Signal Processing for Diagnosis and Treatment of Brain Disorders

Justin Dauwels

www.dauwels.com

Laboratory for Information and Decision Systems (LIDS)
Massachusetts Institute of Technology (MIT)

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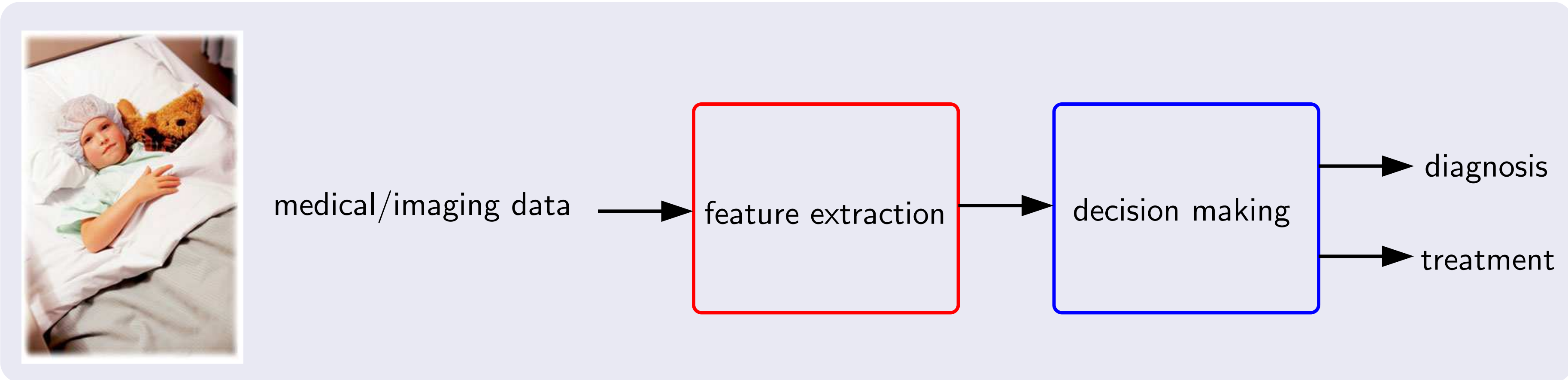
Massachusetts
Institute of
Technology

"With all the tools available to modern medicine—the blood tests, M.R.I.'s and endoscopes—you might think that **misdiagnosis** has become a rare thing. But you would be wrong."

Why doctors so often get it wrong, David Leonhardt, New York Times, Feb. 22, 2006

Proposed: Signal processing aided decision making



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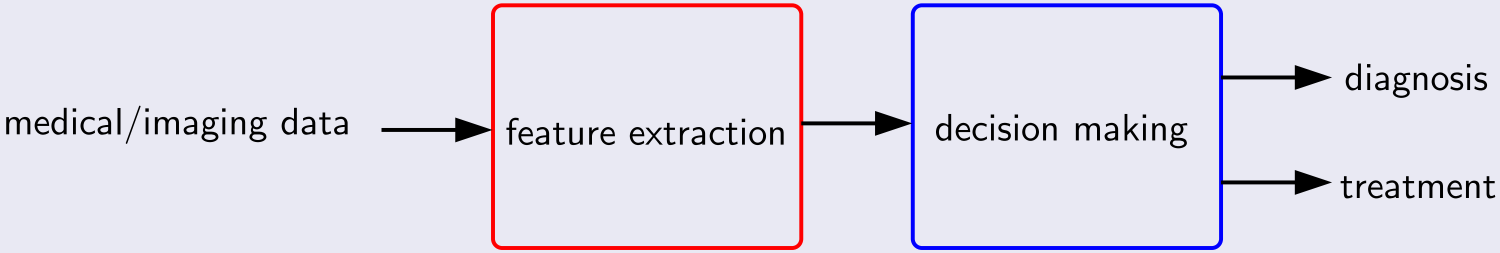


- Signal processing "microscope"
  discovery of **features/patterns** in data associated with certain **disorders**
- Algorithmic decision making
  combine **evidence** "optimally" $\longrightarrow$ **diagnosis** and **treatment**

- More reliable and earlier diagnosis
- More effective treatment (clinical outcome, time and cost)

Synchrony of brain signals is an important feature

- Loss of synchrony of brain signals $\longrightarrow$ brain disorder
- Normal synchrony of brain signals
- Increased synchrony of brain signals $\longrightarrow$ brain disorder

Often subtle effects, requires signal processing

Preview: Topics

Signal Processing Aided Diagnosis

Loss in EEG synchrony → diagnosis of early-Alzheimer's

Signal Processing Aided Treatment

Increased EEG synchrony → localization of epileptic brain tissue

Future Work

Two future research projects

Electroencephalogram (EEG)
= electrical activity along the **scalp** or **brain**

Alzheimer's disease is complex, devastating, and common

- Symptoms: memory loss, language breakdown, loss of motor control, apathy, . . .
- Causes: not well understood, complex molecular mechanisms
- 2-5% of people over 65 years old

Our goal: early diagnosis of AD using EEG

Early diagnosis of AD is important

- medication and other therapies most useful when used early

More precisely: diagnosis of MCI and mild AD

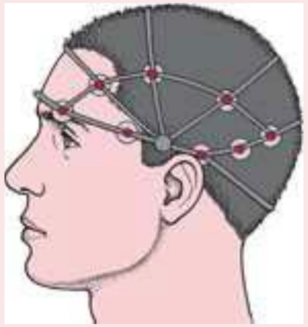
- **predementia** (a.k.a. **mild cognitive impairment**, MCI)
- **mild**–moderate–severe AD

Our goal: early diagnosis of AD using EEG

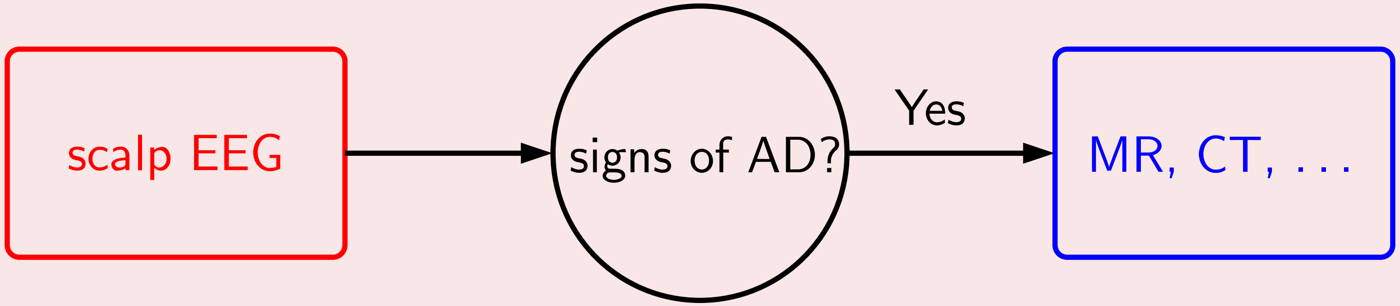
Standard approach

mental testing, MR, CT, SPECT, PET, corticospinal fluid

Scalp EEG is attractive complementary technology

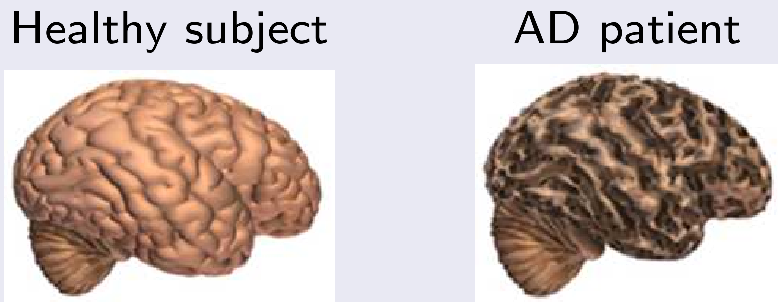


- simple, affordable, mobile
- useful for screening

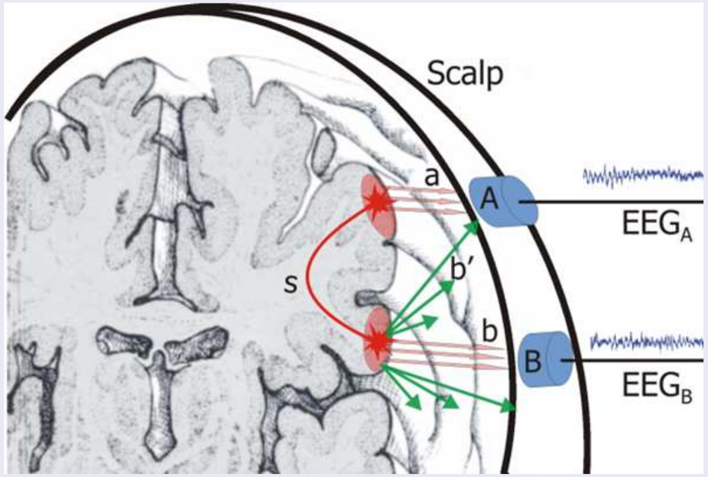


EEG signals of AD patients are less coherent

- Loss of neurons → weaker brain connectivity



- EEG from different brain areas is less correlated in AD patients



- Loss in EEG synchrony → loss in brain connectivity → AD
- How to **detect** loss in EEG synchrony?

How to measure EEG synchrony?

Classical techniques

- correlation coefficient, coherence
- phase synchrony
- Granger causality
- information-theoretic measures
- ...

Few of them applied on **single** data sets of early-AD patients

How to measure EEG synchrony?

Systematic study

30+ measures on **two** data sets (and more to follow)

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Systematic study

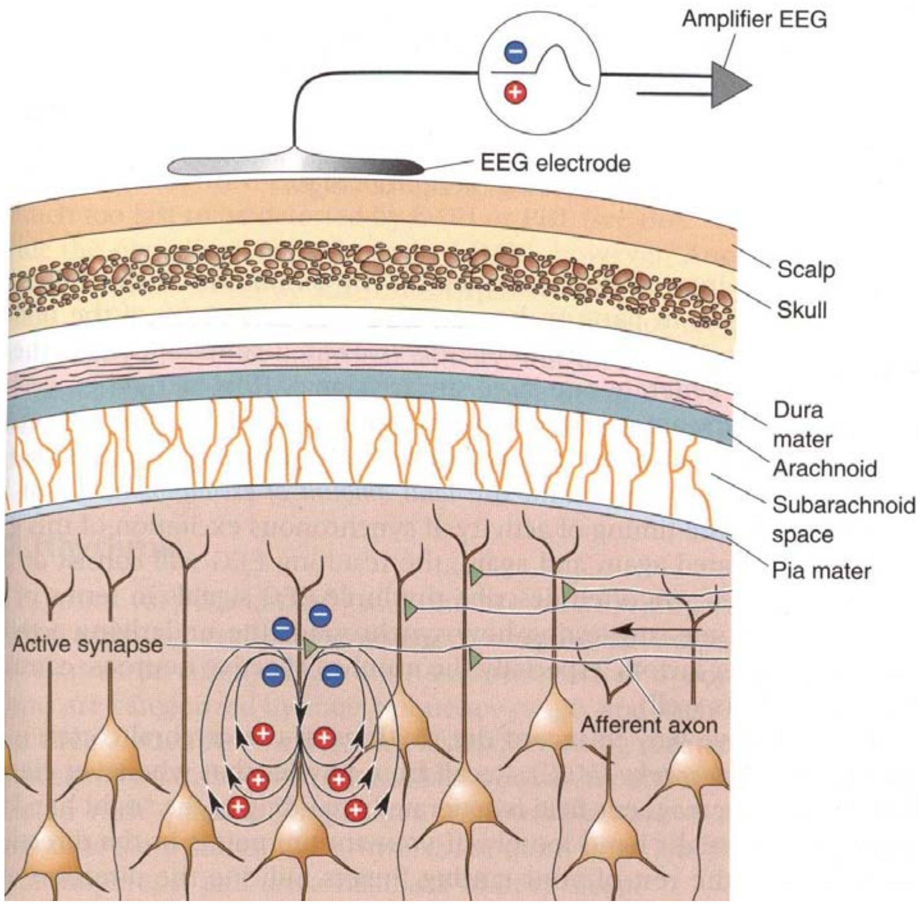
30+ measures on **two** data sets (and more to follow)

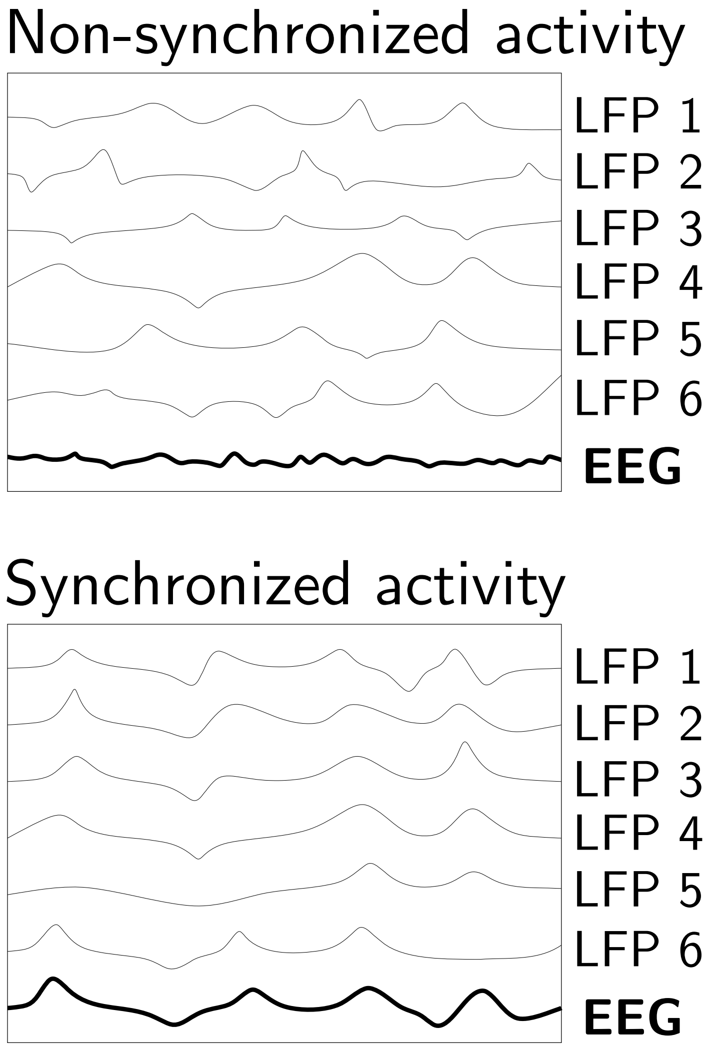
New approach: "Stochastic Event Synchrony (SES)"

- Extracts "events" from EEG signals and aligns those events
- Provides complementary information about synchrony
- Promising results for diagnosing AD
- General formalism for similarity of point processes

In this talk: **pairs** of **two**-dimensional point processes (EEG)

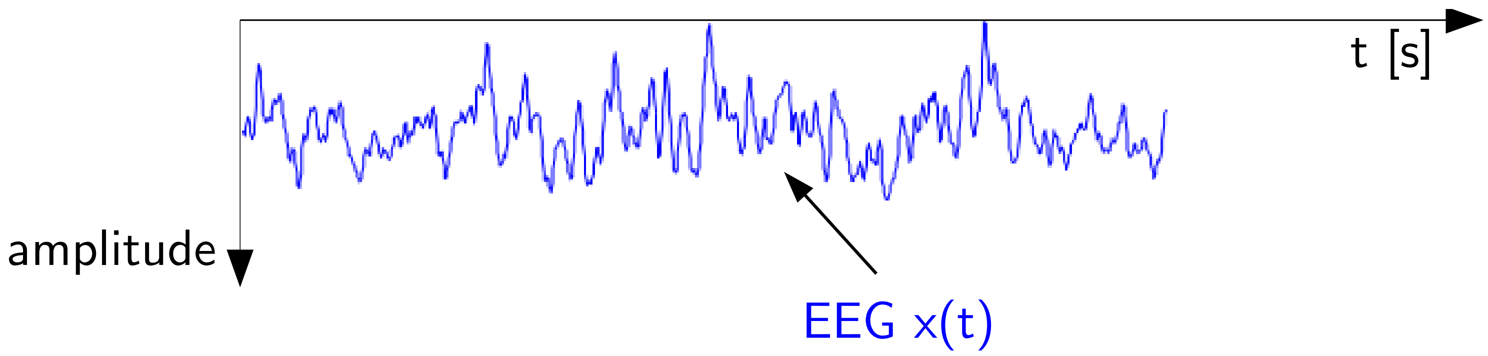
Local synchronous activity leads to "events" in EEG



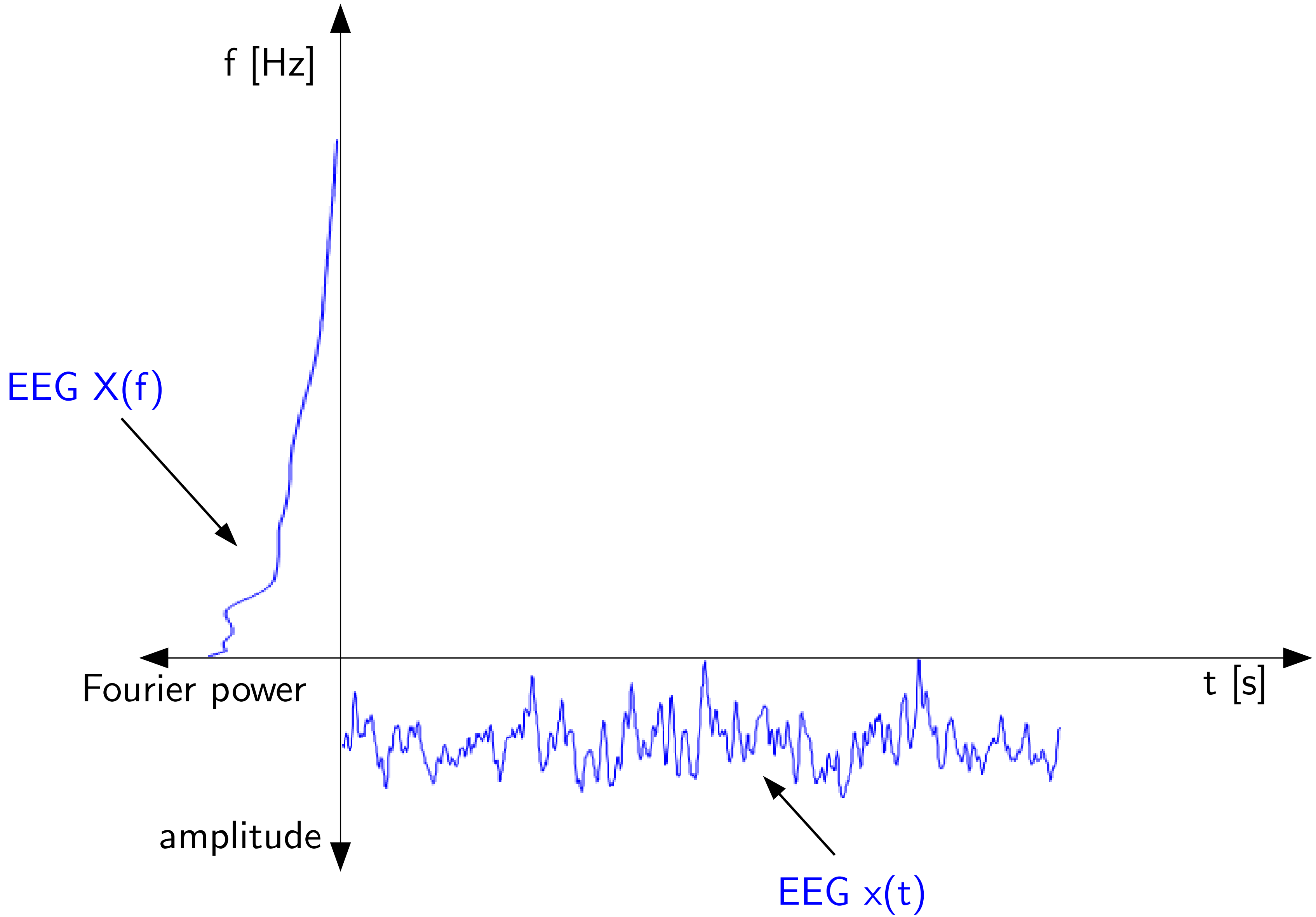


Neuroscience: Exploring the Brain, M. Bear et al.

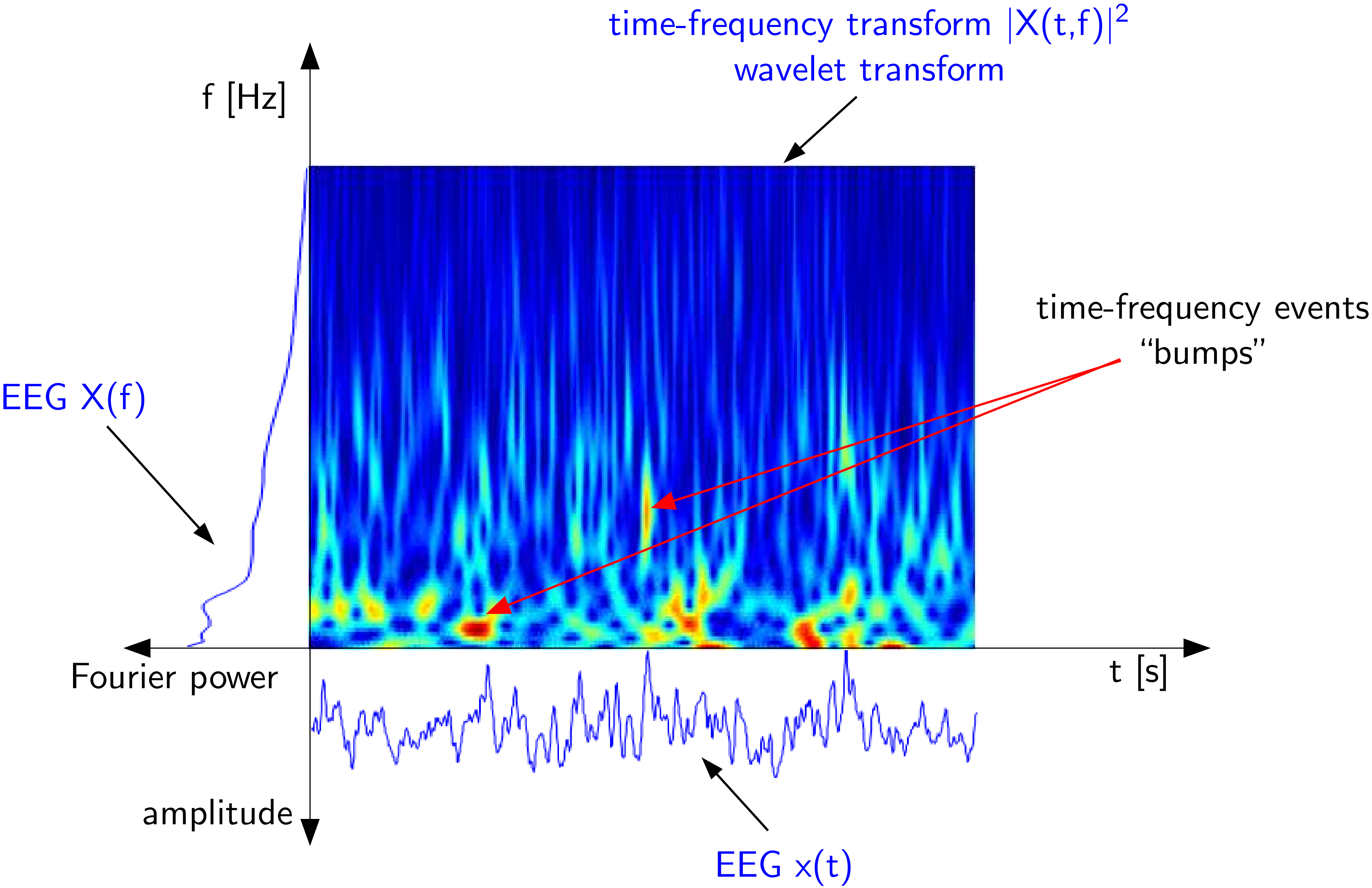
Typical EEG signal in time-domain



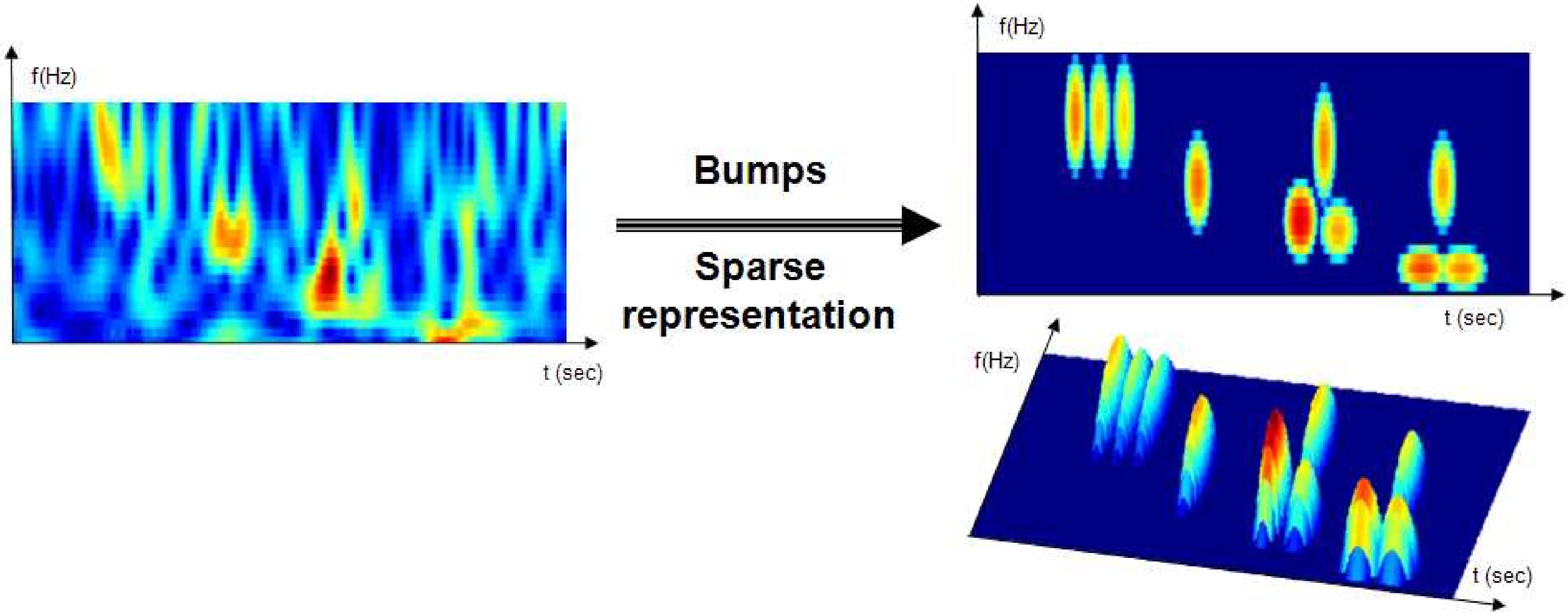
Frequency-domain representation of the same signal



Events can clearly be observed in time-frequency domain



Oscillatory events extracted from time-frequency map

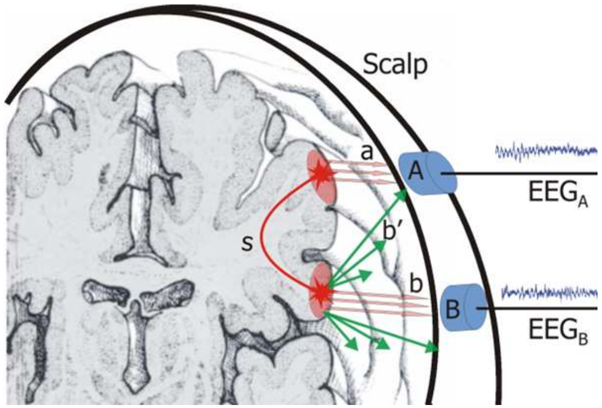


10.000 coefficients → 50 parameters

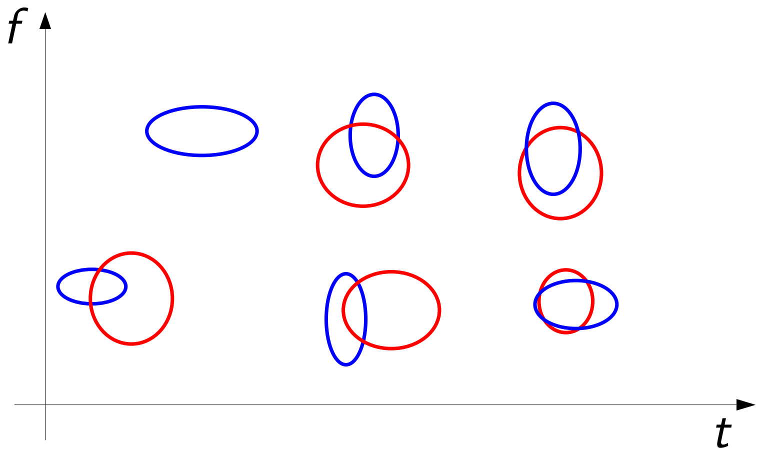
- Bump models are point processes on time-frequency plane
- 5 bump parameters:
  timing, frequency, width in time and frequency, amplitude

F. Vialatte et al., Neural Networks 2007

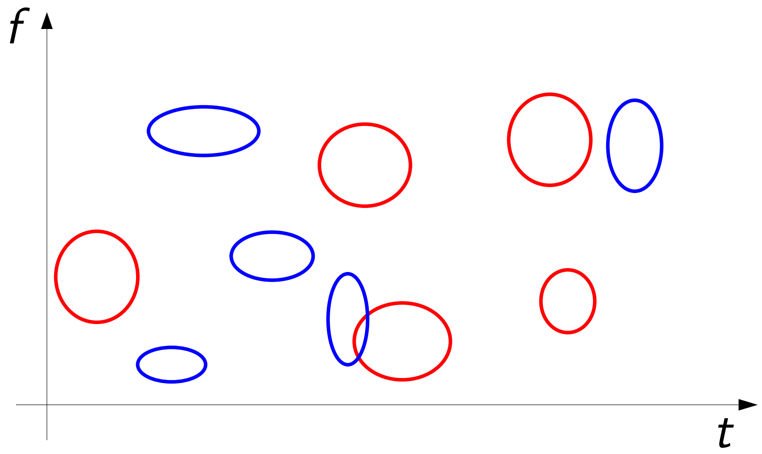
Hypothesis: events are less correlated in AD patients



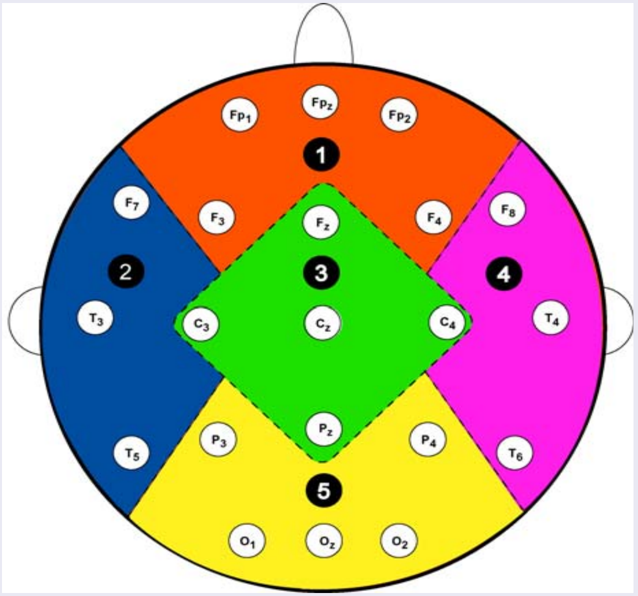
Healthy subject

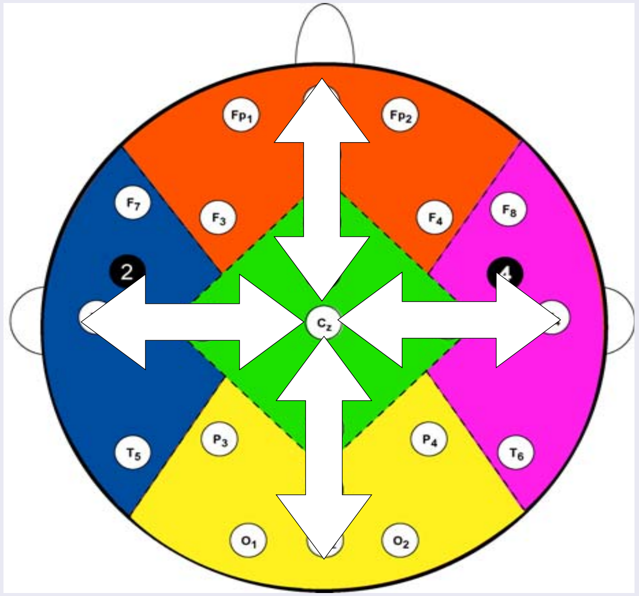


AD patient



How do we compute synchrony of events?



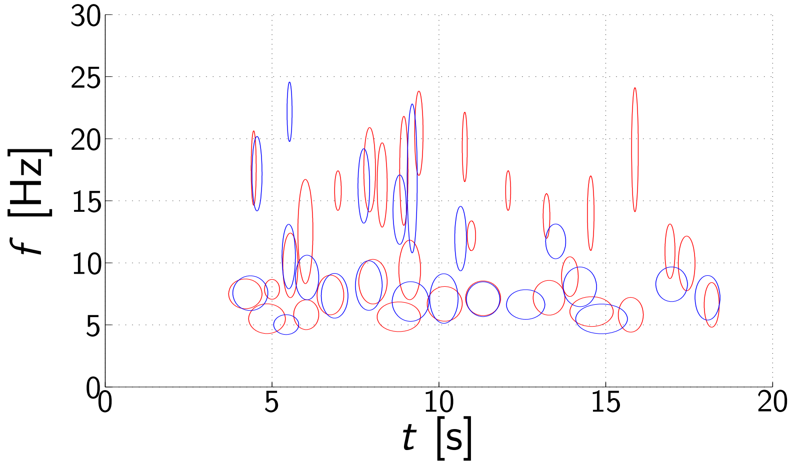


1. Group electrodes in regions
2. Extract bump model for each region
3. Determine similarity of each pair of bump models
4. Average similarity over all pairs

Misalignment of bump models $\longrightarrow$ loss of brain connectivity $\longrightarrow$ AD

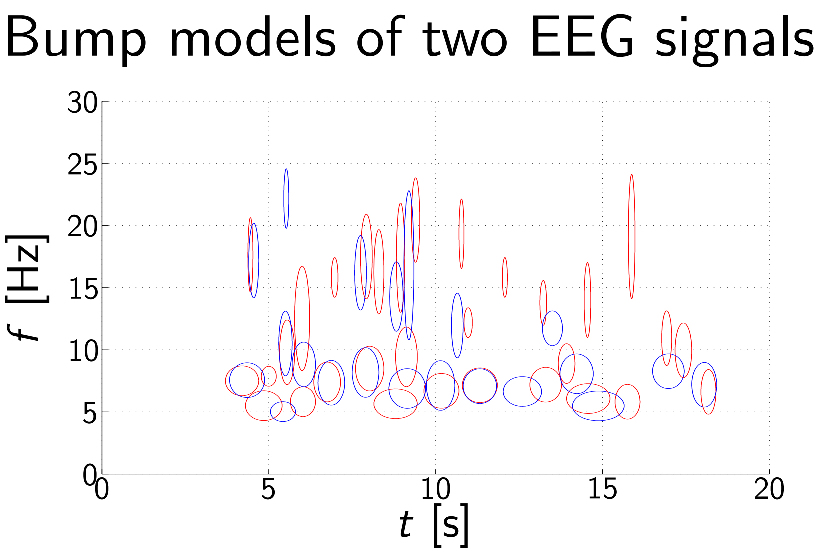
Stochastic Event Synchrony

Bump models of two EEG signals



1. How many bumps coincide?

Stochastic Event Synchrony



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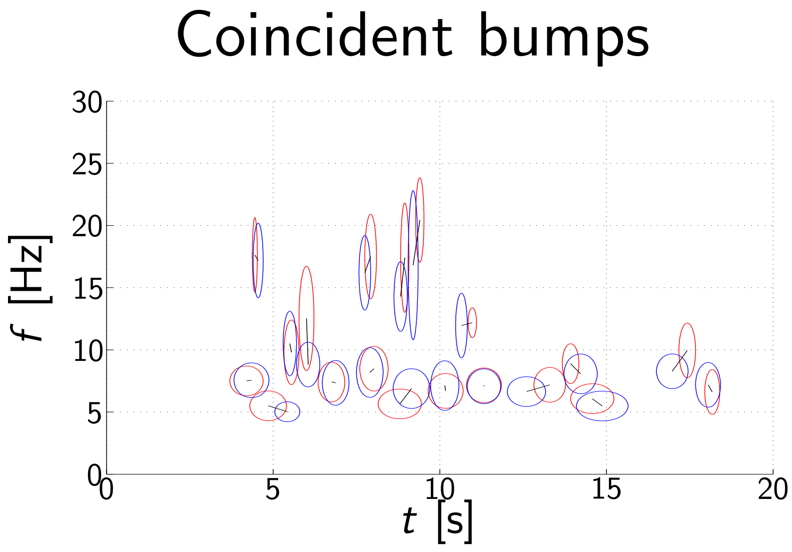
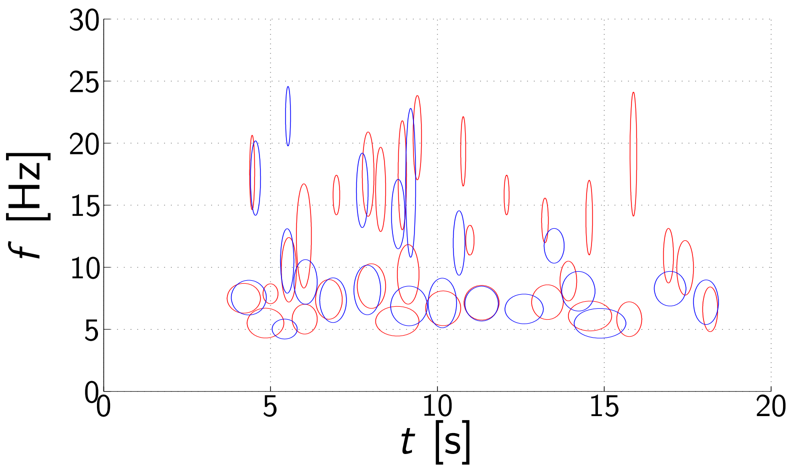


1. How many bumps coincide?
2. How well do the coincident bumps align?

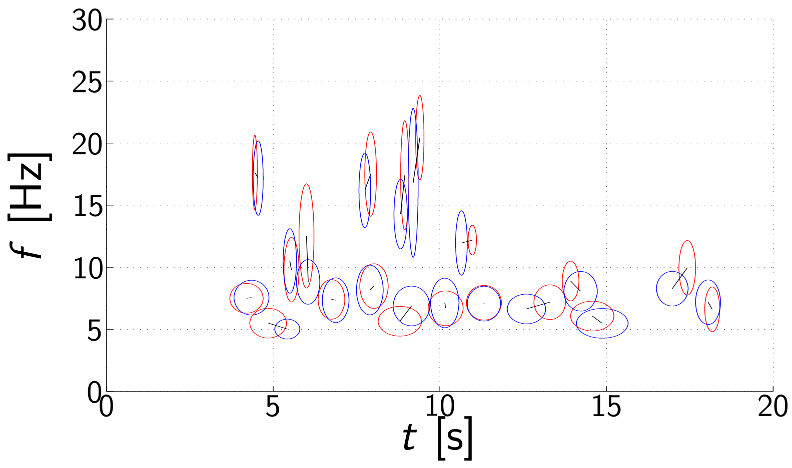
Stochastic Event Synchrony (ρ, δ_t, δ_f, s_t, s_f)

Bump models of two EEG signals



$\Rightarrow$

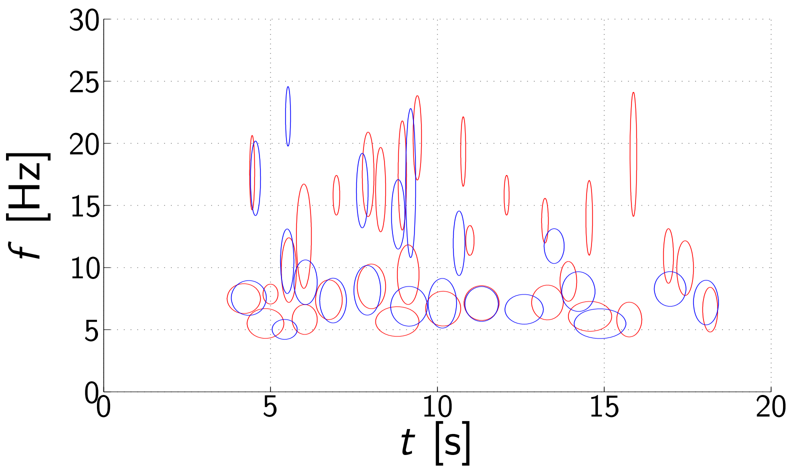
Coincident bumps



1. How many bumps coincide?
   - fraction of non-coincident bumps ρ
2. How well do the coincident bumps align?
   - average t and f offset of coincident bumps (δ_t and δ_f)
   - t and f jitter of coincident bumps (s_t and s_f)

Stochastic Event Synchrony (ρ, δ_t, δ_f, s_t, s_f)

Bump models of two EEG signals



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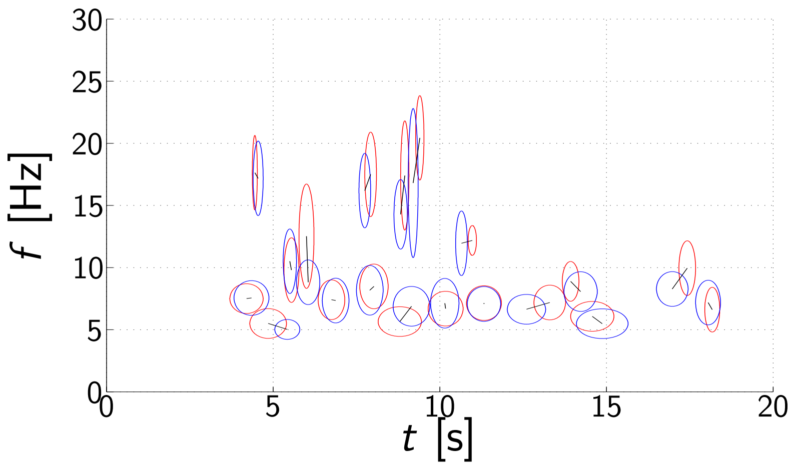

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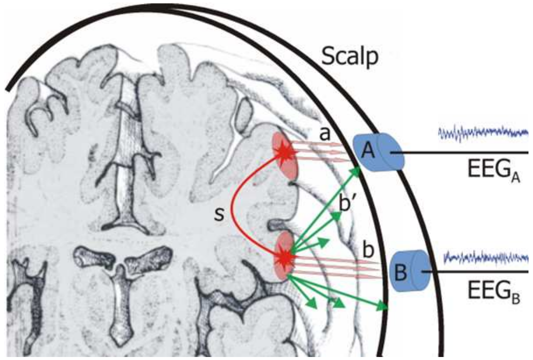
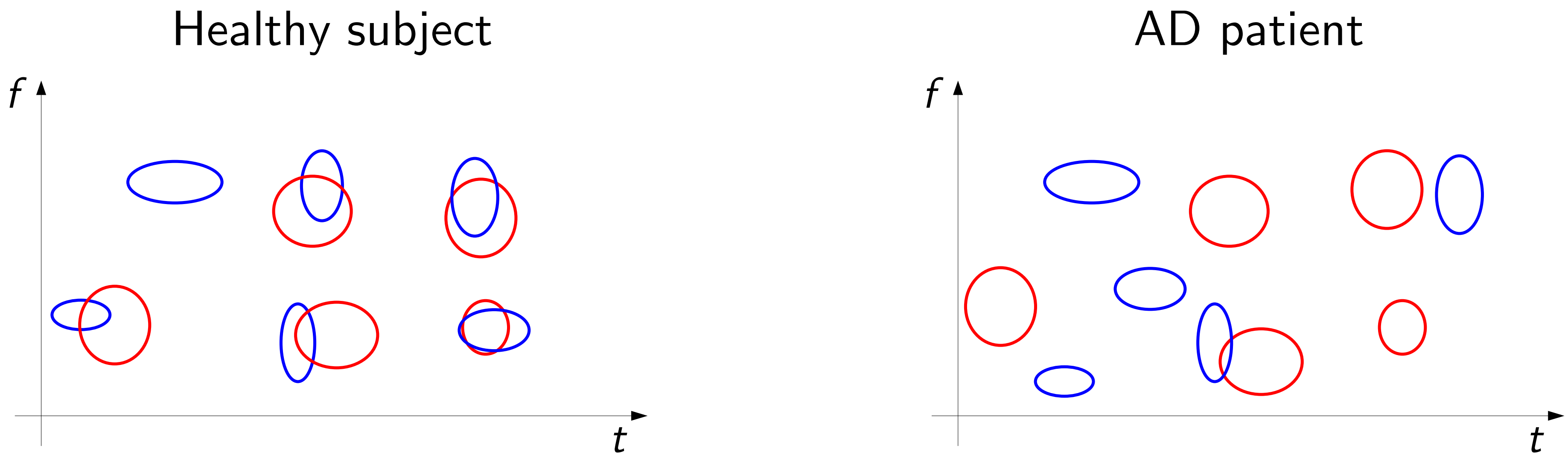
It is natural to **iterate** Step 1 and 2

Want to know more? Want to try it out?

http://www.dauwels.com/SESToolbox/SES.html

Hypothesis: events are less correlated in AD patients





- larger jitter of coincident bumps (s_t)
- larger fraction of non-coincident bumps (ρ)

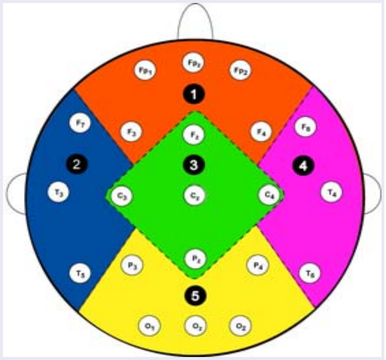
We applied SES to EEG of healthy and early-AD patients

2 data sets, **different** patients/hospitals

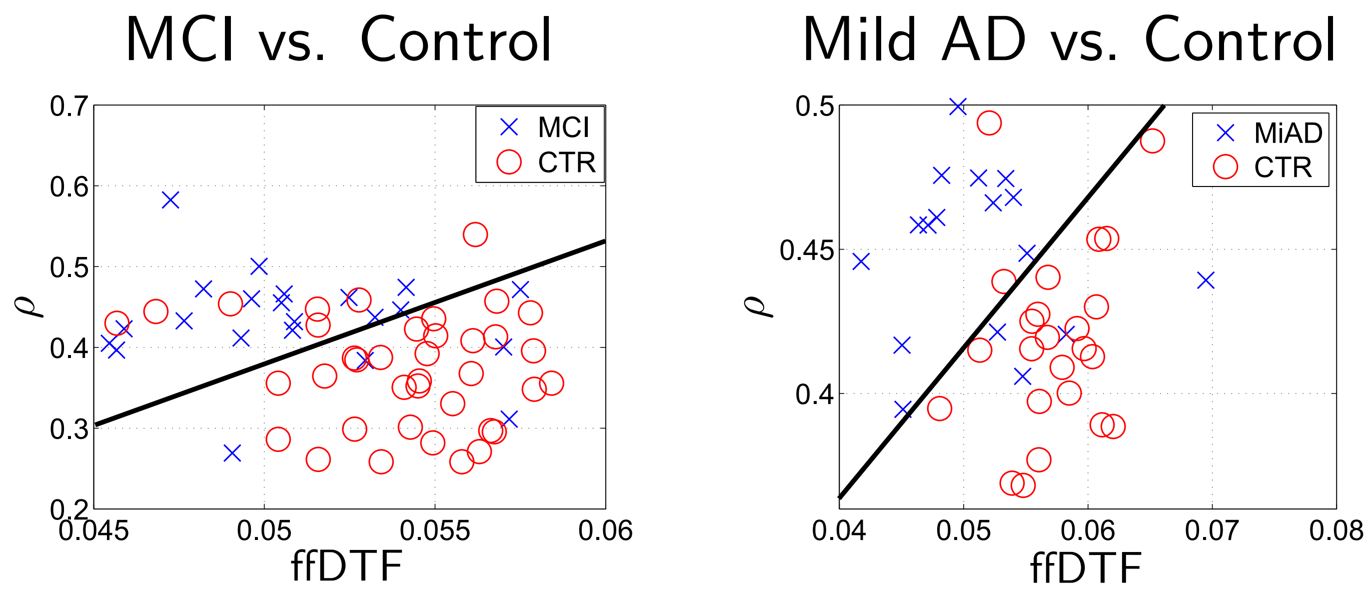
- 22 MCI and 38 Control subjects
- 17 Mild AD and 24 Control subjects

Setup

- spontaneous EEG, in rest with eyes closed
- 21 electrodes (10-20 international system)
- electrodes grouped in 5 zones
- bandpass filtered between 4 and 30Hz
- 20s of artifact-free EEG
- 30+ synchrony measures, including SES



Promising and consistent numerical results



- Only full-frequency direct transfer function (ffDTF) and ρ strongly significant ($p < 0.001$), for **BOTH** data sets
- MCI vs. Control harder than Mild AD vs. Control

Promising and consistent numerical results

Discriminant analysis with leave-one-out crossvalidation

MCI vs. CTR	Linear DA	Quadratic DA
ffDTF	70.0%	70.0%
ρ	68.3%	75%
ffDTF and ρ	**83.3%**	**83.3%**
MiAD vs. CTR	Linear DA	Quadratic DA
ffDTF	82.9%	75.6%
ρ	62.5%	57.5%
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- EEG synchrony loss seems to be strong indicator of early AD
- SES improves diagnosis of AD (for those two data sets)

Preview: Topics

Signal Processing Aided Diagnosis

Loss in EEG synchrony → diagnosis of early-Alzheimer's

We needed to develop **novel** measures of synchrony

Signal Processing Aided Treatment

Increased EEG synchrony → localization of epileptic brain tissue

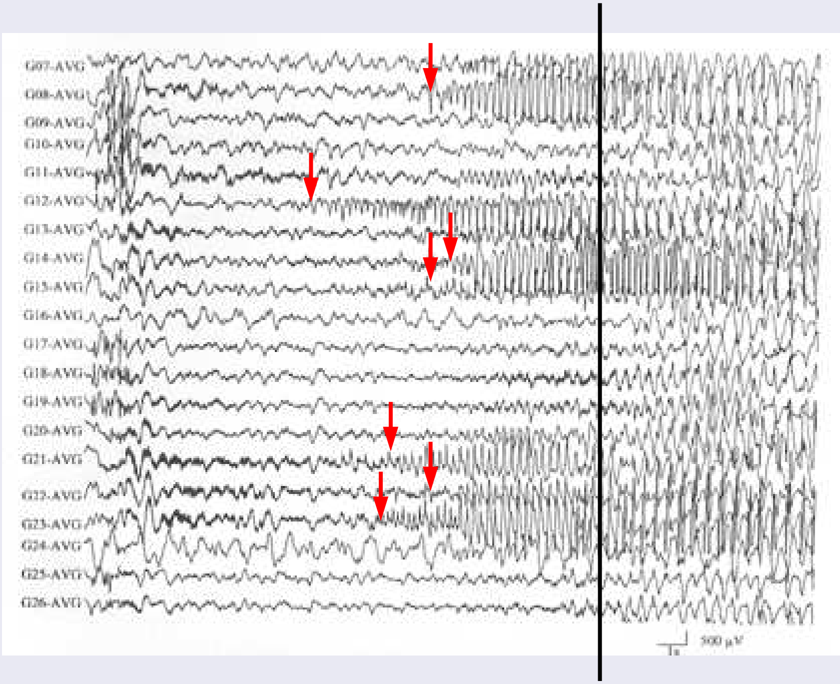
Existing synchrony measures proved to be effective

Future Work

Two future research projects

Epilepsy is common, complex, and devastating

- 2.5 million patients in U.S., 300'000 in U.K., 50 million world
- Heterogeneous group of central nervous system disorders characterized by recurrent unprovoked seizures
- Symptoms: disturbance of consciousness or awareness, alterations of bodily movement, sensation or posture, . . .
- Causes: genetic/metabolic abnormalities, tumors, . . .



Medication is usual treatment but not always effective

- Medication is most common treatment
- However, medication alone not effective for 30% of patients

If medication alone fails, surgery may be solution

Resection if medication alone fails

- Resection may be alternative for location-related epilepsy
- Objective: remove seizure onset zone
- **How to determine the seizure onset zone?**
  - from clinical behavior (e.g., left arm shaking) or scalp EEG
  - from **intracranial** EEG, if everything else fails
    risky, costly, uncomfortable

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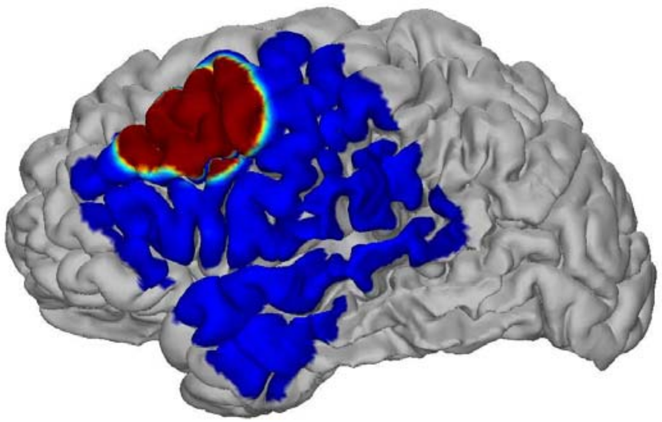
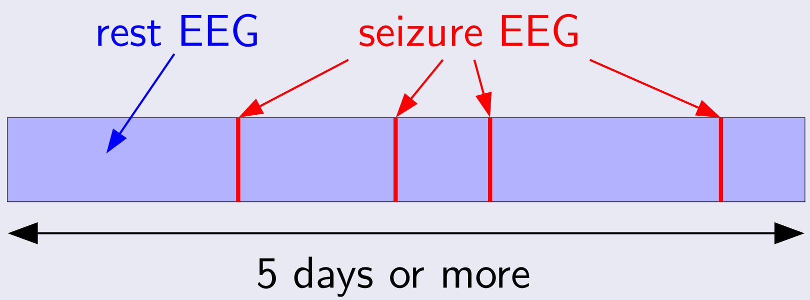
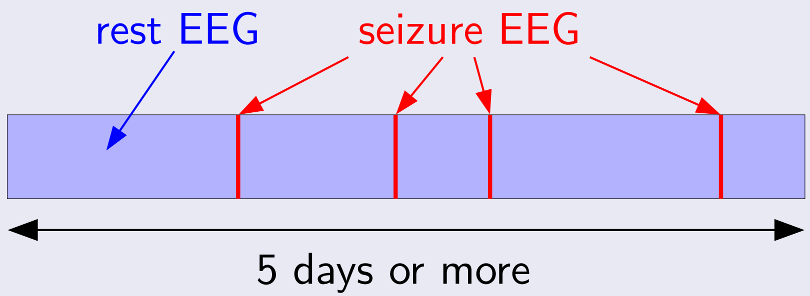


Standard procedure relies mostly on "seizure" EEG

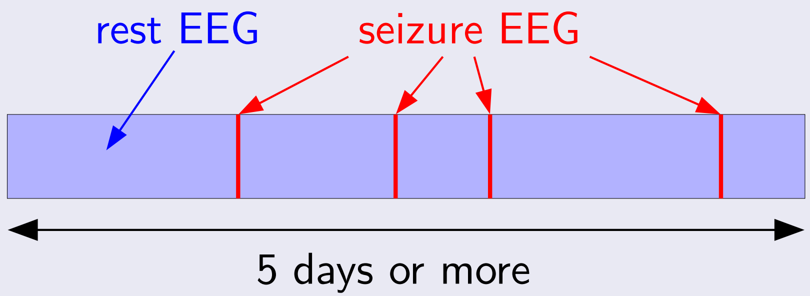


Our approach: exploit rest EEG to shorten hospitalization



We wish to make intracranial recordings as **short** as possible

Our approach: exploit rest EEG to shorten hospitalization



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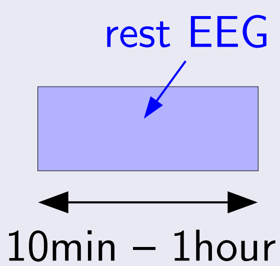


Objective: Seizure Focus Localization

- Use rest EEG only → shorter hospitalization
- Automated procedure → faster and potentially more reliable

Differences with diagnosis of AD project

- Intracanial EEG vs. scalp EEG
- Signal processing to guide surgery vs. diagnosis
- Increased EEG synchrony vs. EEG synchrony loss

Interictal characteristics of seizure onset zone

- Locally enhanced synchrony (“hypersynchrony”)
- Slowing is signature of damaged cortex
- Interictal spikes
- Interictal high-frequency bursts

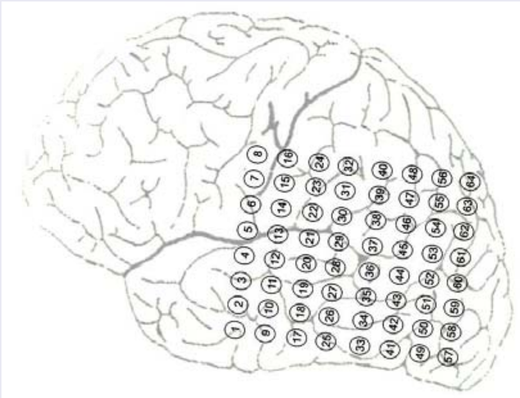
Three main questions

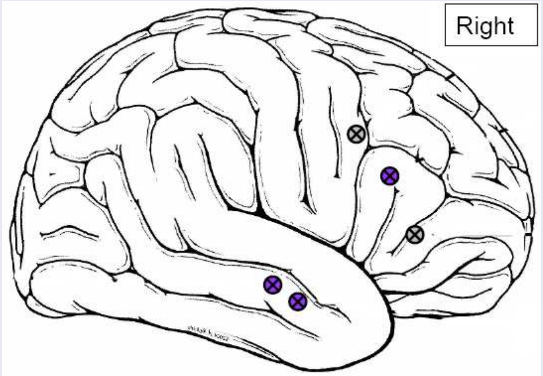
Hypothesis

Seizure onset zone is characterized by hypersynchronous activity even while at **rest**

1. Does hypersynchronous activity occur in rest EEG?
2. Do hypersynchronous areas correlate with seizure onset zone?
3. How to determine seizure onset zone using hypersynchrony?

Our approach



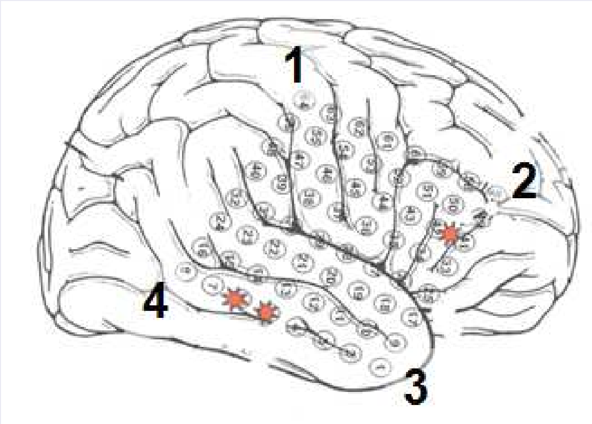


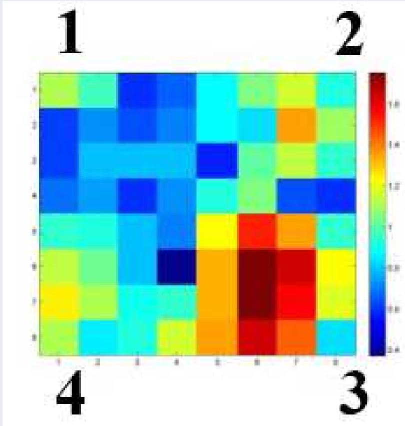
- 6 patients with grid electrodes, 5 with depth electrodes
- 1 hour segment of intracranial **interictal** EEG
- 48 hours between segment and seizures
- bandpass filter between 1–200Hz, notch filter at 60Hz
- no further preprocessing
- several synchrony measures
  correlation coefficient, phase synchrony, Granger causality, ...
- actual seizure focus determined by clinicians from seizure EEG

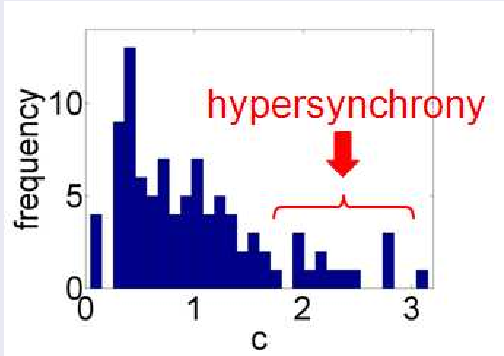
Some brain areas are consistently hypersynchronous

Strong local correlation in anterior temporal lobe

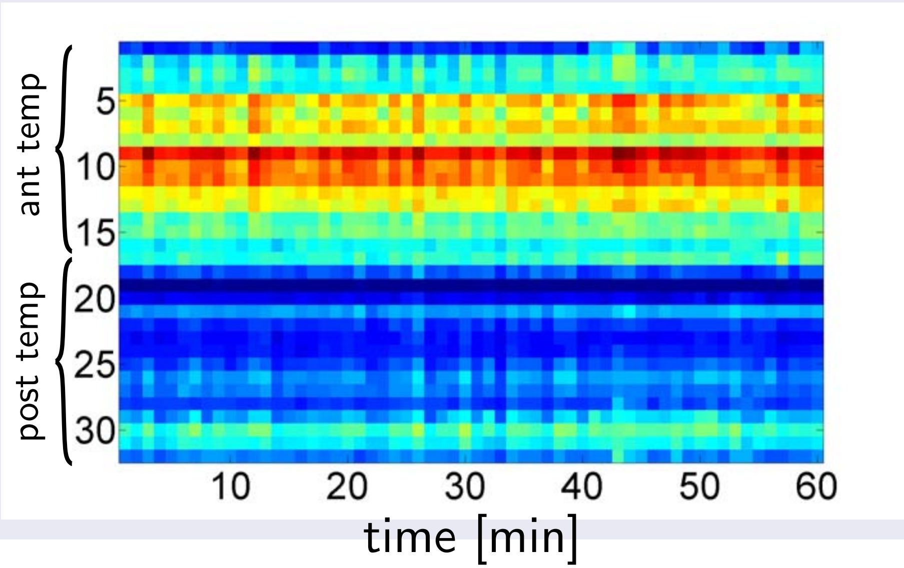
Patient 1 | correlation coeff c | histogram







Variability over time is small (less than 15%)



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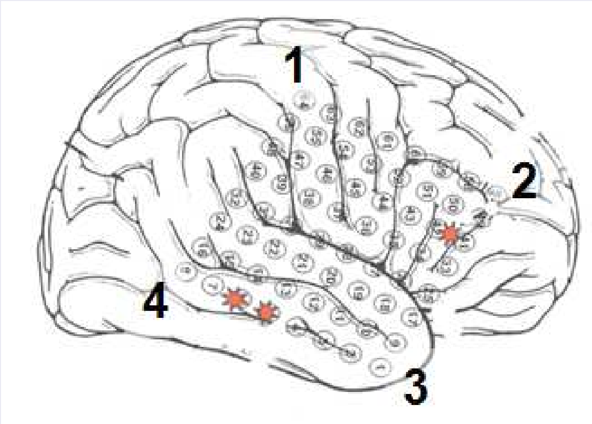
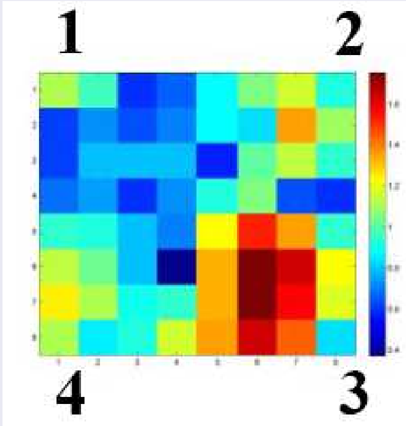
Strong local correlation in anterior temporal lobe

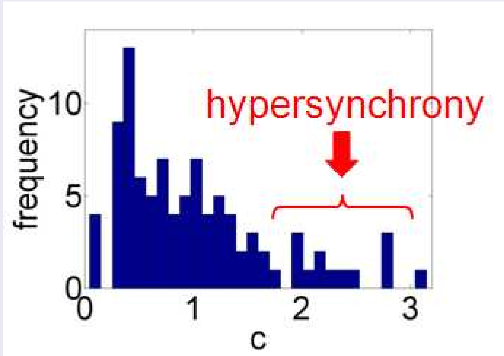
Patient 1



correlation coeff *c*

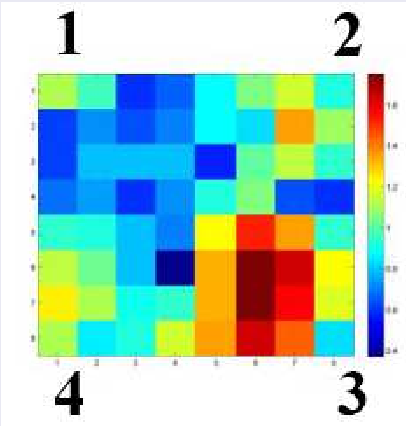


histogram

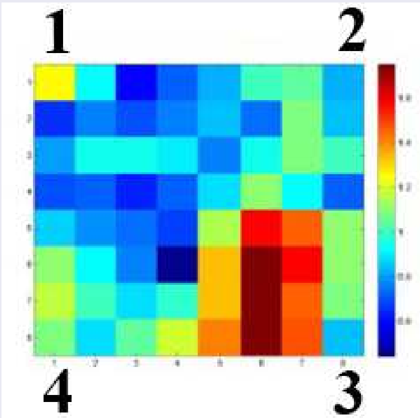


Very similar results for other synchrony measures

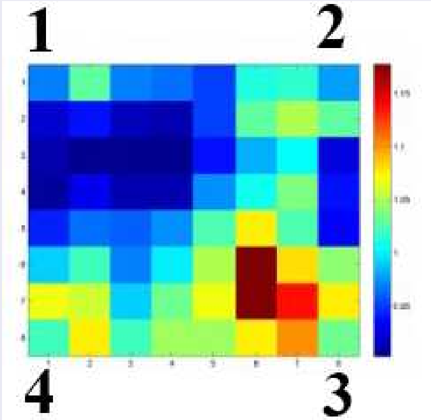
Phase Synchrony



Coherence



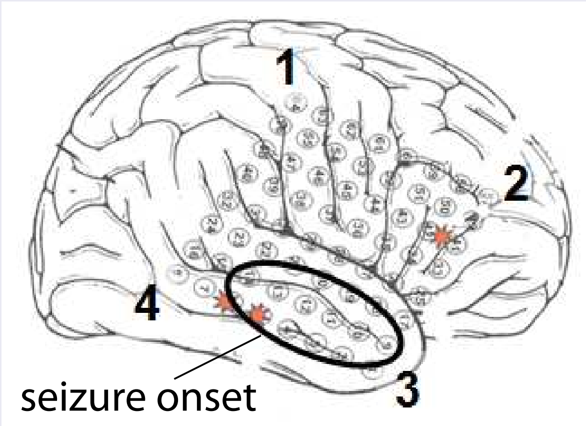
Granger causality (DTF)

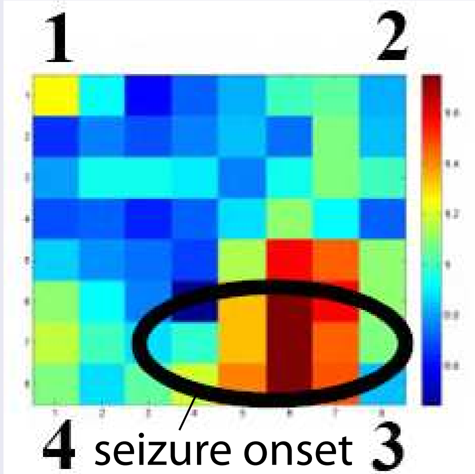


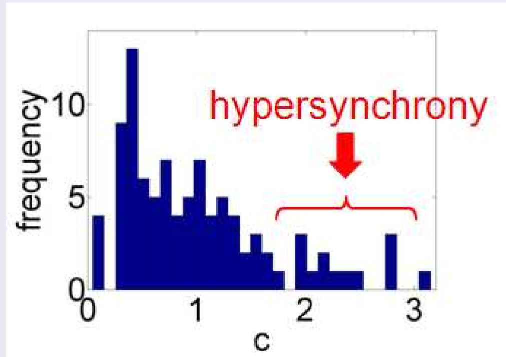
Hypersynchrony correlates strongly with seizure onset zone

Strong local correlation in anterior temporal lobe

Patient 1 | correlation coeff c | histogram

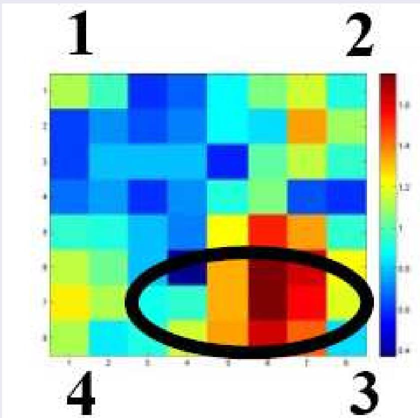


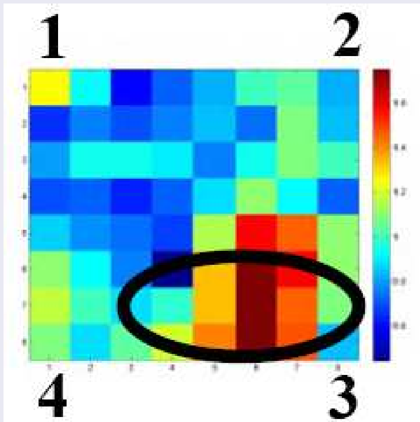


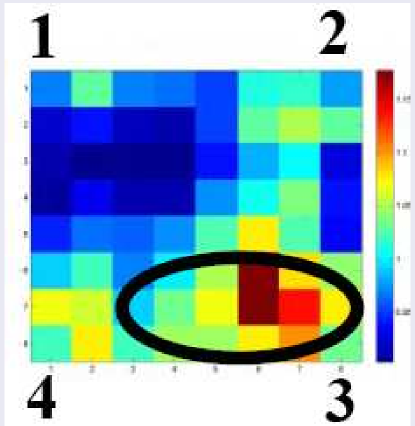


Very similar results for other synchrony measures

Phase Synchrony | Coherence | Granger causality (DTF)

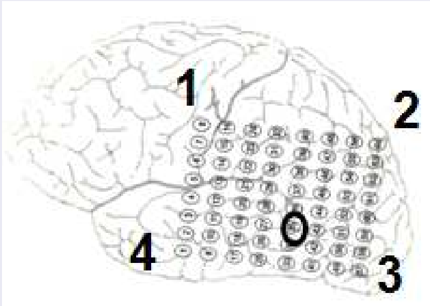


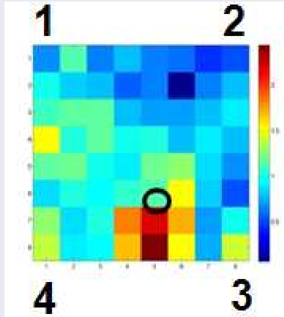




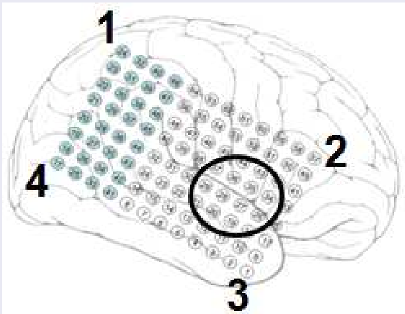
Same phenomenon also occurs in most other patients

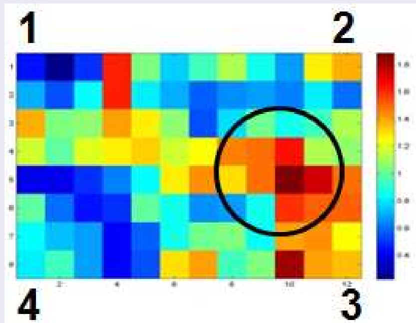
Patient 2 (left hemisphere) correlation coefficient



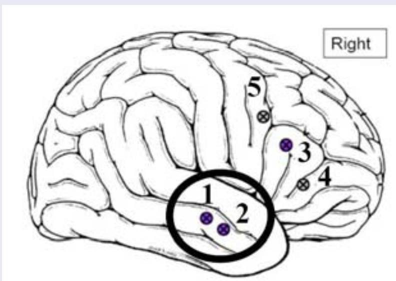


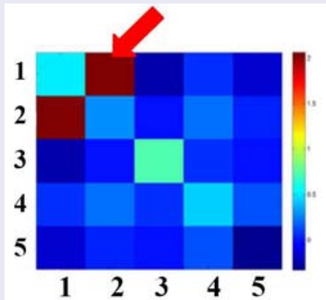
Patient 3 (right hemisphere)





Patient 4 (right hemisphere) (right - left)





Three main questions

1. Does hypersynchronous activity occur in rest EEG?

   Yes! (in **9** of the 11 patients analyzed so far)

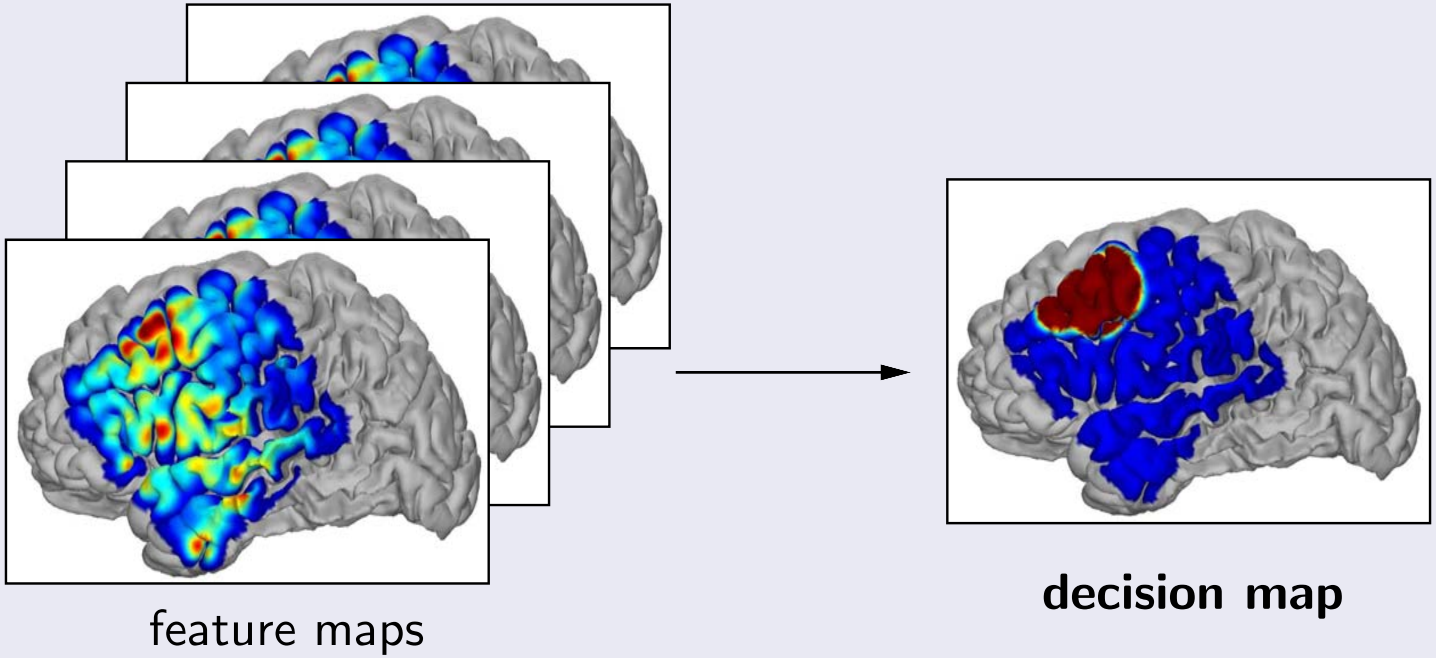
2. Do hypersynchronous areas correlate with seizure onset zone?

   Yes! (in **8** of the 11 patients analyzed so far)

3. How to determine seizure onset zone using hypersynchrony?

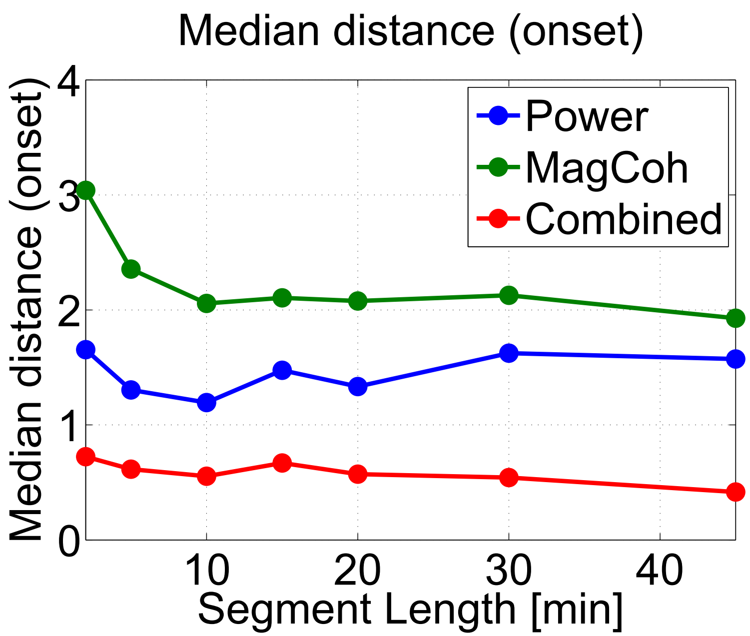
   Statistical decision making, using a **graphical model**

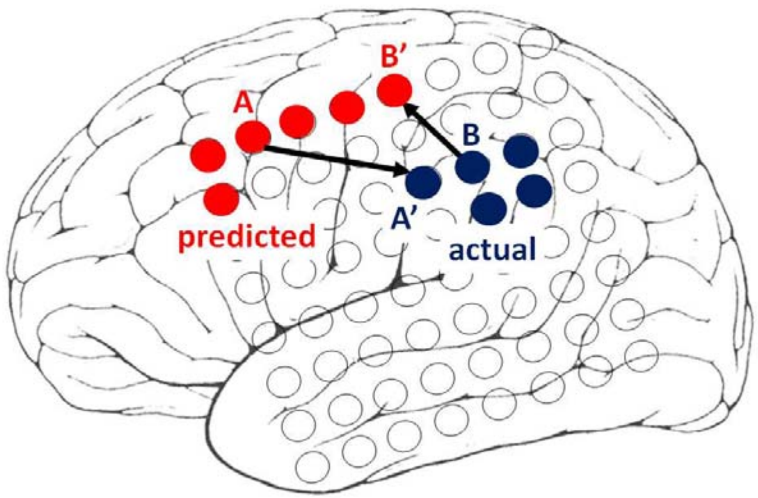
Exploit hypersynchrony to determine seizure onset zone



- Many feature maps
  different frequency bands, different measures
- Noisy!

Reliable localization of seizure focus





- Magnitude coherence in several frequency bands (1–5Hz, 5–20Hz, 20–35Hz, . . . , 80–95Hz)
- Relative power within 1–5Hz band
- Average over segments of length 2min, 5min, . . . , 45min
- Short segment seems to suffice (20 min)

Summary

- **First-ever** automated procedure to detect seizure focus from interictal recordings
- Exploits hypersynchrony and slowing effect
- Straightforward to include additional features
- Reliable estimates of seizure focus
- **Shorter** hospitalization
  5 days to several weeks → 1 day or less.

Topics

Signal Processing Aided Diagnosis

Loss in EEG synchrony → diagnosis of early-Alzheimer's

We needed to develop **novel** measures of synchrony

Signal Processing Aided Treatment

Increased EEG synchrony → localization of epileptic brain tissue

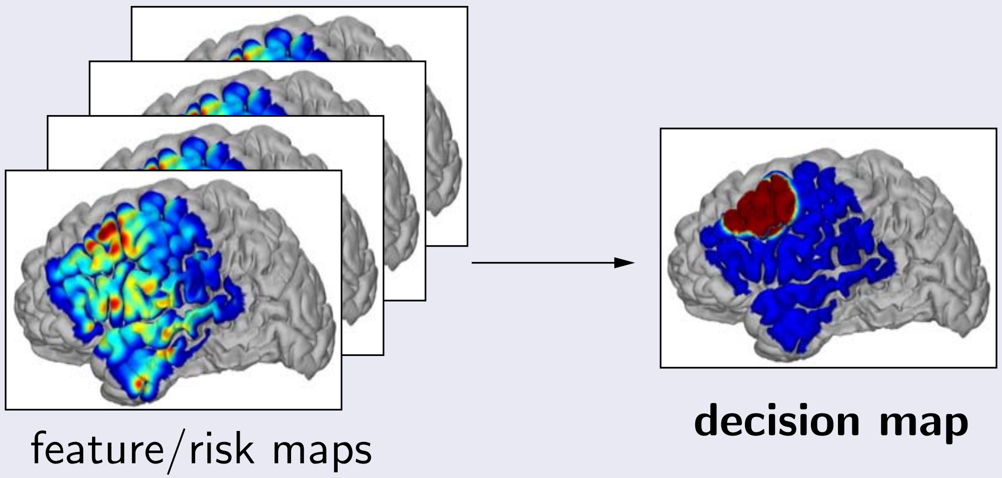
Existing synchrony measures proved to be effective

Future Work

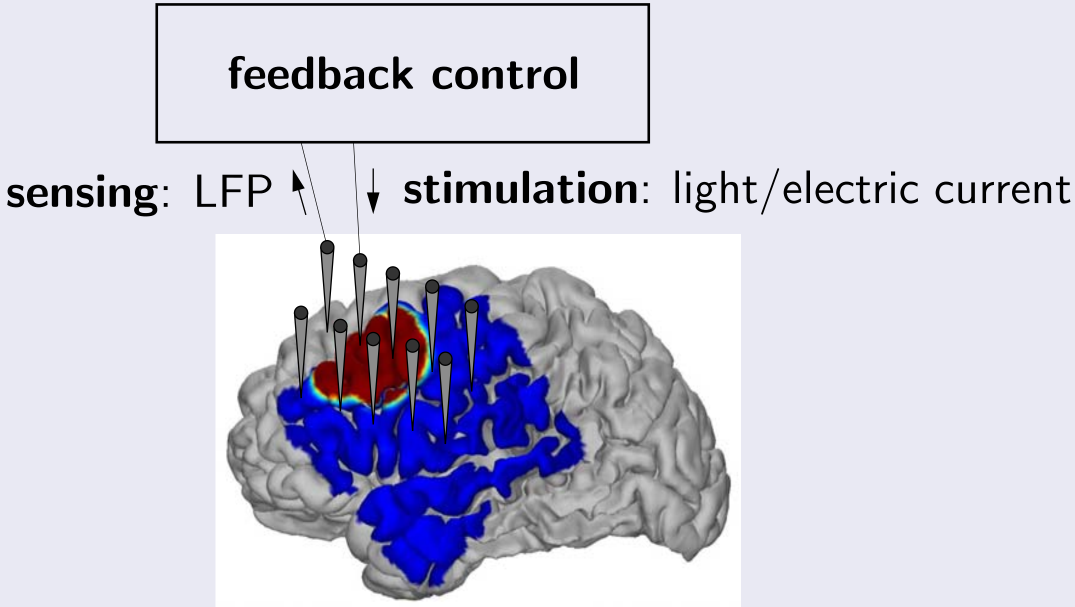
Two future research projects

Localization of Seizure Focus w/o Relying on Seizures

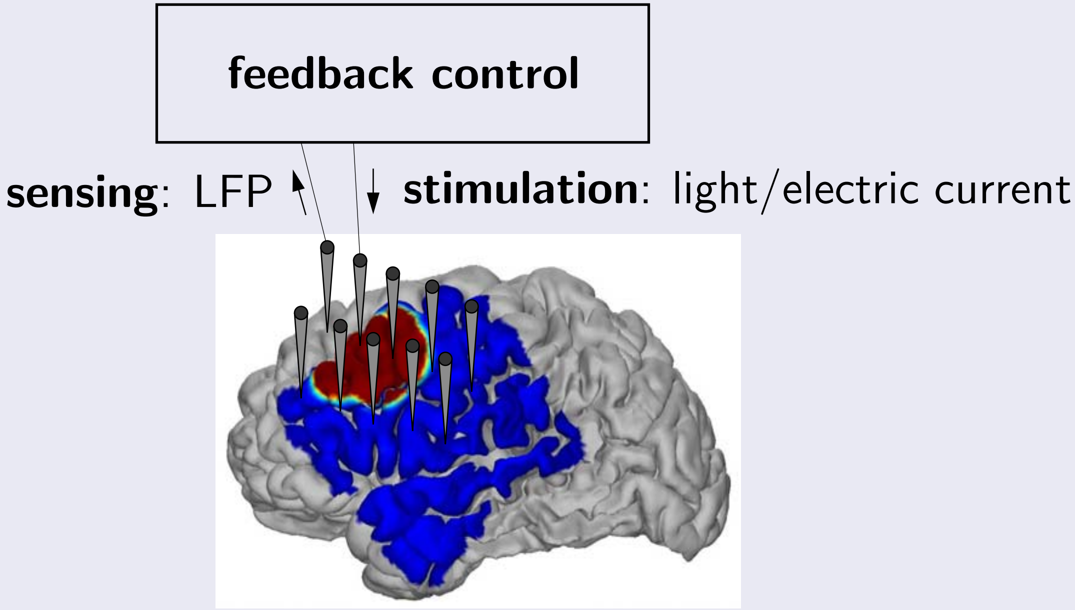
- **Multiple information sources**
  - Brain imaging (EEG, MEG, SPECT, PET, CT, MR, DTI)
  - Clinical behavior
  - Biochemical markers (e.g., neurotransmitters)
  - Genetic data
  - Biophysical models
- **Risk factors**



Brain Implants for Seizure Suppression

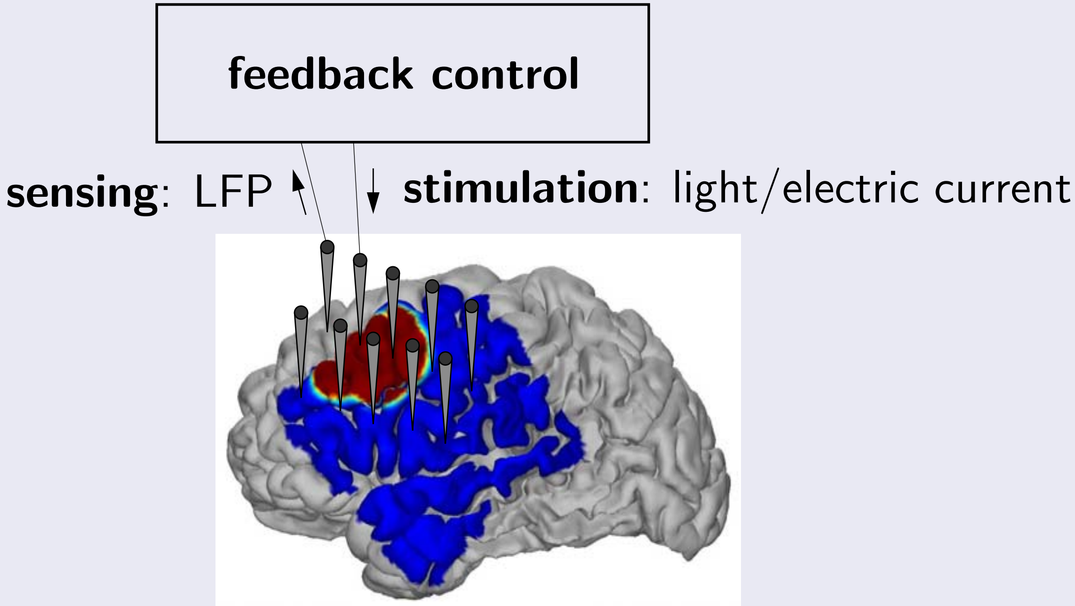


Brain Implants for Seizure Suppression



- **Electrical** stimulation: treatment of PD, recently also epilepsy
- **Photonic** stimulation: optogenetics
  Advantages: better resolution, more specific, less side effects

Brain Implants for Seizure Suppression



- **Electrical** stimulation: treatment of PD, recently also epilepsy
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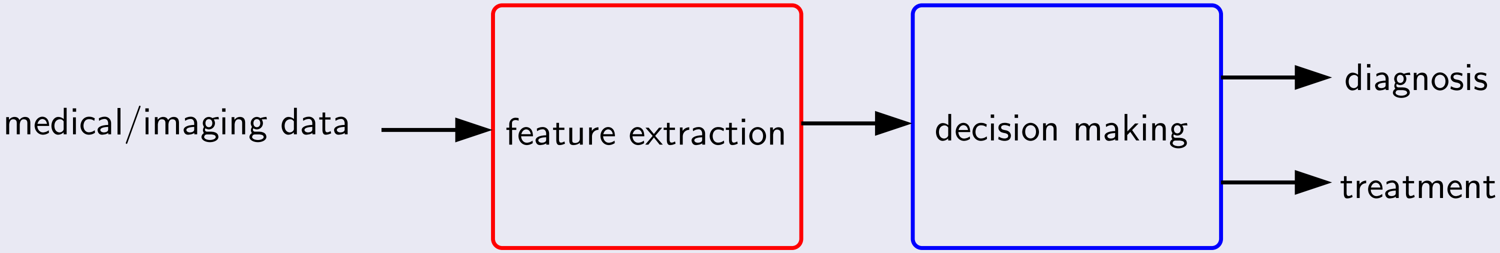
How to design feedback control?

Back to the big picture . . .



- Signal processing "microscope"
  discovery of **features/patterns** in data associated with certain **disorders**
- Algorithmic decision making
  combine **evidence** "optimally" $\longrightarrow$ **diagnosis** and **treatment**

- More reliable and earlier diagnosis
- More effective treatment (clinical outcome, time and cost)

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- François Vialatte (RIKEN)
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SES: Applications beyond AD

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Diagnosis of AD

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- Emad Eskandar (MGH/Harvard)
- Ed Boyden, J.J. Slotine (MIT)
- Al Willsky, Emery Brown (MIT)
- . . .

Analogy: Waiting for a train

- Train may not arrive (e.g., mechanical problem)
  = **event reliability** ρ
- Train may or may not be on time
  = **timing precision** s_t