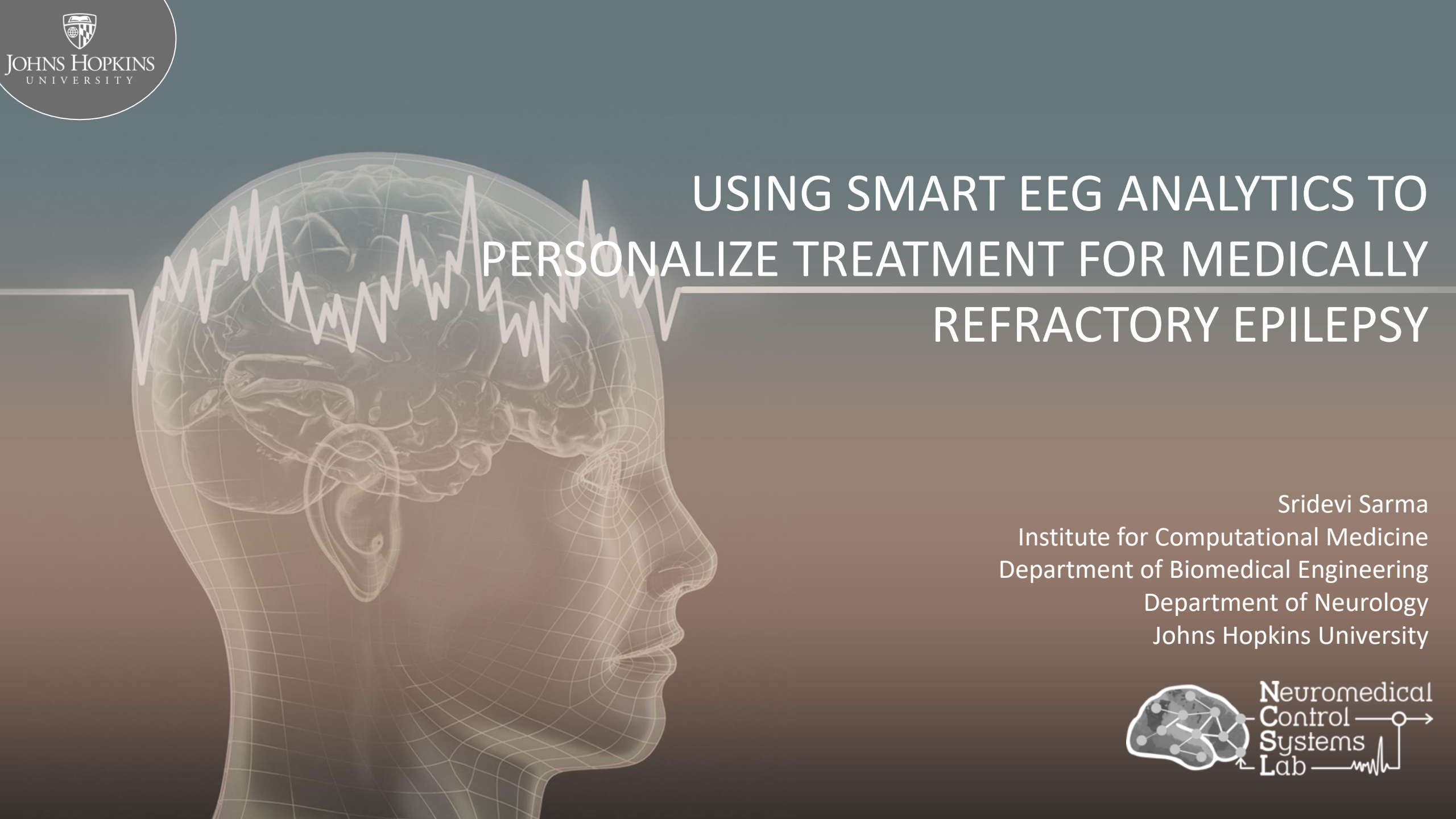

USING SMART EEG ANALYTICS TO PERSONALIZE TREATMENT FOR MEDICALLY REFRACTORY EPILEPSY

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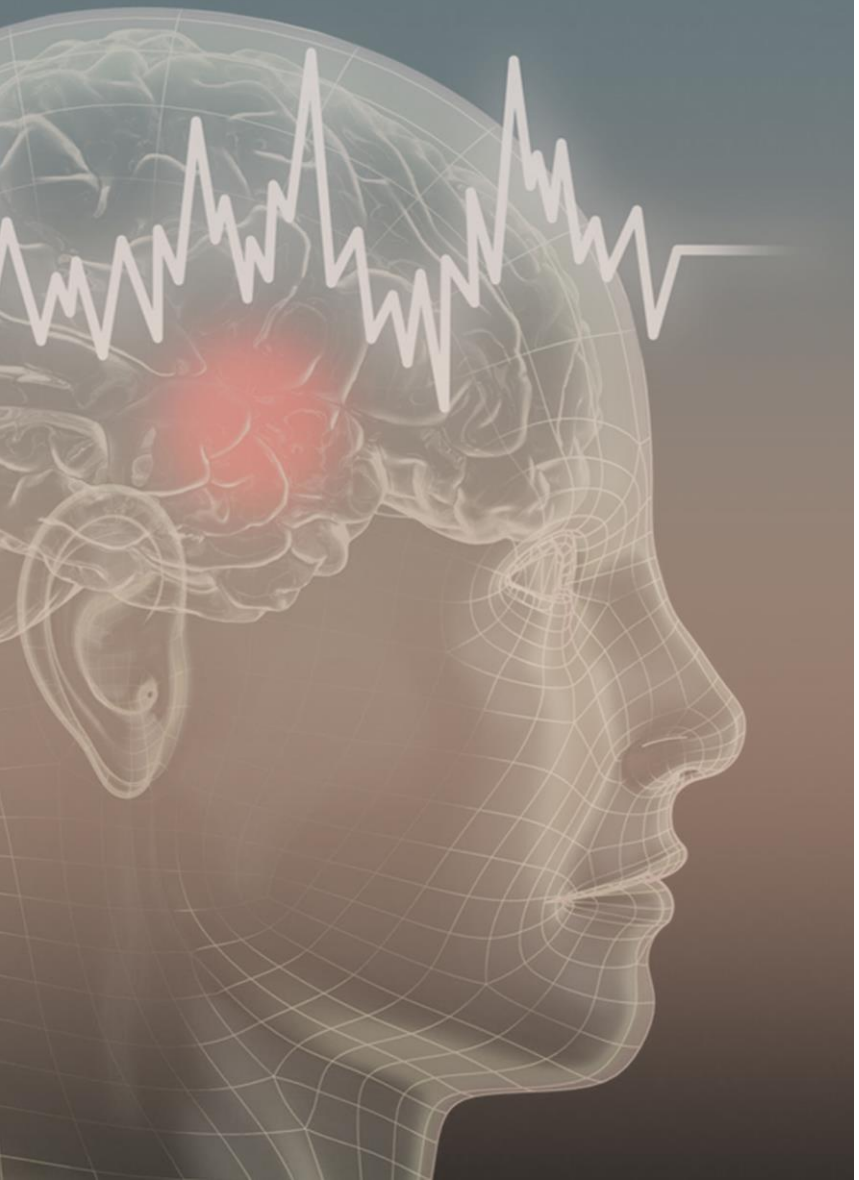
Institute for Computational Medicine
Department of Biomedical Engineering
Department of Neurology
Johns Hopkins University

Neuromedical Control Systems Lab

Disclosure: President and Cofounder of Neurologic Solutions

CLINICAL PROBLEM

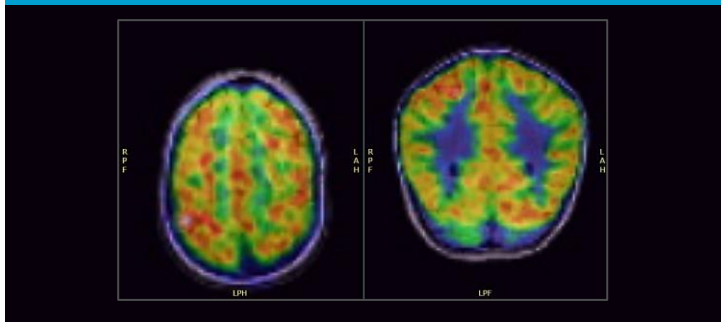


- 60M people suffer from epilepsy
- Over 30% of patients are medically refractory
- Seizures start in the Epileptogenic Zone (EZ), and when focal can be treated with surgery or electrical stimulation
- Both treatments require accurate identification of the EZ
- Surgical success rates average 50%, even after large brain regions are removed

LOCATING EZ NON-INVASIVELY

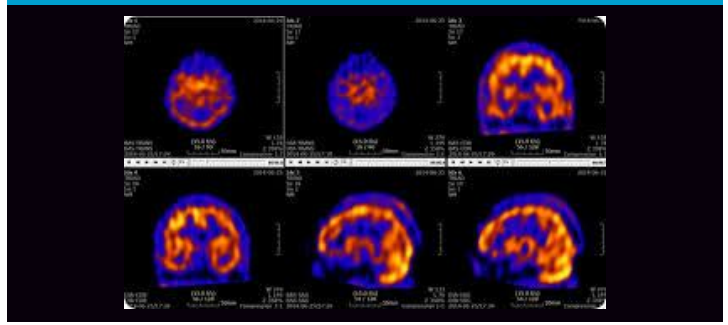
IS TOO COARSE, CAN ONLY PINPONT EZ HEMISPHERE

PET SCAN

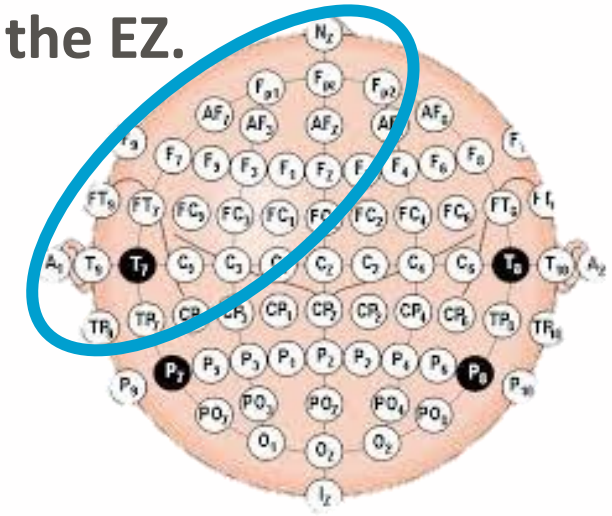


MRI

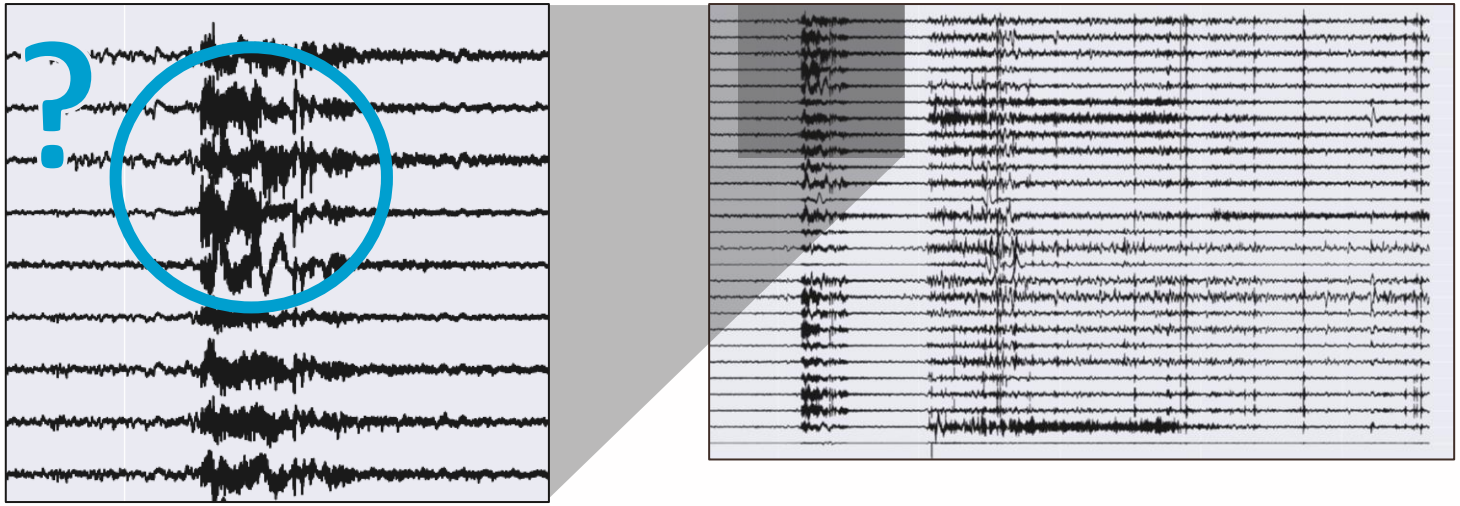
SPECT



Scalp EEG data is too noisy to precisely locate the EZ.



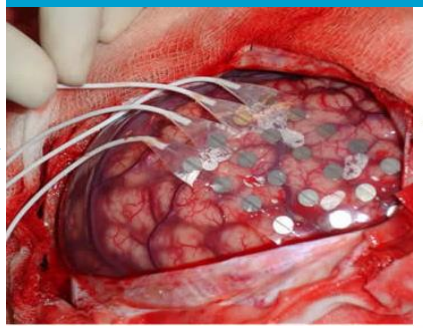
SCALP EEG

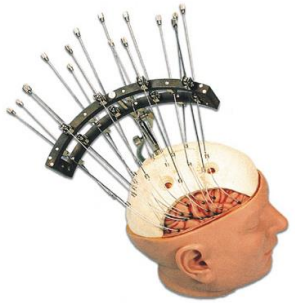


LOCATING EZ INVASIVELY
IS OFTEN REQUIRED BUT PRONE TO HUMAN ERROR

CRANIOTOMY

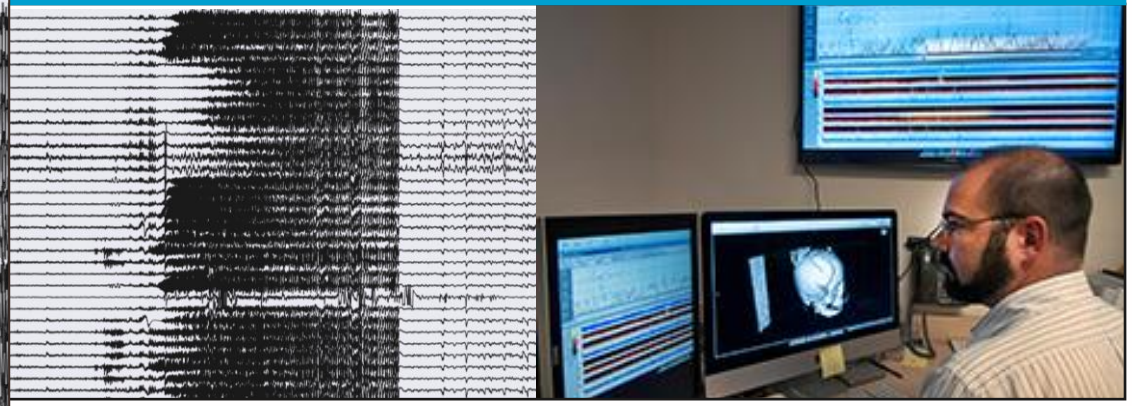
ELECTRODE IMPLANTATION



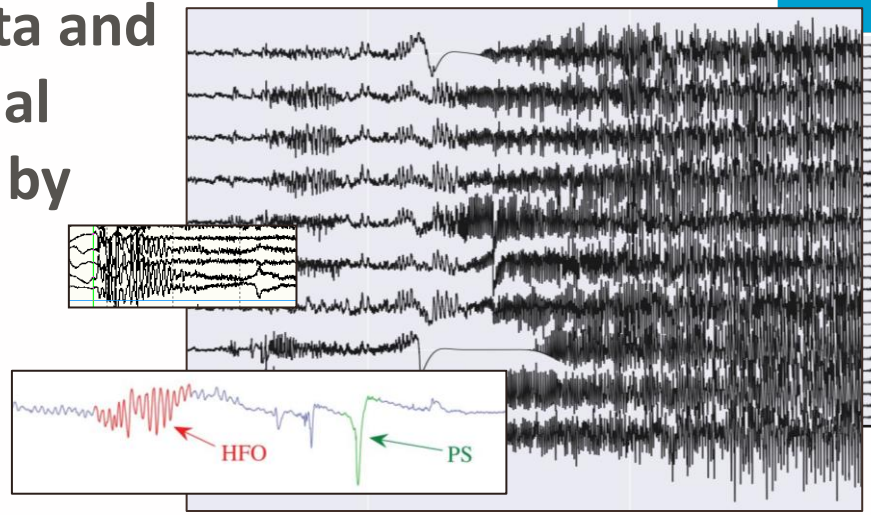


MONITORING
(DAYS/WEEKS)

CLINICAL TEAM ATTEMPTS TO LOCALIZE VISUALLY



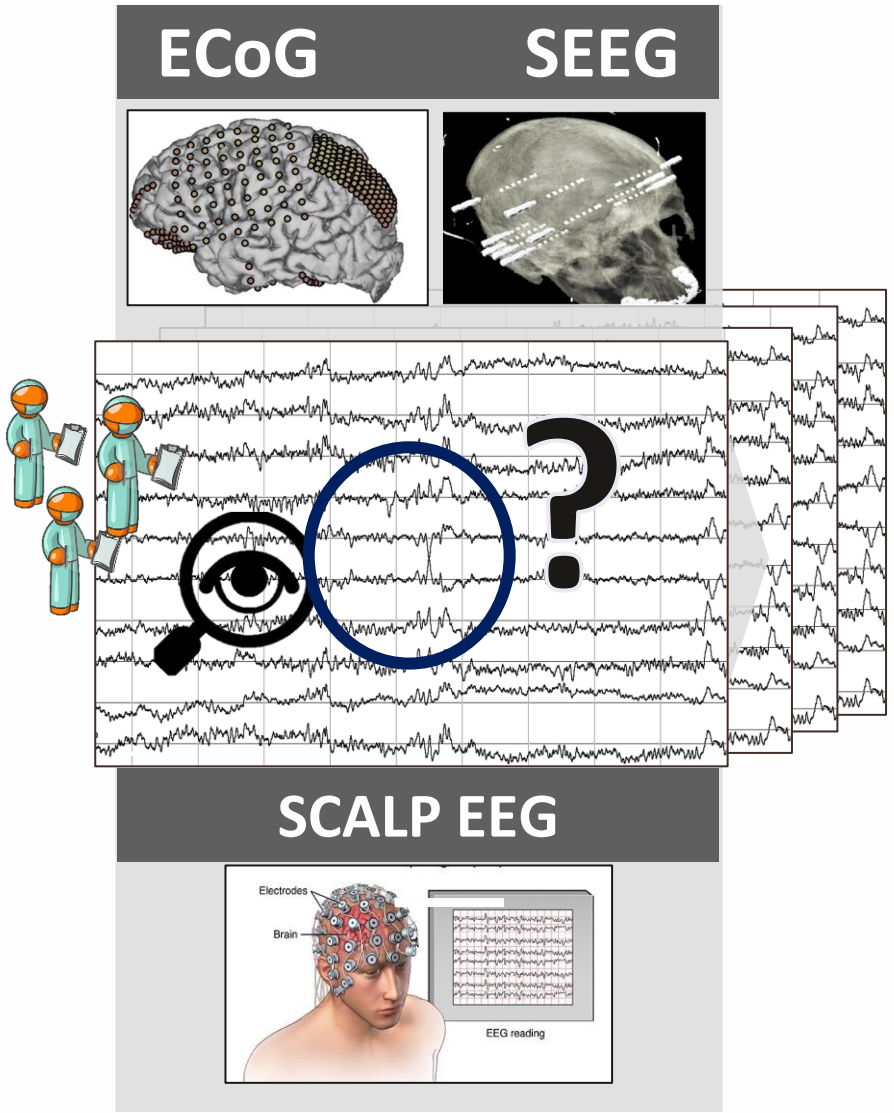
Clinicians visually inspect hours of EEG data and look for abnormal activity channel by channel.



CHALLENGES WITH CURRENT PRACTICE

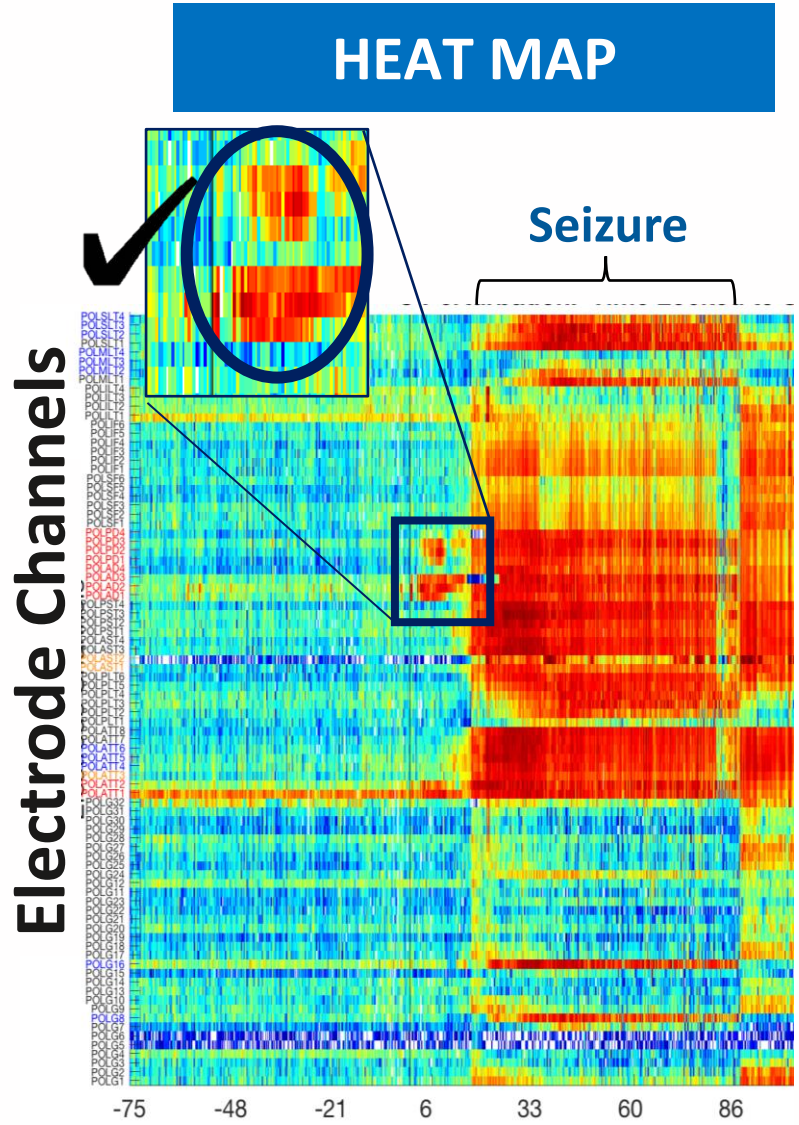
HIGH DEGREE OF PROCESS VARIABILITY	Electrodes must be implanted in the right place
PROLONGED HOSPITAL STAY	Requires days to weeks to observe many seizures
SUBJECTIVE DECISION CRITERIA	No data analytics to interpret signals
OUTCOMES HIGHLY VARIABLE	only 30-70% success
HIGH RISK, HIGH COST	Larger brain area removed to compensate for localization uncertainty; infection risk; $200,000 per treatment

OUR SOLUTION



Network modeling & Systems theory

EZTRACK

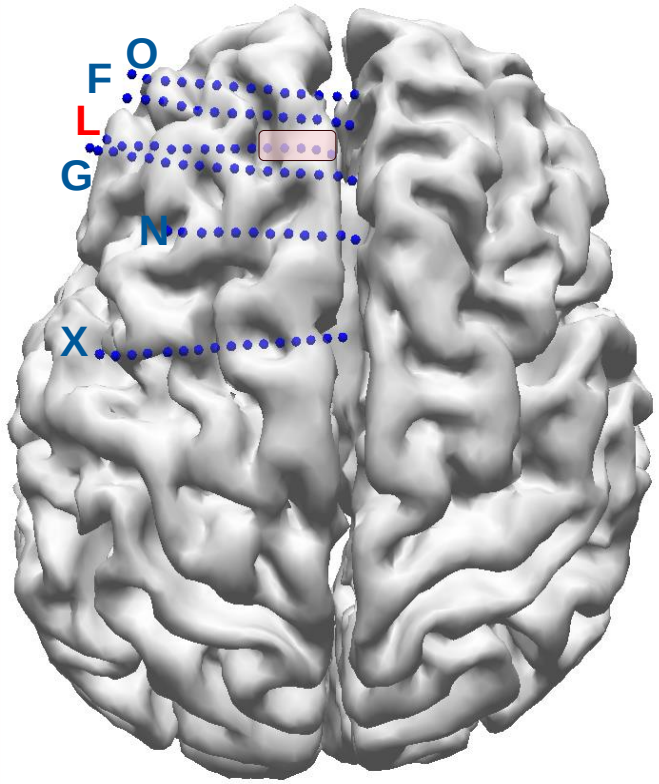


100s of mins, multiple

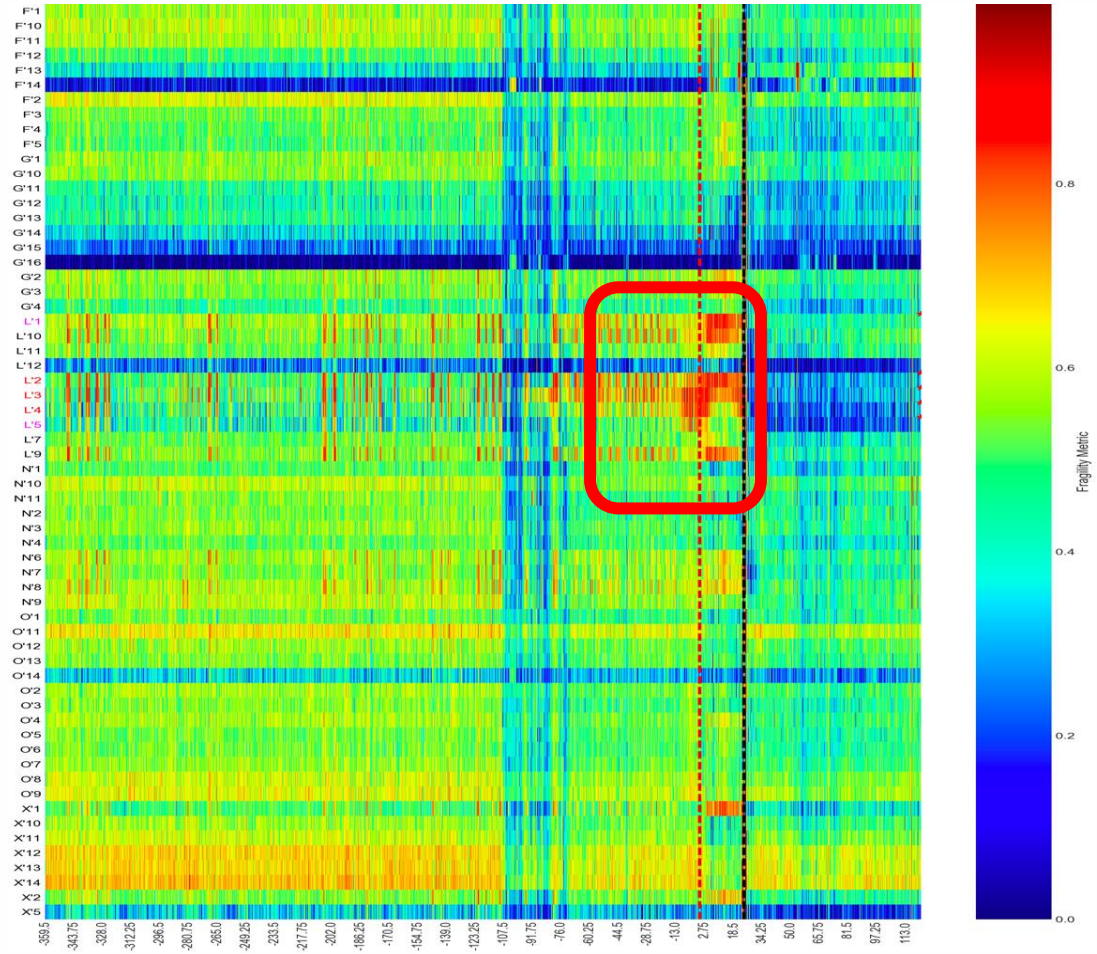
To under 30 secs

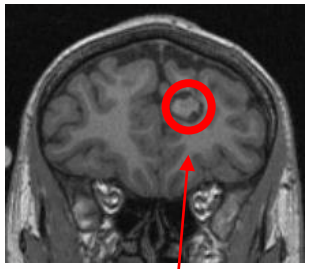
FRAGILITY MAP AGREES WITH CLINICIAN

SUCCESSFUL OUTCOME



O': OrbitoFrontal
G': Anterior Cingulate
X': Mid Cingulate
F': Fronto polar
L': Lesion?
N': Sup Frontal gyrus

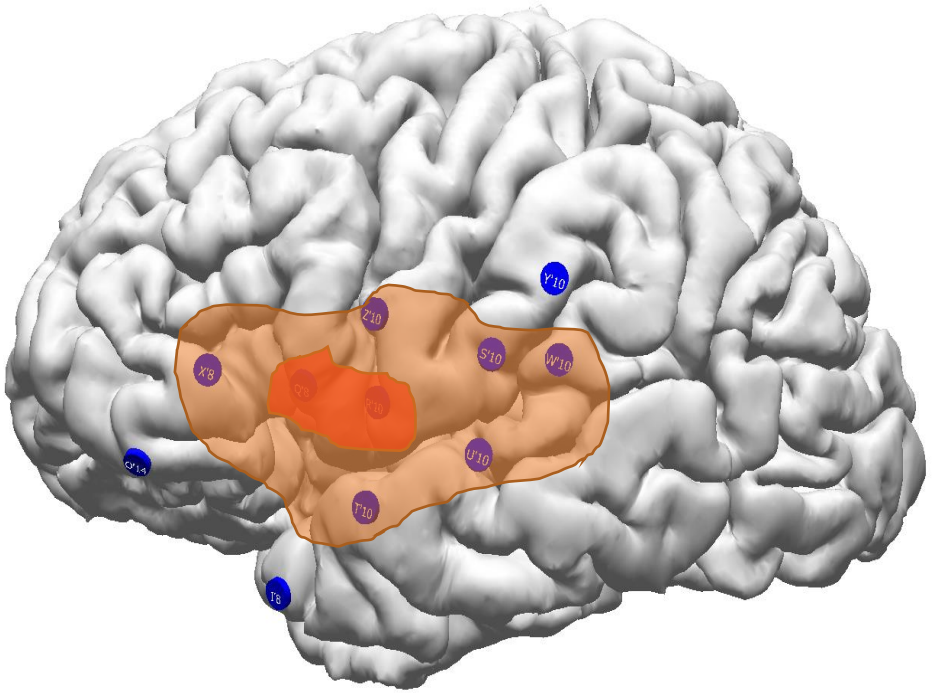


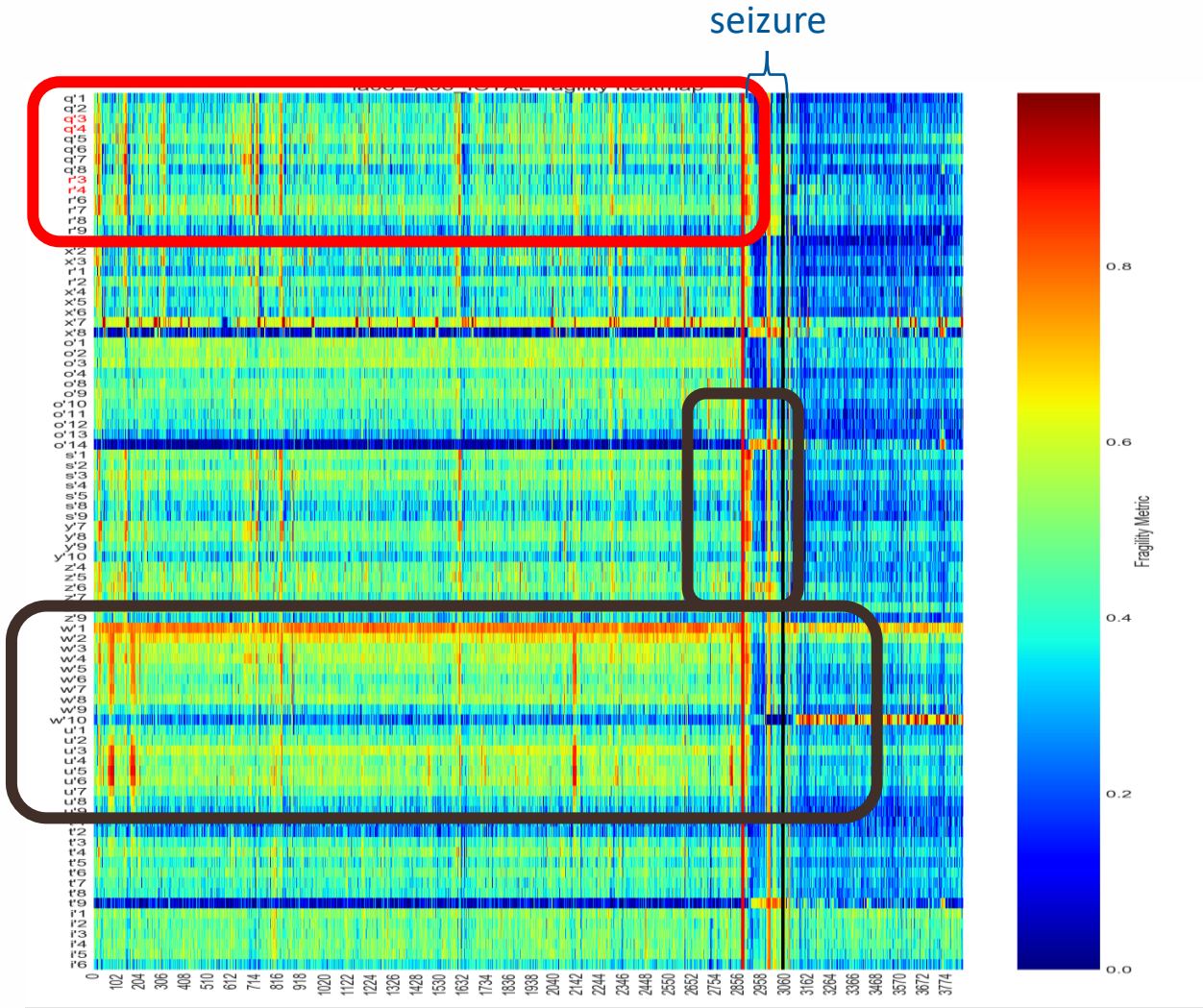


Targeted laser ablation

FRAGILITY MAP DISAGREES WITH CLINICIAN

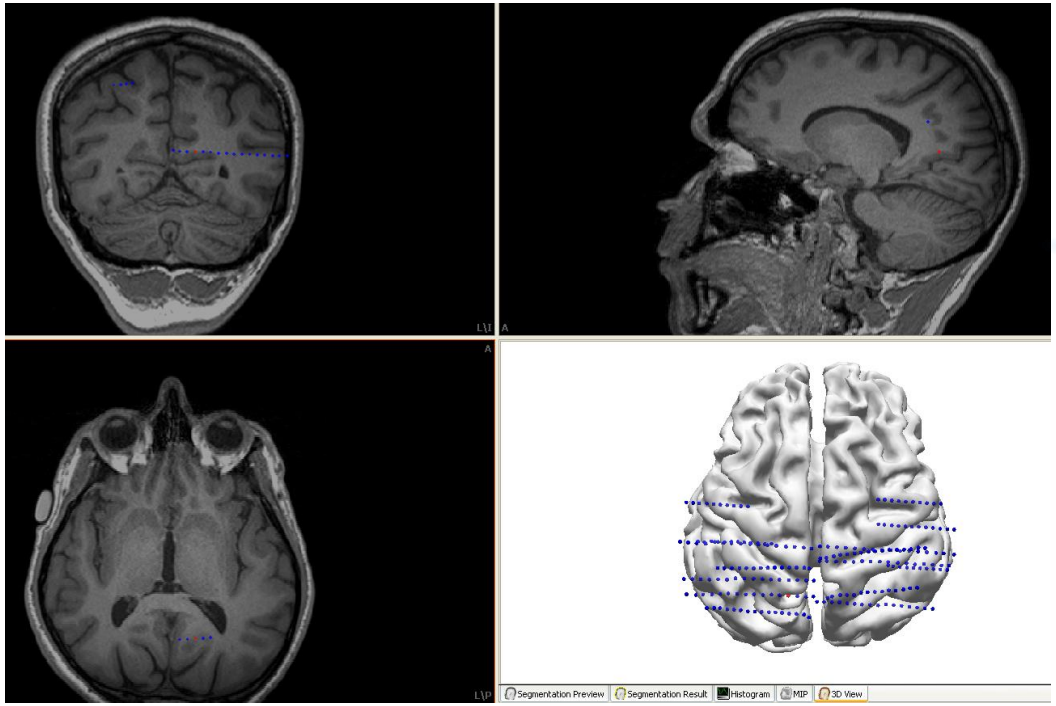
FAILED OUTCOME

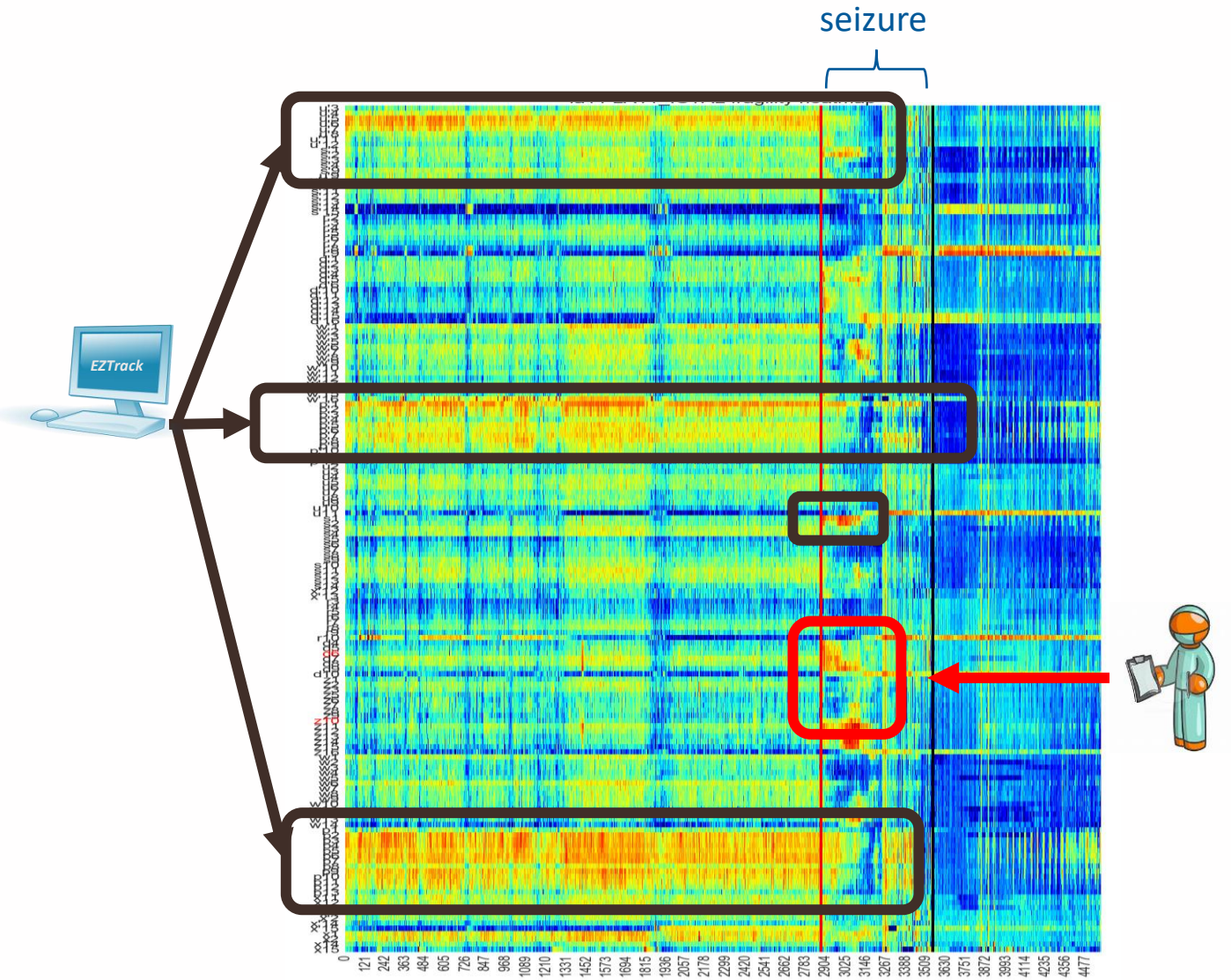




FRAGILITY MAP DISAGREES WITH CLINICIAN

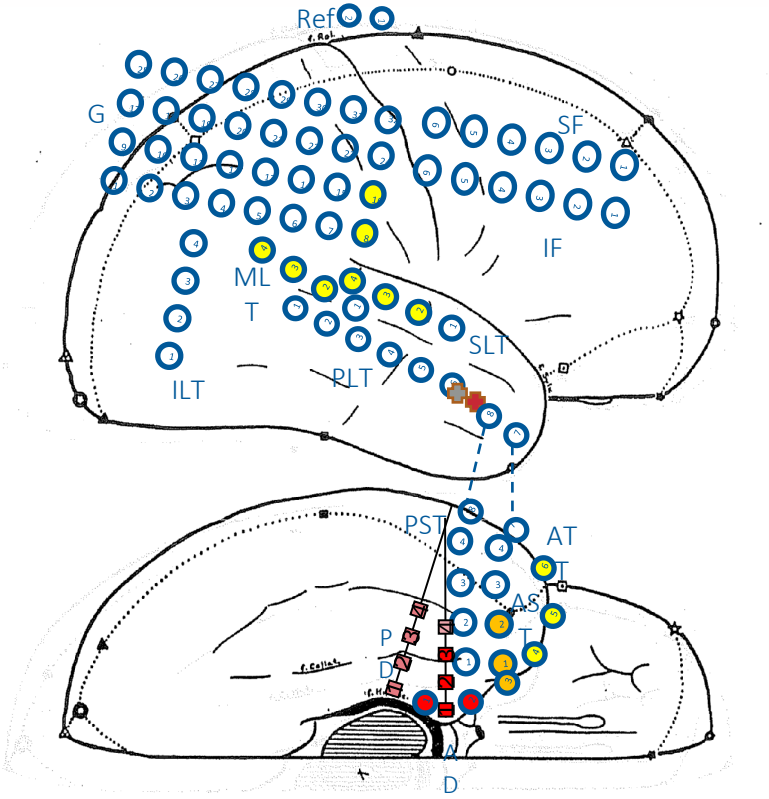
FAILED OUTCOME

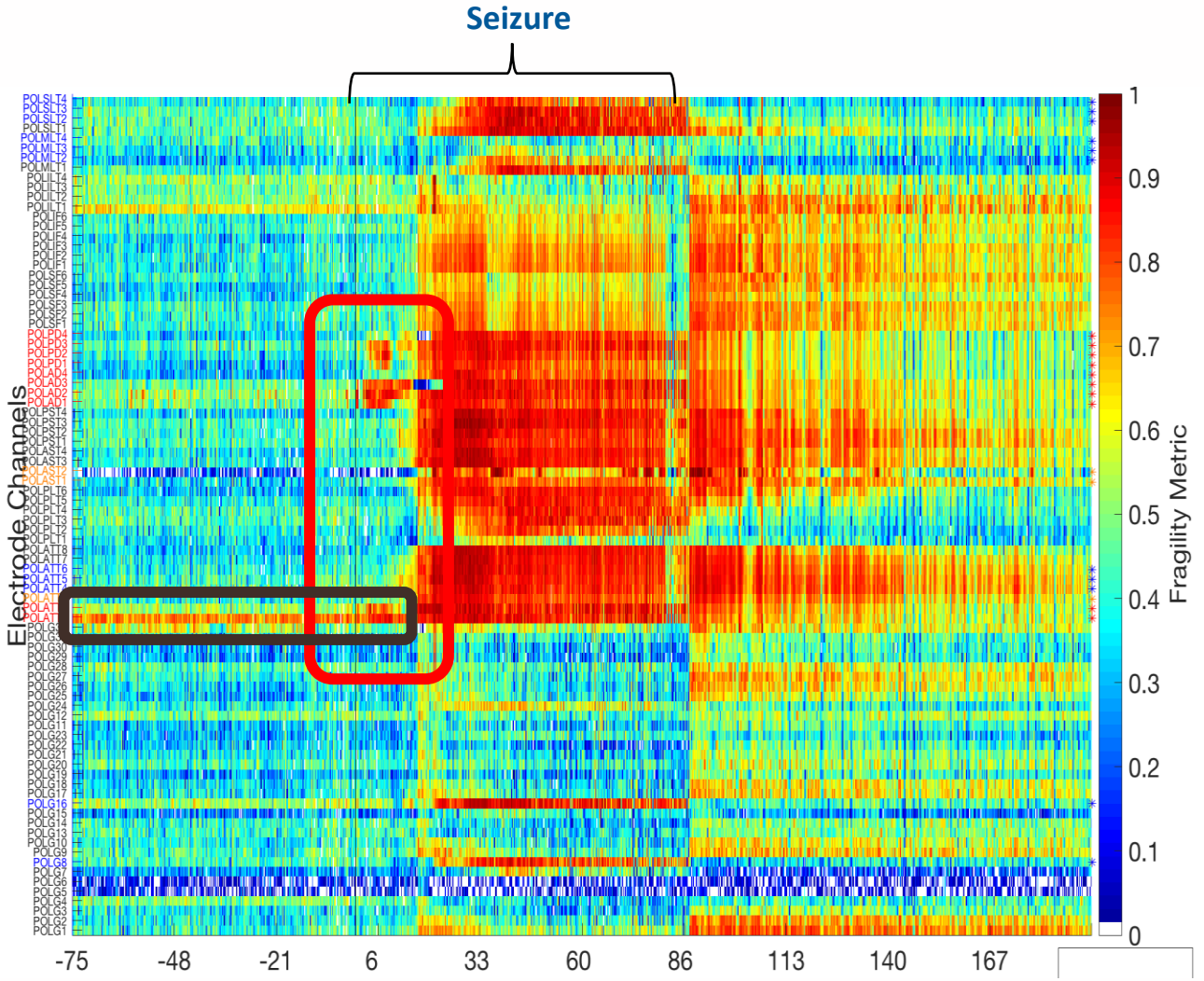




FRAGILITY MAP AGREES WITH CLINICIAN

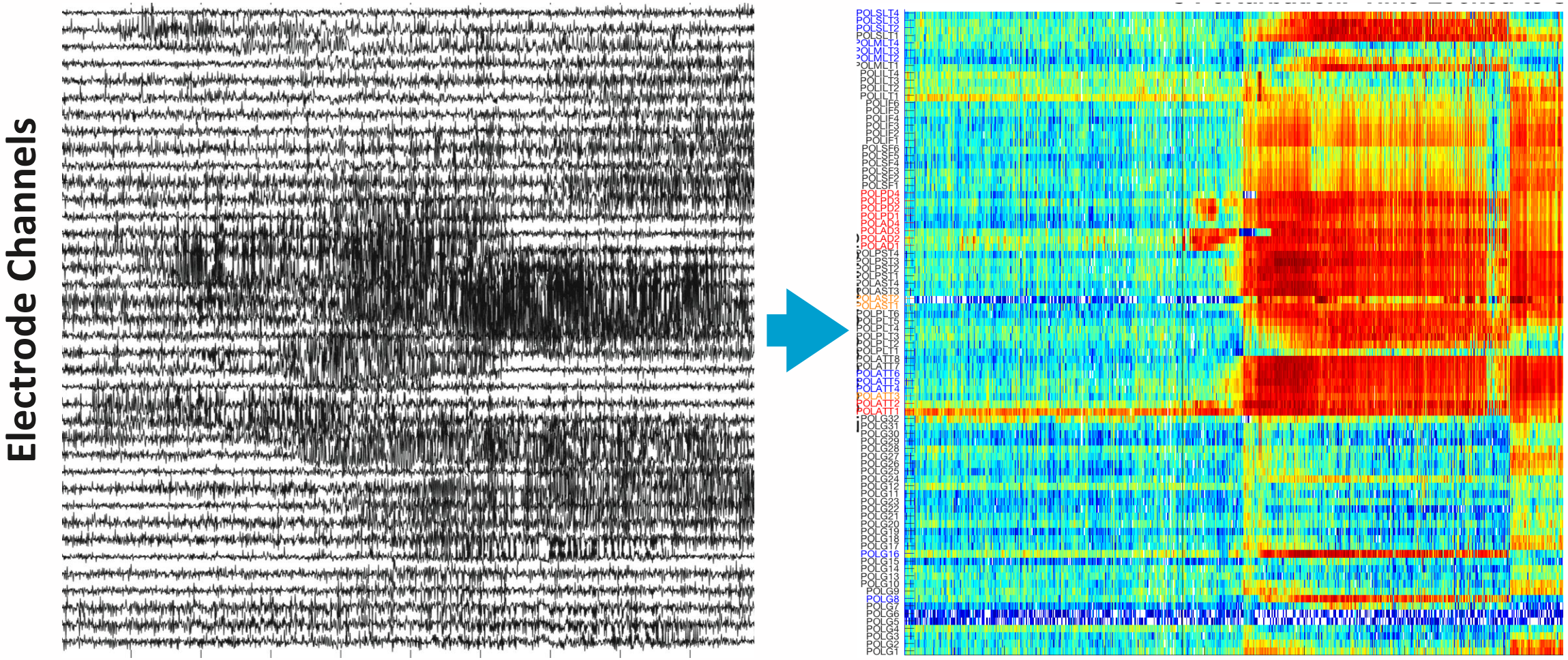
SUCCESSFUL OUTCOME



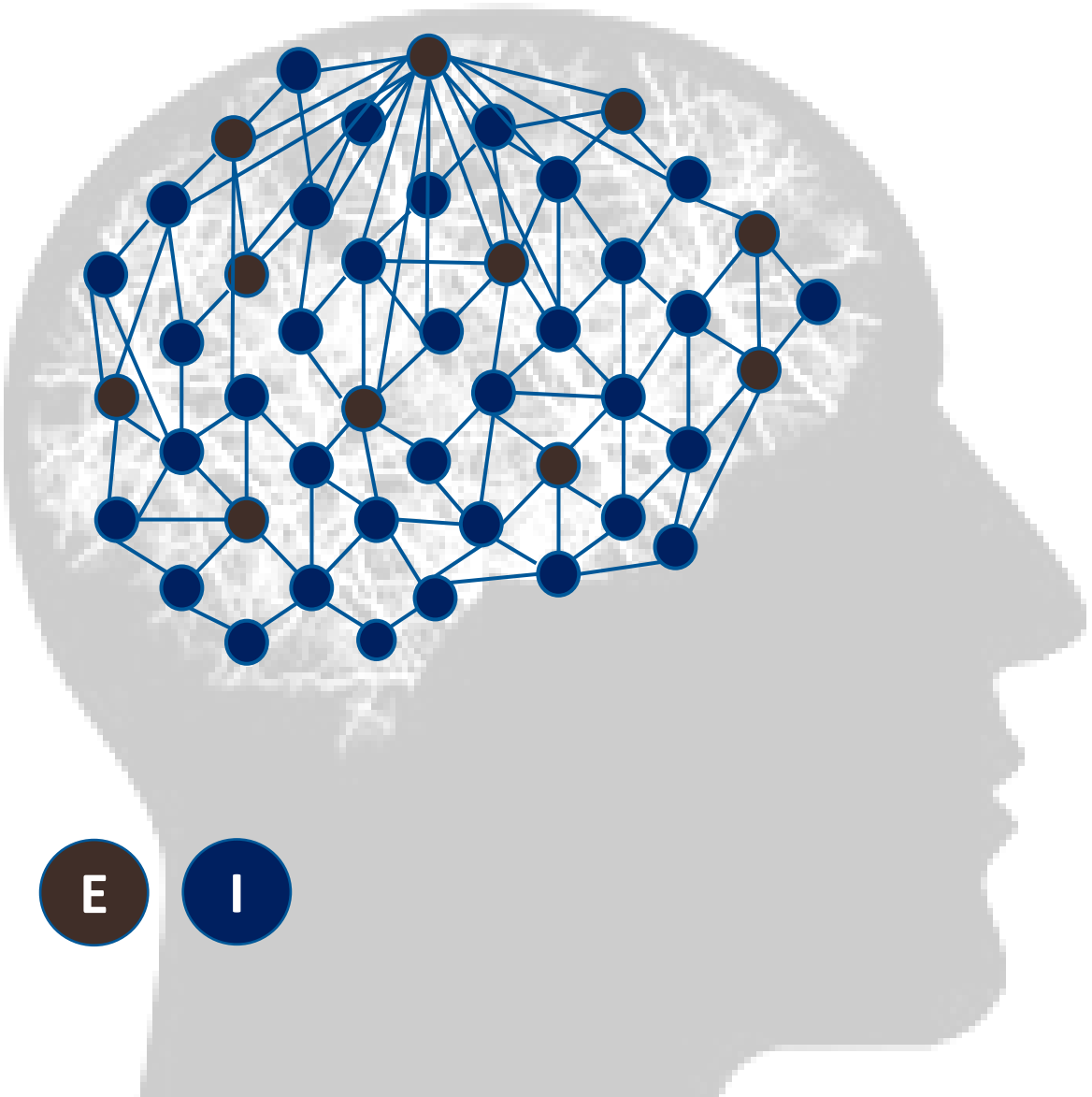


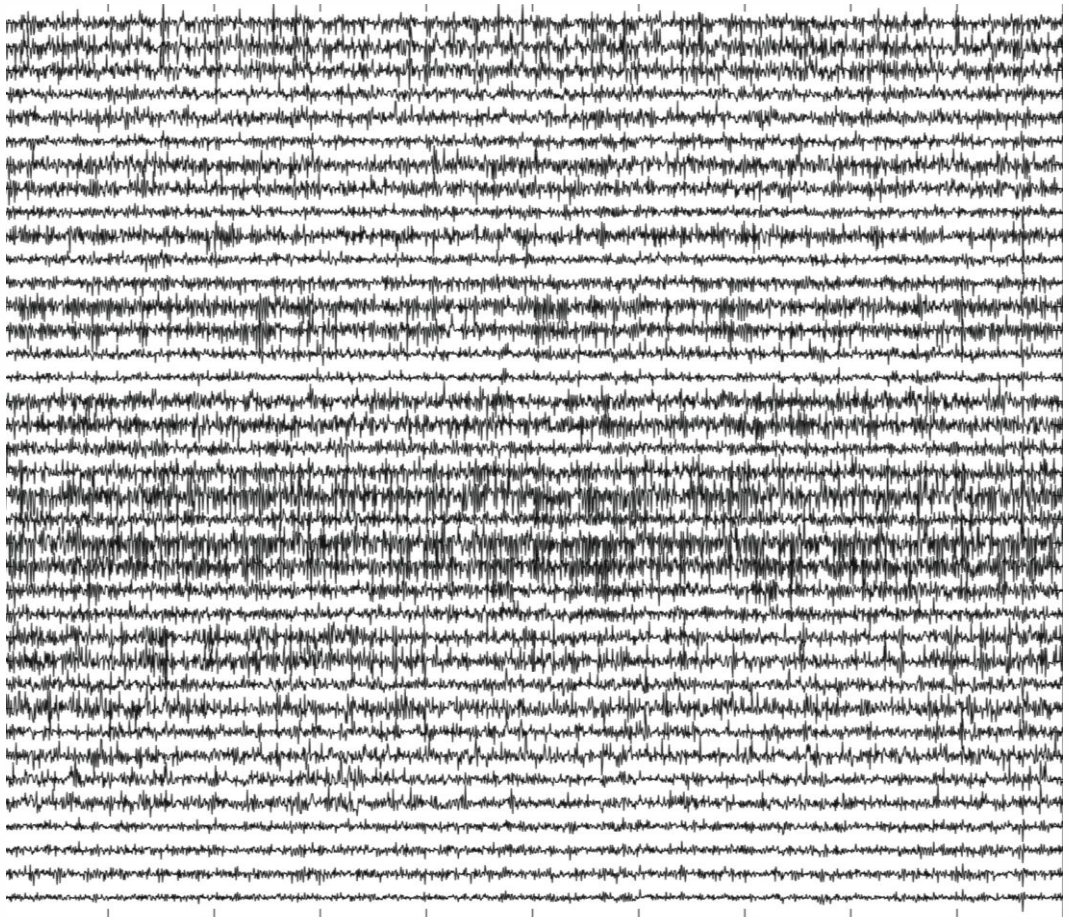
- onset
- early spread
- late spread

HOW DOW WE COMPUTE A HEAT MAP FROM EEG?

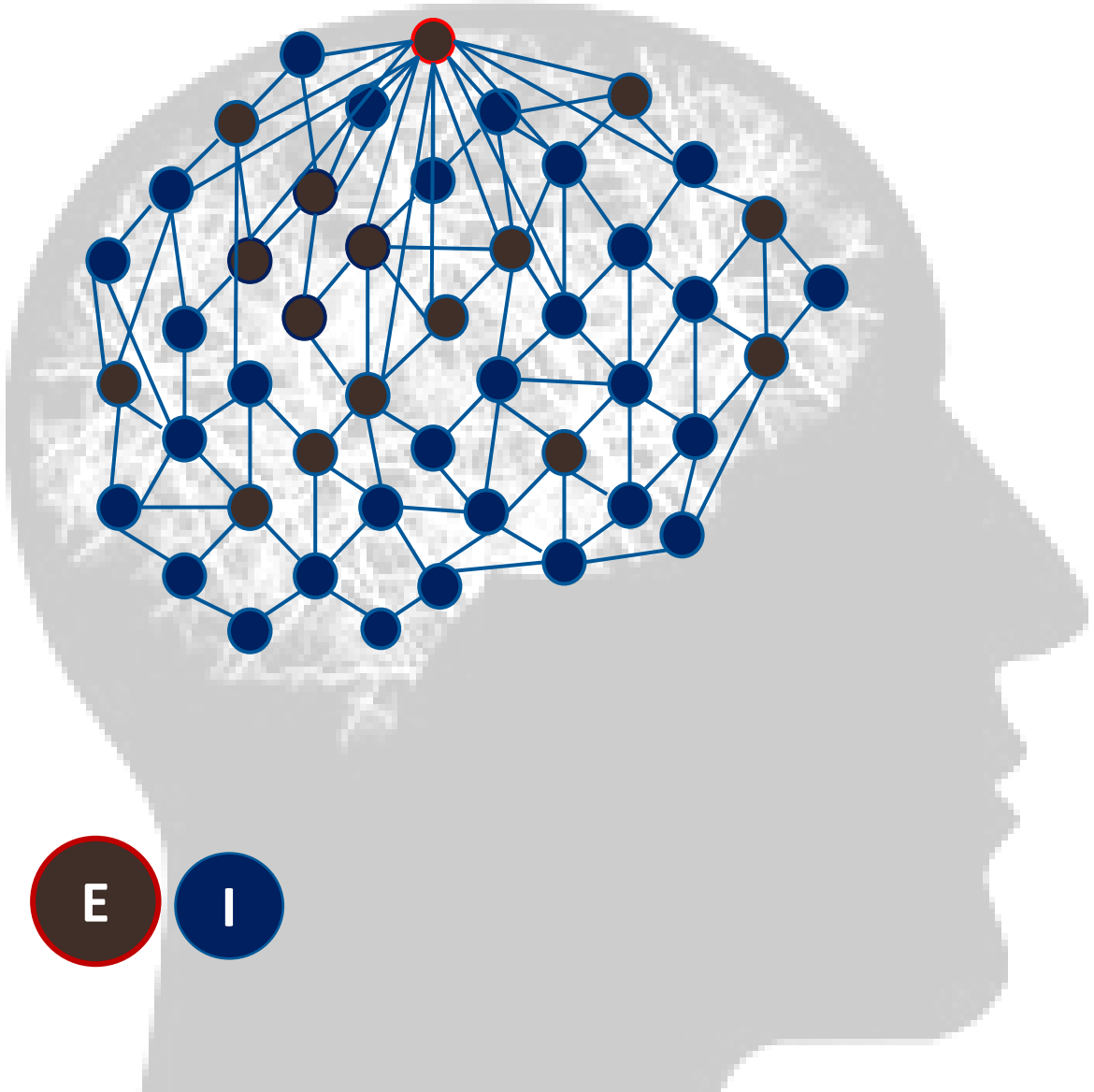


EEG NETWORK IS “BALANCED” IN HEALTH

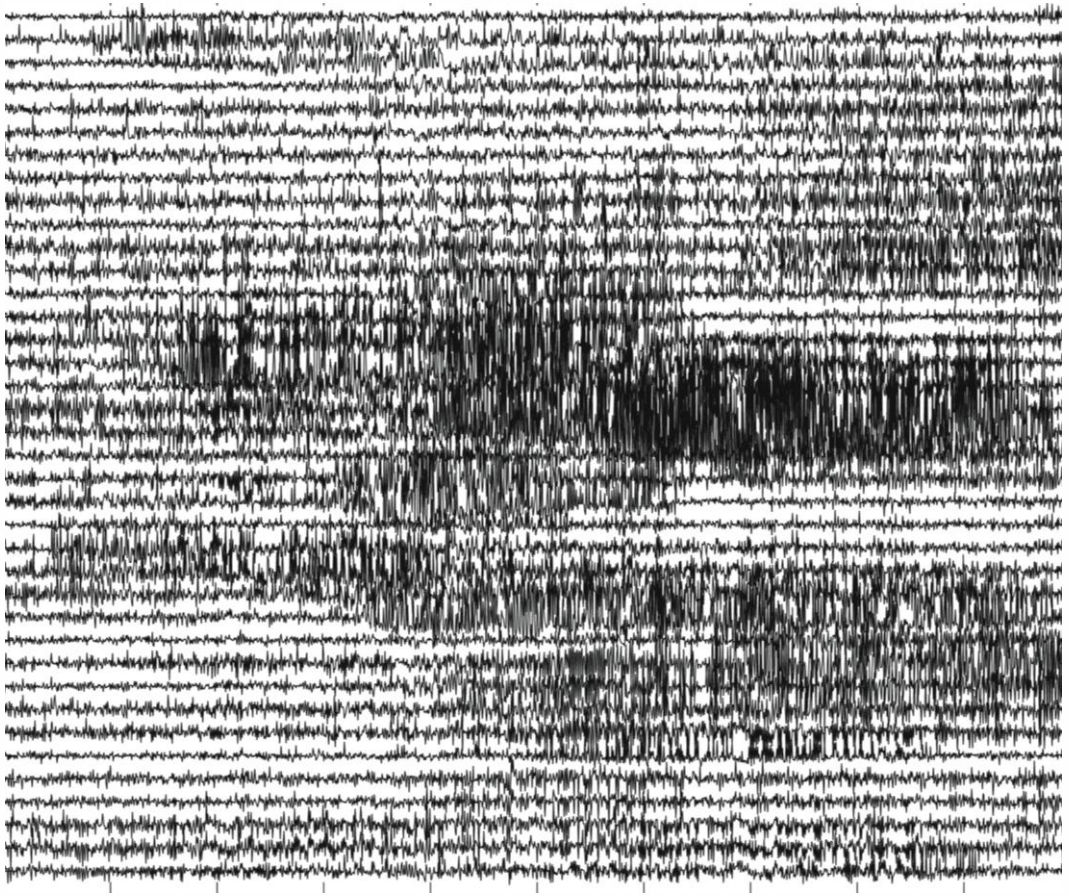




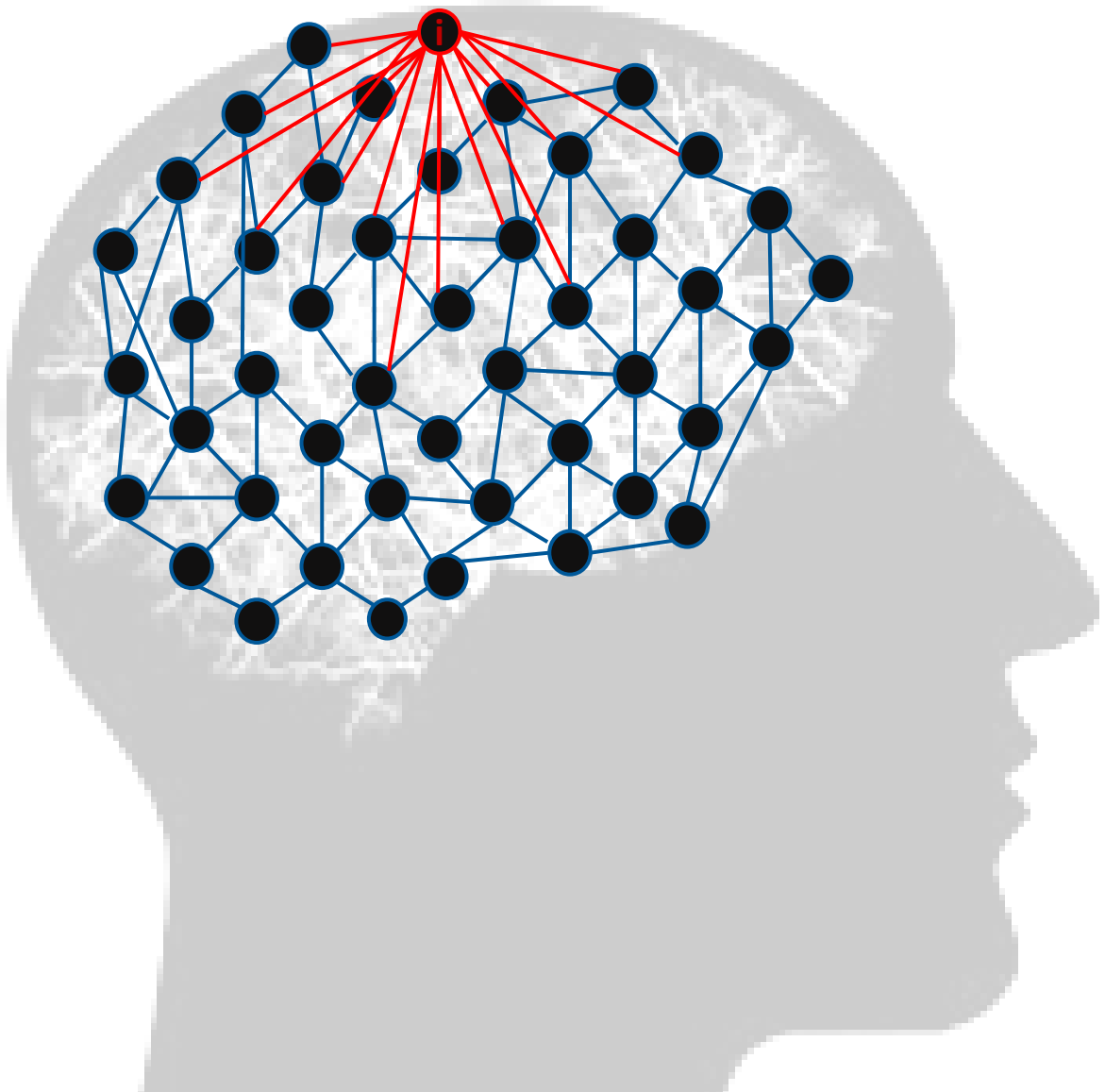
EEG NETWORK IS “IMBALANCED” IN EPILEPSY



Connections at one or more nodes change due to cell death, cell proliferation, inflammation, etc.



FRAGILE NODES CAUSE THIS IMBALANCE

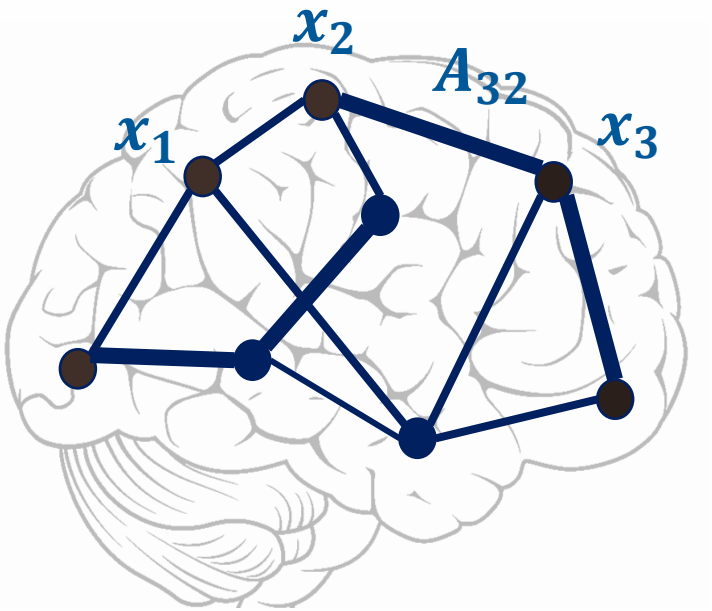


- **Fragility of node i is equal to the smallest amount of change in connections to its neighbors to cause network imbalance**

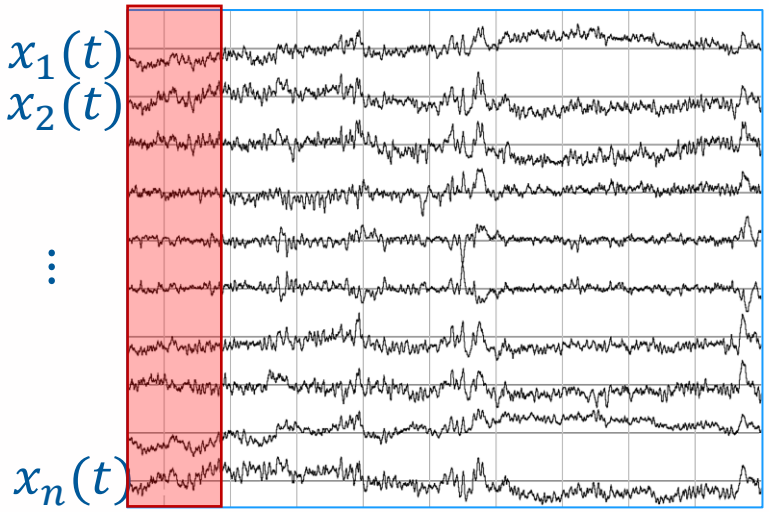
- **We will compute fragility of each node from EEG recordings via an EEG network model**

EEG NETWORK MODEL

EEG Electrode Implantation → **Intracranial EEG Recordings** → **Dynamical Systems Model**



$$x_2(t) \xrightarrow{A_{32}} x_3(t+1)$$

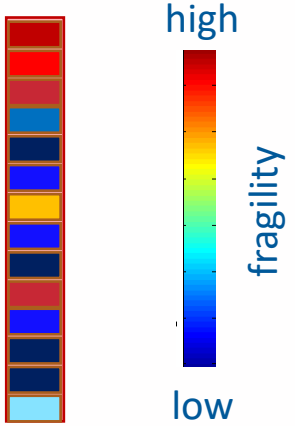


$$x(t) = \begin{bmatrix} x_1(t) \\ \vdots \\ x_n(t) \end{bmatrix}$$

(for each 500 msec window)

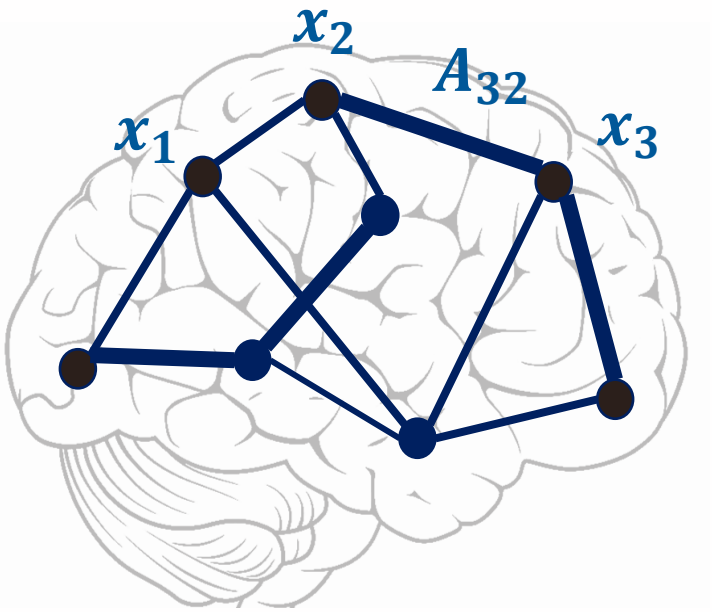
$$x(t+1) = \begin{bmatrix} A_{11} & \cdots & A_{1n} \\ \vdots & \ddots & \vdots \\ A_{n1} & \cdots & A_{nn} \end{bmatrix} \begin{bmatrix} x_1(t) \\ \vdots \\ x_n(t) \end{bmatrix}$$

Fragility of each node in window:

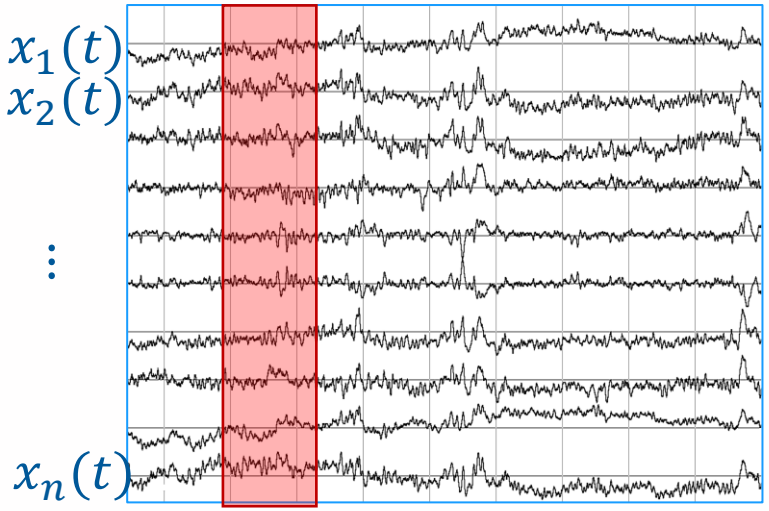


EEG NETWORK MODEL

EEG Electrode Implantation → **Intracranial EEG Recordings** → **Dynamical Systems Model**



$$x_2(t) \xrightarrow{A_{32}} x_3(t+1)$$

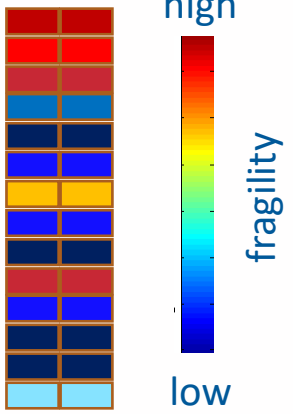


$$x(t) = \begin{bmatrix} x_1(t) \\ \vdots \\ x_n(t) \end{bmatrix}$$

(for each 500 msec window)

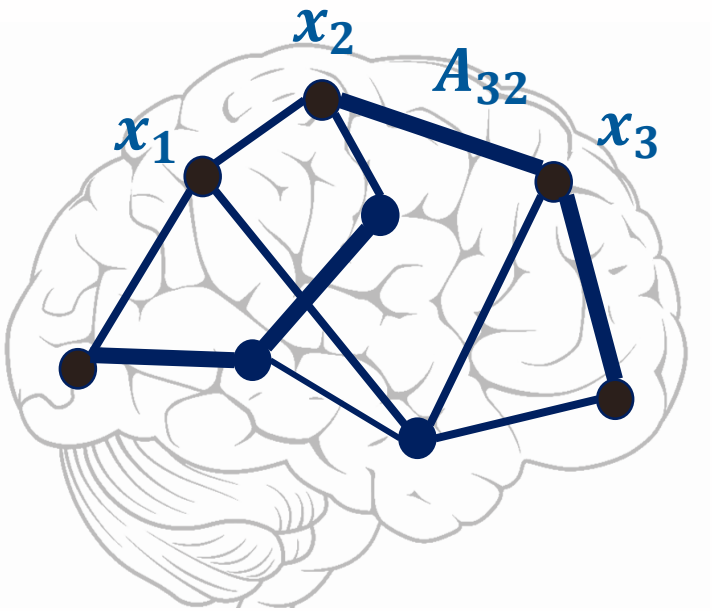
$$x(t+1) = \begin{bmatrix} A_{11} & \cdots & A_{1n} \\ \vdots & \ddots & \vdots \\ A_{n1} & \cdots & A_{nn} \end{bmatrix} \begin{bmatrix} x_1(t) \\ \vdots \\ x_n(t) \end{bmatrix}$$

Fragility of each node in window:

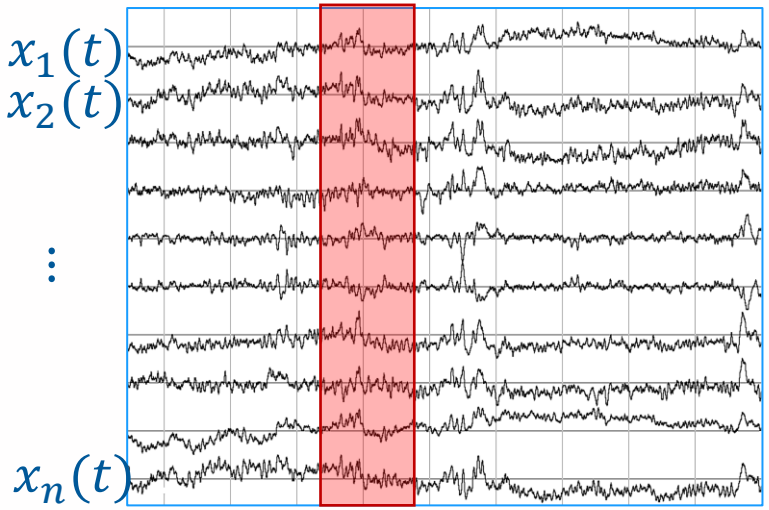


EEG NETWORK MODEL

EEG Electrode Implantation → **Intracranial EEG Recordings** → **Dynamical Systems Model**



$$x_2(t) \xrightarrow{A_{32}} x_3(t+1)$$

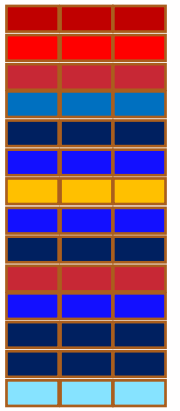


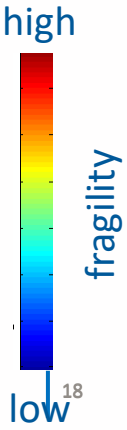
$$x(t) = \begin{bmatrix} x_1(t) \\ \vdots \\ x_n(t) \end{bmatrix}$$

(for each 500 msec window)

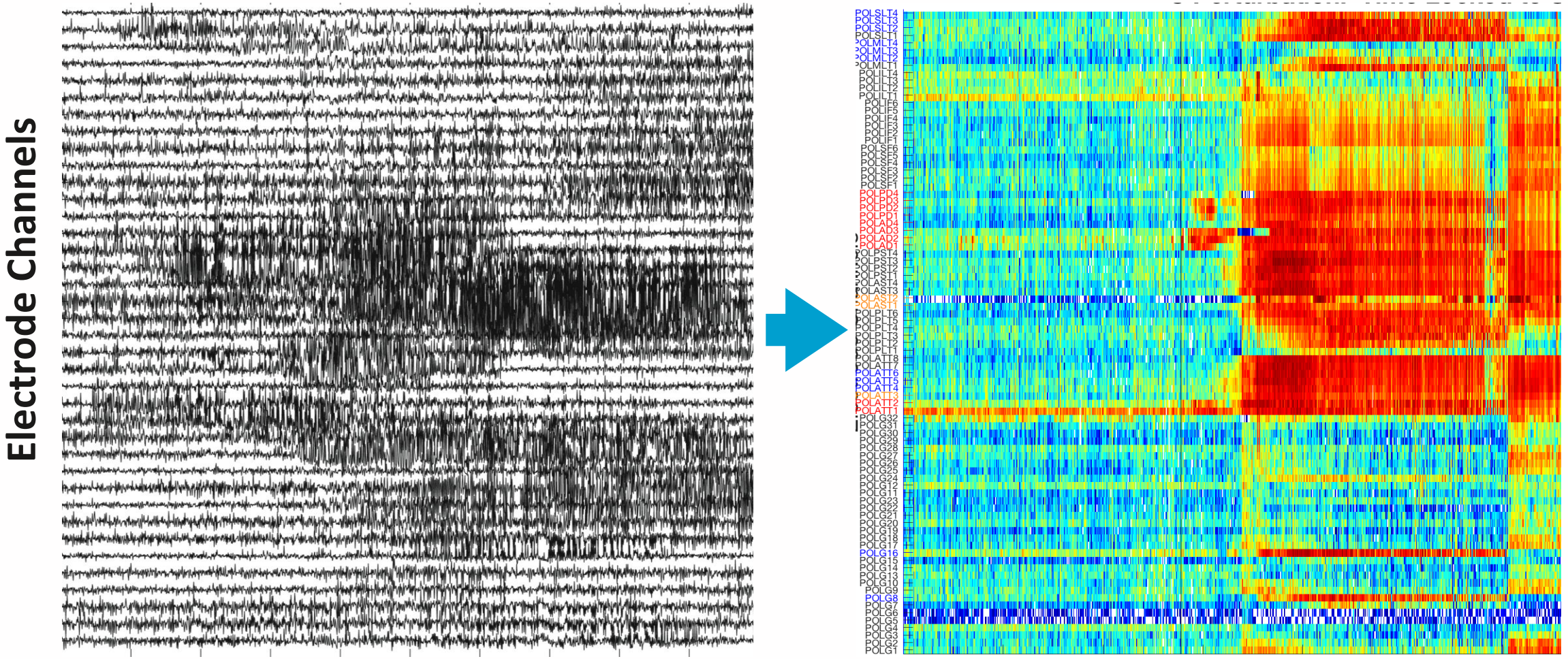
$$x(t+1) = \begin{bmatrix} A_{11} & \cdots & A_{1n} \\ \vdots & \ddots & \vdots \\ A_{n1} & \cdots & A_{nn} \end{bmatrix} \begin{bmatrix} x_1(t) \\ \vdots \\ x_n(t) \end{bmatrix}$$

Fragility of each node in window:





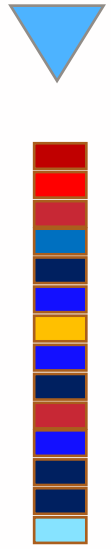
FROM EEG TO FRAGILITY MAP



HOW DO WE COMPUTE FRAGILITY FROM A MODEL?

$$\boldsymbol{x}(t+1) = \begin{bmatrix} A_{11} & \cdots & A_{1n} \\ \vdots & \ddots & \vdots \\ A_{n1} & \cdots & A_{nn} \end{bmatrix} \begin{bmatrix} x_1(t) \\ \vdots \\ x_n(t) \end{bmatrix}$$

Fragility of each node in window:



EEG Network Model

$$\boldsymbol{x}(t+1) = \mathbf{A}\boldsymbol{x}(t)$$

$$\begin{bmatrix} x_I(t+1) \\ x_E(t+1) \end{bmatrix} = \begin{bmatrix} -1 & 3 \\ -3 & -1 \end{bmatrix} \begin{bmatrix} x_I(t) \\ x_E(t) \end{bmatrix}$$

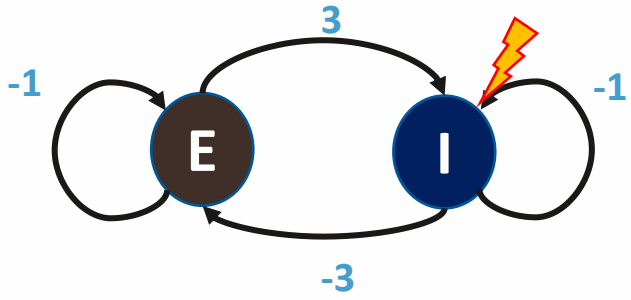
$$\boldsymbol{x}(t+1) = (\mathbf{A} + \boldsymbol{\Delta})\boldsymbol{x}(t)$$

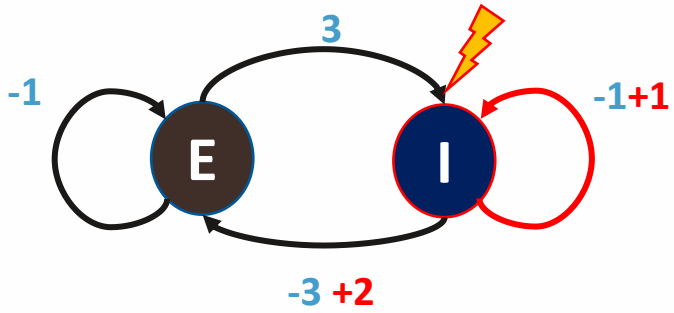
$$\begin{bmatrix} x_I(t+1) \\ x_E(t+1) \end{bmatrix} = \begin{bmatrix} -1+1 & 3 \\ -3+2 & -1 \end{bmatrix} \begin{bmatrix} x_I(t) \\ x_E(t) \end{bmatrix}$$

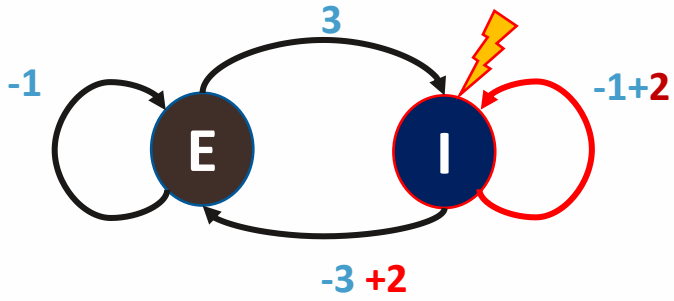
$$\boldsymbol{x}(t+1) = (\mathbf{A} + \boldsymbol{\Delta})\boldsymbol{x}(t)$$

$$\begin{bmatrix} x_I(t+1) \\ x_E(t+1) \end{bmatrix} = \begin{bmatrix} -1+2 & 3 \\ -3+2 & -1 \end{bmatrix} \begin{bmatrix} x_I(t) \\ x_E(t) \end{bmatrix}$$

2 Node EEG Network







Amount of change in connections

$$\|\Delta\| = \left\|\begin{matrix}\Delta_1 \\ \Delta_2\end{matrix}\right\| = \sqrt{\Delta_1^2 + \Delta_2^2}$$

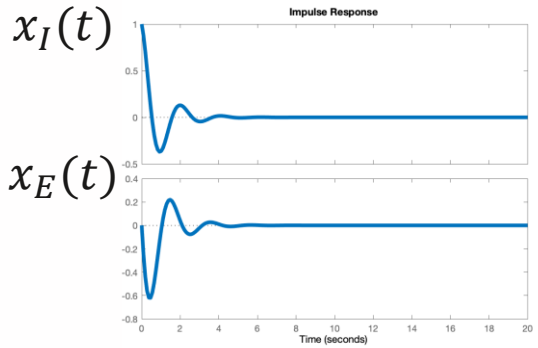
0

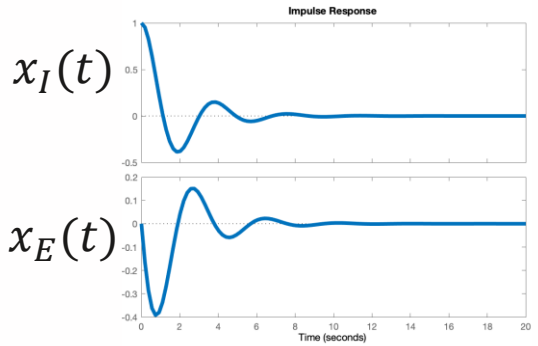
$$\sqrt{5}$$

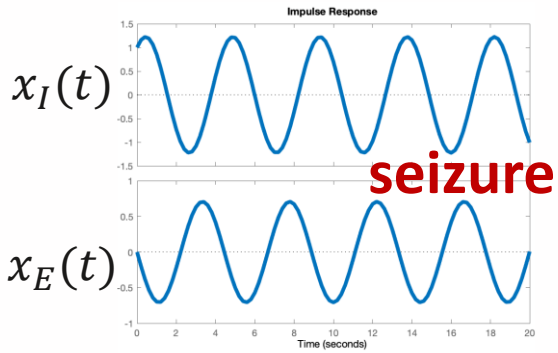
$$\sqrt{8}$$

fragility of node I=$\sqrt{8}$

EEG Responses to Perturbation



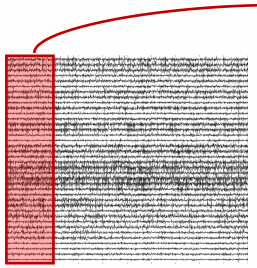




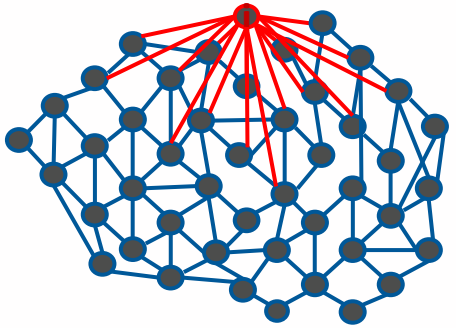
seizure!

COMPUTING FRAGILITY FROM EEG FOR N NODES

1. **Estimate A in each 500msec EEG window**



$$\begin{bmatrix} x_1(t+1) \\ \vdots \\ x_n(t+1) \end{bmatrix} = \begin{bmatrix} a_{11} & \cdots & a_{1n} \\ \vdots & \ddots & \vdots \\ a_{n1} & \cdots & a_{nn} \end{bmatrix} \begin{bmatrix} x_1(t) \\ \vdots \\ x_n(t) \end{bmatrix}$$



2. **For each A matrix, add perturbation to column i**

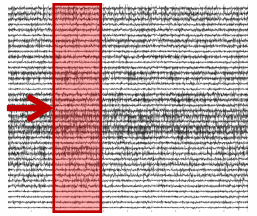
$$\begin{bmatrix} x_1(t+1) \\ \vdots \\ x_n(t+1) \end{bmatrix} = \begin{bmatrix} a_{11} + \Delta_1 & \cdots & a_{1n} \\ \vdots & \ddots & \vdots \\ a_{n1} + \Delta_n & \cdots & a_{nn} \end{bmatrix} \begin{bmatrix} x_1(t) \\ \vdots \\ x_n(t) \end{bmatrix}$$

3. **Optimize over an nx1 Δ vector to find smallest norm to destabilize A+ Δ (seizure)**

$$\min \|\Delta\|_2$$
$$\text{s.t.} \quad \boldsymbol{x}(t+1) = (\boldsymbol{A} + \boldsymbol{\Delta})\boldsymbol{x}(t) \text{ unstable}$$

4. **Repeat steps 2 and 3 for each node up to node n**

5. **Move to next 500 msec window and go to step 1**



***Hypothesis*:** The most *fragile* nodes in the epileptic network correspond to the epileptogenic zone (EZ).

MULTI-CENTER RETROSPECTIVE STUDY

91 PATIENTS

300+ SEIZURES

5 CENTERS

Cleveland Clinic

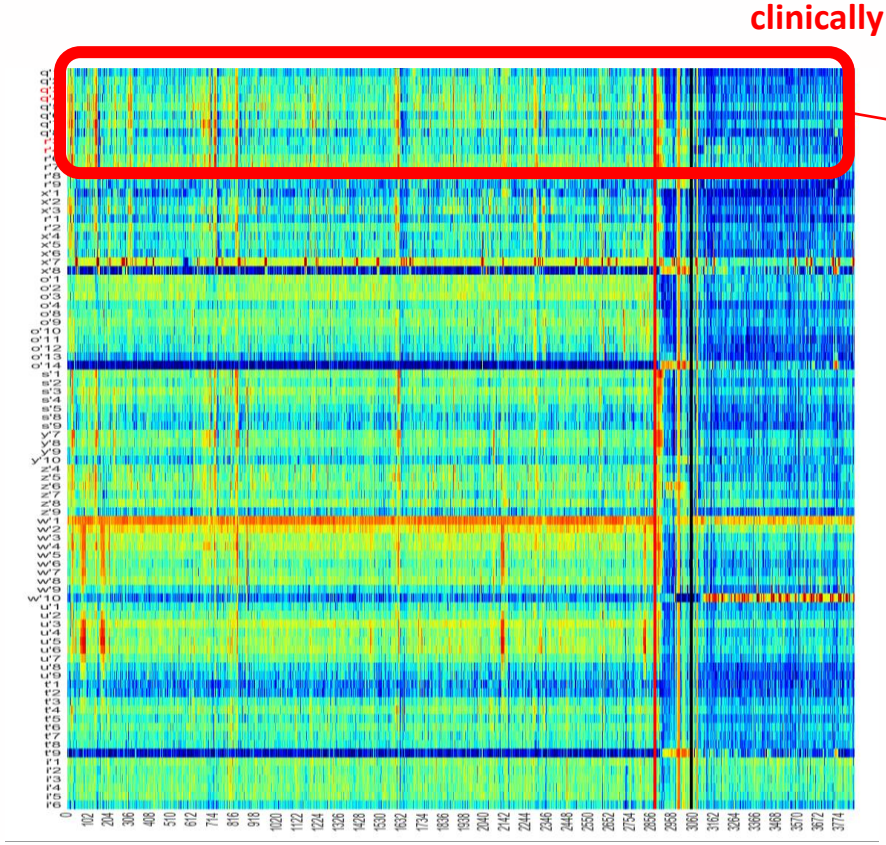
University of Maryland Medical Center

University of Miami Hospital

National Institutes of Health

Johns Hopkins School of Medicine

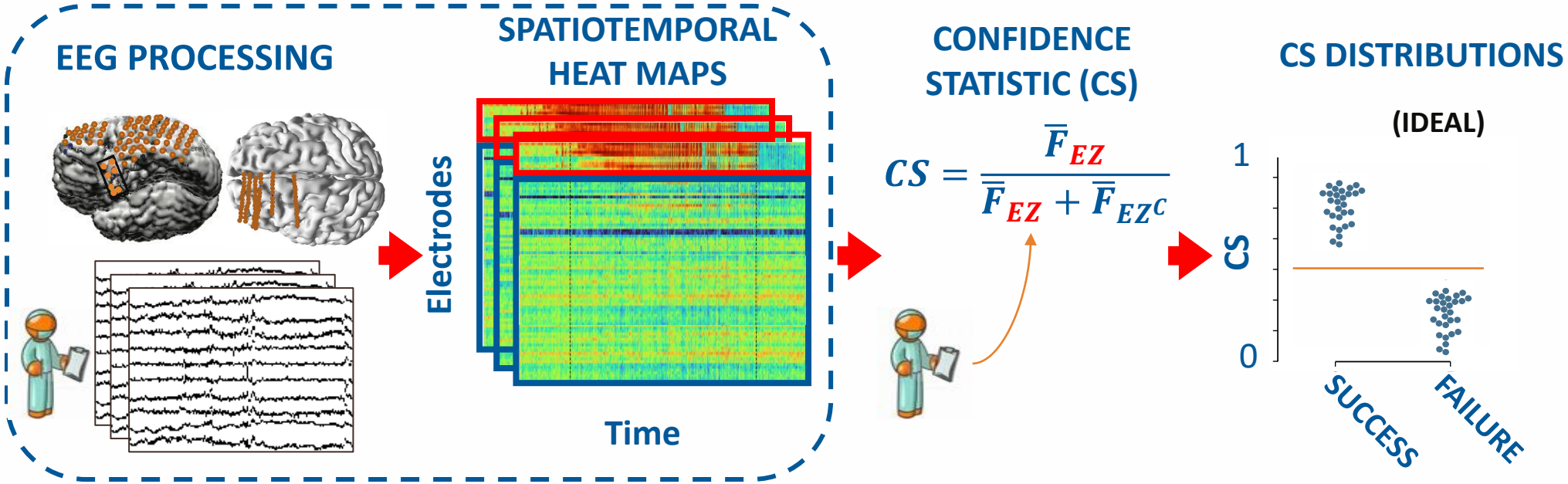
EVALUATING HEATMAPS



$$CS = \frac{\text{mean fragility of CEZ}}{\text{mean fragility of all nodes}}$$

Conjecture: Confidence statistics (CS) will be higher for success and lower for failures

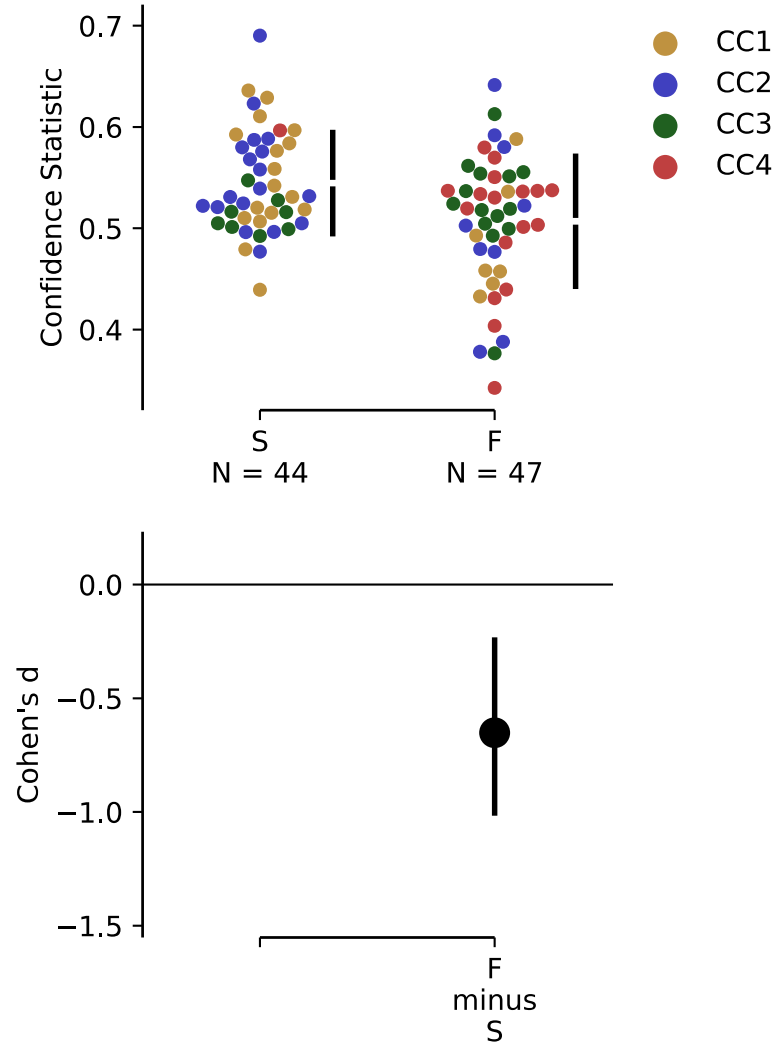
EVALUATING HEATMAPS



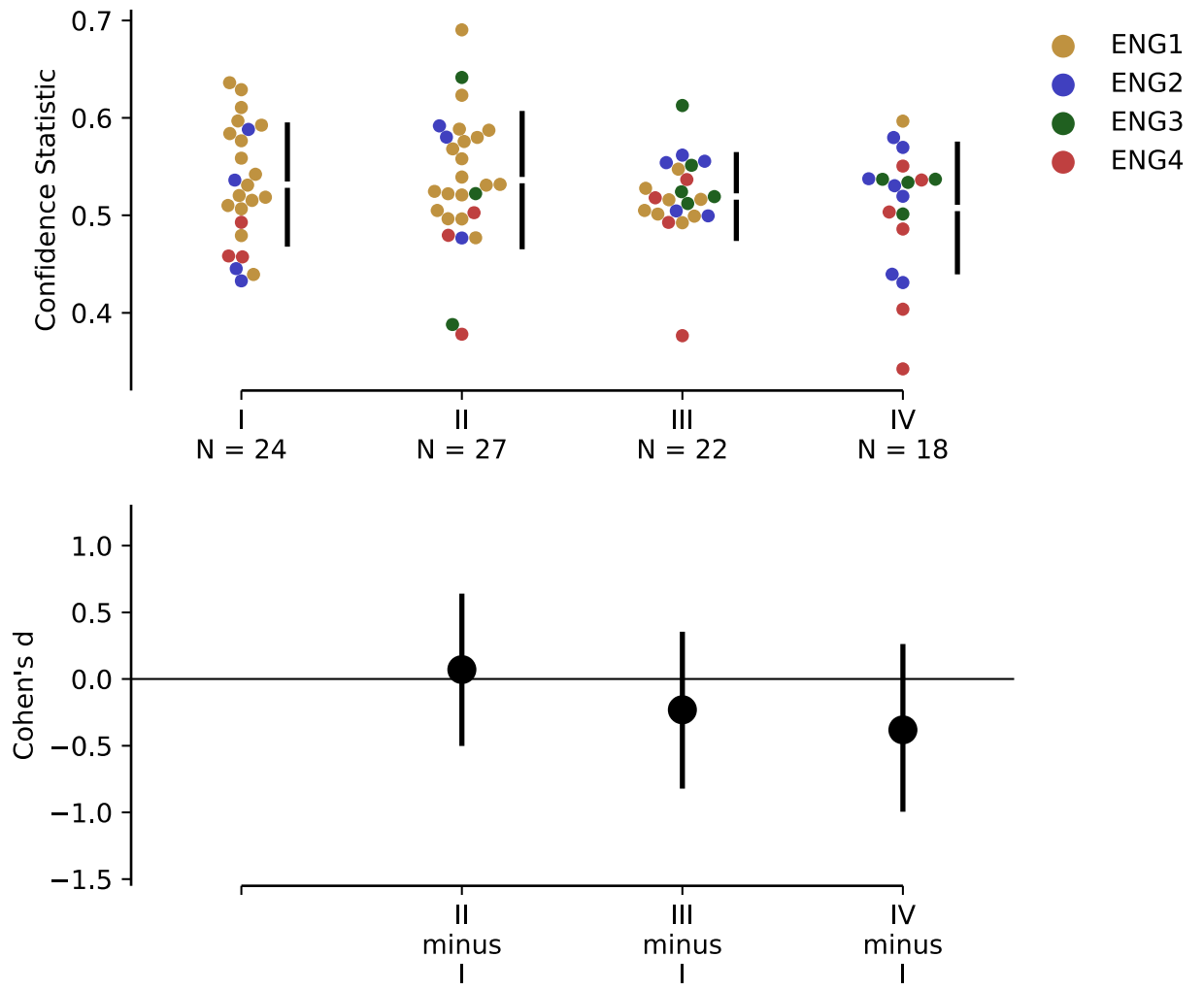
Confidence in a clinically annotated EZ is a way of comparing spatiotemporal feature maps in a systematic way.

FRAGILITY EFFECT SIZE DIFFERENCES BETWEEN OUTCOMES

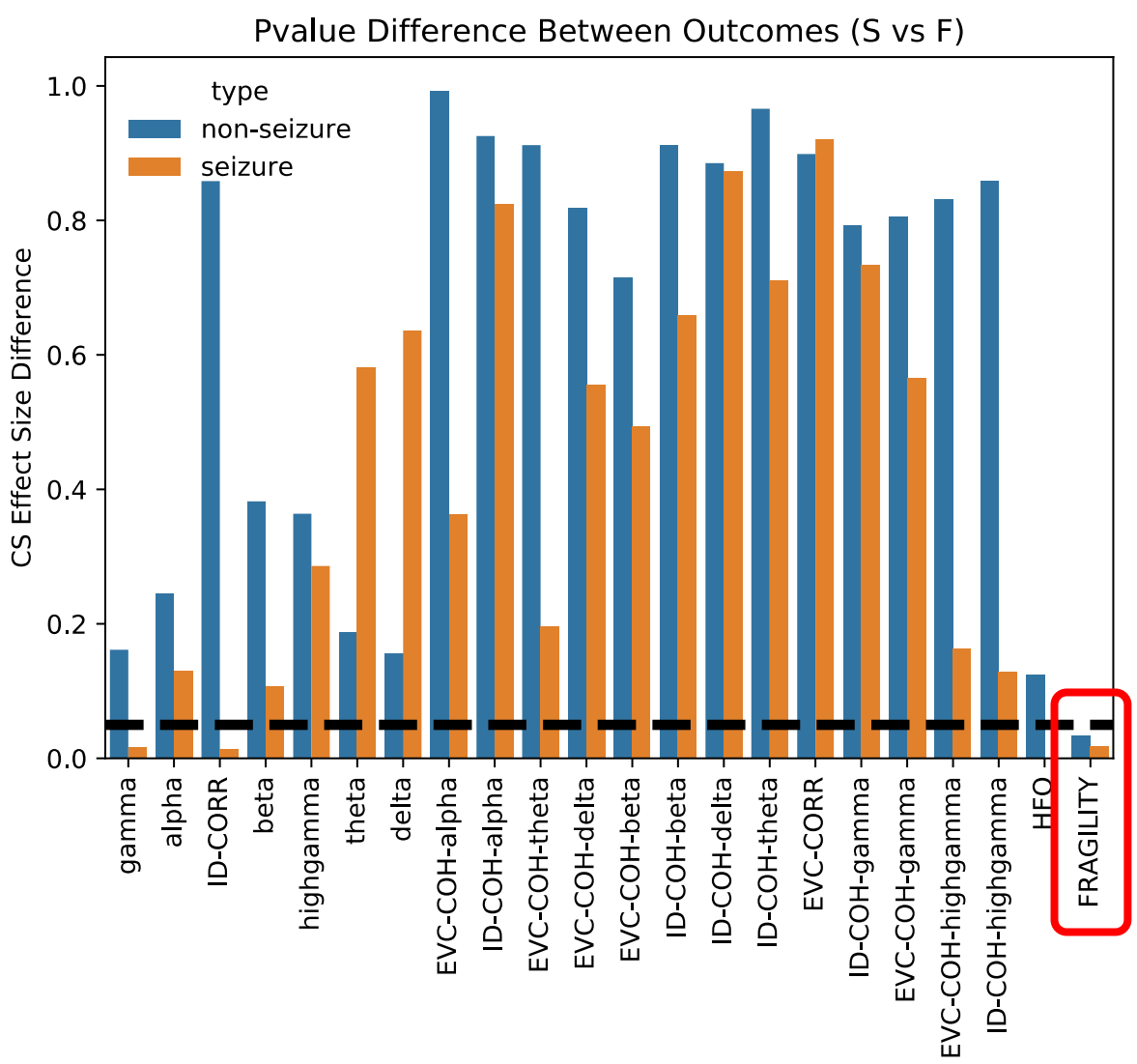
OUTCOME



CLINICAL COMPLEXITY

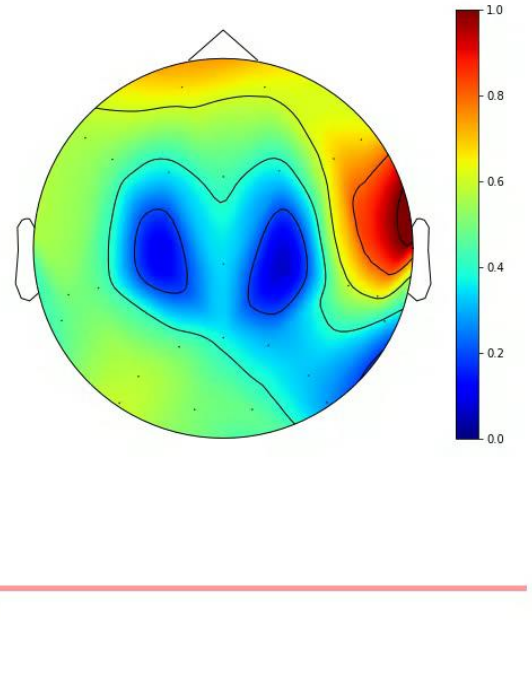


FRAGILITY OUTPERFORMS ALL PROPOSED EEG FEATURES

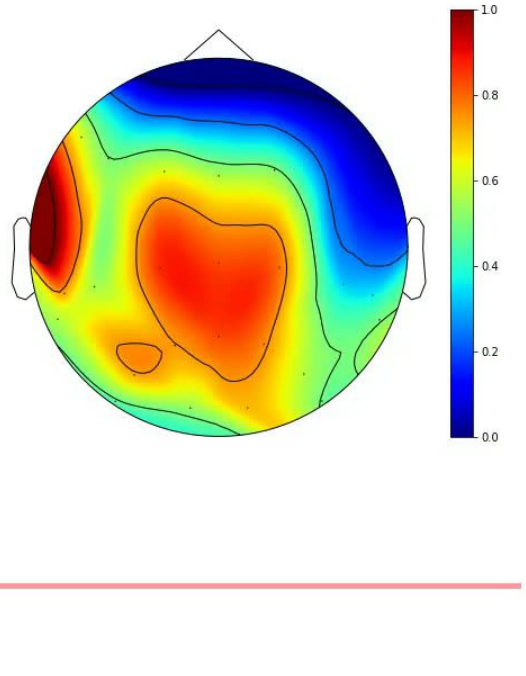


FRAGILITY MAP FOR SCALP
SUCCESSFUL OUTCOME

Fragility Map



Raw EEG



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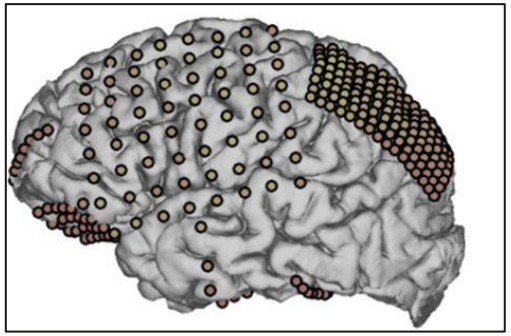
JOHNS HOPKINS SCHOOL of MEDICINE

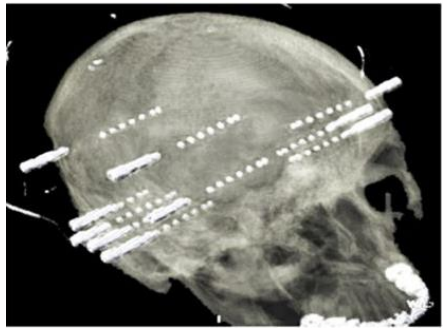
Cleveland Clinic

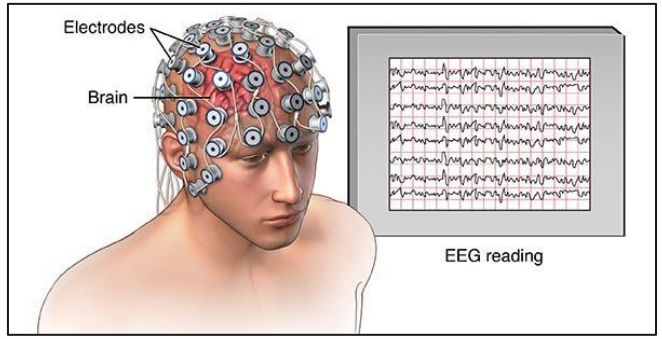
EPILEPSY FOUNDATION

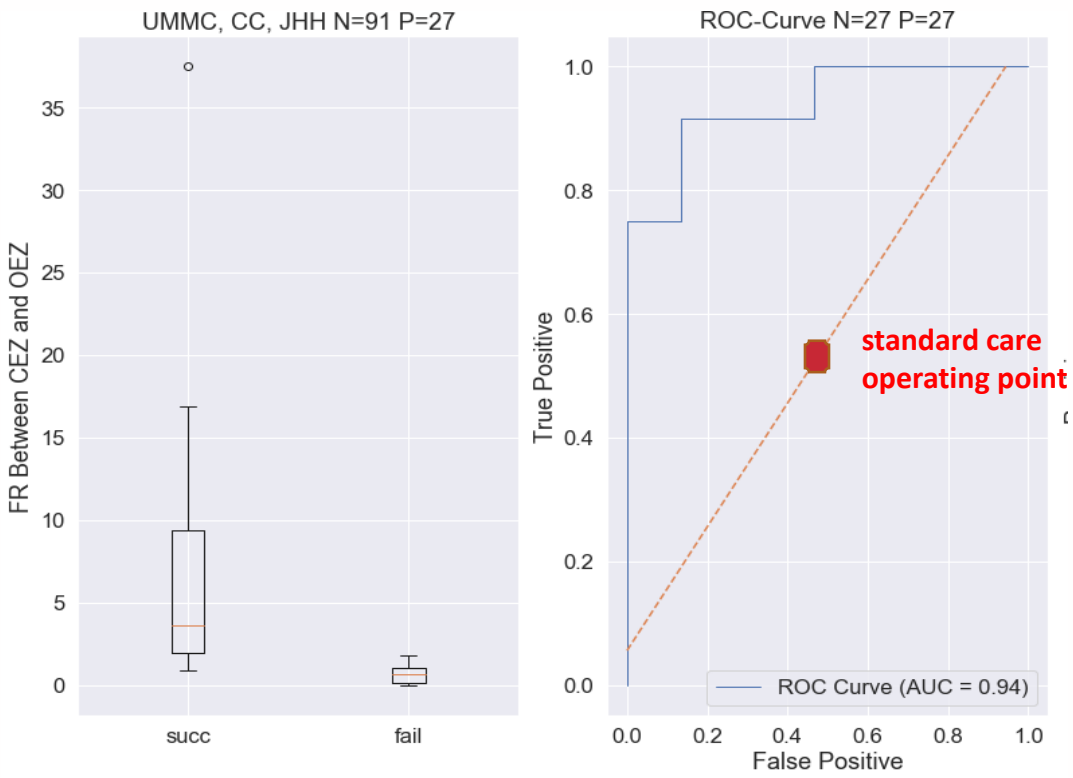
THANK YOU

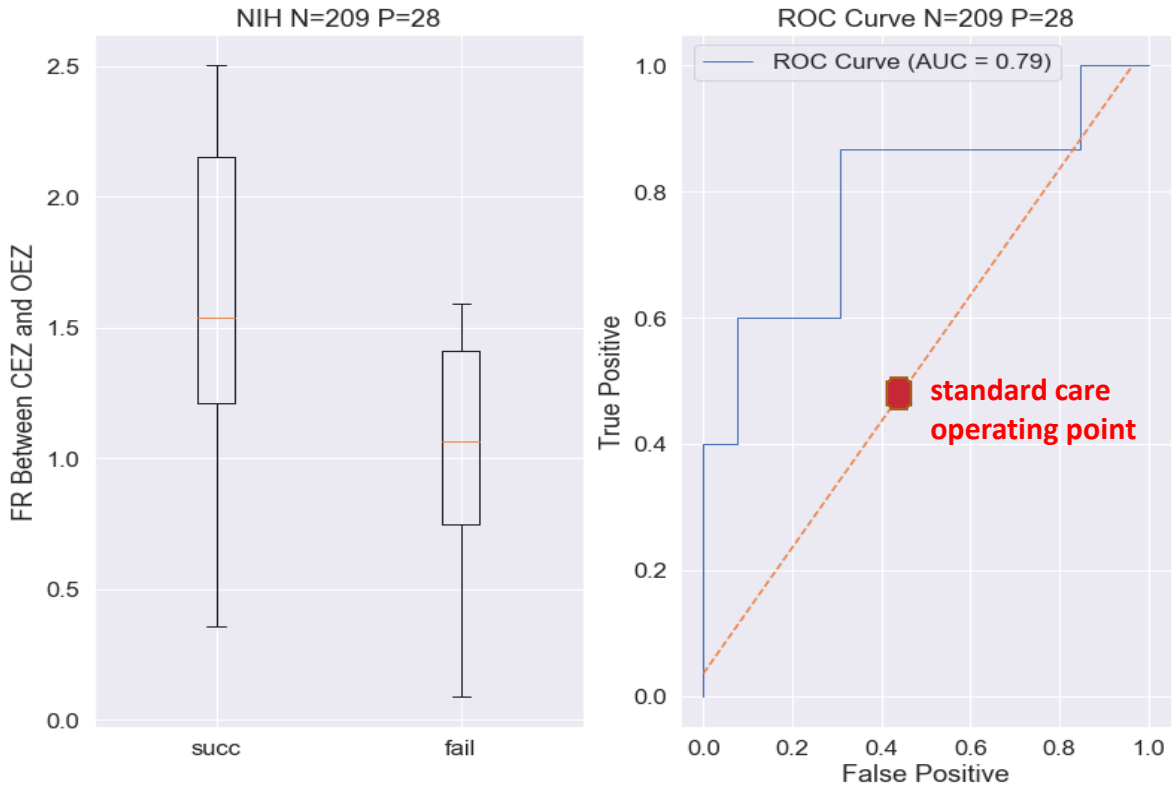
FRAGILITY RATIO PREDICTS OUTCOMES



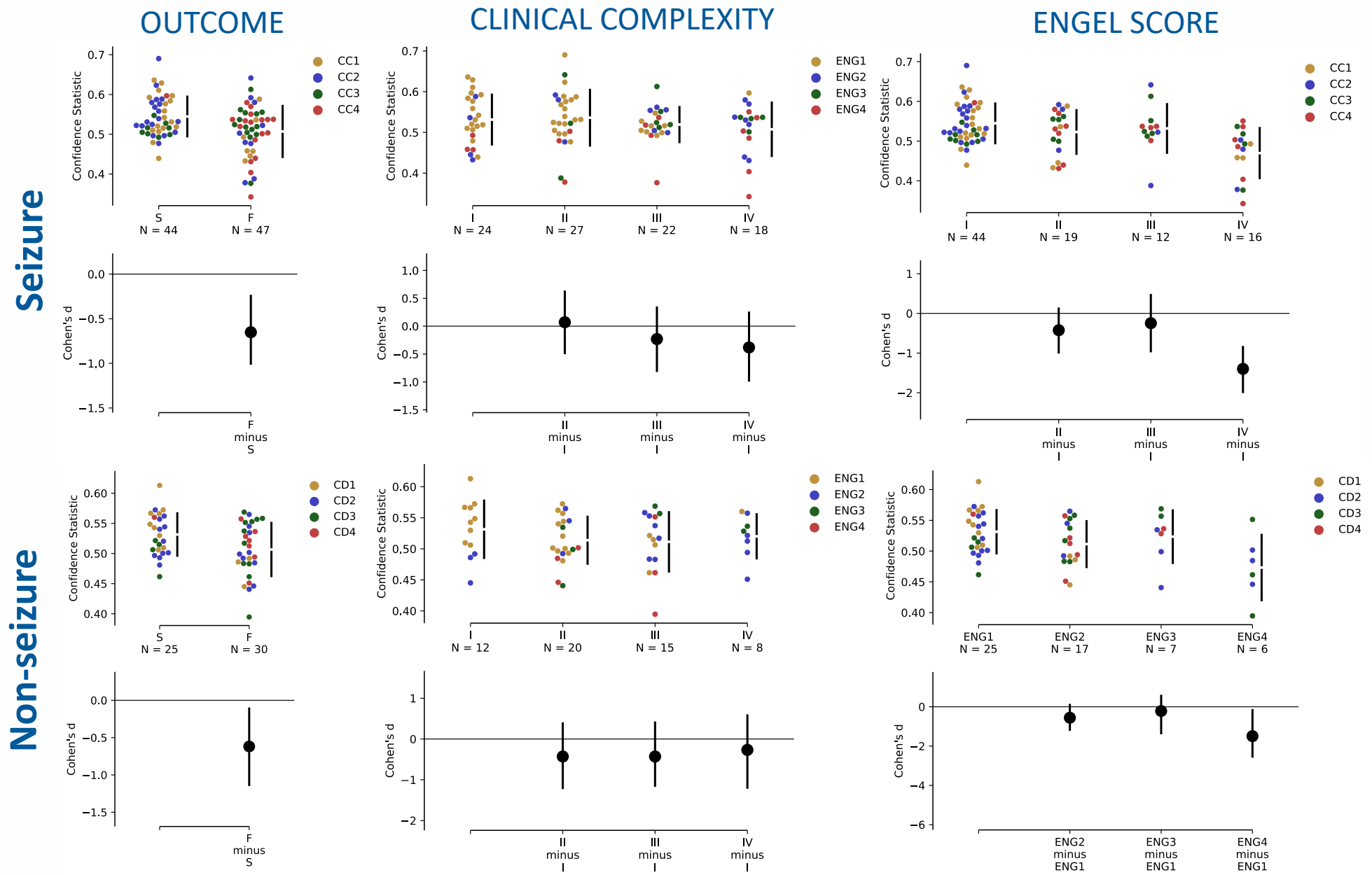








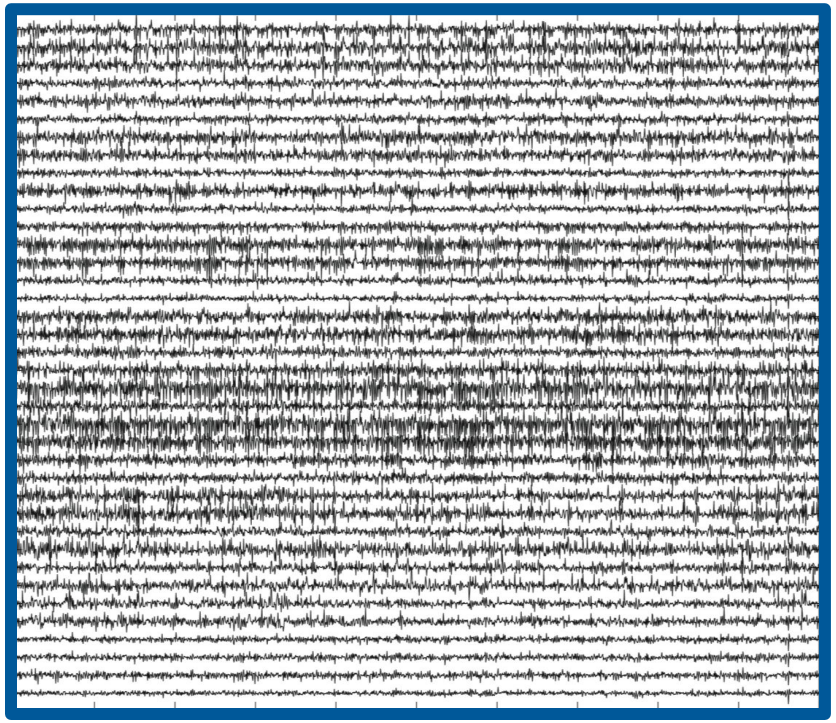
FRAGILITY EFFECT SIZE DIFFERENCES BETWEEN OUTCOMES



Title goes here

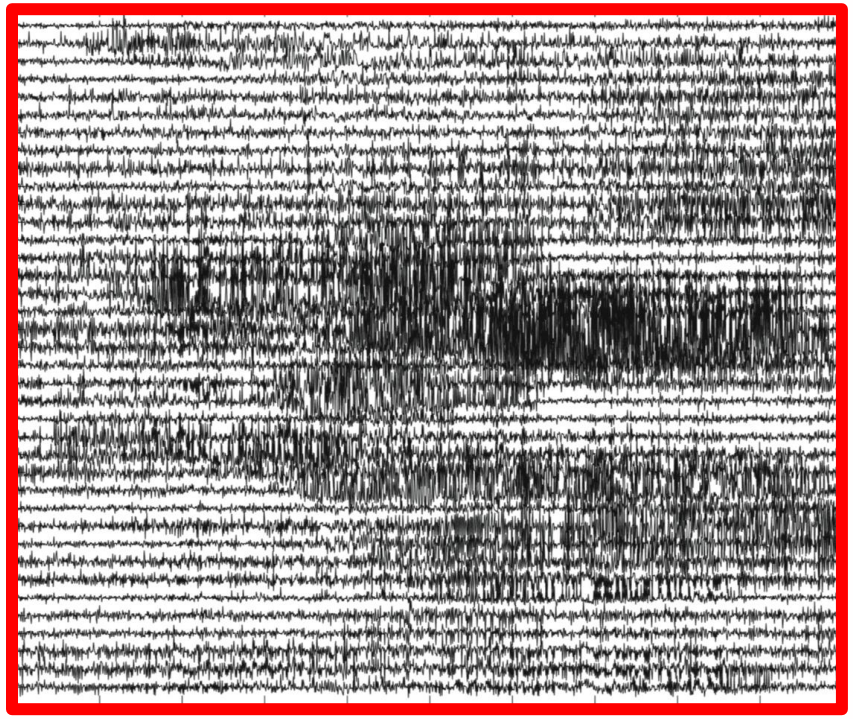
Observation 1: seizure occurs in an *unstable* network

Non-Seizure



STABLE

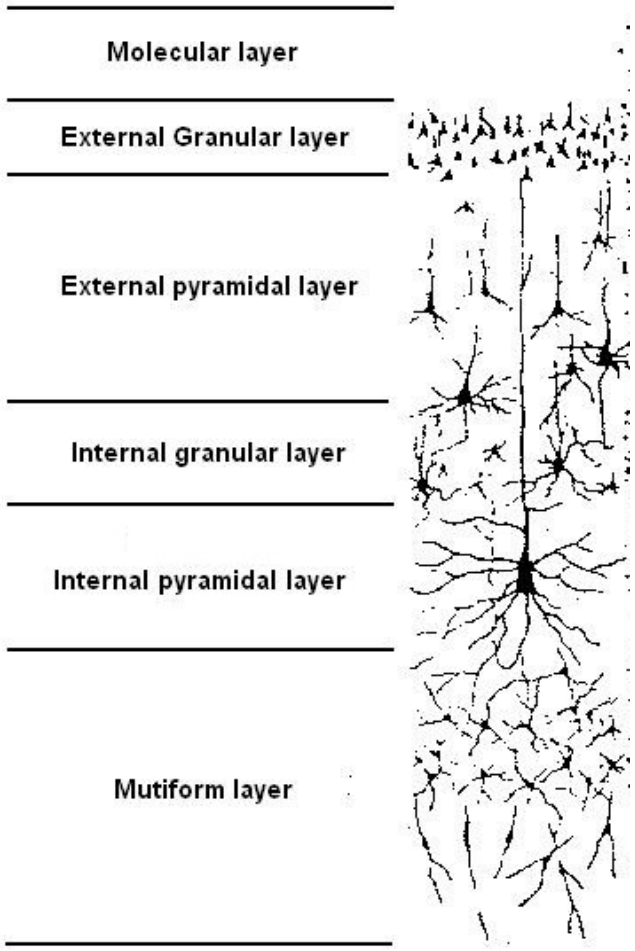
Seizure

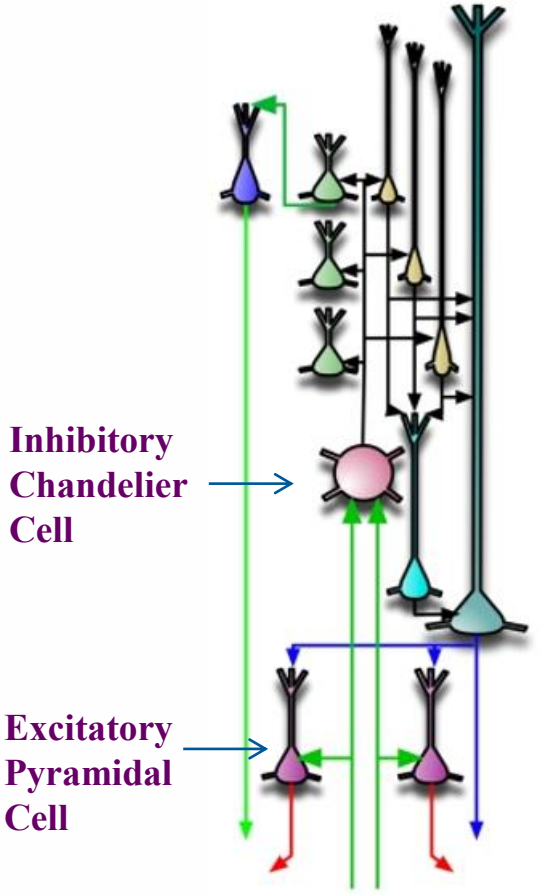


UNSTABLE

Title goes here

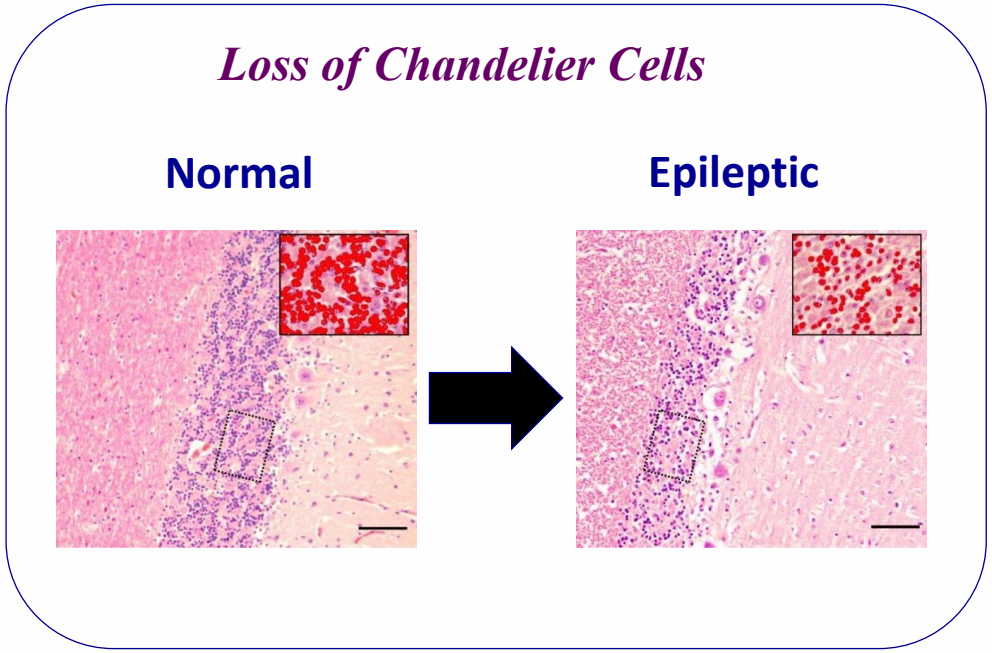
Observation 2: *Destabilization* occurs when neural coupling alters

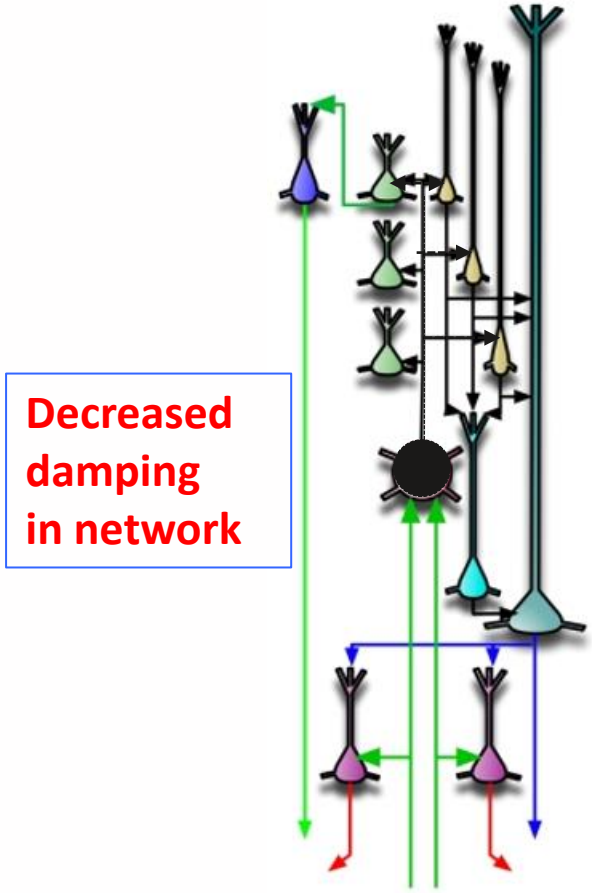




Title goes here

Observation 2: *Destabilization* occurs when neural coupling alters





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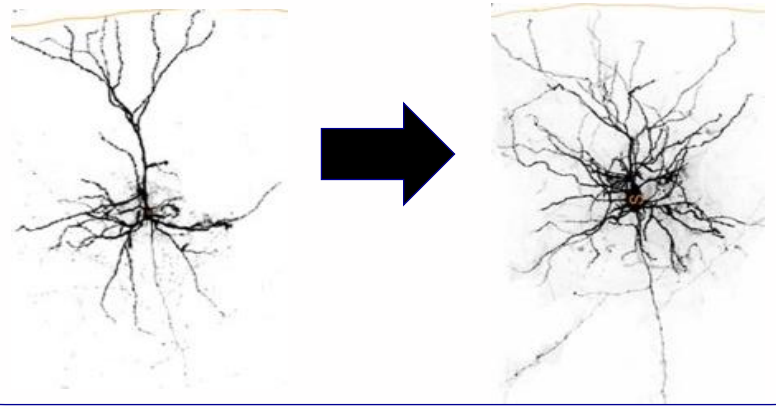
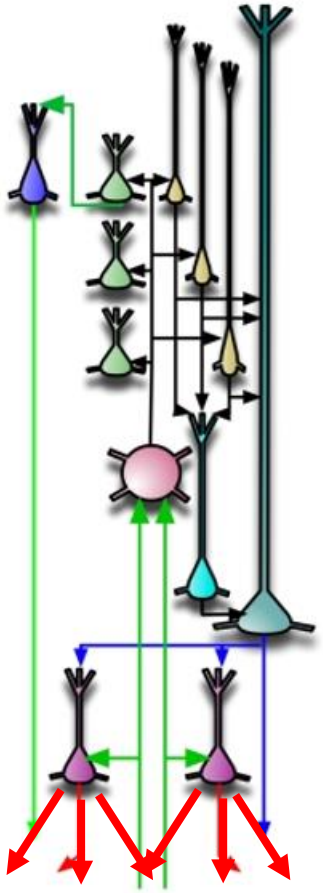
Observation 2: *Destabilization* occurs when neural coupling alters

Abnormal Axonal Spouting of Pyramidal cells

Normal **Epileptic**





Increased excitation in network

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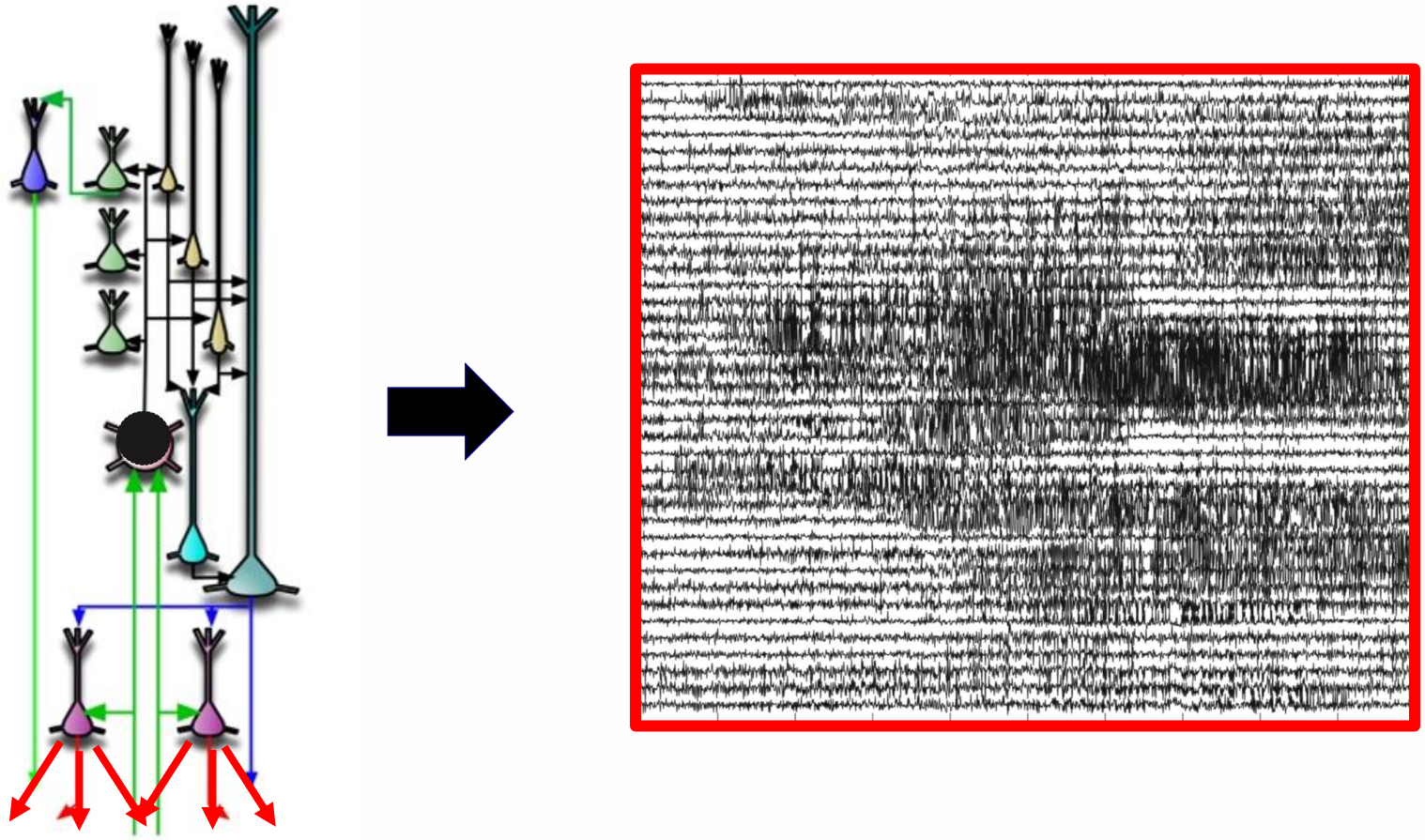
Changes in coupling between neuronal populations (**network nodes**) translates functionally seizures (**instability**)



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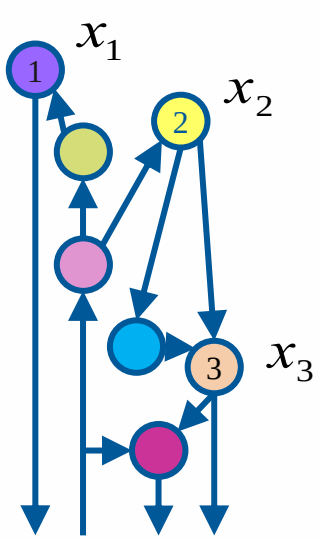
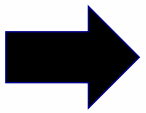
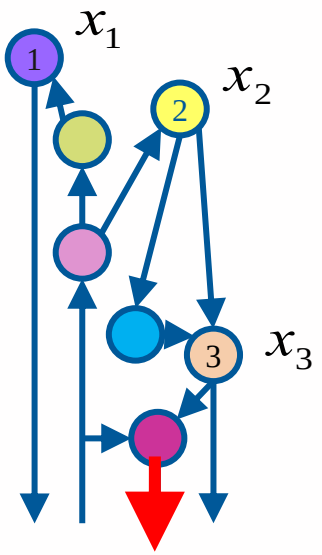
Model seizures as emergent phenomena from functional perturbations



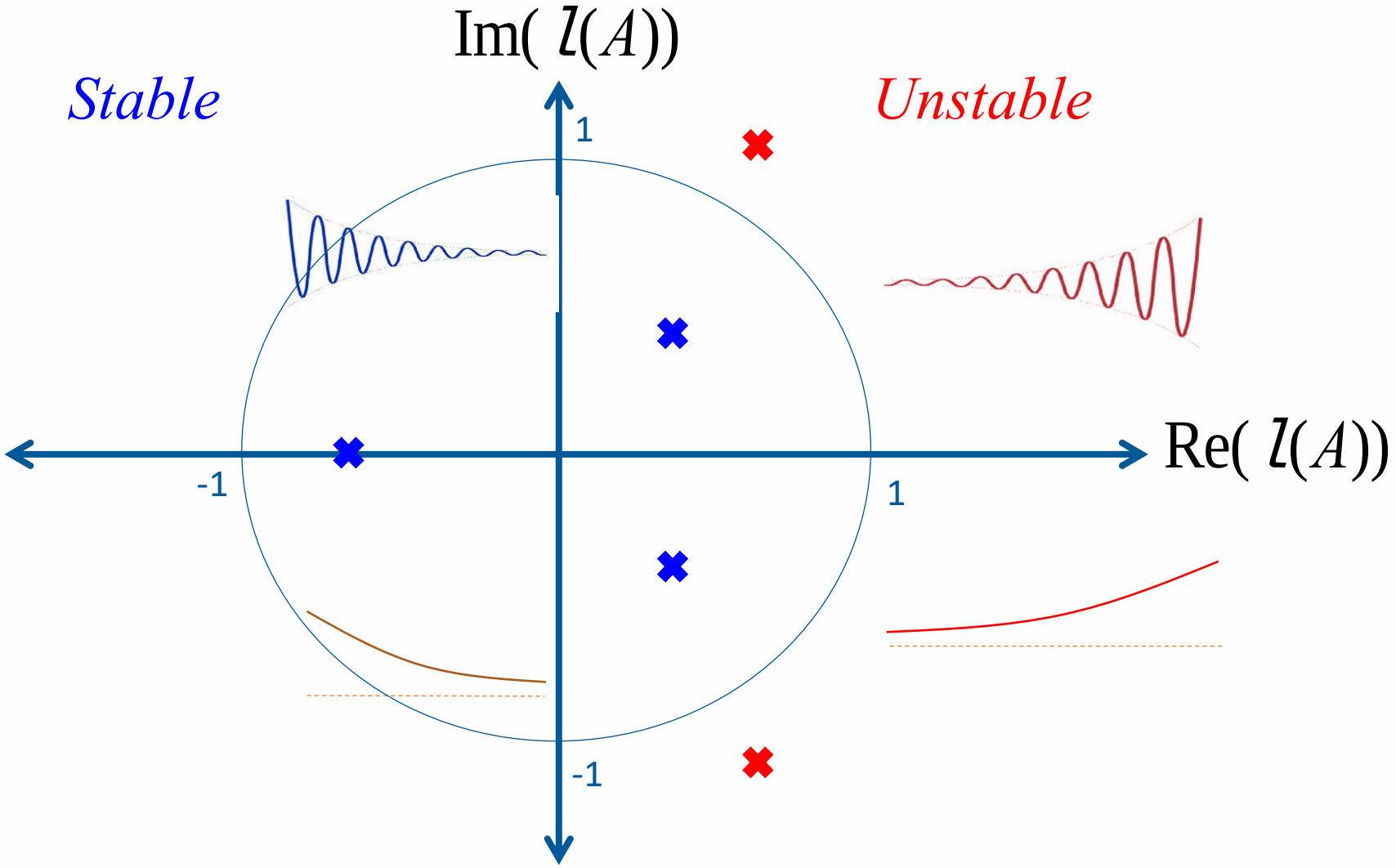




$$\mathbf{x}(t+1) = \mathbf{A}\mathbf{x}(t)$$

$$\mathbf{x}(t+1) = (\mathbf{A} + \mathbf{D})\mathbf{x}(t)$$

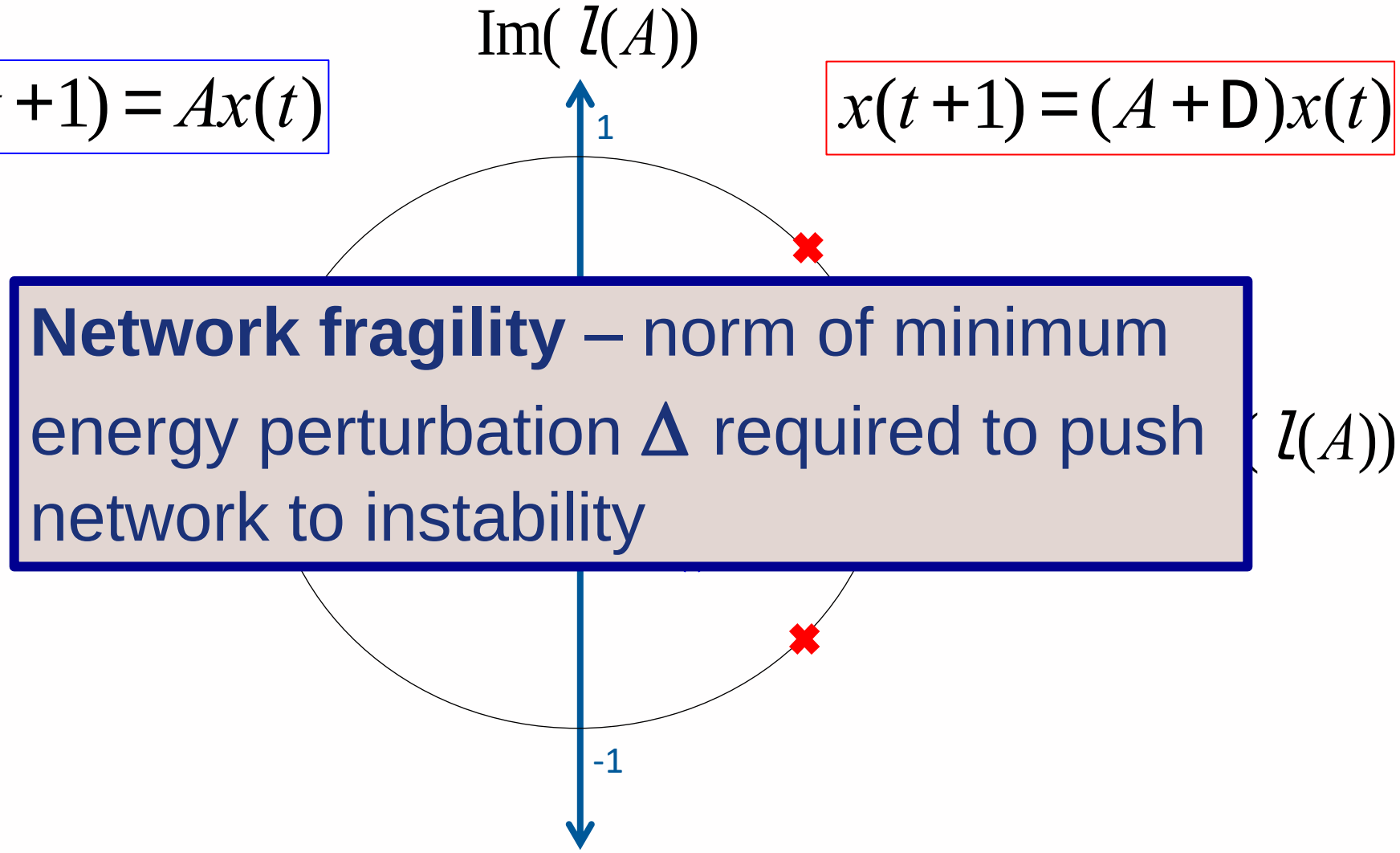
Title goes here



Title goes here

$$x(t+1) = Ax(t)$$

$$x(t+1) = (A + \Delta)x(t)$$



Network fragility – norm of minimum energy perturbation Δ required to push network to instability

Title goes here

Structured perturbation problem

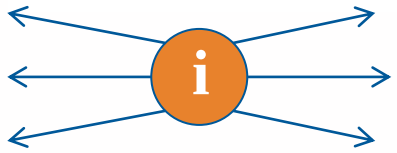
$$x(t+1) = (A + \mathsf{D})x(t)$$

$$\hat{\Delta}(\lambda) = \underset{\Delta \in \Lambda}{\operatorname{argmin}} \{\|\Delta\|_2 \mid \exists\, i : \lambda_i(A+\Delta) = \lambda, \forall\, i : \lambda_i(A) \neq \lambda, i \in 1 \ldots N, A \in \mathbb{R}^{N \times N}\}$$

perturbation on i^{th} column

$$\Delta = \begin{bmatrix} \cdots & | & | & | & \cdots \\ & 0 & \mathbf{r} & 0 & \\ & | & | & | & \end{bmatrix}$$

$\| \hat{\mathsf{D}} \|$ = fragility of i^{th} node



Title goes here

$$\widehat{\Delta}(\lambda) = \underset{\Delta \in \Lambda}{\operatorname{argmin}} \{\|\Delta\|_2 \,|\exists\, i : \lambda_i(A+\Delta) = \lambda, \forall\, i : \lambda_i(A) \neq \lambda, i \in 1 \ldots N, A \in \mathbb{R}^{N \times N}\}$$

$$\left(A + \boldsymbol{\Gamma e_k^T}\right)\boldsymbol{v} = \lambda \boldsymbol{v}$$

$$\left|A - \lambda \mathrm{I} + \boldsymbol{\Gamma e_k^T}\right| = 0$$

$$\left|(A - \lambda \mathrm{I})\left(I + (A - \lambda \mathrm{I})^{-1}\boldsymbol{\Gamma e_k^T}\right)\right| = 0$$

$$\left|I + (A - \lambda \mathrm{I})^{-1}\boldsymbol{\Gamma e_k^T}\right| = 0$$

$$\boldsymbol{\Gamma}^T (A - \lambda \mathrm{I})^{-T} \boldsymbol{e_k} = -1$$

$$\Delta = \begin{bmatrix} \cdots & | & | & | & \cdots \\ & 0 & \boldsymbol{\Gamma} & 0 & \\ & | & | & | & \end{bmatrix}$$

Column Perturbation

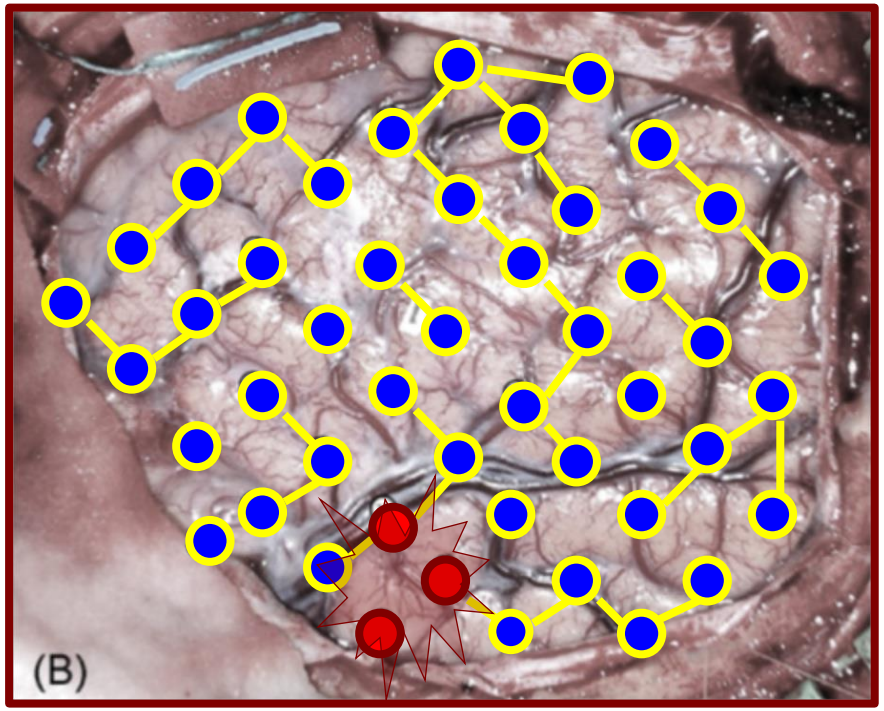
$$\boxed{\min_{\Delta \in \Lambda} \|\Delta\|_2 \Leftrightarrow \min_k \left\{\|\boldsymbol{\Gamma}(k)\|_2 \;\middle|\; \boldsymbol{e_k^T}(A - \lambda \mathrm{I})^{-1}\boldsymbol{\Gamma} = -1\right\}}$$

Least Squares!

Title goes here

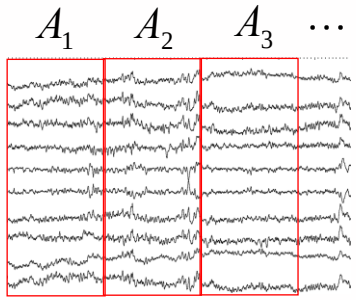
EZ can be localized via fragility analysis (on **non-seizure** data)

Hypothesis: The most *fragile* nodes in the epileptic network correspond to the epileptogenic zone.

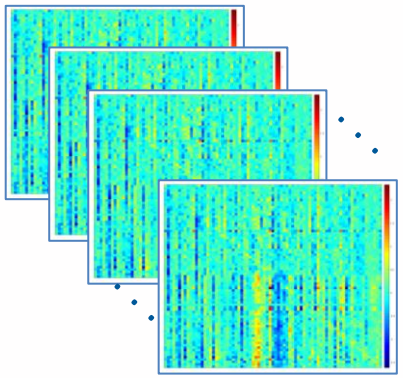


Title goes here

Localization with fragility maps

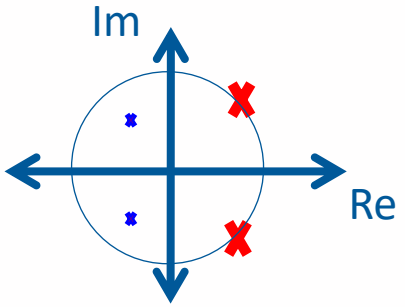


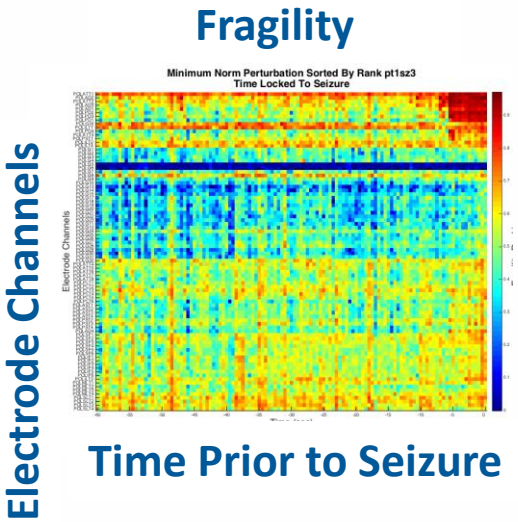
Window size = 500 ms



column perturbations

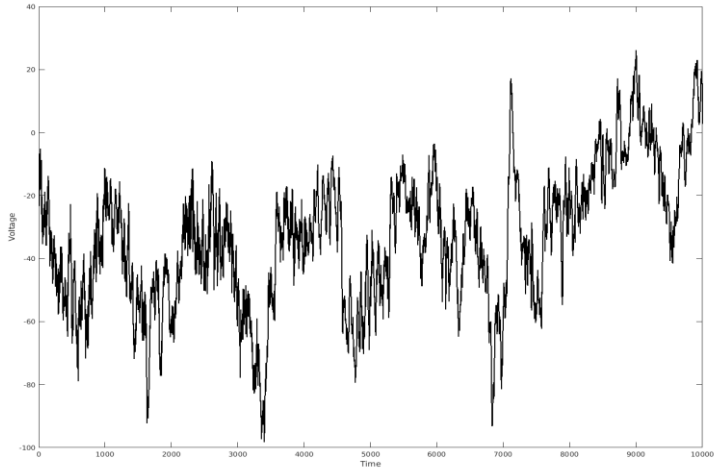
$$\Delta = \begin{bmatrix} \cdots & 0 & \mathbf{r} & 0 & \cdots \end{bmatrix}$$



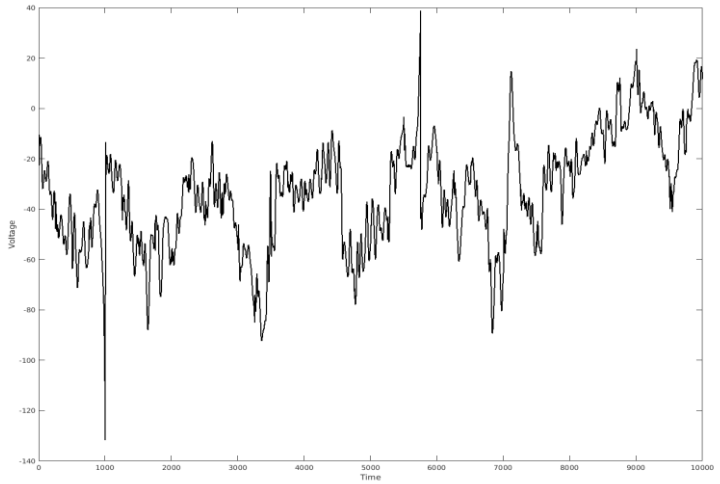


Title goes here

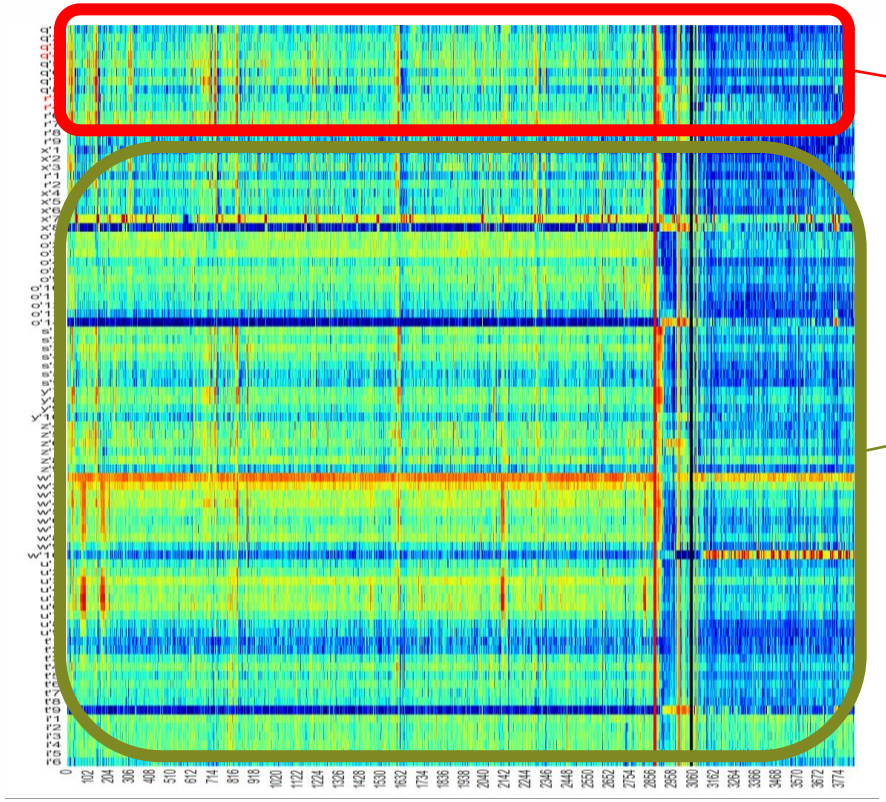
Actual EEG



Simulated EEG



FRAGILITY OF CLINICAL EZ VERSUS REST



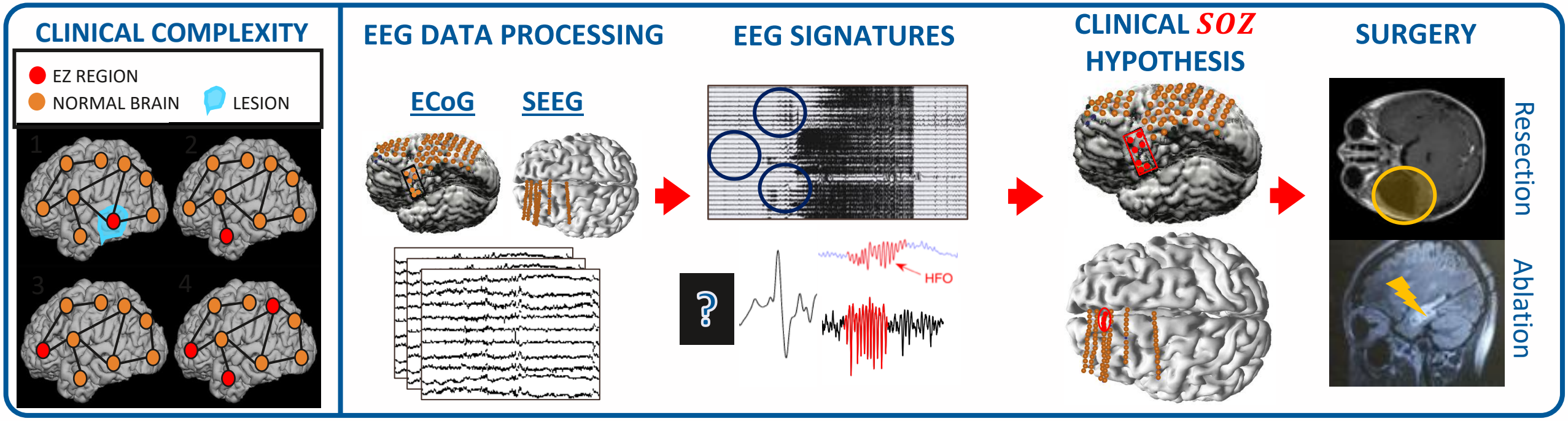
clinically annotated EZ (CEZ)

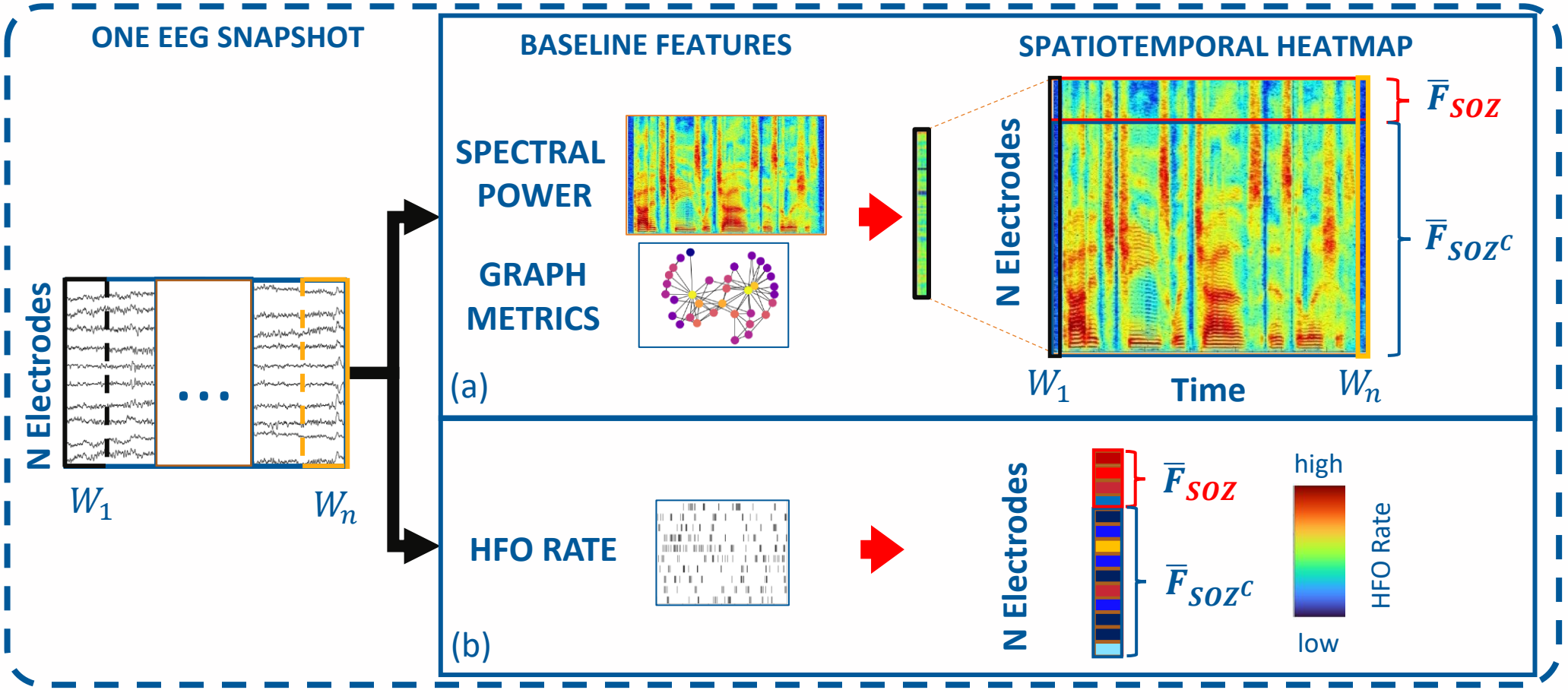
Rest

$$FR = \frac{\text{mean fragility of CEZ}}{\text{mean fragility of rest}}$$

***Hypothesis: Fragility ratio (*FR) is high for successes and low for failures**

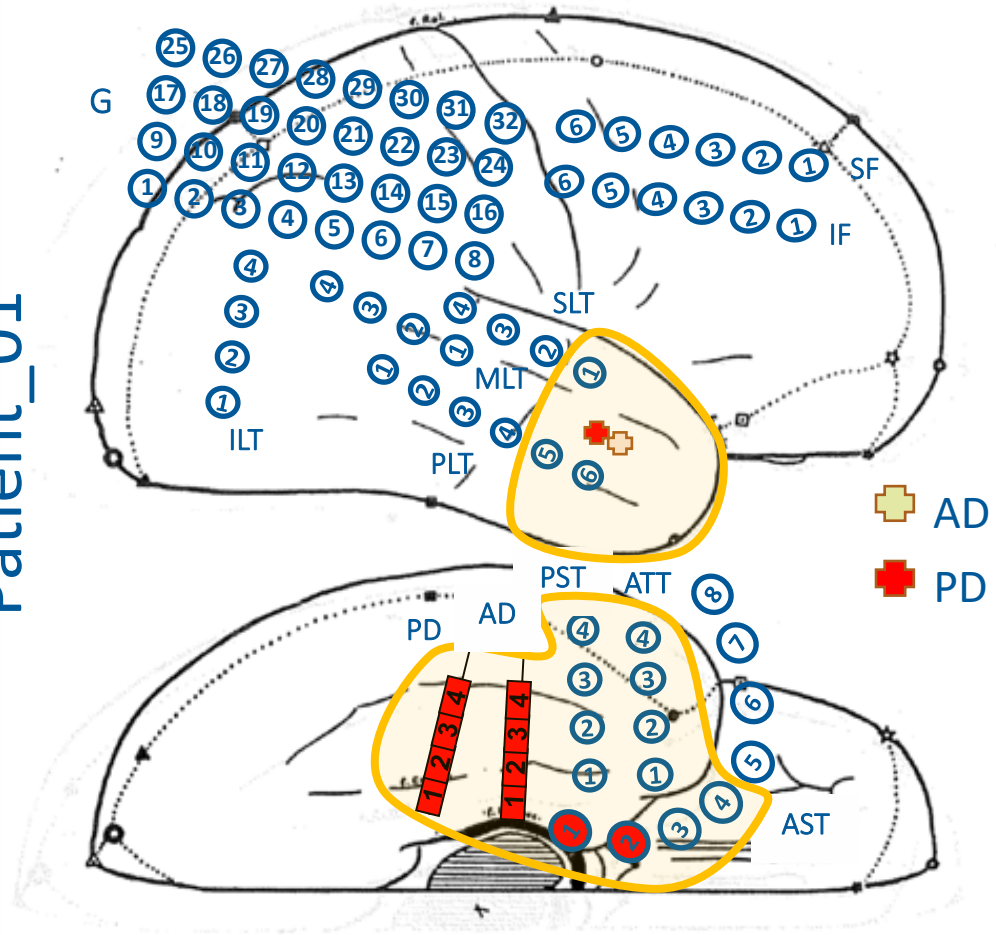
A high-level summary of clinical localization

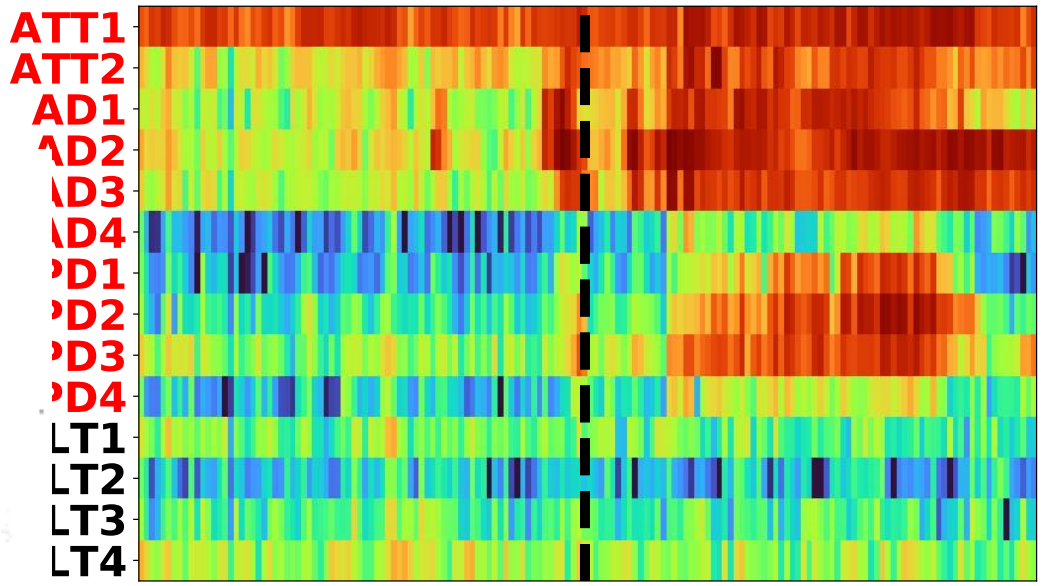


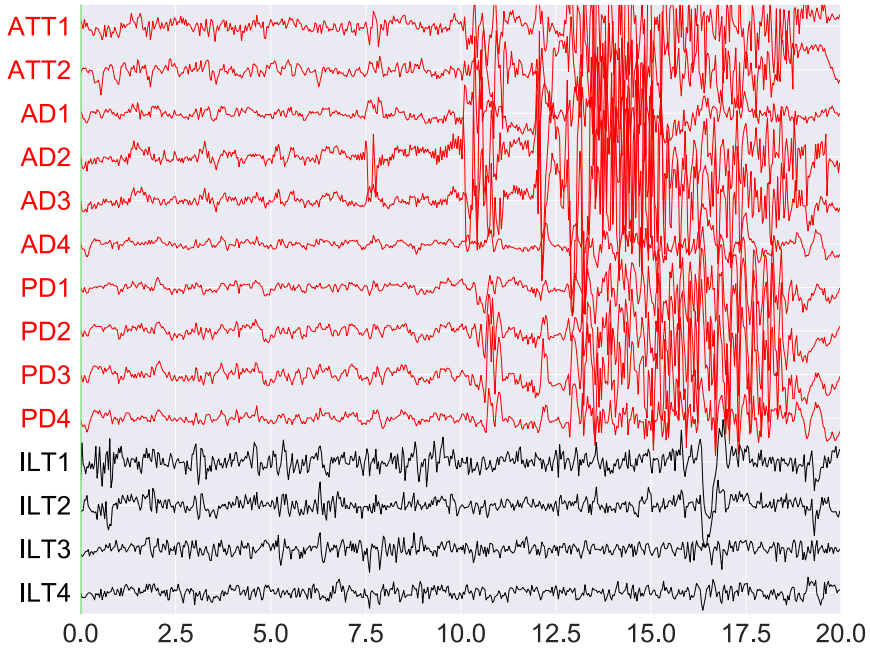

ONE EEG SNAPSHOT
N Electrodes
W_1
W_n
BASELINE FEATURES
SPECTRAL POWER
GRAPH METRICS
(a)
SPATIOTEMPORAL HEATMAP
N Electrodes
$\overline{F}_{soz}$
$\overline{F}_{soz^c}$
W_1
Time
W_n
HFO RATE
(b)
N Electrodes
$\overline{F}_{soz}$
$\overline{F}_{soz^c}$
high
low
HFO Rate


0.0
0.2
0.4
0.6
0.8
1.0
Fragility Metric

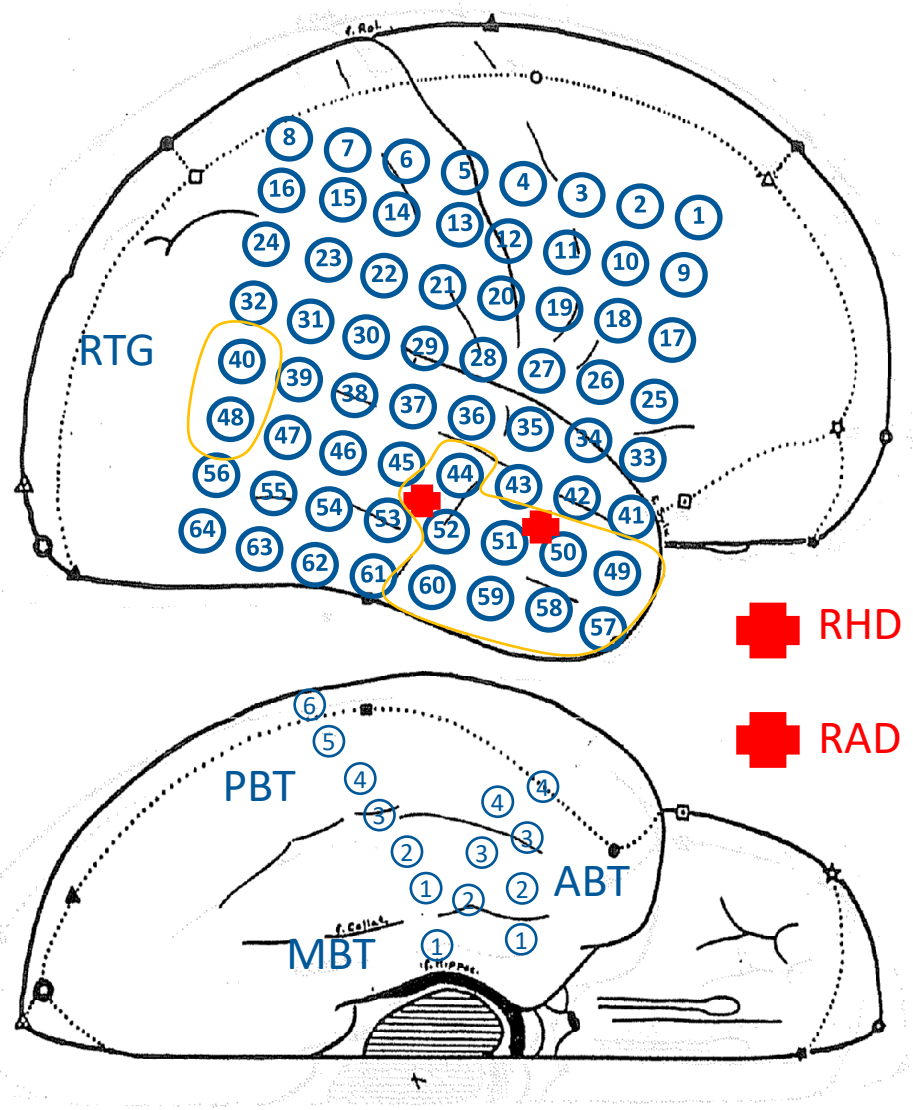
Patient_01

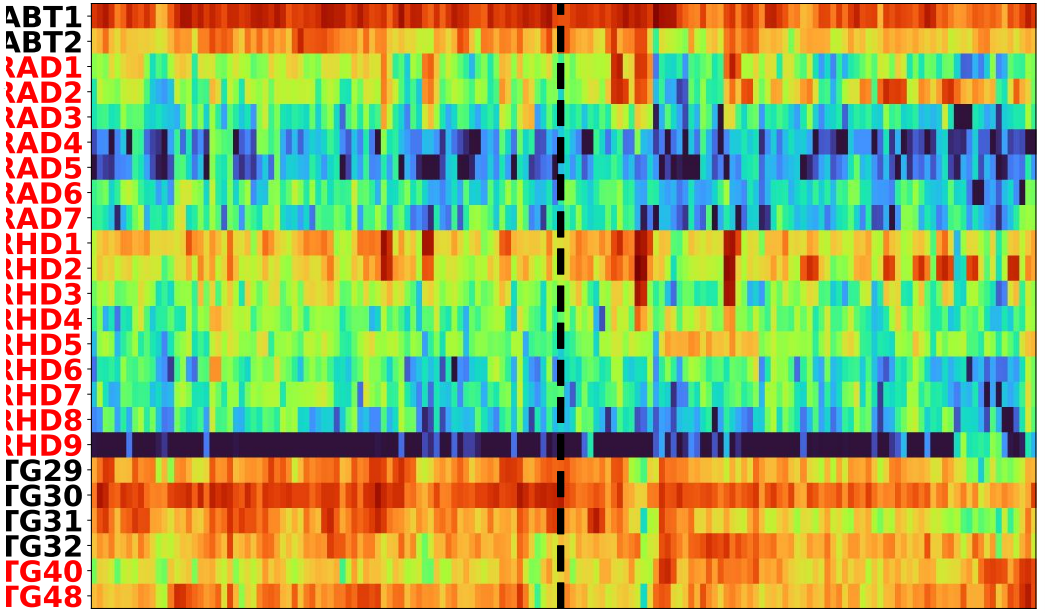

G
SF
IF
SLT
MLT
ILT
PLT
PST
ATT
AST
PD
AD
AD
PD

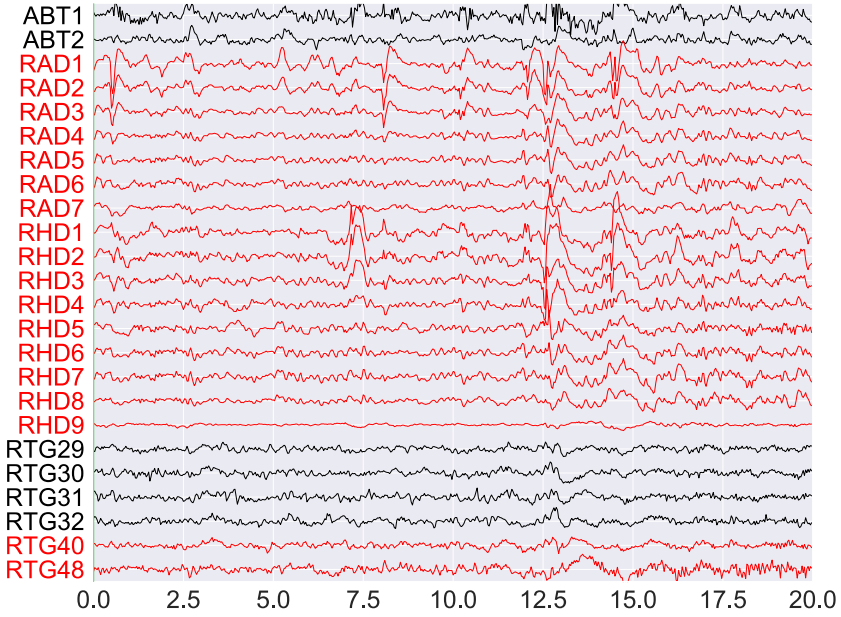

ATT1
ATT2
AD1
AD2
AD3
AD4
PD1
PD2
PD3
PD4
LT1
LT2
LT3
LT4


ATT1
ATT2
AD1
AD2
AD3
AD4
PD1
PD2
PD3
PD4
ILT1
ILT2
ILT3
ILT4
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0

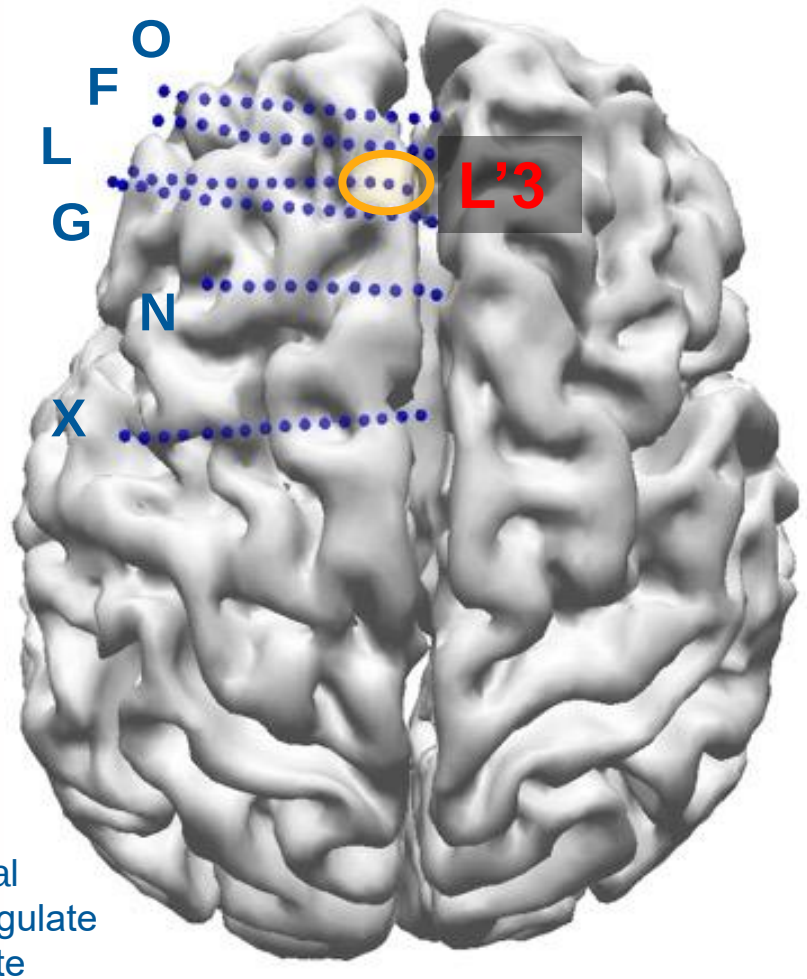
Patient_26

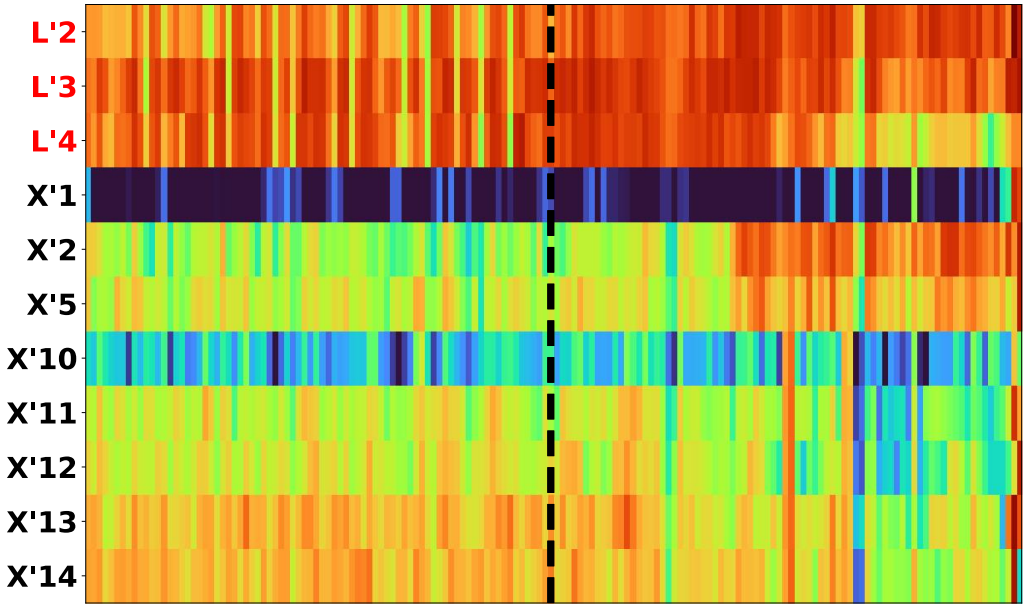

RTG
PBT
ABT
MBT
RHD
RAD

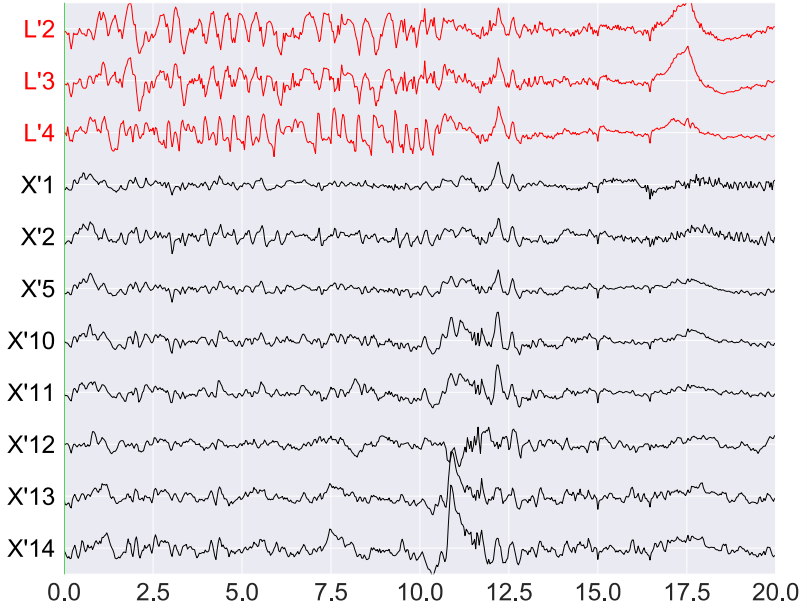

ABT1
ABT2
RAD1
RAD2
RAD3
RAD4
RAD5
RAD6
RAD7
RHD1
RHD2
RHD3
RHD4
RHD5
RHD6
RHD7
RHD8
RHD9
RTG29
RTG30
RTG31
RTG32
RTG40
RTG48


ABT1
ABT2
RAD1
RAD2
RAD3
RAD4
RAD5
RAD6
RAD7
RHD1
RHD2
RHD3
RHD4
RHD5
RHD6
RHD7
RHD8
RHD9
RTG29
RTG30
RTG31
RTG32
RTG40
RTG48
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0

Patient_34

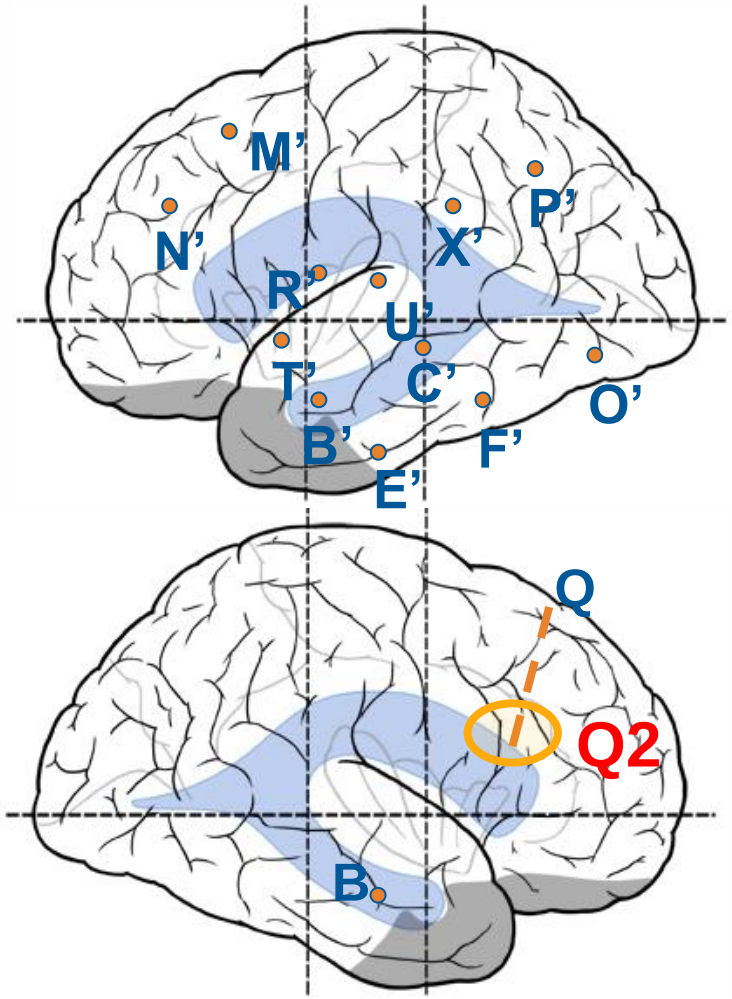


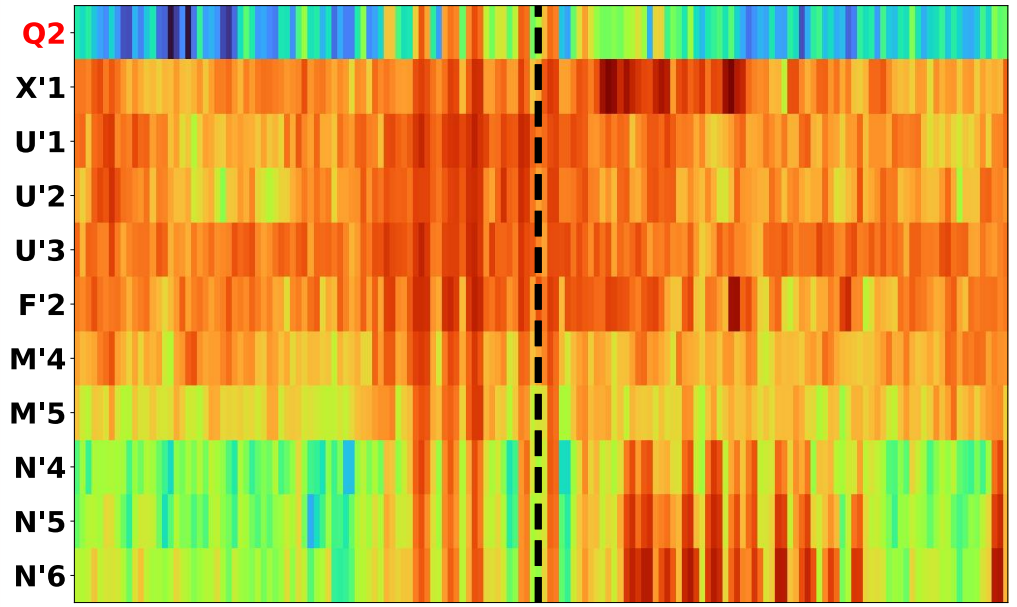


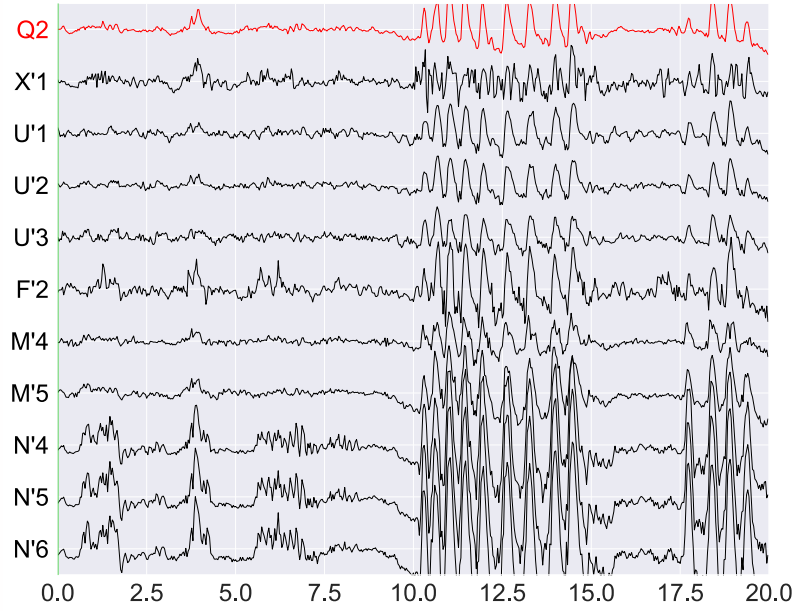


O': OrbitoFrontal
G': Anterior Cingulate
X': Mid Cingulate
F': Fronto polar
L': Lesion?
N': Sup Frontal gyrus

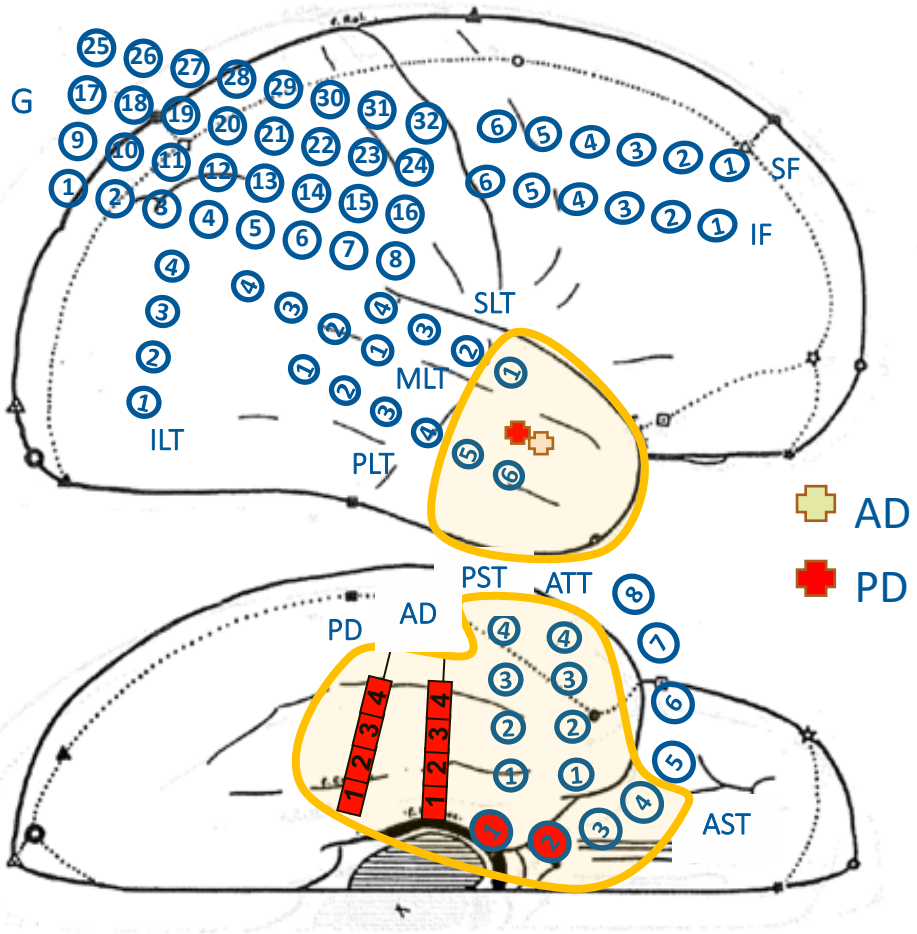
Patient_40

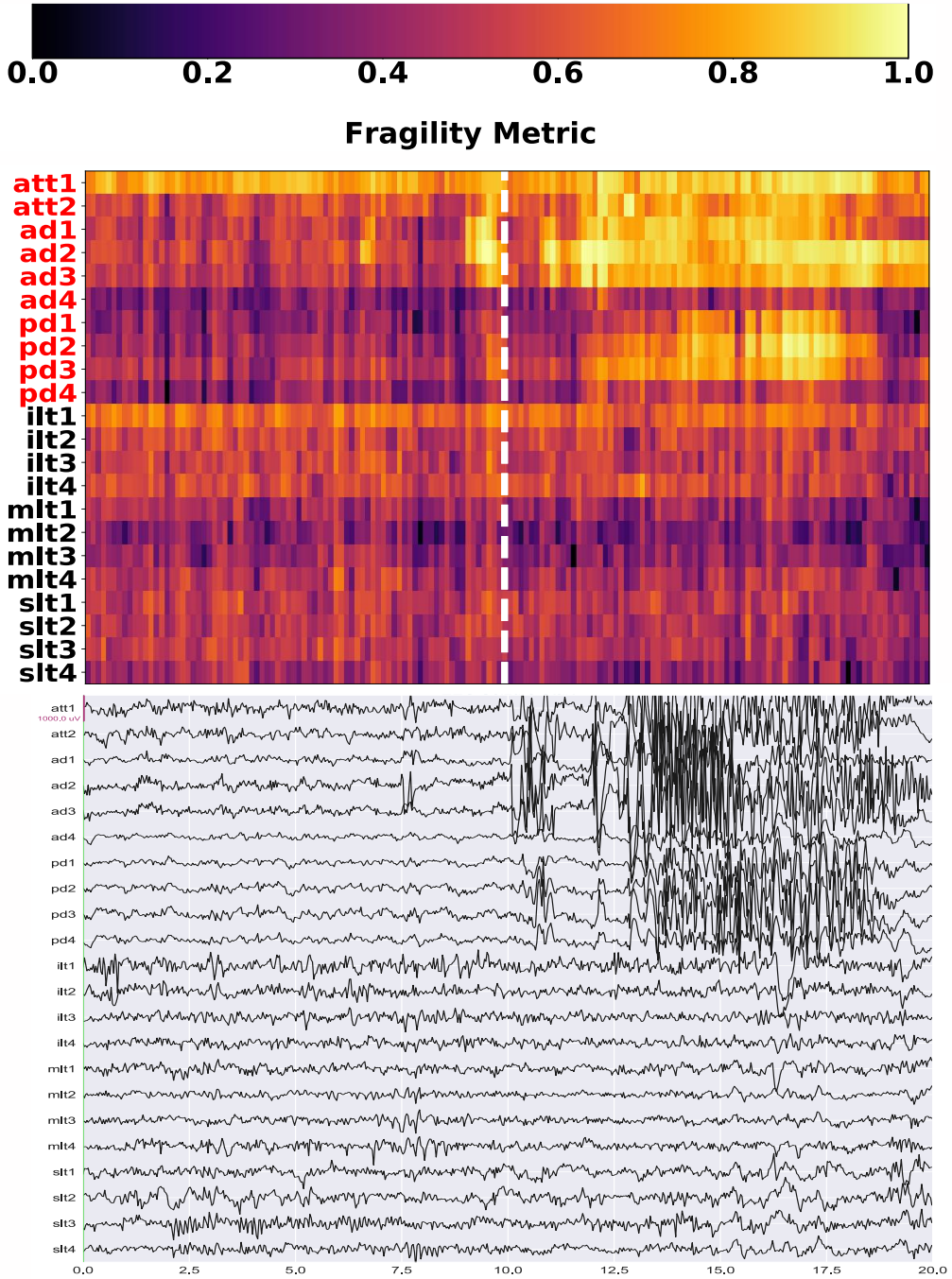

M’
N’
P’
X’
R’
U’
T’
C’
O’
B’
F’
E’
Q
Q2
B


Q2
X'1
U'1
U'2
U'3
F'2
M'4
M'5
N'4
N'5
N'6

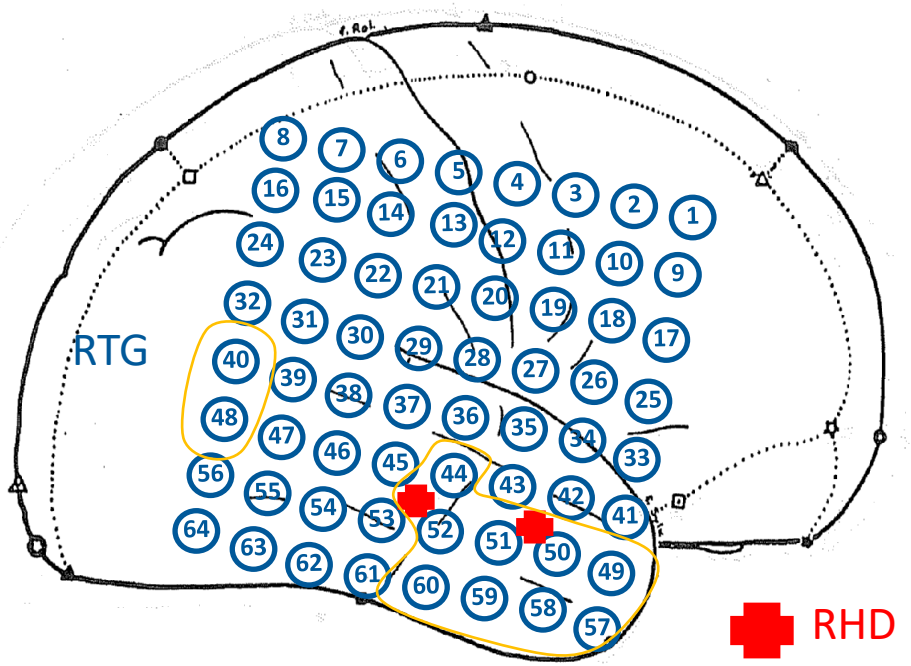

Q2
X'1
U'1
U'2
U'3
F'2
M'4
M'5
N'4
N'5
N'6
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0

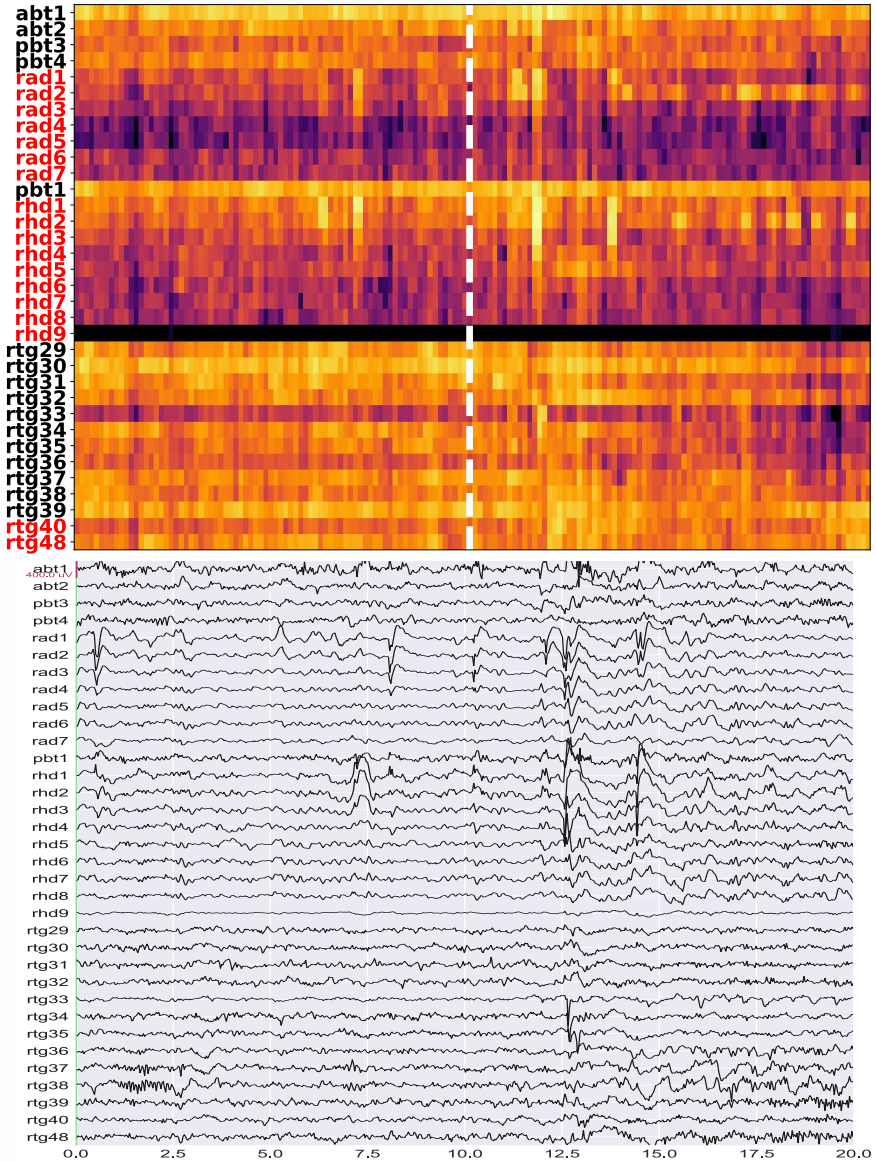
Patient_01


G
SF
IF
SLT
MLT
ILT
PLT
PST
ATT
AST
PD
AD
AD
PD

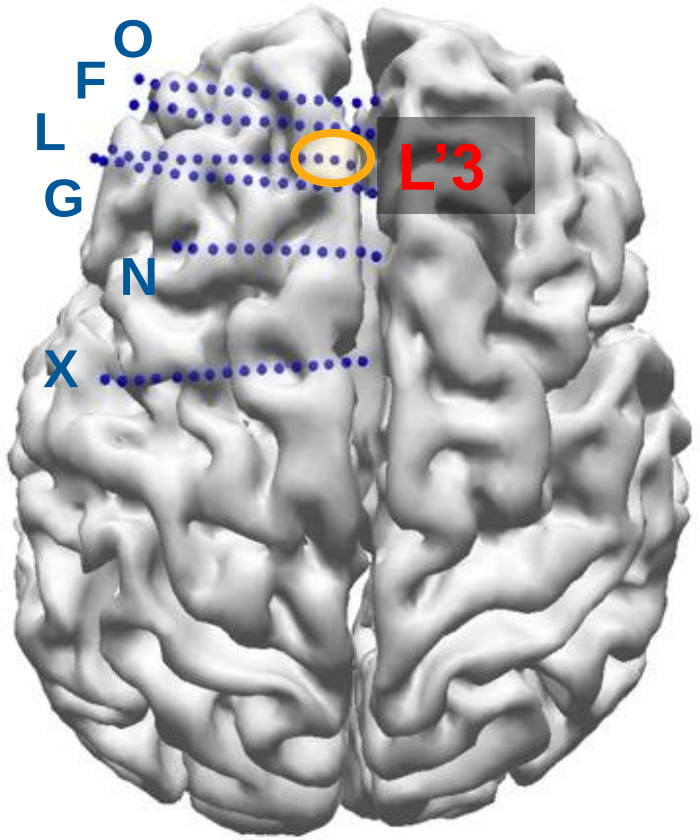

0.0
0.2
0.4
0.6
0.8
1.0
Fragility Metric
att1
att2
ad1
ad2
ad3
ad4
pd1
pd2
pd3
pd4
ilt1
ilt2
ilt3
ilt4
mlt1
mlt2
mlt3
mlt4
slt1
slt2
slt3
slt4
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
Time (secs)

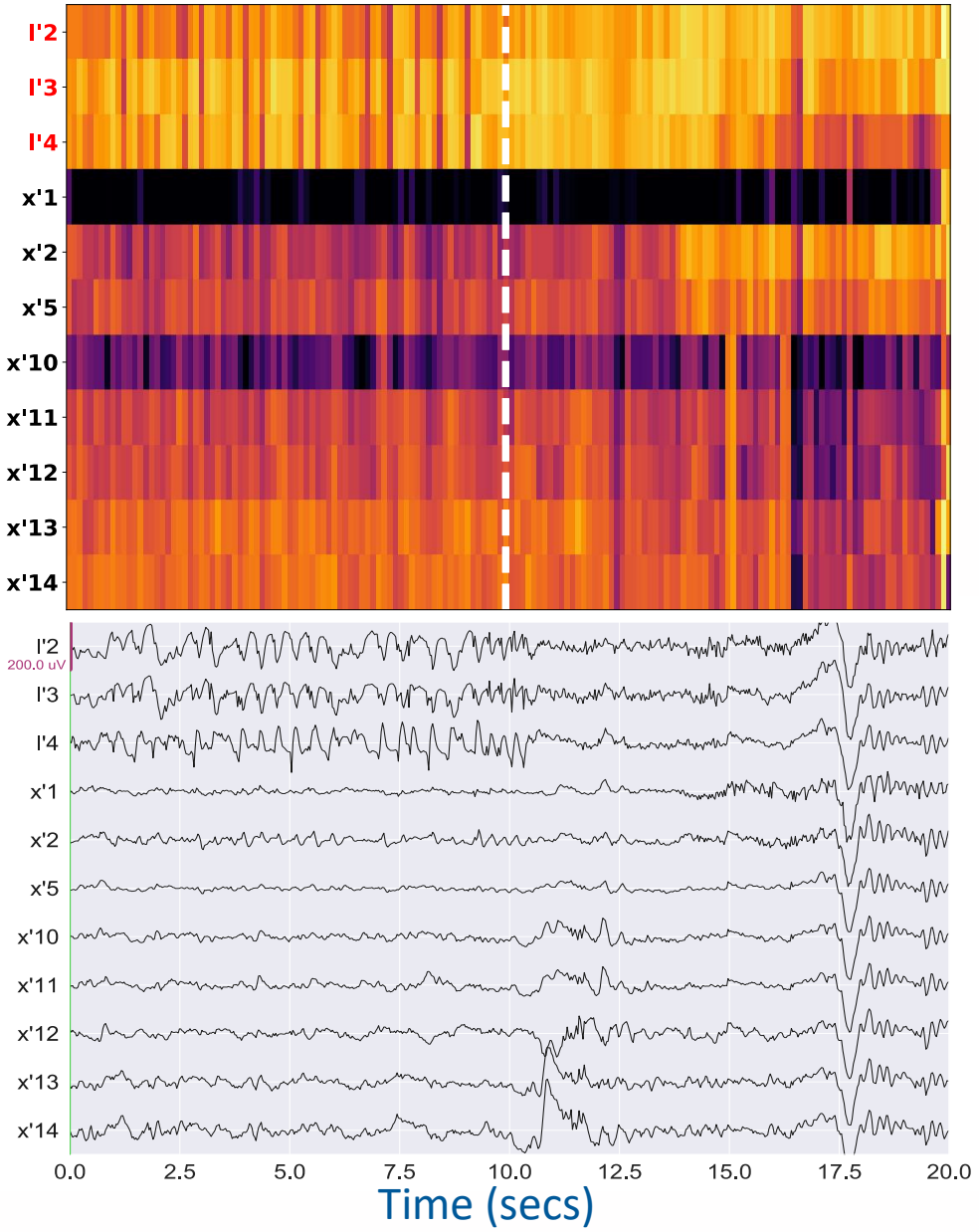
Patient_26


RTG
RHD
RAD
PBT
ABT
MBT


abt1
abt2
pbt3
pbt4
rad1
rad2
rad3
rad4
rad5
rad6
rad7
pbt1
rhd1
rhd2
rhd3
rhd4
rhd5
rhd6
rhd7
rhd8
rhd9
rtg29
rtg30
rtg31
rtg32
rtg33
rtg34
rtg35
rtg36
rtg37
rtg38
rtg39
rtg40
rtg48
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
Time (secs)

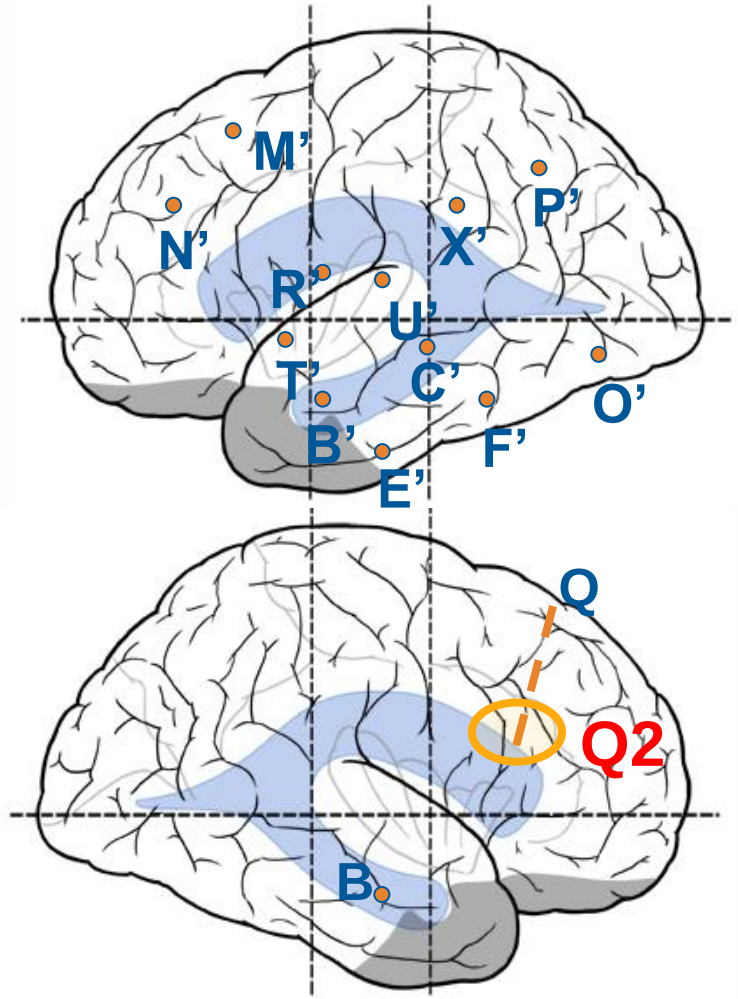
Patient_34

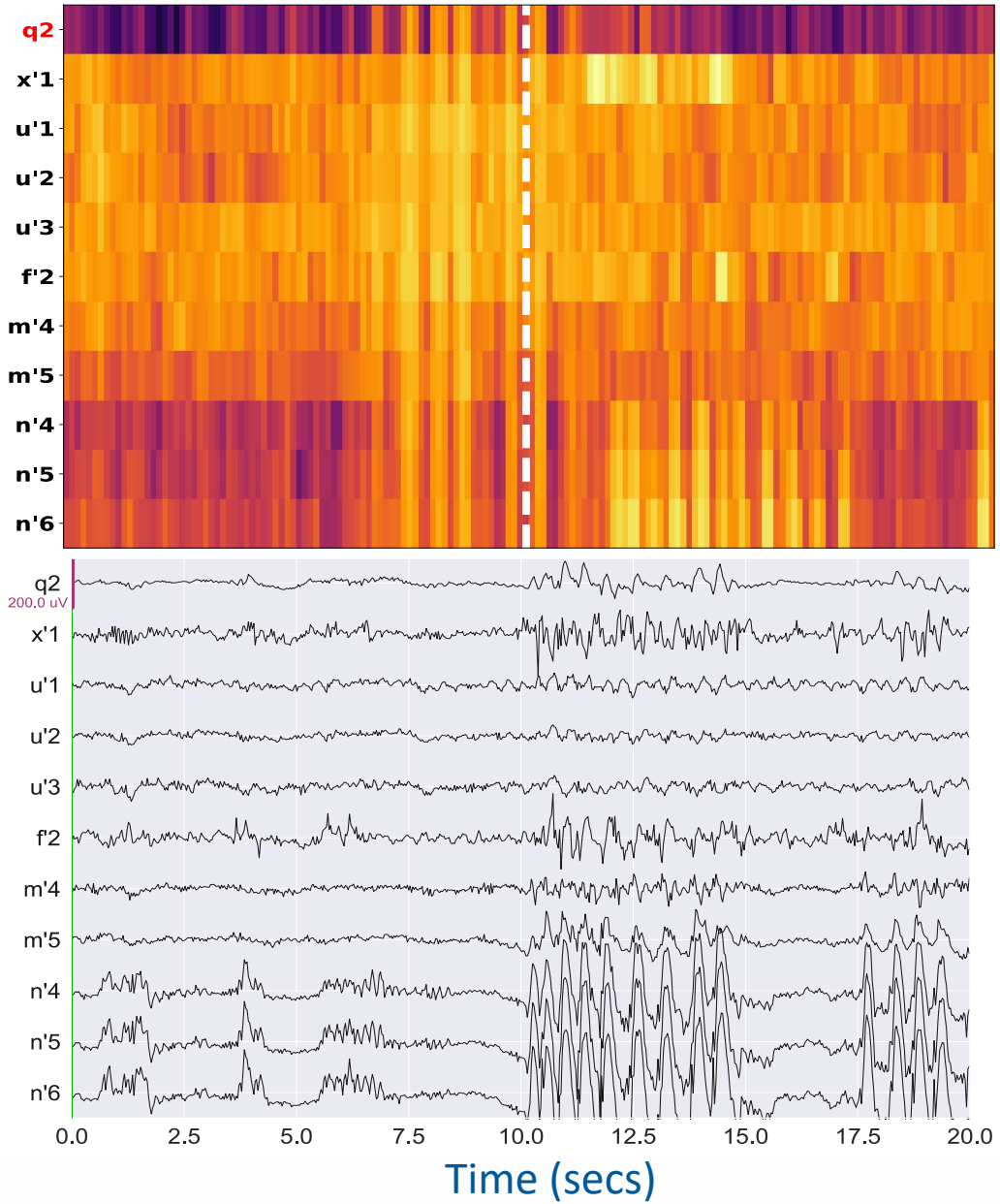




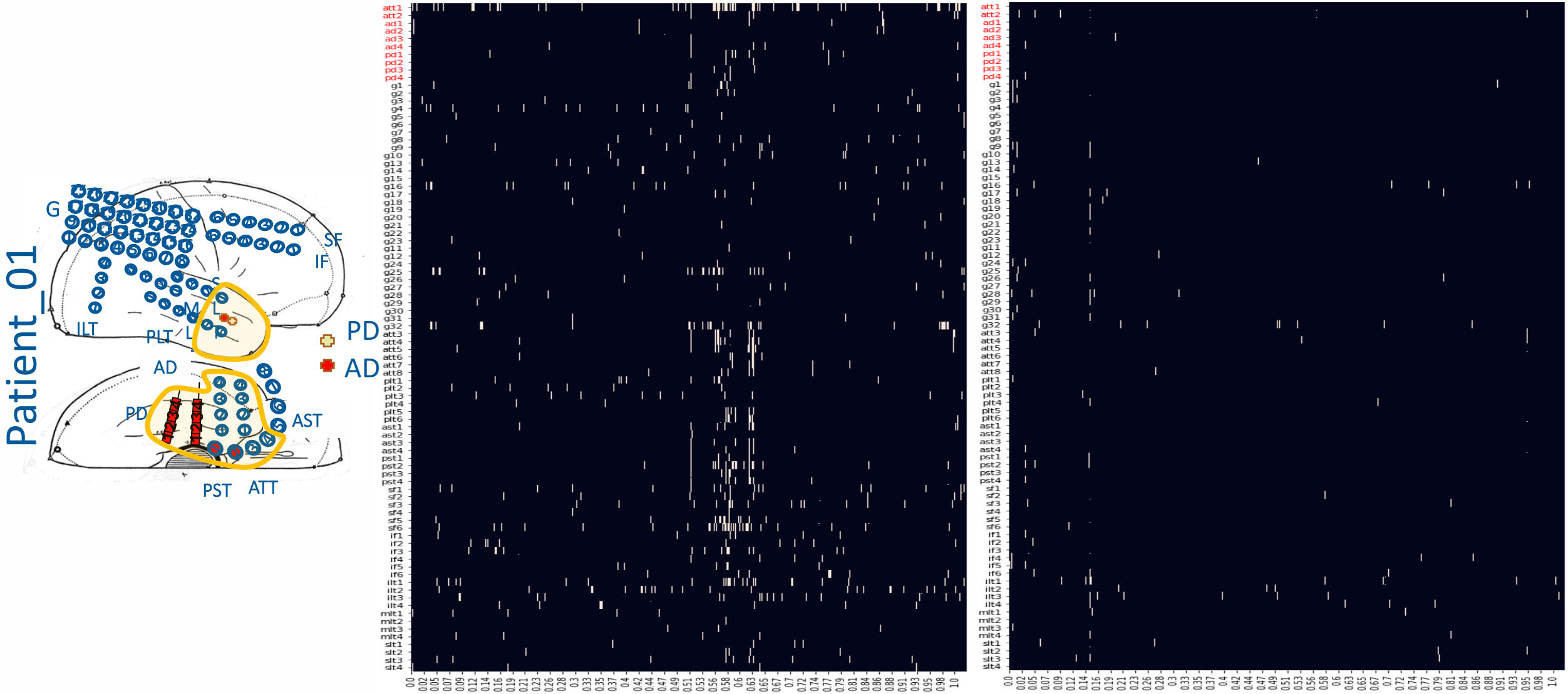
O': OrbitoFrontal
G': Anterior Cingulate
X': Mid Cingulate
F': Fronto polar
L': Lesion?
N': Sup Frontal gyrus

Patient_40

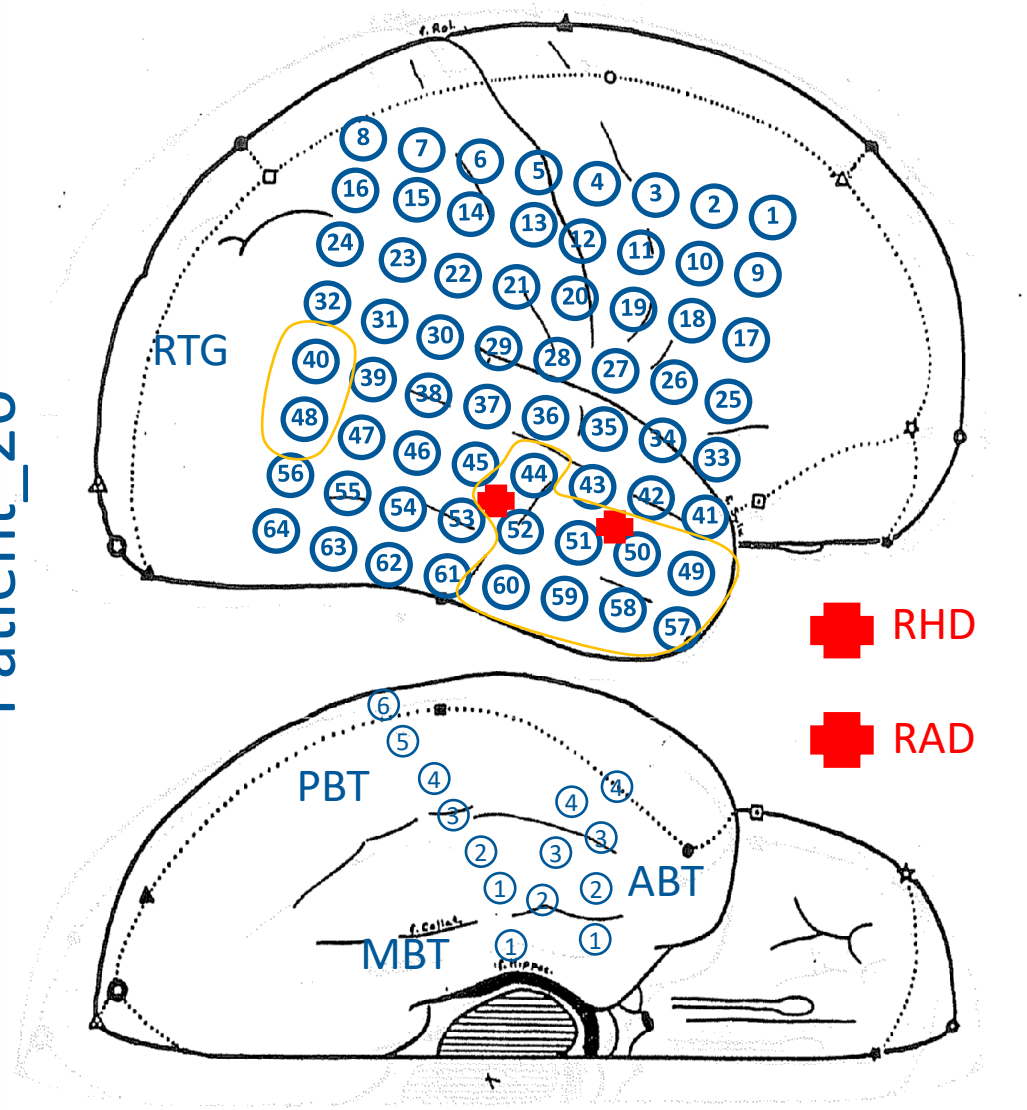

M’
N’
R’
X’
P’
U’
T’
C’
O’
B’
F’
E’
Q
Q2
B

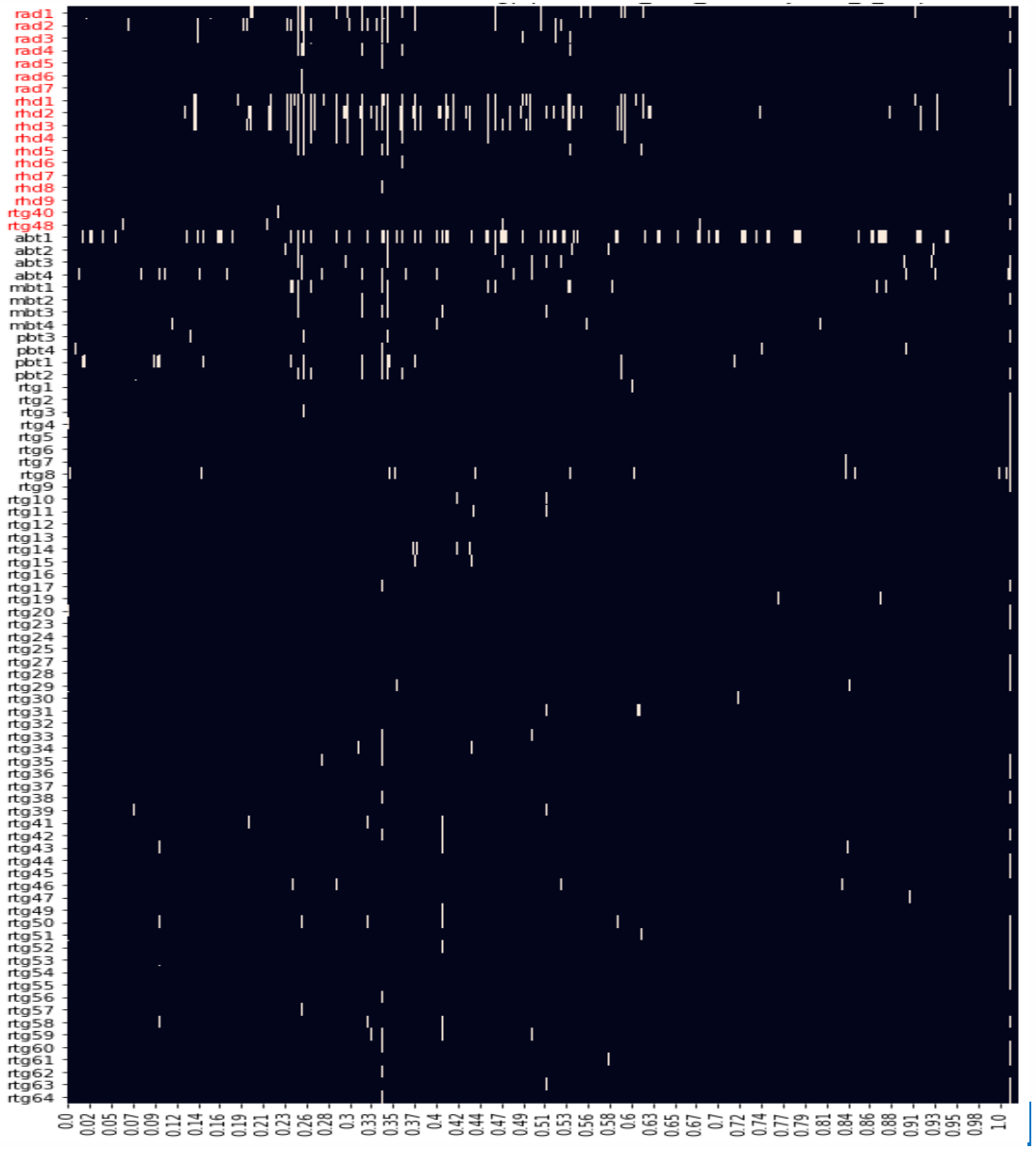

q2
x'1
u'1
u'2
u'3
f'2
m'4
m'5
n'4
n'5
n'6
200.0 uV
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
Time (secs)

HFO rate of successful patient outcome with lesion



Patient_26


RTG
RHD
RAD
PBT
ABT
MBT


rad1
rad2
rad3
rad4
rad5
rad6
rad7
rhd1
rhd2
rhd3
rhd4
rhd5
rhd6
rhd7
rhd8
rhd9
rtg40
rtg48
abt1
abt2
abt3
abt4
mbt1
mbt2
mbt3
mbt4
pbt3
pbt4
pbt1
pbt2
rtg1
rtg2
rtg3
rtg4
rtg5
rtg6
rtg7
rtg8
rtg9
rtg10
rtg11
rtg12
rtg13
rtg14
rtg15
rtg16
rtg17
rtg19
rtg20
rtg23
rtg24
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rtg28
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rtg39
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rtg42
rtg43
rtg44
rtg45
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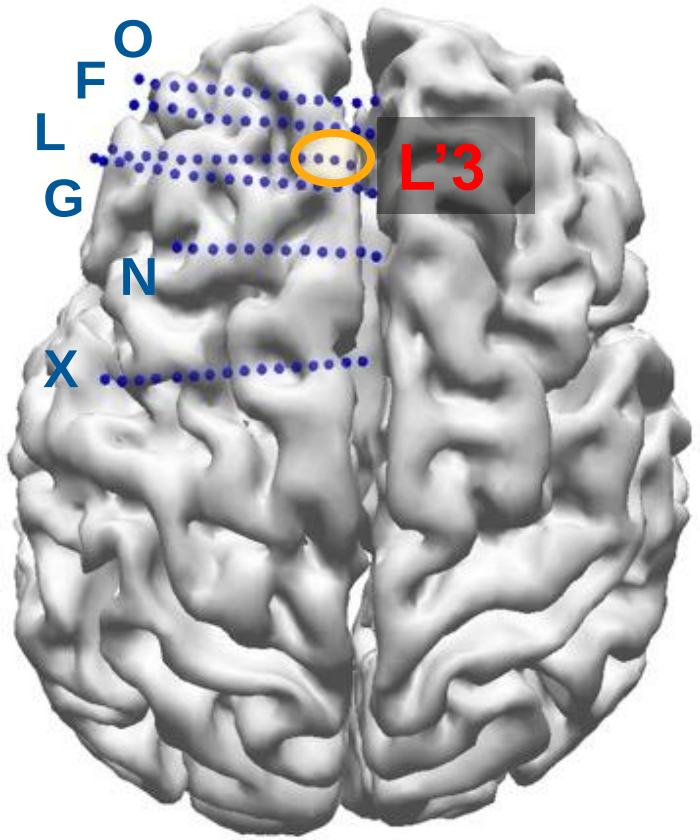
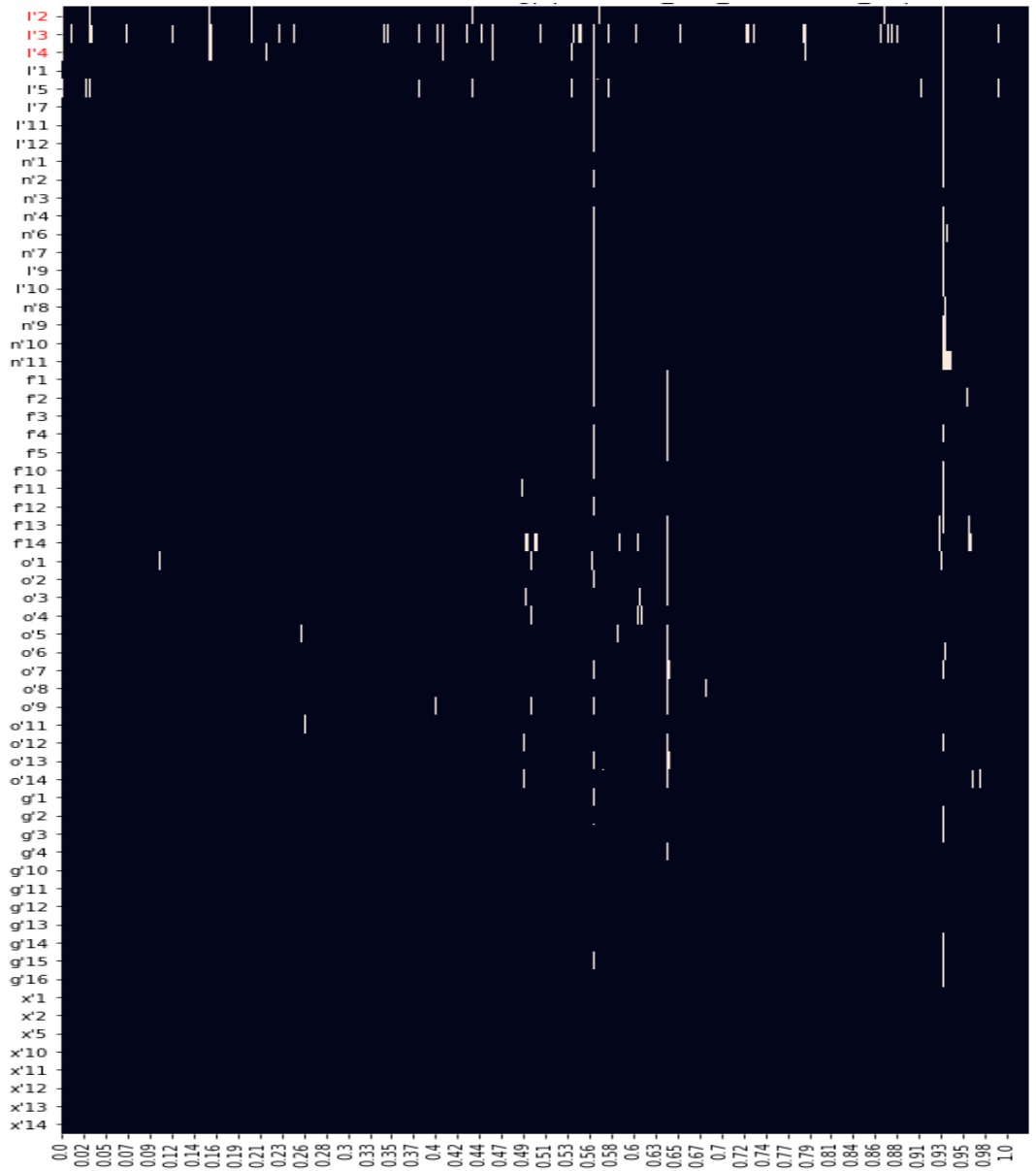
rtg50
rtg51
rtg52
rtg53
rtg54
rtg55
rtg56
rtg57
rtg58
rtg59
rtg60
rtg61
rtg62
rtg63
rtg64
0.0
0.02
0.05
0.07
0.09
0.12
0.14
0.16
0.19
0.21
0.23
0.26
0.28
0.3
0.33
0.35
0.37
0.4
0.42
0.44
0.47
0.49
0.51
0.53
0.56
0.58
0.6
0.63
0.65
0.67
0.7
0.72
0.74
0.77
0.79
0.81
0.84
0.86
0.88
0.91
0.93
0.95
0.98
1.0

Patient_34





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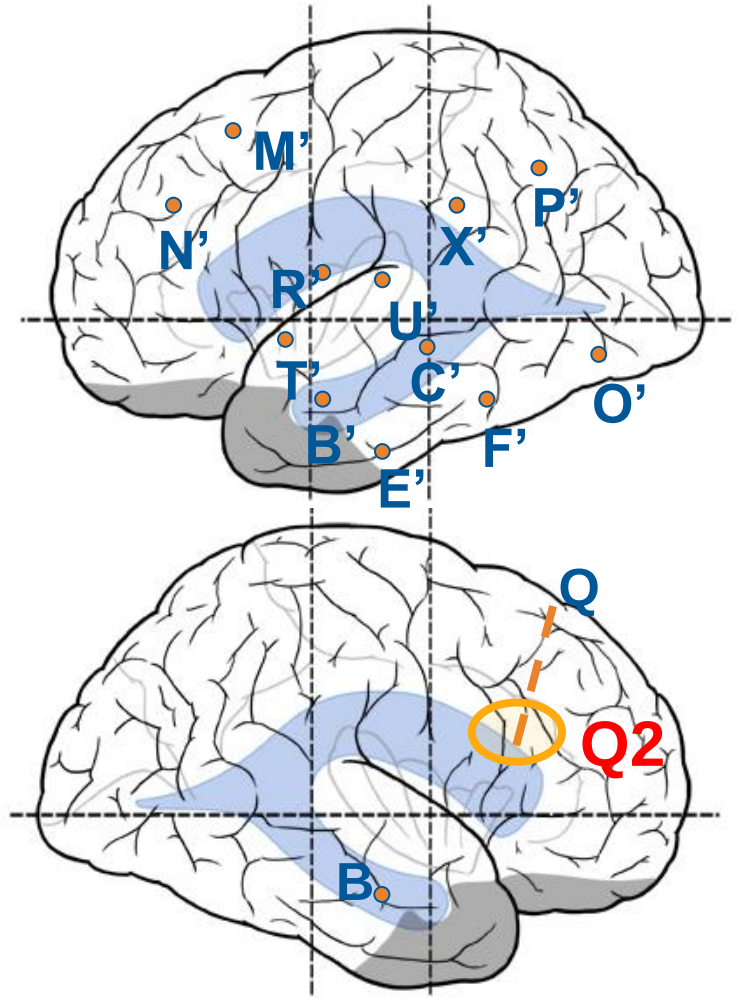
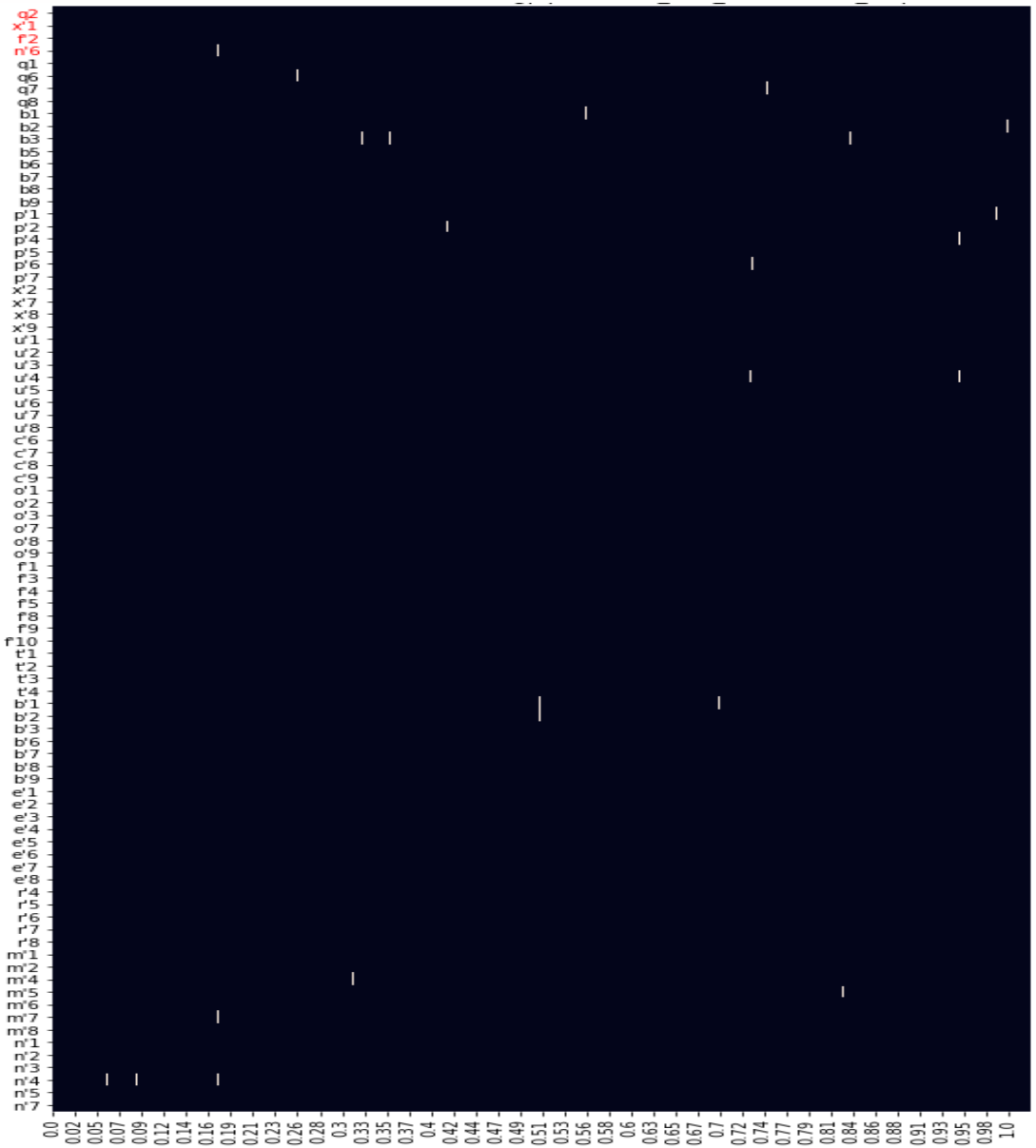
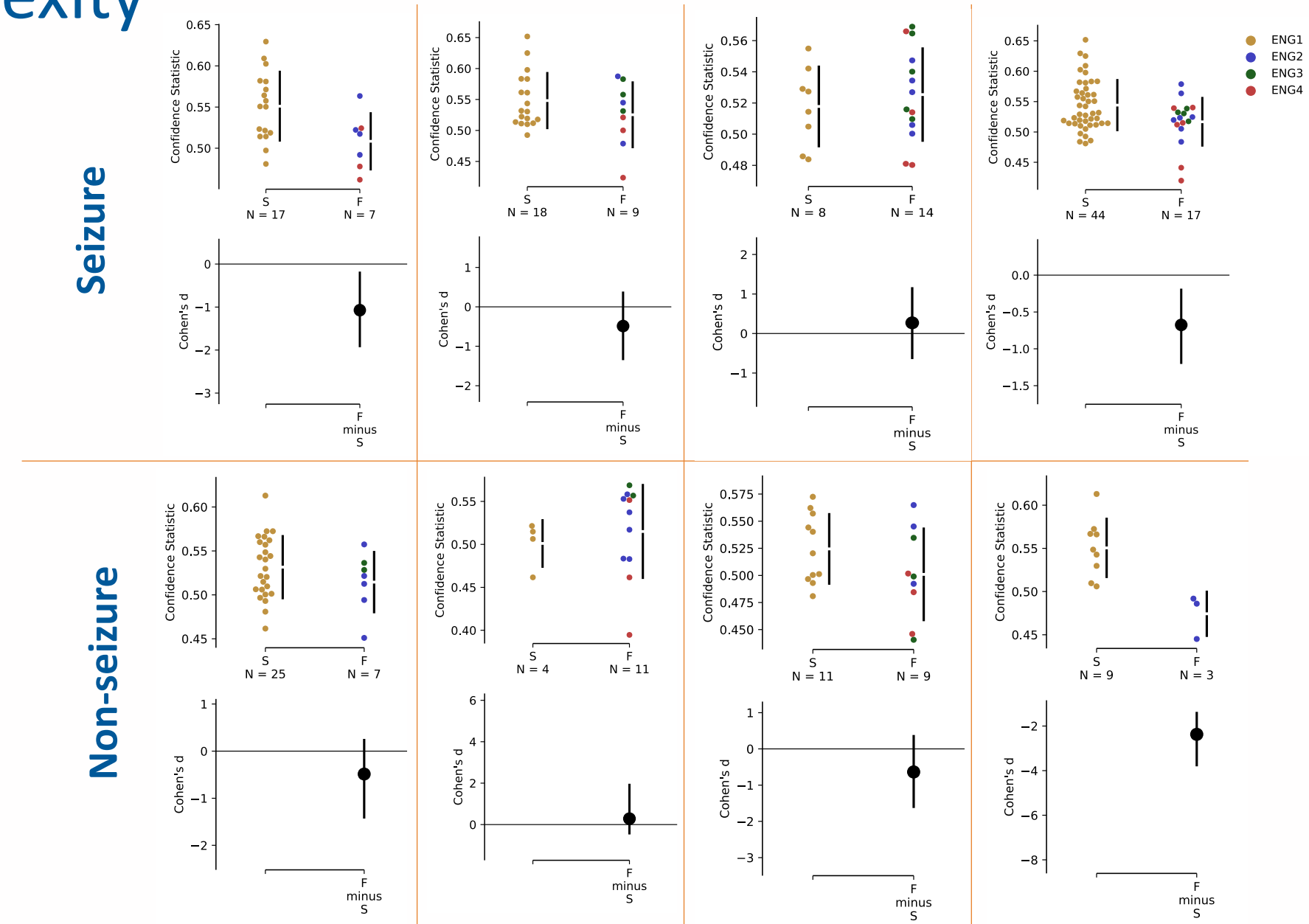
F': Fronto polar
L': Lesion?
N': Sup Frontal gyrus

Patient_40





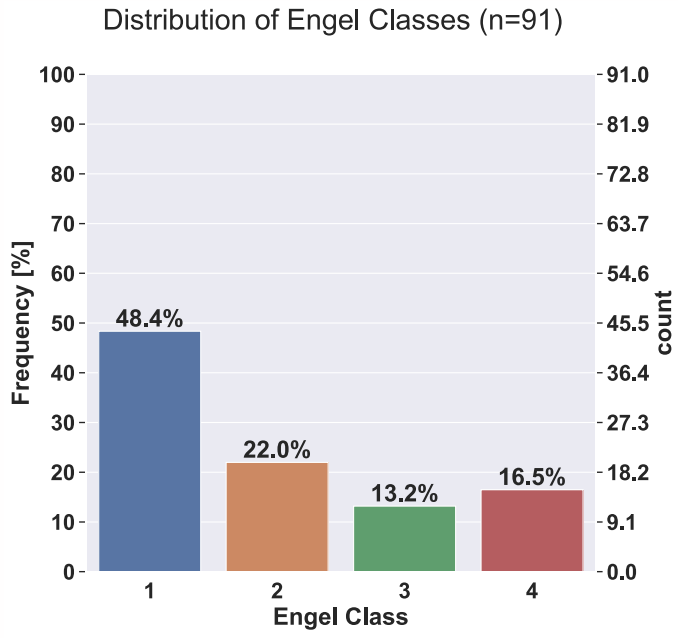
Effect size differences between outcomes within a complexity

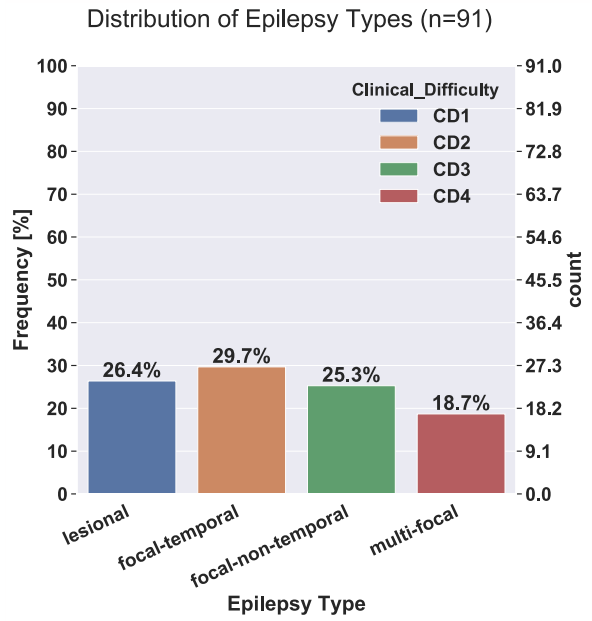


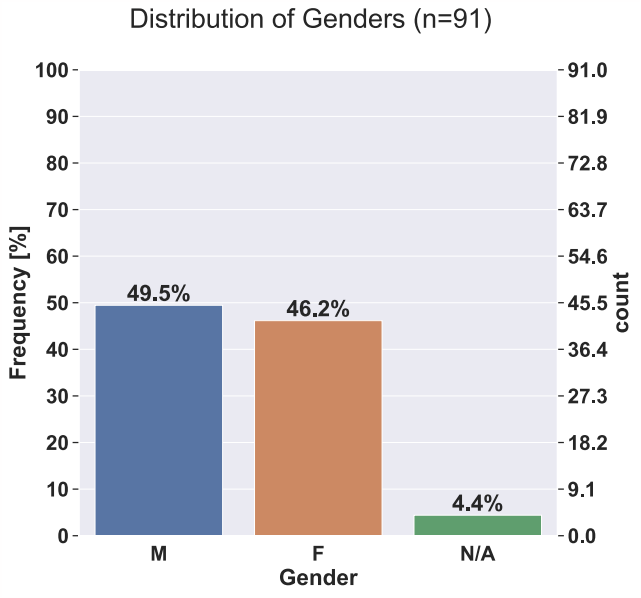
Clinical population summary

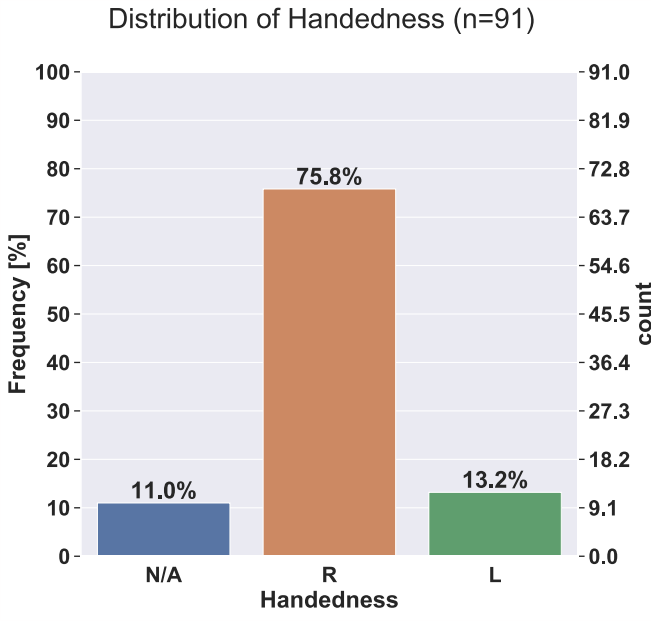
Center	UMH	NIH	UMMC	JHH	CC	Total
# Ictal Patients	5	14	7	4	61	91

Center	UMH	NIH	UMMC	JHH	CC	Total
# Interictal Patients	5	3	0	2	45	55



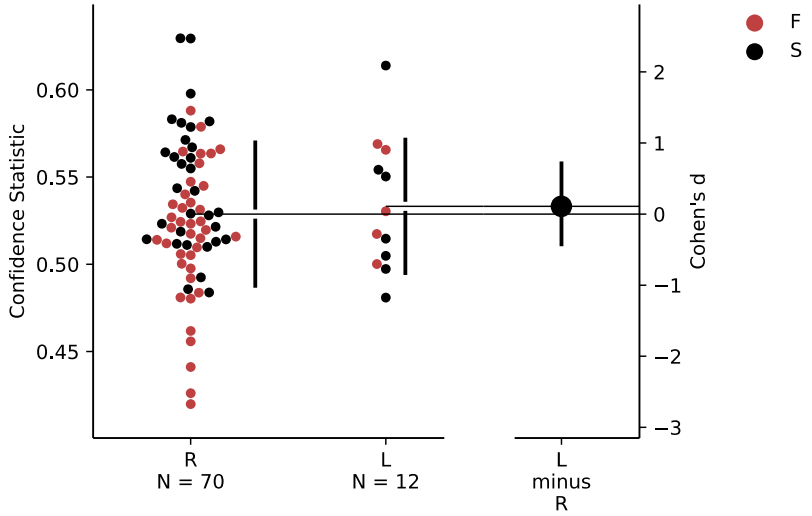




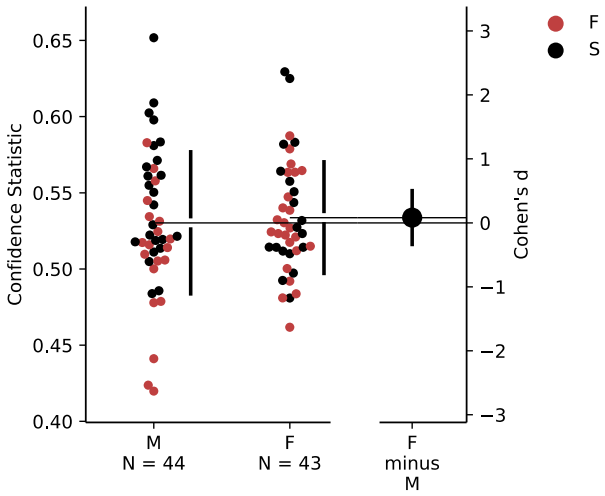


Does it matter across factors that may not vary with epilepsy?

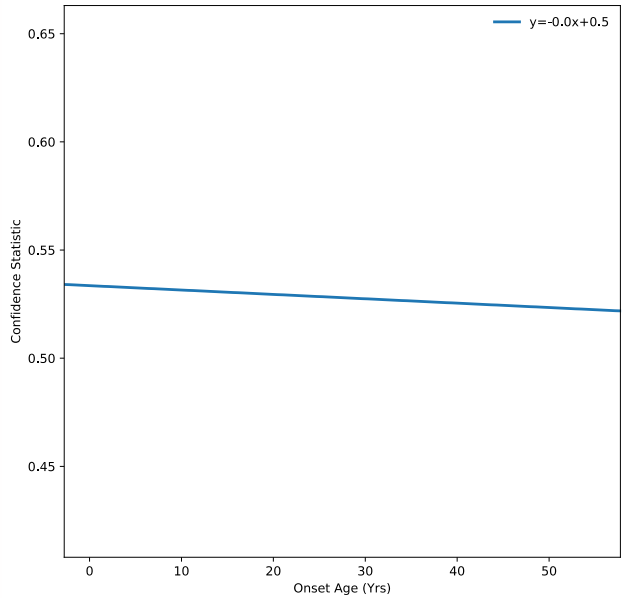
Handedness



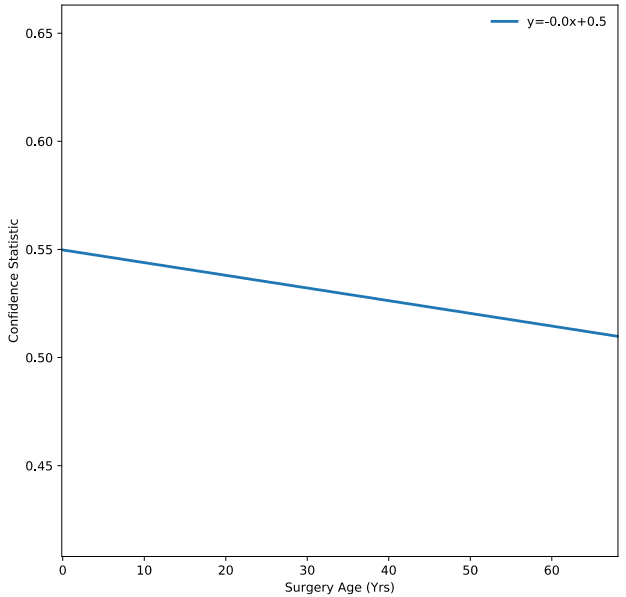
Gender



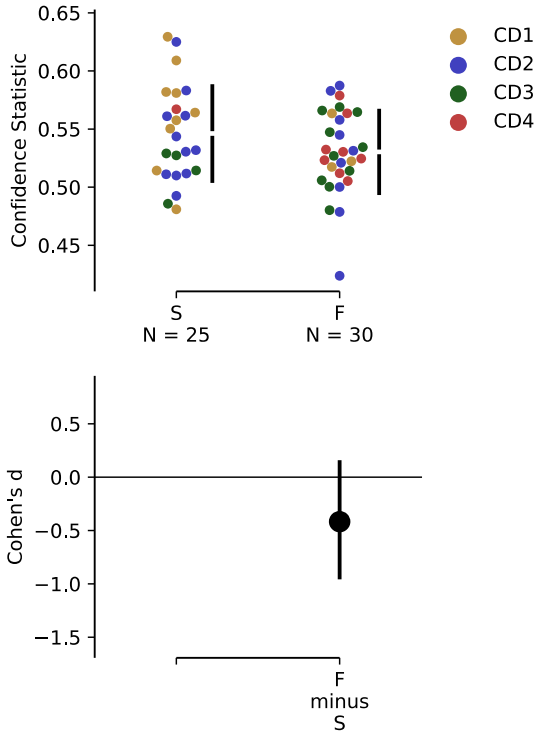
Onset Age

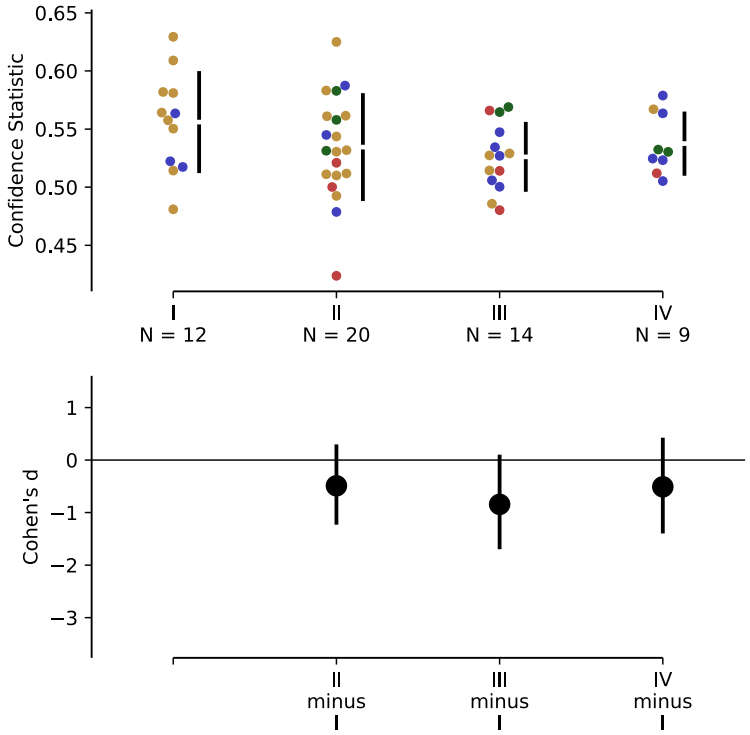


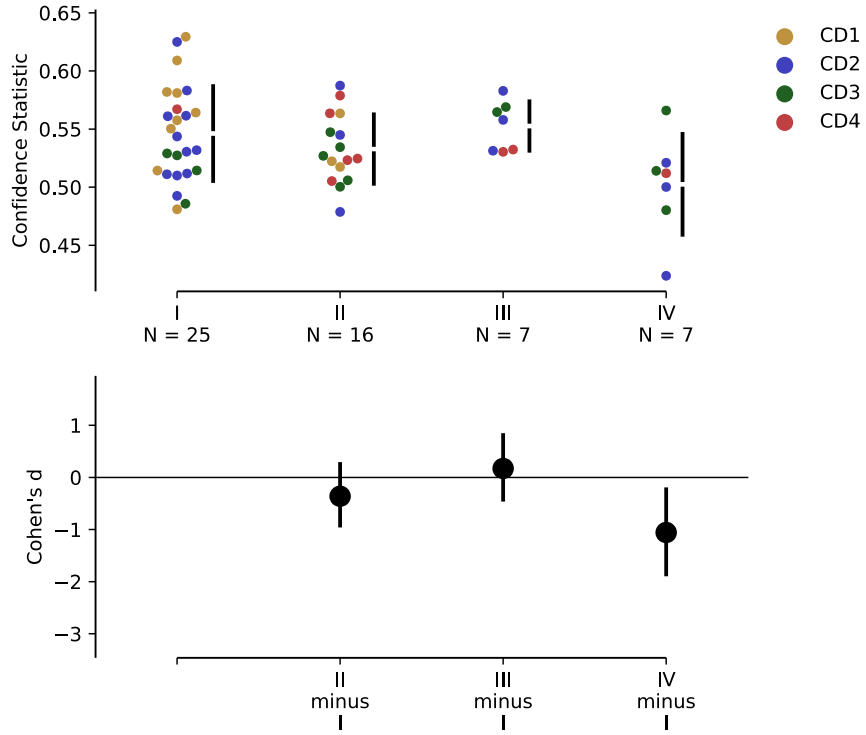
Surgery Age



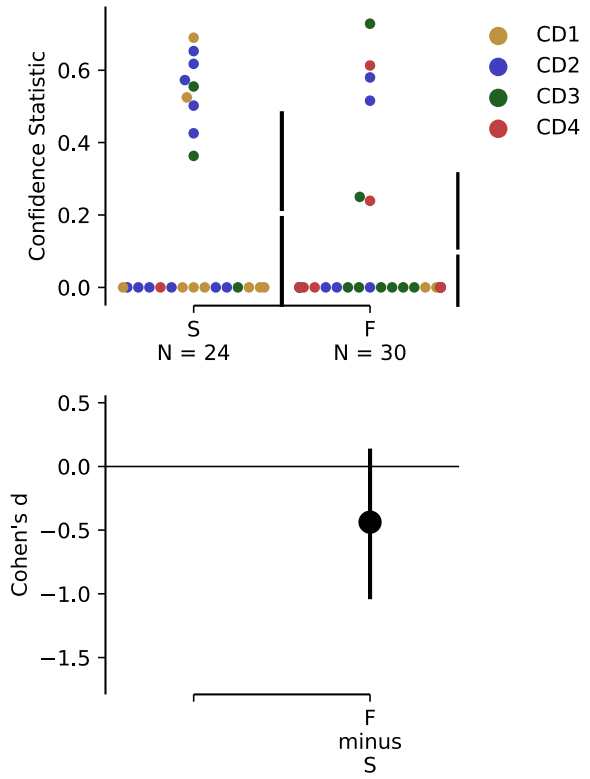
Ictal matched results with interictal data

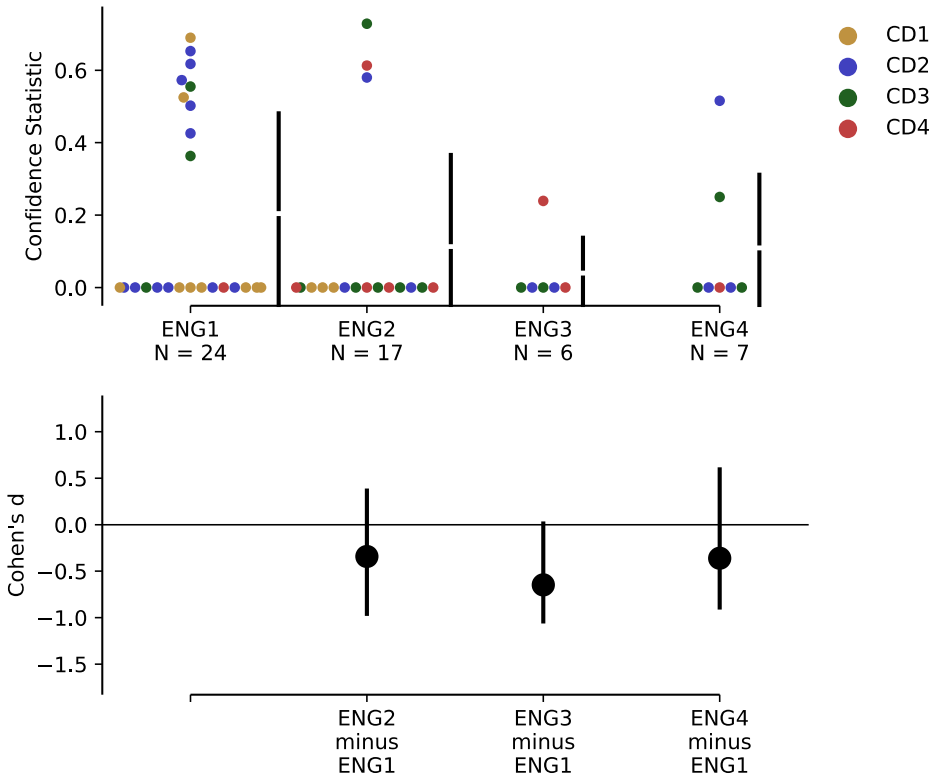






Interictal results using HFOs

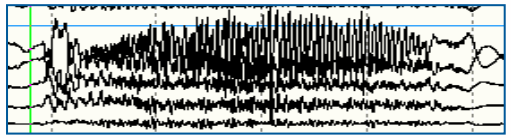


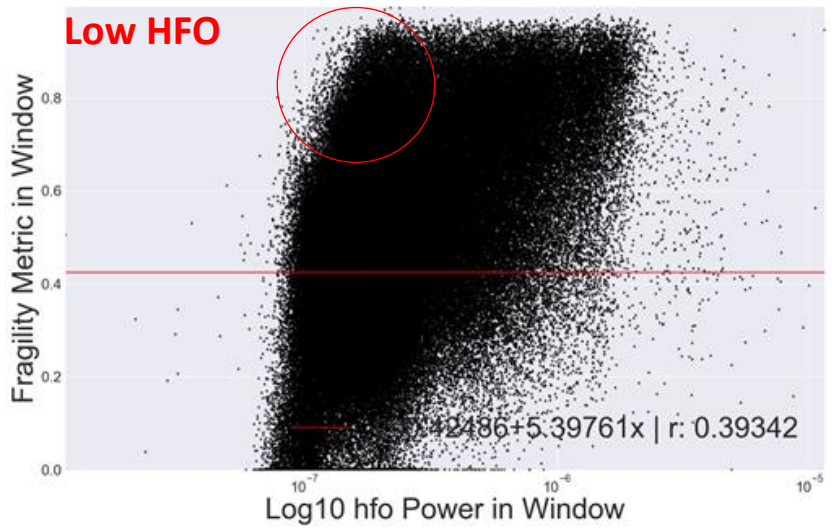


DOES FRAGILITY ADD PREDICTIVE POWER?

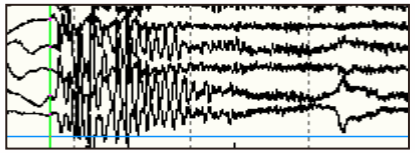
FRAGILITY IS NOT THE SAME AS CLINICAL EEG SIGNATURES

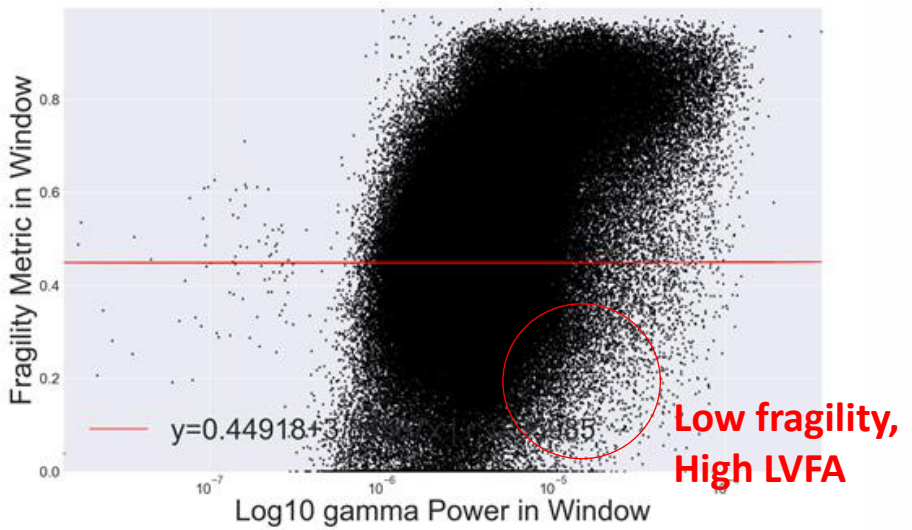
High Frequency Oscillations (HFOs)





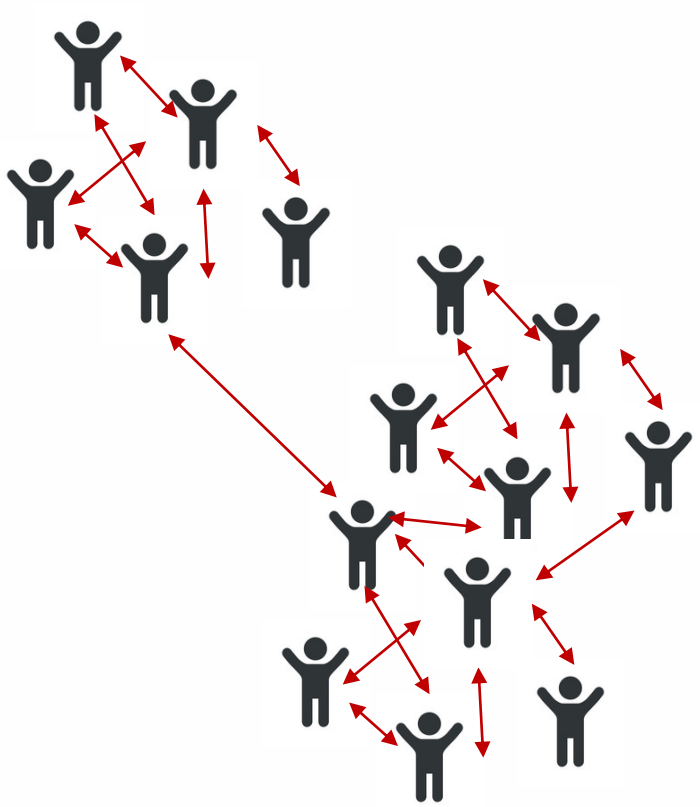
Low Voltage Fast Activity (LVFA)



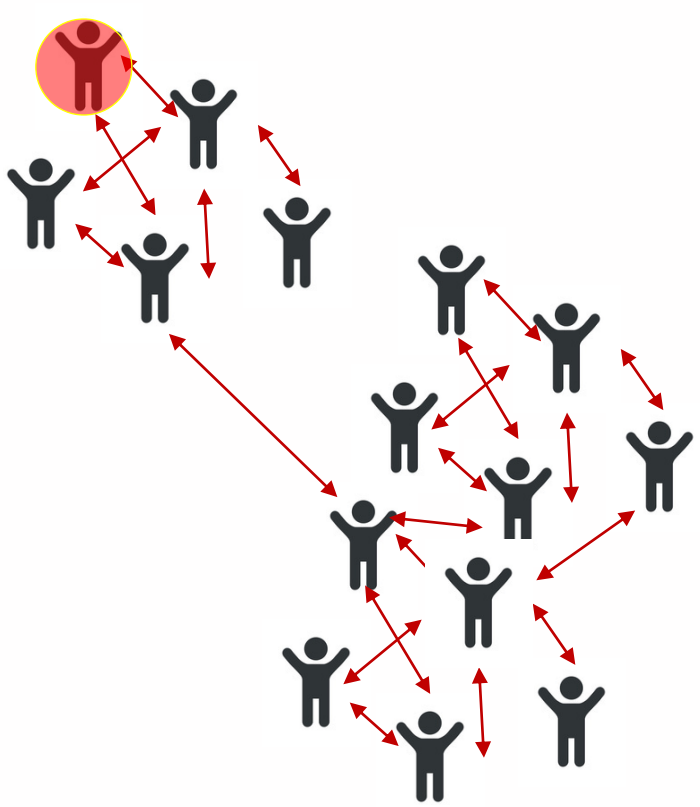


Technology

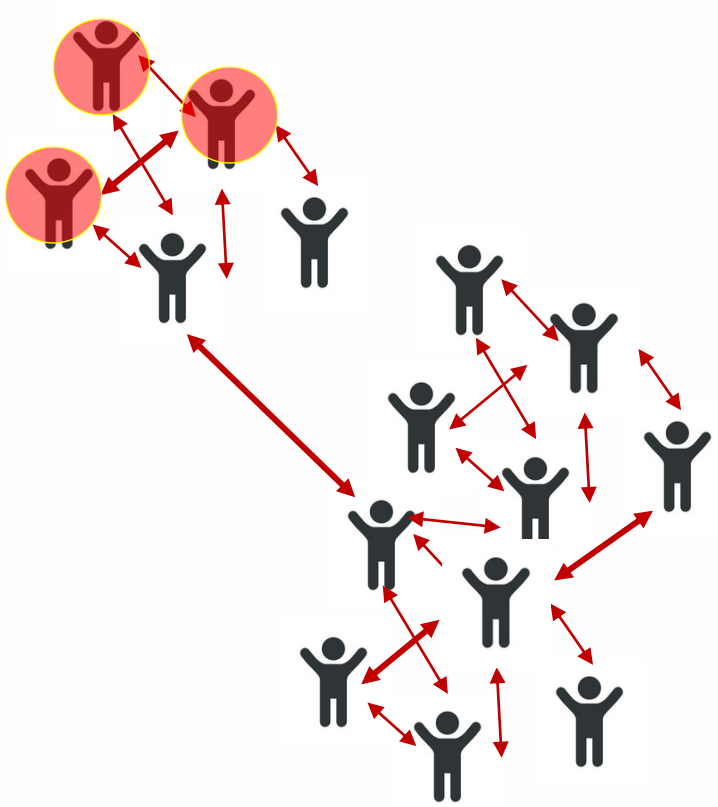
Node 1

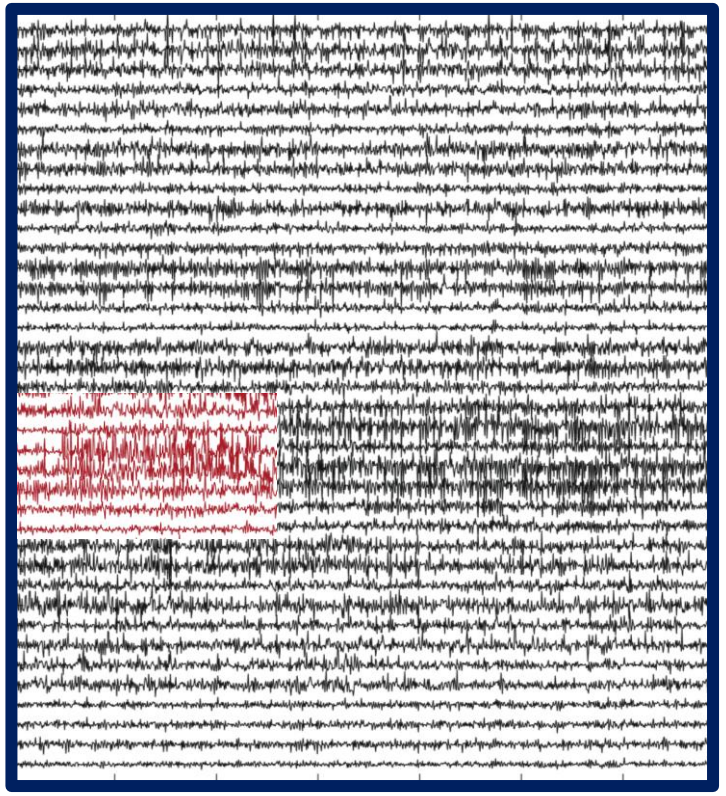


Node 1

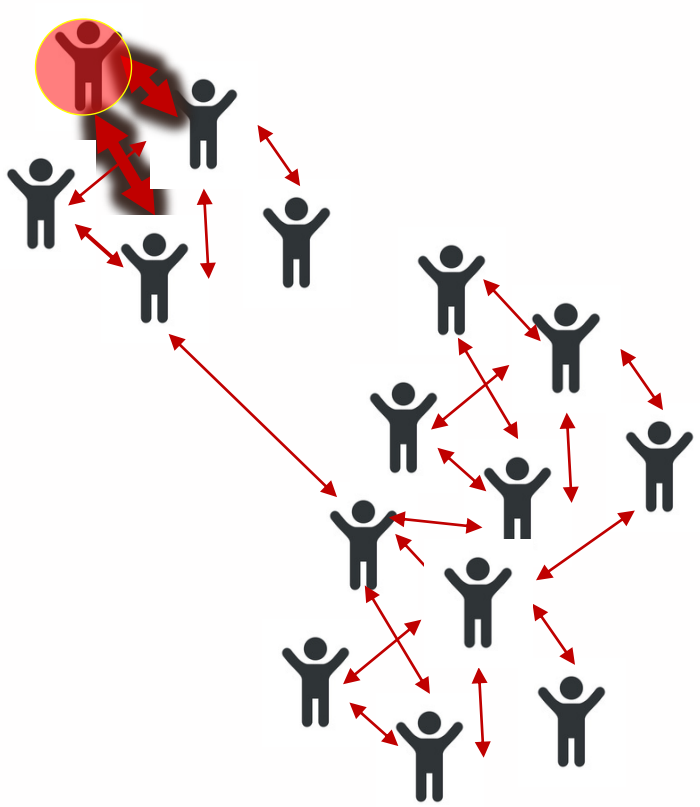


Node 1

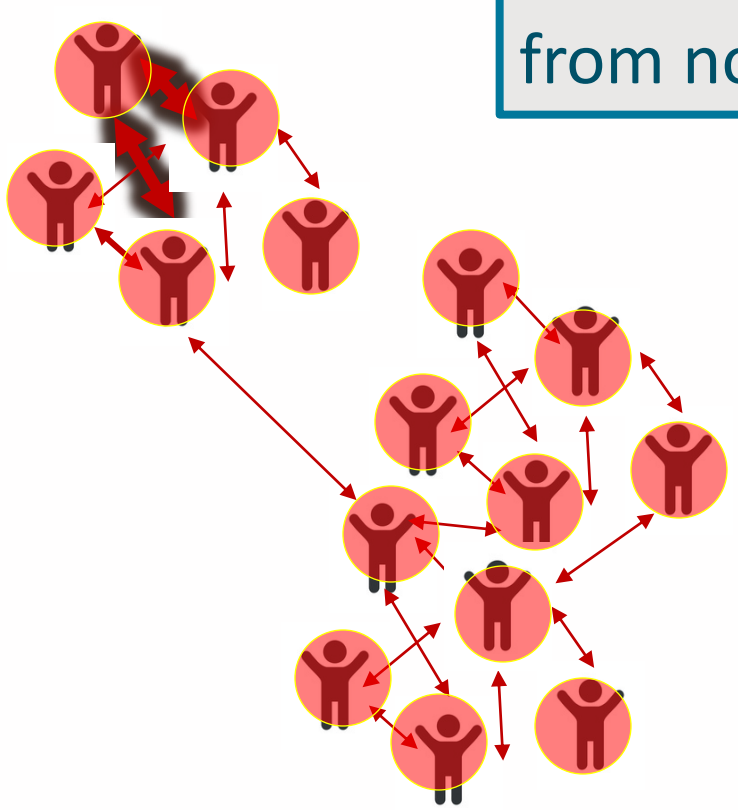




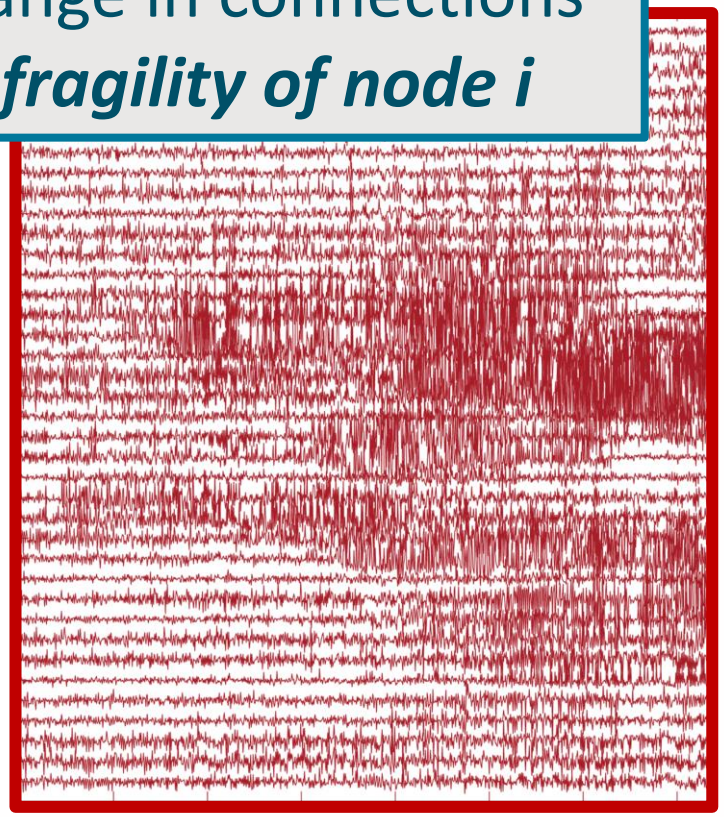
Node 1



Node 1



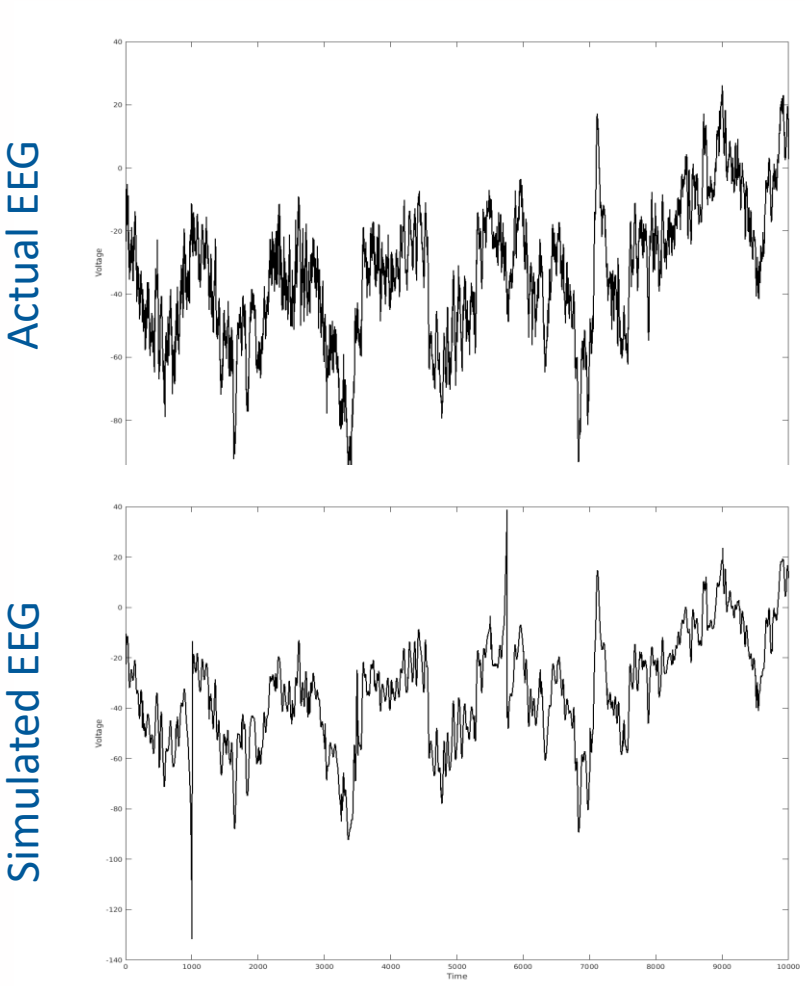
amount of change in connections from node i = ***fragility of node i***



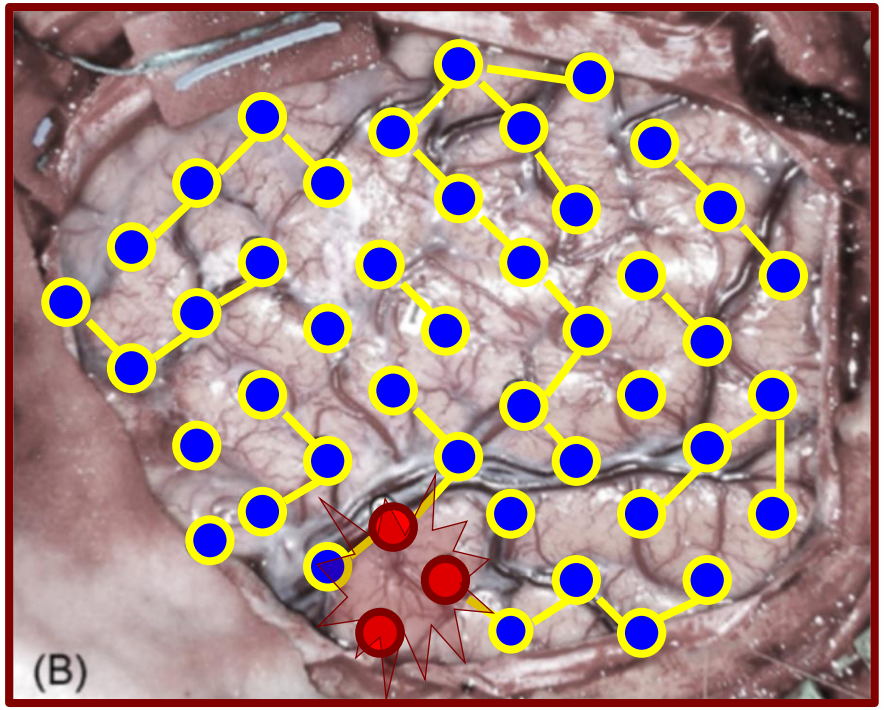
LTV network model accurately reconstructs SEEG data

Actual EEG

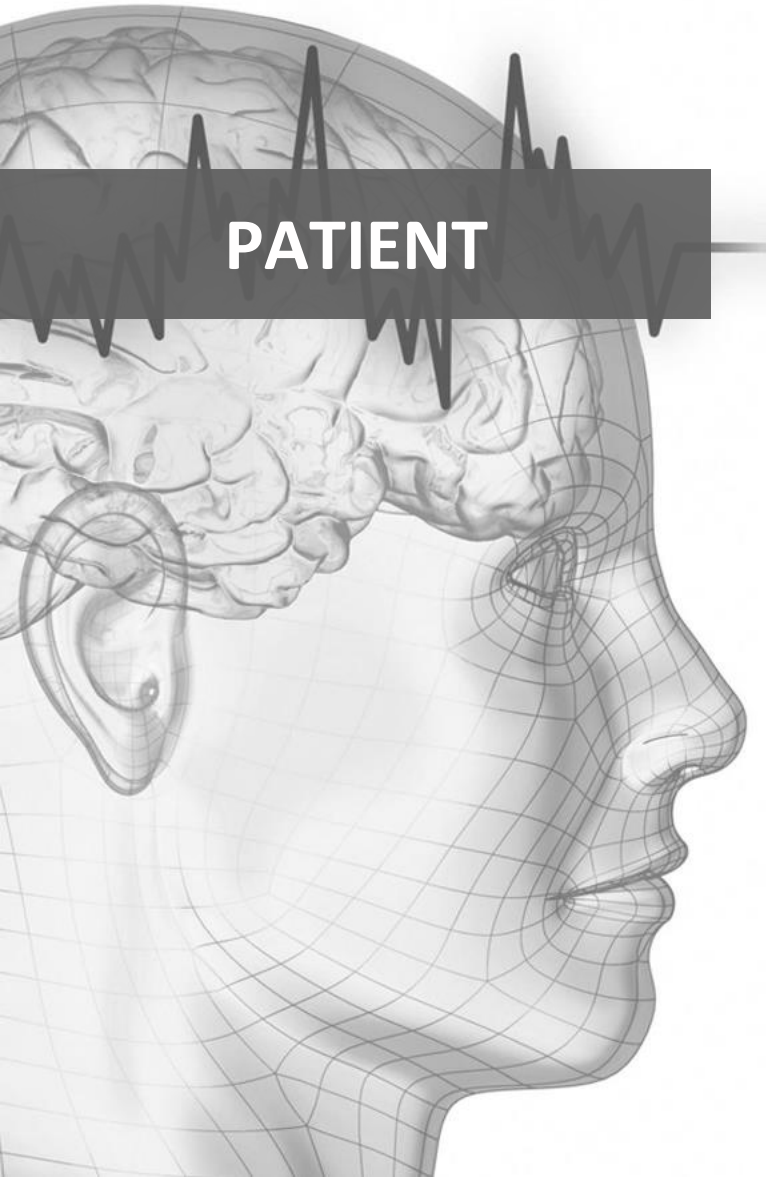
Simulated EEG



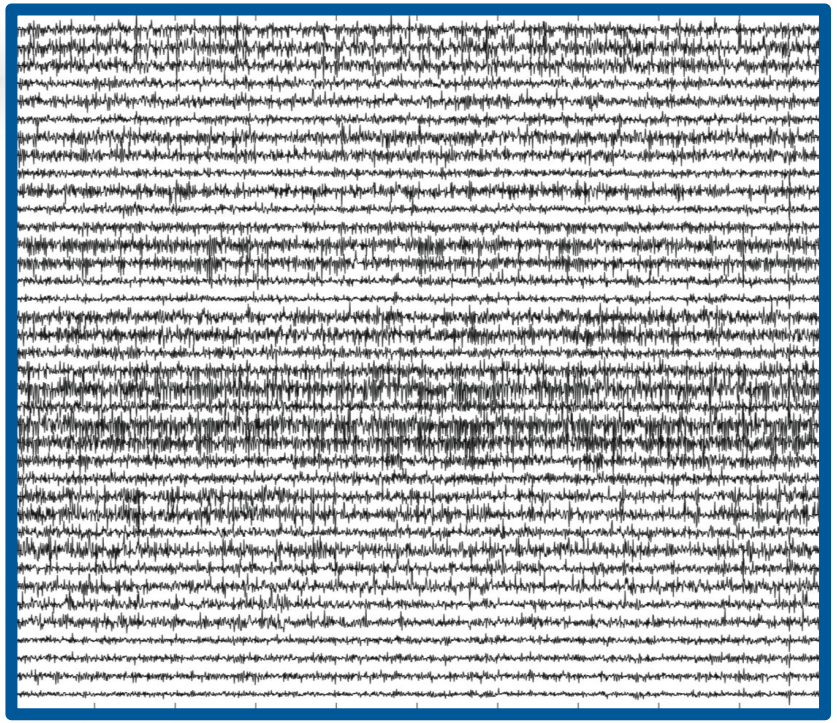
The most *fragile* nodes in the epileptic network correspond to the epileptogenic zone.



OBSERVATION 1: Seizure occurs in unstable network

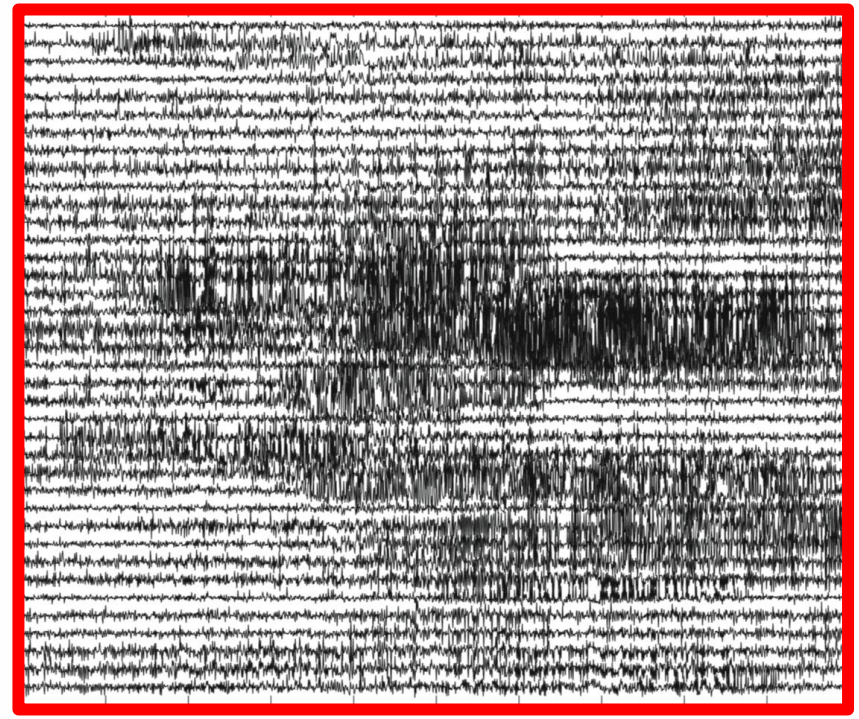


Non-Seizure



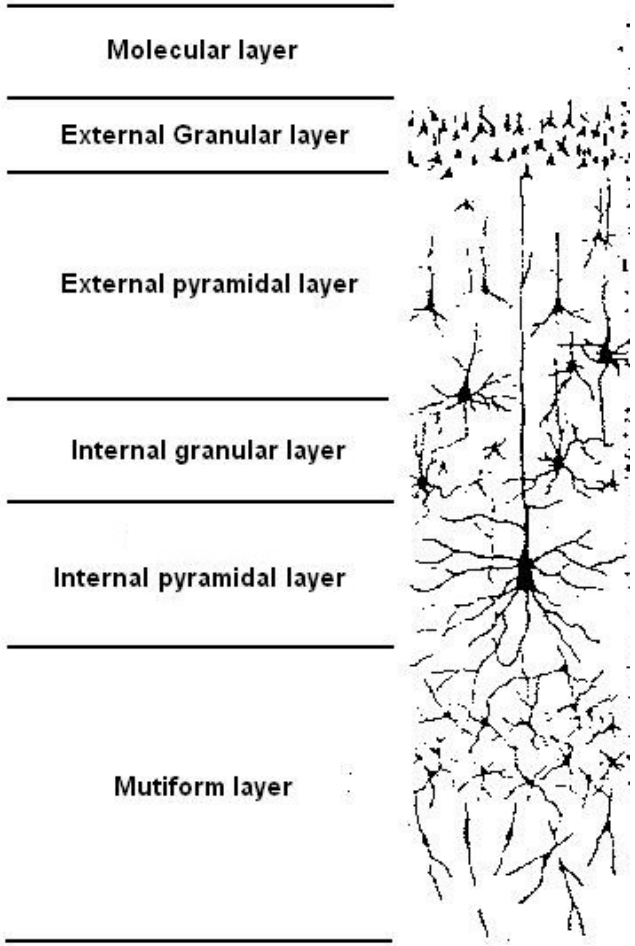
STABLE

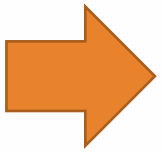
Seizure

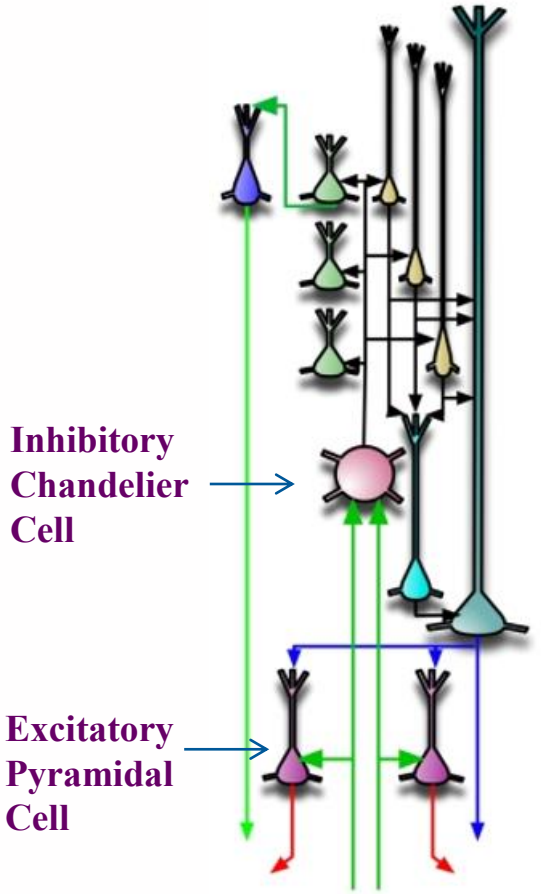


UNSTABLE

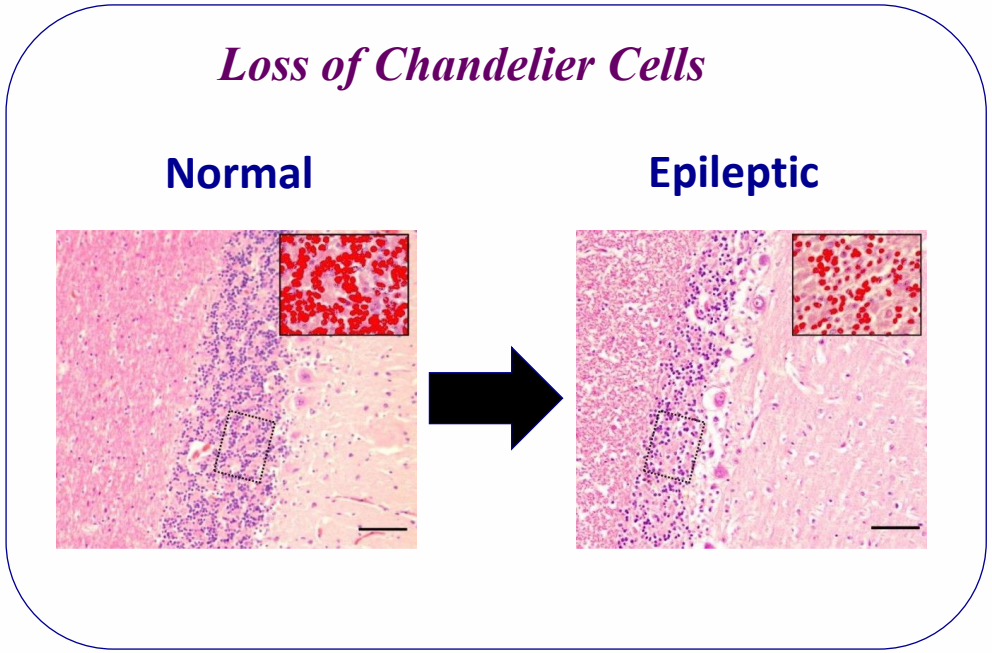
OBSERVATION 2: Destabilization occurs when neural coupling alters



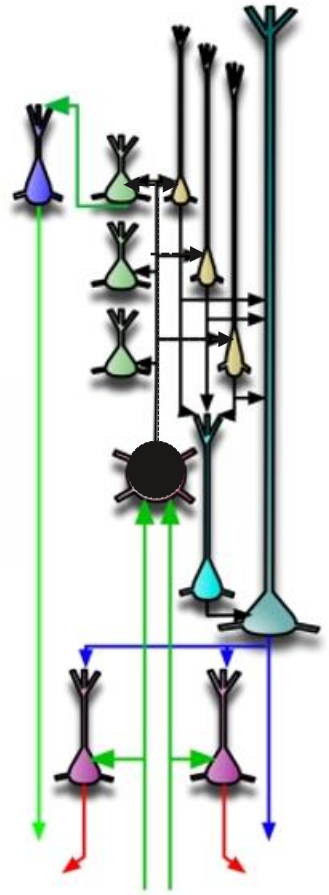




OBSERVATION 2: Destabilization occurs when neural coupling alters



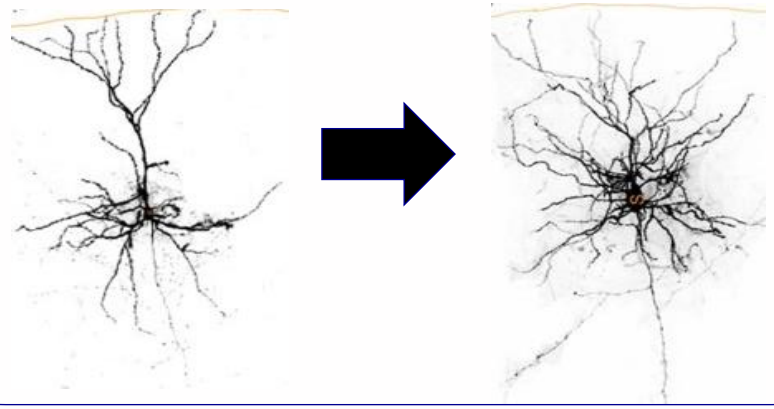
Decreased damping in network

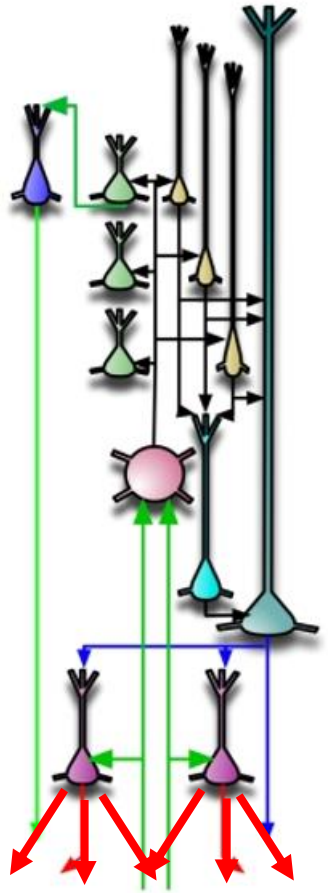


OBSERVATION 2: Destabilization occurs when neural coupling alters

Abnormal Axonal Spouting of Pyramidal cells

Normal **Epileptic**

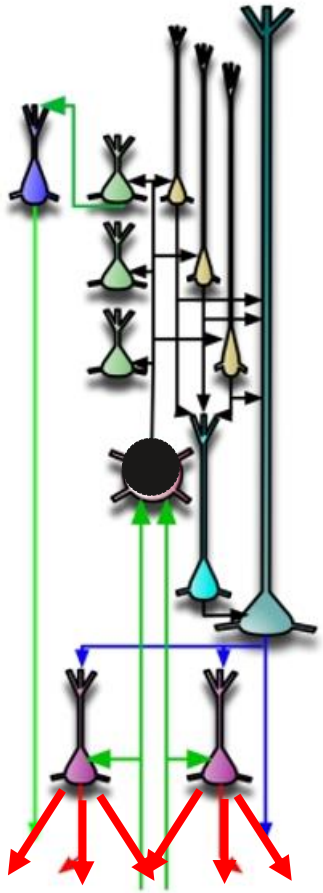


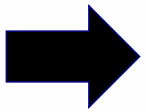


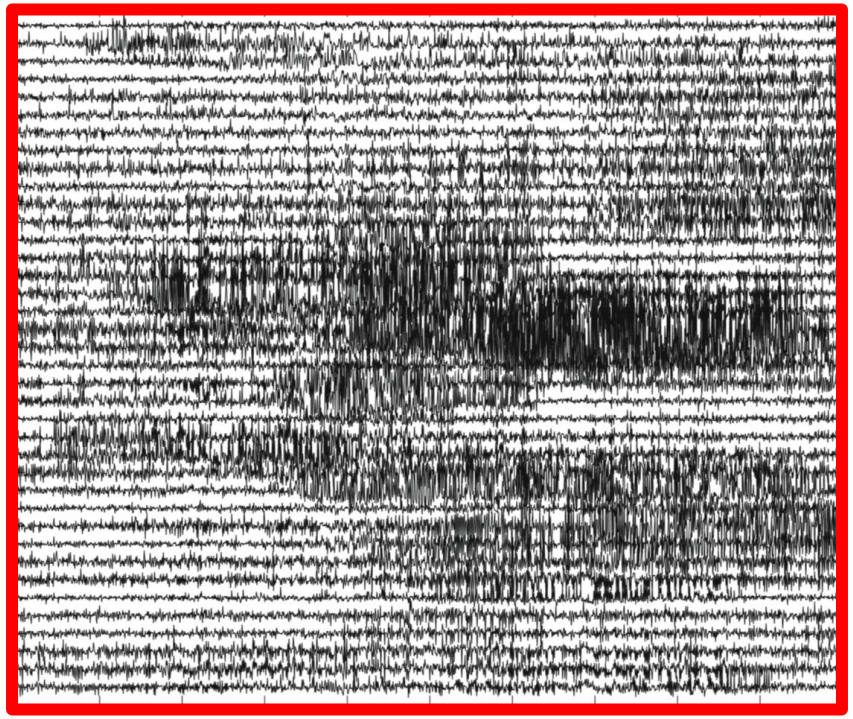
Increased excitation in network

OBSERVATION 2: Destabilization occurs when neural coupling alters

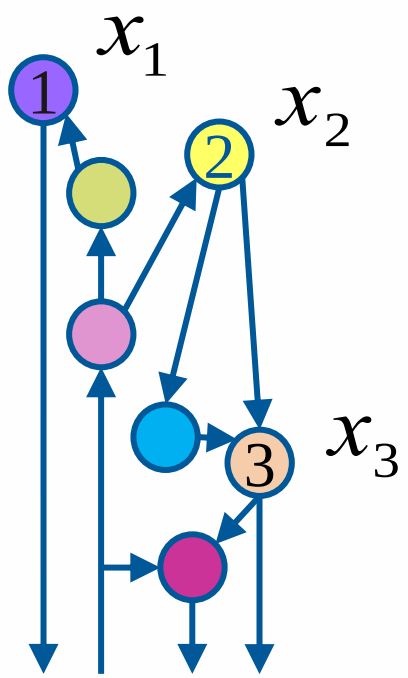
Changes in coupling between neuronal populations (**network nodes**) translates functionally seizures (**instability**)

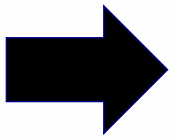


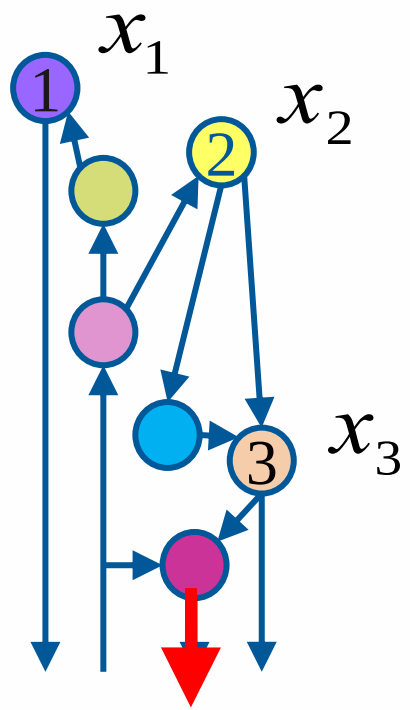




MODEL SEIZURES AS EMERGENT FROM FUNCTIONAL PERTURBATIONS



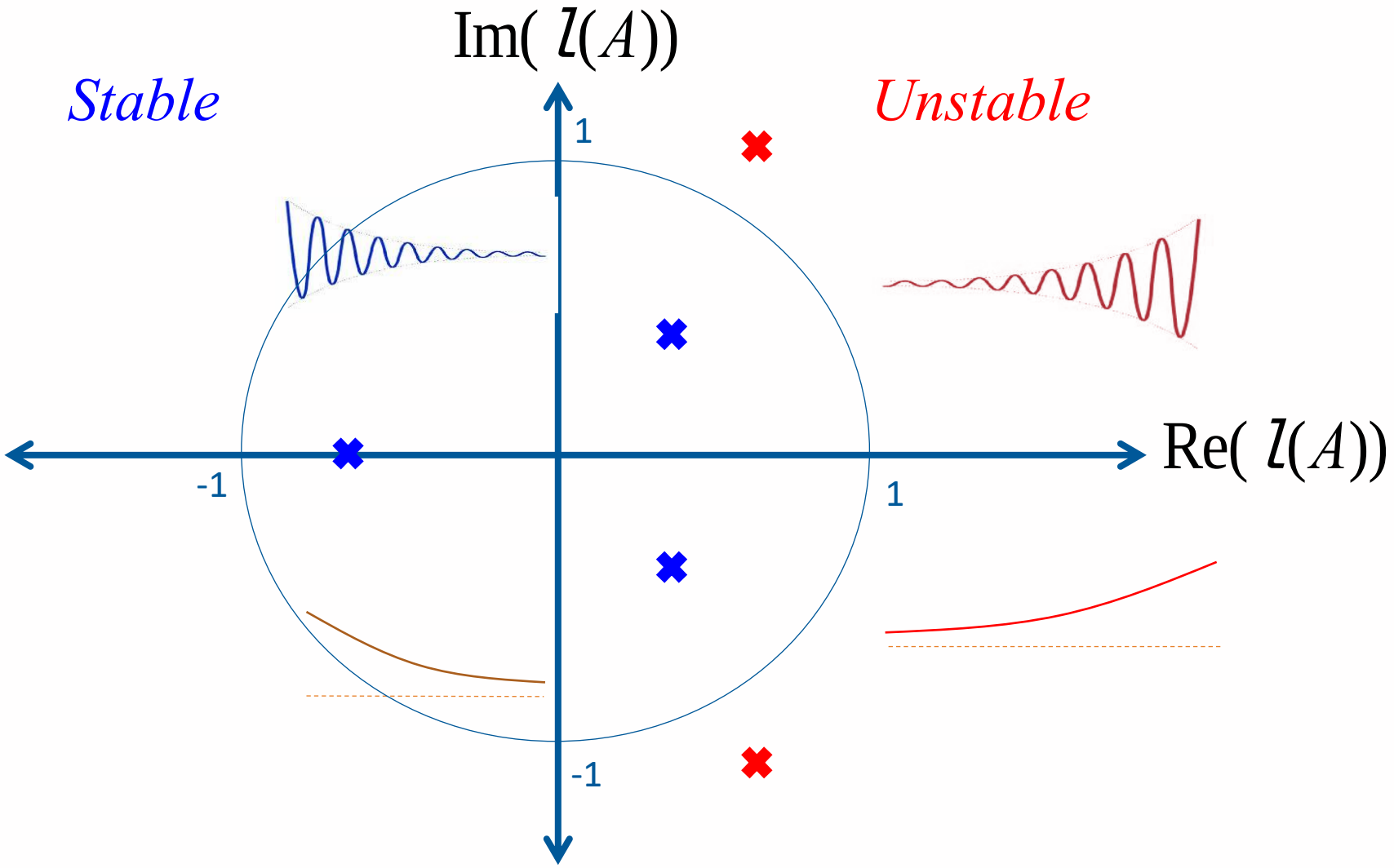




$$\mathbf{x}(t+1) = \mathbf{A}\mathbf{x}(t)$$

$$\mathbf{x}(t+1) = (\mathbf{A} + \mathrm{D})\mathbf{x}(t)$$

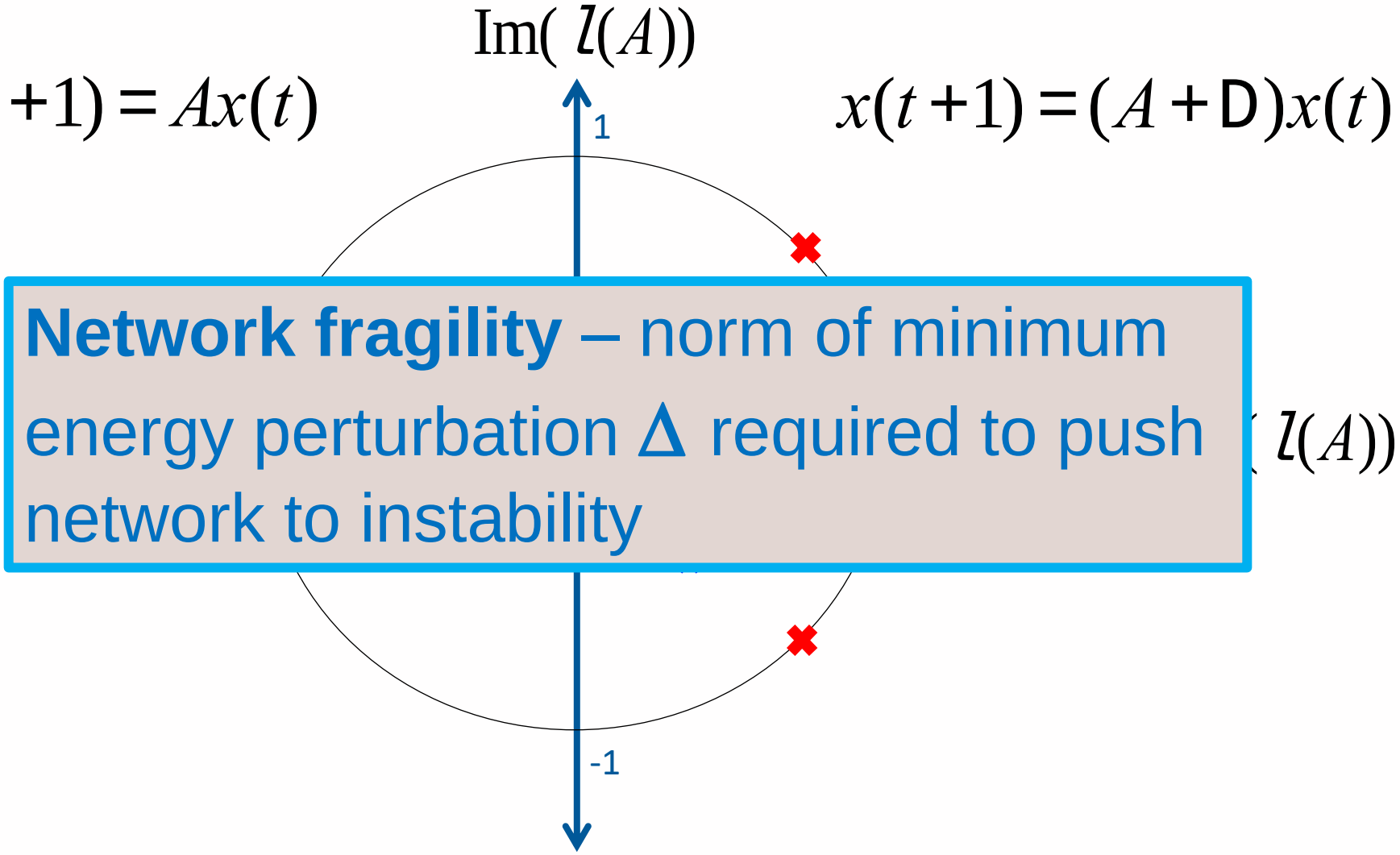
STABILITY OF DISCRETE-TIME LTI SYSTEMS



STABILITY OF DISCRETE-TIME LTI SYSTEMS

$$x(t+1) = Ax(t)$$

$$x(t+1) = (A + \mathrm{D})x(t)$$



Network fragility – norm of minimum energy perturbation Δ required to push network to instability

STRUCTURED PERTURBATION PROBLEM

$$x(t+1) = (A + \mathsf{D})x(t)$$

$$\hat{\Delta}(\lambda) = \underset{\Delta \in \Lambda}{\operatorname{argmin}} \{\|\Delta\|_2 \mid \exists\, i : \lambda_i(A+\Delta) = \lambda, \forall\, i : \lambda_i(A) \neq \lambda, i \in 1 \ldots N, A \in \mathbb{R}^{N \times N}\}$$

perturbation on i^{th} column

$$\Delta = \begin{bmatrix} \cdots & | & | & | & \cdots \\ & 0 & \mathbf{r} & 0 & \\ & | & | & | & \end{bmatrix}$$

$\| \hat{\mathsf{D}} \|$ = fragility of i^{th} node

STRUCTURED PERTURBATION PROBLEM

$$\widehat{\Delta}(\lambda) = \underset{\Delta \in \Lambda}{\operatorname{argmin}} \{\|\Delta\|_2 \mid \exists\, i : \lambda_i(A+\Delta) = \lambda, \forall\, i : \lambda_i(A) \neq \lambda, i \in 1 \ldots N, A \in \mathbb{R}^{N \times N}\}$$

$$(A + \boldsymbol{\Gamma e_k^T})\boldsymbol{v} = \lambda \boldsymbol{v}$$

$$\left|A - \lambda \mathrm{I} + \boldsymbol{\Gamma e_k^T}\right| = 0$$

$$\left|(A - \lambda \mathrm{I})\left(I + (A - \lambda \mathrm{I})^{-1}\boldsymbol{\Gamma e_k^T}\right)\right| = 0$$

$$\left|I + (A - \lambda \mathrm{I})^{-1}\boldsymbol{\Gamma e_k^T}\right| = 0$$

$$\boldsymbol{\Gamma}^T (A - \lambda \mathrm{I})^{-T} \boldsymbol{e_k} = -1$$

$$\Delta = \begin{bmatrix} \cdots & | & | & | & \cdots \\ & 0 & \boldsymbol{\Gamma} & 0 & \\ & | & | & | & \end{bmatrix}$$

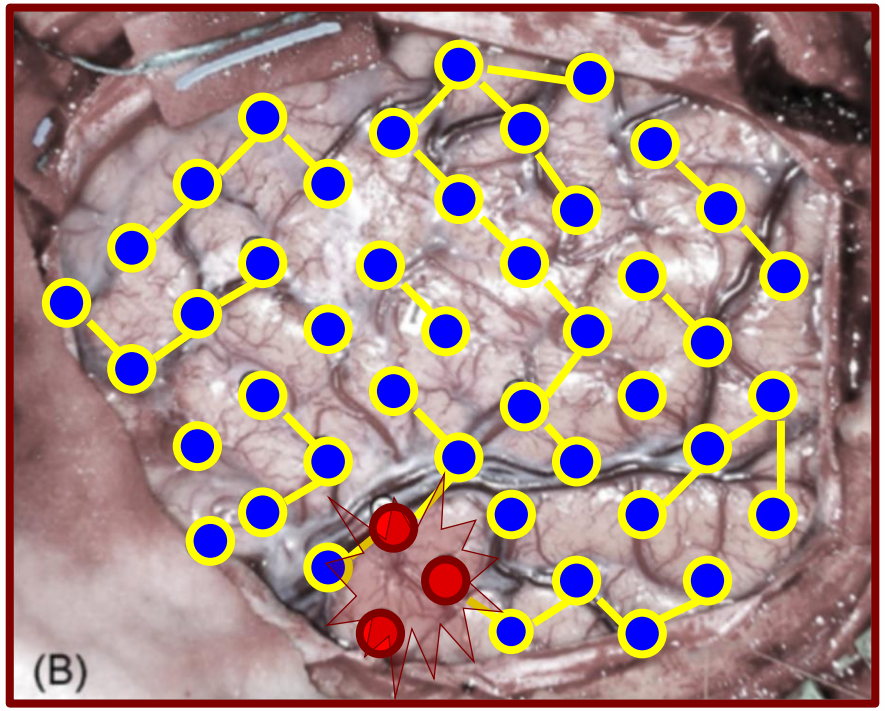
Column Perturbation

$$\min_{\Delta \in \Lambda} \|\Delta\|_2 \Leftrightarrow \min_k \left\{\|\boldsymbol{\Gamma}(k)\|_2 \;\middle|\; \boldsymbol{e_k^T}(A - \lambda \mathrm{I})^{-1}\boldsymbol{\Gamma} = -1\right\}$$

Least Squares!

EZ CAN BE LOCALIZED VIA FRAGILITY ANALYSIS ON NONSEIZURE DATA

Hypothesis: The most *fragile* nodes in the epileptic network correspond to the epileptogenic zone.



LOCALIZATION VIA FRAGILITY MAPS