Received: August 21, 2015 Revised: December 23, 2015 Accepted: February 28, 2016

(onlinelibrary.wiley.com) DOI: 10.1111/ner.12435

Low and High Frequency Hippocampal Stimulation for Drug-Resistant Mesial Temporal Lobe Epilepsy

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Objective: Electrical stimulation of the hippocampus offers the possibility to treat patients with mesial temporal lobe epilepsy (MTLE) who are not surgical candidates. We report long-term follow-up results in five patients receiving low or high frequency hippocampal stimulation for drug-resistant MTLE.

Materials and Methods: The patients underwent stereotactic implantation of quadripolar stimulating electrodes in the hippocampus. Two of the patients received unilateral electrode implantation, while the other three received bilateral implantation. Stimulation of the hippocampal electrodes was turned ON immediately after the implantation of an implantable pulse generator, with initial stimulation parameters: 1 V, 90–150 μs, 5 or 145 Hz. The frequency of seizures was monitored and compared with pre-implantation baseline data.

Results: Two men and three women, aged 27–61 years were studied, with a mean follow-up period of 38.4 months (range, 30–42 months). The baseline seizure frequency was 2.0–15.3/month. The five patients had an average 45% (range 22–72%) reduction in the frequency of seizures after hippocampal stimulation over the study period. Low frequency hippocampal stimulation decreased the frequency of seizures in two patients (by 54% and 72%, respectively). No implantation- or stimulation-related side effects were reported.

Conclusions: Electrical stimulation of the hippocampus is a minimally invasive and reversible method that can improve seizure outcomes in patients with drug-resistant MTLE. The optimal frequency of stimulation varied from patient to patient and therefore required individual setting. These experimental results warrant further controlled studies with a large patient population to evaluate the long-term effect of hippocampal stimulation with different stimulation parameters.

Keywords: deep brain stimulation, epilepsy, high frequency electrical stimulation, low frequency electrical stimulation, outcomes

Conflict of Interest: The authors reported no conflict of interest.

INTRODUCTION

Mesial temporal lobe epilepsy (MTLE) is the most common focal epilepsy affecting adults, and is often associated with pharmacological resistance. Temporal lobe resection is, thus, an accepted treatment option for the management of drug-resistant MTLE. The ideal candidates for surgical resection are those with unilateral ictal EEG discharges and ipsilateral brain magnetic resonance imaging (MRI) evidence of hippocampal sclerosis, with reported success rates ranging from 70 to 90% in both randomized controlled trials and long-term longitudinal cohort studies (1–5). However, temporal lobectomy and hippocampectomy are not suitable for certain patients due to the bilateral nature of the disease and concerns over the risk of memory deficits or even severe amnesia. Alternative therapeutic strategies are therefore required for these patients to achieve better seizure control.

Deep brain stimulation (DBS) is increasingly recognized to be an attractive treatment option for drug-resistant epilepsy. By directly

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targeting a specific neural region or circuit, DBS can modulate symptoms in a manner that is both adjustable and reversible (6). Various brain targets have been investigated, including the anterior and centromedian thalamic nucleus, the cerebellum, the subthalamic nucleus, the caudate nucleus, the motor cortex and the hippocampus (6,7). Two large randomized controlled trials demonstrated the efficacy and safety of intermittent anterior thalamic nucleus (ATN) stimulation (8), and responsive stimulation at the sites of seizure origin (9). Despite these encouraging results, the optimum stimulation targets and parameters for drug-resistant epilepsy have yet to be elucidated.

In 2000, Velasco et al. proposed the use of amygdalohippocampal DBS to control MTLE (10). In their study, hippocampal stimulation using depth electrodes significantly reduced interictal EEG spikes and improved seizure outcomes in 10 patients scheduled to undergo temporal lobectomy. Subsequently, other research groups have demonstrated the efficacy of chronic hippocampal stimulation, with more than half of the patients experiencing a reduction in the frequency of seizures by more than 50% (11–17). Patients with normal MRI findings have been reported to have better seizure outcomes after hippocampal stimulation compared to those with hippocampal sclerosis on baseline MRI (15). In addition, bilateral hippocampal stimulation has been reported to be more effective than unilateral stimulation (17). Currently, there is no consensus on the most appropriate choice of stimulation parameters. The majority of clinical studies have focused on pulsatile high frequency stimulation of the hippocampus, with frequencies ranging from 130 to 200 Hz (18). One human study reported temporary suppression of interictal epileptic activity for 5–10 sec after short-term low frequency stimulation (1–3 sec, 1–3 Hz) of temporal lobe mesiobasal epileptic foci (19). Experimental evidence in animals has also demonstrated that prolonged low frequency stimulation (1 Hz for 10–15 min) increases seizure threshold and inhibits the development of amygdala-kindled seizures (20). However, the long-term beneficial effect of low frequency hippocampal stimulation has not been confirmed in humans with MTLE. In this study, five patients received electrode implantation for hippocampal stimulation for drug-resistant MTLE. Immediately after system internalization, low frequency hippocampal stimulation was applied to patients with MRI suggestive of hippocampal sclerosis, whereas patients with normal MRI received high frequency stimulation. We report the long-term follow-up results of hippocampal stimulation with regards to seizure reduction.

MATERIAL AND METHODS

Subjects and Study Design

The study protocol was approved by the Institutional Ethics Board of Chang Gung Memorial Hospital, Linkou, Taiwan. The preoperative work-up consisted of carefully describing the seizures, neurological examinations, antiepileptic drug (AED) blood levels, and serial EEG including video-EEG, brain MRI, brain FDG-PET and/or SPECT. Five patients with drug-resistant MTLE were enrolled, and informed consent was obtained. These patients were selected based on the following criteria: a) suspicion of MTLE on the basis of video-EEG monitoring; b) capable of recording reliable seizure diaries and with a prospective seizure frequency of at least two complex partial seizures (CPS) per month during a baseline of three months; c) failed ≥ 3 AEDs and currently receiving 1–3 AEDs. Resective surgery is commonly suggested as the treatment option for such patients, however brain stimulation was chosen for these five patients due to concerns of possible postoperative significant worsening of memory, the presence of bilateral hippocampal sclerosis or because bilateral epileptogenic zones were suspected.

Before electrode implantation, daily seizure diaries were prospectively recorded for 3 months, and this served as seizure baseline data, which were compared with seizure data after electrode implantation. Potential adverse events were closely monitored. All AEDs remained unchanged within the first 6 months after stimulation, however they could be subsequently adjusted to minimize side effects or to achieve seizure control.

Surgical Procedures

The patients underwent preoperative cerebral computed tomography (CT) to determine the targets and anterior commissure/posterior commissure (AC/PC) reference line stereotactically. Under local anesthesia, four contact electrodes (3387, Medtronic, Minneapolis, MN, USA) were implanted stereotactically using a parasagittal occipital approach, directed along the hippocampus with the anterior contact placed in the hippocampus head, and the remaining three contacts fit within the hippocampus. The location of the stimulation leads was further confirmed by postoperative brain MRI.

After electrode implantation, external extension was performed to provide EEG recordings for 5–7 days before internalization. The hippocampal EEG was recorded via the implanted leads at the same time as scalp EEG. A trial of hippocampal stimulation with 2 days of stimulation OFF and 2 days with stimulation ON was performed. Spontaneous clinical seizures were recorded, and the number of interictal epileptiform discharges in the first 3-minute period of every hour was identified visually and counted manually. Seven days after electrode implantation, a pulse generator (IPG; 7426 Soletrea or 7428 Kinetra Neurostimulator, Medtronic) was placed subcutaneously into the infraclavicular pocket and connected to stimulation electrodes via a lead extension (Medtronic 7482 Lead Extension, Medtronic).

Stimulation Parameters

All of the patients received stimulation immediately after system internalization. High frequency (145 Hz) or low frequency (5 Hz) stimulation was applied, with a pulse width of 90–150 μs and pulse amplitude of 1 V. Of note, high frequency stimulation (145 Hz) was initially applied in the patients with normal brain MRI based on previous studies, whereas an initial stimulation frequency of 5 Hz was applied in those with MRI evidence of hippocampal sclerosis. After implantation, the patients were followed up monthly for the first 6 months, and every 3 months thereafter or when clinically required. The aim of this open label study was to improve seizure control for patients with drug-resistant MTLE, therefore ongoing adjustments of the stimulation parameters were allowed to achieve the best medical outcomes. These adjustments included first gradual increasing the voltage by 0.5–1 V to a maximum of 6 V, and then adjusting the frequency using either high (range, 90–180 Hz) or low frequency (range, 3–5 Hz), and finally adjusting the pulse width by 30 μs. Based on the assumption that the current generated should be more localized than monopolar, pairs of adjacent electrode contacts were stimulated in a bipolar manner with the most anterior electrode contact serving as the anode and the third electrode contact serving as the cathode, or vice versa. Intermittent (cycling) stimulation with 1 minute ON and 5 minutes OFF was used.

RESULTS

Postimplantation Video-EEG Monitoring

Each patient received postimplantation video-EEG monitoring, after which unilateral or bilateral interictal epileptiform discharges

were recorded from both DBS electrodes and scalp EEG in all of the patients. Under stimulation with low (patients 3 and 4) or high (patients 1, 2, and 5) frequency, the number of interictal epileptiform discharges reduced by more than 50% compared to no stimulation in all five patients. Throughout the video-EEG recording period, no clinical seizures were recorded in patient 3, whereas the remaining four patients experienced two to six episodes of complex partial seizures. Ictal EEG revealed onset from one or more electrode contacts on one of the DBS electrodes, typically consisting of a high frequency, low voltage discharge, occurring seconds before the onset of a clinical seizure, followed by spread to ipsilateral neocortical areas and the contralateral mesial temporal structures. After stimulation was turned ON, no seizures were recorded in patients 1 and 5, and patient 4 had fewer seizures compared with the period without stimulation (four without stimulation, and two with stimulation). Patient 2 experienced two complex partial seizures when stimulation was turned OFF, involving fast activities and rhythmic sharp waves over the right DBS electrode contacts, which spread to left mesial temporal and bilateral neocortical areas. External stimulation of the right and left hippocampus for 3 sec then stopped the ictal EEG discharges in this patient.

General Results and Seizure Control

Table 1 summarizes the clinical characteristics, imaging studies, individual AED treatment, electrode implantation side, postimplantation AED adjustments, and initial and final stimulation parameters of the patients. One patient had bilateral hippocampal sclerosis with EEG showing interictal and ictal onset foci in the right hippocampus only (patient 3), while one patient had left hippocampal sclerosis, which correlated with the onset of interictal and ictal epileptic activity in the left hippocampus (patient 4). The remaining three patients had non-lesional MTLE with seizures arising from the right hippocampus in two (patients 1 and 2) and left hippocampus in one (patient 5); these three patients also had interictal independent bilateral hippocampal epileptic activity. Two patients received unilateral implantation (patients 1 and 4) and three patients bilateral implantation (patients 2, 3 and 5). Patient 1 had normal brain MRI with bilateral interictal epileptic activity, and a unilateral quadripolar electrode was implanted over the right hippocampus based on the ictal EEG recordings that showed seizures arising mainly from the right. In the subsequent study, bilateral electrode implantation was used in the patients with either bilateral interictal epileptic activity (patients 2 and 5) or bilateral hippocampal sclerosis (patient 3). Patient 4 received unilateral electrode implantation in the left sclerotic hippocampus that correlated with the onset of interictal and ictal epileptic activity in the left hippocampus. Table 2 summarizes the interictal and ictal EEG findings, stimulation side and frequency applied.

Seizure frequency at baseline and during follow-up was highly variable among the patients, and this variability was reflected in the results (Table 3). The baseline seizure frequency was 2.0–15.3/month, and the average postoperative follow-up period was 38.4 months (range, 30–42 months). The frequency of seizures improved after hippocampal stimulation in all of the patients, with a mean reduction of 45% (range, 22–72%). Two patients (patients 1 and 5) with a baseline seizure frequency of 2 per month only achieved a 22% reduction after hippocampal stimulation, whereas the three remaining patients (patients 2–4) with higher frequencies of baseline seizures had a reduction of more than 50%. Age, seizure duration and whether unilateral or bilateral stimulation was applied were not correlated with a specific response.

Figure 1 shows the temporal pattern of the reduction in seizures from baseline to 42 months of stimulation treatment. There was an initial reduction in the frequency of seizures in the first 9 months, which transiently increased by 12–18 months and was then followed by a prolonged period of relatively stable seizures reduction. Figure 2 further demonstrates changes in the incidence rates of seizures and the corresponding stimulation frequency for each patient. The two patients with hippocampal sclerosis (patients 3 and 4) received low frequency stimulation and experienced a 54% and 72% reduction in seizure frequency after hippocampal stimulation, respectively. Although the stimulation frequency was transiently increased to 90 Hz from months 3 to 5 in patient 4, there was no significant change in the frequency of seizures between high and low frequency stimulation in this patient. For the three patients with normal brain MRI, patient 5 received high frequency stimulation throughout the follow-up period and only achieved a 22% reduction in the frequency of seizures, whereas the remaining two patients received high frequency stimulation initially which was then adjusted according to their seizure frequency. Patient 1 experienced an increase in seizure frequency in the first 6 months after high frequency stimulation, and therefore low frequency stimulation was applied, after which there was a gradual reduction in the frequency of seizures. However, as only a 25% reduction had been achieved after 18 months, high frequency stimulation was subsequently applied again with a modest effect. A dramatic reduction in seizures was noted during the first 3 months in patient 2, after which the frequency of her seizures gradually increased, and therefore low frequency stimulation was applied from month 6 to 12. However, the frequency of her seizures continued to increase, so we changed back to high frequency stimulation which resulted in better seizure control.

AEDs Adjustment

For at least the first 6 months postimplantation, no changes were made in the AEDs for any of the patients. Comparing the seizure frequency between the periods of each AED adjustment revealed an increased seizure frequency in patient 1 with a decrease in clonazepam dose (2.5/M vs. 5/M) at month 7, a decrease in seizure frequency with a low dose of valproic acid at month 8 (2/M), and adjustments were made to maintain the therapeutic level at month 17 (1/M) with the addition of pregabalin at month 42 (1/M). Patient 2 had an increase in the doses of oxcarbazepine at month seven with the addition of levetiracetam at month 24. An increase in seizure frequency was noted after the addition of levetiracetam (8/M vs. 11/M), and it was therefore discontinued at month 25. Patient 3 was given oxcarbazepine with the discontinuation of valproic acid due to pregnancy at month 38. Oxcarbazepine was then discontinued at month 39 and levetiracetam was added at month 40, and no significant changes in seizure frequency were noted during these periods. Patient 4 had no changes in medication, and patient 5 had small adjustments in the dose of topiramate at month 19, with the addition of oxcarbazepine at month 27 and a decrease in the dose of topiramate at month 29. Most adjustments did not seem to affect seizure frequency except for an exacerbation of seizure control with levetiracetam in patient 2 (month 24). The duration of AED adjustment did not allow for statistical analysis.

Complications

All of the five patients tolerated both the surgical procedure and electrical stimulation well. Postsurgical MRI did not show evidence of either intracranial hemorrhage or edema. No adverse effects were reported and no new seizure types emerged during follow-up. In addition, no disturbances in sleep patterns or behavioral changes were reported.

Table 1. Clinical Patient Characteristics, Presurgical Evaluation Results, and Postsurgical Adjustment.

Characteristic	Patient no.				
	1	2	3	4	5
Age (years)	61	27	27	29	32
Sex	M	F	F	F	M
Seizure onset age	30 year old	14 year old	4 year old	6 year old	25 year old
Etiology	Cryptogenic	Cryptogenic	Cryptogenic	Cryptogenic	Cryptogenic
Seizure type	CPS, secondarily GTCS	CPS	CPS, secondarily GTCS	CPS	CPS, secondarily GTCS
Video-EEG monitoring					
Interictal EEG	B MT independent SW	B MT independent sharp wave (L > R)	R MT SW	L MT SW	B MT independent SW
Ictal EEG	R MT	R MT	R MT	L MT	L MT
Seizure semiology	No aura, staring, vocalization, orobuccal automatism, bilateral hand automatism; occasional L version of head, followed by L hand twitching and GTCS; postictal confusion	No aura, staring, stand up, bilateral hand automatism	Autonomic aura, complex motor, GTCS	Fearful sensation	Orobuccal automatisms; turn to left and right hand automatism, GTCS
Brain MRI	Normal	Normal	Bilateral hippocampal sclerosis (R > L)	L hippocampal sclerosis	Normal
Stimulation side	R	B	B	L	B
Baseline AEDs (mg/day)	PHT (350), TPM (600), CNZ (4)	OXC (1500)	VPA (1500), LTG (200), CNZ (1)	OXC (1800)	TPM (200)
Poststimulation AEDs adjustment					
First adjustment	Month 7: PHT (350), TPM (600), CNZ (3)	Month 7: OXC (1800)	Month 38: LTG (100), CNZ (1), OXC (600) (Discontinue VPA due to pregnancy)		Month 19: TPM (250)
Second adjustment	Month 8: PHT (350), TPM (600), CNZ (3), VPA (500)	Month 24: OXC (1800), LVT (500)	Month 39: LTG (150), CNZ (1)		Month 27: TPM (250), OXC (600)
Third adjustment	Month 17: PHT (350), TPM (300), CNZ (3), VPA (1500)	Month 25: OXC (1800)	Month 40: LTG (150), CNZ (1), LVT (1000)		Month 29: TPM (200), OXC (600)
Fourth adjustment	Month 42: PHT (350), TPM (300), CNZ (3), VPA (1500), PGB (225)				
Stimulation parameters					
Initial	Cycling (1 min ON, 4 min OFF), bipolar, 1 V, 150 μs, 145 Hz	Cycling (1 min ON, 5 min OFF), bipolar, 1 V, 90 μs, 145 Hz	Cycling (1 min ON, 5 min OFF), bipolar, 1 V, 90 μs, 5 Hz	Cycling (1 min ON, 5 min OFF), bipolar, 1 V, 90 μs, 5 Hz	Cycling (1 min ON, 5 min OFF), bipolar, 1 V, 90 μs, 145 Hz
Last	Cycling (1 min ON, 5 min OFF), unipolar, 6 V, 180 μs, 145 Hz	Cycling (1 min ON, 5 min OFF), bipolar, 6 V, 120 μs, and 180 Hz	Cycling (1 min ON, 5 min OFF), bipolar, 1 V, 90 μs, 5 Hz	Continuous, bipolar, 4 V, 120 μs, and 5 Hz	Cycling (1 min ON, 5 min OFF), bipolar, 5 V, 90 μs, and 145 Hz

CPS, complex partial seizures; GTCS, generalized tonic-clonic seizures; B, bilateral; L, left-sided; R, right-sided; MT: mesial temporal; SW, spike-and-wave discharge; MRI, magnetic resonance imaging; AEDs, antiepileptic drugs; PHT, phenytoin ; TPM, topiramate; CNZ, clonazepam; OXC, oxcarbazepine; VPA, valproic acid; LTG, lamotrigine; LVT, levetiracetam; PGB, pregabalin.

Table 2. Clinical and Stimulation Characteristics.

Patient no.	Interictal EEG	Ictal EEG	Brain MRI	Side of stimulation	Initial stimulation frequency
1	B MT	R MT	Normal	R	High (145 Hz)
2	B MT	R MT	Normal	B	High (145 Hz)
3	R MT	R MT	B hippocampal sclerosis	B	Low (5 Hz)
4	L MT	L MT	L hippocampal sclerosis	L	Low (5Hz)
5	B MT	L MT	Normal	B	High (145 Hz)

B, bilateral; MT, mesial temporal; R, right; L, left.

DISCUSSION

The results of this study suggest that long-term hippocampal stimulation may be safe and effective for patients with drug-resistant MTLE. Comparisons of the frequency of seizures at baseline and during the postimplantation period revealed a mean reduction in seizures of 45% (range 22–72%), including two patients with MRI evidence of hippocampal sclerosis. To the best of our knowledge, this article is the first to demonstrate that chronic low frequency hippocampal stimulation can decrease seizure frequency in patients with drug-resistant MTLE. Our results suggest that brain stimulation should be tailored individually and that stimulation parameters should also be taken into consideration when interpreting the efficacy of hippocampal stimulation, especially in those with hippocampal sclerosis.

There was an initial reduction in seizure frequency in both the patients with or without hippocampal sclerosis, which increased transiently by 12–18 months and was then followed by a prolonged period of relatively stable seizure reduction. Because all of the patients received active stimulation immediately after internalization of IPG, we cannot rule out factors other than the stimulation as the cause of the improvements. The "implant effect" ("insertional effect") caused by electrode implantation may have contributed to the initial seizure reduction, and thus a double-blind controlled study with active stimulation and a control group is required to clarify the therapeutic effect achieved by insertion of DBS electrodes alone, with active hippocampal stimulation, or interactions between these factors. It is nonetheless encouraging that the benefits observed during the early phase of this study did not diminish, and in fact seemed to increase over time. Although the mechanism remains unknown, steady improvements have been reported with VNS (21), ATN (8), and responsive stimulation (9) for epilepsy. Our results and the observations from a recent long-term study (17) suggest that hippocampal stimulation should be added to this list. Given the long duration and severity of epilepsy in our five patients, and that treatment with many AEDs failed, the sustained reduction in seizures with hippocampal stimulation is clinically meaningful.

Among our patients, responses to stimulation were highly variable and individualized. The patients with hippocampal sclerosis had a 54–72% reduction in seizures, compared to 22–55% in the three patients with normal MRI, which is in contrast with findings from a previous report (15). Using high frequency (130 Hz) hippocampal stimulation in both patients with or without hippocampal sclerosis, Velasco and colleagues found that improvements occurred sooner and were more significant in the patients with normal MRI in a follow-up period of 18–84 months compared with those with hippocampal sclerosis. The authors speculated that in order to achieve a satisfactory response to stimulation, it is important that the neuronal network be preserved in the stimulated area, and that the severe neuronal reduction that accompanies hippocampal sclerosis may represent a less satisfactory tissue for modulation with stimulation. A recent study by Boëx reported that a large zone of stimulation with either high voltage bipolar DBS ($\geq$1 V) or quadripolar stimulation is required for patients with hippocampal sclerosis, while a limited zone of stimulation or even a microlesional effect could be sufficient in patients with normal brain MRI (11). However, it must be emphasized that the small number of patients and limited data preclude any definite conclusions regarding the effective parameters for patients with or without hippocampal sclerosis.

It is generally accepted that stimulus parameters, and particularly frequency, have a profound impact on the effects of the stimulation (22). The mechanism behind this frequency-dependent effect on brain stimulation is unclear, and the parameter selection process is still largely empirical. A frequency range between 10 and 70 Hz is commonly used to induce kindling and is generally avoided as it may induce seizures. This leaves a high frequency range ($>$70 Hz) and a low frequency range ($<$10 Hz) (23). It has been suggested that high frequency stimulation-induced EEG desynchronization has a

Table 3. Effects of Hippocampal Stimulation in Seizure Control.

Patient no.	Patient sex/age (year)	Baseline seizure frequency/month	Post-DBS seizure frequency/month (mean seizure reduction)	Total follow-up (month)
1	M/61	2.3 ± 1.2	1.8 ± 1.2 (−23%)	42
2	F/27	15.3 ± 7.5	7.0 ± 3.9 (−55%)	42
3	F/27	4.0 ± 2.6	1.8 ± 1.7 (−54%)	42
4	F/29	13.0 ± 2.6	3.7 ± 3.1 (−72%)	36
5	M/32	2.0 ± 0.0	1.5 ± 1.2 (−22%)	30

Seizure frequency is expressed as mean ± standard deviation.

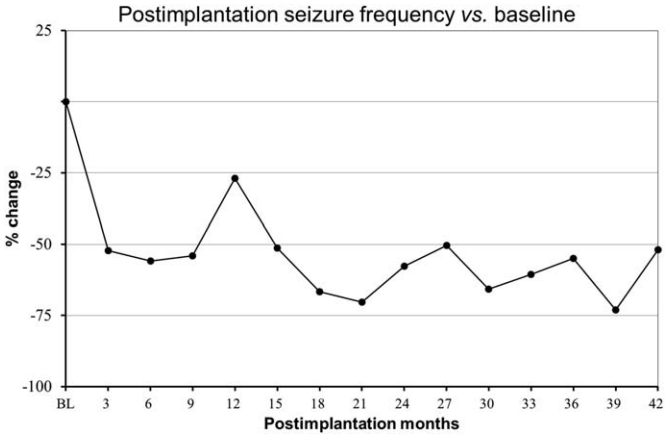

Figure 1. Frequency of seizures over time after stimulator implantation, expressed as a percentage of that at baseline (BL). A negative value indicates a reduction in the frequency of seizures compared with baseline.

beneficial therapeutic effect in patients with epilepsy, and the antiepileptic effect of high frequency hippocampal stimulation has been widely studied in both clinical and preclinical studies (6,7,18). In contrast, relatively few reports have studied the efficacy of low frequency stimulation, which is still under debate, even though it is assumed to have an antiepileptic effect. Animal studies have concluded that high frequency stimulation at 130 Hz is more effective than low frequency stimulation (5 Hz) in affecting excitability in epileptic rats (23). The beneficial effect of high frequency stimulation but not low frequency stimulation in nonlesional MTLE was described by Boëx and colleagues (24). In this short-term study, stimulation to the hippocampus with 130 Hz for 3–6 hours significantly reduced interictal discharges and abolished seizures in three patients with non-lesional MTLE, whereas persistent interictal discharges and habitual seizures still occurred despite low frequency stimulation (5 Hz). Furthermore, low frequency stimulation of either the kindling focus (25) or areas that participate in the spread of seizures (26) delayed the development of seizures in a hippocampal epilepsy model in rats. Even in fully kindled animals, preemptive low frequency at the kindling focus dramatically decreased stage 5 seizures (27). Nevertheless, studies supporting the efficacy of low frequency stimulation in humans are rare (19,28,29). Recently, Koubeissi et al. found that low frequency stimulation of the hippocampal fiber tract reduced interictal spikes and lowered the chances of a seizure by 92% in the subsequent 48 hours (30). However, long-term follow-up was not performed for these patients. Our results demonstrated that for patients with hippocampal sclerosis, low frequency hippocampal stimulation was tolerable and reduced the frequency of seizures in long-term follow-up. Due to the small sample size and a number of uncontrolled variables, including the stimulation settings (voltage and pulse width, bilaterally or unilaterally) and short duration of treatment with each stimulation parameter, more clinical data are still needed before drawing any adequate conclusions. In addition, whether patients with normal MRI findings respond better to high or low frequency stimulation remains undetermined. A double-controlled, randomized, prospective study with systemic switching between low and high frequency stimulation over a longer time period across subjects is warranted to elucidate the effect of stimulation frequency in different etiologies of MTLE. Furthermore, as the selection of the optimal frequency may be based on its ability to induce EEG-desynchronization and reduce interictal epileptic activity, a double-blind controlled study with EEG monitoring is needed to clarify the effect of each stimulation parameter for EEG desynchronization and seizure control.

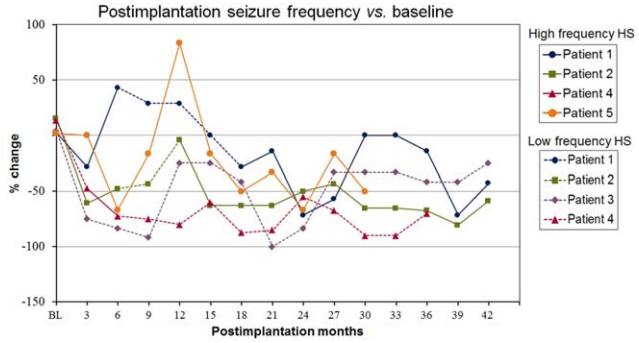

Figure 2. Postimplantation frequency of seizures in each patient. Solid lines represent high frequency hippocampal stimulation (HS). Dotted lines represent low frequency HS.

In this study, we used electrodes developed for Parkinson's disease, and being implanted on ATN for epilepsy treatment. These quadripolar electrodes span a length of 10.5 mm, which did not cover the whole hippocampus. This indicated that we only stimulated the anterior portions of the hippocampus, therefore a longer electrode (11,31), or more contacts (12) would possible needed in the future study to cover the hippocampal formation more adequately.

An obvious question is whether adjustments in AEDs accounted for the improvements in seizure control in the long-term follow-up phase. It is important to note that all five patients had tried at least three AEDs without major benefits before hippocampal stimulation. In addition, the AEDs were kept constant during the first 6 months, and improvements were evident during this phase. Thus, although we cannot completely rule out the effect of changes in AEDs, the findings suggest that adjustments in the medications did not have a major effect on seizure control.

Memory decline following temporal lobectomy has been documented in several studies; however no patients receiving hippocampal stimulation have been reported to experience such a decline, not even with bilateral stimulation (31). There was no apparent difference in the report of memory related adverse events, including the three patients who received bilateral hippocampal stimulation. Indeed, a recent study reported significant improvements in the memory in MTLE patients treated with responsive stimulation to mesial temporal regions (32).

The most significant potential complication of DBS is hemorrhage, which has been reported in 5% of patients. Mechanical equipment problems, skin erosion, infection or foreign body reactions are the other main complications of the placement of stimulation devices, particularly in thin patients (6). In our cases, none of these side-effects were observed. In addition, depression has been noted with ATN stimulation (33), however, none of our patients reported any emotional problems. Our findings suggest that hippocampal stimulation may be safe in patient with MTLE.

CONCLUSIONS

For patients with drug-resistant MTLE, resective surgery is a successful treatment strategy with good outcomes. Nevertheless, many patients with drug-resistant epilepsy are unsuitable for resective surgery or are reluctant to undergo brain surgery. For patients in whom

it is not advisable to perform resective surgery, hippocampal stimulation seems to be a promising alternative. The 38.4-month follow-up period in this study provides some evidence of proof of concept of the role of hippocampal stimulation in the treatment of drug-resistant MTLE, and provides support for ongoing investigations into this treatment modality.

Acknowledgements

This work was funded by the National Science Council of the Republic of China, Taiwan (NSC91-2314-B-182A-039), the National Health Research Institutes, Taiwan (NHRI-GT-EX89S926P), and Chang Gung Memorial Hospital, Taiwan (CMRPG3C0451).

Authorship Statement

Dr. Tony Wu conducted the study. Drs. Siew-Na Lim, Bao-Luen Chang, Chih-Hong Lee, Mei-Yun Cheng, Chun-Wei Chang, Wei-En Johnny Tseng, Hsiang-Yao Hsieh and Hsing-I Chiang were involved in patient recruitment, data analysis and manuscript writing. Drs. Ching-Yi Lee, Shih-Tseng Lee and Po-Hsun Tu assisted with surgical procedure and protocol development. All authors provided intellectual contributions to the manuscript and reviewed the final manuscript prior to submission. All authors contributed to the manuscript in accordance with ICMJE guidelines for authorship.

How to Cite this Article:

Lim S.-N., Lee C.-Y., Lee S.-T., Tu P.-H., Chang B.-L., Lee C.-H., Cheng M.-Y., Chang C.-W., Tseng W.-E.J., Hsieh H.-Y., Chiang H.-l., Wu T. 2016. Low and High Frequency Hippocampal Stimulation for Drug-Resistant Mesial Temporal Lobe Epilepsy.
Neuromodulation 2016; 19: 365–372

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COMMENTS

The authors of this study have performed important work by taking the analogous approach that we have taken with other disorders treated using Neuromodulation. Basically, what is the physiological effect of frequency in different disease states? In this study, the authors favor a low frequency stimulation approach in the two patients with hippocampal sclerosis and a high frequency approach in patients with non-lesional disease. The important observation to note is that there is a real insertional effect noted in the 4 patients described. And further, there is fluctuation in seizure frequency compared to baseline over the follow-up period. There is not full description of what the fluctuation of the seizure frequency was before intervention and these are quite important variables to track.

Nevertheless, it is important for exploratory studies such as this to occur. It raises questions, which may result in future therapies and understanding. The conclusions of this study given the sample size are limited and the reader must still realize that the published results of responsive stimulation still reveal more robust clinical responses over continuous deep brain stimulation in the hippocampus.

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Over one-third of patients with epilepsy do not have their seizures controlled with medications [1, 2]. For many of these drug-resistant patients, surgical removal of epileptogenic brain tissue is an effective and well-tolerated treatment that remains underutilized [3]. However, resective surgery is often not an option for patients with seizures that are multifocal or that arise from eloquent brain regions. The challenge of treating this patient population motivated the development of neurostimulation for epilepsy, now a burgeoning field [4–6]. Diverse cerebral structures, including thalamus, hippocampus, cerebellum, and neocortex [7], have been used as targets for neurostimulation, and devices to deliver electrical brain stimulation are also varied. For example, the NeuroPace RNS® System includes a neurostimulator that functions in a responsive (closed-loop) manner, continuously sensing brain activity through electrodes placed at the seizure onset zone(s) and, in response to detection of abnormal activity, stimulating at these sites to inhibit seizures. By contrast, several other devices have been developed to treat seizures without a feedback signal using fixed (open-loop) patterns of brain or cranial nerve electrical stimulation [8–12].

With ever-increasing clinical use of these devices, new challenges have emerged. Closed-loop and open-loop devices have comparable efficacy [9, 13], but head-to-head trials have not been done to establish superiority of either approach. Furthermore, for both types of devices, the stimulation parameter space is vast, and selection of stimulation parameters is largely empiric. High-frequency (> 100 Hz) stimulation is most often used in clinical settings, and experimental results with low-frequency (< 5 Hz) stimulation have been mixed, though chronic human data are lacking. Despite its clinical relevance, direct electrical brain stimulation is poorly understood with regard to mechanistic effects at the level of neural circuits [14], hampering our ability to efficiently determine optimal stimulation parameters for a given patient. Thus, 'rational electrotherapy' for epilepsy remains elusive [15].

The concept of chronic hippocampal stimulation for drug-resistant mesial temporal lobe epilepsy (MTLE) is not new, and there are several limitations to the small, uncontrolled, open label study by Lim and co-workers. However, an important finding is that chronic, open-loop, low-frequency hippocampal stimulation can reduce seizure frequency in drug-resistant MTLE. Mean seizure frequency was nearly halved compared to pre-stimulation baseline, and the authors are to be commended on the long period of follow-up (mean 38.4 months). Notably, clinical responses to high- vs. low-frequency stimulation were highly variable among the five subjects. There are hints that the underlying pathology (e.g. mesial temporal sclerosis vs. non-lesional) might explain some of this variation, but the small number of subjects precludes any firm conclusions. Clinical trials of the RNS® System and other neurostimulation devices were also not adequately powered to determine subgroup effects based on pathology, but such analyses may be possible with more widespread commercial use of these devices. Ideally, rapid determination of optimal stimulation parameters would be guided by electrophysiological biomarkers of treatment response, and identifying a control signal to take the guesswork out of neurostimulation remains a major goal of this field.

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Comments not included in the Early View version of this paper.

