

# Critically Appraised Topic

## Temporal Lobe Epilepsy and Hippocampal Stimulation

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### Hippocampal stimulation in medically intractable mesial temporal lobe epilepsy may be effective in reducing seizure frequency in patients for a period of up to 18 months

**Clinical Scenario:** A 55-year-old man has had temporal lobe epilepsy for 20 years and has failed treatment with multiple antiepileptic medications. He has on average 20 complex partial seizures per month. He does not have mesial temporal sclerosis on magnetic resonance imaging (MRI). He is not considering surgery. Video electroencephalogram (EEG) and electrode depth recording has confirmed a left mesial temporal lobe (MTL) focus.

**Clinical Question:** What is the safety, efficacy, and long term seizure control in patients with MTL epilepsy treated with hippocampal stimulation?

**Search Strategy:** Medline was used to search for articles by combining “epilepsy, Temporal lobe/th [therapy]” with hippocampal stimulation which mapped to “electric stimulation/ or hippocampus”. This yielded 51 articles; when English language and humans were used as limits yielded 35 articles. Three articles were relevant. The first article by Boon et al (2007) was an open pilot study and two of the 12 consecutive patients with refractory MTL seizures underwent resective surgery. The other study by Tellez-Zenteno et al (2006) used an individual patient randomized-controlled trial design (N of 1), but only included 4 patients. It was felt that the study by Velasco et al (2007) was the best evidence having the largest published study using a double-blinded protocol.

### Clinical Bottom Lines:

1. A seizure reduction of 79% ( $p < 0.0005$ ) occurred in all patients with electrical stimulation of the hippocampus. In patients without mesial temporal sclerosis (MTS) compared to those with MTS, seizure reduction appeared earlier (at 1 mo vs. 8 mo) and to a greater extent (95%,  $p < 0.0005$  vs. 69%,  $p < 0.05$  at 18 months).
2. There was a significant rate of complication consisting of skin erosion resulting in infection requiring removal of the stimulation device in three out of nine participants (33%).

**The evidence:** Velasco et al (2007) evaluated the safety, efficacy of hippocampal electrical stimulation and long-term follow-up in nine non-consecutive patients with medically refractory mesial temporal lobe epilepsy. All patients had complex partial seizures with 7/9 also having secondary generalized tonic-clonic seizures. Patients were selected from a larger group of patients who underwent bilateral hippocampal electrode implantation for diagnostic purposes. The study group consisted of nine patients (six male, three female) between the ages of 14-43 years. Average number of seizures per month was 28 (15-70) measured within a three month period. Five had normal MRIs and the remaining four had mesial temporal sclerosis. Three patients had bilateral foci and six had a unilateral focus of MTL seizure activity. Patients were randomized to a double blind stimulation protocol: five of the patients had an initial one month “off” period and the remaining four initiated stimulation immediately after implantation. Patients were evaluated at baseline (three months prior to electrode implantation) and subsequently every three months up to 84 months (mean-37 months). Every three months, up to 18 months patients were evaluated with EEG, neuro-psychological testing, neurophysiological testing, seizure frequency and complications. No changes were made to antiepileptic therapy. For the purpose of the study all participants were evaluated up to month 18 for main outcome measures (seizure frequency and neuropsychological performance) in addition to three months of baseline. Complications were reported regardless of duration of follow-up.

### RESULTS

	Mean Seizure frequency per month at baseline	Mean Seizure frequency per month at 18 months
Combined Group	28 [15-70]	6 [0-23] (significant from month 2); $p < 0.0005$ from month 6
Normal MRI (n=5)	37 [15-50]	0.2 [0-1] (significant from month 1); $p < 0.0005$ from month 3
MTS (n=4)	39 [23-70]	12 [6-23] (significant from month 8) $P < 0.05$

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- \* seizure count regardless of on or off group assignment was reduced in both groups. Statistical analyses could not be performed because of a small number of observations
- \*\* 3/9 patients had skin erosion with infection requiring removal of hardware at 24 months
- \*\*\* no deterioration in memory deficit following implantation. Trend at 18 months for improvement in all tests, but small numbers did not permit statistical analyses

#### Comments:

1. There was an attempt at double blinding, but patients were aware of allocation.
2. Patient selection was non consecutive, inclusion and exclusion criteria were not clearly defined, and the characteristics of the patients in the two groups were not specified.
3. One month follow-up was not sufficient to see effect of hippocampal stimulation in the MTS group.
4. Statistical comparisons could not be made for the efficacy of hippocampal stimulation within the various subgroups (bilateral vs. left vs. right implantation) or on neuropsychological changes over time by group because of the small sample size of the study.
5. No confidence intervals or effect sizes were calculated.
6. It is unclear what neuropsychological cut-offs (i.e. Standard deviation on tests) were used for degree of memory impairment.
7. A complete follow-up in all patients of 18 months (18-84) was short.
8. Limited information was given on patient's antiepileptic medications and whether they were changed during the baseline period.

#### Reference Article Appraised

Velasco AL, Velasco F, Velasco M, et al. Electrical stimulation of the Hippocampal epileptic foci for seizure control: a double-blind, long term follow-up study. *Epilepsia*. 2007;48:1895-1903.

#### Articles of Interest

1. Boon P, Vonck K, De Herdt V, et al. Deep brain stimulation in patients with refractory temporal lobe epilepsy. *Epilepsia*. 2007; 48:1551-60.
2. Tellez-Zenteno JF, McLachlan RS, Parrent A, et al. Hippocampal electrical stimulation in mesial temporal lobe epilepsy. *Neurology*. 2006;66:1490-4.

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#### EXPERT OPINION

##### Hippocampal stimulation: are we there yet?

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##### When hippocampal stimulation is an option

Temporal lobectomy may lead to successful seizure control in patients with pharmacoresistant mesial temporal lobe epilepsy (MTLE). So why would anyone consider hippocampal stimulation? Not all patients are candidates to a surgical resective

procedure. Ineligibility includes seizures originating from both mesial temporal lobes and/or unacceptable memory deficits caused by resection of the seizure-generating hippocampus. In these two situations, neuromodulation may be considered. In this issue, This clinically appraised topic (CAT) evaluates the published literature on the efficacy of hippocampal stimulation (HS) in patients with pharmacoresistant MTLE.

##### Efficacy of hippocampal stimulation

As this CAT shows, the results can vary from 80% seizure-freedom in patients with MTLE and normal MRI<sup>1</sup> to minimal improvements of only 15-30% reduction in seizure frequency<sup>2,3</sup>. Study design may not be the only reason for the discrepancy. So far the precise mechanism through which neuromodulation affects seizures is unknown. Additionally, there are too many variables that can be manipulated in order to deliver the electrical stimulation, and the number of treated patients so far is too small, making it difficult to interpret the results of the studies in this area.

##### Knowledge of mechanism of action is evolving

There is some evidence that electric stimulation may affect neurophysiology, synaptic plasticity, non-linear dynamics, gene expression, and tissue metabolism. We are only starting to understand how changes in electrical stimulation parameters may affect some of these systems. For example, high frequency stimulation (100Hz minimum) can induce synaptic plasticity in the form of short-term depression, long-term depression or both<sup>4,5</sup>. High frequency stimulation also upregulates glutamic acid decarboxylase and downregulates calcium- and calmodulin-dependent protein kinase II. The overall effect of these gene expression changes is enhancement of inhibition around the stimulated site<sup>6</sup>.

##### Neuromodulation remains a challenge

Even when high frequency is used, a number of other parameters can be changed (intensity, wave form, pulse width, length of stimulation, etc) affecting the overall current charge density delivered to the epileptogenic tissue. Furthermore, hippocampal stimulation can be delivered through many combinations of four electrode contacts and the pulse generator's case. Therefore, the limbic structures can be differently affected by the location, size and strength of the electric field. Since limbic seizures can arise (a) within a trisynaptic loop involving mainly the entorhinal cortex, dentate gyrus and hippocampus; or (b) from multiple limbic sites including amygdala, piriform cortex, entorhinal cortex, and hippocampus<sup>7</sup>, the area receiving most of the electric stimulation may not necessarily be the seizure-onset zone. In addition, there is a complex interplay between seizure onset and spread to different, closely related structures that occupy a small physical space.

The type of neuromodulation may also influence the results. Previous studies using closed loop or seizure-detection responsive stimulation demonstrated a moderate short-term efficacy to control limbic seizures<sup>8</sup>. The NeuroPace trial will provide long-term data in this respect<sup>9</sup>. So far, no open and closed loop stimulation paradigms were ever compared in the same patient, where all other variables are kept constant.

*Patient-dependent variables*

Another variable is tissue pathology: if electric stimulation works through GABAergic systems, as previously suggested<sup>10,11</sup>, then patients with hippocampal sclerosis should have a poorer response, since they have less of this neuronal population. This may be at least partially true, as it has been observed that patients without MTS have a better response to HS. On the other hand, this may simply be a red herring. We may find (through technological advances such as 7 Tesla MRI or genetic studies) that the so-called “non-lesional” epilepsy tissue has molecular or structural pathologies which are much more susceptible to electrical stimulation.

Neuromodulation for the treatment of seizures is not new<sup>12</sup>, but has not yet reached its full potential. Developments in basic science research should lead to a better understanding of neuromodulation’s mechanism of action. This will have to be integrated with large (likely multicentre) clinical studies with appropriate design to avoid confounding factors. Once neuromodulation is perfected more patients will benefit from this form of treatment.

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