Intracranial stimulation studies of brain connectivity in epilepsy

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4 Neurosurgery Department, Bagdasar-Arseni Hospital, Bucharest, Romania
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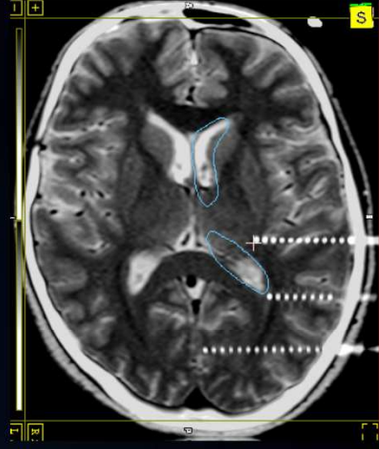
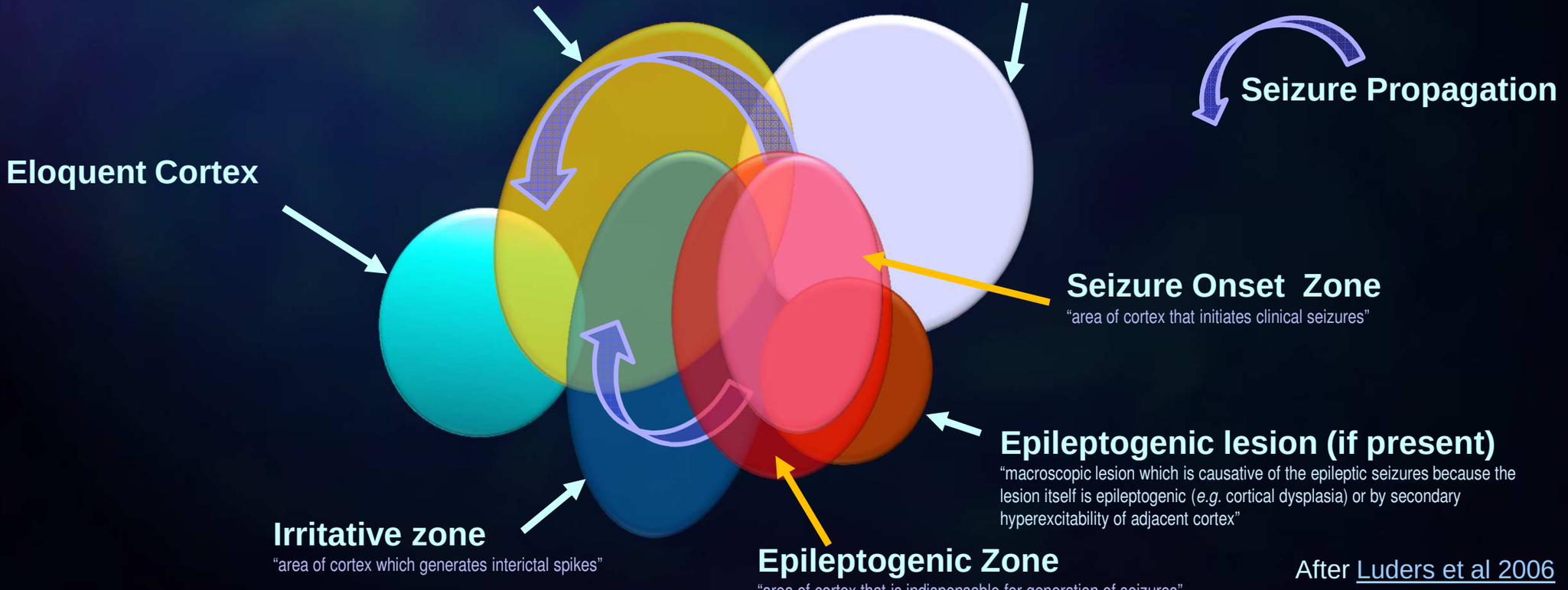
4th Conference of the National Neuroscience Society of Romania, IBRO symposium "Abnormal Brain Connectivity"
Bucharest, October 17th-19th 2013

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



After Luders et al 2006
& Kahane, AES 2012

Brain (2001), **124**, 1683–1700

INVITED REVIEW

Presurgical evaluation of epilepsy

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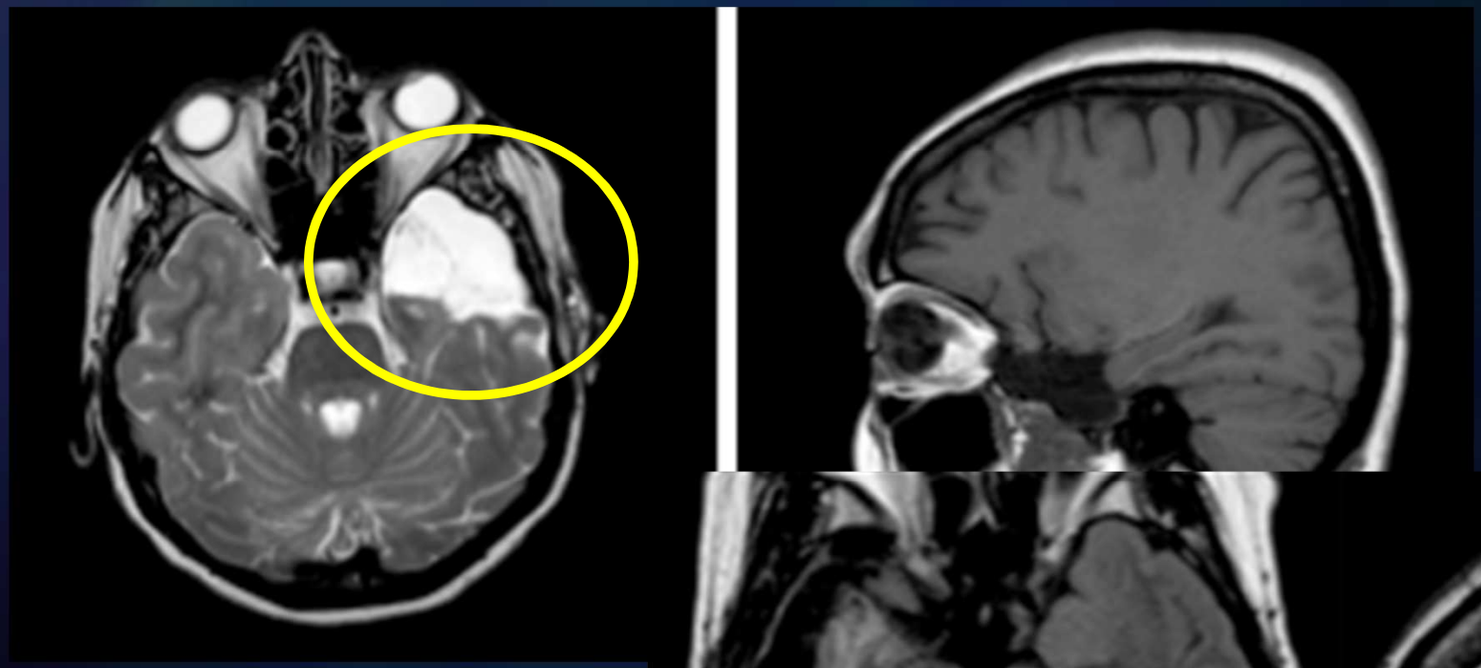
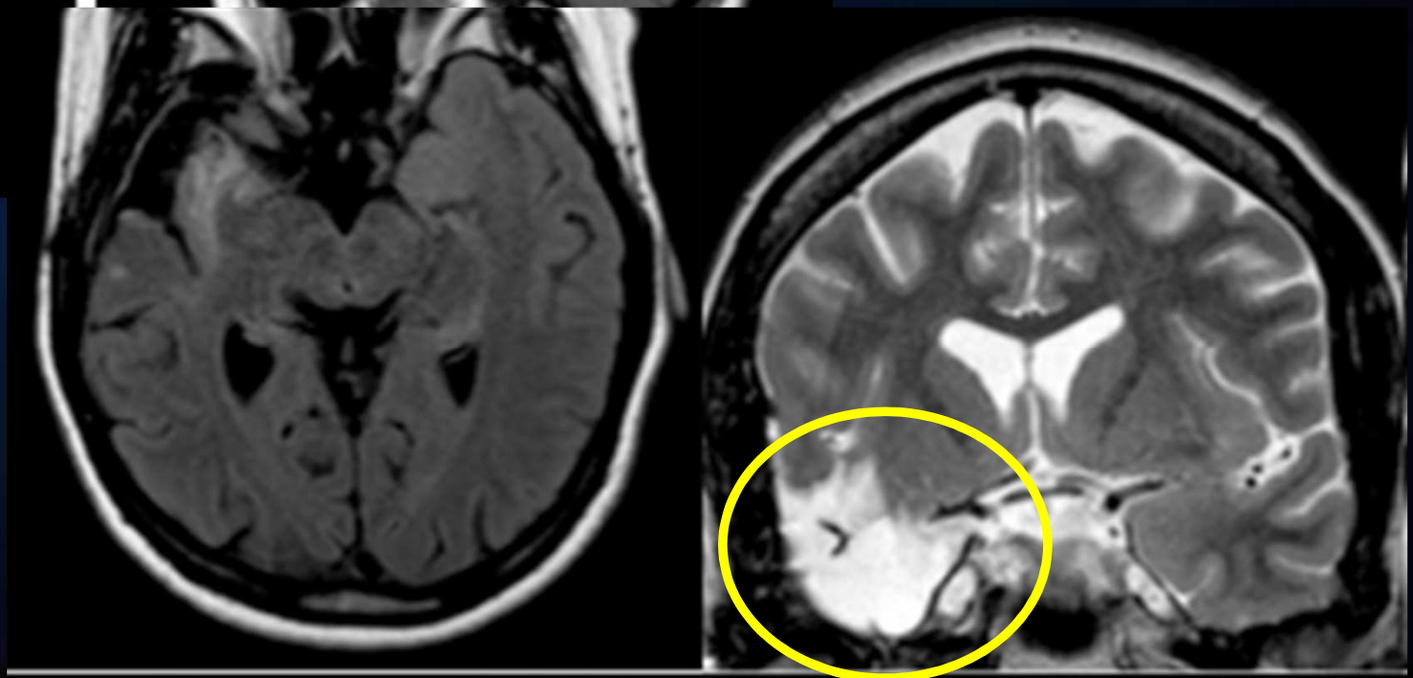
Table 1 *Descriptions of zones and lesions of the cortex (adapted from Lüders and Awad, 1992)*

Epileptogenic zone	Region of cortex that can generate epileptic seizures. By definition, total removal or disconnection of the epileptogenic zone is necessary and sufficient for seizure-freedom
Irritative zone	Region of cortex that generates interictal epileptiform discharges in the EEG or MEG
Seizure onset zone	Region where the clinical seizures originate
Epileptogenic lesion	Structural lesion that is causally related to the epilepsy
Ictal symptomatogenic zone	Region of cortex that generates the initial seizure symptoms
Functional deficit zone	Region of cortex that in the interictal period is functionally abnormal, as indicated by neurological examination, neuropsychological testing and functional imaging or non-epileptiform EEG or MEG abnormalities
Eloquent cortex	Region of cortex that is indispensable for defined cortical functions

Goal - Identify the epileptogenic zone and perform functional mapping in order to:

- determine whether or not epilepsy surgery can be undertaken and to define its chances of risk and benefit
- recommend tailored resections

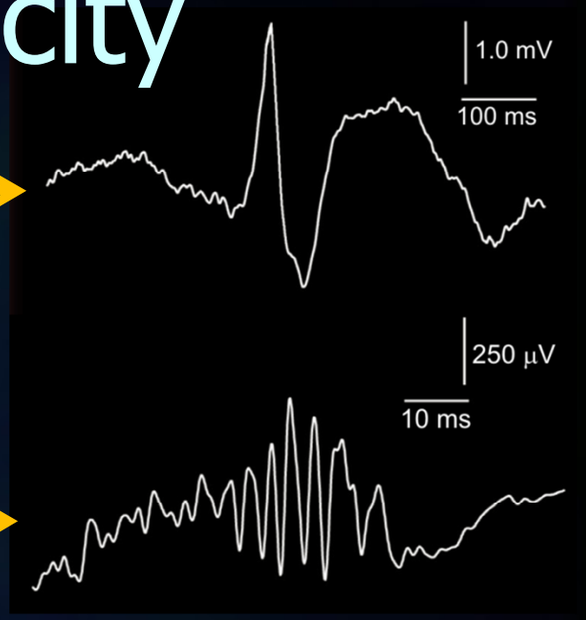




Example: Temporal lobe pole resection

Biomarkers of epileptogenicity

- **Inter-ictal spikes**



- **High-frequency oscillations:**
  - **Ripples 80(100) - 250 Hz**
  - **Fast Ripples >250 Hz**

- **High-frequency oscillations (HFO) - in normal brain**
  - Spontaneous ripples (100–200 Hz) are present in area CA1 of the hippocampus, as well as CA3, subiculum and the entorhinal cortex ripple frequency and sensory-evoked high-frequency oscillations (HFOs) occur in neocortex.
  - Ripples in area CA1 of stratum radiatum, and possibly neocortical HFOs, reflect inhibitory postsynaptic potentials of discharging interneurons that regulate pyramidal cell firing.
  - Hippocampal ripples and neocortical evoked HFOs are believed to play a role in sensory information processing.

After Staba and Bragin, *Biomarkers Med.* **5**(5), 2011

Biomarkers of epileptogenicity

Pathological HFOs in epileptic brain (pHFO)

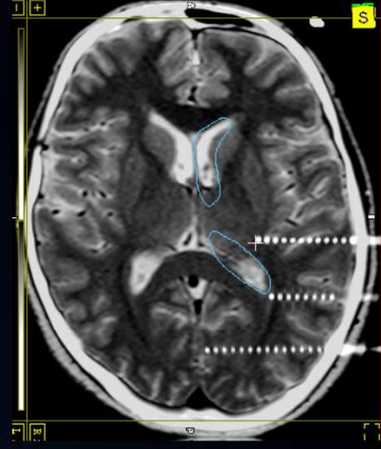
- Interictal fast ripples (250–600 Hz) are strongly associated with brain areas capable of generating spontaneous seizures.
- Ripple frequency HFOs in epileptogenic dentate gyrus and the neocortex should be considered pathological HFOs (pHFOs).
- Hippocampal pHFOs reflect bursts of population spikes arising chiefly from synchronously firing principal cells.

Interictal pHFOs as a biomarker of epilepsy

- The association between pHFOs and epileptogenicity suggest pHFOs could help localize the seizure onset zone and might identify the epileptogenic zone more accurately.
- The appearance of pHFOs after epileptogenic injury, for example status epilepticus, and before spontaneous seizures suggests pHFOs could be a biomarker of epileptogenesis in acquired epilepsy.

After Staba and Bragin, *Biomarkers Med.* **5**(5), 2011

Biomarkers of epileptogenicity



Interictal spikes as a biomarker of epilepsy

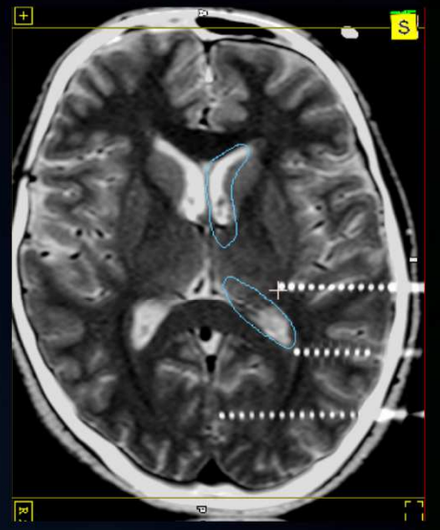
- Interictal spikes (IIS) represent a good spatial biomarker for the SOZ and the irritative zone
- However, there is little evidence that IIS predict seizure frequency or severity of epilepsy.
- The functional role of IIS in epilepsy is not known, but some IIS might reduce ictal discharges.
- The presence and clustering of IIS after status epilepticus could indicate the subsequent appearance of spontaneous seizures.

Conclusion

- Interictal pHFOs reflect basic neuronal disturbances in brain areas capable of generating spontaneous seizures that could identify the epileptogenic region, determine the severity of epileptogenicity and possibly predict the development of epilepsy.

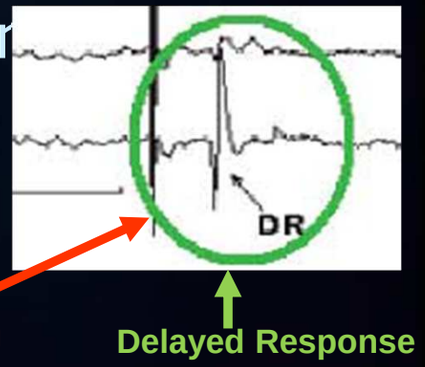
After Staba and Bragin, *Biomarkers Med.* **5**(5), 2011

Invasive recordings and stimulation: *StereoElectroEncephaloGraphy* - **SEEG**

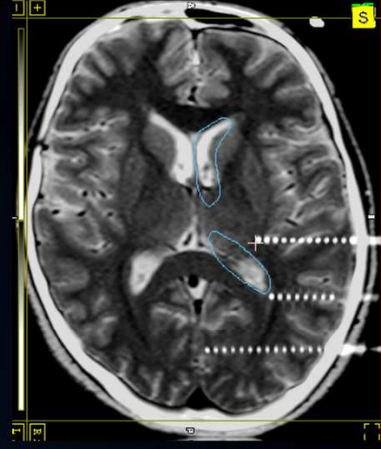


- SEEG
  - Provides direct access to electrophysiological recordings in the seizure onset zone, when located in deep brain structures
  - Allows delineation of the epileptogenic area in 3D volume
  - Provides excellent time & space resolution
  - HFOs and spikes are well evidenced

- Direct Electric Stimulation (DES)
  - Uses different stimulation protocols to map epileptogen brain connectivity
  - Functional mapping of eloquent cortex



SEEG + DES



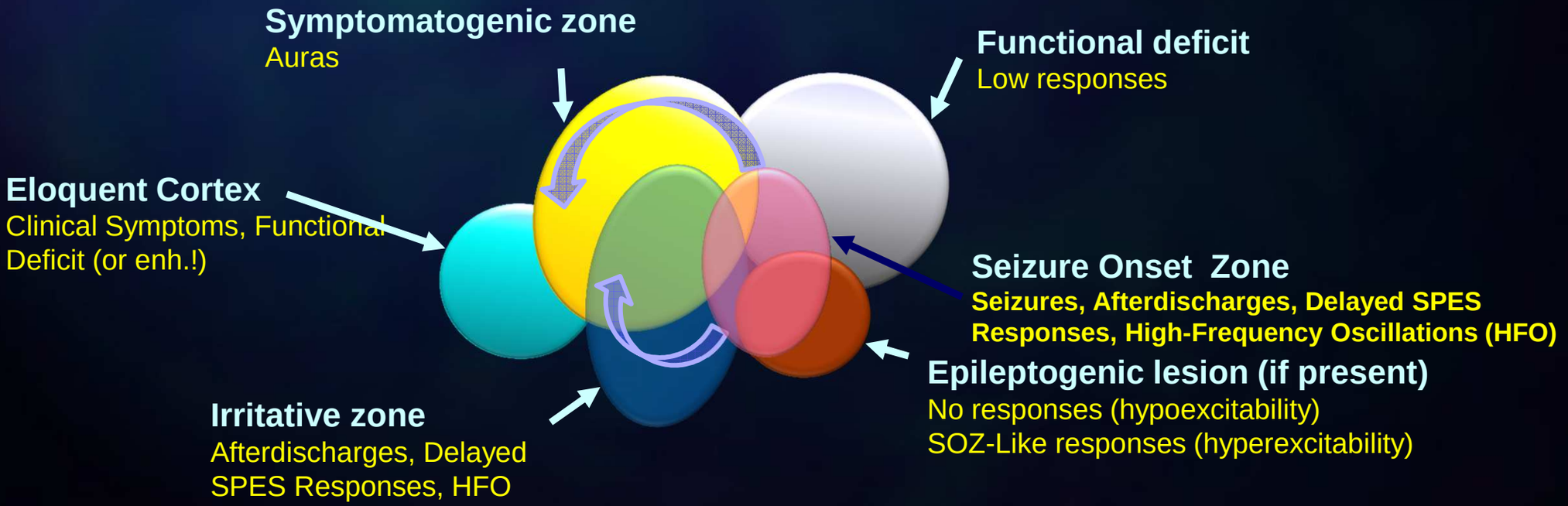
Each zone has specific EEG markers

- 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.”

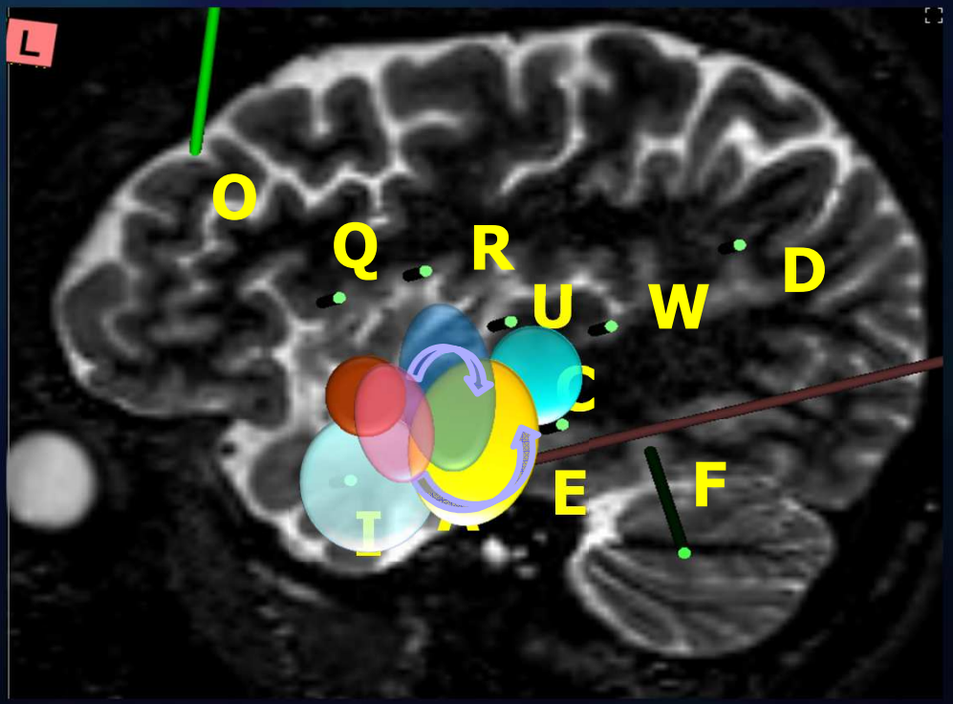
- van ’t Klooster et al, 2011



Imaging the Seizure Onset Zone

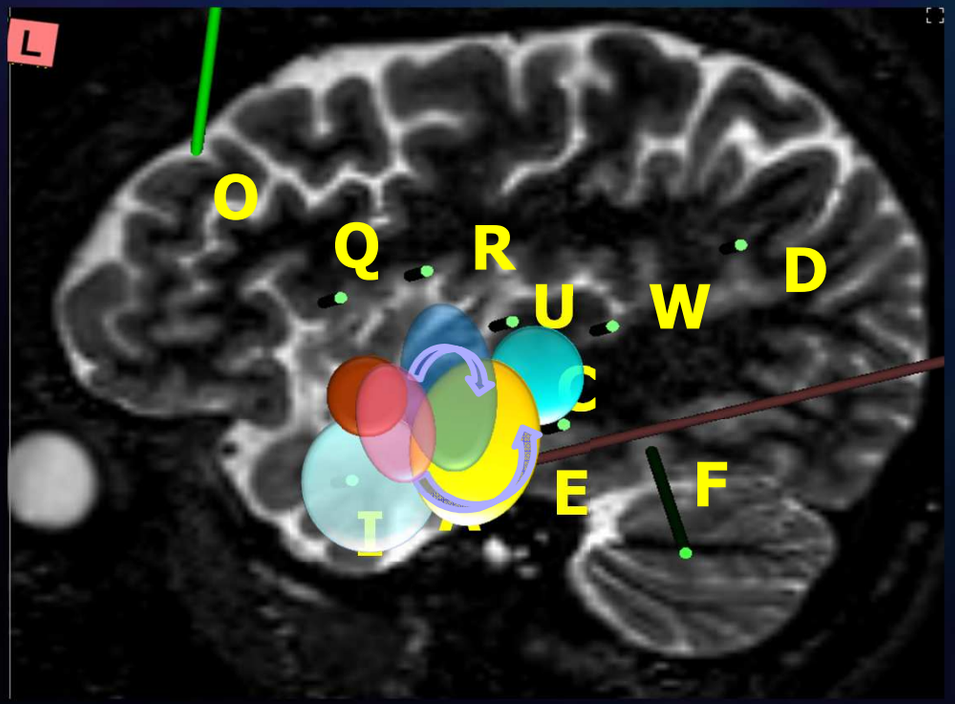
- MRI – shows anatomical data based on probing the response of protons (H+) in the water using variable magnetic fields applied in various sequences and radiofrequency signals

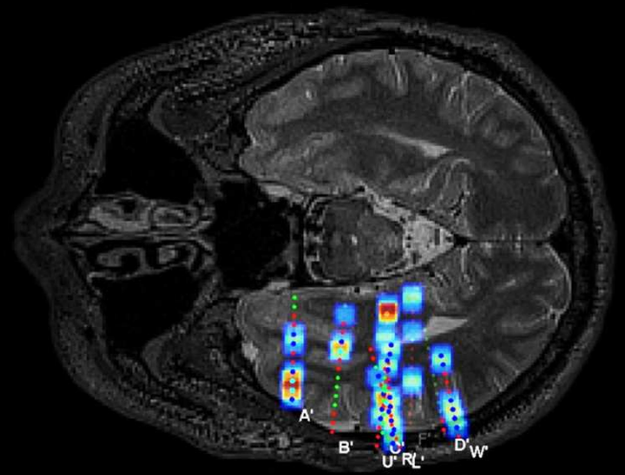
- DES – shows functional connectivity based on electrophysiological responses to electrical stimulation, imaging the epileptogenic areas.

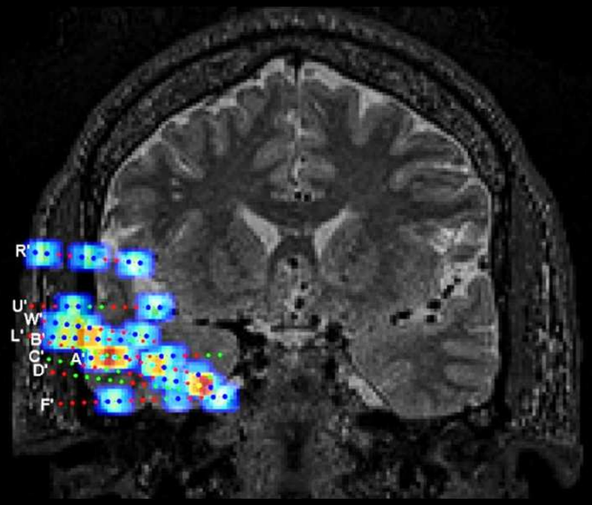


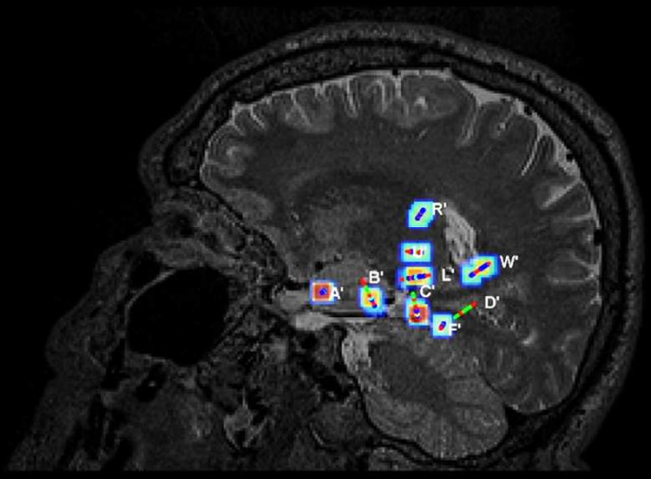
Our Aim

- To combine stereotactic information regarding each electrode's position within the brain with measurements of epileptogenicity biomarkers, to create exact 3D activation and connectivity maps for each patient



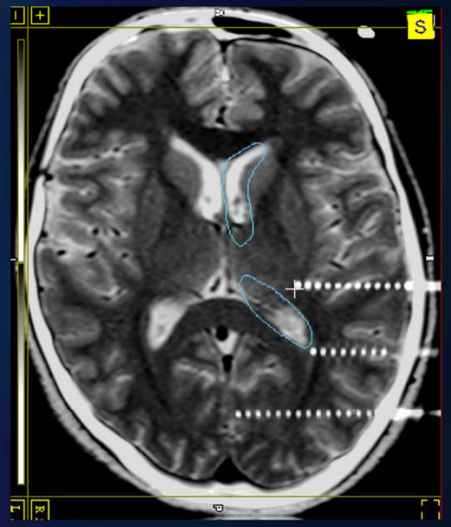


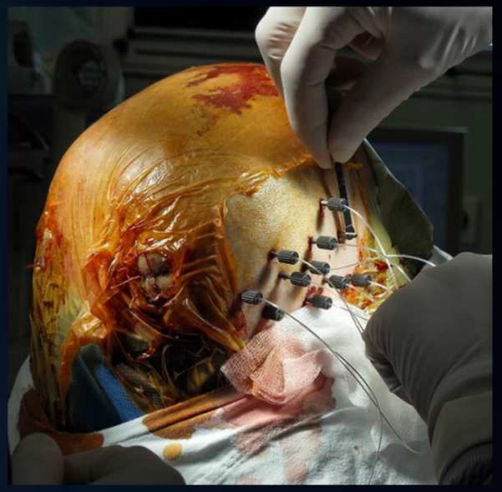


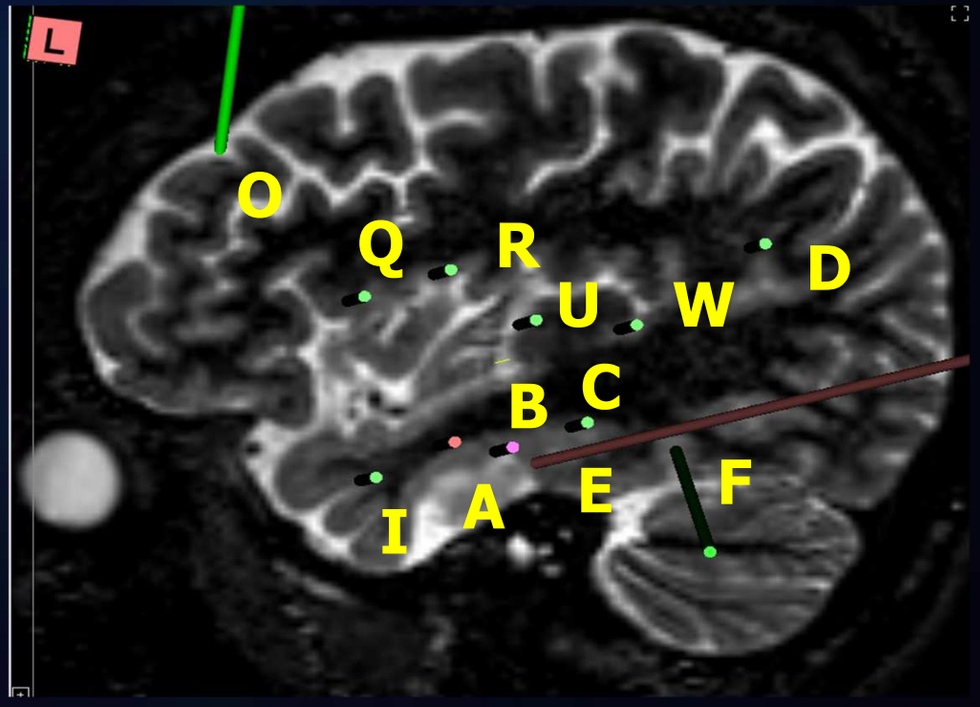


Subjects and Methods

- 13 patients with drug-resistant epilepsy
- 8-17 SEEG electrodes stereotactically implanted
- Data recorded using
  - 64 channels amplifier
  - Sampling rate 4096 Hz
    - allows visualization of High-Frequency Oscillations (HFO) with f>100 Hz
- Stimulation: Programmable stimulator (Guideline LP+, FHC Inc)

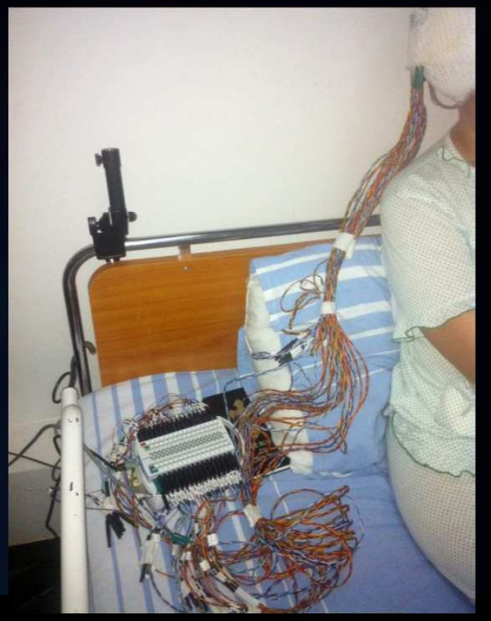






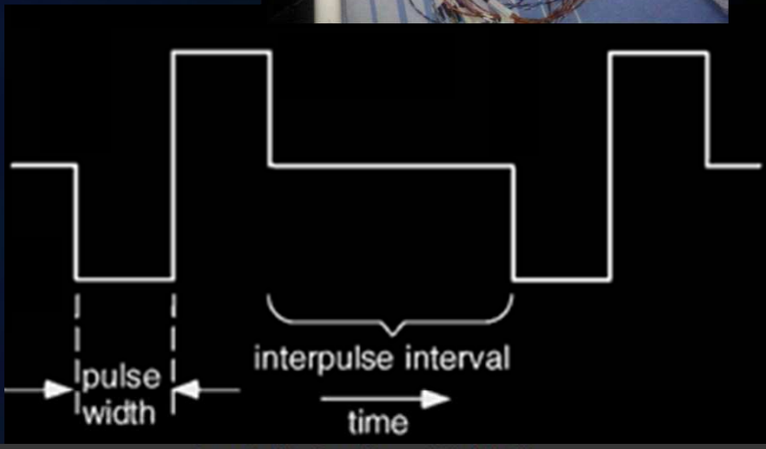
A - Amygdala; B – Anterior Hippocampus;
C – Posterior Hippocampus;
E – Entorhinal Cortex; U – Superior Temporal Gyrus;
D - Retrosplenial cortex; S - Suprasylvian;
I – Temporal Pole; O - Orbitofrontal; F - Fusiform gyrus;
R – Rolandic Operculum; W – Wernicke;

Subjects and Methods

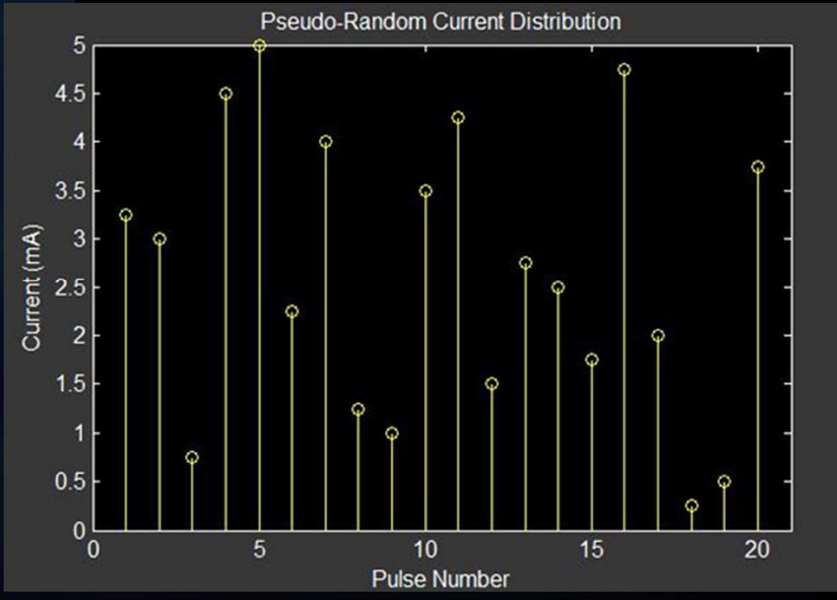


Stimulation protocols:

- Standard
  - 1 Hz: biphasic, 3 ms pulse width, 40 s stimulation length, 0.5 - 3 mA current range - used for mapping brain connectivity *(Enatsu et al., 2012, David et al, 2013)*
  - 50 Hz functional mapping: biphasic, 1 ms pulse width, 5 s stimulation length, 0.5 - 3 mA current range (Kahane et al, 2004)



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



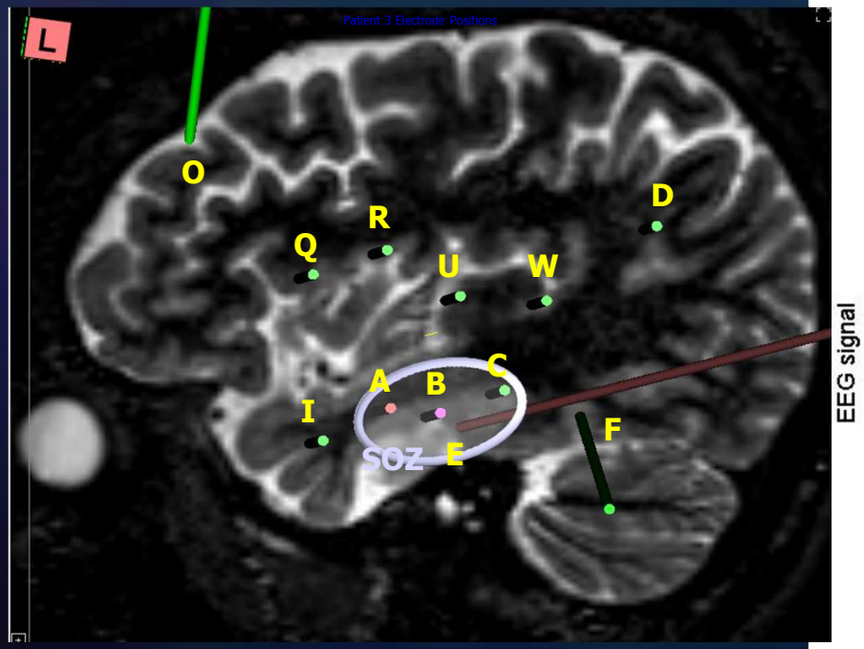
Presurgical video-EEG monitoring:

- 5-14 days

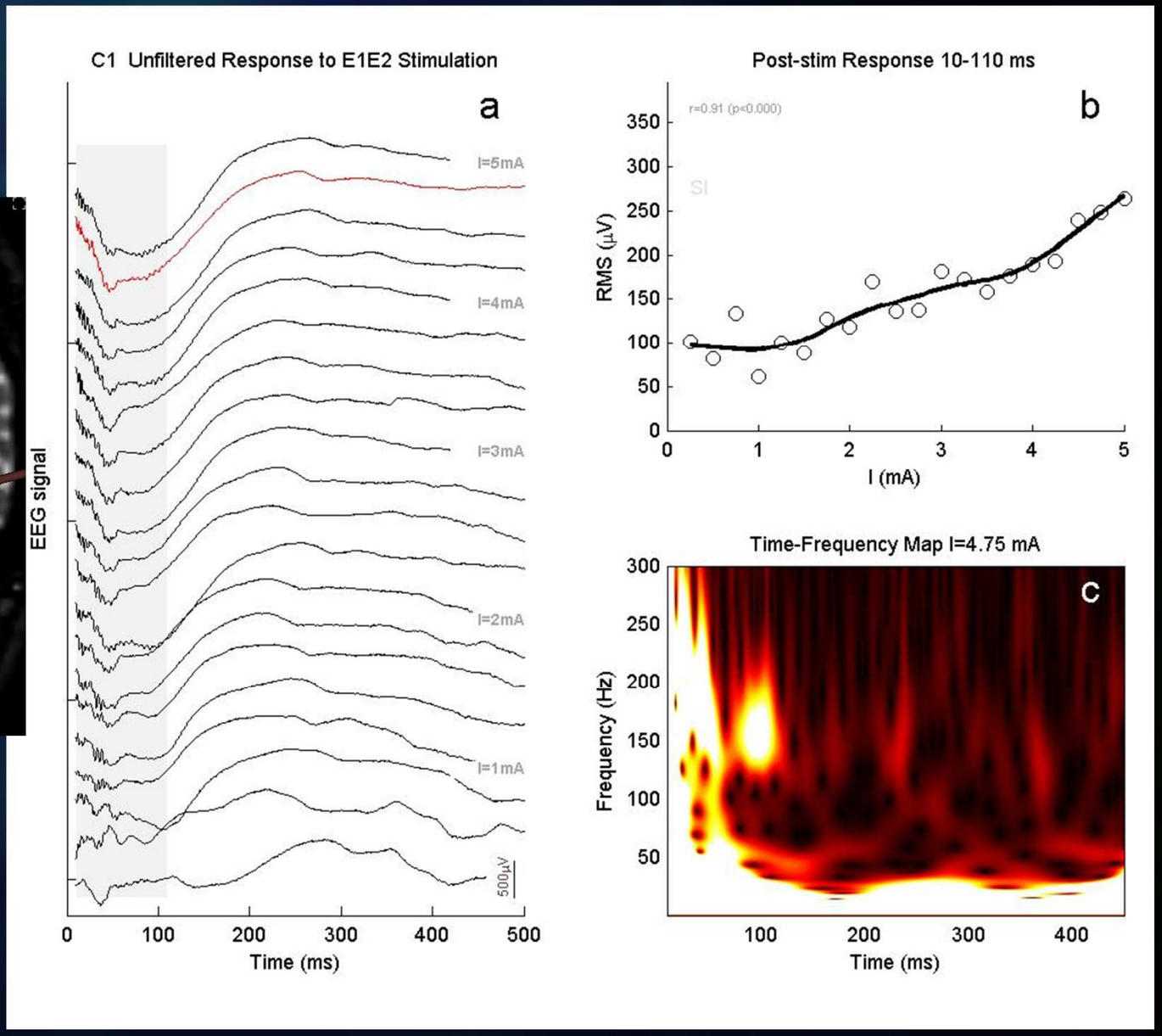
SPES

C1 (Post Hc) response to E1-E2 (Entorhinal Cortex) stimulation

Raw signal



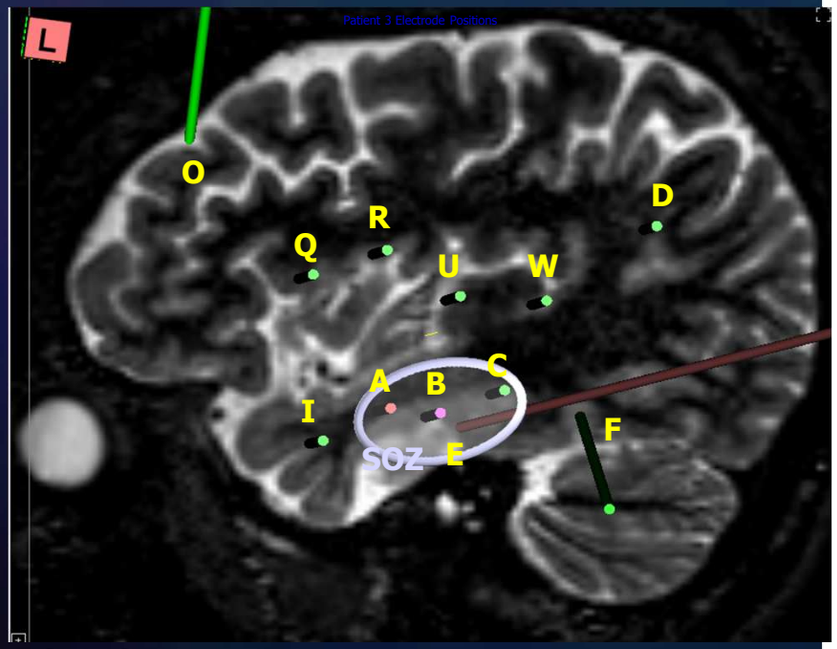
SEEG electrode implantation pattern in patient 3. A - Amygdala; B – Anterior Hippocampus; C – Posterior Hippocampus; E – Entorhinal Cortex; U – Superior Temporal Gyrus; D - Retrosplenial cortex; S - Suprasylvian; I – Temporal Pole; O - Orbitofrontal; F - Fusiform gyrus; R – Rolandic Operculum; W – Wernicke.



a) EEG traces; (b) - stimulus response curve; (c) – Time-frequency map (Morlet)

SPES

C1 (Post Hc) HFOs ~150 Hz evoked by E1-E2 (Entorhinal Cortex) stimulation



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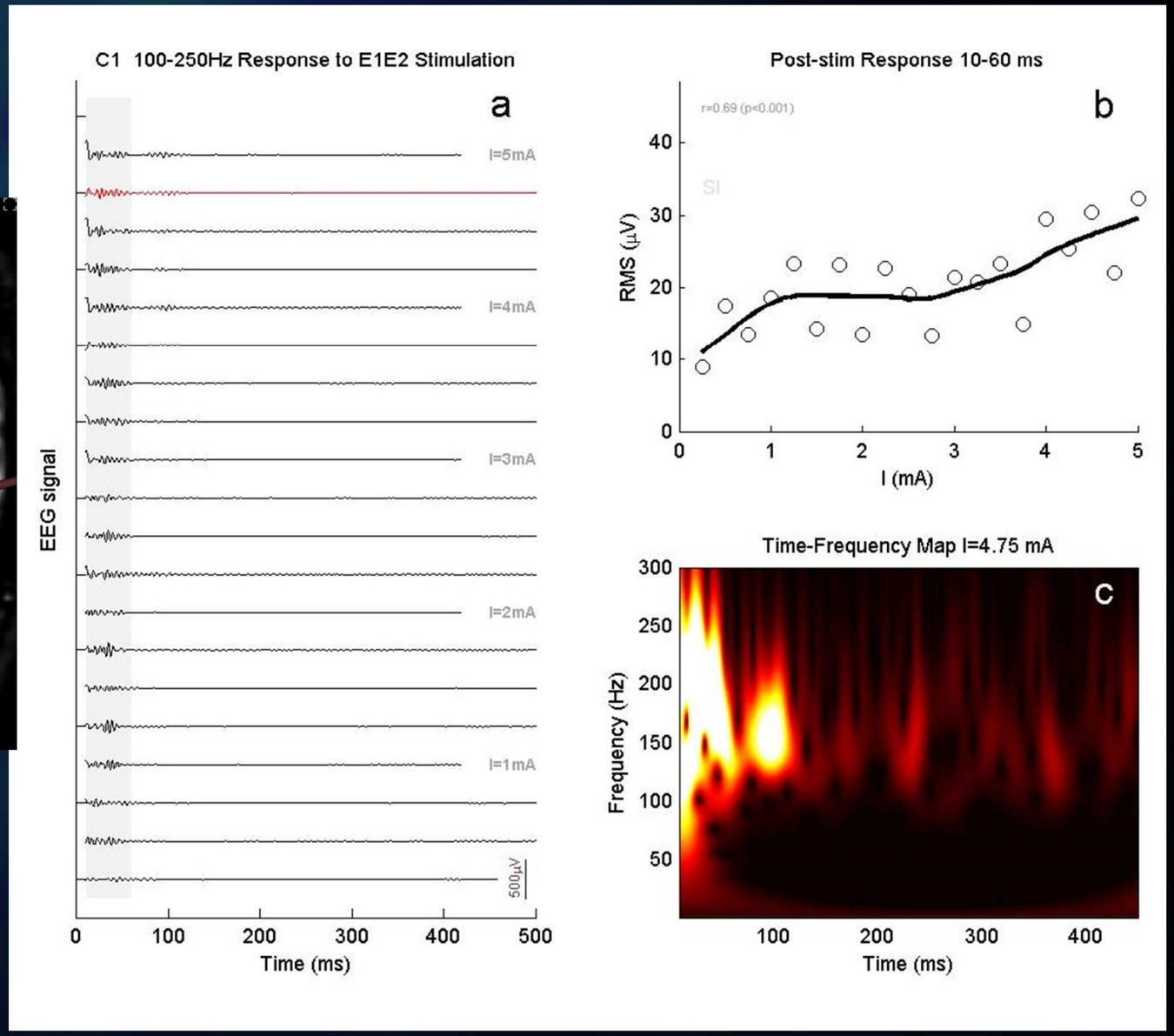
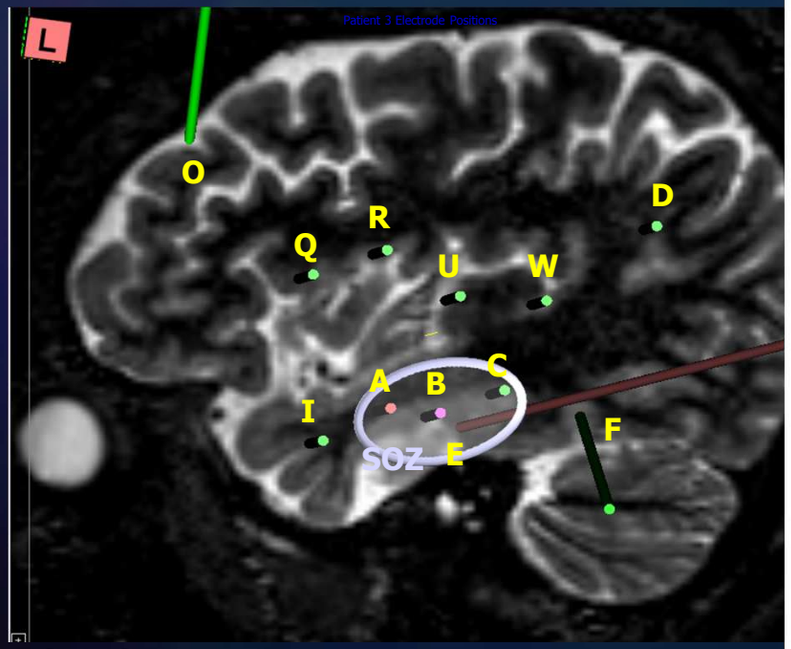


a) EEG filtered in the 100-250 Hz range; (b) - stimulus response curve; (c) – Time-frequency map (Morlet)

SPES

Delayed Responses: D01 (Retrosplenial Cortex) evoked by stimulating contacts B03-B04 (Anterior Hippocampus)



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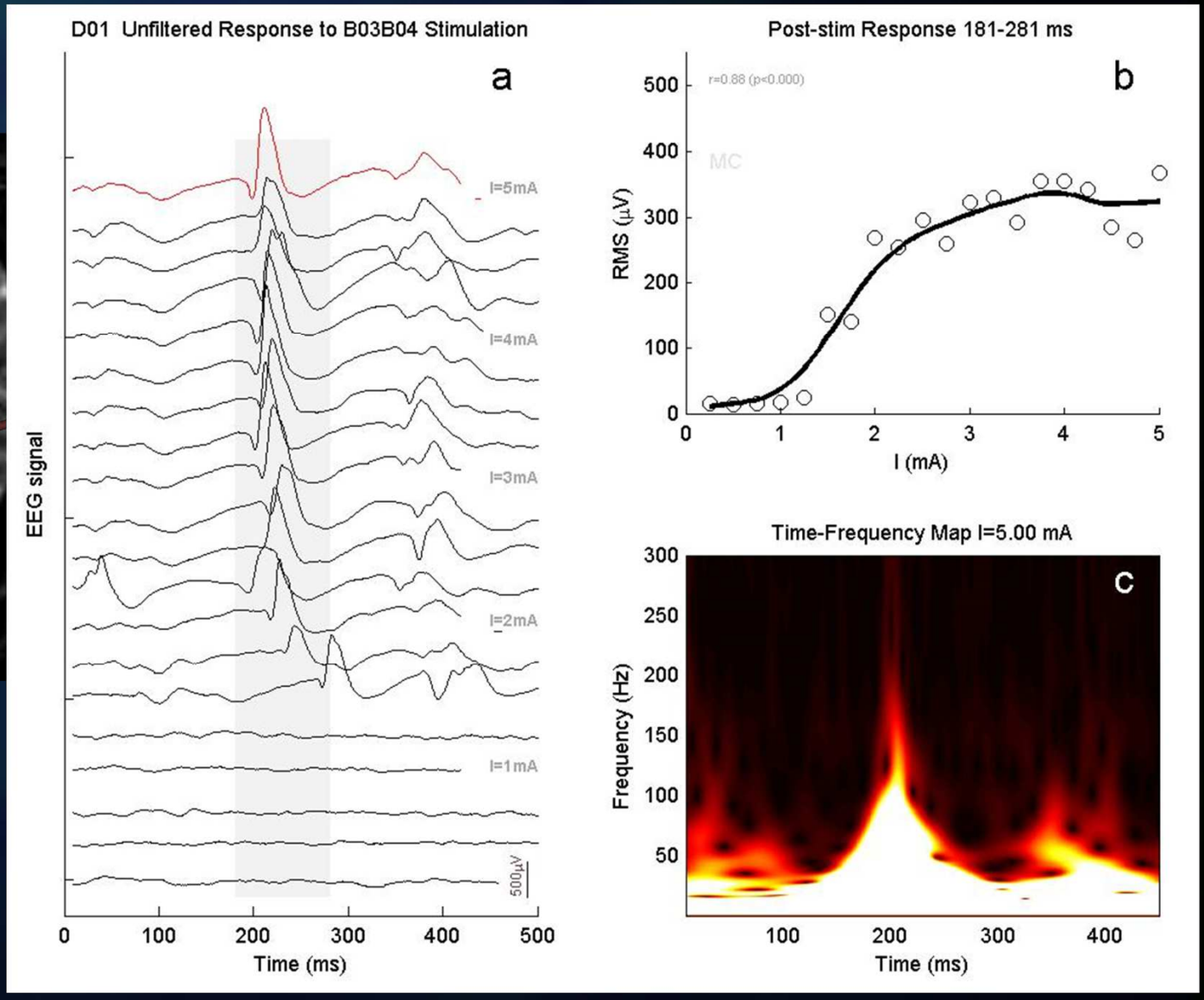


a) Raw EEG traces; (b) - stimulus response curve; (c) – Time-frequency map (Morlet)

Sensitivity, specificity and predictive value of the responses for EZ delineation

- Sensitivity
  - Sens = [positive channels within SOZ /(positive channels within SOZ + negative channels within SOZ] x 100,

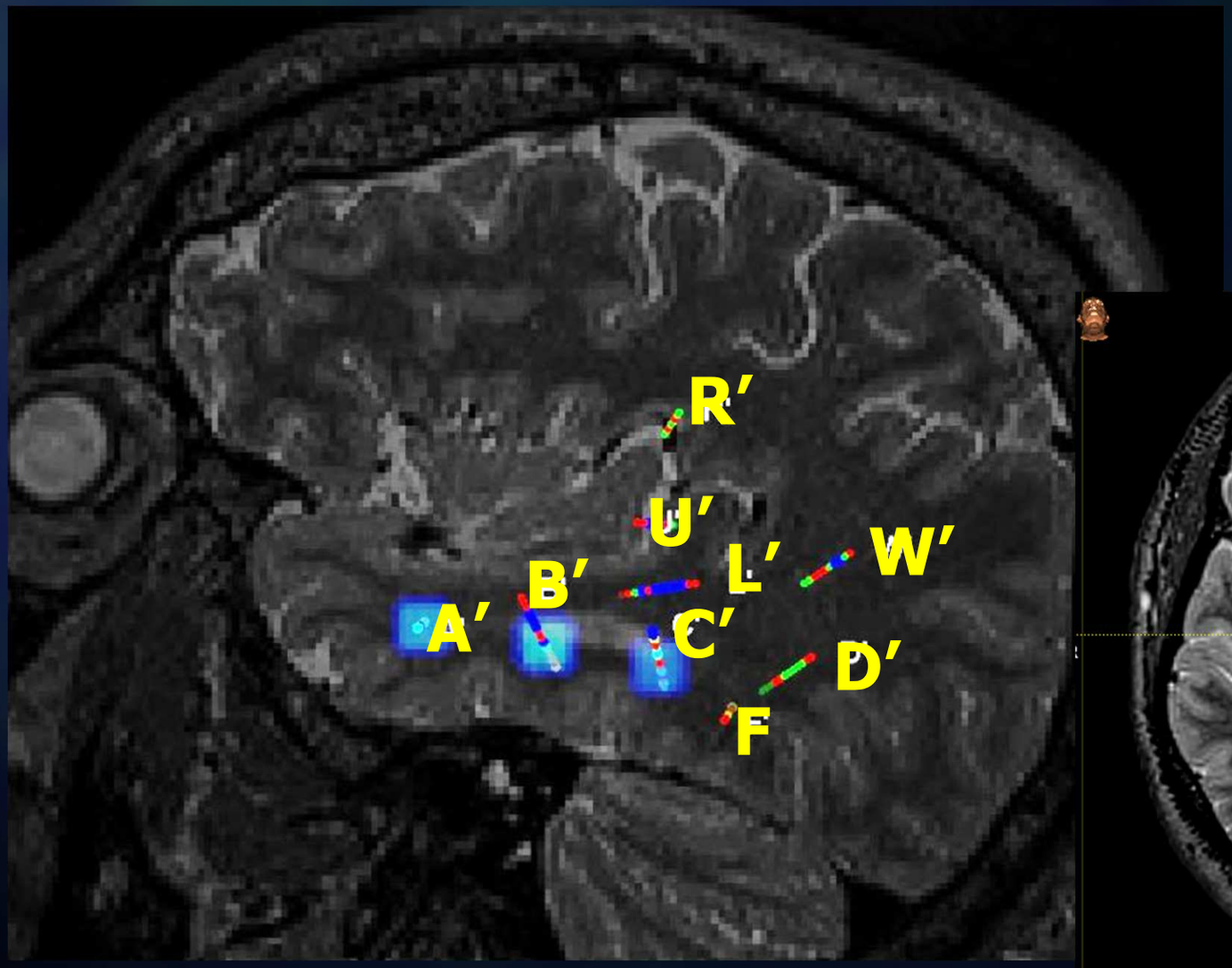
  or
  - Sens = (positive channels within SOZ /channels within SOZ) x 100
- Specificity
  - Spec = [negative channels outside SOZ / (negative channels outside SOZ + positive channels outside SOZ)] x 100,

  or
  - Spec = (negative channels outside SOZ / channels outside SOZ) x 100
- Accuracy
  - Acc = [(positive channels within SOZ + negative channels outside SOZ)/total channels] x 100,
- PPVel is defined as
  - number of positive electrodes within SOZ / number of positive electrodes
- NPVel is defined as
  - number of negative electrodes within SOZ / number of negative electrodes

Andrade-Valenca, Dubeau, Mari, Zelmann, Gotman, Neurology 2011

Results (continued)

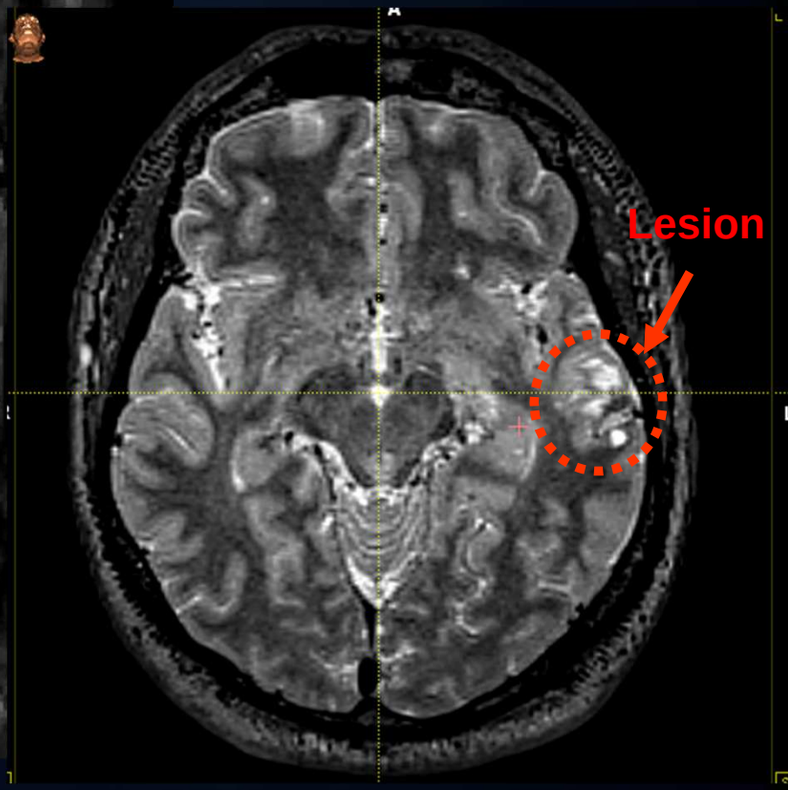
Pat 10 (BF): M, 47y, DNET, Left Middle Temp. Gyr. (T2)



SEEG:

9 electrodes

95 contacts

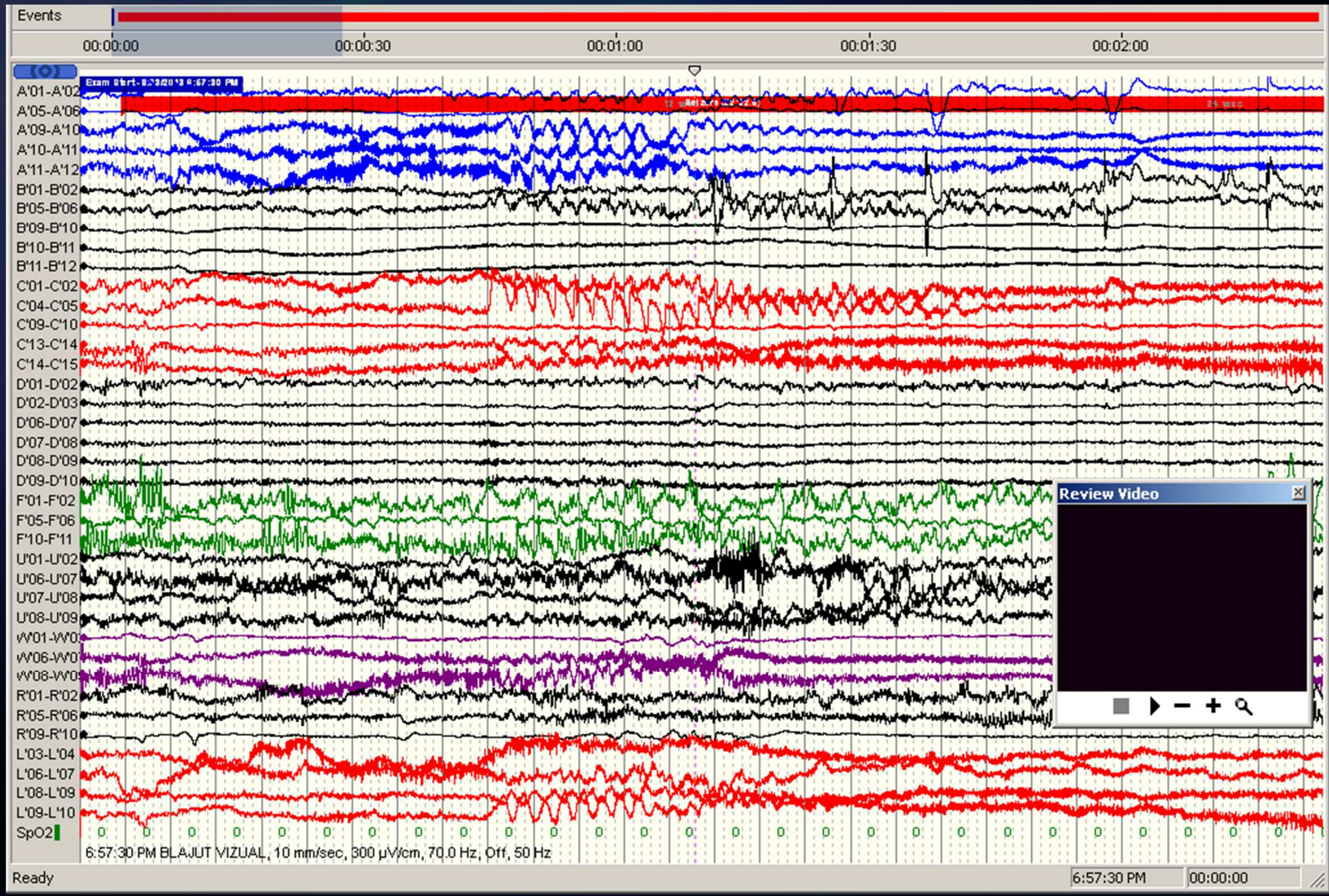


A’ - Amygdala; B’ – Anterior Hippocampus; C ‘– Posterior Hippocampus; U’ – Superior Temporal Gyrus;

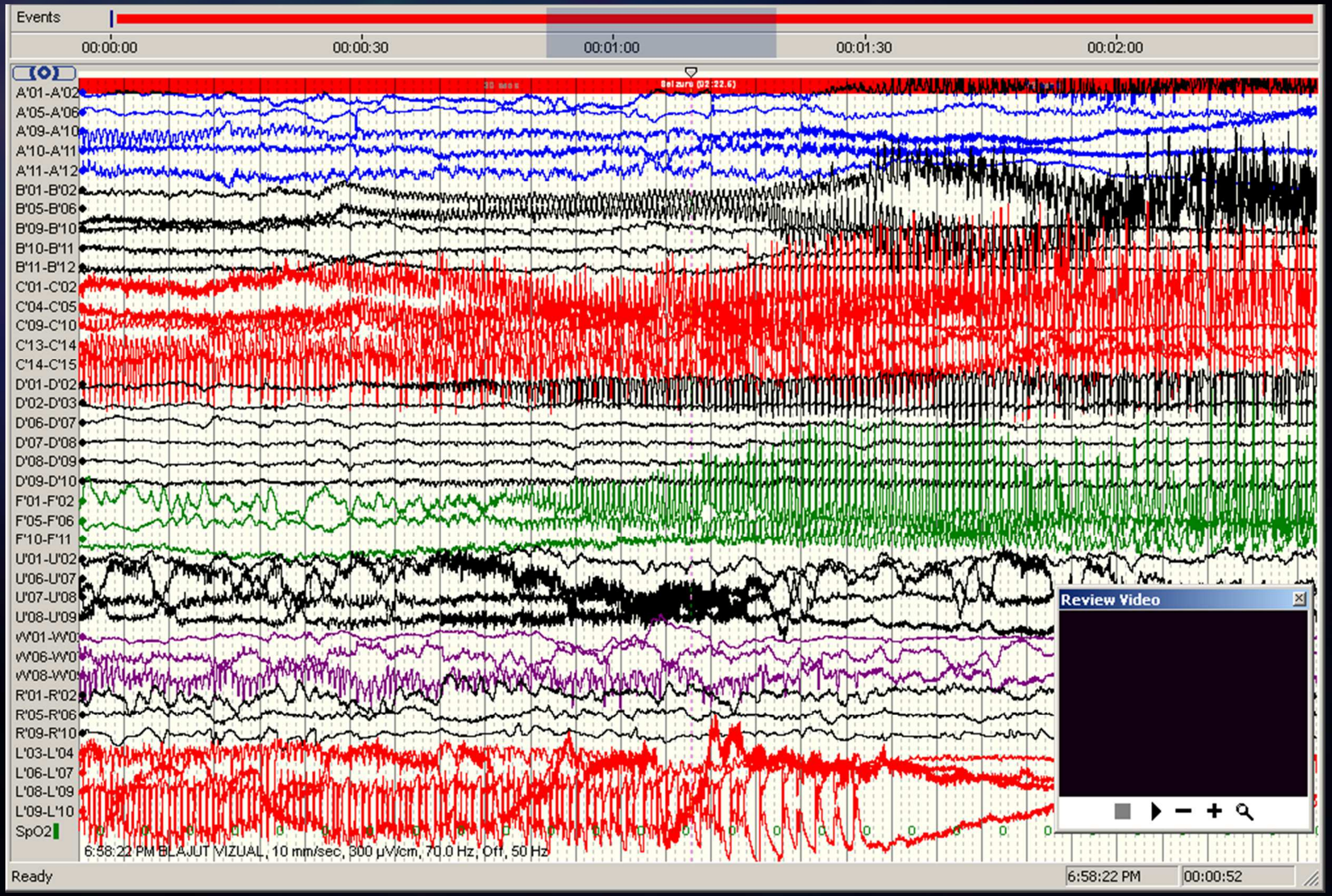
L – Middle Temporal Gyrus (Lesion); D’ – Posterior to Lesion; F’ - Fusiform gyrus; R’ – Rolandic Operculum;

W’ – Wernicke;

Spontaneous Seizure

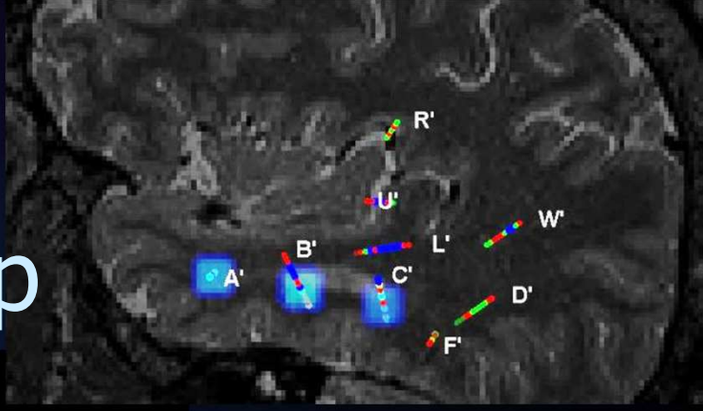


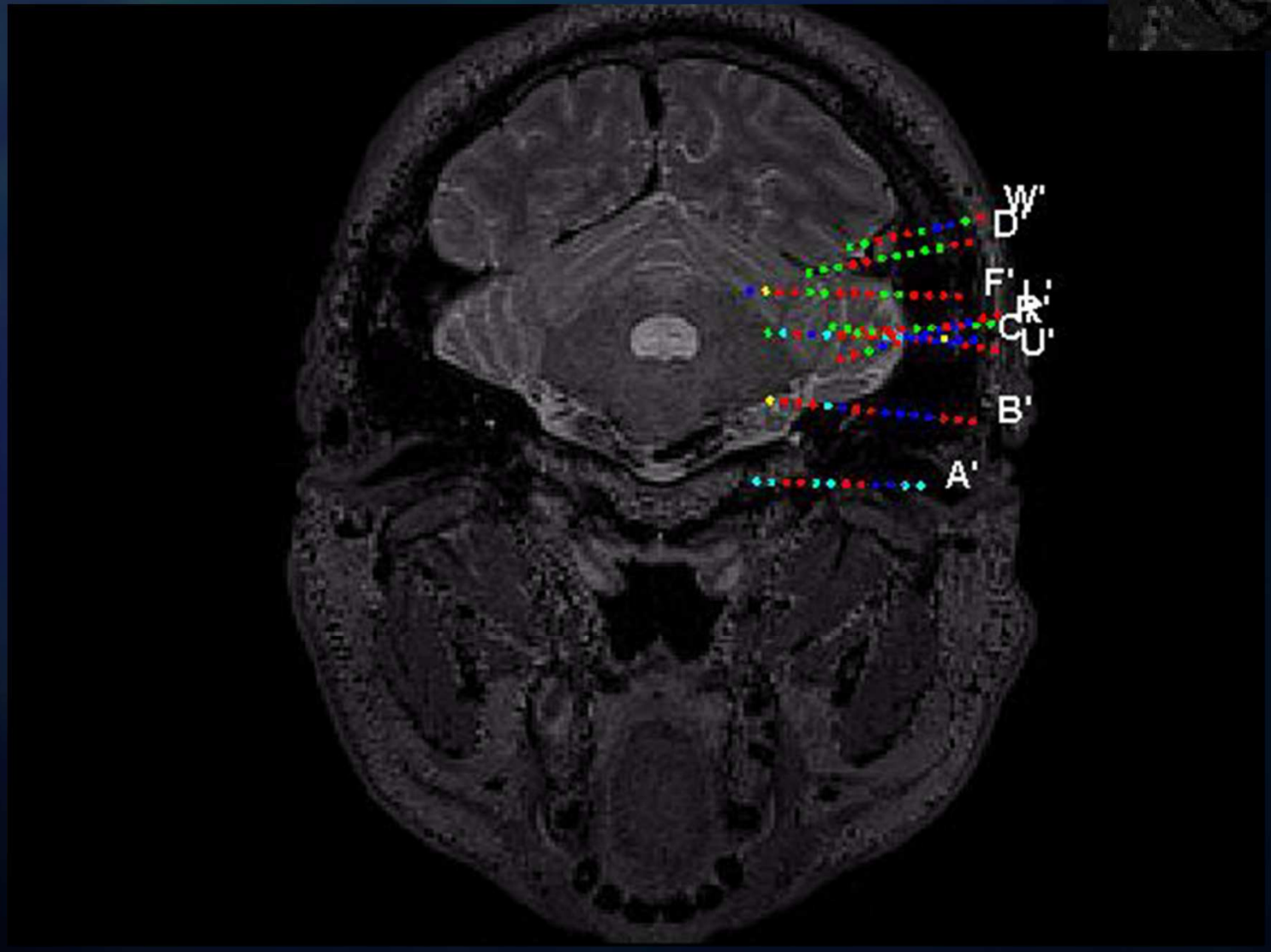
Spontaneous Seizure



Results

- SPES Delayed Response Map





Patient 10

BF: M, 47y, DNET, MTG

SEEG:

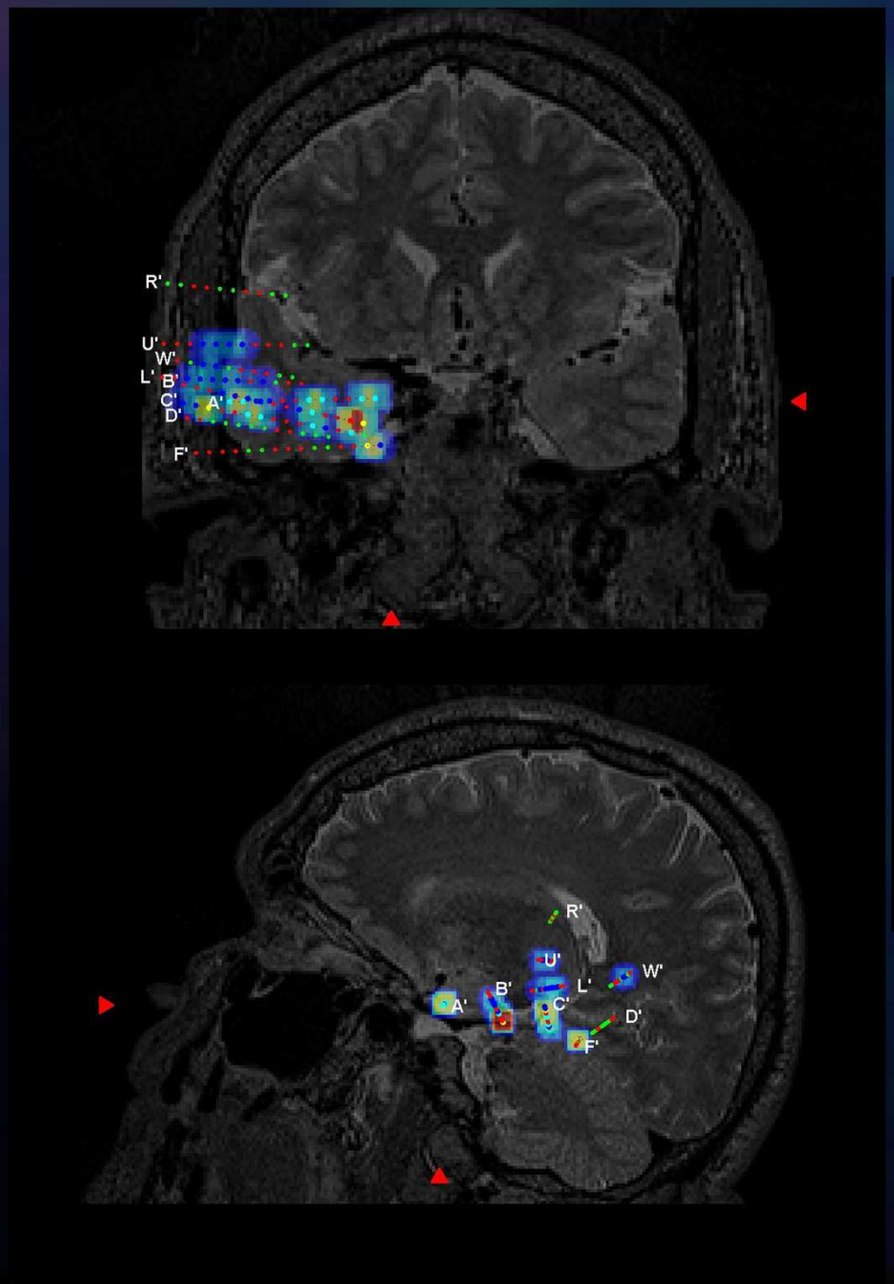
9 electrodes

95 contacts

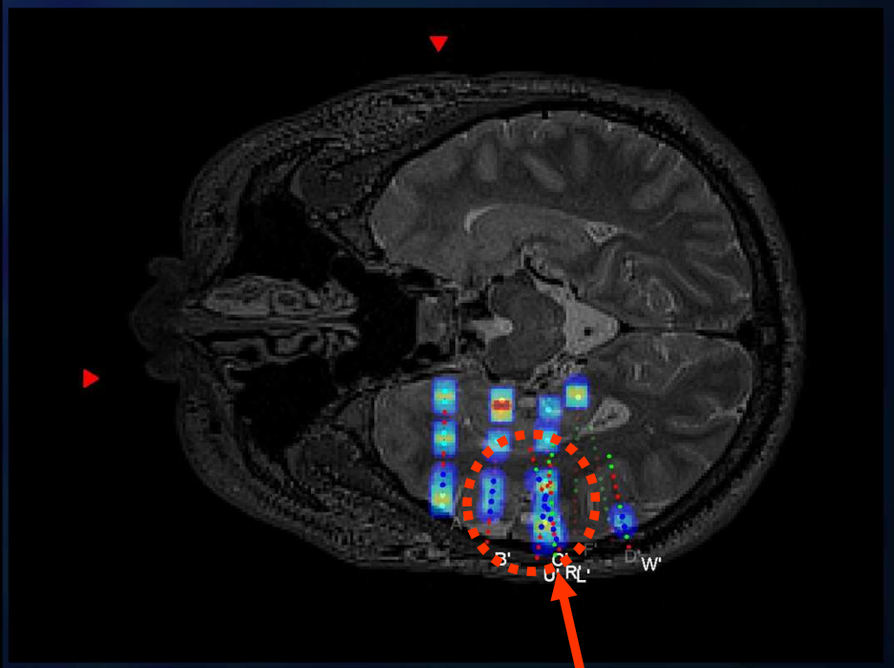
A' - Amygdala; B' – Anterior Hippocampus; C '– Posterior Hippocampus; U' – Superior Temporal Gyrus; L – Middle Temporal Gyrus (Lesion); D' - Retrosplenial cortex; F' - Fusiform gyrus; R' – Rolandic Operculum; W' – Wernicke;

Delayed Responses Map

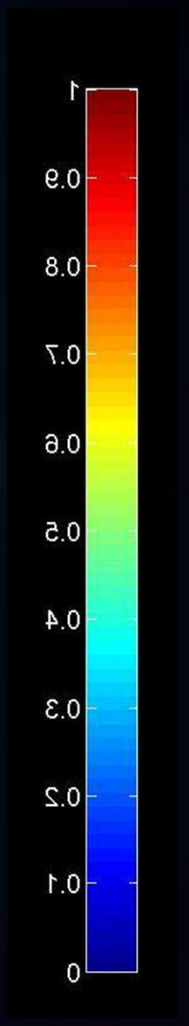
Pat 10 (BF): M, 47y, DNET, Left Middle Temp. Gyr. (T2)



Maximum Intensity Projection (MIP)

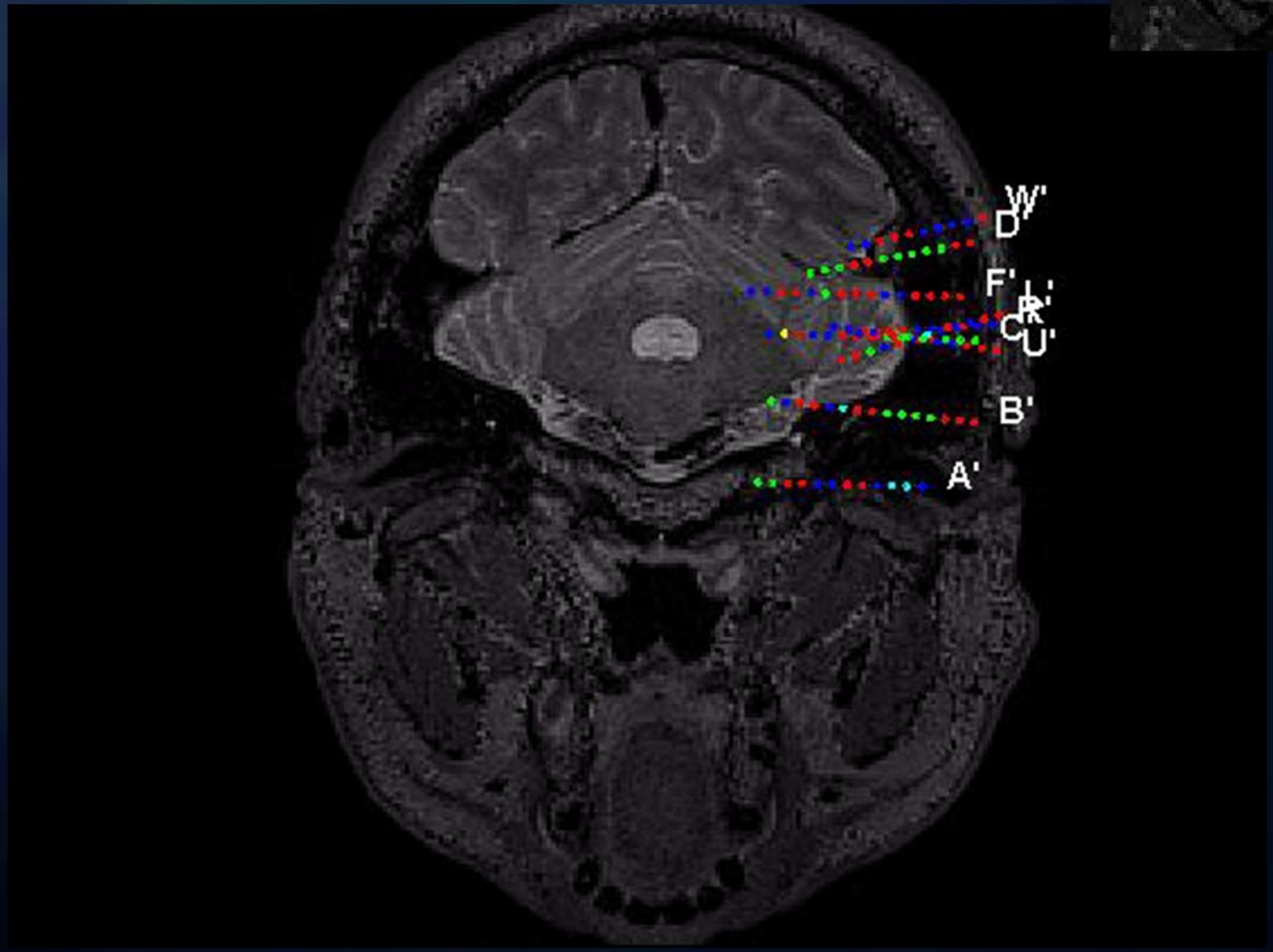


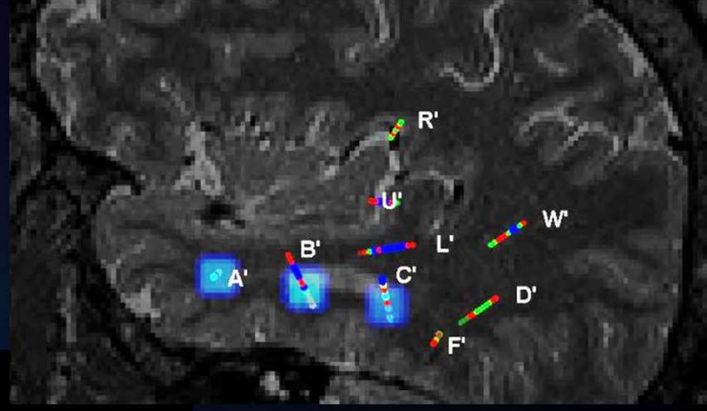
Lesion



Results

- SPES HFO Map





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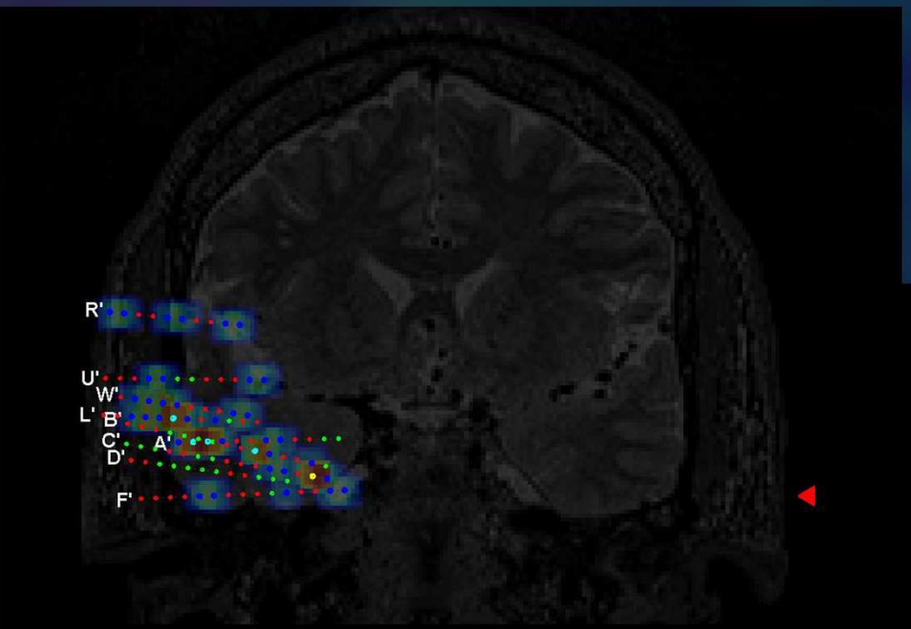
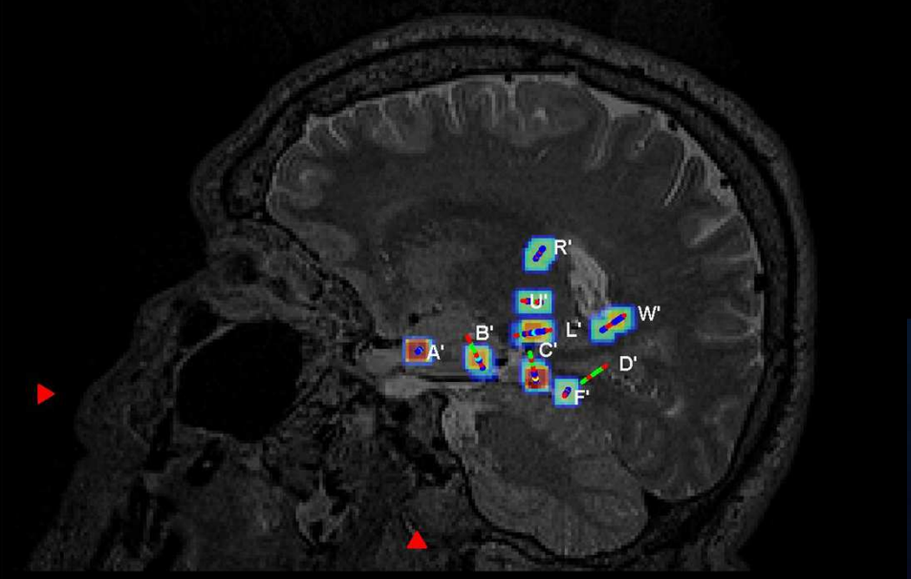
95 contacts

A' - Amygdala; B' – Anterior Hippocampus; C '– Posterior Hippocampus; U' – Superior Temporal Gyrus;
L – Middle Temporal Gyrus (Lesion); D' - Retrosplenial cortex; F' - Fusiform gyrus; R' – Rolandic Operculum;
W' – Wernicke;

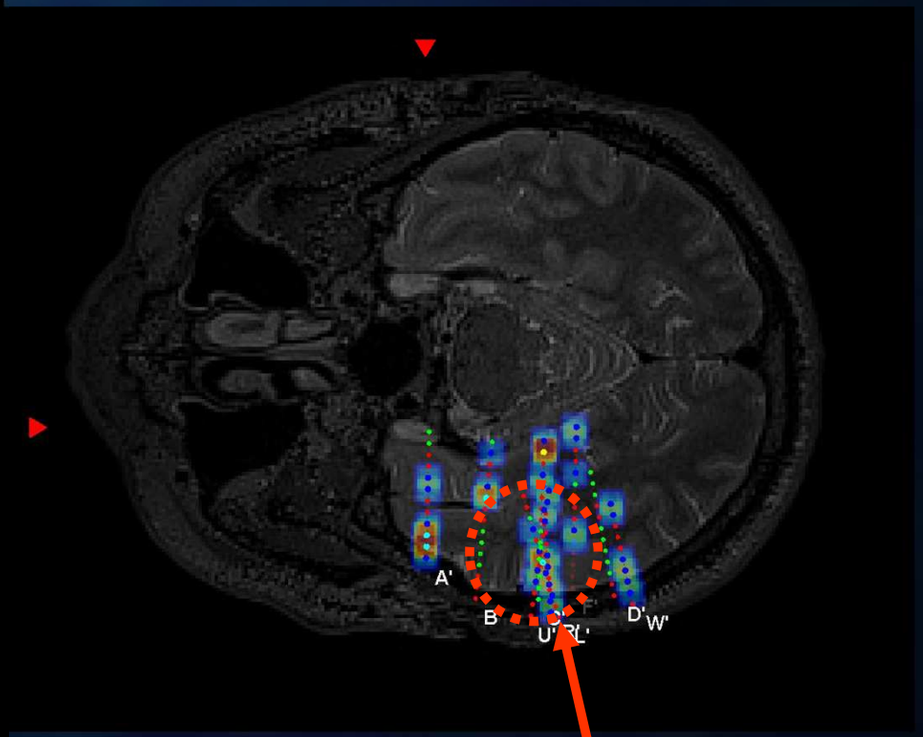
HFO Map

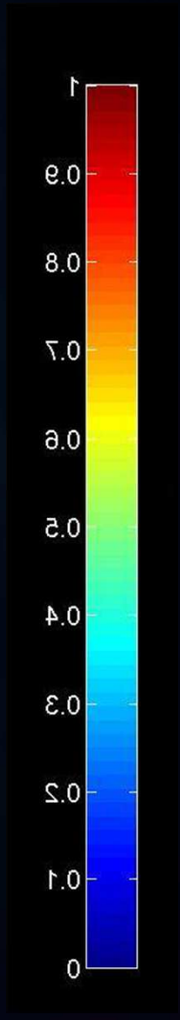
Pat 10 (BF): M, 47y, DNET, Left Middle Temp. Gyr. (T2)





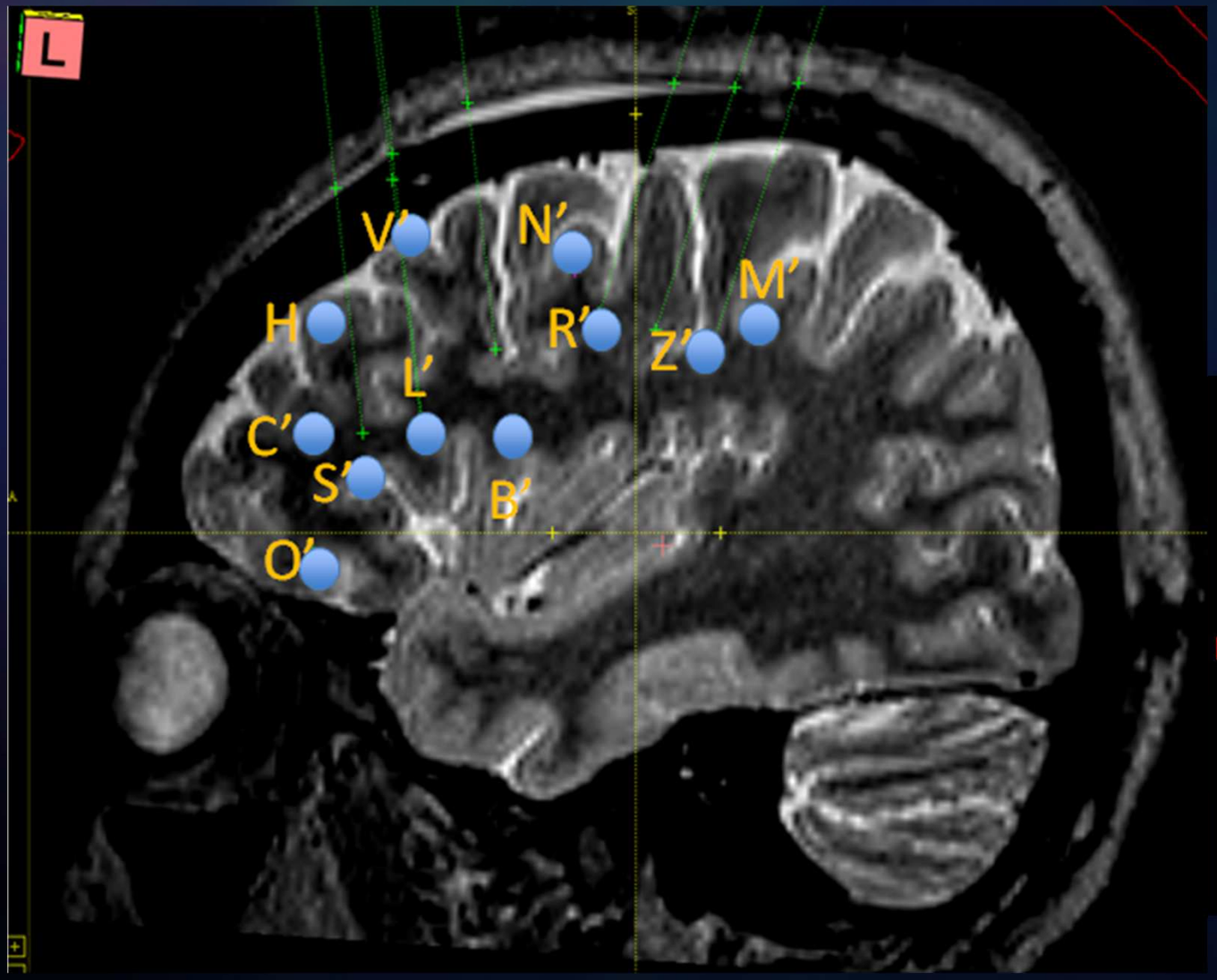
Maximum Intensity Projection (MIP)





Results (continued)

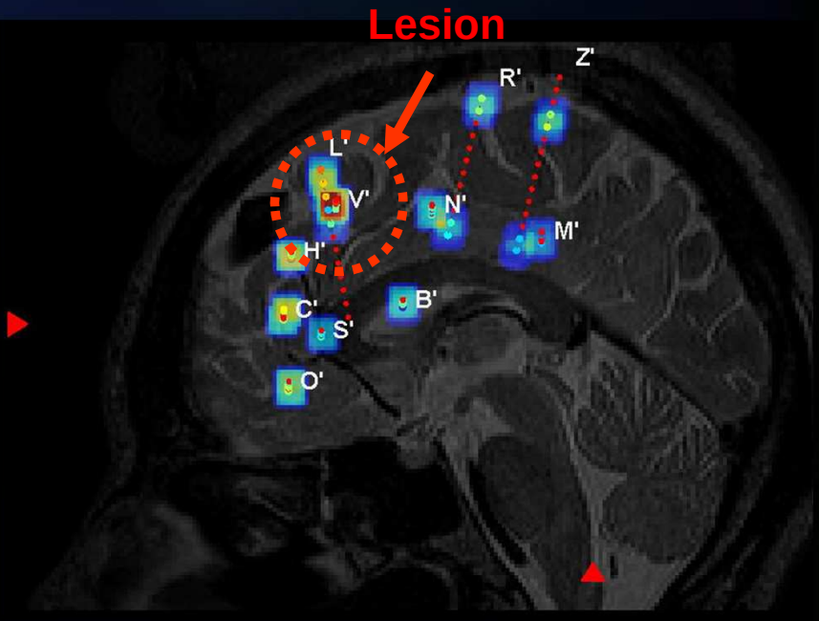
Pat 12 (BM): F, 40y, Focal Dysplasia, Frontal - Premotor



SEEG:

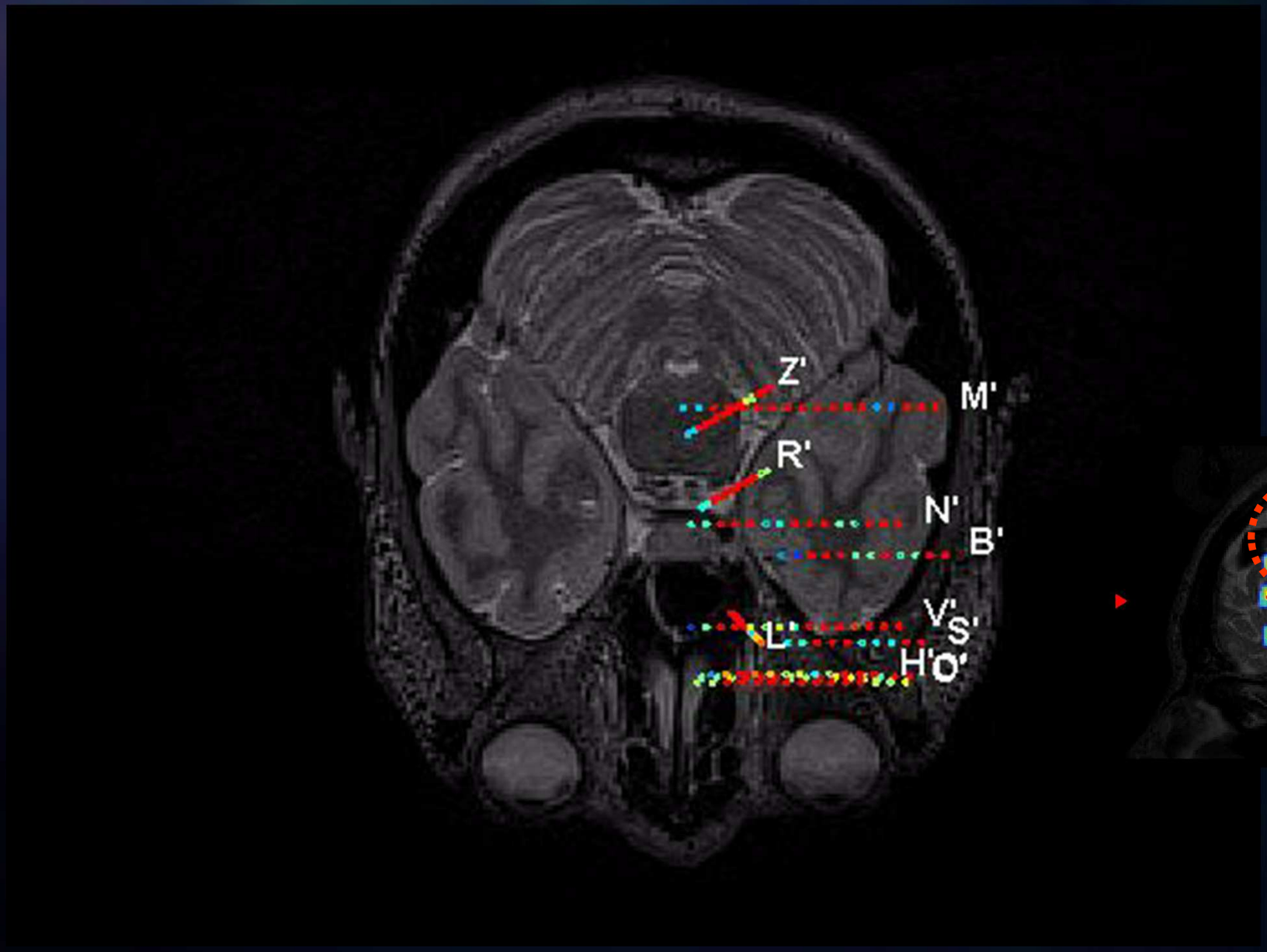
11 electrodes

146 contacts



Results

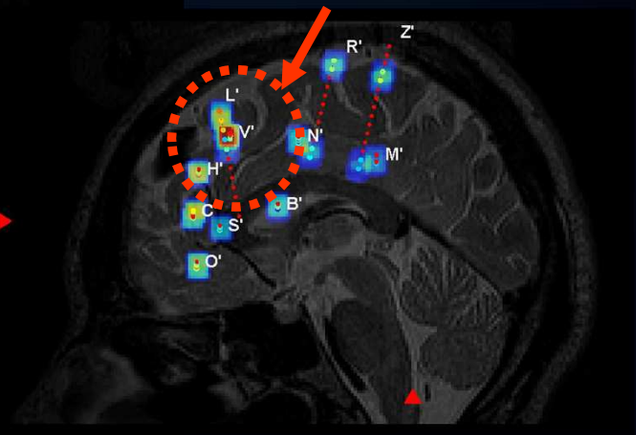
- SPES Delayed Response Map



Patient 12

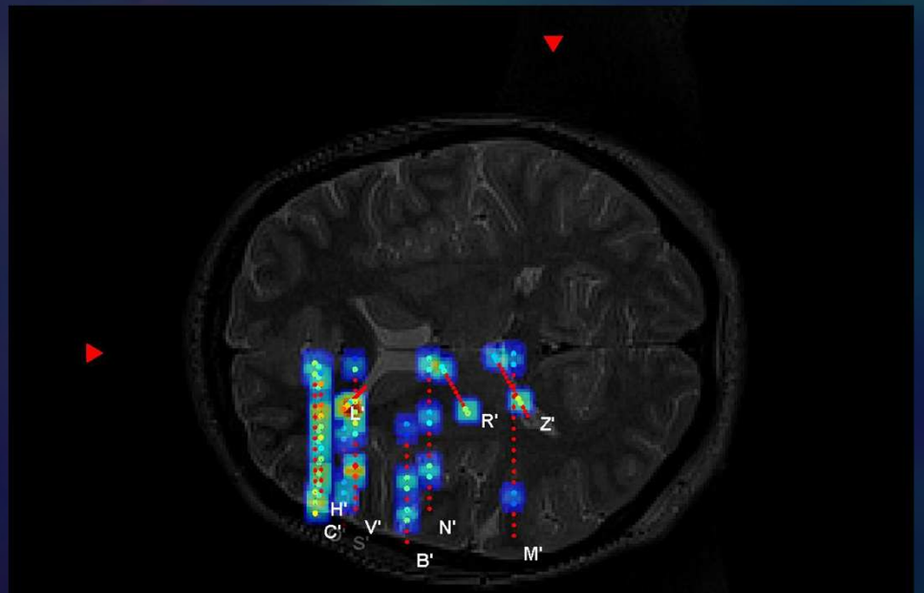
F, 40y, Focal Dysplasia Frontal Lobe

Lesion

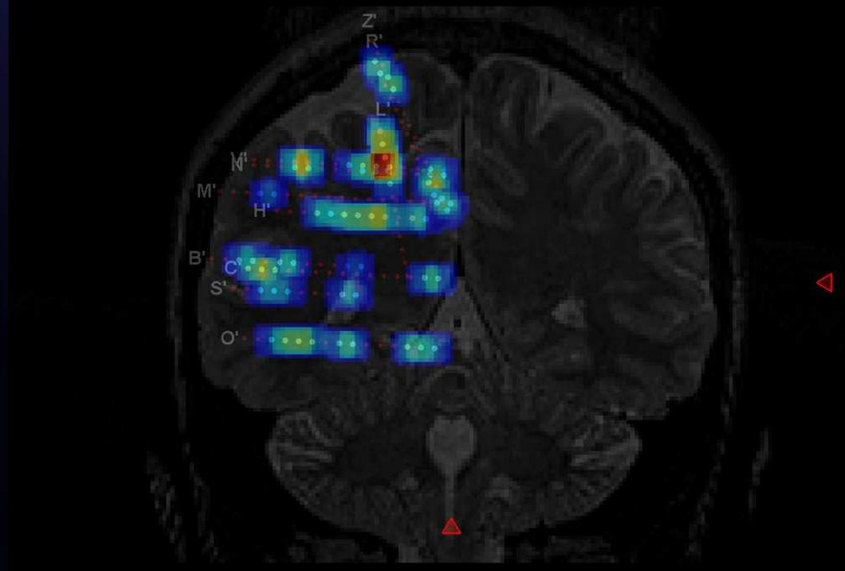


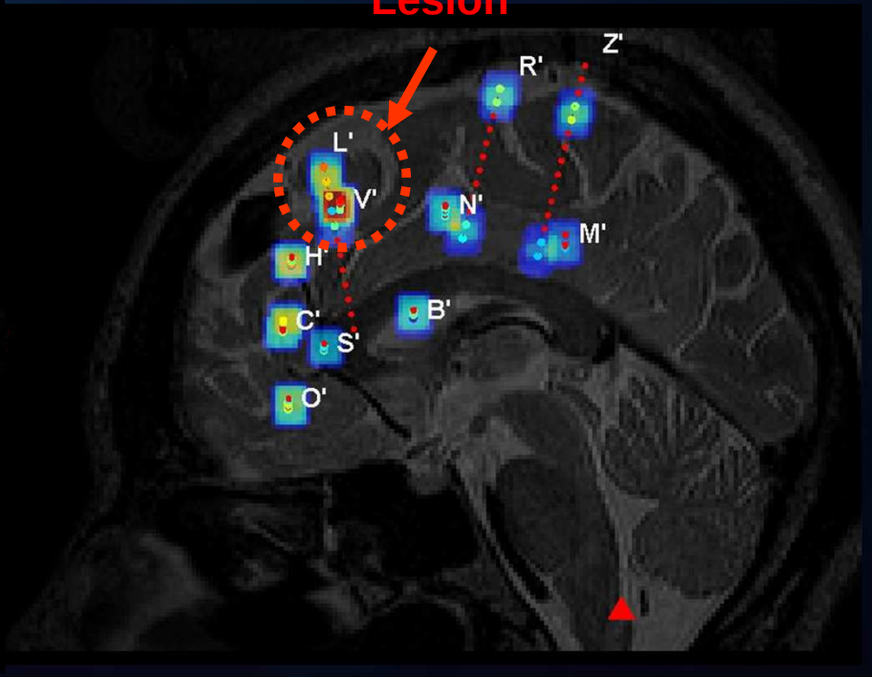
Delayed Responses Map

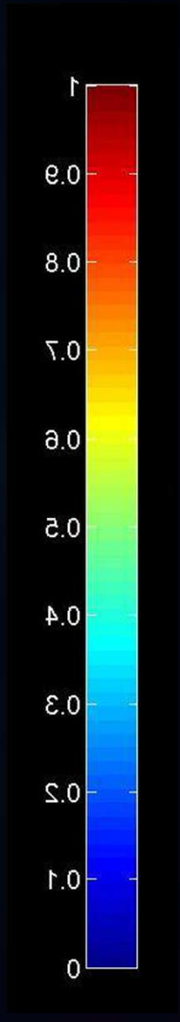
Pat 12 (BM): F, 40y, Focal Dysplasia, Frontal - Premotor



Maximum Intensity Projection (MIP)

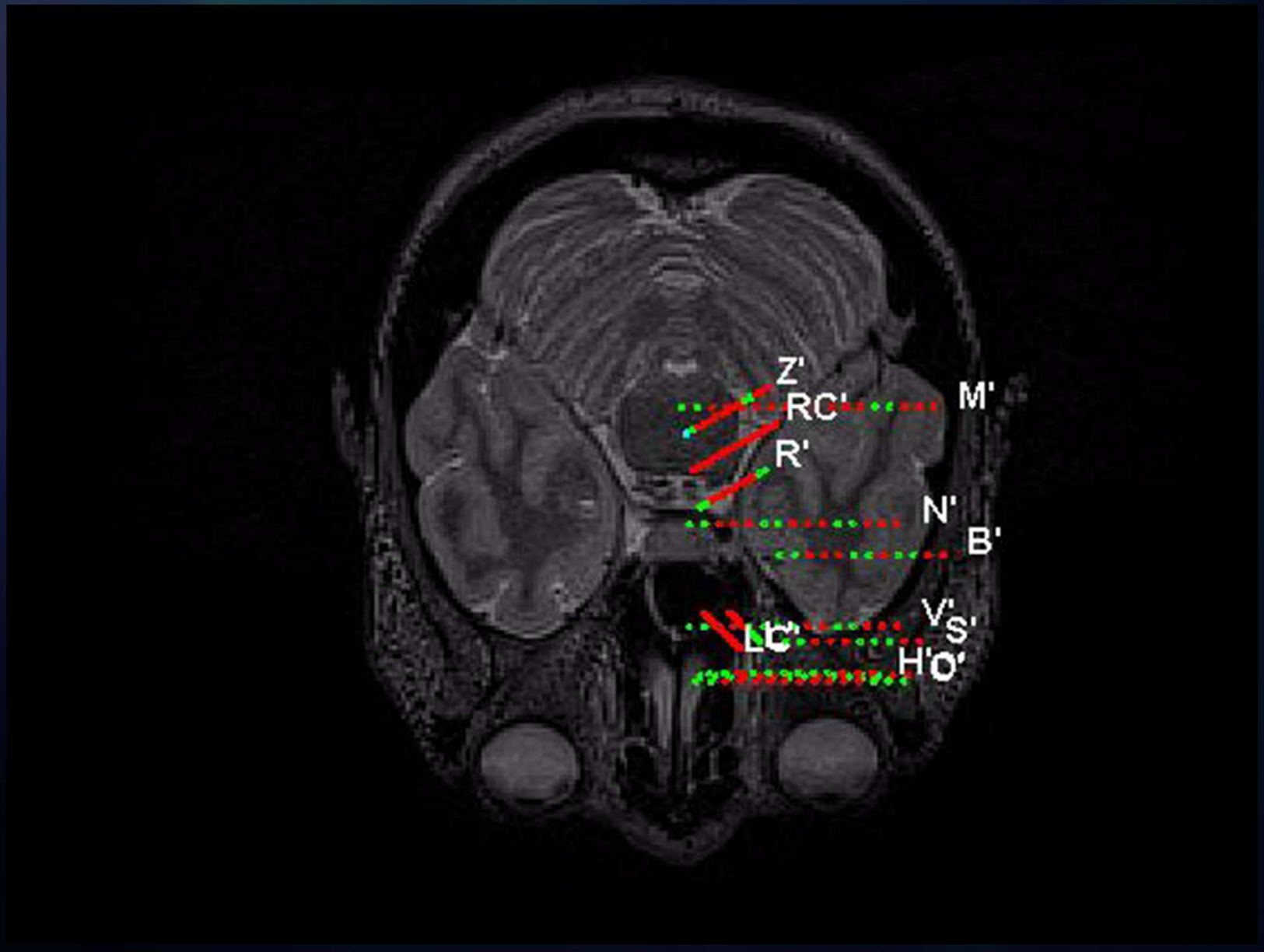






Results

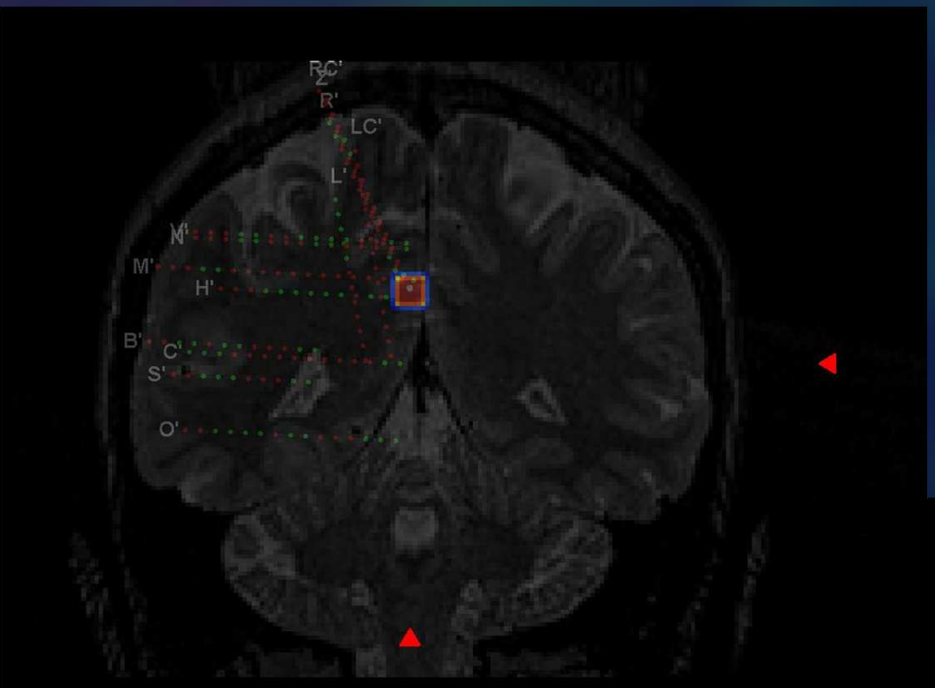
- SPES HFO Map

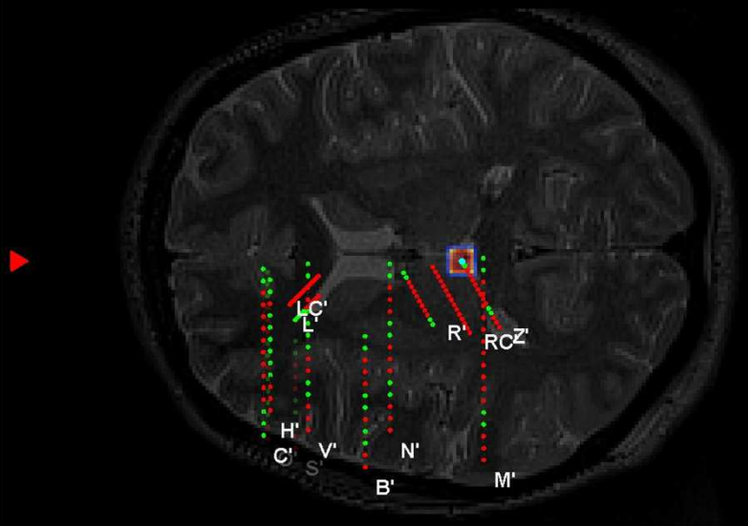


Patient 12

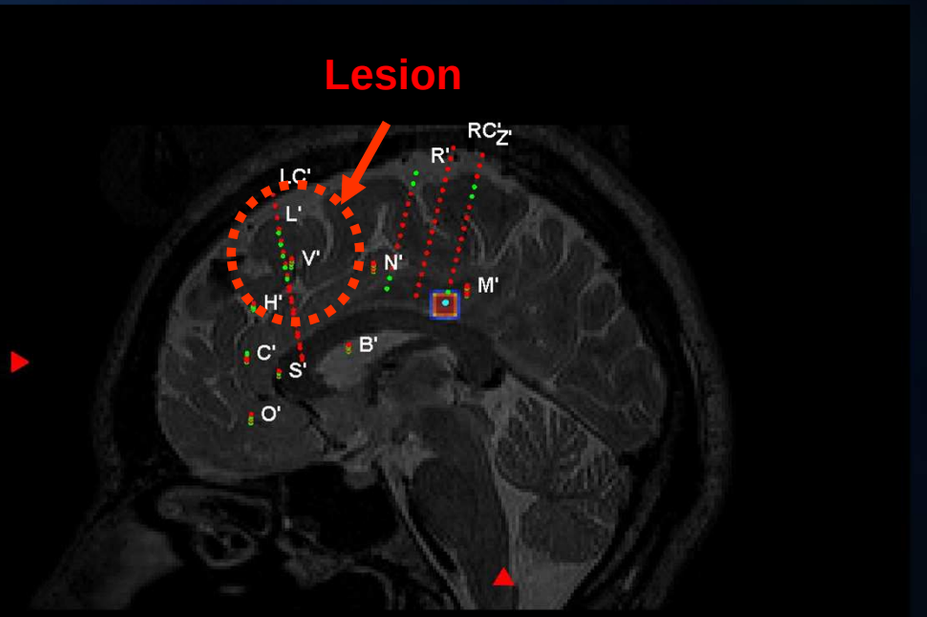
HFO Map

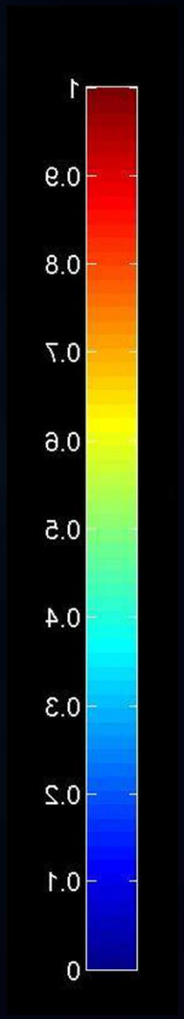
Pat 12 (BM): F, 40y, Focal Dysplasia, Frontal - Premotor





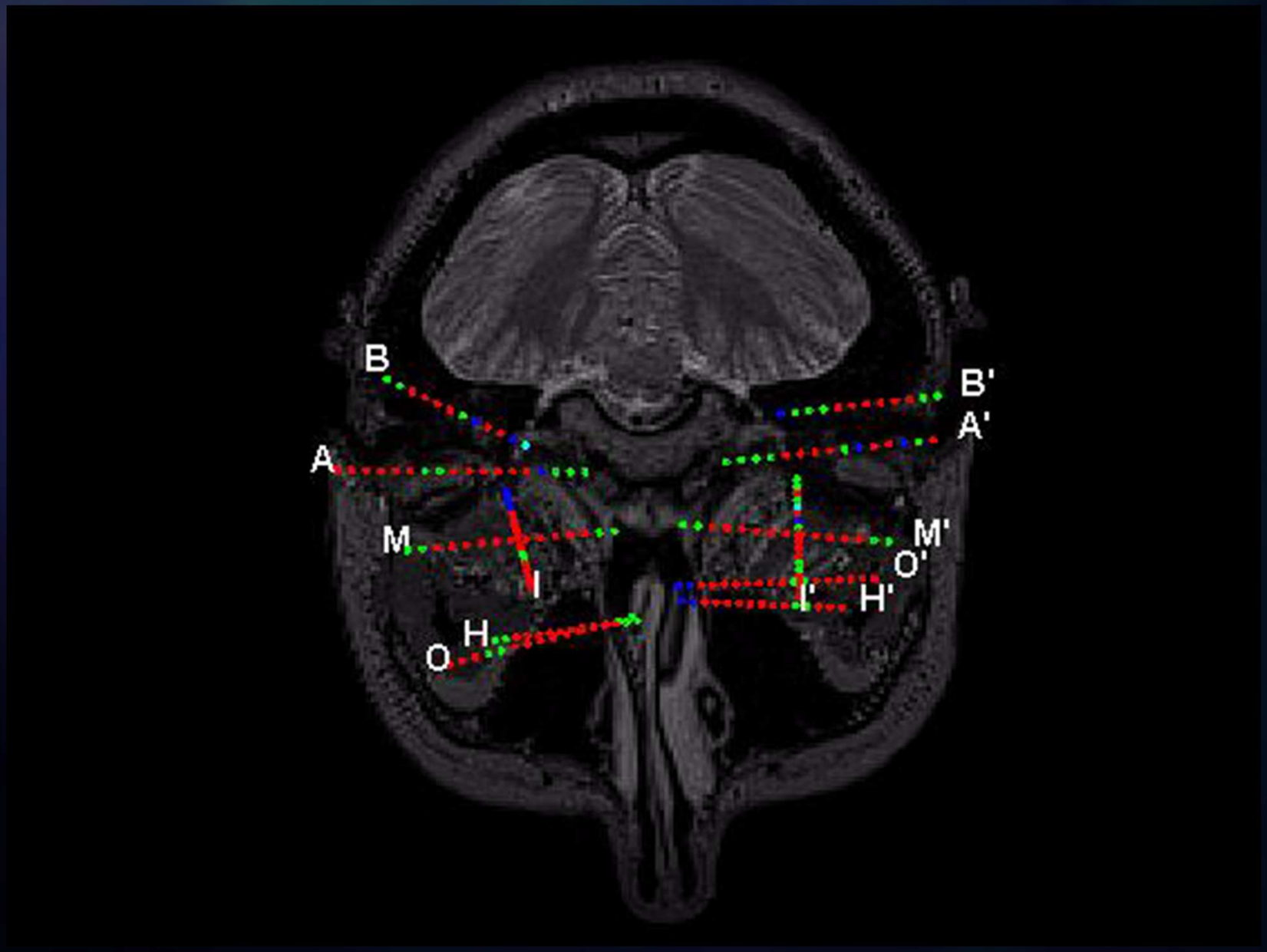
Maximum Intensity Projection (MIP)





Results

- SPES Delayed Response Map

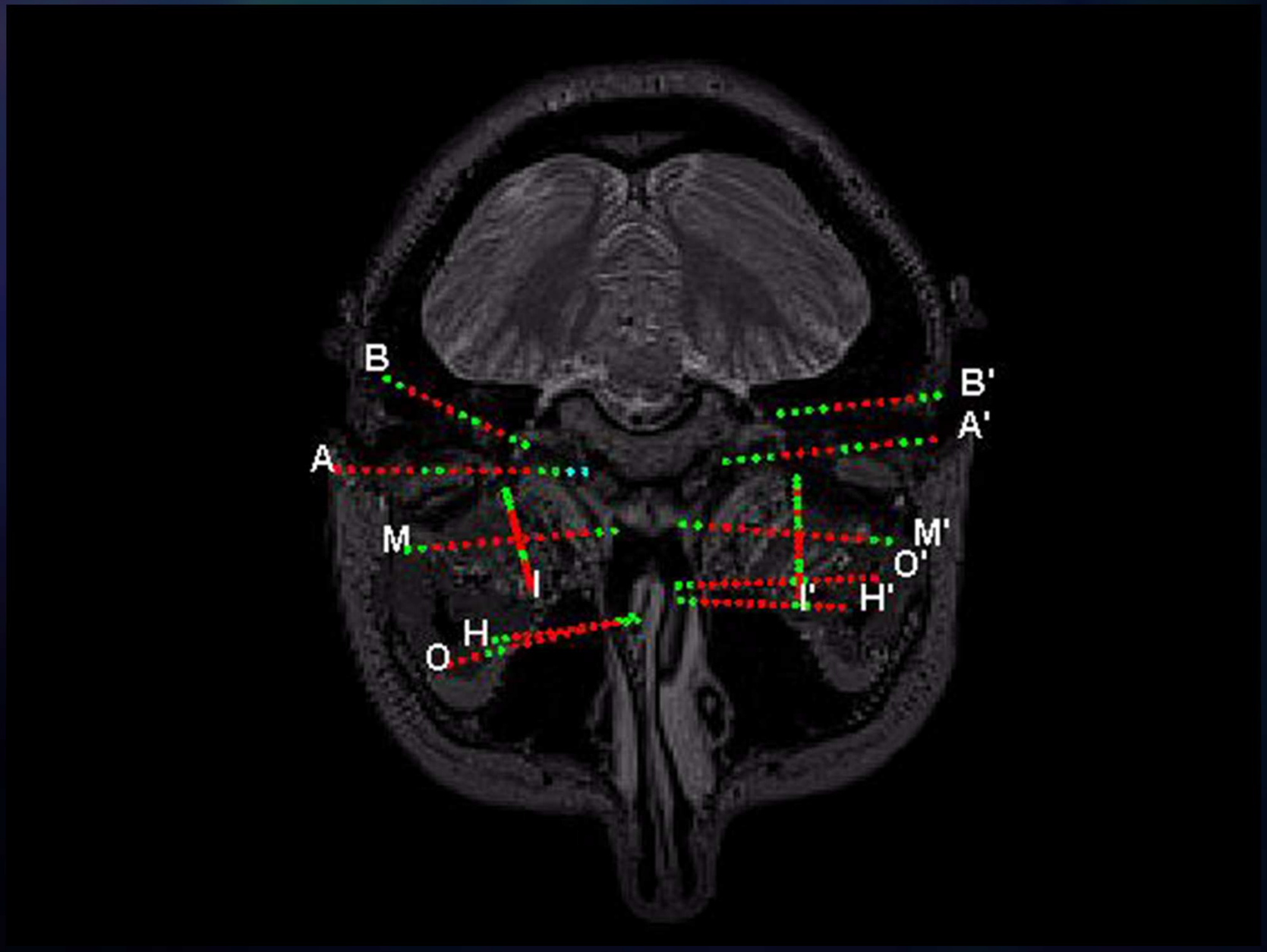


Patient 13

DD, 32y, MRI Negative

Results

- SPES HFO Map



Patient 13

Conclusions

- Intracranial Single Pulse Electrical Stimulation (SPES) helps in highlighting brain connectivity and identifying the epileptogenic network, while reducing the reliance on spontaneous activity
- Evaluation of delayed response curves as well as oscillations in various frequency bands provide valuable complementary information to recording spontaneous activity.
- Exact 3D activation maps provide connectivity information, helping in delineating the epileptogenic zone, for tailored resections for each patient.

Thank You !

Funding:

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