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Epilepsy (E Waterhouse, Section Editor)

Deep Brain Stimulation for Epilepsy: Biomarkers for Optimization

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Abstract

Purpose of review Two large-scale controlled clinical trials have provided Class I evidence for the benefit of deep brain stimulation (DBS) as a therapy for refractory epilepsy. However, the efficacy has been variable, with some patients not achieving any improvement in their seizure control. This disparity could be the result of suboptimal stimulation parameters/electrodes or alternatively a difference in the type of seizures being treated. This review presents the most recent clinical results with a focus on two major targets for DBS, the anterior nucleus of the thalamus (ANT) and the hippocampus. We detail the etiologies where DBS might work best, and provide evidence for the use of recorded neural responses for the optimization of stimulation parameters and closed-loop control of devices.

Recent findings Stimulation of the hippocampus may work well for both focal and generalized seizures, whereas ANT stimulation may be best for focal seizures only. Studies have demonstrated that changes in stimulation-evoked response shape can be used as a biomarker for stimulation efficacy. Furthermore, new biomarkers have been identified that could be used for closed-loop stimulation.

Summary Improvements in patient screening and stimulation optimization are needed for patients to achieve optimal seizure control. Furthermore, therapy should be adjusted to suit individual patient needs. Recording evoked responses during the application of DBS could be used to measure the effectiveness of DBS and titrate stimulation as needed.

Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent seizures, affecting over 60 million people worldwide (1% of the population) [1]. The occurrence of seizures is a major source of stress, injury, and reduced quality of life for those affected by the disorder [2]. As many as a third of patients with epilepsy are resistant to available medications, a statistic that has not changed in over several decades despite the development of numerous new antiepileptic drugs [3]. Alternative therapies are clearly required for patients with drug-resistant epilepsy.

For many refractory patients, deep brain stimulation (DBS) has proven to be an effective treatment. DBS involves the application of electrical stimulation in a pre-programmed manner to deep brain structures via chronically implanted electrodes. DBS has proven to be remarkably effective and safe in the treatment of movement disorders such as Parkinson's disease, dystonia, and essential tremor. This success has encouraged the use of DBS across a broad range of neuropsychiatric disorders including depression, Tourette syndrome, obsessive-compulsive disorder, as well as epilepsy [4].

Promising though variable antiepileptic effects have been observed in both clinical and animal studies of epilepsy across a number of stimulation targets including the anterior nucleus of thalamus (ANT), cerebellum, hippocampus, subthalamic nucleus, centromedian nucleus of the thalamus, caudate nucleus, and trigeminal nerve [5, 6]. In 2018, the USA Food and Drug Administration granted approval for the use of DBS in the ANT to treat medically refractory seizures in adults (> 18 years). Currently, the mechanisms through which DBS can reduce seizure frequency are unclear. Furthermore, many patients respond exceptionally well to DBS, while others achieve little benefit. Reducing this discrepancy may come down to tailoring individualized stimulation parameters. However, testing for potential efficacy with any set of parameters is difficult unless neural recordings can also be obtained.

This review focuses on the effects of DBS in two primary target regions, the ANT and the hippocampus. We discuss the mechanisms behind seizure control and key human clinical results. Additionally, we present evidence for potential improvements that could be obtained through the recording of evoked neural responses and closed-loop electrical stimulation.

The circuit of Papez and its role in seizures

The circuit of Papez was conceived by James Papez in 1937 [7]. He first suggested that this circuit was devoted to emotional experience and expression [8]. It is now known that this circuit, which forms part of the limbic system, is responsible for a range of functions, such as expression of emotion and the formation of episodic and spatial memories. The circuit of Papez forms a closed loop circuit starting at the hippocampus, travelling through to the fornix, mammillary bodies, mammillothalamic tract, anterior nucleus of the thalamus (ANT), cingulate cortex, entorhinal cortex, and back to the hippocampus (Fig. 1a; Shah et al. [10]). The ANT and the hippocampus share a particularly strong connection, as demonstrated by a highly correlated theta rhythm (synchronous firing of neurons that give rise to regular oscillations) between these areas [11].

The circuit of Papez plays an important role in the synchronization of pathological signals, spread of seizures, and loss of consciousness during seizures [12]. Several projections also radiate from the ANT to the retrosplenial and prefrontal cortex, providing a pathway for the generalization of seizures [13]. Limbic structures are known to atrophy in mesial temporal lobe epilepsy, including the hippocampus, fornix, and thalamic nuclei [14–16]. The atrophy leads to pathological signaling and the formation of interictal spiking emerging from the hippocampal formation and surrounding areas. The Papez circuit is an

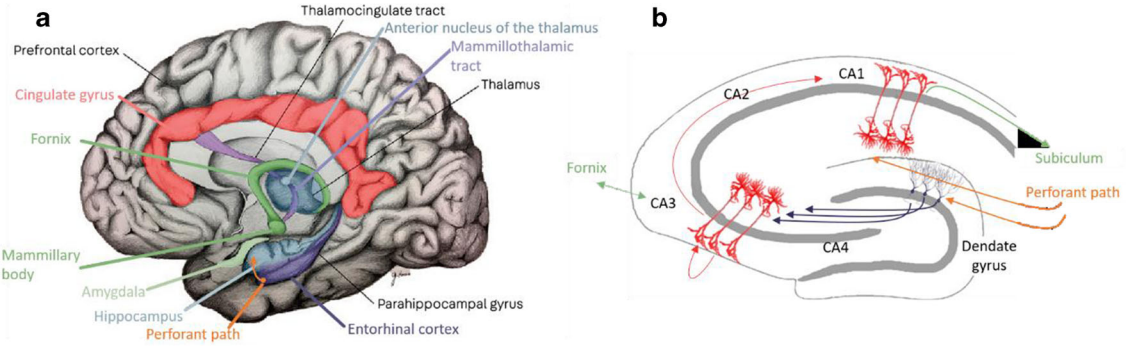

Fig. 1. The circuit of Papez. **a** The circuit of Papez forms a closed loop between various neural components of the limbic system (colored regions) [image adapted from [9]]. **b** The hippocampus plays a vital role in the generation and propagation of seizures. Hippocampal cells form microcircuits that relay signals to the entorhinal cortex, subiculum, and to the thalamus via the fornix. (Figure 1a reprinted from Gliebus, G.P., Memory dysfunction. Behavioral Neurology and Psychiatry, 2018. 24(3): p. 727–744, with permission from Wolters Kluwer Health, Inc.).

attractive target for the treatment of seizures as modulation of circuitry components can result in modulation of hippocampus and cortical areas, which serves to interrupt pathological signaling and seizure propagation [17–19]. Herein, we describe two components in the circuit of Papez, the hippocampus and the ANT, which are two major targets for DBS.

Hippocampus

The hippocampus plays an important role in spatial navigation, the formation and consolidation of memories, and learning [20–23]. The hippocampus has input connections stemming from the amygdala, entorhinal cortex through the perforant path, and the fornix [10, 24]. It is made up of four regions: CA1, CA2, CA3, and CA4, which form local GABAergic (inhibitory) and glutamatergic (excitatory) microcircuits (Fig. 1b). CA1 is characterized by a heterogeneous assortment of GABAergic cells which entrain synchronized activity in hippocampal pyramidal neurons [25, 26]. For example, sharp waves occurring during sleep are thought to originate from a coordinated interplay between CA3 and CA1 pyramidal cells [27]. The interaction between glutamatergic neurons and GABAergic interneurons sculpts the precisely timed firing patterns of the hippocampus and gives rise to various network oscillations, each correlated with a specific function [28].

There is considerable evidence that the hippocampus is involved in seizure propagation and initiation [29–31]. In temporal lobe epilepsy, hippocampal tissue often shows distinctive patterns of cell loss, particularly in area CA1 [30, 32, 33]. This "sclerosis" is associated with an increased glutamate/GABA ratio, often reaching levels that likely fuel further cell death [33]. In vitro models have shown that the loss of pyramidal cells in CA1 can affect signaling in the subiculum, resulting in the generation of interictal epileptiform activity [30]. Interictal epileptiform activity and seizures can also be generated in CA1, CA3, and entorhinal cortex [34] and in corticothalamic regions [35]. The hippocampus also plays a vital role in the propagation of seizure activity in other types of epilepsy. In occipital lobe epilepsy, the hippocampus is one of the first areas to be activated [36–38]. Experiential phenomena such as hallucinations and

voices are common to seizures with an occipital lobe origin [38] and early hippocampal involvement likely reflects this. Seizures with a frontal origin also often involve limbic structures. The prefrontal cortex receives inputs from various limbic areas, and so a large class of seizures with a frontal lobe origin involve limbic structures [39, 40].

Anterior nucleus of the thalamus

The ANT is formed by a collection of nuclei located at the anterior region of the thalamus, each with its own distinctive connectivity. There are extensive reciprocal connections between the ANT and the anterior cingulate, along with connections to subcortical areas such as the subiculum and CA1 [10, 13, 41]. As a major node in both the circuit of Papez and thalamocortical pathways, the ANT is thought to function as a relay structure, amplifying and synchronizing activity within these circuits.

The ANT plays an important role in the generalization of seizures from subcortical to cortical structures [18, 42–44]. High spectral EEG coherence between electrodes placed in the ANT and at the cortical surface during seizures has been observed in rodents, demonstrating the special role played by the ANT in the propagation of seizure activity [42]. Comparatively, other thalamic areas played little role in the cortical spread of seizure activity. This may suggest the ANT's connections to the cingulate and prefrontal cortex are important for the generalization of seizures. Furthermore, lesions and high-frequency stimulation of the ANT have been shown to disrupt the spread of seizures in animal models, which provides further evidence of the role the ANT plays in seizure propagation [44–46].

Treatment options

Deep brain stimulation

The hippocampus is often involved in the generation of seizures and hence makes an attractive target for deep brain stimulation. Therapeutic effects of hippocampal stimulation are thought to result from an increased inhibition of the hippocampal formation. In a pilot study, Velasco et al. [47] showed that high-frequency electrical pulse stimulation (> 100 Hz) abolished clinical seizures, increased the threshold for seizures, and significantly reduced the number of interictal spikes after 5–6 days of stimulation. The authors discovered an increase in the amount of benzodiazepine receptor binding (GABA receptor) in the stimulated hippocampus compared to the unstimulated tissue. They postulated that the antiepileptic effect was due to an increase in neuronal inhibition, which regulated the initiation and propagation of seizures. Subsequent human [48] and animal [49] studies have reinforced this finding by showing that high-frequency DBS increases GABA tissue levels and upregulates GABA receptor expression. It is also possible that hippocampal stimulation works best when the stimulating electrode is close to the subiculum [50]. This finding may result from the fact that the changes in GABAergic signaling cause hyperexcitability in the subiculum [30]. Neuromodulation of the subiculum may reduce excitability and interrupt the propagation of seizures through the perforant path.

The activity of the ANT is highly correlated with that of the hippocampus [51] and stimulation of the ANT influences both the superior-mesial frontal and mesial temporal cortices [52]. Thus, the ANT is also an attractive target for regulating the excitability in both the limbic system and the cortex. Additionally, the ANT provides some practical advantages over other possible target areas in the limbic system. The ANT has a well-defined stereotaxy and is more distant from sensory and motor specific thalamic nuclei which enables the use of higher intensity currents [53].

Stimulation of the ANT was first trialed in humans in the 1980s [54]. Since then, numerous trials have been conducted, all indicating some reduction in the mean seizure rate, but with a variable responder rate [55, 56••, 57••, 58••, 59–62, 63•]. For many of these trials, simply inserting the electrodes caused a reduction in seizure frequency, thus suggesting a placebo or microthalotomy effect [64–67]. This made it difficult to determine if stimulation of the ANT provided any additional benefits. However, the SANTE study, a randomized double-blind clinical trial, and its long-term follow-up excluded a simple microthalotomy effect [68, 69]. In this study, the decline in seizure frequency was greatest for seizures classed as "most severe," perhaps suggesting that stimulation of the ANT successfully prevented the propagation of seizure activity to other brain regions [68, 70].

The mechanisms through which ANT stimulation reduces seizure frequency remain uncertain. It is a common view that seizures result from an imbalance of excitatory and inhibitory activity, and some hypothesize that ANT stimulation restores the balance between inhibitory and excitatory processes. This may be achieved through the generation of new synapses [71] or an alteration of neurotransmitter release. For example, animal studies have shown that stimulation of the ANT can increase adenosine levels in the hippocampus and that the reduction in excitability caused by DBS can be abolished by adenosine receptor antagonists [72]. Furthermore, like DBS, increased serotonergic activity in the ANT can reduce seizure likelihood [73]. Thus, it is possible that the benefits of ANT stimulation arise through changes in the activity of neurotransmitters like serotonin and adenosine, which help restore the balance between excitatory and inhibitory activity.

An alternate hypothesis is that ANT stimulation reduces seizure occurrence by desynchronizing network activity [52]. A recent study in humans has demonstrated that high-frequency stimulation of the ANT can desynchronize local field potentials over a broad frequency range within the ipsilateral hippocampus, reducing the occurrence of interictal spikes and high-frequency oscillations within the hippocampus [74]. This agrees with several animal investigations which have shown an attenuation of background activity in the hippocampus during ANT stimulation [75–77] and desynchronization between limbic and cortical areas during DBS [42]. Interestingly, stimulation not only desynchronized activity in local networks but also large-scale networks involving multiple cortical areas. This suggests that ANT stimulation could act by lowering the overall network excitability.

Clinical results

DBS for epilepsy has been trialed in numerous controlled and uncontrolled trials and shown to be safe and for many patients efficacious. To date, there have

been two ANT [56, 68] and four hippocampal [78–81] controlled DBS clinical trials. The SANTE study was the first controlled ANT study and consisted of 110 participants divided into two arms. The control arm of the study did not have stimulation turned on until 3 months following implantation whereas the experimental group had stimulation turned on immediately. During this blinded period, patients with stimulation showed a 40.4% drop in seizure occurrence compared to a 14.5% drop in the control group. Interestingly, the 50% responder rate (at least 50% seizure reduction) increased from 43% at year one to 67% at year three suggesting improved benefit of DBS over time. Similar improvements over time have also been reported in other uncontrolled trials [78, 82, 83]. More recently, Herrman et al. [56] investigated ANT stimulation in 18 participants. This trial came to an early halt as only 4 patients (22%) were considered responders, and the majority of patients showed no significant improvement and some even showed a possible worsening of their condition.

For hippocampal DBS, the responder rates have also been variable. Velasco et al. [78] reported a trial involving 9 participants in which all had a seizure reduction of at least 50%. Conversely, a trial with 4 participants [80] and another with 2 [79] reported no significant change in seizure rate during stimulation. The largest controlled study using hippocampal stimulation has been from the responsive neural stimulation system (NeuroPace, USA), where 191 participants were implanted with a closed-loop device stimulating either hippocampal structures (50% of patients), or other seizure foci [81, 83, 84]. The 2-year responder rate for this study was 55%.

It is not clear why DBS is ineffective for some patients and effective for others. It could be that specific DBS targets work better for patients with particular pathologies. For example, patients with temporal onset seizures in the SANTE study had a 76% seizure reduction, compared to 59% for frontal onset epilepsies and 68% for other onset locations at a 5-year follow-up [68]. Similarly, a recent study with 17 participants found that patients with temporal lobe, frontal lobe, and parietal lobe and occipital lobe epilepsy had seizure reductions of 67%, 51%, and 35%, respectively. Table 1 shows the variation in efficacy across seizure types for several trials where the seizure types have been identified and long-term (> 6 months) follow-ups were conducted. In general, ANT stimulation appears to work best for focal seizures (FIA and FA, with and without impaired awareness, respectively) and is less effective for generalized tonic-clonic (GTC) seizures. However, the study by Herrman et al. [56] is a clear exception to this. They suggested the efficacy was lower compared to that of the SANTE study due to important cohort differences; their study included patients with much higher seizure rates, taking a higher number of antiepileptic drugs and with previous resective surgeries or VNS implants. Hippocampal stimulation appears to work well for both focal and generalized seizures. However, these findings should be taken with caution. Every study relied on patient diaries in order to assess efficacy, which have been shown to be a poor marker of actual seizure rates [89].

In general, DBS of limbic structures is well tolerated with few reported adverse effects. In addition to a reduction in seizure frequency, DBS of limbic structures can result in other positive side effects. For example, many patients have reported improved cognitive abilities, less emotional and physical discomfort, and generally feeling more positive [61, 62, 83, 90]. However, given that the limbic system is implicated in emotional and memory processing, it is

Table 1. Efficacy of stimulation across different types of seizures

Study	Seizure type	% change in seizure rate
[66]– 5 participants, ANT	GTC (2 patients)	– 29
	FIA and secondarily GTC (3 patients)	– 72
[65]– 4 participants, ANT	GTC (1 patients)	– 35
	FA with motor and secondarily GTC (2 patients)	– 61
	FIA and secondarily GTC (1 patients)	– 43
[85] – 4 participants, ANT	FIA and secondarily GTC (3 patients)	– 79
	FA and FIA (1P)	– 91
[56] – 18 participants, ANT*	GTC (11 patients)	– 34
	FIA (18 patients)	– 17
[86], 3 participants, hippocampus*	FIA (3 patients)	– 78
	GTC (1 patients)	– 95
[78], 9 participants, hippocampus	FIA and secondarily GTC (7 patients)	– 82
	FIA (2 patients)	– 92
[87], 10 participants, hippocampus*	FIA (10 patients)	– 60
	FA (2 patients)	– 74
	GTC (3 patients)	– 75
[88], 2 participants, hippocampus	GTC (1 patients)	– 65
	FIA and secondarily GTC (1 patients)	– 90

FIA focal with impaired awareness, *FA* focal without impaired awareness, *GTC* generalized tonic-clonic
*Studies separate patients with multiple seizure types. Hence, they appear twice according to the seizures they present

not surprising that DBS can affect, for better or worse, memory and psychiatric condition. The SANTE study reported side effects of depression (14.8%), memory impairment (13%) anxiety (9.3%), paraesthesia (9.3%), dizziness (5.6%), and headaches (3.7%) to have occurred throughout the cohort [68]. Furthermore, uncontrolled trials have reported symptoms such as psychosis and sleep fragmentation in patients receiving DBS [58••, 63•, 91]. In some cases, psychiatric symptoms could be resolved by changing the stimulating electrode or stimulation parameters [56, 58••, 68, 80], highlighting the importance of stimulation electrode and parameter selection for optimal patient outcomes.

Optimizing stimulation

To date, no "optimal" stimulation parameters have been identified for DBS in epilepsy. The effects of frequency, pulse width, voltage, and cycling on stimulation efficacy remain poorly understood. Typically, many studies begin with the recommended settings stemming from the SANTE study: 5-V pulse amplitude, 145-Hz stimulation frequency, 90-μs pulse width and cycling of 1 min on, 5 off. However, more clinical and animal studies that systematically modulate each parameter are clearly required.

Studies suggest the frequency of stimulation could be of particular importance in the efficacy of treatment. However, the effects of stimulation frequency may differ between DBS targets. For example, low-frequency (< 10 Hz) stimulation of the ANT has been shown to increase the synchronization between brain regions, the number of interictal spikes, and the risk of seizure [46, 74, 92]

(but see [57••, 93]), whereas high-frequency stimulation (> 100 Hz) has the opposite effect, reducing the risk of seizure [55]. Both high- and low-frequency stimulation of the hippocampus may have beneficial effects. Several rodent studies have shown that low-frequency stimulation of the hippocampus results in fewer seizures and an increase in the seizure threshold [94–99], although when directly compared to higher frequency stimulation, it was found to be less effective [99]. Similarly, Boëx et al. [100] found that high-frequency stimulation, but not low-frequency stimulation, was associated with a reduction in interictal discharges and absence of clinical or sub-clinical seizures during stimulation in three patients with temporal lobe epilepsy.

Both continuous and cycling stimulation have been trialed in the treatment of epilepsy and found to be effective [68, 101], though their relative efficacy has rarely been compared. One human clinical trial stimulating the ANT revealed a reduction in seizure frequency for both continuous and cycling stimulation with no clear differences in the efficacy of either regime [55, 65]. However, these results are difficult to interpret as cycling was implemented immediately following continuous stimulation and thus may have been confounded by carry over effects of the continuous stimulation. A separate trial found that continuous stimulation actually exacerbated seizures in one patient, while cycling with the same parameters did not [57••]. Regardless, the use of cycling may pose some practical advantages over continuous stimulation, as it is theoretically safer for the brain tissue and can prolong the battery life of the device [5]. Though if a cycling regime is implemented, the duration of the stimulation ON phase may be an important consideration; Osorio et al. [82] found that applying stimulation for 2.5 s was ineffective but observed considerable improvements when increased to 30 s. Furthermore, the waveform shape could also influence the response to stimulation. Biphasic pulses (positive pulse followed by a negative pulse or vice-versa) have been shown to produce greater reductions in interictal discharges compared to that of monophasic pulses in some patients [102]. There has also been very little comparison between unilateral versus bilateral stimulation. In two rat epilepsy models, the application of bilateral stimulation of the ANT was found to produce a greater reduction in seizure activity than unilateral stimulation [45, 103]. These findings are supported by a human clinical trial that found that switching from unilateral to bilateral stimulation could further improve the outcome. However, as with the other stimulation parameters, a more thorough investigation is required to draw any meaningful conclusions.

Ultimately, it is likely that selecting the stimulating electrodes and stimulation parameters in a patient-specific manner will produce the best results. The trial by Herrman et al. [56] stimulated the ANT using the same set of electrodes and parameters across all patients regardless of their response and concluded the trial early due to poor responder rates and in some cases a possible worsening of patient condition. In contrast, trials that have adjusted stimulation electrodes and parameters according to individual patient needs have produced much more promising results [67, 85, 93, 101]. Currently, clinicians tend only to adjust the stimulating electrodes or parameters when there is a lack of improvement in seizure frequency or if negative side effects arise [57••, 58••, 63•]. Consequently, it is likely that for most patients, the ideal stimulating electrodes or parameters are not being used. Optimizing stimulation for each patient is an important aspect of DBS for epilepsy that requires attention.

Closed-loop DBS

Unlike movement disorders such as Parkinson's disease, where optimal stimulation parameters can be identified almost immediately via the cessation of tremor and other motor effects, the sporadic nature of seizures makes it difficult to determine if DBS treatment is effective over short time frames. Consequently, clinical studies have been forced to assess treatment efficacy over months to years of trial-and-error parameter adjustment. DBS devices that include recording capabilities may be key in improving stimulation optimization by providing more immediate feedback. However, first we must identify suitable markers of stimulation efficacy.

Implantation of DBS electrodes into regions of the limbic system provides the perfect opportunity to assess excitability and measure the efficacy of DBS. The circuit of Papez forms a closed-loop neural circuit within which the propensity of seizures to initiate and propagate can be directly measured. DBS trials have demonstrated clear patterns between stimulation-evoked responses and the suppression of seizures [47, 74, 104, 105]. Van Gompel et al. [93] used evoked responses recorded in the hippocampus to identify ANT electrodes that optimally activated the Papez circuit. Furthermore, Velasco et al. [47] showed that the evoked responses recorded between the amygdala and hippocampus flattened out after high-frequency stimulation of the hippocampal region, and that this was a marker for anti-epileptic inhibition of the hippocampus. Our own experience with DBS has confirmed these findings. In one patient with DBS devices implanted bilaterally into the ANT and hippocampus, we observed that stimulating with high frequency (150 Hz) and voltage (5 V) in either the hippocampus or ANT caused an increase in the evoked potential size and had a seizure promoting effect. However, lower stimulation frequency (120 Hz) and voltage (2.5 V) combinations instead caused a flattening of the evoked potentials and have produced a significant reduction in seizure rates (– 96% in the last month). Figure 2 shows how a small voltage change can lead to a large change in the evoked responses.

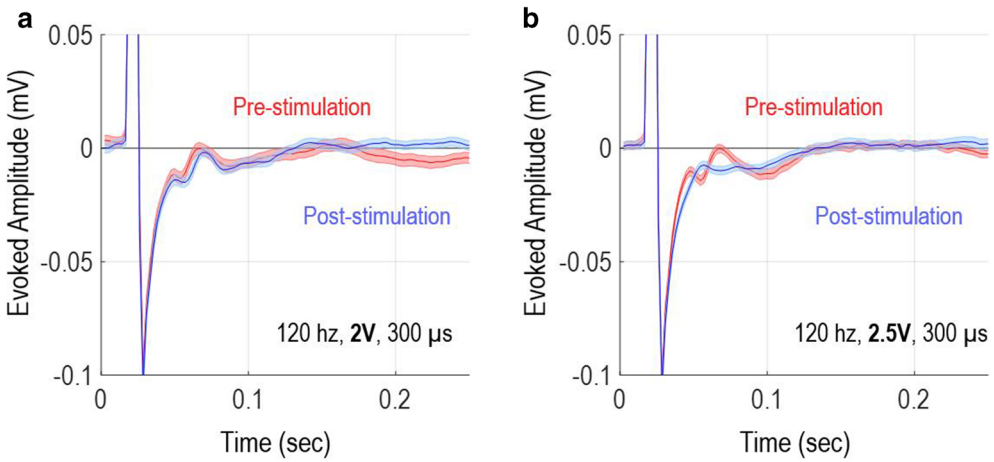

Fig. 2. Changes in evoked responses prior to (red) and after (blue) high-frequency stimulation of the hippocampus. **a** When stimulating the hippocampus with 120 Hz, 2 V and 300 µs pulse width, the pre- and post-stimulus evoked responses showed little difference. **b** Increasing the stimulation amplitude to 2.5 V caused a reduction the evoked response amplitude and has resulted in an effective therapy for this patient.

Desynchronization between regions in the circuit of Papez has been suggested to be a possible mode of action of DBS for epilepsy [74, 86, 106]. Yu et al. [74] demonstrated that recordings between different regions could be used to measure synchronization and thereby the effectiveness of DBS. The study found that low synchronization between regions was correlated with a suppression of seizures. Desynchronization in network activity may therefore offer a powerful method of assessing the efficacy of stimulation parameters.

There are some known side effects that can result from stimulation, including memory impairment and sleep fragmentation [68, 91]. We know that the brain goes though natural cycles that influence seizure likelihood [107•], and stimulation at times where there is already a low risk of a seizure occurring may not be beneficial. By only stimulating when needed, in a closed-loop system, we could potentially reduce the prevalence and severity of stimulation-related side effects.

The RNS system (NeuroPace, Inc) is an example of a closed-loop system that operates responsively using epileptiform activity as a biomarker for the state of the brain. This system detects when abnormal activity is identified, as defined by a neurologist and often constituting of interictal spikes or electrographic seizures, and then applies electrical stimulation to abate the activity. It is interesting that the results in this closed-loop study were not very different from open-loop DBS trials. Osorio et al. [82] also attempted closed-loop stimulation based on interictal spikes in 8 patients, where stimulation was either applied at the ANT or cortical surface. The mean seizure reduction was 58%, and 5 patients were considered responders. The poor efficacy observed in some patients in these studies may be due to the biomarker used to regulate stimulation.

Whether interictal spiking is seizure preventing or seizure facilitating remains controversial. Gotman et al. [108] showed that seizures could be preceded by increases or decreases in interictal activity and overall there was no clear relationship between seizures and interictal spikes. Baud et al. [109] investigated the time course of interictal spiking rates in 37 participants with the RNS implant. Of these, only 14 participants had detected events that were reliably linked to seizures. In these 14 patients, seizures were positively correlated with increases in interictal spiking. However, this may not generalize to other patients. Interictal spikes have been found to be both pro- and anti-seizure [110••]. In vitro and in vivo studies have confirmed this finding and suggest that the effect of interictal spikes depends on the dynamical state of the brain at the time of the event [111••]. If an interictal spike occurs at a highly susceptible time, seizures can be facilitated, otherwise they can be prevented. Nevertheless, clear relationships between spiking and seizures are apparent in most subjects [109, 110••, 112–114] and closed-loop stimulation needs to be flexible enough to respond to patient specific changes in biomarkers of seizure risk.

Future outlook

Deep brain stimulation provides a safe and effective therapeutic option for many patients with refractory epilepsy. The future of DBS looks particularly promising as patients tend to see continued improvements in their condition over long-term periods (> 5 years) [69, 115, 116]. Furthermore, DBS may prove effective for etiologies that are difficult to treat via other options [117•]. However, DBS is not effective for all patients with epilepsy. It remains unclear why some patients achieve a high reduction in seizure rates, while others do not. Given the risks

and costs associated with the implantation of DBS, more work is clearly required to better screen potential candidates and optimize stimulation parameters.

Improvements in patient outcome will likely come from the use of closed-loop stimulation. Devices that can record brain activity create new opportunities to monitor the effects of stimulation, tune stimulation parameters for individual patients, and automatically titrate stimulation for when it is needed. However, further investigations into clinically relevant biomarkers are sorely needed. Implanted DBS electrodes may provide a unique opportunity to determine seizure risk and monitor stimulation efficacy relative to a range of biomarkers such as interictal spikes [109, 110••, 111••], statistical markers [118–123], and circadian rhythms [107•, 124]. Biomarkers of seizure likelihood are likely to differ between patients and accurately gauging the seizure risk may require several different biomarkers. DBS devices tuned to each patient's condition will undoubtedly pave the way for improved outcomes and provide relief for patients still awaiting seizure control.

Compliance with Ethical Standards

Conflict of Interest

Katrina L. Dell and Mark J. Cook each declare no potential conflicts of interest. Matias I. Maturana reports grants from National Health and Medical Research—GNT1130468 and grants from Melbourne Neuroscience Institute Fellowship, during the conduct of the study.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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