excitability, as well as modulation of the limbic seizure network [21]. Early lesion studies of the ANT in cats and nonhuman primates demonstrated effective reduction in seizure frequency and duration [106], and human studies began as early as the 1960s [107, 108]. Several small, open-label studies throughout the 2000s showed promising decreases in seizure frequency—between ~30 % and 90 %—with prominent implantation, as well as carryover, effects with 2–3 months of stimulation cessation [103, 109–112].

The promising results of these initial open-label studies were the foundation for the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy trial (SANTE; NCT00101933, Medtronic, Minneapolis, MN, USA), a multicenter, randomized, double-blind trial of bilateral stimulation of ANT for localization-related epilepsy [23]. Participants (n= 110) with medically refractory partial seizures—including secondarily generalized seizures—were implanted with bilateral ANT DBS leads and randomized at 1 month postsurgery to receive either 3 months of stimulation at 5 V (90 μs pulse

duration, 145 Hz frequency, 1 min on alternating with 5 min off) or 3 months of sham stimulation. Following the 3-month double-blind period, all patients received open-label stimulation for 9 months, with 2 interspersed office visits at which stimulation parameters could be adjusted in a limited fashion. Following the first year, antiepileptic drugs and stimulation parameters could be freely adjusted. Of the 110 patients implanted, 108 completed the blinded evaluation period, 105 patients were evaluated at the 1-year outcome point, and 102 evaluated at 2 years. Two of the implanted patients were excluded from the analysis owing to explant of an infected device, 1 of whom was explanted prior to randomization, and 1 of whom was randomized to sham-stimulation and—importantly—had only 66 of the prespecified 70 days of required postrandomization seizure diaries prior to explanation.

There were some important statistical issues that warrant discussion. First, as in previous studies, an appreciable implantation effect was noted (although placebo and/or regression to the mean effects could also have been factors): 1 month following implantation and prior to initiation of the treatment phase patients assigned to both the stimulation and sham stimulation groups experienced a median reduction in seizures of 21–22 %. As shown in Fig. 2, the 2 groups began to separate beginning with the first month after active or sham stimulation and continuing to the end of the blinded period. However, only in the third (and final) month of blinded stimulation was there an unequivocal statistical difference in seizure frequency between the 2 groups (median 40.4 % reduction in seizures in active stimulation compared with 14.5 % reduction with sham stimulation, $p=0.0017$; Fig. 2), evidently due to continued reduction in the active group and regression towards baseline in the sham group. This finding was in the group of 108 randomized patients who had at least 70 diary days, as prespecified in the statistical analysis plan. However, this was not the actual prespecified primary outcome measure, which was a generalized estimating equation (GEE) model encompassing the entire 3-month blinded evaluation period. The GEE is a useful tool in evaluating biological count data that has a very high variance, as in seizure counts. However, the GEE could not generate a result for this group of 108 patients owing to a treatment-by-visit (i.e., months follow-up) interaction resulting from the lack of a significant difference between the groups prior to the third month of treatment. This presented a critical challenge in determining whether the study was a success.

To address this issue, two *post hoc* analyses were additionally performed. First, 1 patient in the stimulated group was statistically determined to be an "outlier": when first activated at the protocol-determined 5 V this patient had 210 brief partial seizures during the 1-minute on-stimulation phases over 3 days. Although the stimulator was inactivated (and later restored at 4 V with good clinical effect), these seizures disproportionately decreased the difference between the active and sham stimulation groups. However, when this outlier was excluded from the analysis, the difference between the groups was increased during the first month, but was still not statistically significant until the third month ($p=0.0023$), and the GEE model still indicated a treatment-by-visit effect and again failed to generate a result. The second *post hoc* analysis excluded the outlier patient, but additionally *included* the patient in the sham stimulation group who had only had 66 of the 70 required days of seizure diaries prior to explantation, in an "intent-to-treat" analysis. With this group of 108 patients, the treatment-by-visit interaction was no longer in the GEE model, and a statistically significant treatment effect became evident over the entire blinded evaluation phase ($p=0.039$).

This use of a *post hoc* analysis has raised a good degree of debate as to whether this was a successful trial. The primary outcome measure, rather than generating a negative result, simply could not generate a result owing to the time course over which the treatment and placebo groups diverged. In the absence of a result from the prespecified primary outcome measure, should we discard the important *post hoc* secondary outcome measure (statistically significant group difference at 3 months) and the non-prespecified intent-to-treat GEE result? Although "*post hoc*", does this truly increase the chance that this finding ($p=0.039$) represents a type I error? Or is it more likely that adopting the stance that the primary outcome measure was not met and the trial was a failure represents a type II error?

Arguably more relevant than this unresolvable question is the implication that the results are not sufficiently robust to support the usefulness of this treatment. As there clearly was a statistically significant difference between the groups in the third month of treatment, but not in the first 2, it was not the robustness per se that impaired the GEE analysis, but rather the progressive improvement in the treated group and decline of effect in the nonstimulated group. In fact, seizure frequency continued to decline during the open-label stimulation phase: median seizure frequency decreased by 41 % at 1 year, 56 % at 2 years [23], and 69 % at 5 years ($n=74$), whereas the 50 % responder rate increased from 43 % at 1 year to 54 % at 2 years [23] and 68 % at 5 years ($n=59$) (Salanova et al., in preparation). Nevertheless, seizure freedom was relatively low, with 16 % becoming seizure-free for at least 6 months during the first 5 years of the trial. Six patients (5.5 %) were seizure free for >2 continuous years and 11 (10 %) were seizure free over the last 6 months at the 5 year follow-up.

Complaints of memory impairment occurred in 27 % of patients over the course of the trial (Salanova et al., in preparation). Impairment, which could be confirmed in 50 % of the cases, was never serious and occurred in the context of baseline memory impairment in 50 %. Conversely, overall group

statistics did not show decline in memory measures, but did show improvement in various measures, including attention, executive function, and mood.

The complicated statistical issues discussed above may have obfuscated the analysis of the clinical significance of the trial by the US Food and Drugs Administration advisory panel. Although the panel ultimately recommended approval by a 7:5 margin, premarket approval was not granted and the status of ANT DBS remains in limbo in the USA. Nevertheless, approval was granted by the regulatory agencies in Canada, Europe, Australia, and elsewhere. In the wake of the recent approval of RNS therapy on improbably similar data (Fig. 2), it may be worthwhile for the FDA to revisit its decision with respect to ANT DBS.

Future Directions

Despite these significant clinical successes, DBS therapy for epilepsy remains in its infancy. Our limited understanding of the mechanisms of DBS action [113–115], the epileptogenic networks themselves, and their interaction, as well as the nonselective effects of DBS on heterogeneous populations of neurons, combine to make this promising therapy still relatively unrefined and dependent on careful empirical progress.

Further incremental advances may be gained through technological innovations, such as constant current and novel devices that may enable more predictable and directed stimulation volumes, and better avoidance of stimulation side effects [116–118]. Additional benefits in device longevity, and perhaps effectiveness and tolerability, may be gained through the use of closed-loop (feedback-controlled) neurostimulation devices and alternative stimulation parameters. One form of closed-loop therapy is the RNS (discussed in Morrell et al. [46]), which activates electrical stimulation of the previously defined seizure onset zone upon detection of electrophysiological signatures of a seizure. Presently applied directly to the epileptic focus or foci, similar technology could conceivably be applied to modulatory nodes, such as ANT, in response to seizure detection.

However, an alternate approach is to characterize states that are associated with seizures and mitigate those states with,

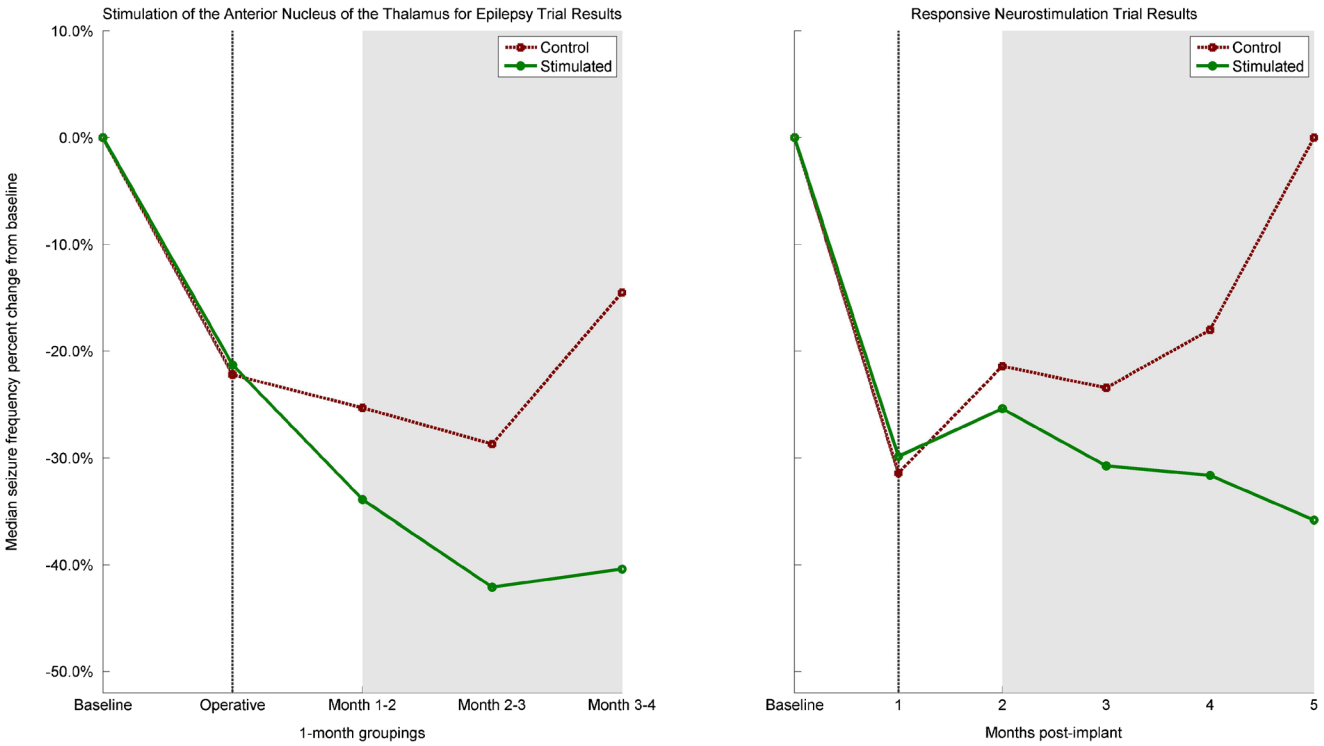

Fig. 2 Median percentage change in seizure frequency from baseline during the Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy (SANTE) and Responsive Neurostimulation System (RNS; Neuropace, Mountainview, CA, USA) trials. In both trials, stimulation was started 1 month after implantation (vertical dashed line). (Left) Despite an appreciable reduction in seizure frequency with implantation, control patients (red, dashed line) in the SANTE trial did not improve in seizure reduction during the blinded phase of the trial (gray). This is in contrast to stimulated patients (green, solid line), who underwent a median 40.4 % reduction in seizure frequency in the final blinded month as compared with a 14.5 % reduction in controls. (Right) Stimulated patients in the RNS trial also demonstrated an appreciable reduction in seizure frequency with implantation. Stimulation was optimized for 1 month before the blinded evaluation phase (gray). During this phase, stimulated patients underwent a mean 37.9 % reduction in seizure frequency compared with a 17.3 % reduction in controls ($p=0.012$). (Adapted from [23] and [46])

amongst other approaches, DBS. For example, theta band activity within the septo-hippocampal circuit has been associated with decreased seizures [119, 120], and continuous multimicroelectrode electrical stimulation using theta frequencies in a rat model of temporal lobe epilepsy decreases seizures (Desai et al., in preparation). Conceivably, the RNS could be adapted to accomplish this. Alternatively, using a novel bidirectional stimulation and recording pulse generator unit approved for research in humans (Activa PC+S; Medtronic, Minneapolis, MN, USA), a closed loop state control algorithm was recently tested in a large animal (sheep) model [121]. One DBS electrode was implanted in the ANT and a second one in the hippocampus. Spectral power was examined in the latter, which was decreased by stimulation in ANT [122]. The sensitivity for evoking seizure activity by stimulation in the hippocampus was decreased in the low-power state associated with ANT stimulation as well. Moreover, the power could be continuously kept low in the hippocampus by a closed-loop algorithm that titrated ANT stimulation to hippocampal power, thereby keeping the hippocampus in the less sensitive state for seizure evocation. This paradigm may easily be tested in animal models of epilepsy, or, indeed, in humans with epilepsy, as the safety of both ANT and hippocampal electrode implantation has been thoroughly established. A similar approach is under study and promising in a nonhuman primate model of seizures (S. Chabardes, personal communication).

The success to date in ANT DBS for refractory epilepsy likely results in part from the stereotyped pathways for seizure propagation through the ANT in MTLE (60 % of patients in the SANTÉ trial had onsets in the temporal lobe [23]) and perhaps forms of frontal lobe epilepsy that may share those pathways. Many foci outside the mesial temporal lobe likely have different propagation networks; in vivo studies of epileptogenic networks may therefore allow more rational and patient-specific targeting for DBS placement in this heterogeneous and more difficult to treat group of patients [113]. Thus, a true leap forward in neuromodulation therapy will require both a more detailed understanding of epileptogenic networks and the ability to selectively modulate different cell populations within those networks.

Optogenetics, a novel molecular technology utilizing cell type-specific expression of light-sensitive ion channels, is not only capable of millisecond-level precision control, but can also selectively activate and inhibit particular genetically defined subpopulations of neurons within a larger circuit [123]. Activated by particular wavelengths of light, these channels selectively conduct cations or anions across the cell membrane, producing defined depolarization or hyperpolarization in the expressing cells. The resulting technique combines the specificity of pharmacological therapies with the temporal control of electrical stimulation. Several early studies of optogenetics in vitro and in animal models of epilepsy have shown promising results. The earliest application of optogenetics to epilepsy was by Tønnesen et al. [33], who demonstrated that halorhodopsin—an inhibitory chloride pump—was capable of suppressing epileptiform activity in hippocampal organotypic slice cultures. More recently, 3 groups have demonstrated that inhibition of particular targets can interrupt seizures in vivo in rat models of epilepsy. Paz et al. [124] took advantage of the thalamocortical circuit, inhibiting hyperexcitable thalamocortical neurons in response to epileptic activity in the cortex, arresting the seizure. However, Wykes et al. [125] targeted the seizure foci directly, again successfully inhibiting seizures. Similarly, Krook-Magnuson et al. [126] used a closed-loop approach to target directly the subpopulations of the hippocampus to detect and arrest spontaneous temporal lobe seizures. These early results suggest that optogenetics could play a greater role in future therapeutics. However, there are a number of challenges that currently limit its implementation, such as issues with gene therapy [128], miniaturization of light sources, and channel and light distribution in primate brains. While not insurmountable, these limitations necessitate greater research, particularly with nonhuman primates, which will better reflect the limitations on human optogenetic therapies.

Concluding Remarks

The use of electrical stimulation for epilepsy has been explored for half a century, and only recently have 2 therapies successfully obtained regulatory approval for more widespread use in patients: ANT DBS outside of the USA (but not within), and RNS within the USA (but not outside). Given the complementarity of these 2 approaches, it would be ideal if all patients in all geographical locations had access to either. For patients with identified foci within functional regions, RNS may be preferable, but is not indicated for multiple (>2) foci, whereas ANT DBS may be effective in the latter. However, this is conjecture, and will remain so for a long period to come. Most proximately, we hope that ANT DBS attains approval in the USA, either on the basis of a more rational evaluation of the results of the controlled multicenter trial, or as a result of a new trial (which we do not anticipate). While ANT DBS has been approved in Europe and elsewhere, postapproval surveillance data will not likely contribute to US approval, as it is open label and uncontrolled. RNS, however, is approved only in the USA and has not been studied in Europe. The regulatory hurdles for CE Mark-approval require safety, but not effectiveness, data, so it is anticipated that the way forward will be less burdensome for RNS approval outside the USA. Finally, prospects for targets other than the cortex (RNS) and ANT (DBS) are dim, given the difficulty with ANT approval to date and the limited pilot data for alternative targets. CMT DBS holds the most promise as an

adjunct in the treatment of generalized epilepsy, in particular Lennox–Gaustaut syndrome. Generalized epilepsy remains amongst the most challenging of epileptic syndromes, for which neither RNS nor ANT DBS are likely to be effective, and for which novel therapeutics are much needed.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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