Brain Stimulation in epilepsy: where are we?

Philippe Kahane, MD, PhD

Pole de Neurologie-Psychiatrie, Grenoble
GIN INSERM U836-UJF-CEA, Grenoble
CTRS-IDEE, Lyon
Prevalence: 4-10 / 1000
Incidence: 20-70 / 100000

Drug-resistance: 30%

Indication of resective surgery in 30% of medically intractable partial epilepsies

- eloquent cortex
- multifocal
- bilateral - generalized

--> alternative treatment
DBS CxS

Non responsive

Responsive
Deep brain stimulation
Cerebellum

Cooper IS, Amin I, Riklan M, Waltz JM, Poon TP.

Cerebellar stimulation demonstrated anti-epileptic properties on various animal models in the fifties and sixties *(mostly penicillin and cobalt foci in cats)*

These findings were not confirmed in chronic alumina cream focus in monkey, nor in kindled cats, in the late seventeens

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- Seizures modified / inhibited in 10/15 patients
- No evidence of any adverse effects

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Wright GD, McLellan DL, Brice JG. A double-blind trial of chronic cerebellar stimulation in twelve patients with severe epilepsy.

Twelve patients with severe intractable epilepsy were treated by chronic cerebellar stimulation under double-blind conditions for six months. No reduction in seizure frequency occurred that could be attributed to stimulation, though eleven of the patients considered that the trial had helped them. One patient experienced fewer episodes of incontinence during stimulation. Cerebellar stimulation in its present form cannot be recommended for the treatment of severe intractable epilepsy.

J Neurol Neurosurg Psychiatry 1984; 47: 769-774.
Double-blind, Randomized Controlled Pilot Study of Bilateral Cerebellar Stimulation for Treatment of Intractable Motor Seizures

Epilepsia 2005; 46: 1071-1081


Significant effect on GTCS and TS

% Change GTCS

BASAL St OFF St ON Stimulation ON

n5 n2 n3 n5 n5 n5 n4 n3 n3 n3

Double-Blind Phase

3-month epochs

1 year 2 years

Pt2 Fever

Fever
**Anterior nucleus**

Cooper & Upton, 1985

6 patients: seizures reduced by 60% in 5
EEG spikes reduced in 3
Effect required bilateral DBS

1. Interruption of the mamillothalamic tract prevented seizures in guinea pigs (Mirski & Ferrendelli 1984)

2. ES of the mammilary nuclei increased seizure threshold to PTZ in rats (Mirski & Fisher 1994)

3. Anticonvulsant effect of anterior thalamic HFES in rat (Mirski et al. 1997)
<table>
<thead>
<tr>
<th>Study</th>
<th>Frequency</th>
<th>pts n°</th>
<th>f-up (mths)</th>
<th>szr reduct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodaie et al. 2002</td>
<td>100 Hz</td>
<td>5</td>
<td>15</td>
<td>24-89 %</td>
</tr>
<tr>
<td>Kerrigan et al. 2004</td>
<td>100 Hz</td>
<td>5</td>
<td>6-36</td>
<td>4 / 5</td>
</tr>
<tr>
<td>Lim et al. 2007</td>
<td>90-110 Hz</td>
<td>4</td>
<td>43.8</td>
<td>35-76%</td>
</tr>
<tr>
<td>Osorio et al. 2007</td>
<td>175 Hz</td>
<td>4</td>
<td>36</td>
<td>53-92%</td>
</tr>
</tbody>
</table>

![Graph showing average % change in seizure frequency over time](image)
Mesial Temporal Inhibition in a Patient with Deep Brain Stimulation of the Anterior Thalamus for Epilepsy

Epilepsia 2006; 47: 1958-1962

Dominik Zumsteg, Andres M. Lozano, and Richard A. Wennberg
Centromedian N

= part of a nonspecific reticulothalamocortical system mediating cerebral cortex excitability

= well-defined structure, easily localized by traditional stereotaxic techniques


13 pts with Lennox-Gastaut syndrome
Bilateral HFS stimulation of the CMN
Follow-up from 12 to 94 months

Efficacy on GTCS & atypical absences
No effect on tonic & partial seizures

Fisher et al. 1992 : no benefit in a small (7 pts) placebo-controlled study
## TABLE 4. Improvement of ability scales after 18 months of ESCM

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Onset (yr)</th>
<th>% Sz reduction</th>
<th>Ability scale before ESCM</th>
<th>Ability scale after ESCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>7</td>
<td>100</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>6</td>
<td>100</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>7</td>
<td>70</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>5</td>
<td>80</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>2</td>
<td>50</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>2</td>
<td>70</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
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<td>80</td>
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<td>3</td>
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<td>8</td>
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<td>4</td>
<td>80</td>
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<td>3</td>
</tr>
<tr>
<td>9</td>
<td>19</td>
<td>10 mo</td>
<td>60</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>5 mo</td>
<td>70</td>
<td>0</td>
<td>2</td>
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<td>11</td>
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The "nigral control" of epileptic seizures
(Depaulis et al. 1994)

Caudate N

Subthalamic N

D2 → striatal complex → D1

GABA

Dopamine

GABA

mesencephalic dopaminergic neurons

GABA

GABA

GABA

Glu/Asp

SC

SNpr

D2

pallidum

STN

SNpr

CP CA NC
The "nigral control" of epileptic seizures (Depaulis et al. 1994)

Caudate N

Subthalamic N

Dopamine

GABA

GABA

Glu/Asp

antiepileptic effect

mesencephalic dopaminergic neurons

GABA
Caudate N

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mesencephalic dopaminergic neurons

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GABA

SC

GABA
The “nigral control” of epileptic seizures (Depaulis et al. 1994)
Chkhenkeli & Chkhenkeli
Stereotact Funct Neurosurg 1997; 36: 63-71

38 epileptic pts
4-6 pps - caput nuclei caudati

decrease of focal and generalized interictal discharges (and szrs?)

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<td>27 m</td>
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<td>R C (FCD)</td>
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</tr>
<tr>
<td>38 y</td>
<td>L C (Por cyst)</td>
<td>10 m</td>
<td>67% (p=0.01)</td>
</tr>
<tr>
<td>17 y</td>
<td>L Ins (ADNFLE)</td>
<td>6 m</td>
<td>no change</td>
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Chabardès et al. 2002
### Cleveland experience
Neme et al. 2001
Loddenkemper et al. 2001
- 5 pts
- good response in 2 (-80% and -60%)
- no response in 1

### American University of Beirut
(Alaraj et al. 2001)
- 1 pt (LGS)
- disappearance of GTC sz
  >75% red. in myoclonic & absences sz

### Fribourg-Kehl/Kork experience
(Vesper et al. 2007)
- 1 pt (PME)
- 50% reduction of sz frequency

### Subthalamic N

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Chabardès et al. 2002
Chabardès et al. 2002

Vesper et al. 2007
PET evidence for a role of the basal ganglia in patients with ring chromosome 20 epilepsy

A. Biraben, MD; F. Semah, MD; M.-J. Ribeiro, MD, PhD; G. Douaud; P. Remy, MD, PhD; and A. Depaulis, PhD

Neurology 2004; 63: 73-77
Cortical stimulation

Hippocampal electrical stimulation in mesial temporal lobe epilepsy

J.F. Tellez-Zenteno, MD, PhD; R.S. McLachlan, MD; A. Parrent, MD; C.S. Kubu, PhD; and S. Wiebe, MD

Abstract—Background: Adjustable, reversible therapies are needed for patients with pharmacoresistant epilepsy. Electrical stimulation of the hippocampus has been proposed as a possible treatment for mesial temporal lobe epilepsy (MTLE). Methods: Four patients with refractory MTLE whose risk to memory contraindicated temporal lobe resection underwent implantation of a chronic stimulating depth electrode along the axis of the left hippocampus. The authors used single patient, randomized, double-blind, multiple cross-over design. The active electrode was placed at different locations. Single-blind testing showed no significant differences in other outcomes. There were no adverse effects. One patient has been treated for 4 years and continues to experience substantial long-term seizure improvement. Conclusion: The authors demonstrate important beneficial trends, some long-term benefits, and absence of adverse effects of hippocampal electrical stimulation in mesial temporal lobe epilepsy. However, the effect sizes observed were smaller than those reported in non-randomized, unblinded studies.

NEUROLOGY 2006;66:1490–1494

• 4 patients
• double blind, multiple cross-over, randomized treatment
• mean reduction in seizures of 15% (ns)
• no adverse events
Electrical Stimulation of the Hippocampal Epileptic Foci for Seizure Control: A Double-blind, Long-term Follow-up Study

Ana Luisa Velasco, Francisco Velasco, Marcos Velasco, David Trejo, Guillermo Castro, and José Damián Carrillo-Ruiz

Unit of Stereotactic, Functional Neurosurgery and Radiosurgery, Hospital General de México, Mexico City, Mexico

Summary: Purpose: Our aim was to evaluate the safety and efficacy of electrical stimulation of the hippocampus in a long-term follow-up protocol. Patients attended a medical appointment every 3 months for seizure diary collection, deep brain stimulation parameterization, and evaluation of neuropsychological deterioration. Patients signed the informed consent approved by the Hospital’s Ethics Committee and began a double-blind stimulation protocol. Patients attended a medical appointment every 3 months for seizure diary collection, deep brain stimulation parameterization, and evaluation of neuropsychological deterioration.

- 9 patients
- Double blind
- N MRI group (n=5): reduction in seizures of >95%
- HcS group (n=4): reduction in seizures of 50-70%
- no neuropsychological deterioration
Effect of an external responsive neurostimulator on seizures and electrographic discharges during subdural electrode monitoring.
Patient 2: stimulated and aborted seizure [as seen from the external responsive neurostimulator (eRNS)].
Automated Seizure Abatement in Humans Using Electrical Stimulation

Ivan Osorio, MD¹,²  Mark G. Frei, PhD,²  Sridhar Sunderam, PhD,²  Jonathon Giftakis, PhD,³  Naresh C. Bhavaraju, PhD,²  Scott F. Schaffner, MBA,³  and Steven B. Wilkinson, MD¹,²

The need for novel, efficacious, antiseizure therapies is widely acknowledged. This study investigates in humans the feasibility, safety, and efficacy of high-frequency electrical stimulation (HFES; 100–500Hz) triggered by automated seizure detections. Eight patients were enrolled in this study, which consisted of a control and an experimental phase. HFES was delivered directly to the epileptogenic zone (local closed-loop) in four patients and indirectly, through anterior thalami (remote closed-loop), to the other four patients for every other automated seizure detection made by a validated algorithm. Interphase (control vs experimental phase) and intraphase (stimulated vs nonstimulated) comparisons of clinical seizure rate and relative severity (clinical and electrographic) were performed, and differences were assessed using effect size. Patients were deemed "responders" if seizure rate was reduced by at least 50%; the remaining patients were deemed "nonresponders." All patients completed the study; rescue medications were not required. There were 1,491 HFESs (0.2% triggered after-discharges). Mean change in seizure rate in the local closed-loop group was −55.5% (−100 to +36.8%); three of four responders had a mean change of −86% (−100 to −58.8%). In the remote closed-loop, the mean change of seizure rate was −40.8% (−72.9 to +1.4%); two of four responders had a mean change of −74.3% (−75.6 to −72.9%). Mean effect size was zero in the local closed-loop (responders: beneficial and medium to large in magnitude) and negligible in the remote closed-loop group (responders: beneficial and medium to large). HFES effects on epileptogenic tissue were immediate and also outlasted the stimulation period. This study demonstrates the feasibility and short-term safety of automated HFES for seizure blockage, and also raises the possibility that it may be beneficial in pharmaco-resistant epilepsies.

Ann Neurol 2005;57:258–268
Local closed-loop (n=4)  
-55.5% (-100% / +36.8%)

remote closed-loop (n=4)  
-40.8% (-72.9% / +1.4%)