DEEP BRAIN STIMULATION OF BASAL GANGLIA IN FOCAL MOTOR SEIZURES IN A PRIMATE MODEL

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28 th January 2012, Grenoble
PLAN

Introduction
Pharmacoresistant Epilepsy in humans
Current treatment options
Motor seizures in human epilepsy
DBS in epilepsy
Basal ganglia and epilepsy

Experimental work Part 1: The Model
Characterization of Penicillin induced focal motor seizures in primate
Dynamic changes in basal ganglia during seizures in the model

Experimental Work Part 2: Effects of DBS on seizures
Material and Methods
Results

Discussion

Perspective

Conclusion
Epilepsy: CNS disorder characterized by recurrent seizures

Seizures: Recurrent episodic cerebral dysfunction

Pharmacoresistant epilepsy: a failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (Kwan et al., 2010)

Seizure freedom: freedom from seizures for a minimum of 3 times the longest preintervention interseizure interval or 12 months whichever is longer (Kwan et al., 2010)
Impact

Quality of life

- Anxiety and depression

- Cognitive problems in patients
  (Hermann et al., 1997; Hermann and Seidenberg, 2002)

Employability
  (Leidy et al., 1999)

SUDEP (8-17%)
  (Tomson, 2000)

Economic Burden
  (Jacoby et al., 1998).
TREATMENT OF PHARMACO RESISTANT EPILEPSIES

Surgery

- **Curative**: lobectomy, lesionectomy, and hemispherectomy
- **Palliative**: corpus callosotomy and multiple subpial transections
TREATMENT OF PHARMACO RESISTANT EPILEPSIES

Neuromodulation

• Vagus Nerve Stimulation

• **DBS**: SANTE, Neuropace Clinical trials

Radioneurosurgery

**rTMS** (experimental)
HUMAN MOTOR SEIZURES

Focal Cortical Dysplasia

Inflammation

AV malformation

Cavernous Malformation
Seizures: episodic recurrent cerebral dysfunction, characterised by pathological synchronization

DBS
- Desynchronise
- Inhibit propagation
- Decrease excitability
Possible sites of influence of basal ganglia circuits in Epilepsy

1- Dopaminergic modulation
2- Excitatory influence over STN
3- Excitation of output structure
4- Inhibition of thalamic nuclei
5- Influence of SNr over DMAZ
## DBS STN IN ANIMALS

<table>
<thead>
<tr>
<th>Studies (First Authors)</th>
<th>Model / Animal</th>
<th>Stimulation parameters</th>
<th>Summary of results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vercueil</strong> (1998)</td>
<td>Absence seizures GAERS rats</td>
<td>130Hz, up to 300µA, 60 µs</td>
<td><strong>Bilateral stimulation effective</strong> in suppressing spike wave discharge</td>
</tr>
<tr>
<td><strong>Lado</strong> (2003)</td>
<td>Generalized clonic and tonic-clonic flurothyl seizures Adult rats</td>
<td>130, 260, 800Hz, up to 500µA, 60µs</td>
<td><strong>Bilateral stimulation at 130Hz increased the seizure threshold</strong> 800Hz was proconvulsive</td>
</tr>
<tr>
<td><strong>Feddersen</strong> (2007)</td>
<td>Absence seizures GAERS rats</td>
<td>5 to 500Hz 10 to 100µs</td>
<td><strong>60Hz frequency and the 60µs optimal for controlling SWD.</strong> But repeated stimulation ineffective and might increase seizure number</td>
</tr>
<tr>
<td><strong>Shehab</strong> (2011)</td>
<td>Tonic brain stem seizures Electroshock model: rats</td>
<td>30 or 260Hz</td>
<td>Fails to suppress tonic seizures</td>
</tr>
<tr>
<td><strong>Saillet</strong> (2012)</td>
<td>Absence seizures GAERS rats</td>
<td>Responsive SNr stimulation and auditory</td>
<td><strong>SNr bilateral stimulation effective in 97% seizures</strong></td>
</tr>
</tbody>
</table>
# DBS STN IN HUMANS

<table>
<thead>
<tr>
<th>Studies (First Author)</th>
<th>Number of patients / Trail design</th>
<th>Seizure / epilepsy</th>
<th>Stimulation parameters</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benabid (2002)</td>
<td>1 cortical dysplasia</td>
<td>Refractory partial seizure</td>
<td>HFS STN</td>
<td>80% reduction in number and severity of seizures. Improvement in both motor and cognitive functions</td>
</tr>
<tr>
<td>Chabardès (2002)</td>
<td>5</td>
<td>Medically refractory epilepsy one patient of severe and myoclonic epilepsy (Dravet syndrome) and one had an autosomal dominant frontal lobe epilepsy</td>
<td>HFS STN</td>
<td>67 to 80% reduction in seizure frequency was observed in three patients. Dravets syndrome responded weekly and no effect on patient with autosomal dominant frontal lobe epilepsy</td>
</tr>
<tr>
<td>Shon (2005)</td>
<td>2 already underwent resective surgery on frontal cortex</td>
<td>Bilateral asymmetric tonic seizures (left&gt;right) with rare drop attacks</td>
<td>HFS</td>
<td>One patient had about 50% reduction in seizures other had 33% reduction in frequency but more benefit in seizure severity</td>
</tr>
<tr>
<td>Lee (2006)</td>
<td>3</td>
<td></td>
<td></td>
<td>49.1% reduction</td>
</tr>
<tr>
<td>Wille (2011)</td>
<td>5</td>
<td>Progressive myoclonic epilepsy syndrome</td>
<td>HFS STN/SNr + HFS ventral intermediate nucleus (VIM) (4 patients) VIM stimulation found ineffective, sometimes triggered myoclonia</td>
<td>HFS STN/SNr Produced 30% to 100% reduction in seizure frequency improved capabilities like free standing, walking, improved fine motor skills</td>
</tr>
<tr>
<td>Cappeci (2012)</td>
<td>2</td>
<td>Undergone anterior colostomy but no benefit</td>
<td>Bilateral HFS</td>
<td>First patient had 65% decrease of partial motor seizures and 100% control over tonic-clonic generalized attacks. Second patient: no reduction of fits and an increase atypical absence seizures</td>
</tr>
</tbody>
</table>
BASAL GANGLIA AND EPILEPSY

Newer models of Basal Ganglia (Redgrave et al 2010, Garcia-Munoz et al 2010...)

(A) Alexander et al (1986)
(B) Parent and Hazarati (1993)
(C) Joel and Weiner (1997)
ANIMALS
- Pharmacological studies in animals
- Electrophysiological studies in animals
- Metabolic studies in animals
- Experimental Cell transplantations

HUMANS
- Structural MRI
- Functional MRI
- EEG coregistered with fMRI
- PET and SPECT studies
EXPERIMENTAL WORK PART I

THE MODEL
PENICILLIN INDUCED FOCAL SEIZURES

METHODS

CHARACTERIZATION OF MODEL IN NON-HUMAN PRIMATES

- **Macaca fascicularis**
- 2 animals
- 11 experiments
- Action of Penicillin
  - GABA blocker
  - Mechanism: paroxysmal depolarization in the injection zone
  - Lateral inhibitory interneurons affected
  - Deeper neurons hyperpolarized
  - Strictly local – focal effects

*Elger, C. E. and Speckman, E. J. (1983)*

Protocol reviewed by local ethics committee – protocol XXXX
METHODS: RECORDINGS

**ECoG features**: Spikes, polyspikes, seizures

**Polyspikes and beginning of seizure**

**End of a seizure**
A seizure

Median normalised amplitude of 17 seizures
RESULTS
RESULTS: SEIZURES

Characterization of model: 2 animals, 8 experiments
RESULTS: EFFECT OF DIAZEPAM

Characterization of model: 1 animal, 3 experiments

(A) Effect of Diazepam on total time spent in seizure

(B) Effect of Diazepam on average duration of seizure
RESULTS: HISTOPATHOLOGY

Coronal sections of brains of monkeys *(Cresyl Violet Stain)*

No gliosis at injection site
MULTI UNIT ACTIVITY OF BG AND COHERENCE FUNCTION BETWEEN LFP AND ECOG DURING MOTOR SEIZURE

Cortex and STN

Cortex and GPe

Strong coherence during the course of the seizure in gamma and beta bands

Devergnas et al, Brain 2012
COHERENCE BETWEEN CORTEX AND PUTAMEN

Devergnas et al, Brain 2012

Significant coherence in the second half of the seizure in 20-45 Hz band
CHANGES IN MEAN FIRING RATE DURING MOTOR SEIZURE

Mean firing rate

Devergnas et al, Brain 2012
CHANGES IN PERCENTAGE OF OSCILLATORY NEURONS

Devergnas et al, Brain 2012
SUMMARY

- Easy to generate, stable, reproducible model
- Safe to the primate
- With evidence of changes in basal ganglia during focal motor seizures
- STN and Putamen activity modified during seizures
EXPERIMENTAL WORK PART II

THE STIMULATION
WORKING HYPOTHESES

• High Frequency Stimulation (HFS) of STN may modulate the motor seizure

• Putamen may participate additionally in modulation

• Chronic High Frequency Stimulation (HFS) STN

• Preventive HFS STN

• Low Frequency Stimulation (LFS) Putamen

• Combined HFS STN+LFS Putamen
METHODS: DETERMINATION OF TARGETS (STN)

Atlas + Ventriculography
Electrophysiology
METHODS: SURGERY

- Ventriculography
- Electrophysiology
- Electrode & stimulator placement
METHODS: TARGETING PUTAMEN, PUTAMEN+STN

Putamen: ventriculography

A: lateral Xray
B: AP Xray

Putamen: final placement

STN+Putamen: final placement
## Stimulation Parameters

<table>
<thead>
<tr>
<th>Animal</th>
<th>Best contact point</th>
<th>Threshold Voltage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STN HFS</strong>&lt;br&gt;pulse width 60µs, frequency 130Hz</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal 1</td>
<td>Monopolar (case +)&lt;br&gt;Contact 2 -</td>
<td>2.4V</td>
</tr>
<tr>
<td></td>
<td>Bipolar&lt;br&gt;Contact 0 + / Contact 2 -</td>
<td>3V</td>
</tr>
<tr>
<td>Animal 2</td>
<td>Monopolar (case +)&lt;br&gt;Contact 3 -</td>
<td>2V</td>
</tr>
<tr>
<td></td>
<td>Bipolar&lt;br&gt;Contact 2 + / Contact 3 -</td>
<td>2V</td>
</tr>
<tr>
<td>Animal 3</td>
<td>Monopolar (case +)&lt;br&gt;Contact 3 -</td>
<td>2.8V</td>
</tr>
<tr>
<td></td>
<td>Bipolar&lt;br&gt;Contact 2 + / Contact 3 -</td>
<td>3.3V</td>
</tr>
<tr>
<td><strong>Putamen LFS</strong>&lt;br&gt;pulse width 60µs, frequency 5Hz, 20Hz</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal 4</td>
<td>Monopolar (case +)&lt;br&gt;Contact 3 -</td>
<td>3.4V</td>
</tr>
<tr>
<td></td>
<td>Bipolar&lt;br&gt;Contact 2 + / Contact 3 -</td>
<td>3.8V</td>
</tr>
<tr>
<td>Animal 2</td>
<td>STN Monopolar (Case +)&lt;br&gt;Contact 3 -</td>
<td>2V</td>
</tr>
<tr>
<td></td>
<td>Putamen (case +)&lt;br&gt;Contact 2 - / Contact 3 -</td>
<td>3V</td>
</tr>
</tbody>
</table>
METHODS: PROTOCOL AND RECORDINGS

Chronic HFS STN

- Induction and Stim: 0
- Stim Stop: 4 hrs
- Record (specimen 1 and 2): 6 hrs

Preventive HFS STN

- Stimulation: -36 hrs
- Induction: 0
- Stim Stop: 4 hrs
- Record: 6 hrs

Chronic LFS Putamen

- Induction and Stim: 0
- Stim Stop: 4 hrs
- Record (specimen 1 and 2): 6 hrs
RESULTS: CONFIRMATION OF IMPLANTED DEPTH ELECTRODES

Fig A: A lateral X-ray projection obtained after completion of surgery shows the location of the depth electrode in STN.

Fig B: Sagital T2W post mortem MRI in same specimen showing the tract and placement of depth electrode.

Final placement (fig A) + Post mortem MRI coronal (fig B)

T2W images, Very high resolution MRI protocols specifically developed at MRI facility, GIN, Grenoble
## HFS STN STIMULATION

<table>
<thead>
<tr>
<th>Animal</th>
<th>Number of experiments</th>
<th>Number of Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Control 6</td>
<td>473</td>
</tr>
<tr>
<td></td>
<td>Stimulation 8</td>
<td>290</td>
</tr>
<tr>
<td>2</td>
<td>Control 5</td>
<td>280</td>
</tr>
<tr>
<td></td>
<td>Stimulation 3</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>Control 4</td>
<td>328</td>
</tr>
<tr>
<td></td>
<td>Stimulation 4</td>
<td>160</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>1572</td>
</tr>
</tbody>
</table>
RESULTS: EFFECT OF STN DBS
NUMBER OF SEIZURES

Animal 1 (6 control + 8 stim.)

Animal 2 (5 control + 3 stim.)

Animal 3 (4 control + 4 stim.)

** X axis: hours after injection
** Y axis: Number of seizures

Hou Hours

Specimen Specimen

39
RESULTS: EFFECT OF STN DBS
TOTAL DURATION OF SEIZURES

Animal 1 (6 control + 8 stim.)
Animal 2 (5 control + 3 stim.)
Animal 3 (4 control + 4 stim.)

X axis: hours after injection
Y axis: total duration in seconds
RESULTS: EFFECT OF STN DBS
AVERAGE DURATION OF SEIZURES

Animal 1 (6 control + 8 stim)

Animal 2 (5 control + 3 stim)

Animal 3 (4 control + 4 stim)

X axis: hours after injection
Y axis: Average duration in seconds
RESULTS: EFFECT OF STN DBS ON INTERICTAL SPIKES

Animal 1 (6 control+8 stim.)

Animal 2 (5 control+3 stim.)

Animal 3 (4 control+4 stim.)

X axis: hours after injection
Y axis: Number of interictal spikes
RESULTS: EFFECT OF PREVENTIVE STN STIMULATION

X axis: hours after injection
Y axis: Number of seizures

X axis: hours after injection
Y axis: total duration in seconds

X axis: hours after injection
Y axis: Average duration in seconds

1 primate,
10 experiments (5 control, 5 stimulation)
454 seizures.
### LFS PUTAMEN STIMULATION

<table>
<thead>
<tr>
<th>ANIMAL</th>
<th>NUMBER OF EXPERIMENTS</th>
<th>NUMBER OF SEIZURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Control 5</td>
<td>118</td>
</tr>
<tr>
<td></td>
<td>Stimulation 5</td>
<td>109</td>
</tr>
<tr>
<td>4</td>
<td>Control 2</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Stimulation 2</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>289</td>
</tr>
</tbody>
</table>
RESULTS: EFFECT OF LFS OF PUTAMEN ON NUMBER OF SEIZURES

Animal 1 (5 control + 5 stim.)

Animal 4 (2 control + 2 stim.)

X axis: hours after injection
Y axis: Number of seizures
RESULTS: EFFECT OF LFS OF PUTAMEN ON TOTAL DURATION OF SEIZURES

X axis: hours after injection
Y axis: total duration in seconds
EFFECT OF LFS OF PUTAMEN ON AVERAGE DURATION OF SEIZURES

X axis: hours after injection
Y axis: Average duration in seconds

Animal1 (5 control+5 stim.)

Animal4 (2 control+2 stim.)
RESULTS: EFFECT OF HFS STN + LFS PUTAMEN

X axis: hours after injection
Y axis: Number of seizures

X axis: hours after injection
Y axis: total duration in seconds

1 primate
10 experiments (5 controls, 5 stimulations) 477 seizures
SUMMARY OF RESULTS

- **Chronic HFS STN** was most effective in controlling number of seizures and the total time spent in seizures.

- **Preventive HFS STN (in one animal)** was not found to be superior to acute stimulation.

- **LFS Putamen** alone was effective but mainly in first two hours of stimulation.

- **In a combined HFS STN and LFS Putamen stimulation** tested in one animal the effect of stimulation in terms of seizure control was modest and poor compared to HFS STN alone or LFS Putamen alone.
DISCUSSION

Part A) Normal Part B) Modification in focal motor seizures Part C) Possible effect of HFS DBS of STN

STN subthalamic nucleus GPe Globus Pallidus externa GPI Globus Pallidus interna Th Thalamus STR Striatum PUT Putamen SNr Substantia Nigra glu Glutamate. Filled black arrows inhibitory pathway, hollow arrows excitatory pathways.
MacKinnon et al., 2005).
LFS STN- burst in ventral thalamus
Barth et al., 2002
GABAergic output from ZI-thalamus

Whitmer et al., 2012
HFS STN-β synchrony in Parkinson’s

Devergnas and Wichmann, 2011
Primate LFS of STN—evoked potentials in motor cortex

Fraix et al., 2008,
Dauper et al., 2002
rTMS cortical silent period
DISCUSSION

HFS STN effects

Cortical Excitability

Decreased Metabolism
SPECT+PET (Haegelen et al., 2010, ) FDG PET Le June et al 2010

rCBF
Cilio et al 2009

PET
Limousin et al 1997 Hershey et al., 2003

Thalamo cortical relay
Guo et al., 2008

M1 motor cortex excitability
Santaniellio et al., 2012

Computational modelling
In PD primates
DISCUSSION

- Gale, Ladorla, Systemic GABA transaminase (1980)
- Local GABA mimetic drugs (1982)
- Deransart et al (GAERS) NMDA antagonist (1996)
- Fedderson et al (GAERS) DBS
- Saillet et al (GAERS) Bilat DBS 2012
- Shehab (electroshock) 2011

Endogenous Nigral Control of Epilepsy (Depaulis et al 1994)
DISCUSSION

• Results of Preventive STN stimulation
• Results of Putaminal stimulation

D2
Anticonvulsant

D1
Proconvulsant

D2,D3 altered


Starr, 1996


Different Neuronal Types
LIMITATIONS

• A model of seizure
• Just reducing number ?
• Unilateral ??
• Precision of implantation ?
DISCUSSION
OUR RESULTS AND HUMAN STN DBS FOR EPILEPSY

- 5 patients Chabardes (Chabardes et al., 2002) 1 Rt premotor resection, 1 with VNS.
- 5 patients Willi (Willi et al., 2011) 1 with VNS.
- 2 cases Shon (Shon et al., 2005) both had resective surgery
- 2 cases Capecci (Capecci, 2012) had anterior callosotomy

- 1 case Hammer (Hammer et al 2003) a bilateral STN stimulation in a refractory seizure patient; unsatisfactory results (This patient had left fronto-central epilepsy due to cortical dysplasia in this region. He already had undergone multiple subpial resections of the face and motor area and focal cortical excision anterior to eloquent cortex.)

Seizures originating from the central region are POSSIBLY the best candidates for STN-DBS
CONCLUSION

• Chronic HFS STN was most effective in controlling numbers and the total time spent in focal motor seizures in primate model
• Results are in accordance with published human cases
• Translational Therapeutic Potential
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