What We Have Learned From Intracranial Direct Electrical Stimulation (SEEG Studies)

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Identifying the epileptogenic network



Epileptogenic Zone:

"the minimum amount of cortex that must be resected

(inactivated or completely disconnected) to produce seizure freedom"

Luders et al., 2006 **Functional deficit** Symptomatogenic zone "area of cortex which, when activated, produces the "area of cortex that is not functioning normally in the interictal period" initial ictal symptoms or signs" **Seizure Propagation Eloquent Cortex** Seizure Onset Zone "area of cortex that initiates clinical seizures" **Epileptogenic lesion (if present)** lesion itself is epileptogenic (e.g. cortical dysplasia) or by secondary hyperexcitability of adjacent cortex" Irritative zone "area of cortex which generates interictal spikes" After Luders et al 2006

& Kahane, AES 2012

StereoElectroEncephaloGraphy



- Provides direct access to electrophysiological recordings in the seizure onset zone, when located in deep brain structures
- Allows delineation of the epileptogenic area in 3D volume
- Provides excellent time & space resolution
- Direct Electric Stimulation (DES)
 - Uses different stimulation protocols to map epileptogenicity and brain connectivity
 - Functional mapping of eloquent cortex



SEEG + DES

Each zone has specific EEG markers

- during spontaneous activity ictal or inter-ictal
- as a response to stimulation



Analysis of the electrophysiological responses to DES:

"Its major advantage is that it covers the full spectrum of events (spikes, ripples and fast ripples) that can be used to delineate the epileptogenic cortex without depending on their spontaneous occurrence and the occurrence of seizures." - van 't Klooster et al, 2011



Imaging the Seizure Onset Zone

- MRI shows anatomical data based on probing the response of protons (H+) in the water using variable magnetic fields applied in various sequences and radiofrequency signals
- DES could show functional data electrophysiological responses – to electrical stimulation, imaging the epileptogenic areas.

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DES Protocols

- Repetive low- (1Hz) and highfrequency (50 Hz) stimulation
- Single Pulse Electric Stimulation (SPES)
 - intracranial electrodes, Monophasic pulse, 0.3 - 3ms pulse width, 5-30 s interpulse interval, up to 8mA currents
 - Early Responses (ER) and sometimes Delayed Responses (DR)
 - DR are a marker specific to seizure onset zone SOZ (2002, Valentin et. al)
 - subdural grid electrodes, similar stimulation protocol
 - Similar results (2009, Flanagan et al.)





2008 Valontin and Alarcon

DES Protocols



• SPES

 Grid electrodes, monophasic square wave, 0.3 ms pulse width, 1 s interpulse interval, 1 – 10mA currents

Results:

- Response amplitude varies with current amplitude (2010, Iwasaki et. al)
- Grid electrodes, biphasic pulse, 0.3 ms pulse width, 1 s interpulse interval, 1 – 15mA currents

Results:

• Response amplitude varies with current amplitude (2012, Enatsu et. al)



Subjects and Methods

Subjects:

- 4 patients with refractory epilepsy
- Stimulation done during presurgical evaluation

Equipment used:

- Nicolet wireless 64channel amplifier
- Programmable stimulator (Guideline LP+, FHC Inc)





Methodology

• SEEG electrodes

- Data recorded using
 - 64 channels
 - Sampling rate 4096 Hz - allows visualization of
 - High-Frequency Oscillations (HFO) with f>100 Hz
- A Amygdala; B Anterior Hippocampus;
- **C Posterior Hippocampus;**
- E Entorhinal Cortex; U Superior Temporal Gyrus;
- **D** Retrosplenial cortex; **S** Suprasylvian;
- I Temporal Pole; O Orbitofrontal; F Fusiform gyrus;
- **R Rolandic Operculum; W Wernicke;**







Methods

Stimulation protocols:

• 1 Hz: biphasic, 3 ms pulse width, 40 s stimulation length, 0.5 - 3 mA current range



50 Hz functional mapping: biphasic, 1 ms pulse width,
5 s stimulation length, 0.5 - 3 mA current range

• SPES: monophasic & biphasic, 3 ms pulse width, 15 s interpulse interval, currents in the 0-5mA range (0.25mA step)

• Paired Pulse (PP) : biphasic, 3 ms pulse width, 10-200ms pair delay, 1 mA current

 Variable Pulse Width (VPDES): biphasic, 0.25 – 3ms pulse witdh (0.25ms step), 15 s interpulse interval, 1 mA current

Methods

SPES

biphasic, 3 ms pulse width, 15
s inter-pulse interval,
variable amplitude in the 05mA range (0.25mA step)
pseudo-random sequence for a total of 5 min to factor out time



- peri-stimulus response: early, delayed, HFO's
- stimulus response-curves

1 Hz Stimulation

- Common practice
- Used for mapping brain connectivity (electric responses) (2012, Enatsu et al.)
- Sometimes a seizure can occur: E1-E2 – Entorhinal Cortex stimulated (see attached video)



50 Hz Stimulation

- Common practice
- Used for functional mapping (clinical responses)
- Can produce auras and seizures
- Other clinical response: muscle contractions, auditory / visual / olfactive hallucinations, verbal arrest,etc
- Case study: (see attached video)
 - Wernicke stimulation causes verbal arrest
 - Entorhinal Cortex stimulation causes aura during stimulation
 - 1 mA a mild aura
 - 2 mA a stronger aura like the one before seizure

SPES High frequency oscillations (HFO, 100-250Hz) strong marker for epileptogenic area. (2012 Enatsu et all.; 2012 da Silva et al.)



SPES

E1-E2 – Entorhinal Cortex

C2 – Posterior Hippocampus





SPES – HFO (100-250 Hz)

E1-E2 – Entorhinal Cortex

C2 – Posterior Hippocampus







SPES – Fast Ripples (>250 Hz)

E1-E2 – Entorhinal Cortex

C2 – Posterior Hippocampus



Fast Ripples (FR, >250Hz) are even more specific to the epileptogenic area than HFOs (2012 Cho et al.)



DES Case Study

Responses, HFO's



Seizure Onset Zone

- A Amygdala;
- B Anterior Hippocampus;
- C Posterior Hippocampus;

Irritative zone:

• E - Entorhinal Cortex;

Functional Deficit: • I - Temporal Pole;

• F - Fusiform gyrus;

Eloquent Cortex:

R – Rolandic Operculum;

(hyperexcitability)

• W - Wernicke;

No responses:

- O Orbitofrontal;
- U Superior Temporal Gyrus;

SPES Monophasic



Monophasic pulse

Biphasic pulse

• Our data showed that brain responses are similar for both monophasic and biphasic SPES (results are shown on a future slide)

VPDES B1 B2 – Hippocampus VPDES 1.5mA





A4 - Amygdala

C2 - Posterior Hippocampus

SPES vs. VPDES

Injected current or "charge per phase" is the most relevant parameter in SPES





A7 - Amygdala

C2 - Posterior Hippocampus

SPES vs. VPDES

Injected current or "charge per phase" is the most relevant parameter in SPES







B5 – Hippocampus

B6 – Hippocampus

Conclusions

- Intracranial Direct Electric Stimulation (iDES) helps in delineating the epileptogenic network
- Evaluation of stimulus-response curves as well as oscillations in various frequency bands triggered by iDES provide valuable complementary information to recording spontaneous activity.
- The most relevant parameter in SPES is the injected current ("charge per phase")

