

# The Human Brain Project, a high-impact playground for quantitative sciences

25 Gennaio 2015 ore 14.00 - Aula Conversi, Dipartimento di Fisica, "Sapienza" Univ. di Roma



## Human Brain Project

Unify our understanding of the human brain

## Misurare la coscienza: un approccio perturbazionale

Marcello Massimini MD, PhD

Mario Rosanova MD, PhD

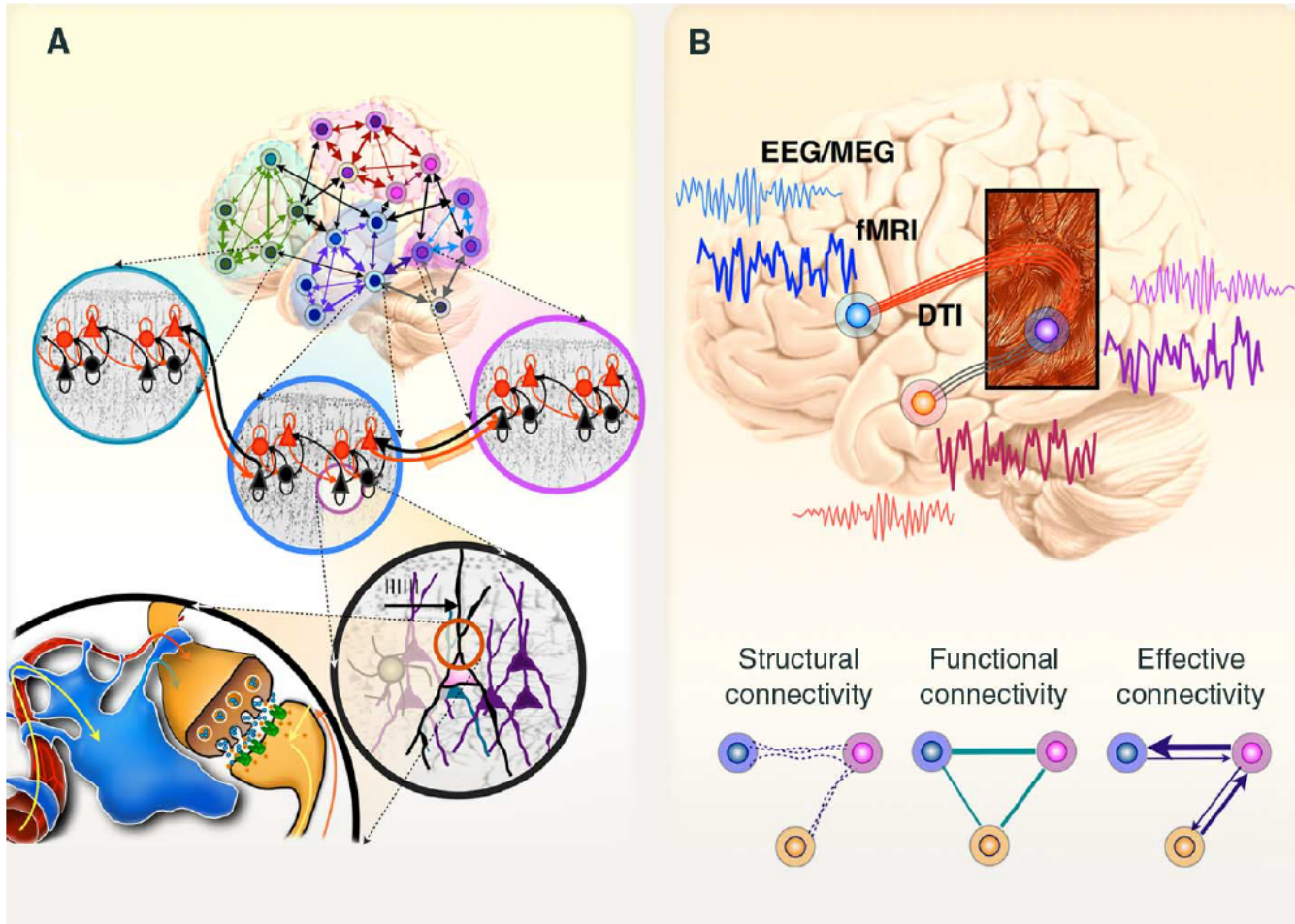


UNIVERSITÀ DEGLI STUDI DI MILANO

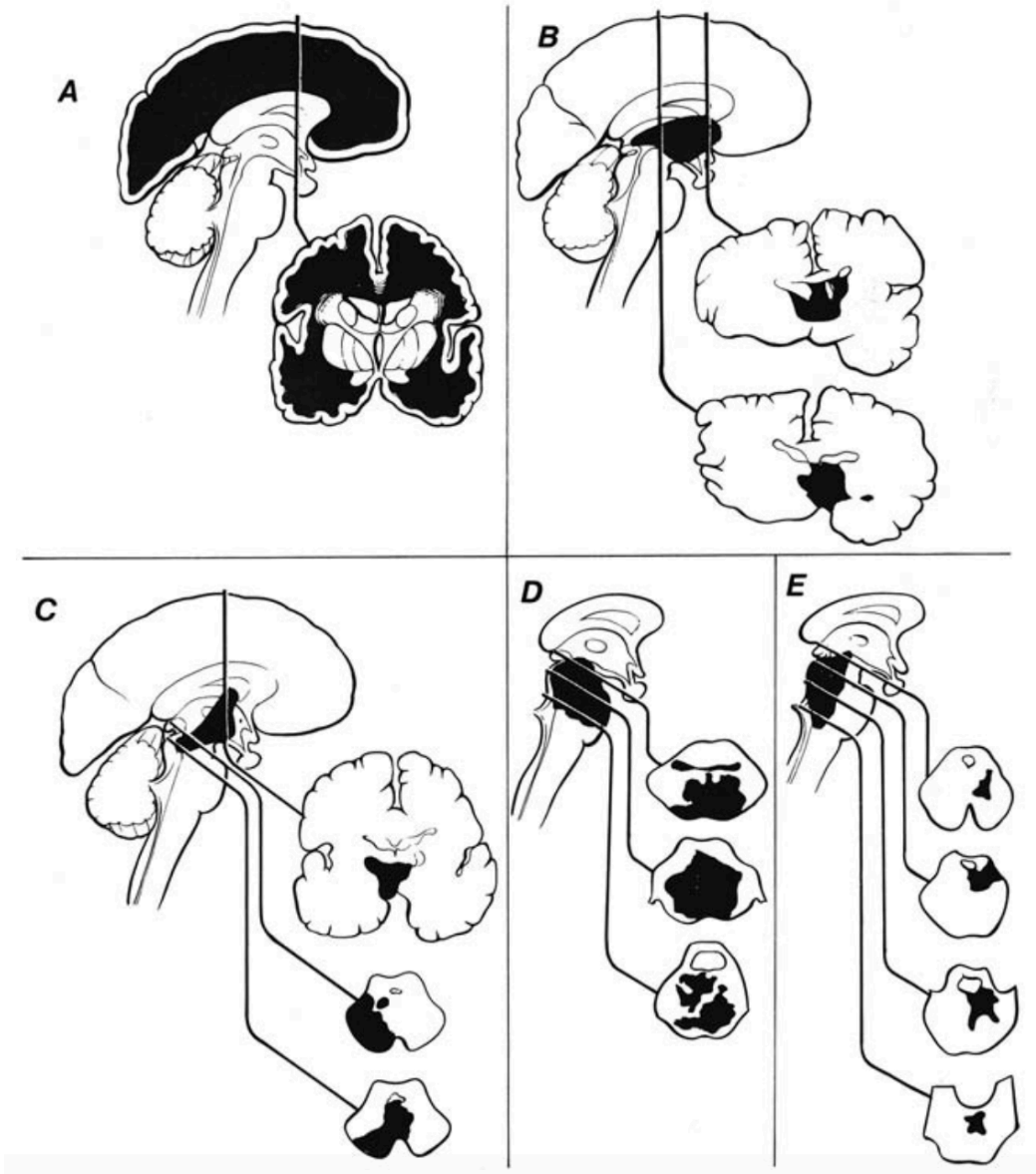
DIPARTIMENTO DI SCIENZE BIOMEDICHE  
E CLINICHE "LUIGI SACCO"

*marcello.massimini@unimi.it*

*mario.rosanova@unimi.it*







# Coma



*With the patient's family permission*

?



*With the patient's family permission*

# Coma

## CRS-R

### COMA RECOVERY SCALE-REVISED

©2004

#### Administration and Scoring Guidelines

Joseph T. Giacino, Ph.D. and Kathleen Kalmar, Ph.D.

*Center for Head Injuries  
Edison, New Jersey*



Johnson Rehabilitation Institution  
Affiliated with JFK Medical Center



Updated 11-1-05

### JFK COMA RECOVERY SCALE - REVISED ©2004

Record Form

*This form should only be used in association with the "CRS-R ADMINISTRATION AND SCORING GUIDELINES" which provide instructions for standardized administration of the scale.*

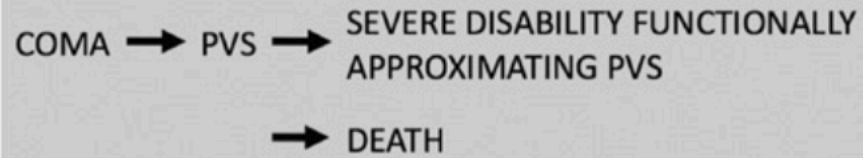
Patient:		Diagnosis:		Etiology:																
Date of Onset:		Date of Admission:																		
	Date																			
	Week	ADM	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16			
<b>AUDITORY FUNCTION SCALE</b>																				
4 - Consistent Movement to Command *																				
3 - Reproducible Movement to Command *																				
2 - Localization to Sound																				
1 - Auditory Startle																				
0 - None																				
<b>VISUAL FUNCTION SCALE</b>																				
5 - Object Recognition *																				
4 - Object Localization: Reaching *																				
3 - Visual Pursuit *																				
2 - Fixation *																				
1 - Visual Startle																				
0 - None																				
<b>MOTOR FUNCTION SCALE</b>																				
6 - Functional Object Use †																				
5 - Automatic Motor Response *																				
4 - Object Manipulation *																				
3 - Localization to Noxious Stimulation *																				
2 - Flexion Withdrawal																				
1 - Abnormal Posturing																				
0 - None/Flaccid																				
<b>OROMOTOR/VERBAL FUNCTION SCALE</b>																				
3 - Intelligible Verbalization *																				
2 - Vocalization/Oral Movement																				
1 - Oral Reflexive Movement																				
0 - None																				
<b>COMMUNICATION SCALE</b>																				
2 - Functional: Accurate †																				
1 - Non-Functional: Intentional *																				
0 - None																				
<b>AROUSAL SCALE</b>																				
3 - Attention																				
2 - Eye Opening w/o Stimulation																				
1 - Eye Opening with Stimulation																				
0 - Unarousable																				
<b>TOTAL SCORE</b>																				

Denotes emergence from MCS †

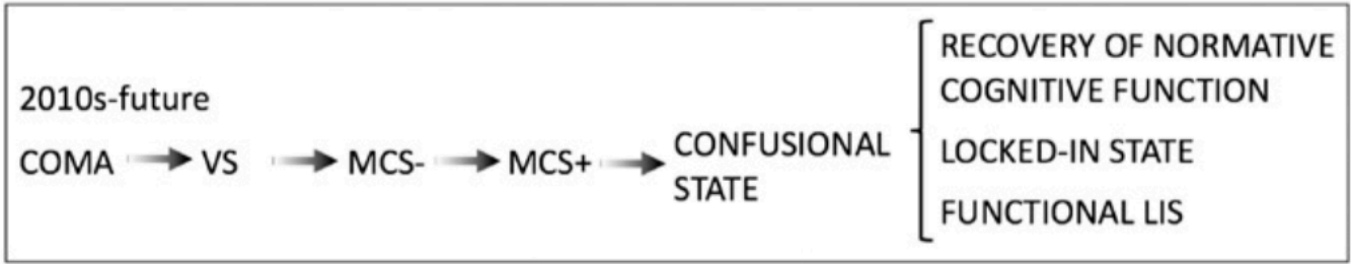
Denotes MCS \*

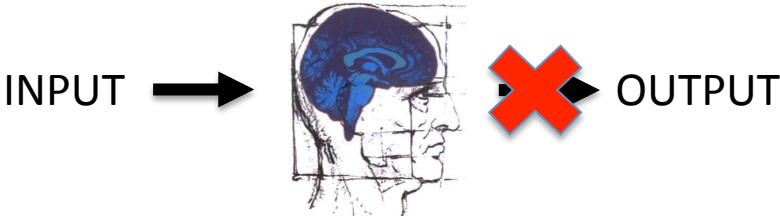
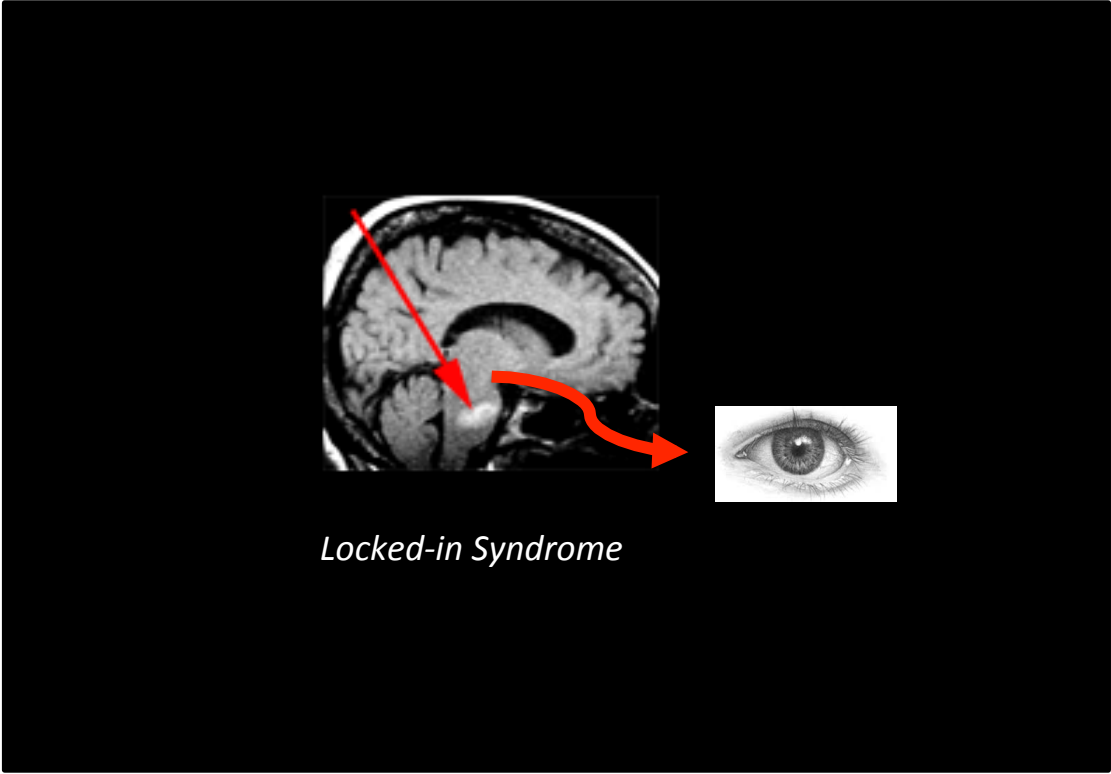


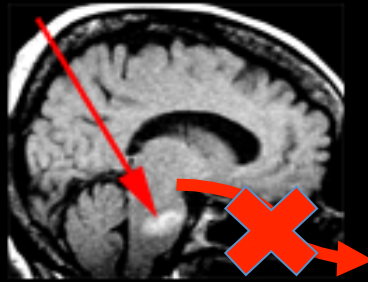
1970-90s



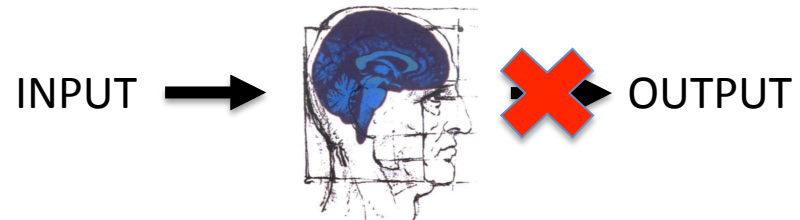


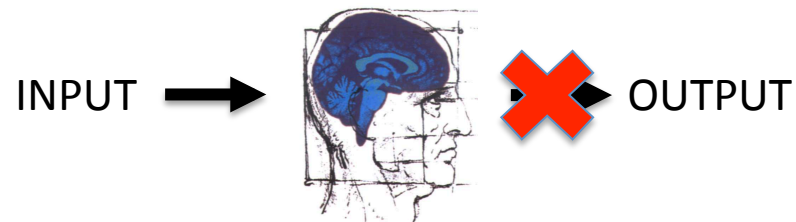
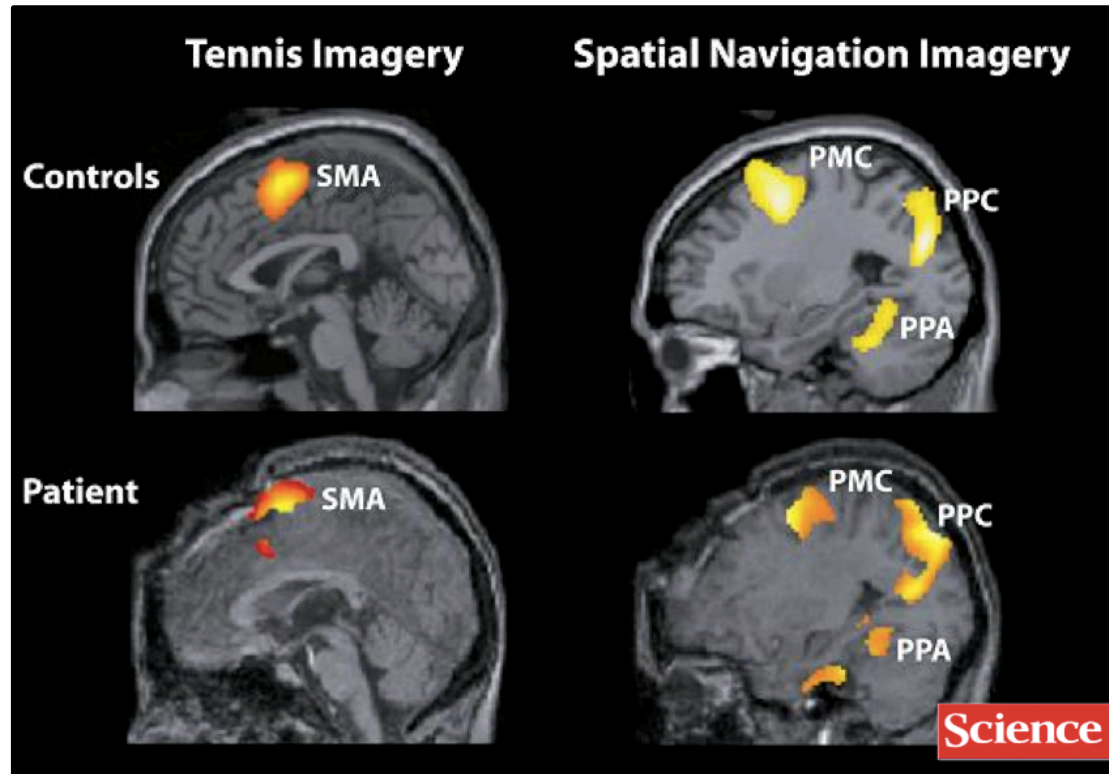






*Complete Locked-in Syndrome*

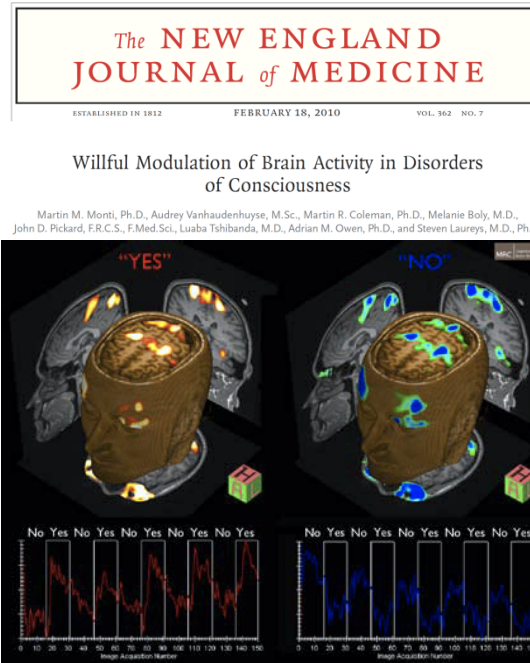
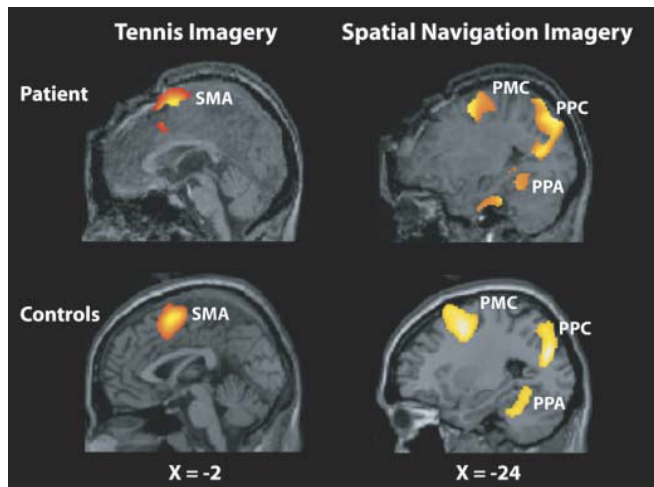




# Probe the subject to elicit a neural response

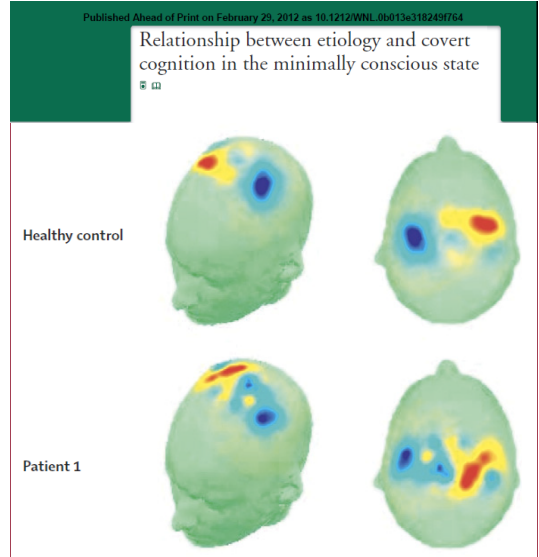
## Detecting Awareness in the Vegetative State

Adrian M. Owen,<sup>1\*</sup> Martin R. Coleman,<sup>2</sup> Melanie Boly,<sup>3</sup> Matthew H. Davis,<sup>1</sup> Steven Laureys,<sup>3</sup> John D. Pickard<sup>2</sup>



## Bedside detection of awareness in the vegetative state: a cohort study

Damian Cruse, Srivas Chennu, Camille Chatelle, Tristan A Bekinschtein, Davinia Fernández-Espejo, John D Pickard, Steven Laureys, Adrian M Owen

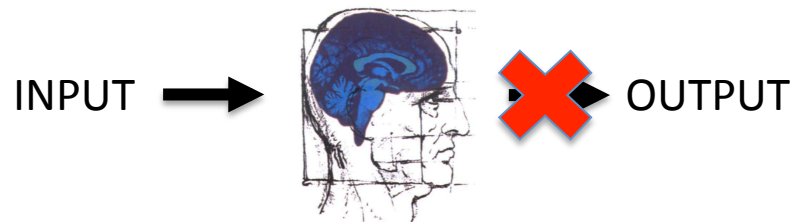
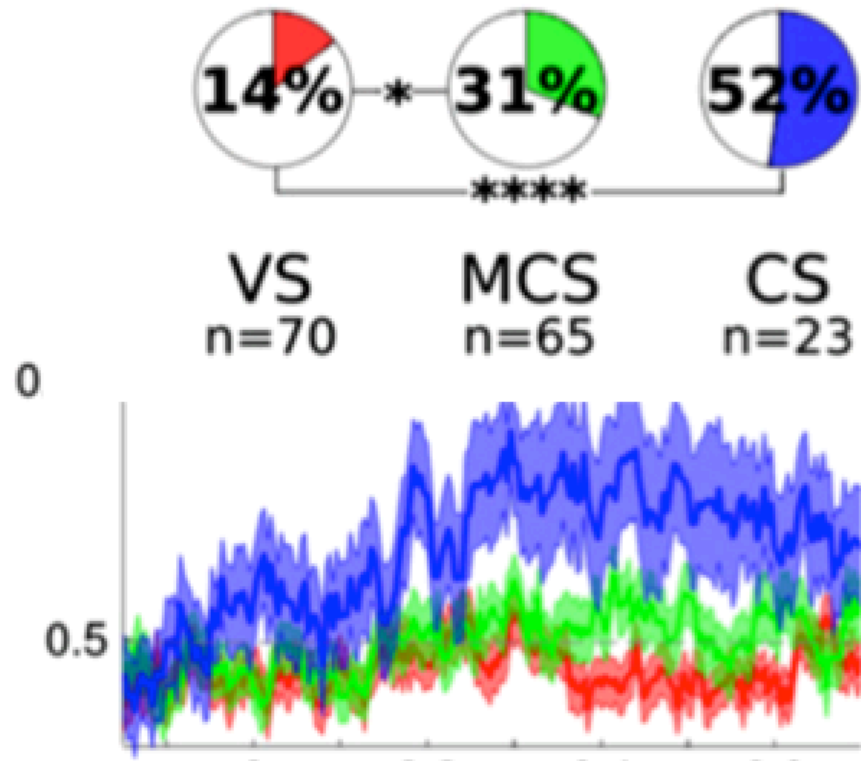


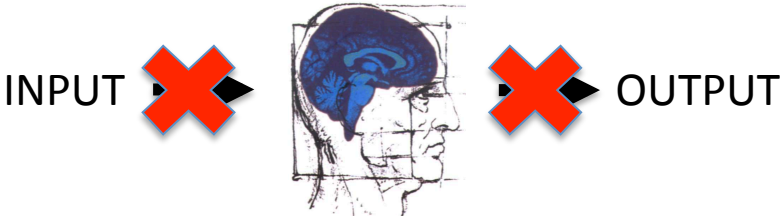
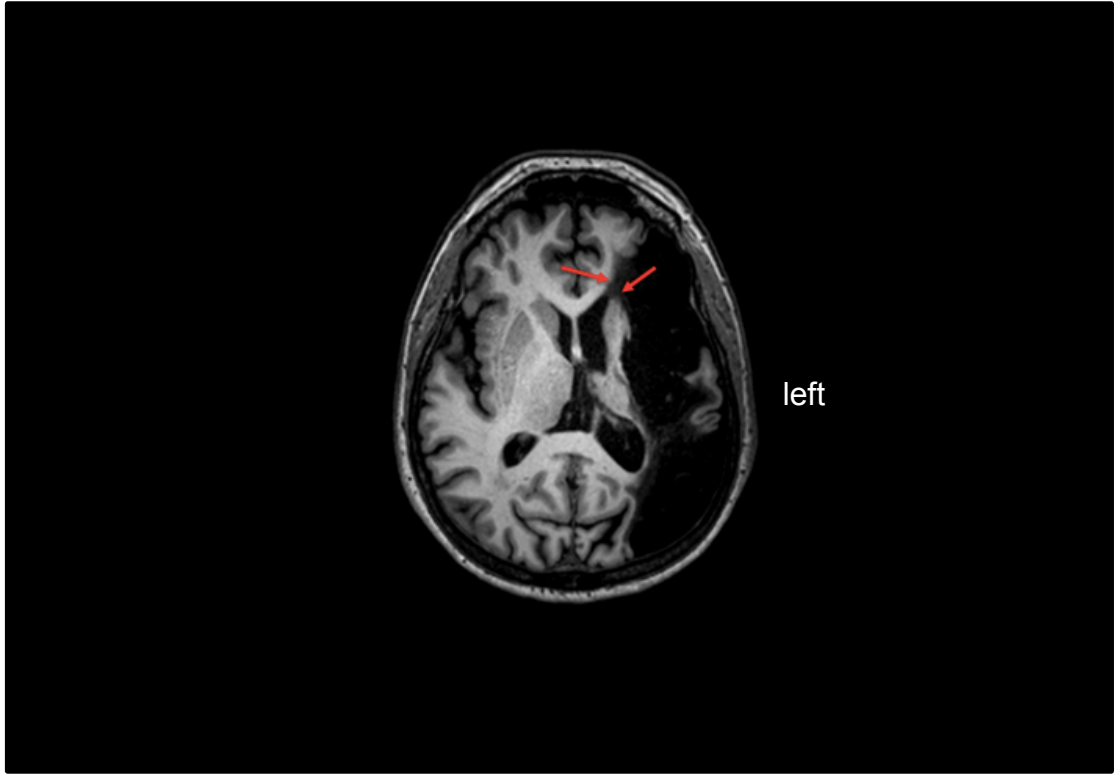
Owen et al., *Science* 2006; Boly et al., *Neuroimage* 2007; Monti et al., *NEJM* 2010; Monti et al., *BMJ* 2010; Cruse et al., *Lancet* 2011; Cruse et al., *Neurology* 2012

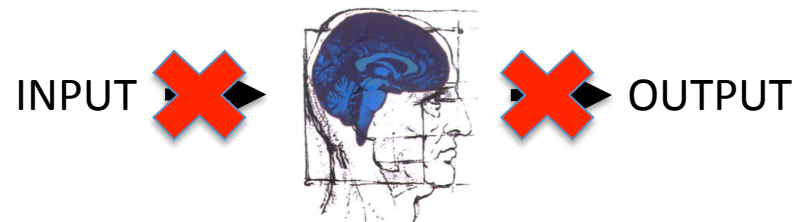


Patient No.	Location	Age	Sex	Diagnosis on Admission	Cause of Disorder	Interval since Ictus	Response on Motor Imagery Task	Response on Spatial Imagery Task
24	Cambridge	23	Male	MCS	TBI	11.0	No	No
25	Cambridge	38	Female	MCS	TBI	3.0	No	NA
26	Cambridge	18	Male	MCS	TBI	8.0	No	No
27	Cambridge	26	Male	MCS	TBI	11.0	No	NA
28	Cambridge	64	Male	MCS	TBI	6.0	No	No
29	Cambridge	54	Female	MCS	Brain-stem stroke	5.0	No	No
30	Cambridge	29	Female	MCS	TBI	2.0	No	NA
31	Cambridge	19	Female	MCS	TBI	1.0	No	No
32	Cambridge	34	Male	MCS	TBI	52.0	No	NA
33	Cambridge	17	Male	MCS	TBI	7.0	No	NA
34	Cambridge	56	Male	MCS	Anoxic brain injury	6.0	No	No
35	Cambridge	21	Male	MCS	TBI	51.0	No	No
36	Cambridge	53	Female	MCS	Anoxic brain injury	13.0	No	No
37	Cambridge	36	Male	MCS	TBI	30.0	No	NA
38	Cambridge	25	Male	MCS	TBI	8.0	No	No

# ERP: P3b



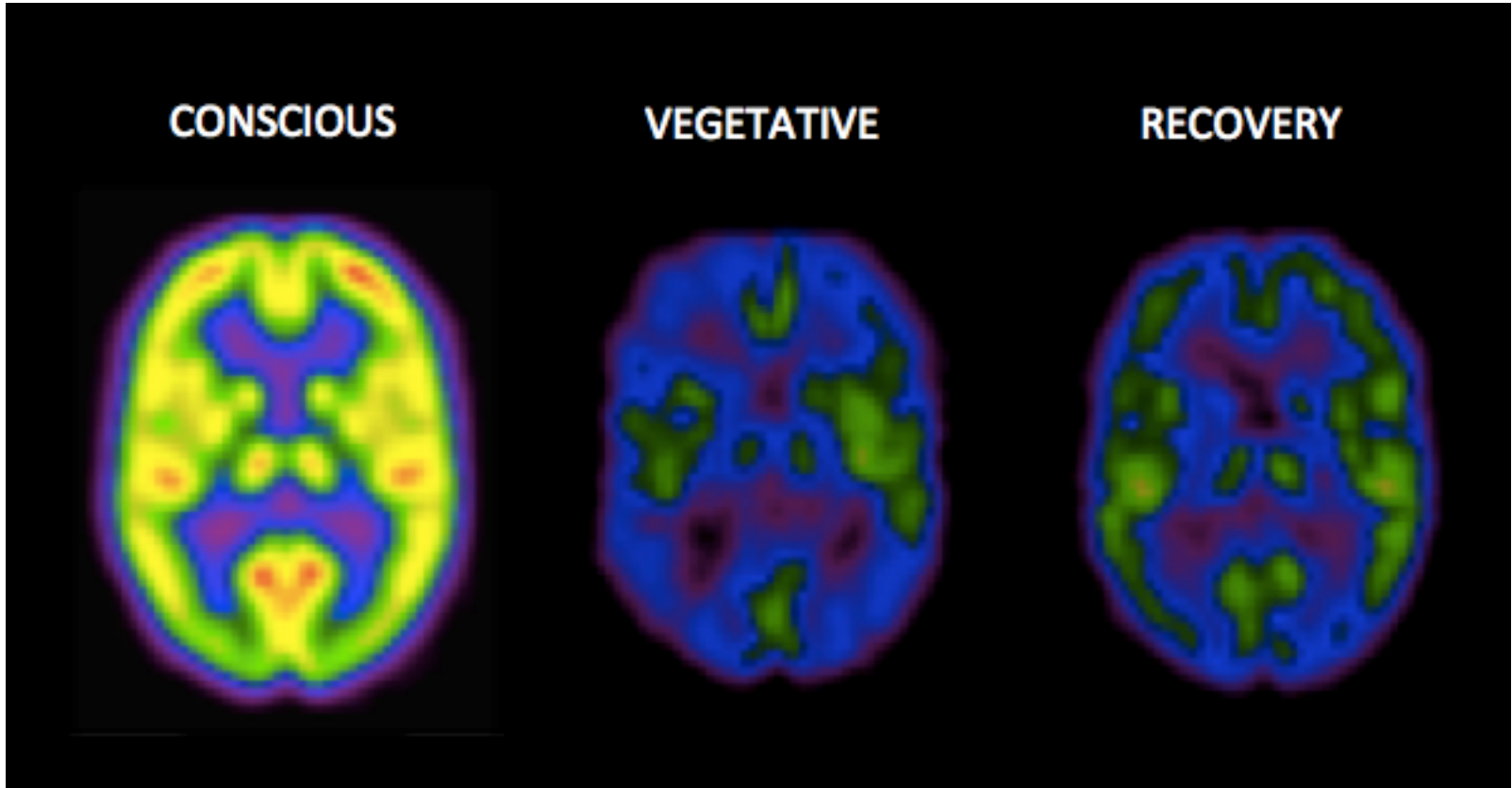




*Modified from S. D'Alì "The dream"*



level of neural activity?

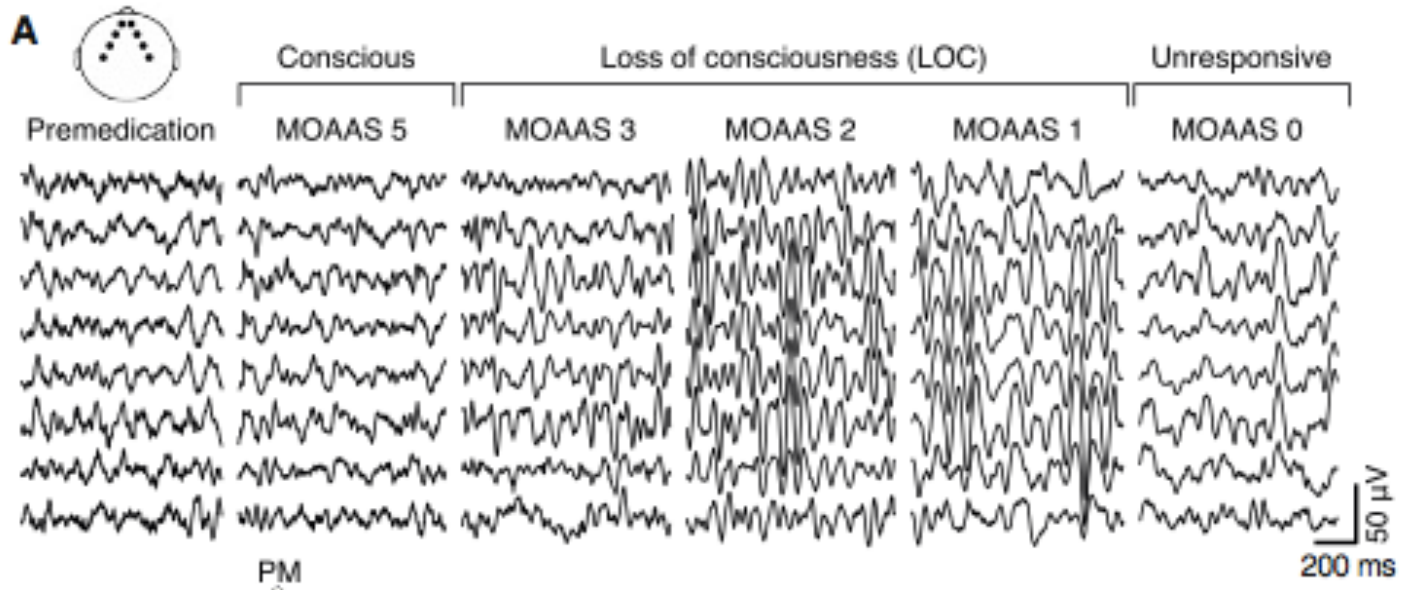








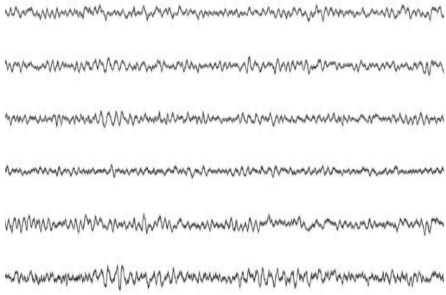
# synchrony of neural activity?





# spectral features?

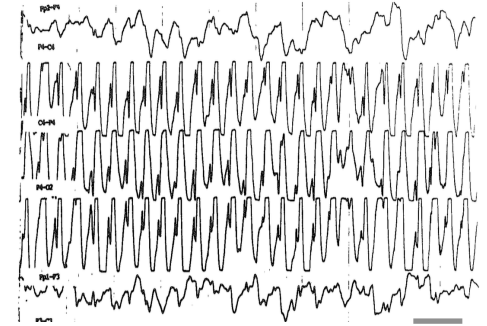
## Alpha Coma



1 s



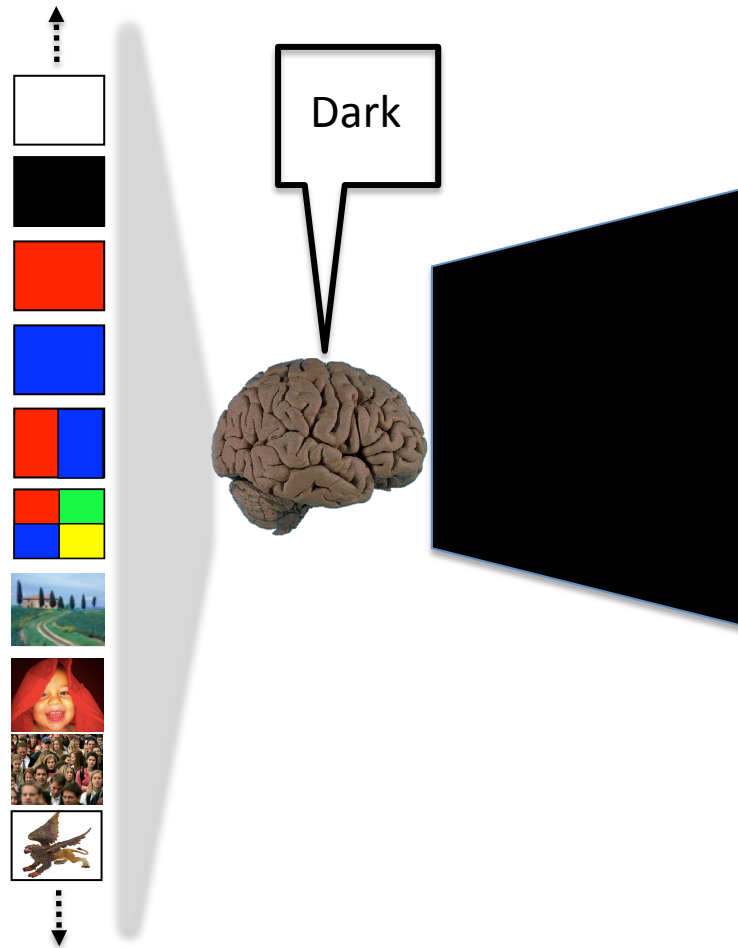
## Status Epilepticus



1 s

# IITC

PHENOMENOLOGY: CONSCIOUS EXPERIENCE IS, AT ONCE, DIFFERENTIATED and INTEGRATED



# IITC

PHENOMENOLOGY: CONSCIOUS EXPERIENCE IS, AT ONCE, DIFFERENTIATED and INTEGRATED

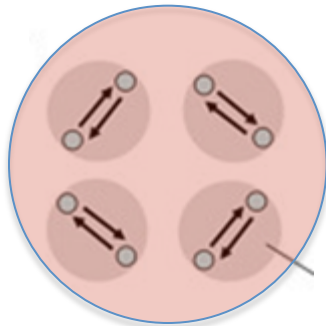




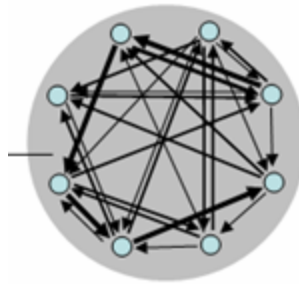
**Consciousness** in the brain depends on the optimal **balance**  
between functional integration and differentiation  
 $\cong$  *Complexity*

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between functional integration and differentiation  
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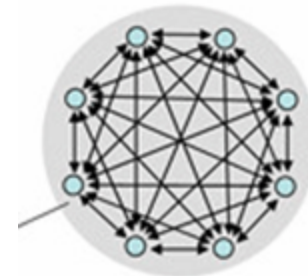
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no integration

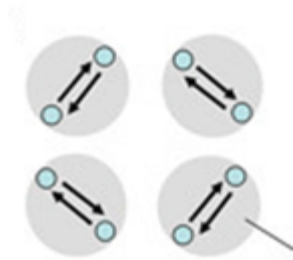


complexity

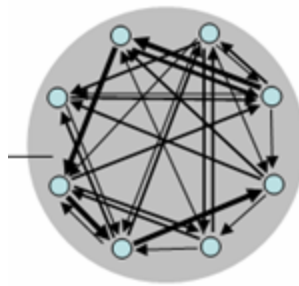


no differentiation

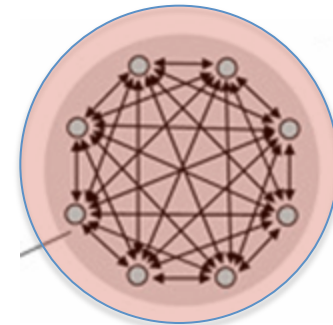
**Consciousness** in the brain depends on the optimal **balance** between functional integration and differentiation  
 $\cong$  *Complexity*



no integration

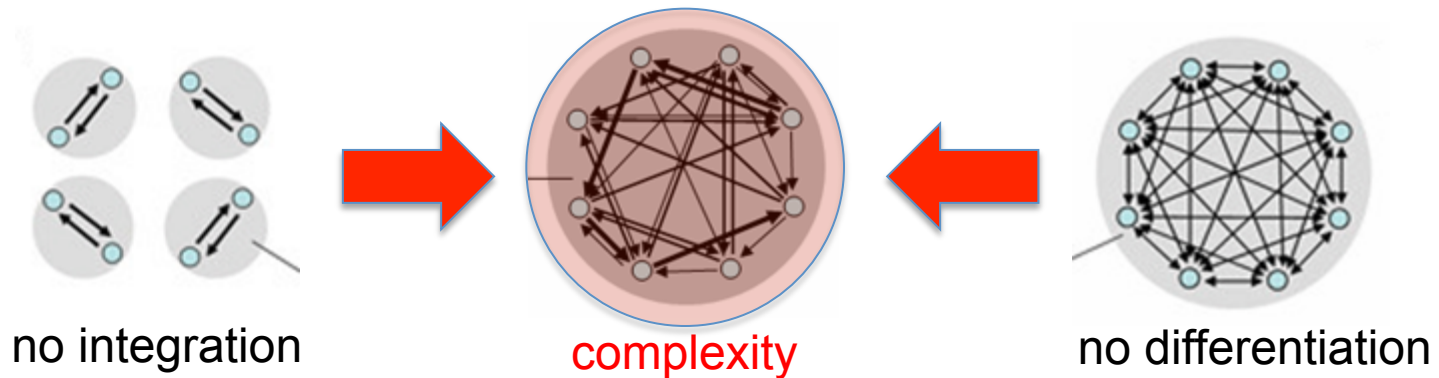


complexity



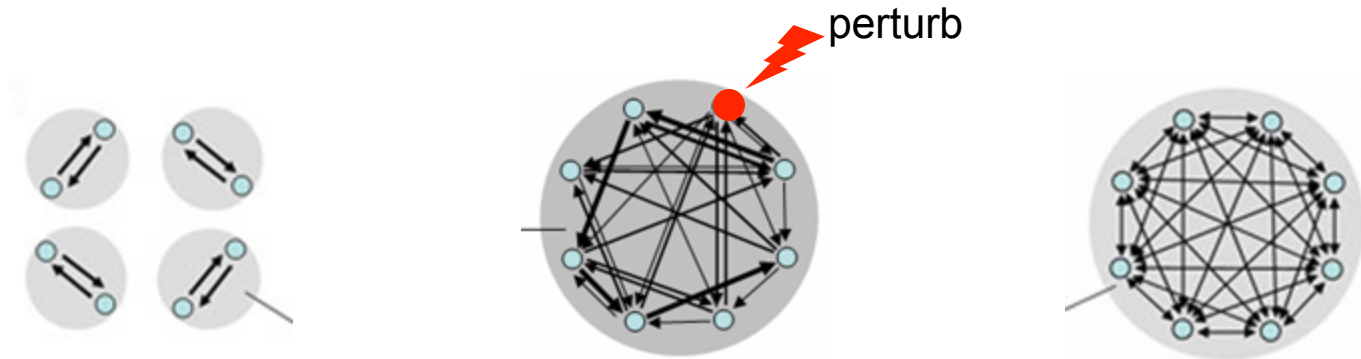
no differentiation

**Consciousness** in the brain depends on the optimal **balance** between functional integration and differentiation  
 $\cong$  *Complexity*



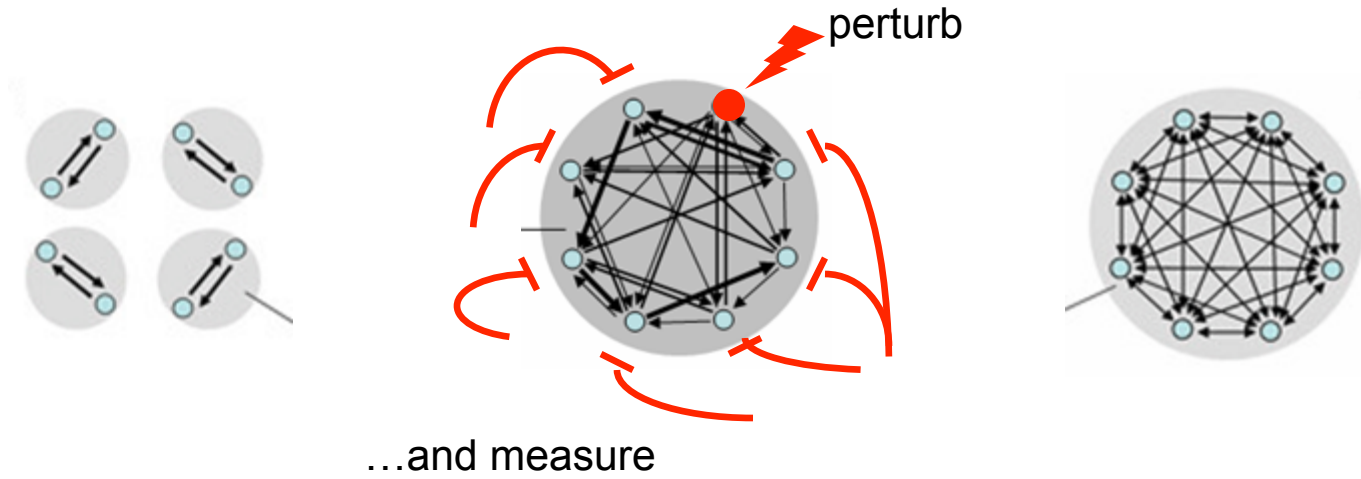
## an empirical approximation

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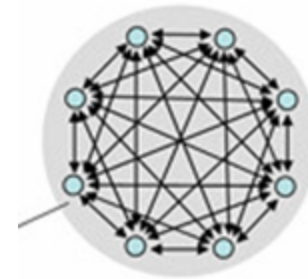
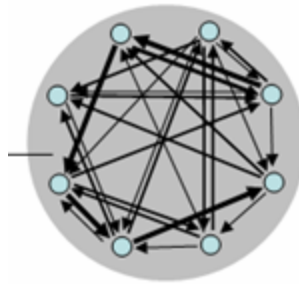
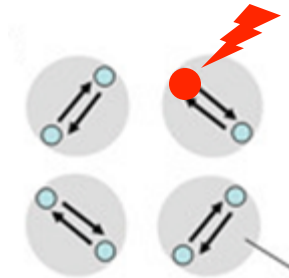
an empirical approximation

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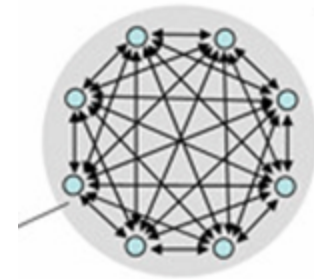
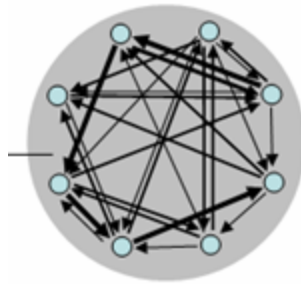
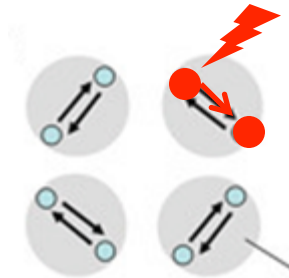
## an empirical approximation

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## an empirical approximation

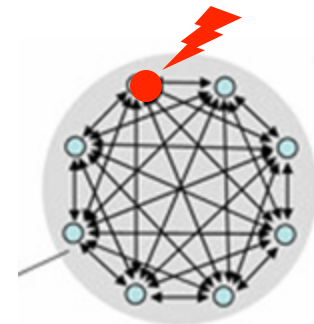
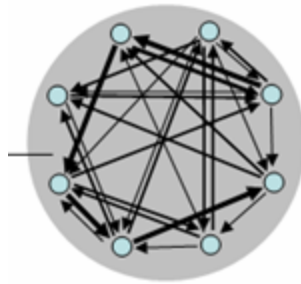
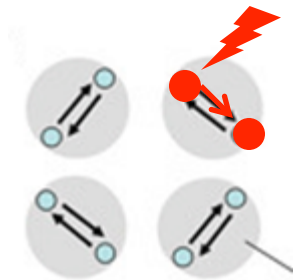
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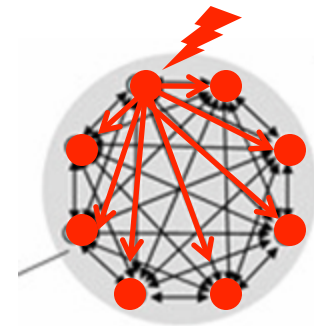
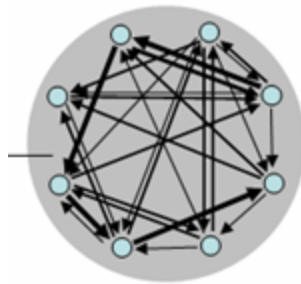
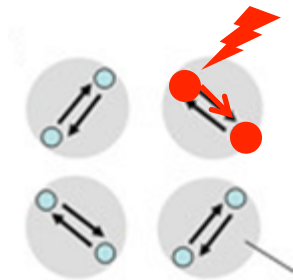
## an empirical approximation

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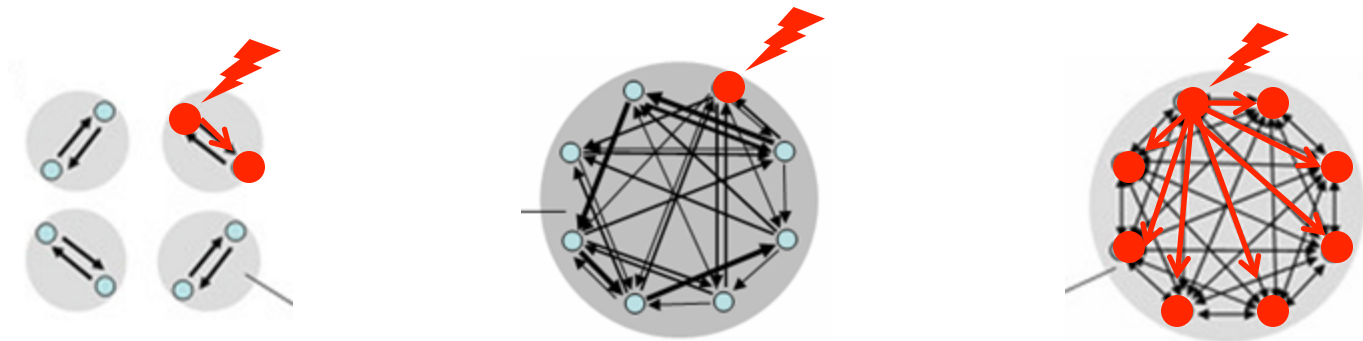
## an empirical approximation

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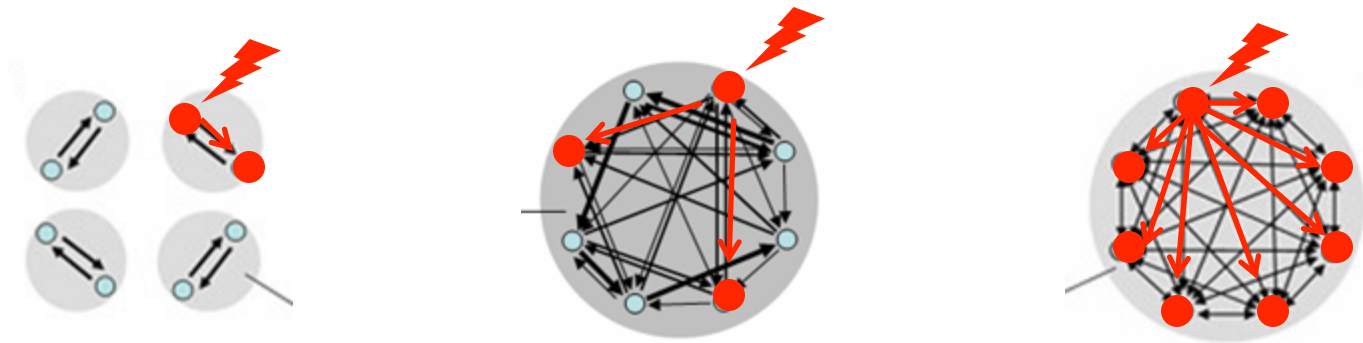
## an empirical approximation

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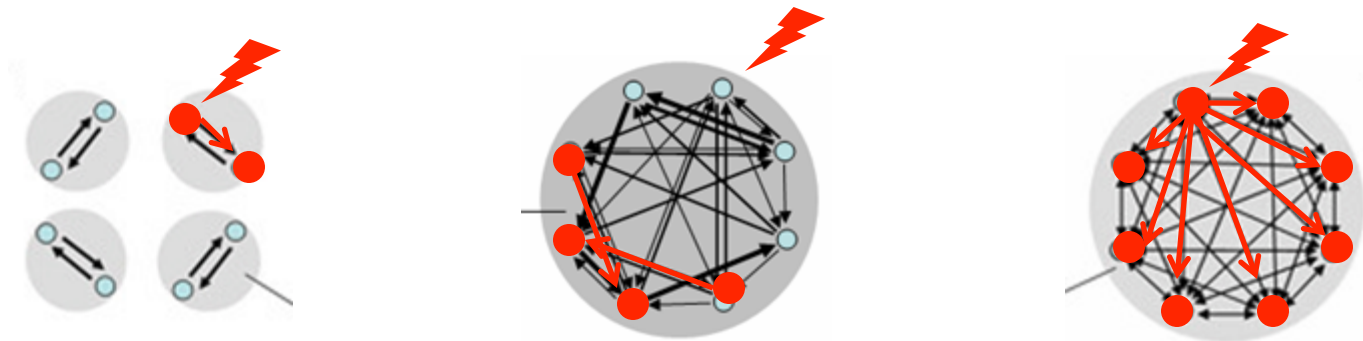
## an empirical approximation

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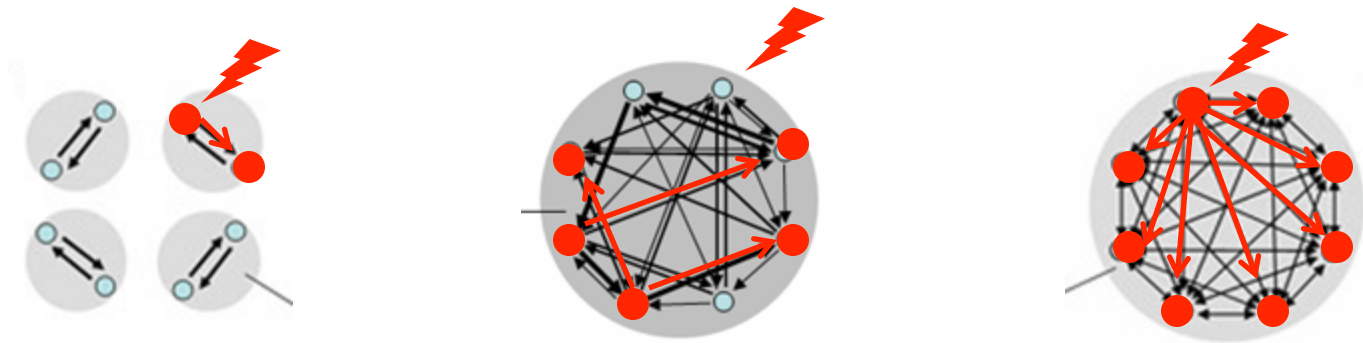
## an empirical approximation

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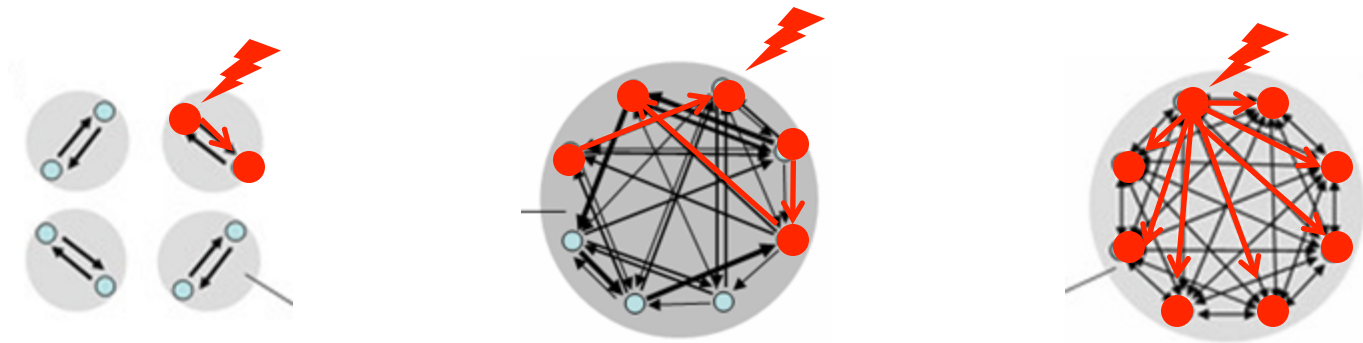
## an empirical approximation

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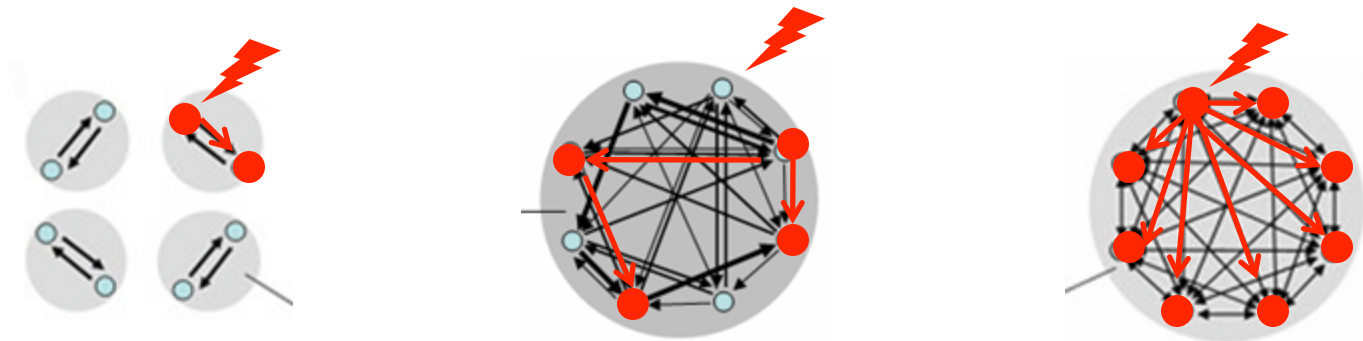
## an empirical approximation

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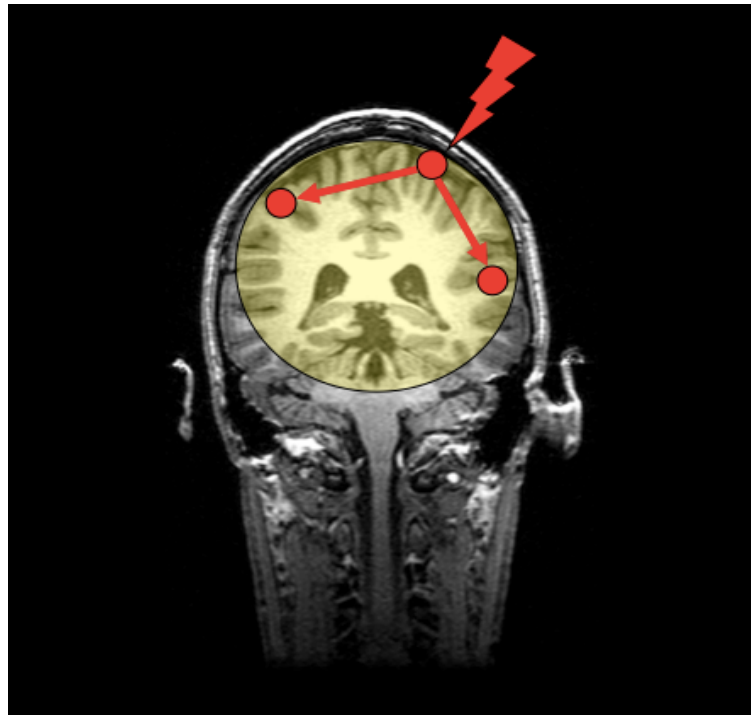
## an empirical approximation

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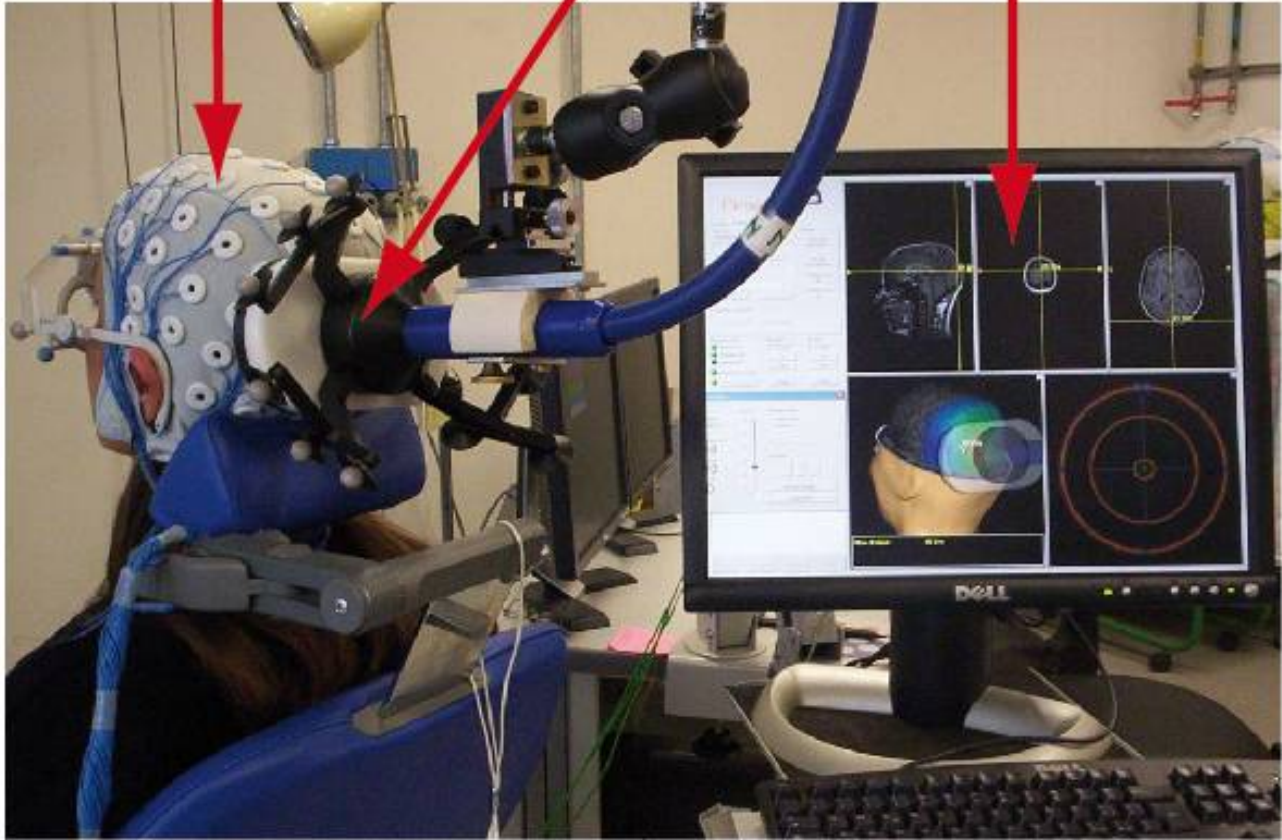
an empirical approximation



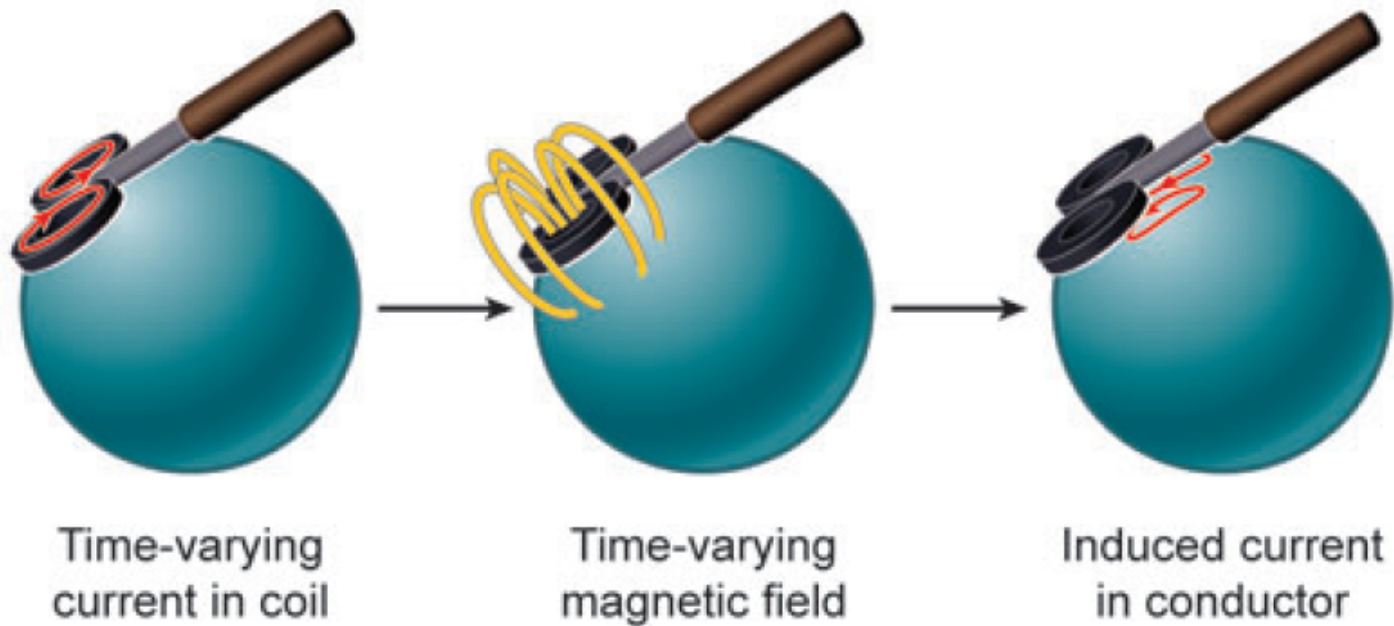
**hd-EEG**

**TMS**

**NBS**

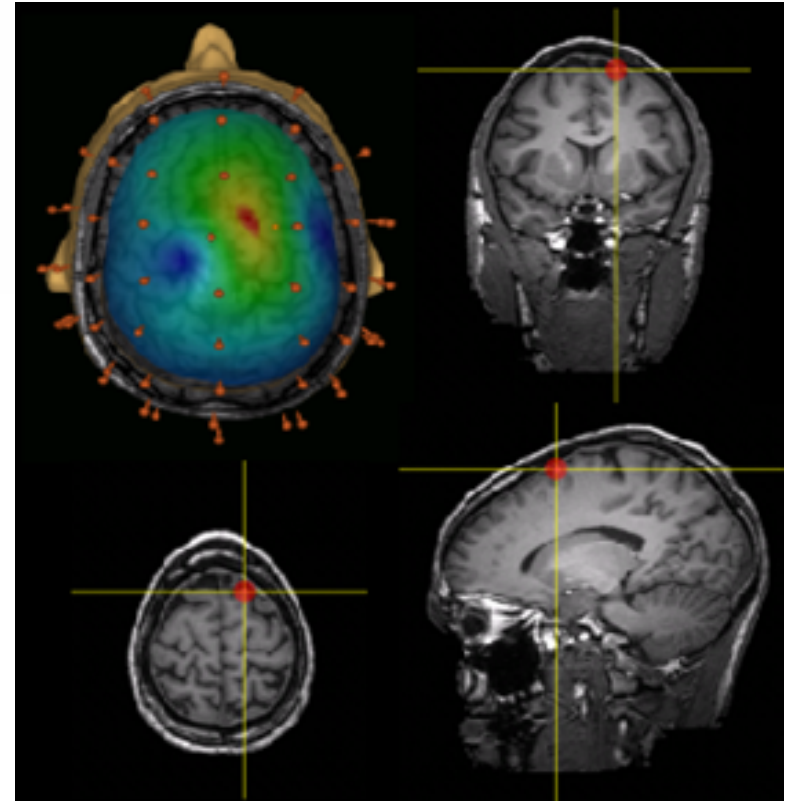
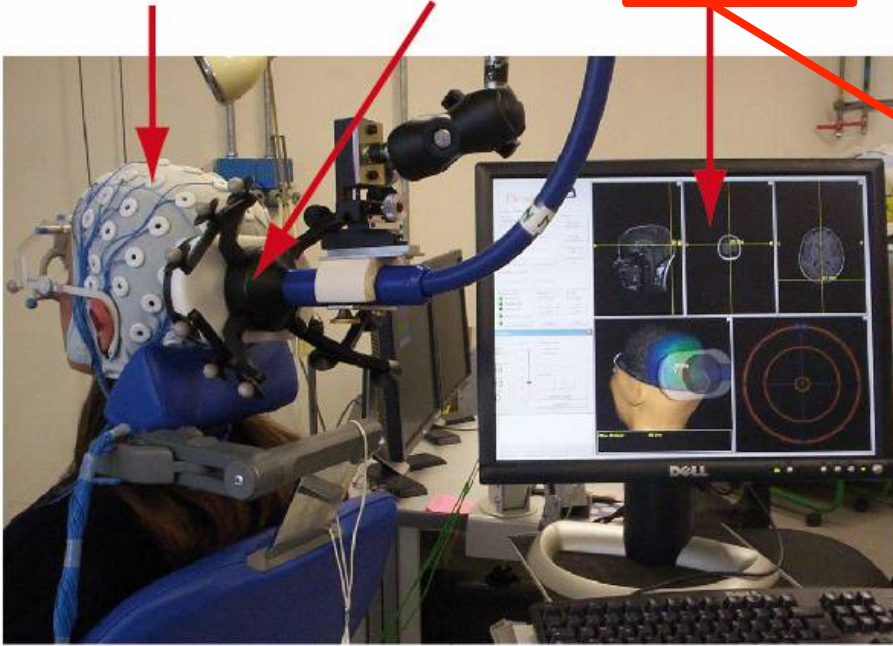


# TMS

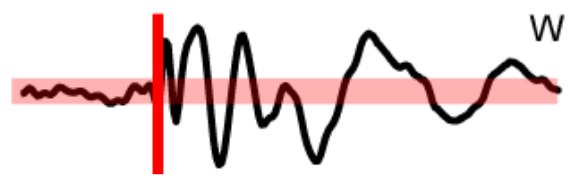
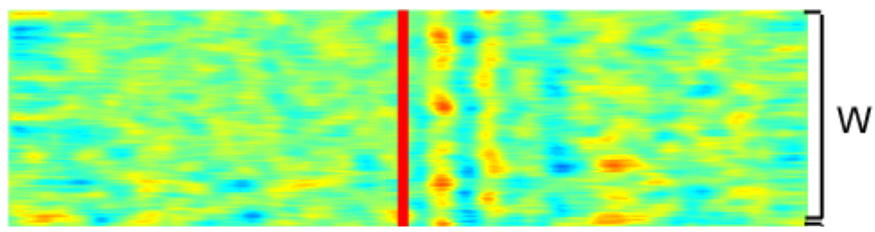
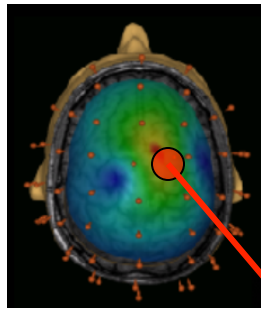


hd-EEG TMS

**NBS**

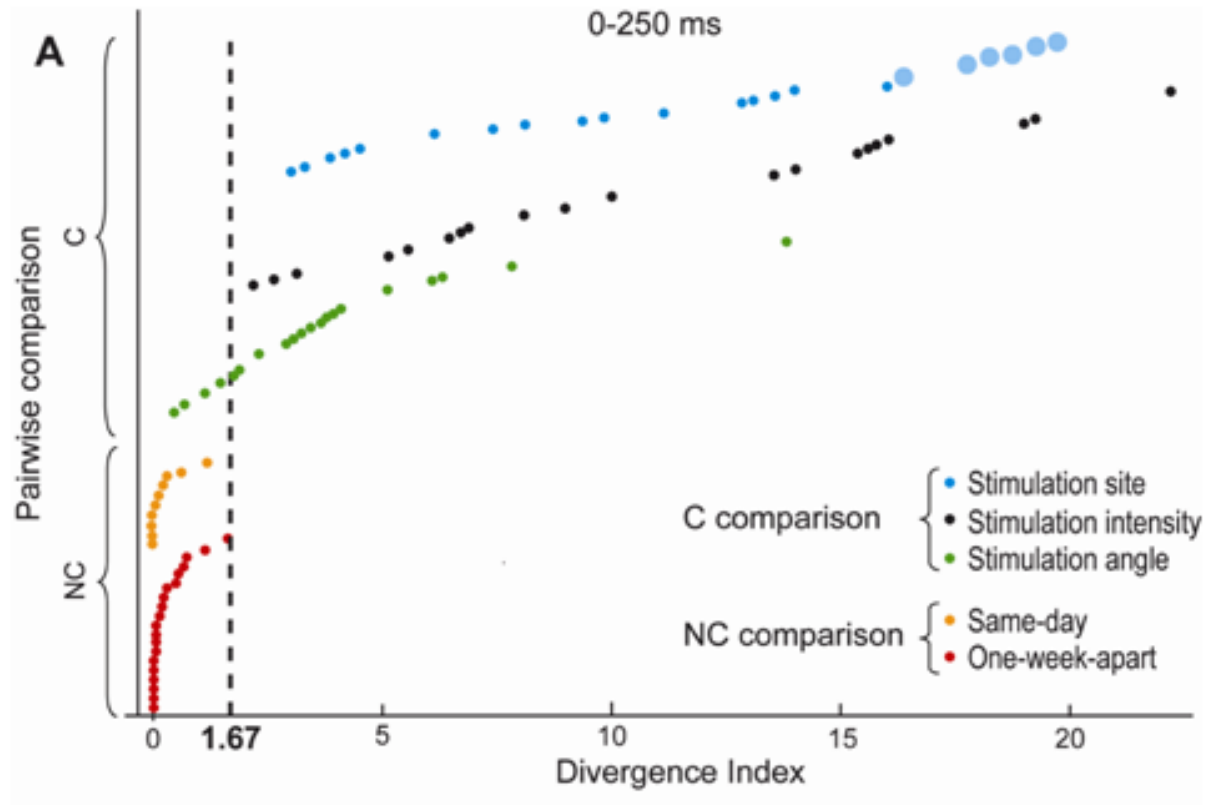


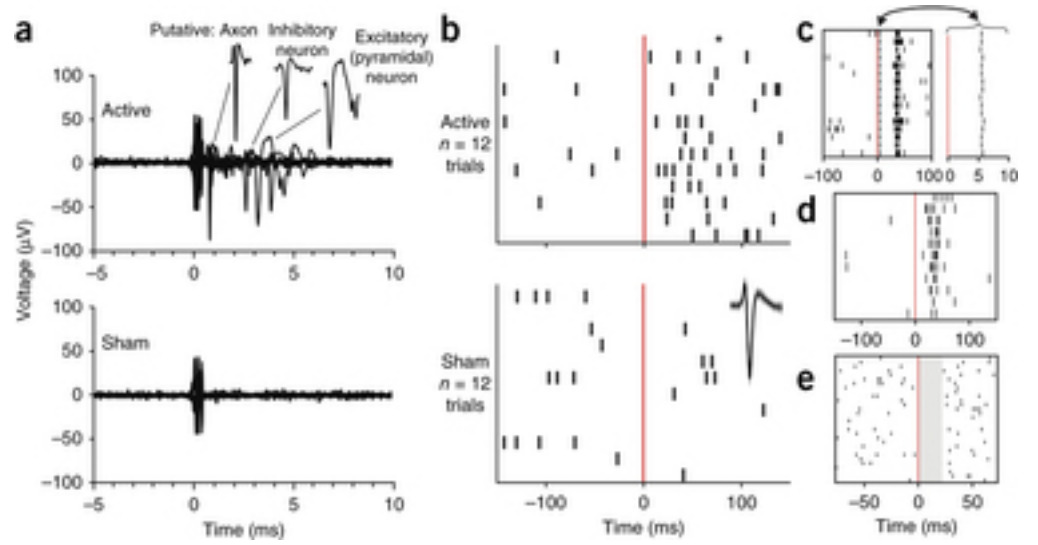
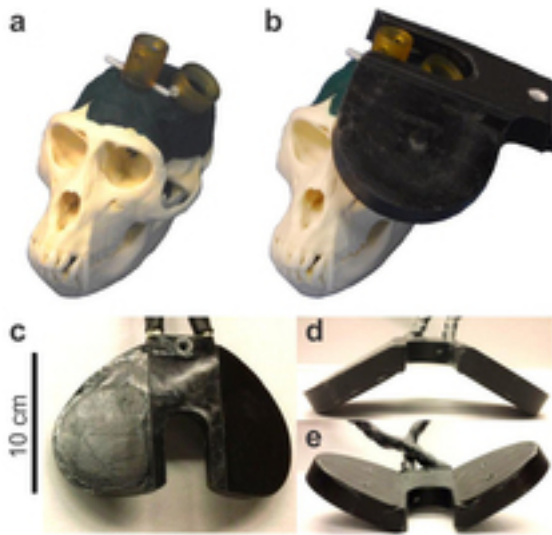
# hd-EEG



300 200 100 **TMS** ↑ 100 200 300  
Time (ms)

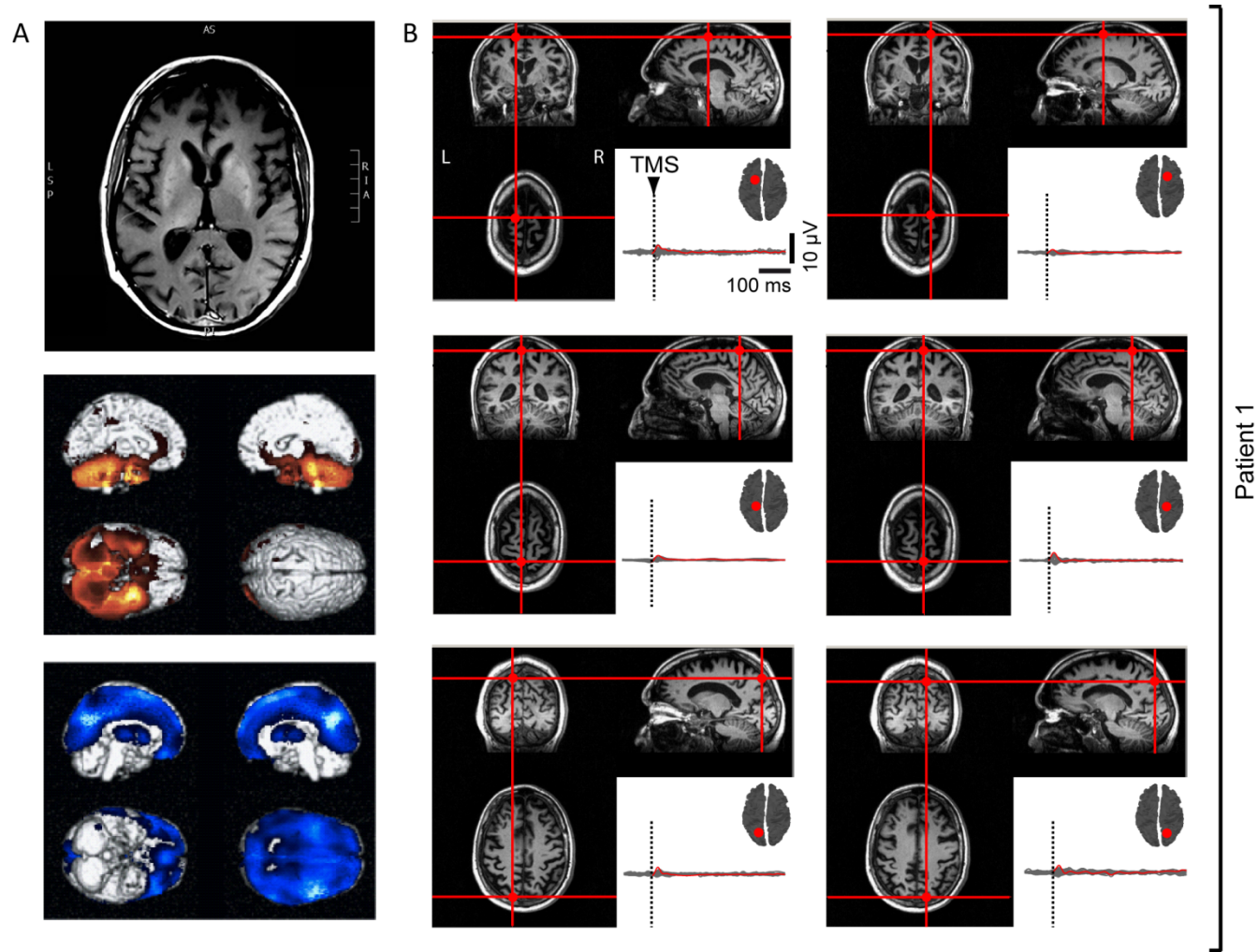
**TMS** ↑ 100 ms **8 μV**





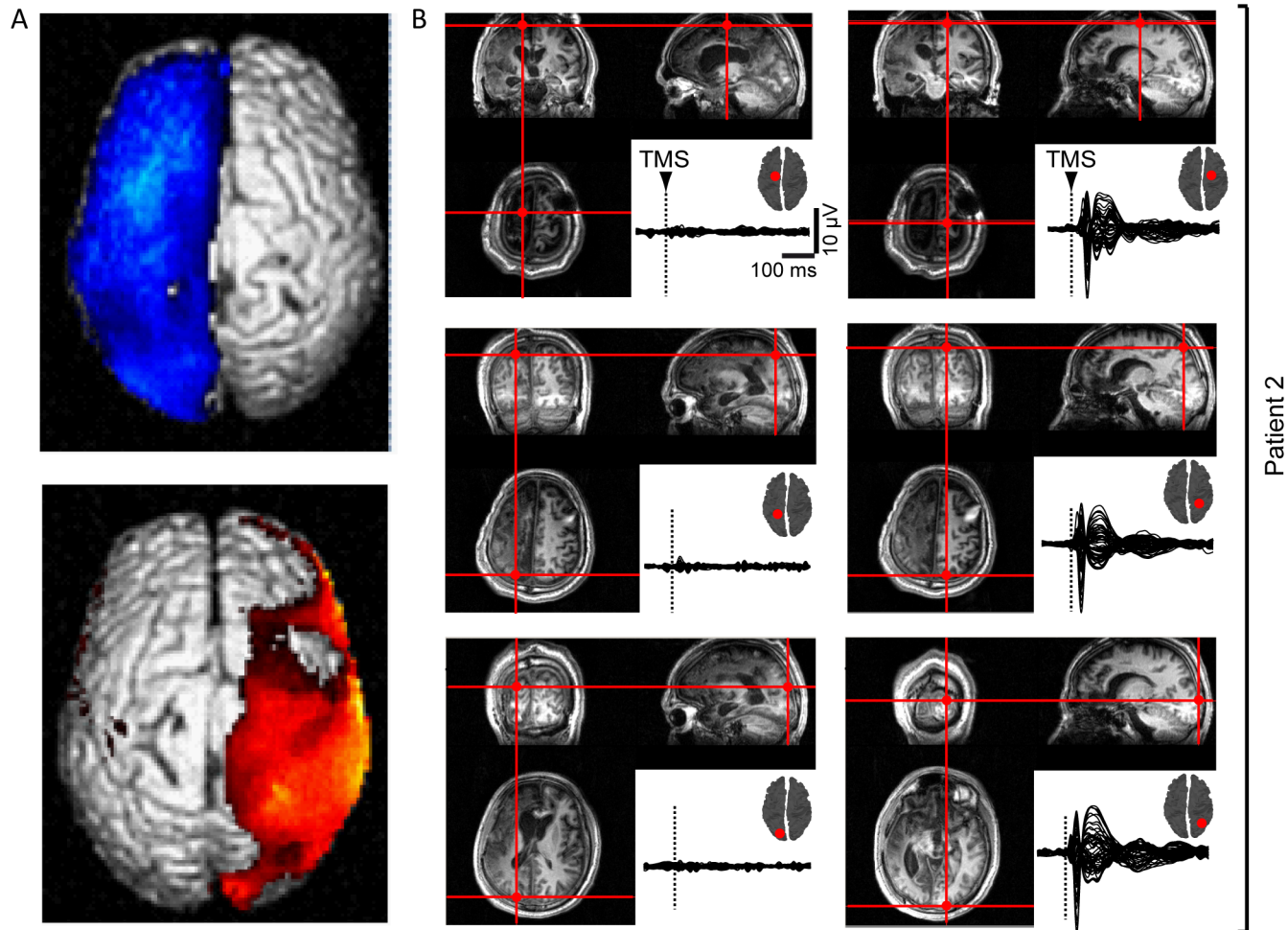


# Anoxic: diffuse cortical lesion (apallic)

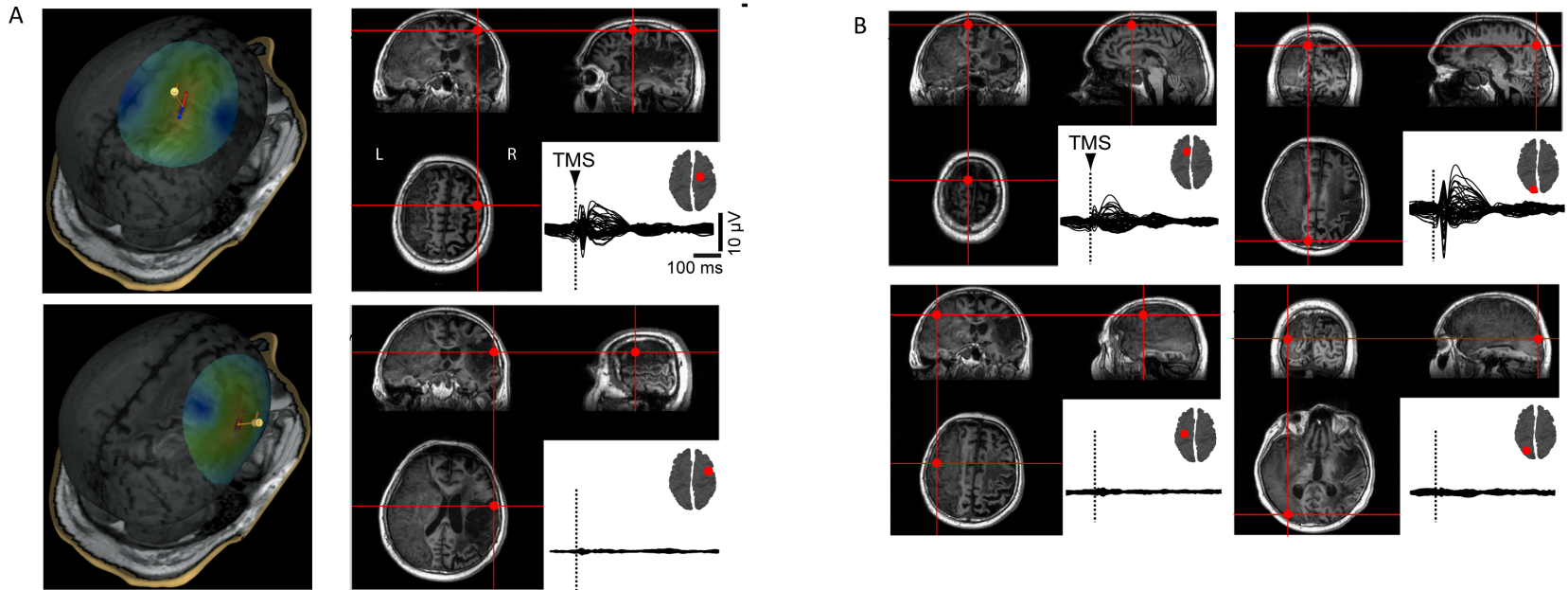




# Large lesion involving an entire hemisphere



# Multiple focal lesions



A genuine response to cortical stimulation

Gosseries, Sarasso et al., *Brain Stim.* 2015

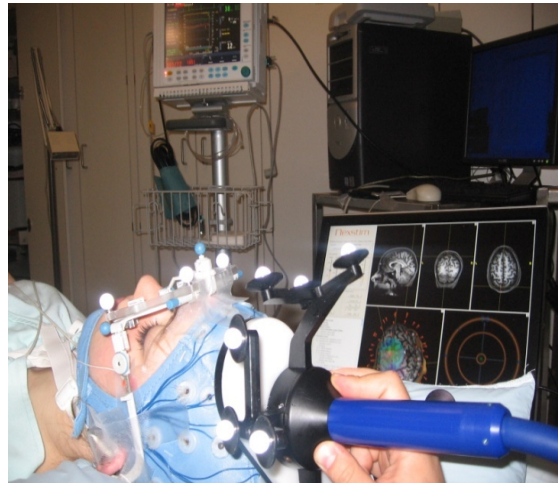
VALIDATION/CALIBRATION



APPLICATION



Sleep

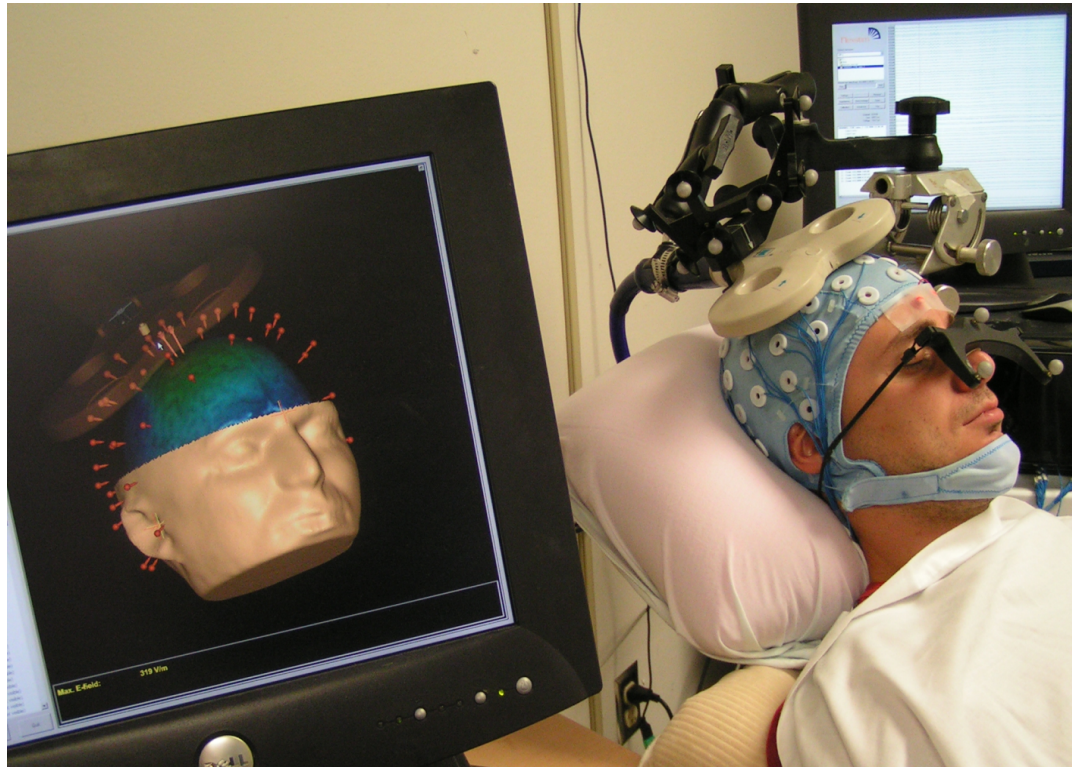


Anesthesia  
*Midazolam*  
*Propofol*  
*Xenon*  
*Ketamine*



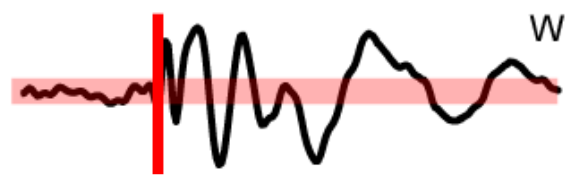
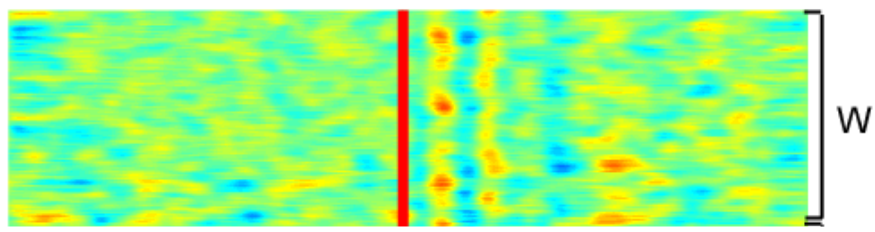
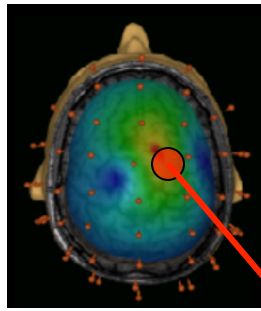
DOCs

# Sleep



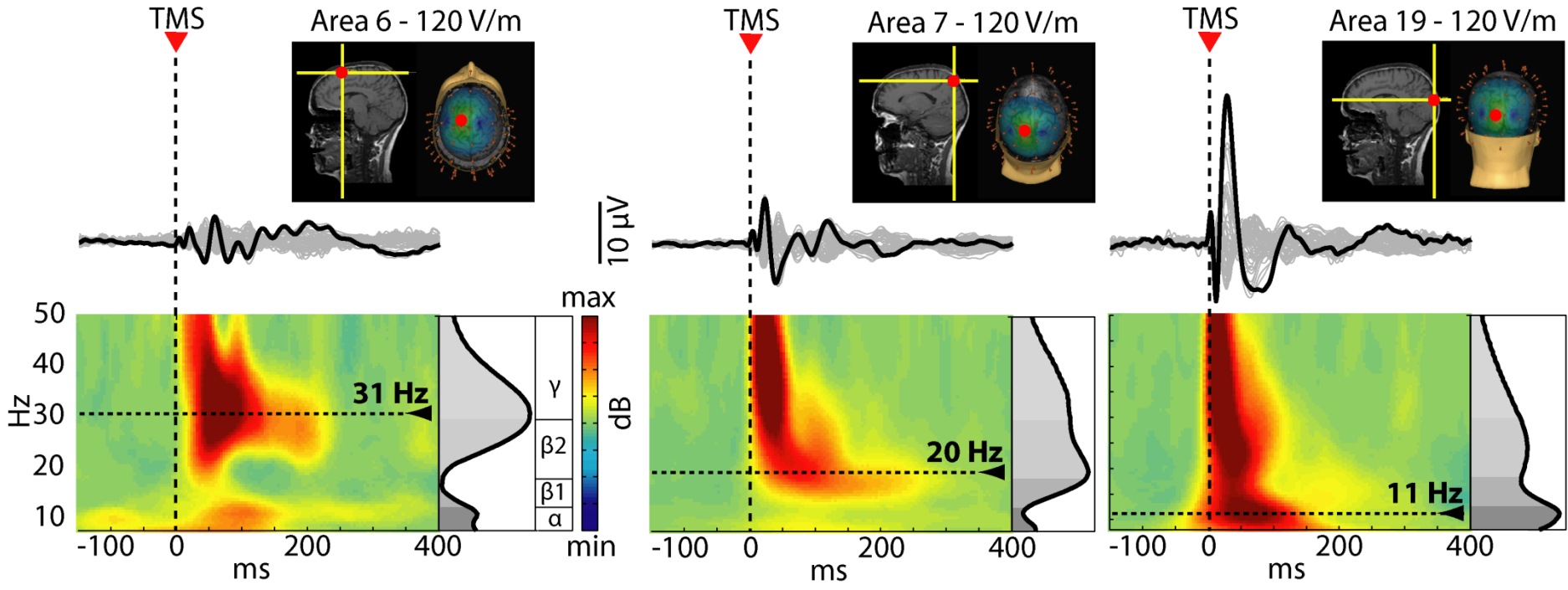


# hd-EEG



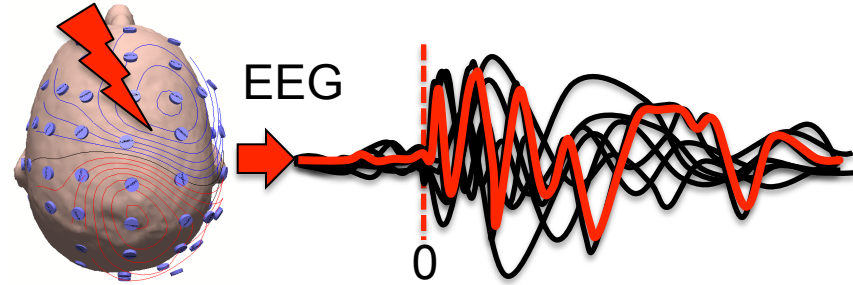
300 200 100 **↑** TMS 100 200 300  
Time (ms)

**↑** TMS  
100 ms  
8  $\mu$ V



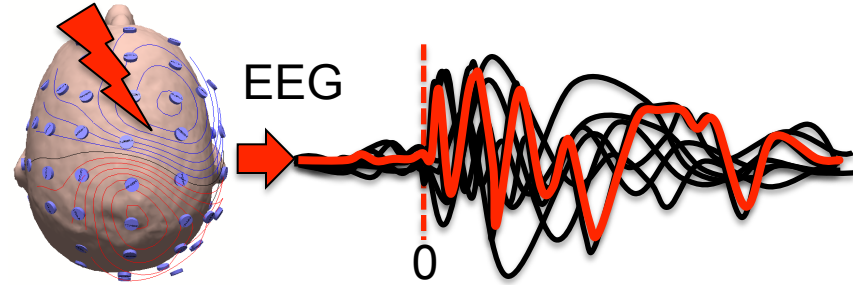
# Wakefulness

TMS

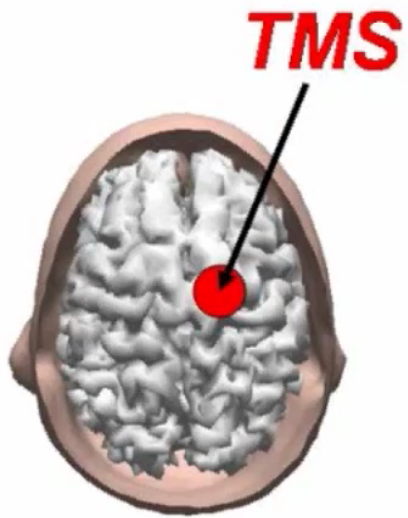


# Wakefulness

TMS



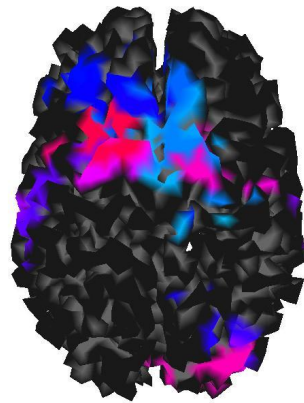
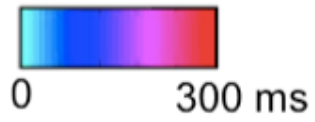
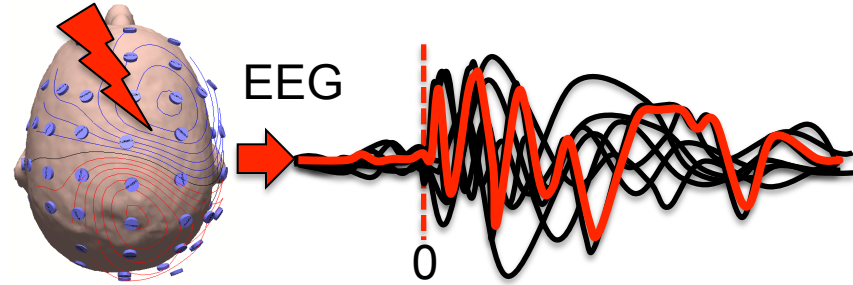
0 ms



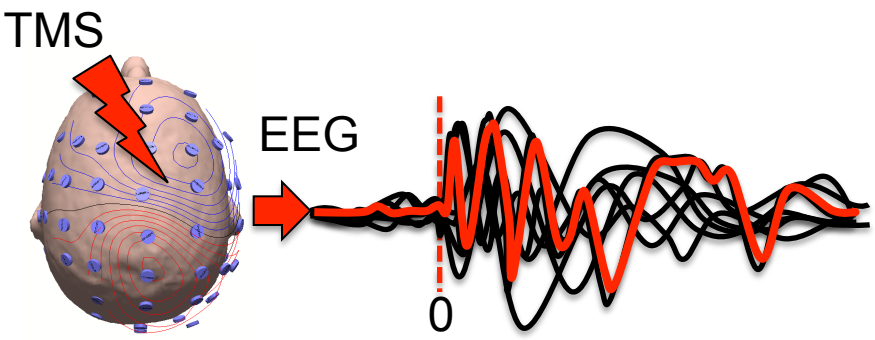


# Wakefulness

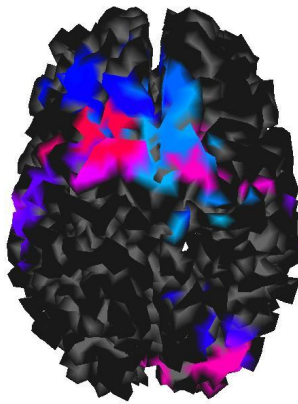
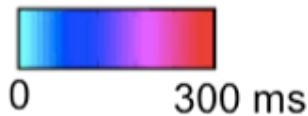
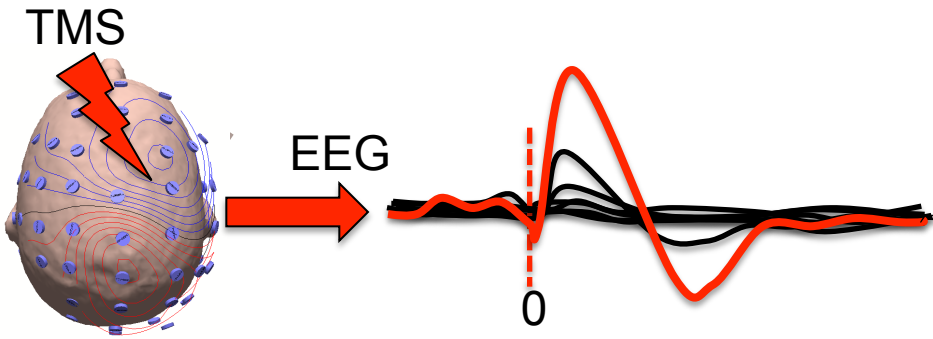
TMS



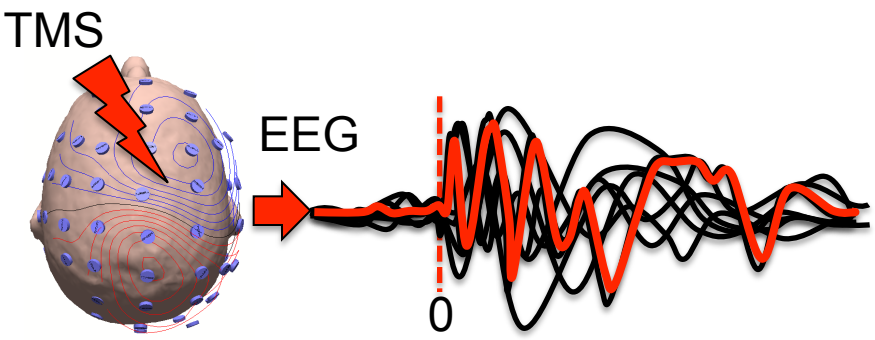
**Wakefulness**



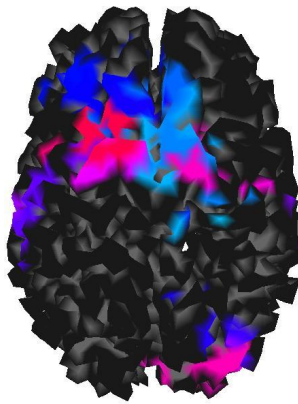
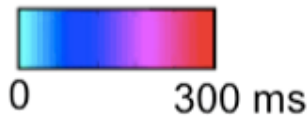
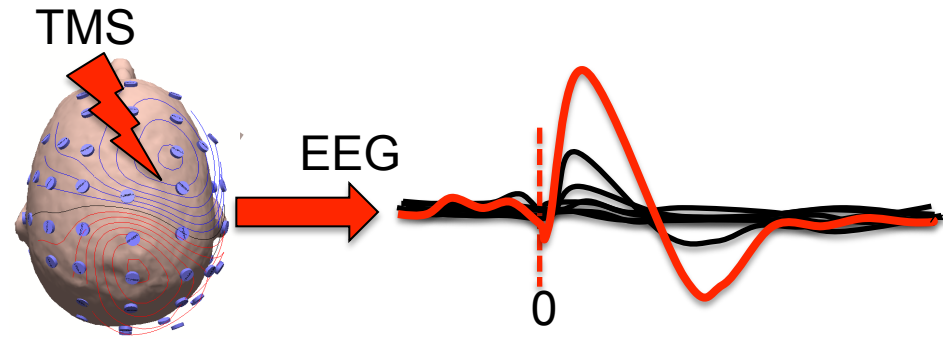
**Sleep**



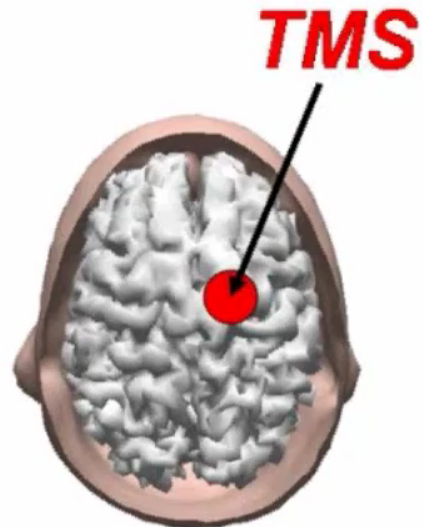
**Wakefulness**



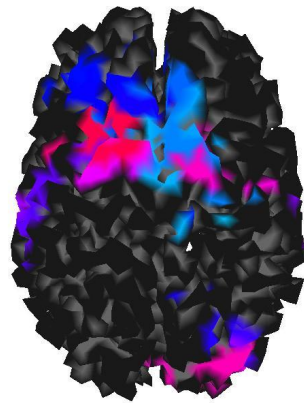
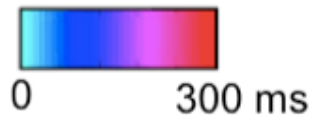
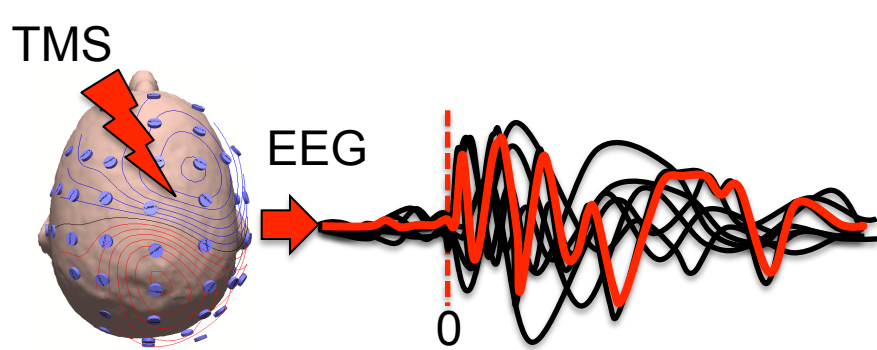
**Sleep**



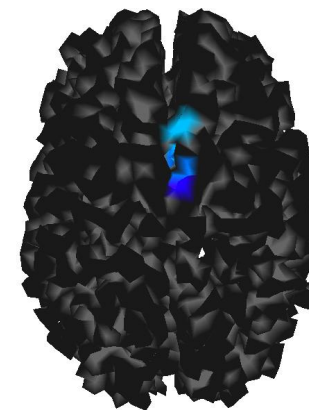
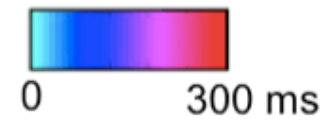
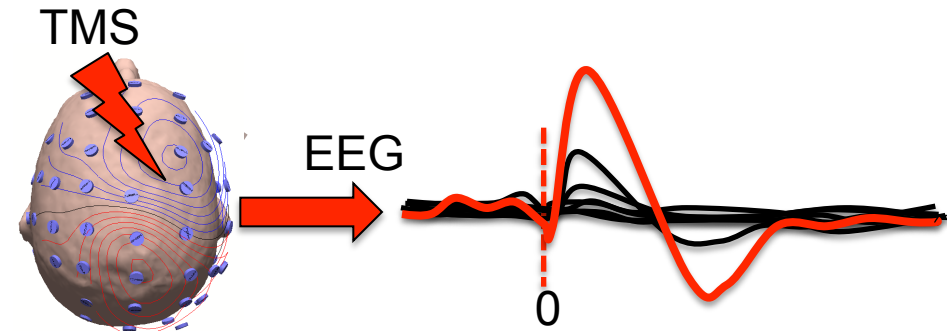
0 ms



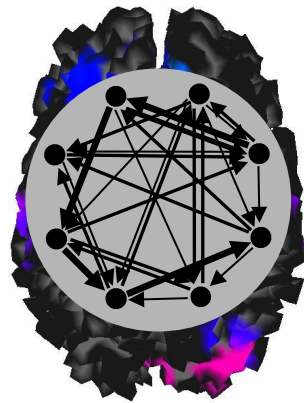
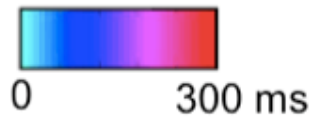
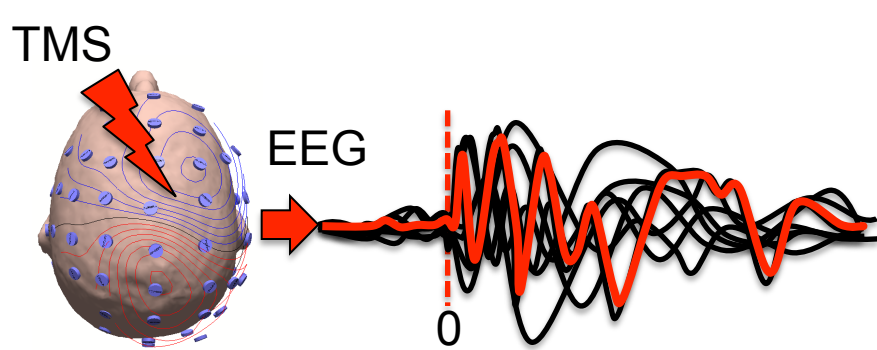
## Wakefulness



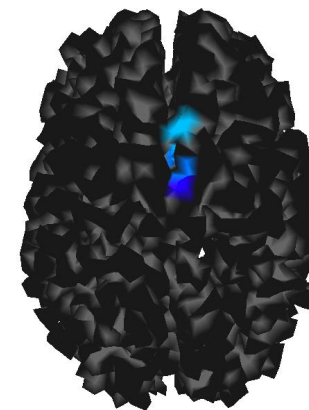
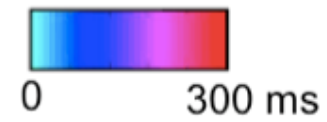
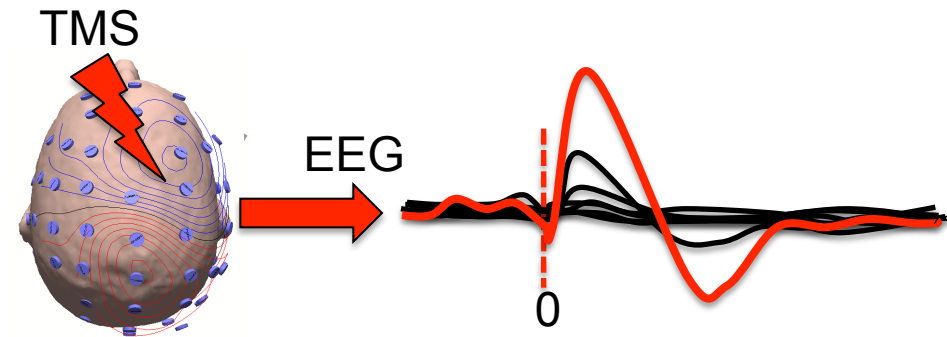
## Sleep



## Wakefulness

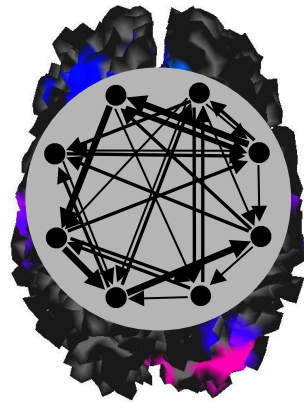
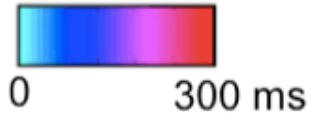
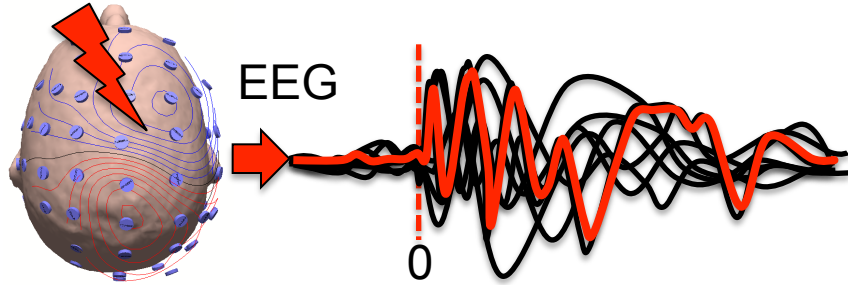


## Sleep



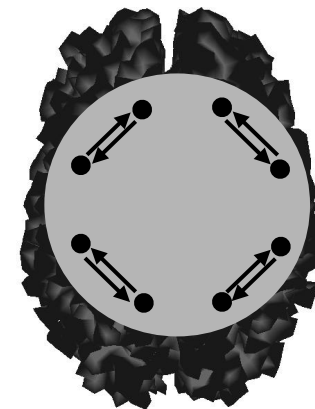
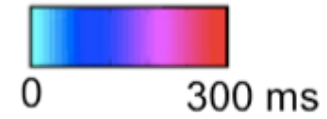
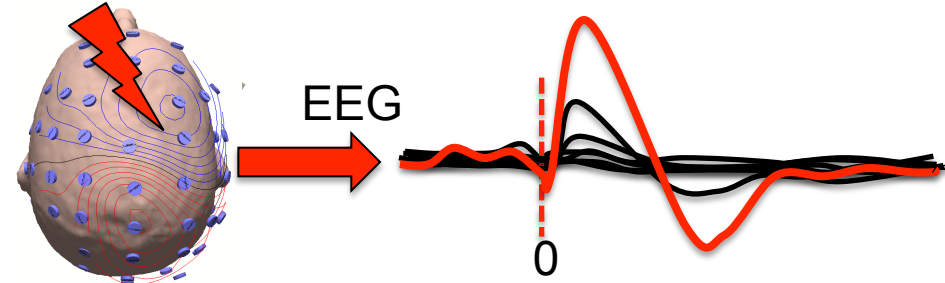
## Wakefulness

TMS

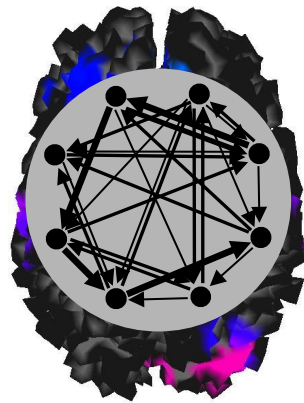
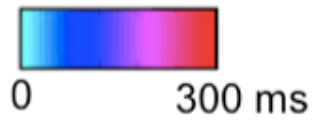
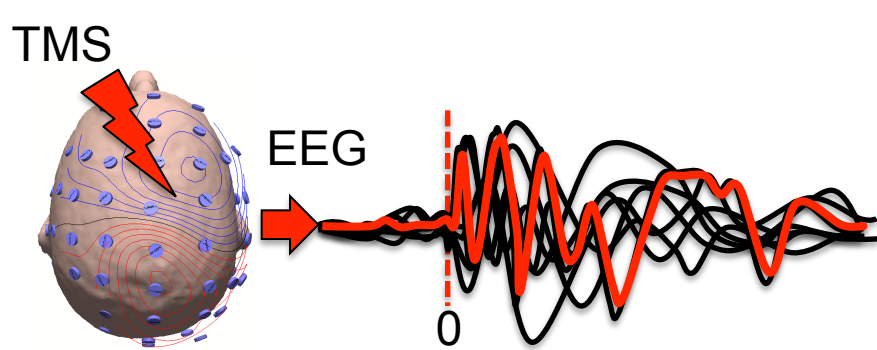


## Sleep

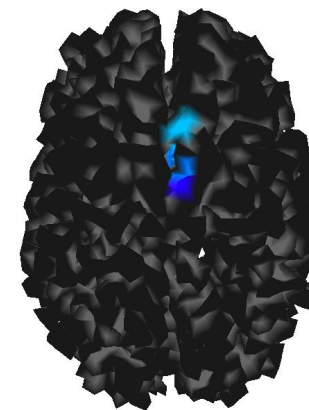
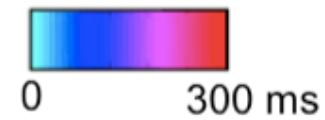
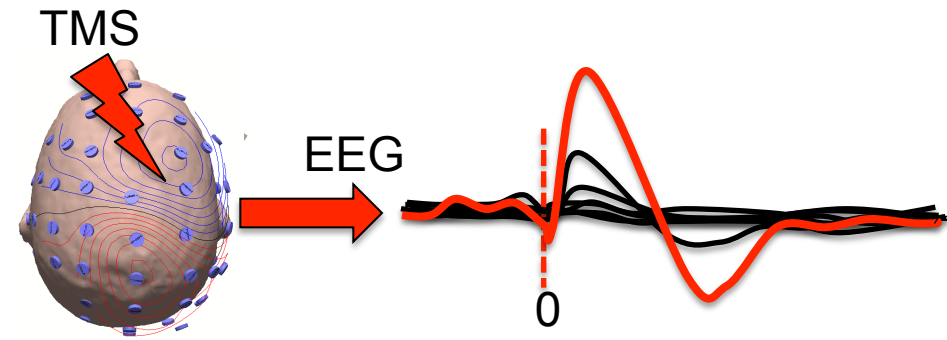
TMS



## Wakefulness



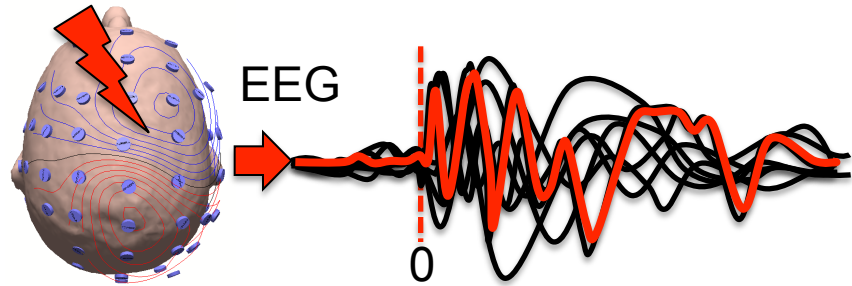
## Sleep





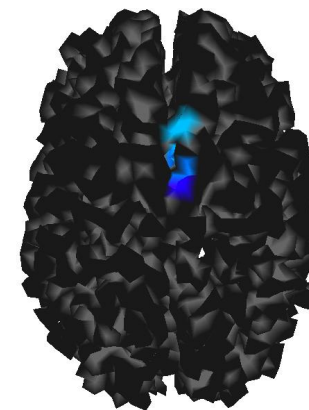
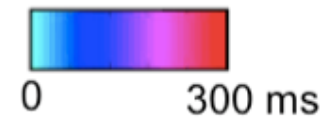
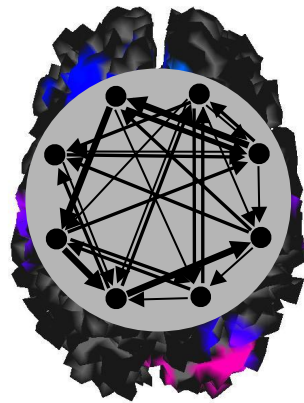
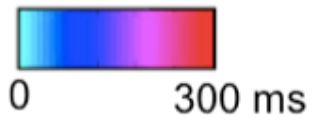
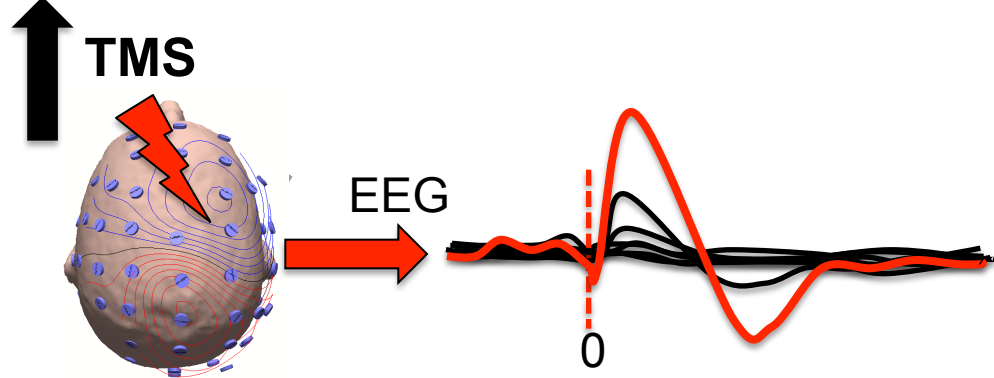
Wakefulness

TMS



Sleep

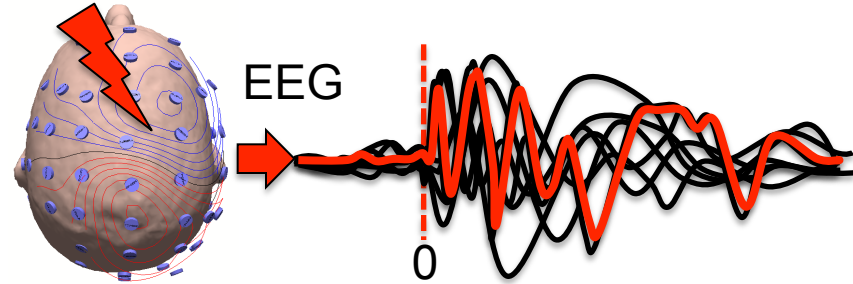
TMS





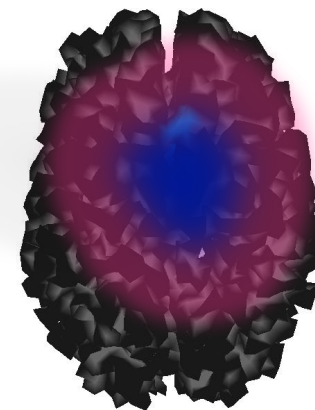
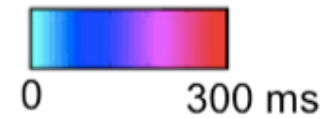
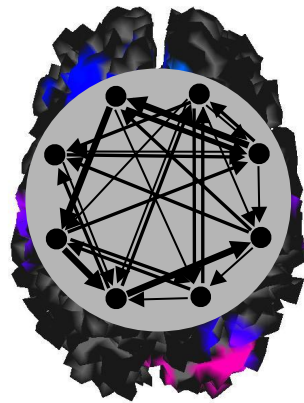
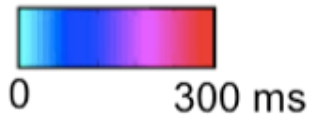
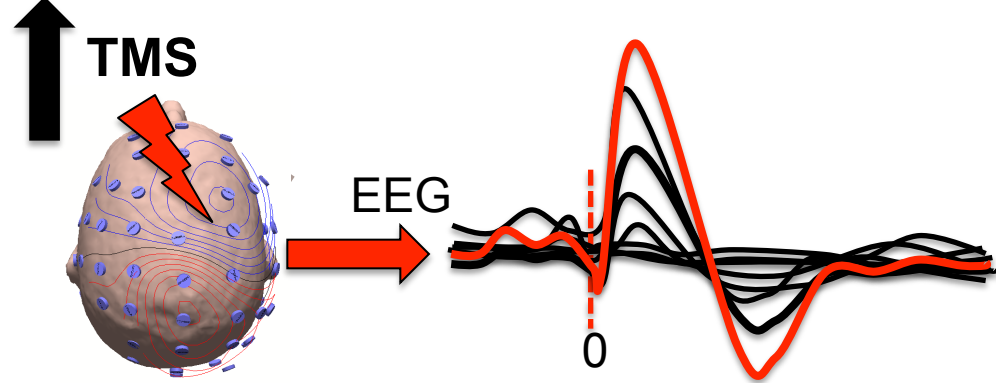
Wakefulness

TMS



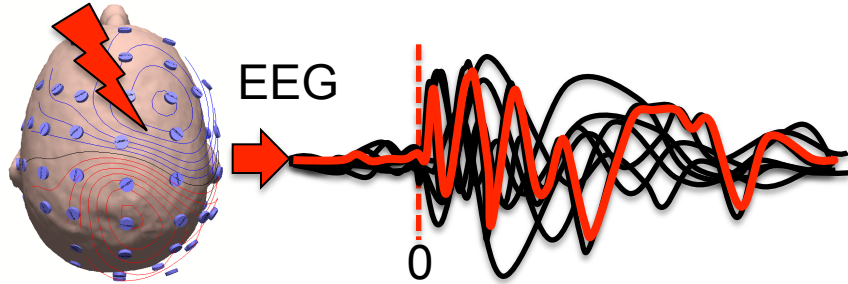
Sleep

TMS



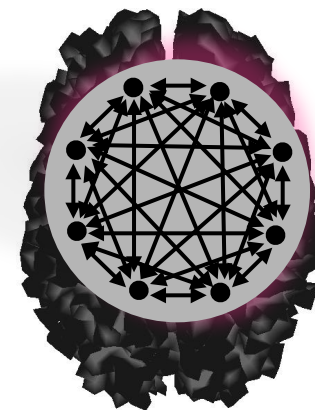
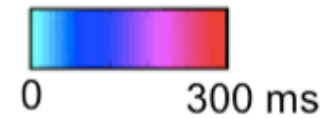
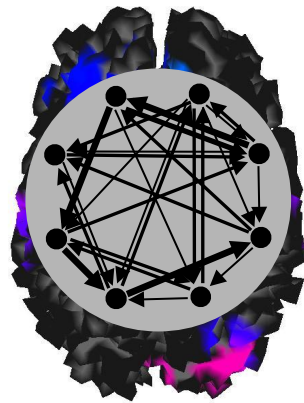
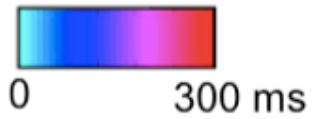
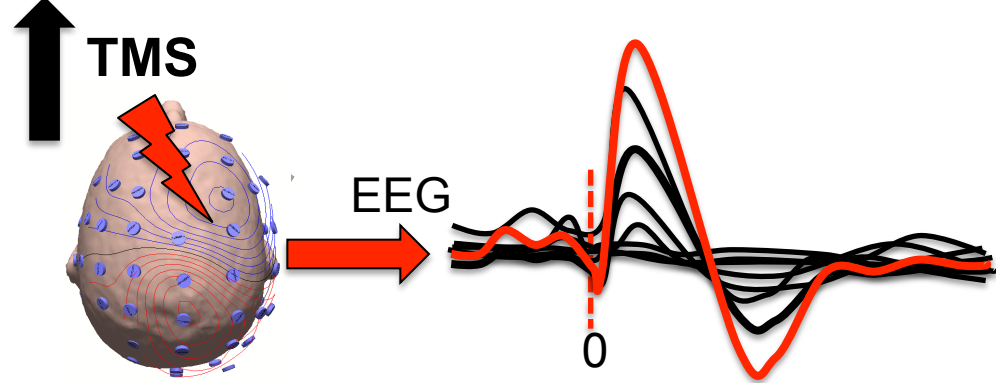
Wakefulness

TMS

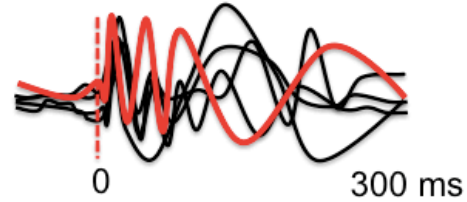
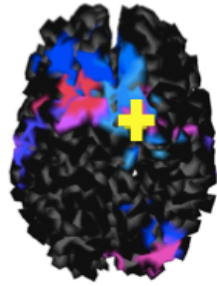


Sleep

TMS

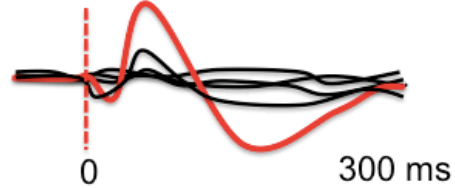
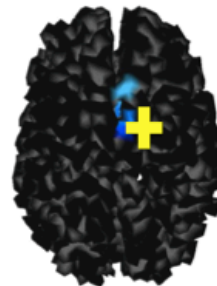


**Wakefulness**



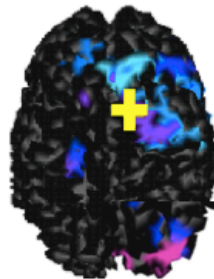
**Immediate Report**

**NREM**

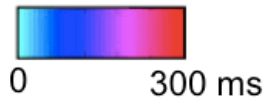


**No Report**

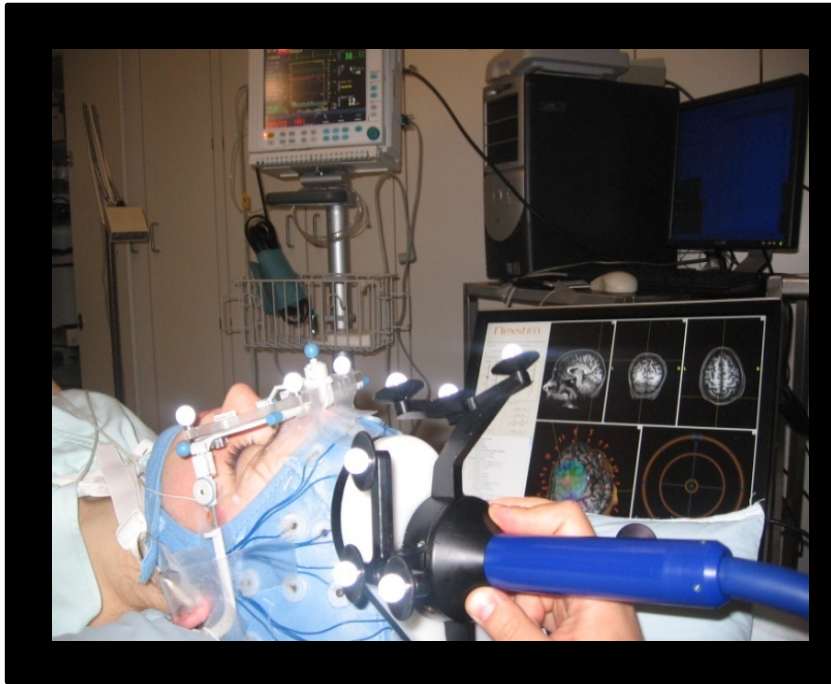
**REM**



**Retrospective Report**

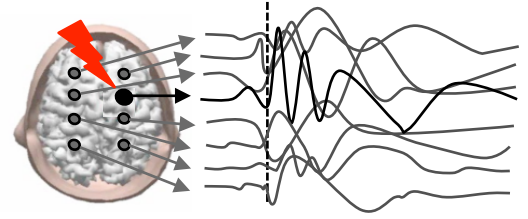


# Anesthesia

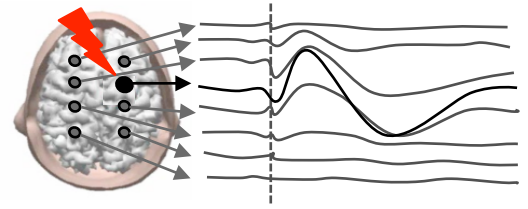


Immediate Report

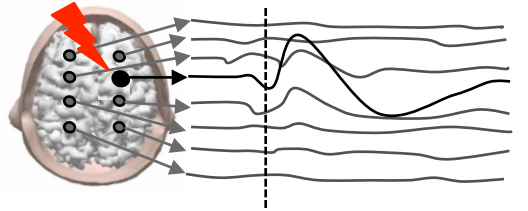
Awake



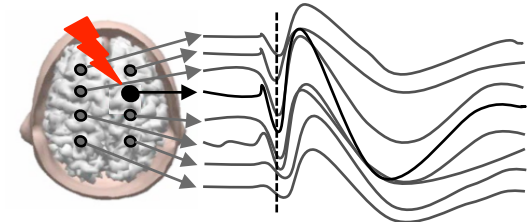
Midazolam



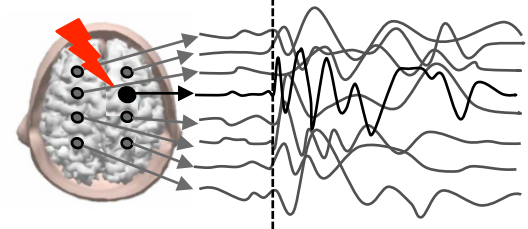
Propofol



Xenon

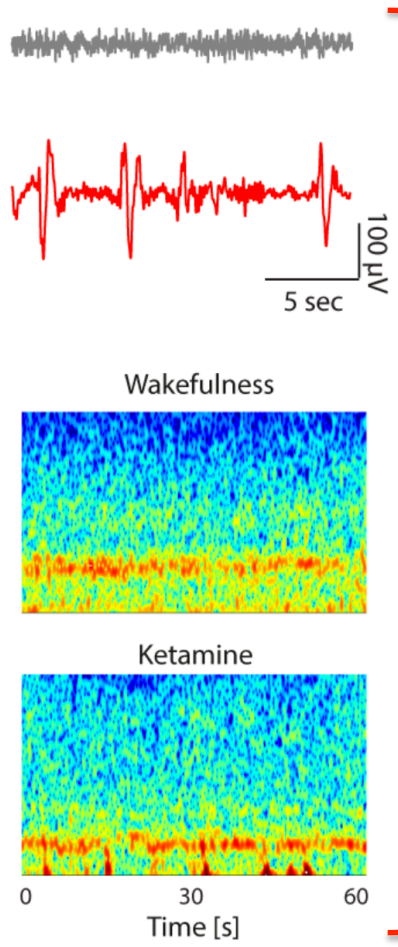


Ketamine



No Report

Retrospective Report

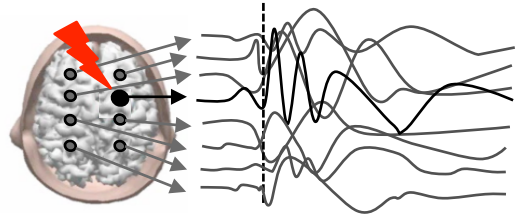


Immediate Report

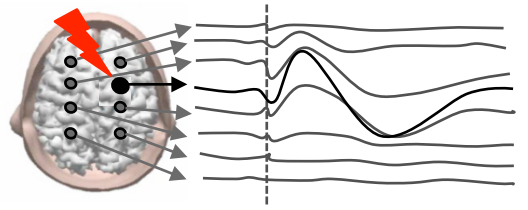
No Report

Retrospective Report

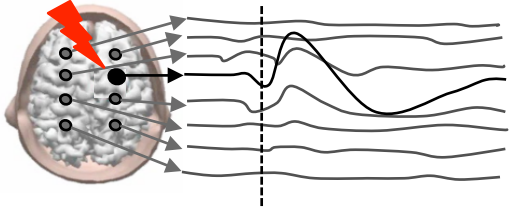
Awake



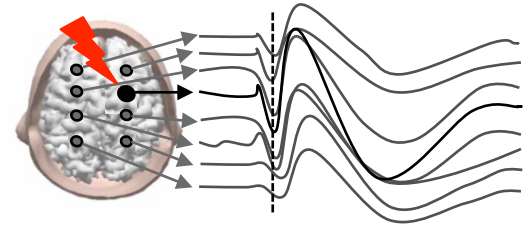
Midazolam



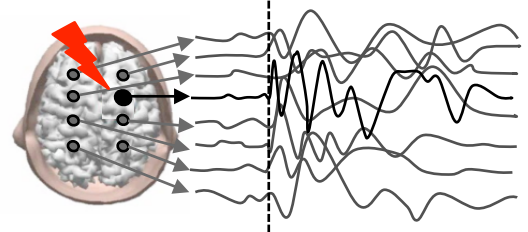
Propofol



Xenon



Ketamine





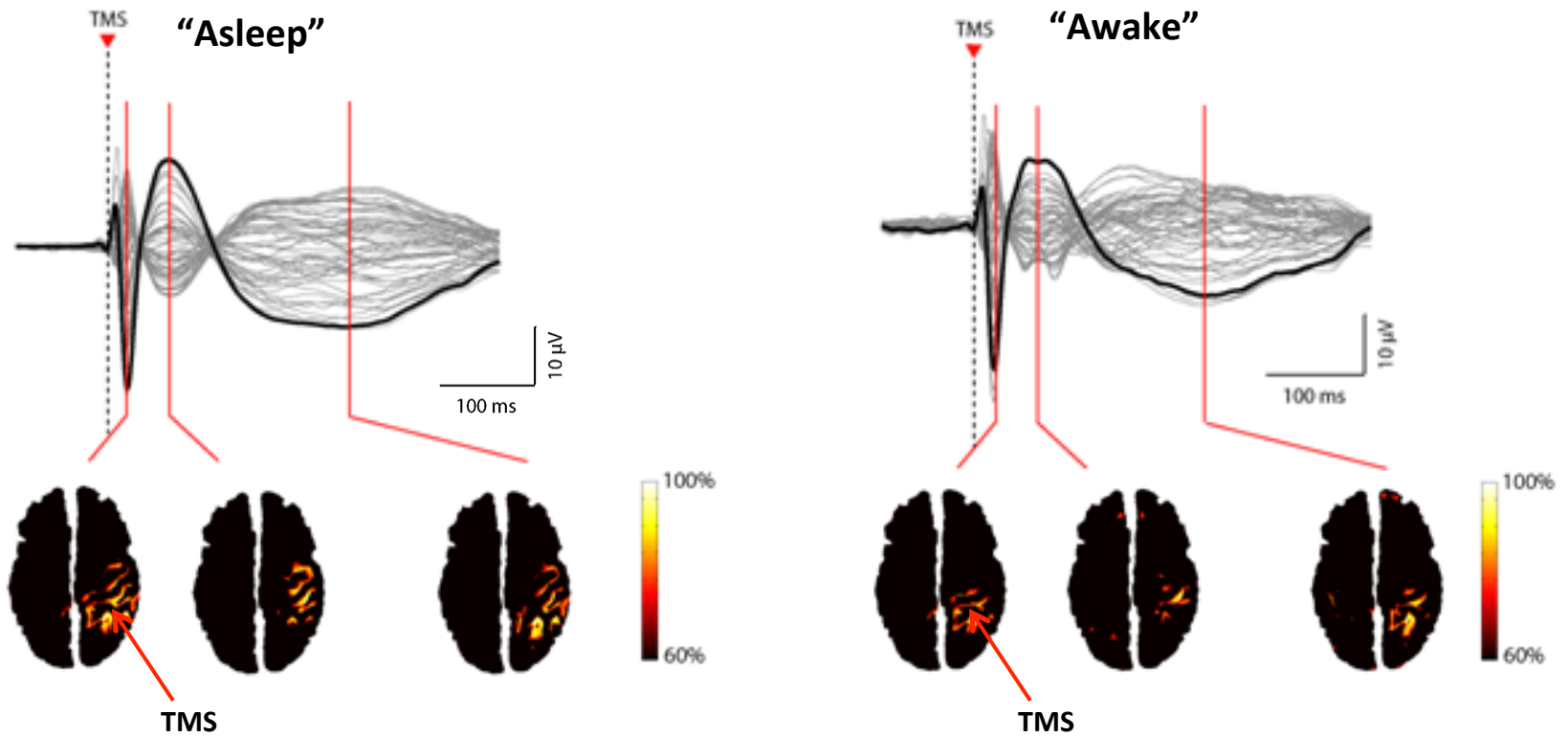
# Disorders of Consciousness



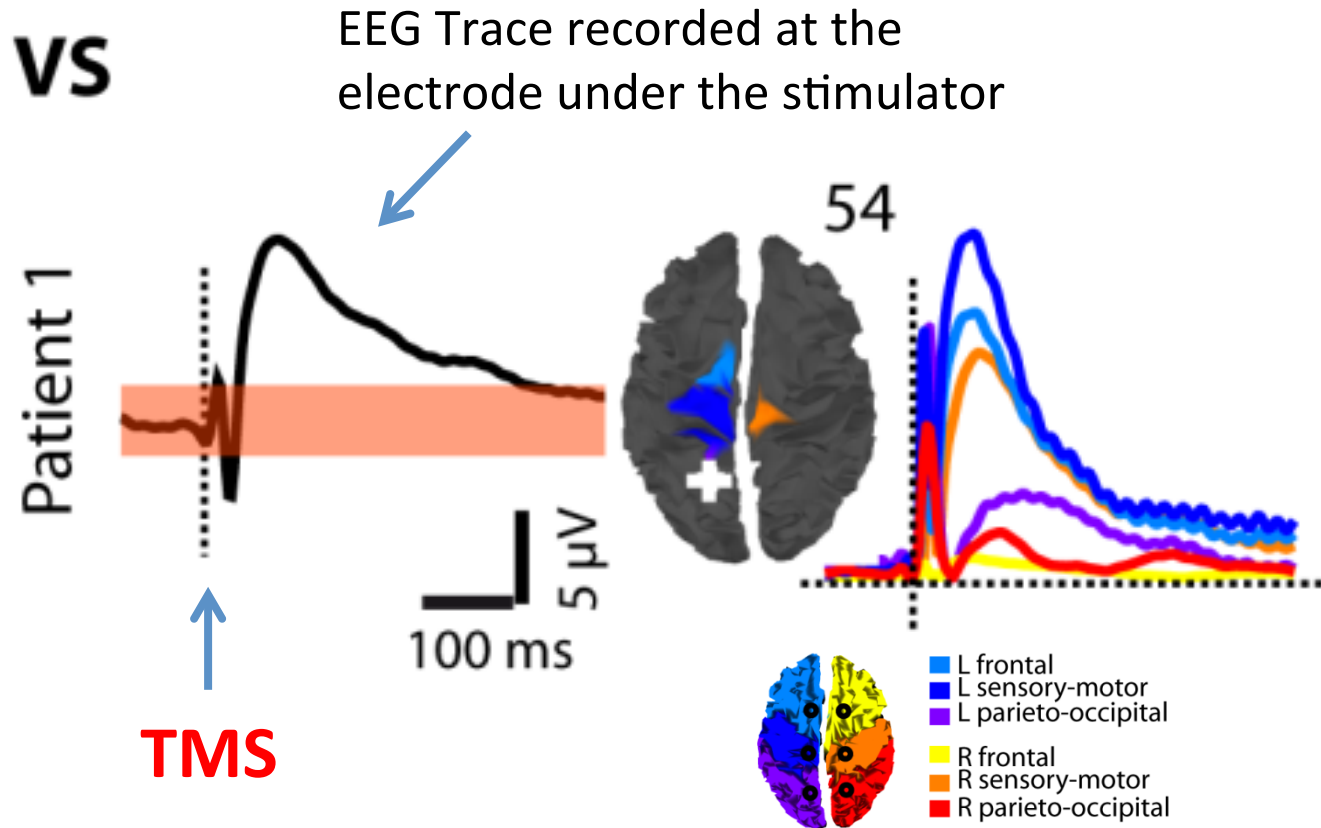
**Vegetative State**  
(vigilance without awareness)



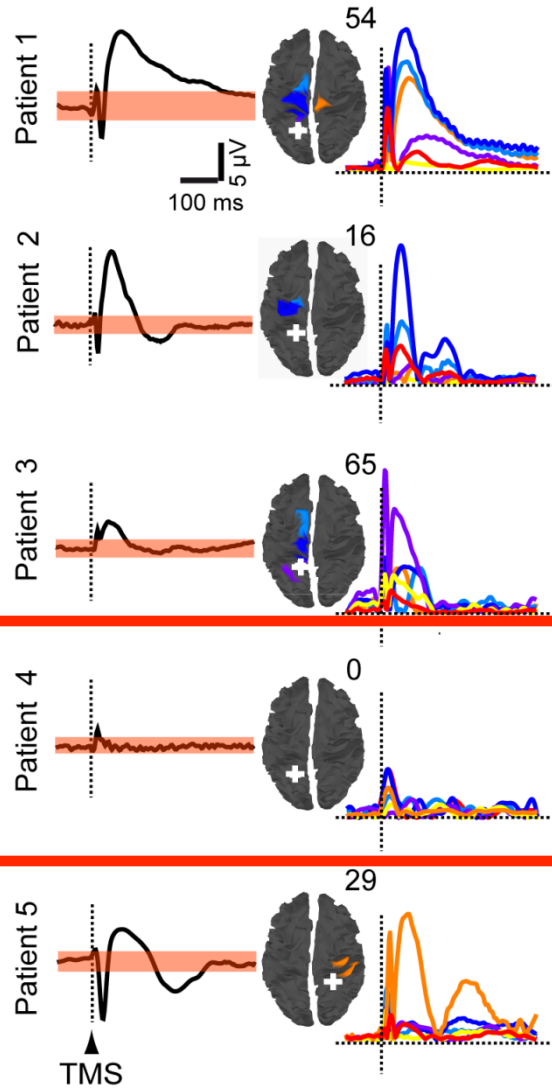
## Vegetative State (vigilance without awareness)



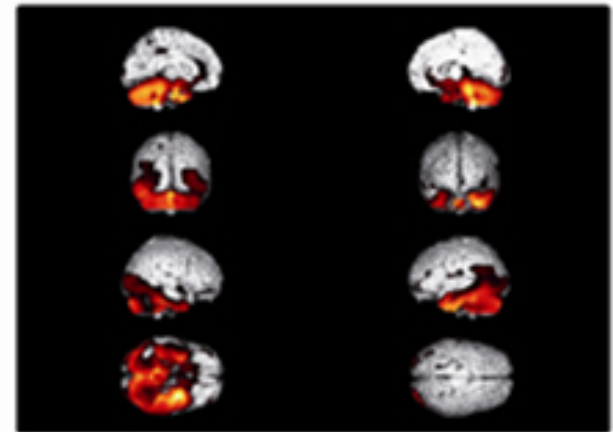


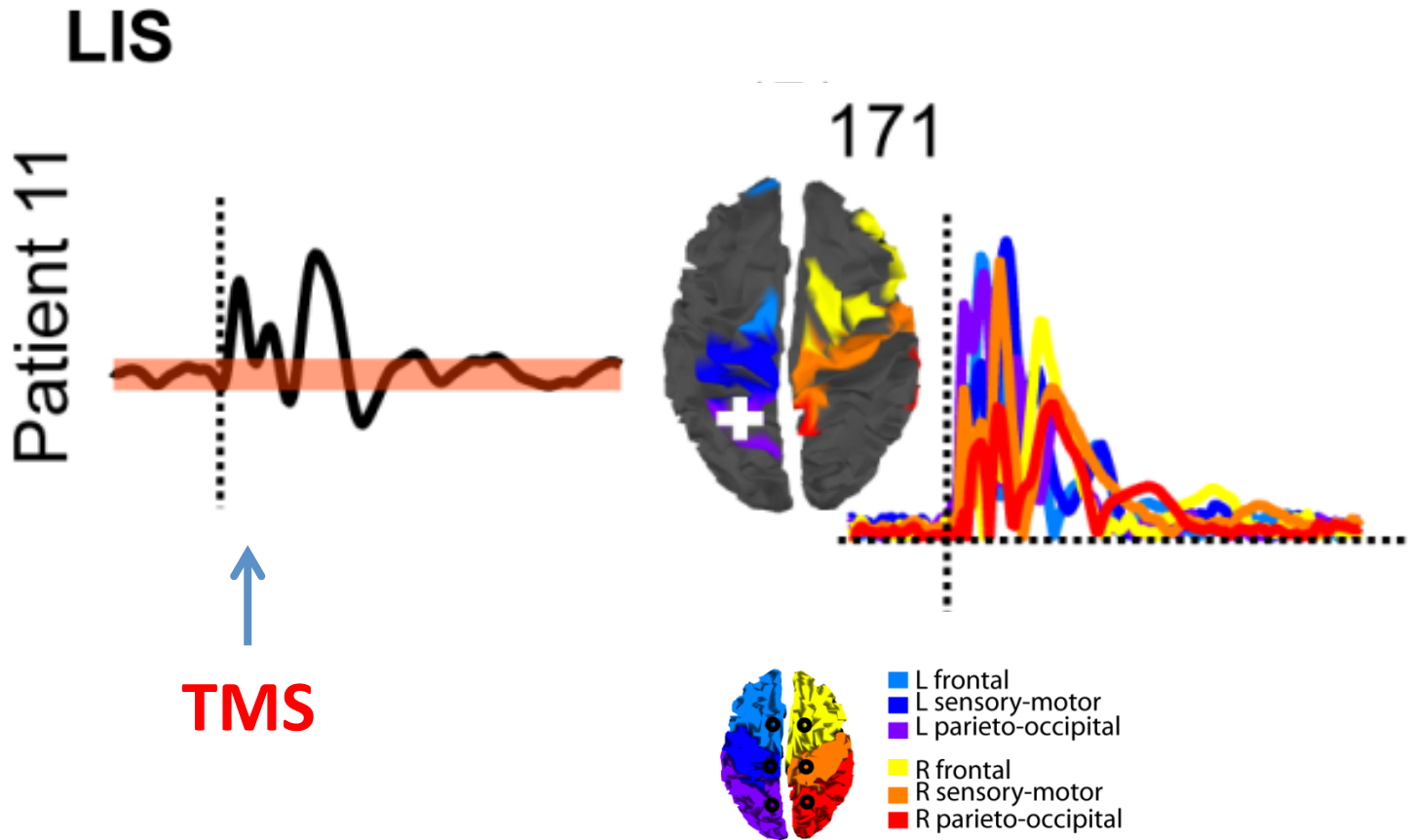


**Vs**



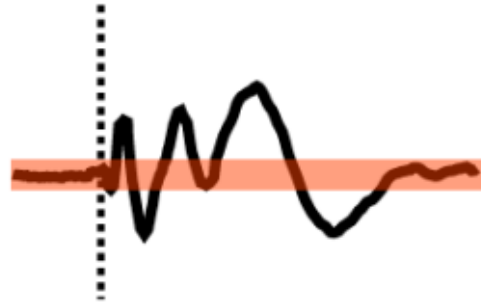
Preserved regions



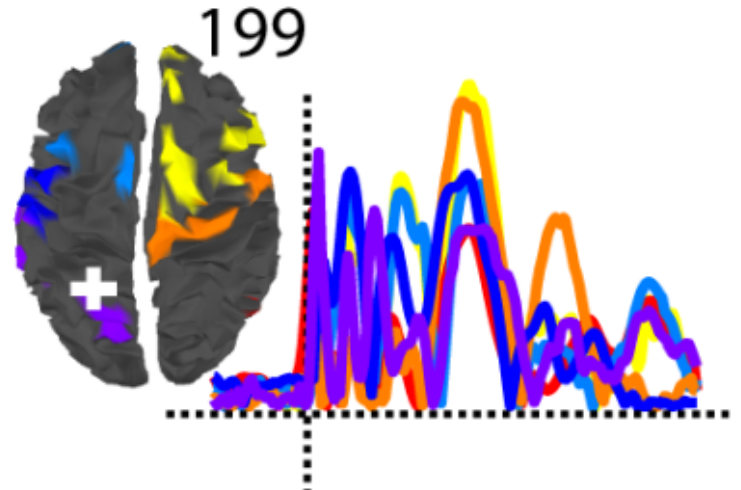


# MCS

Patient 7



TMS

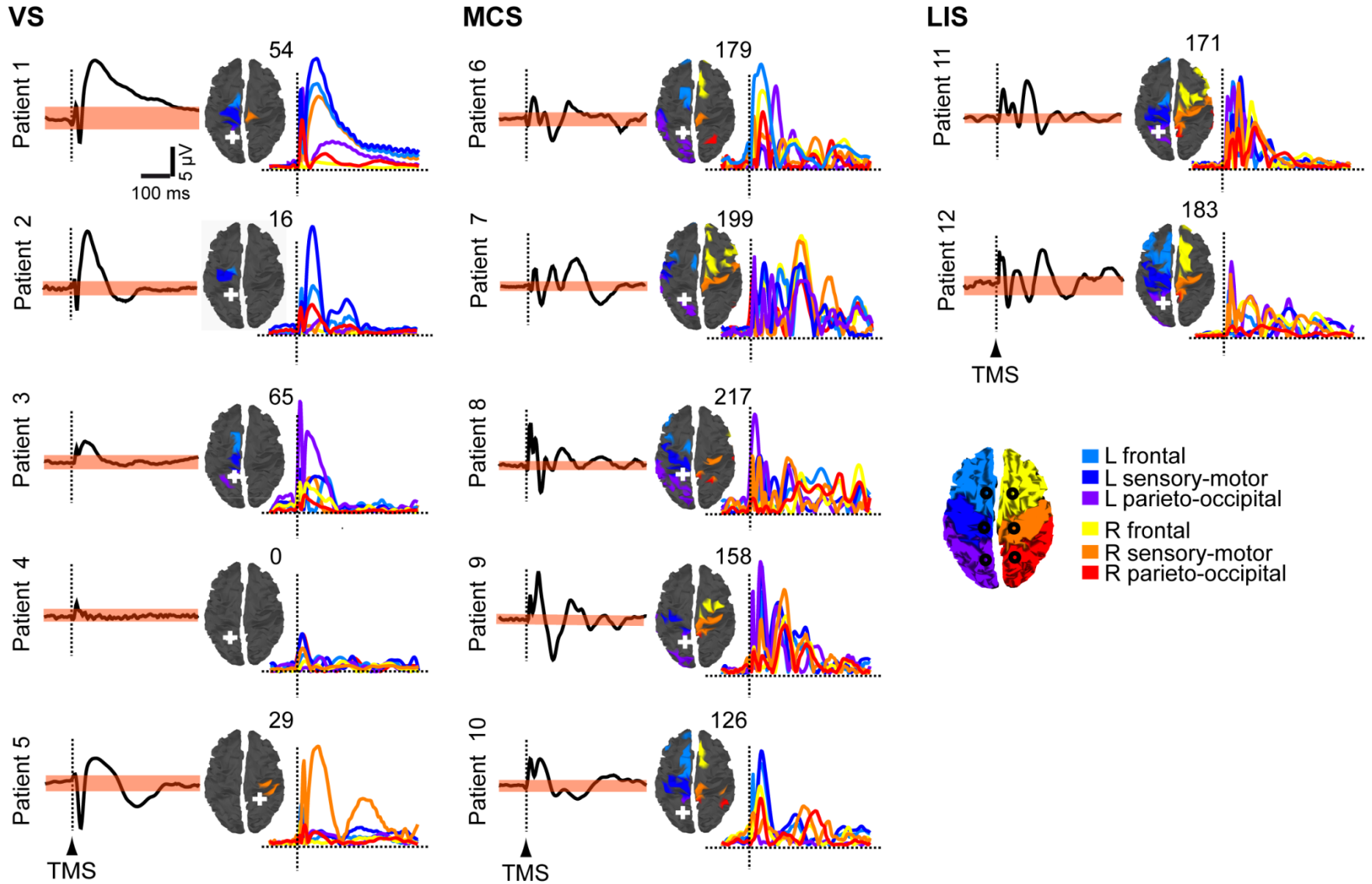


- L frontal
- L sensory-motor
- L parieto-occipital
- R frontal
- R sensory-motor
- R parieto-occipital

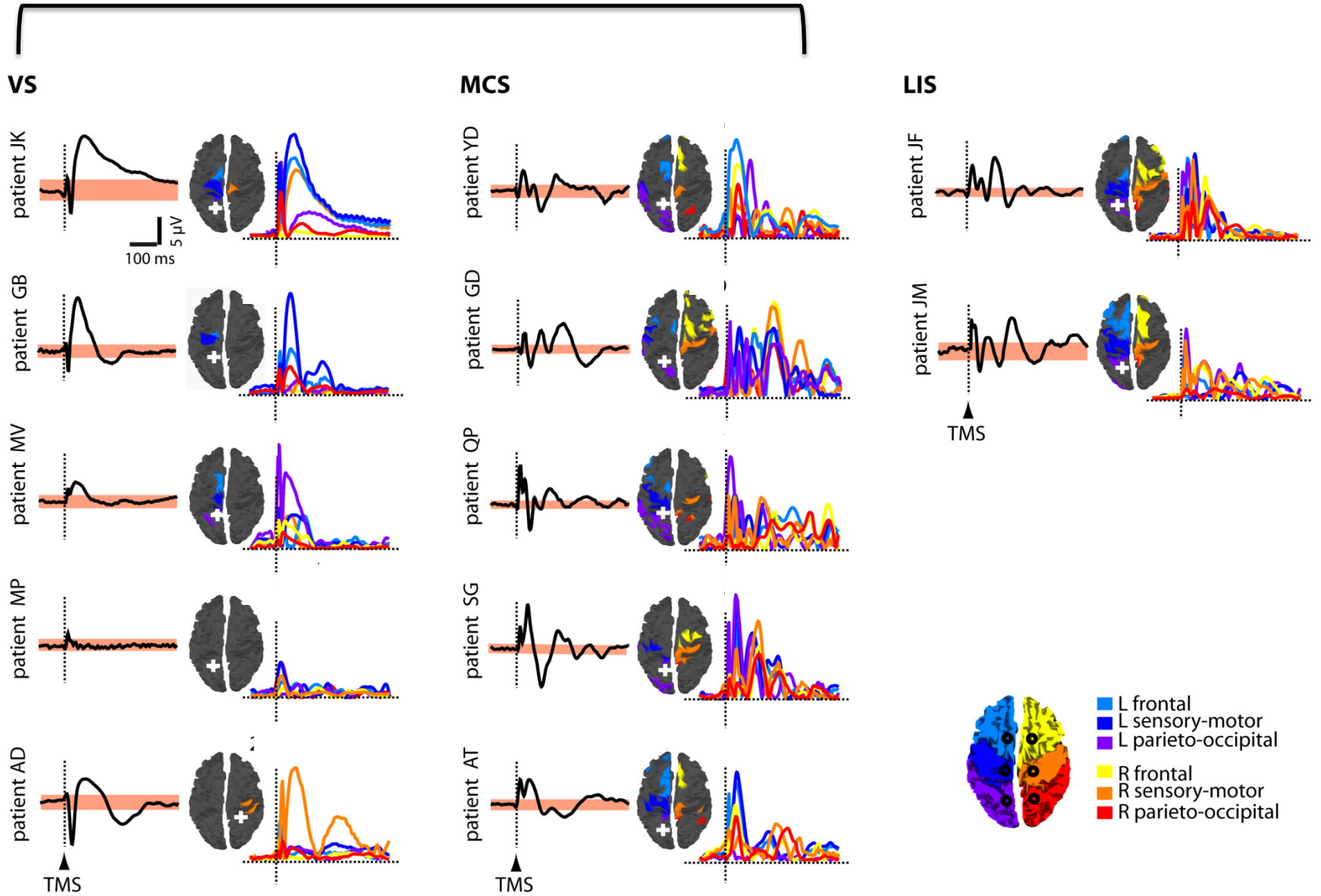
Awake, unconscious

Awake, minimal signs

Awake, fully conscious



# 40% diagnostic error



## Consciousness Absent

Sleep

Anesthesia

Vegetative State

## Consciousness Present

Wakefulness

Dreaming

Locked-in Syndrome

Minimally Conscious State



Massimini et al *Science*, 2005;  
Massimini et al., *PNAS* 2007  
Massimini et al. *Cog. Neurosci*, 2010  
Rosanova et al., *J Neurosci*. 2010  
Ferrarelli et al., *PNAS* 2010  
Rosanova et a., *Brain*, 2012

## Consciousness Absent

Sleep

Anesthesia

Vegetative State

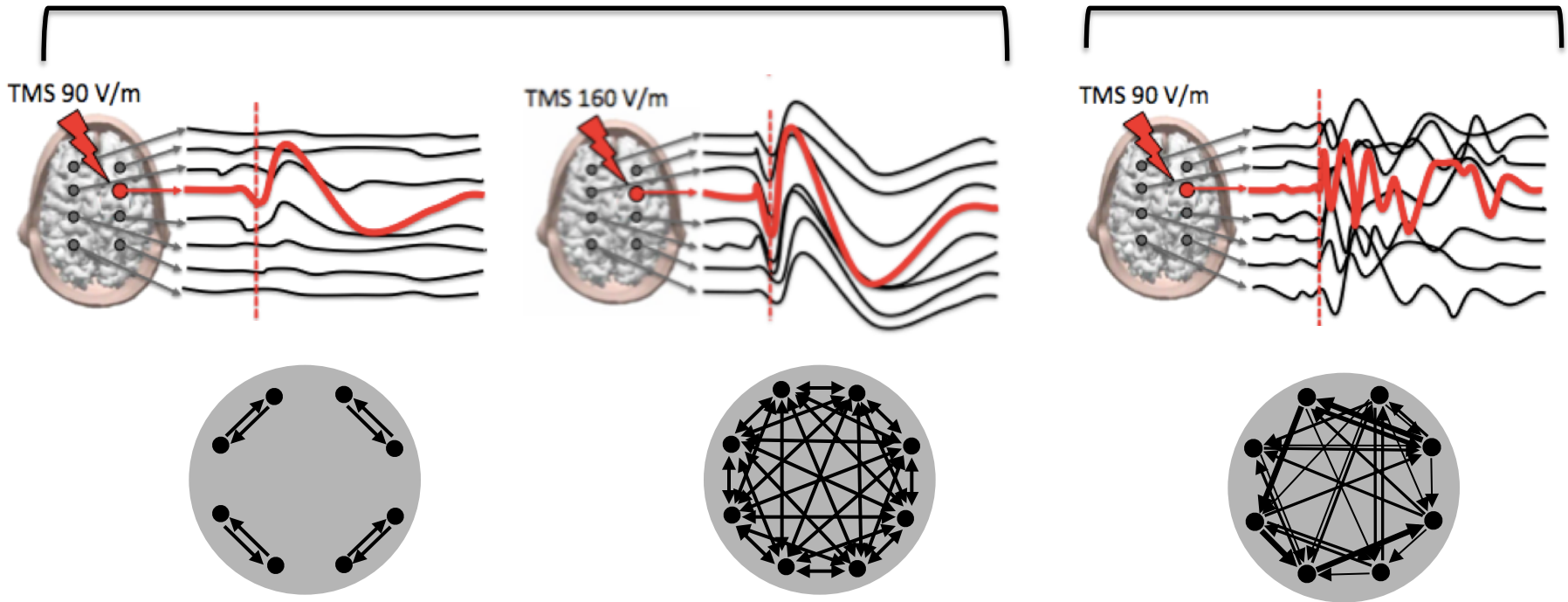
## Consciousness Present

Wakefulness

Dreaming

Locked-in Syndrome

Minimally Conscious State





## Consciousness Absent

Sleep

Anesthesia

Vegetative State

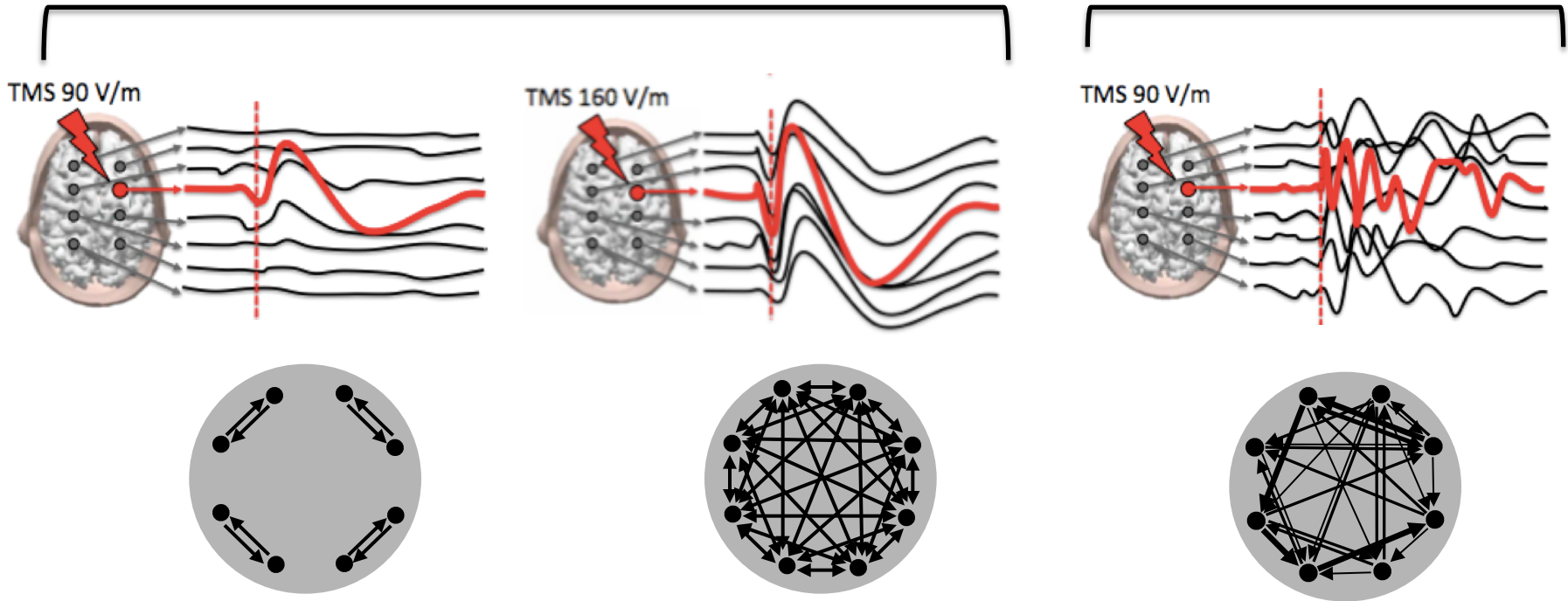
## Consciousness Present

Wakefulness

**Dreaming/Ketamine**

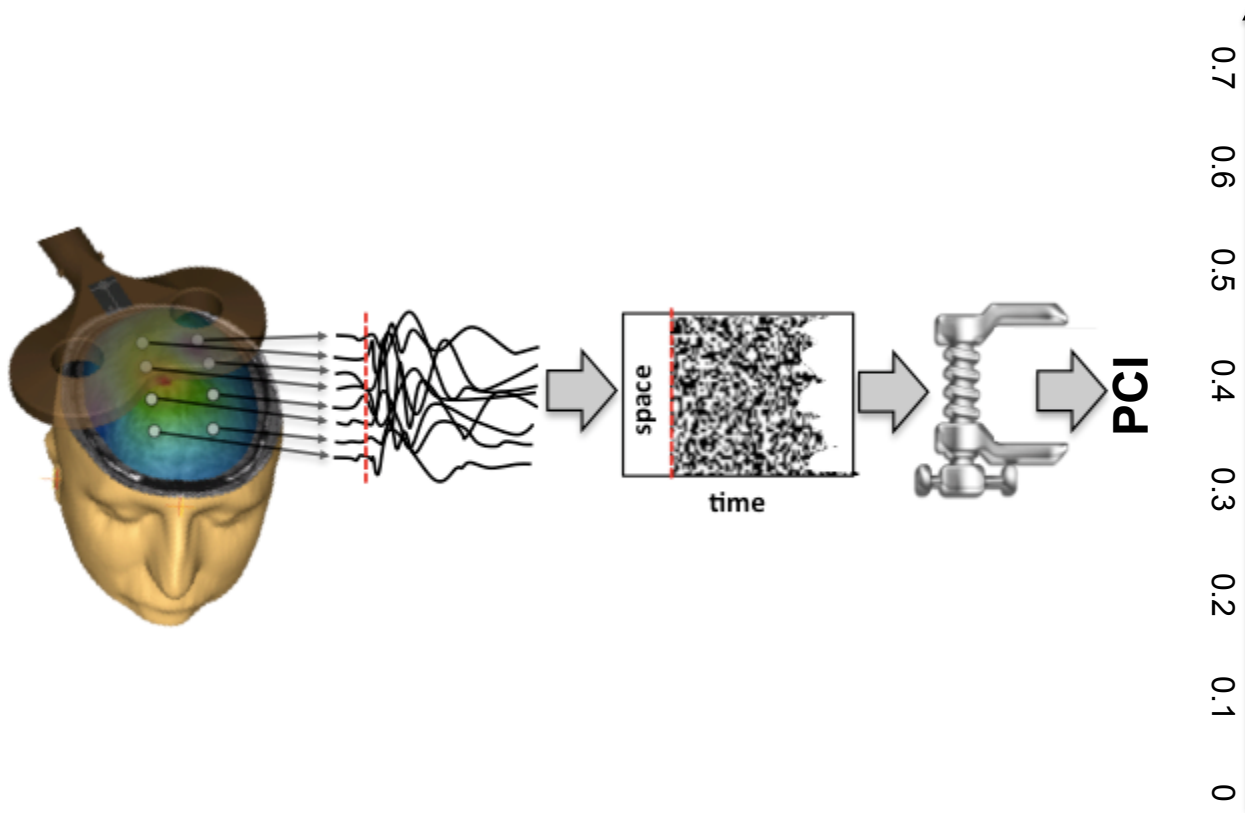
**Locked-in Syndrome**

**Minimally Conscious State**

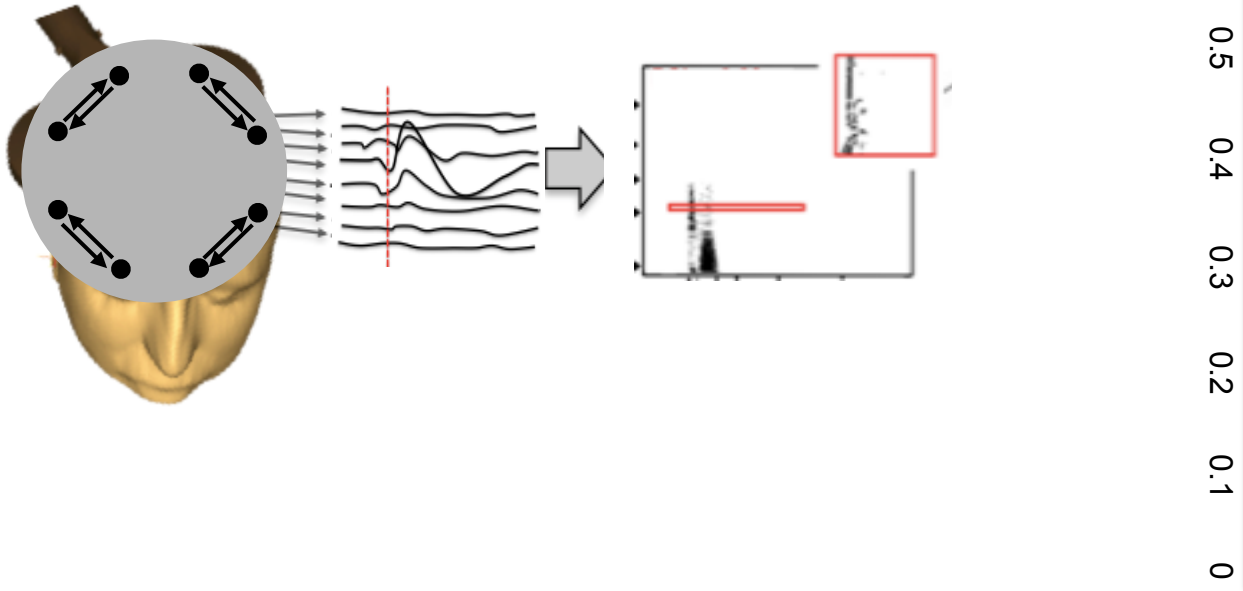


A quantification: the Perturbational Complexity Index

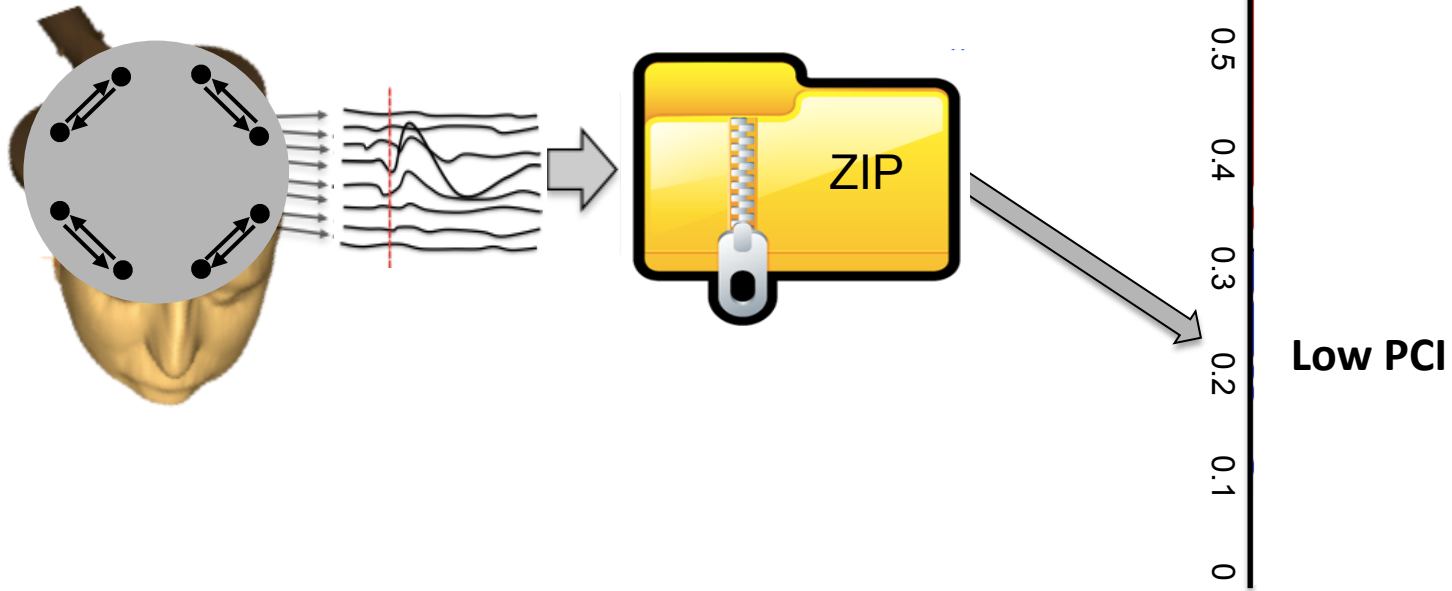
## A quantification: the Perturbational Complexity Index (PCI)



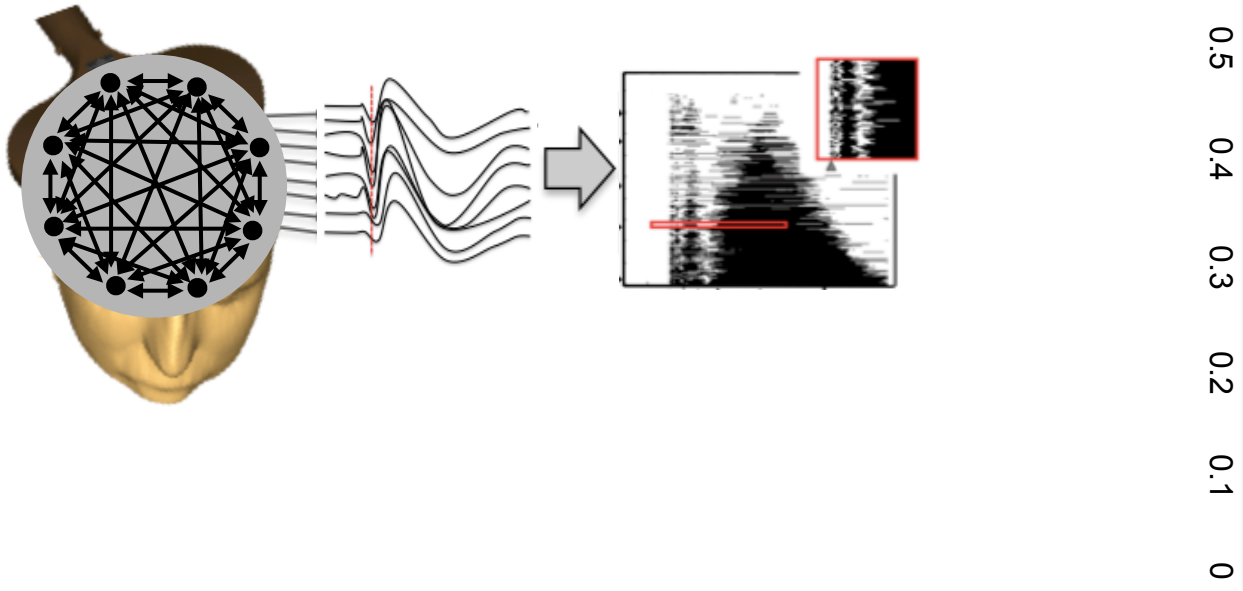
No Integration



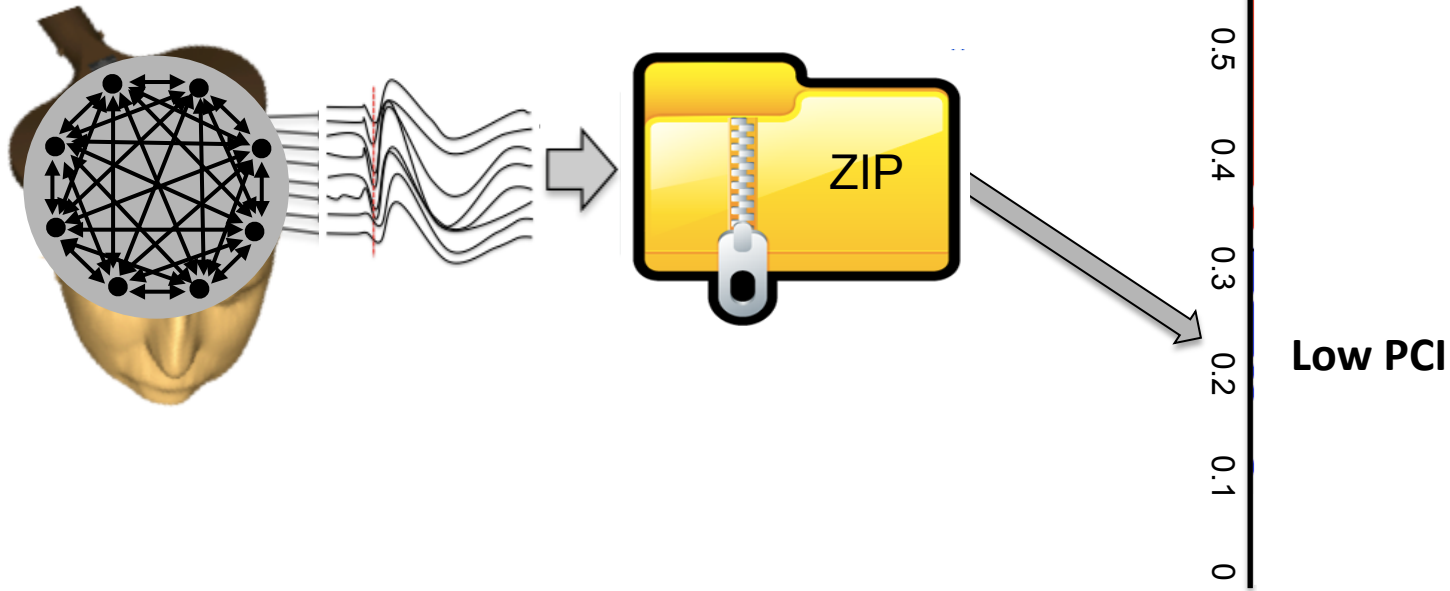
**No Integration**



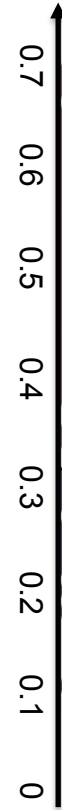
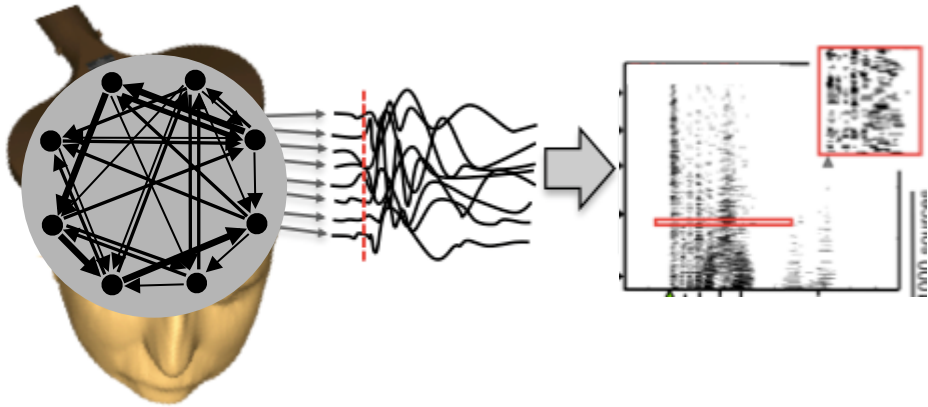
## No Differentiation



**No Differentiation**

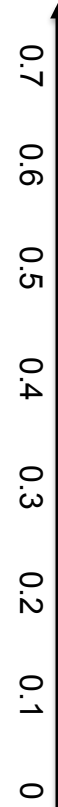
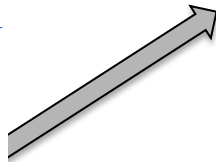
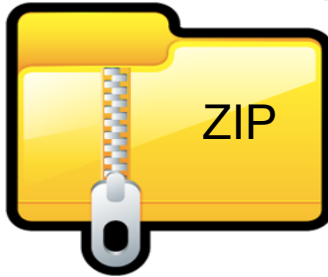
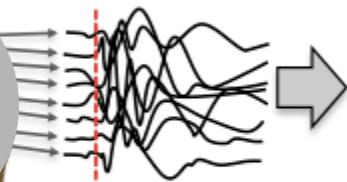
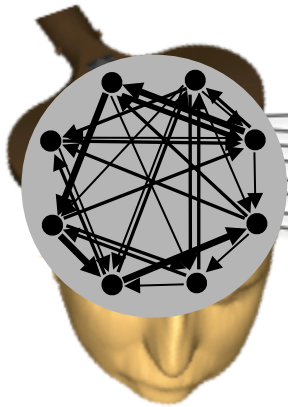


# Integration & Differentiation

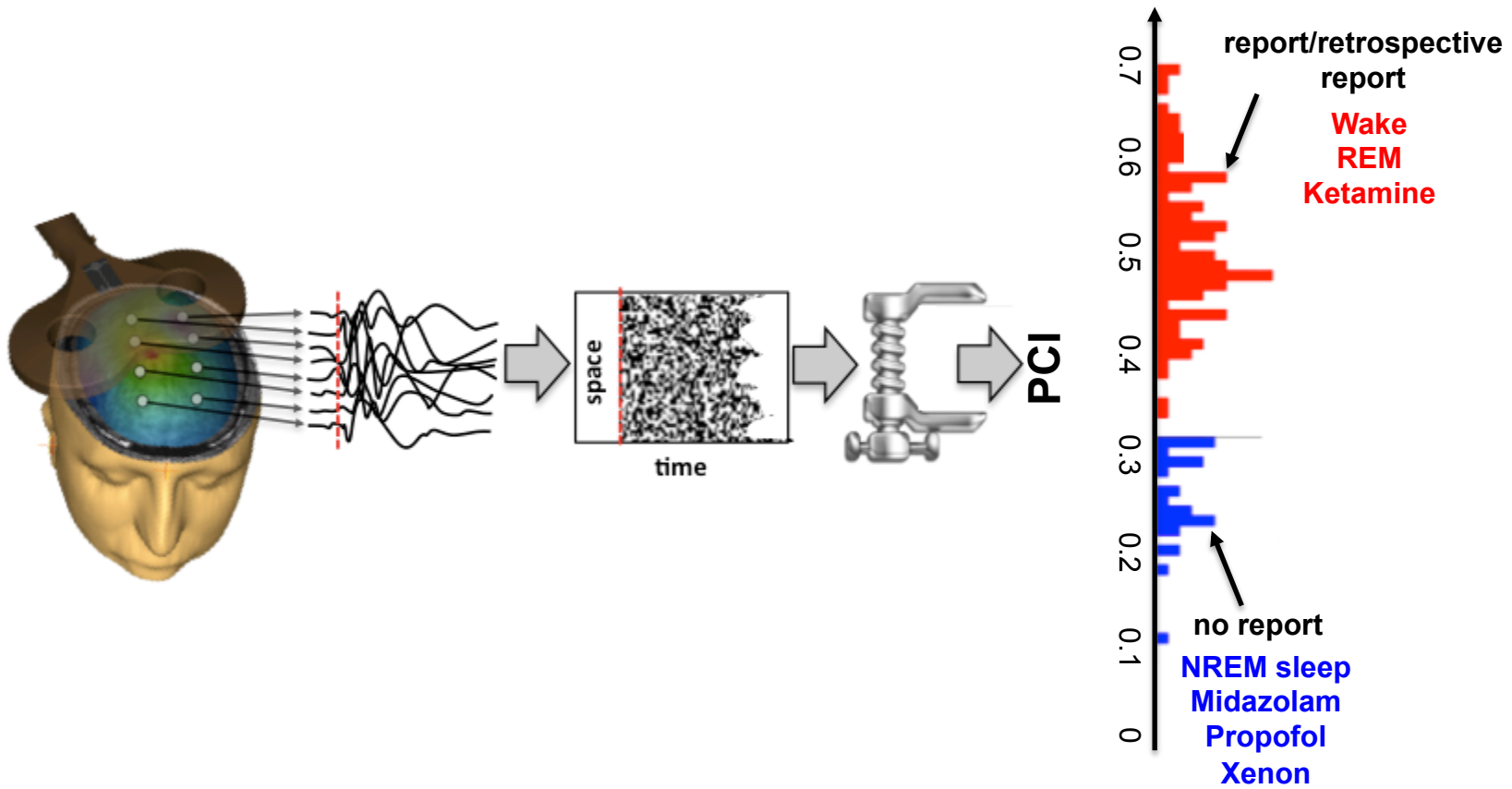


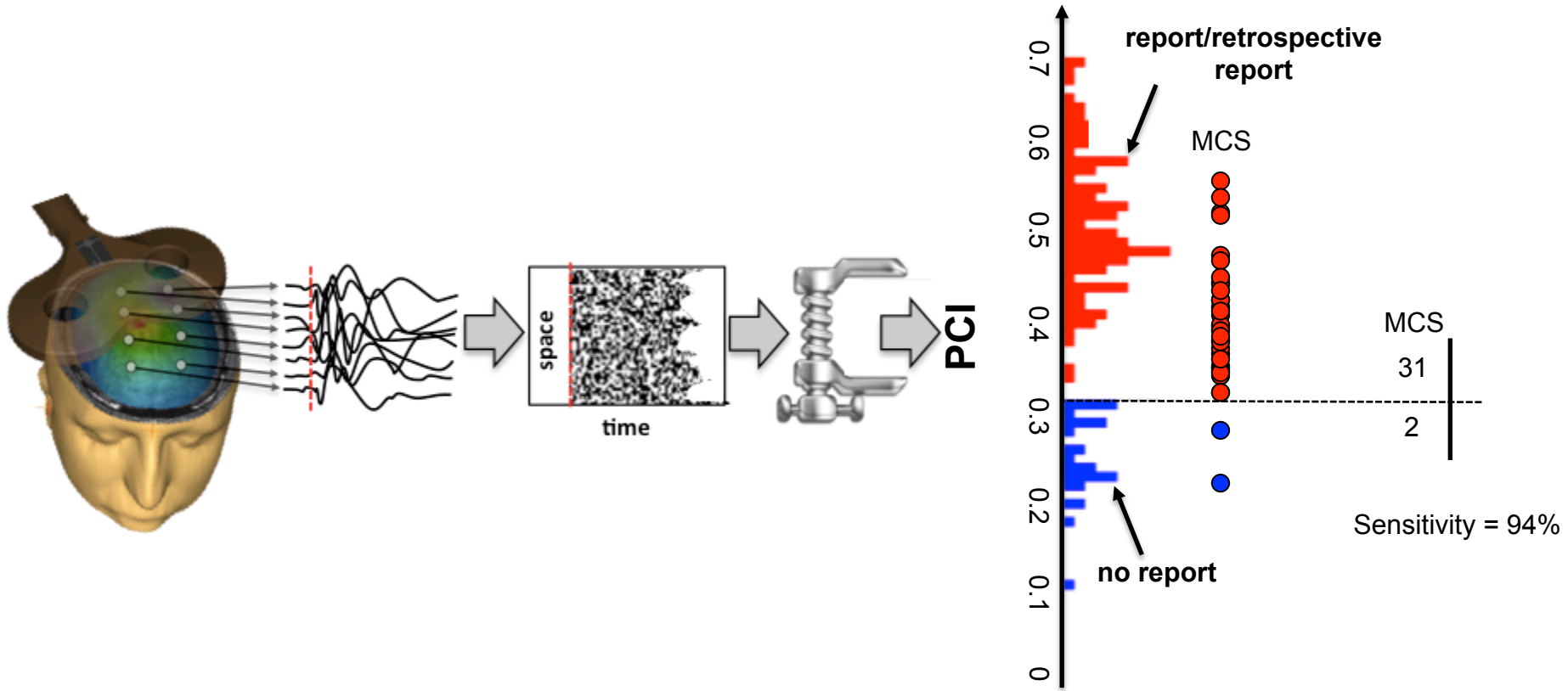


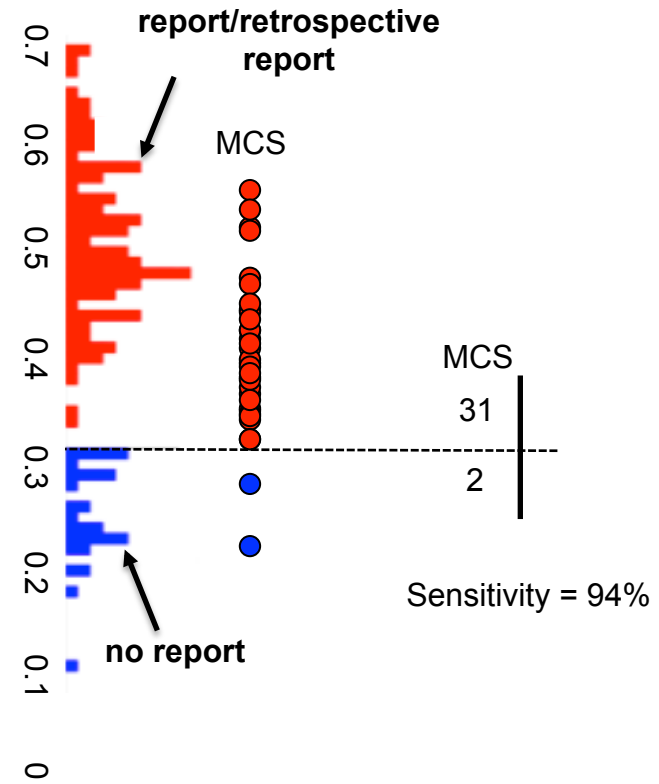
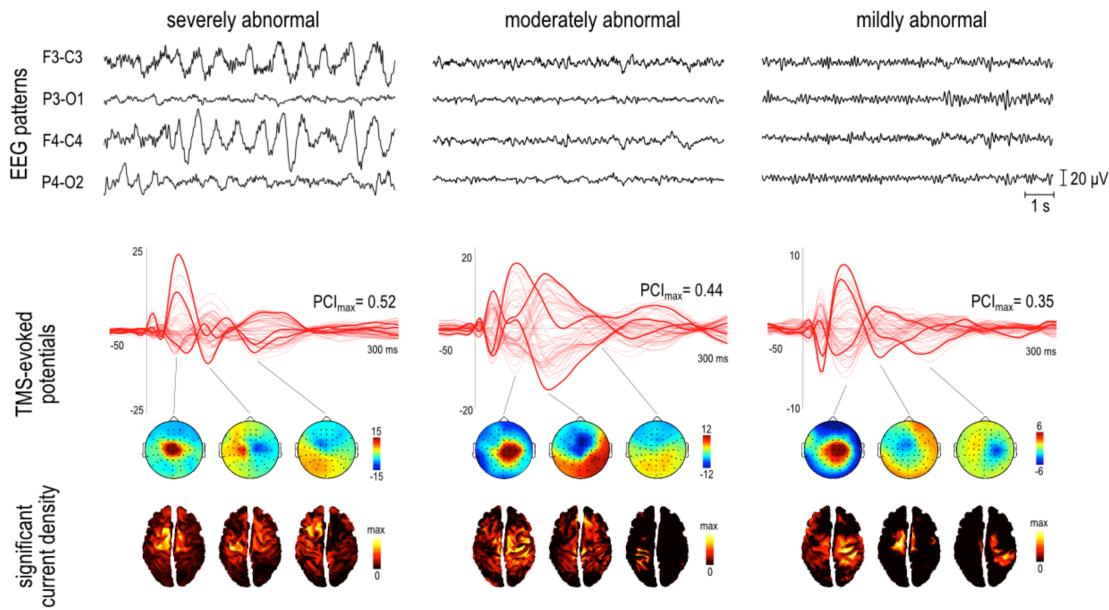
**Integration  
&  
Differentiation**

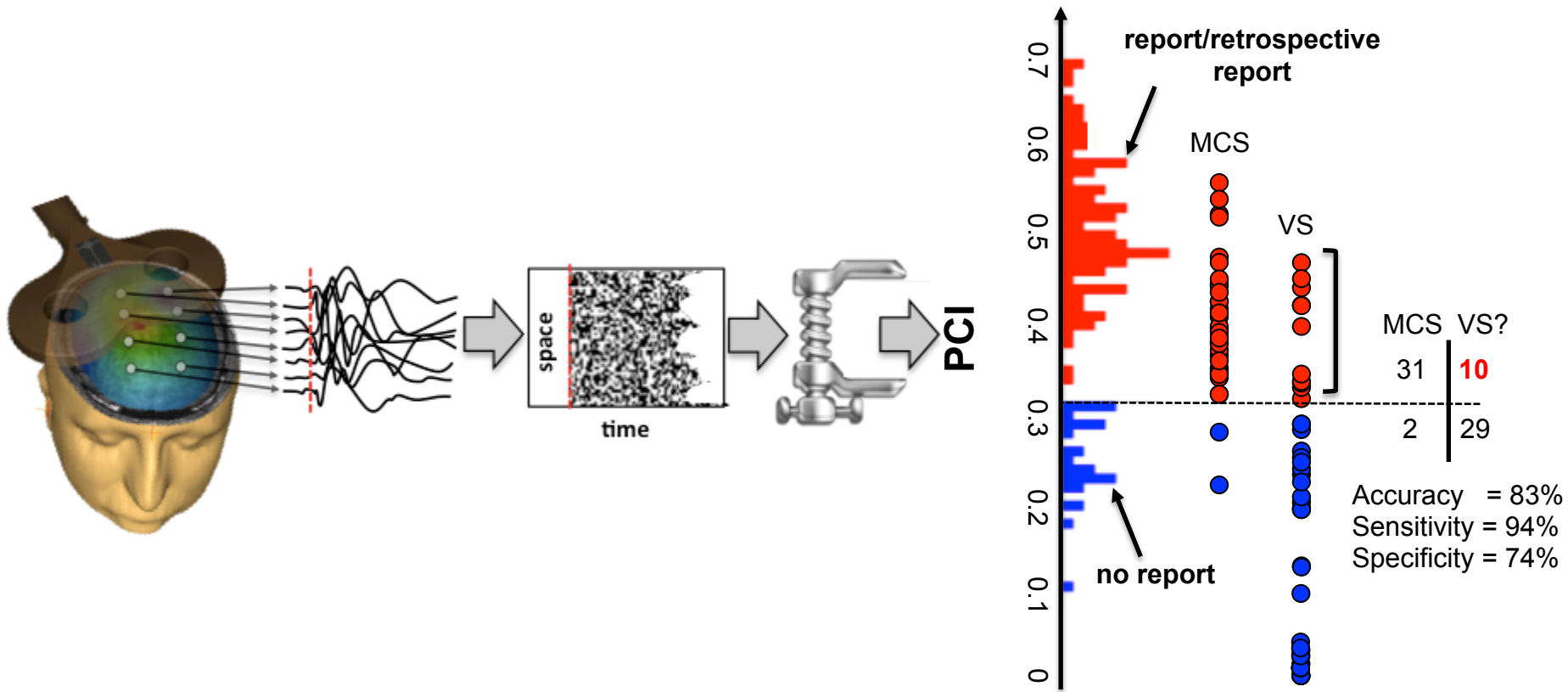


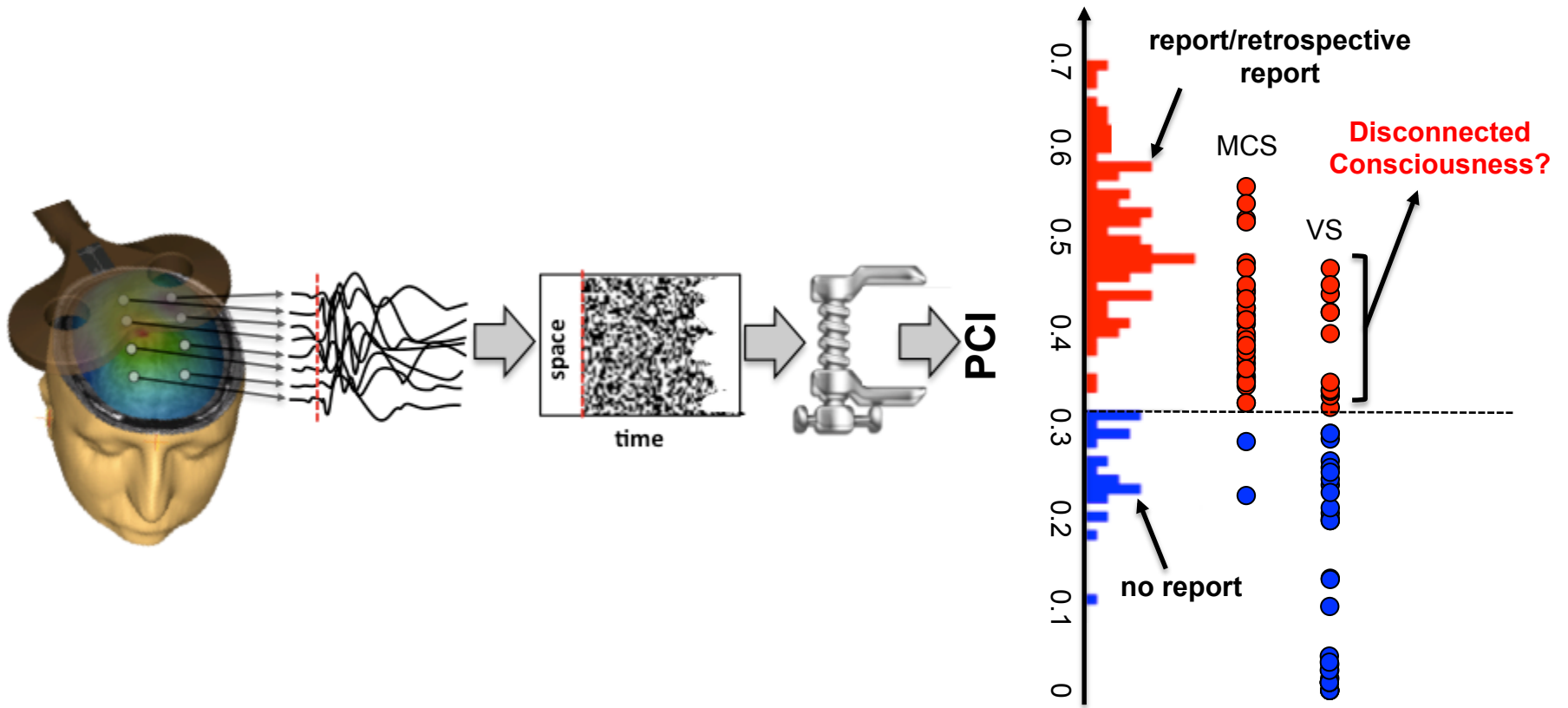
**High PCI**

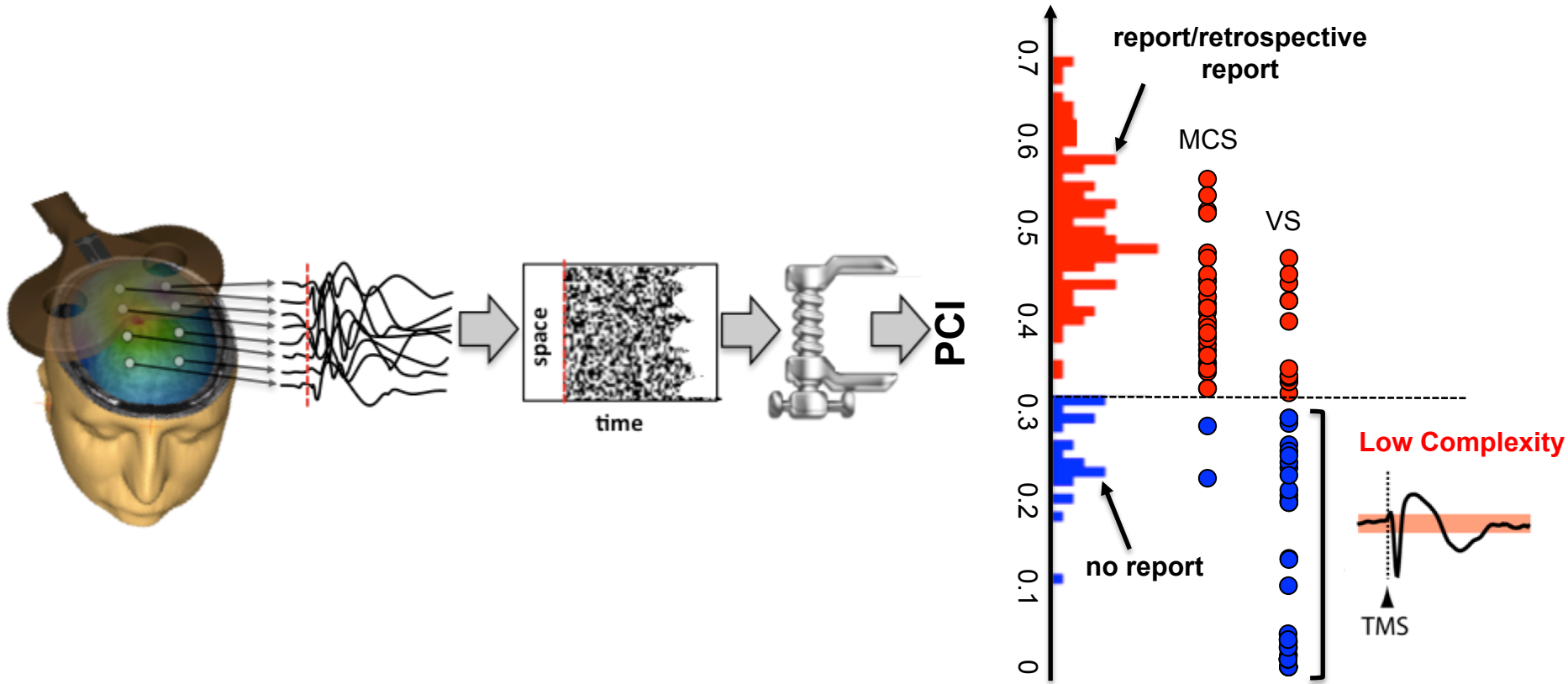












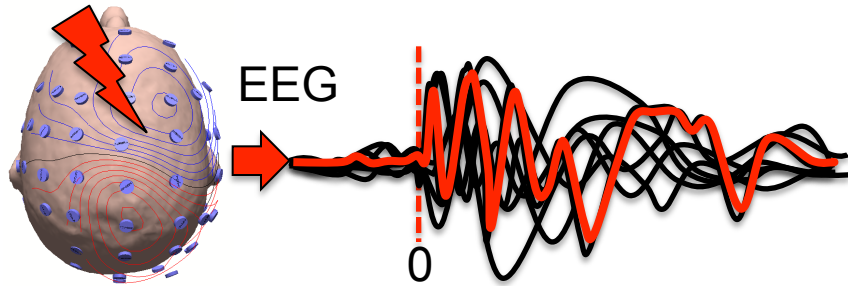
# Sleep





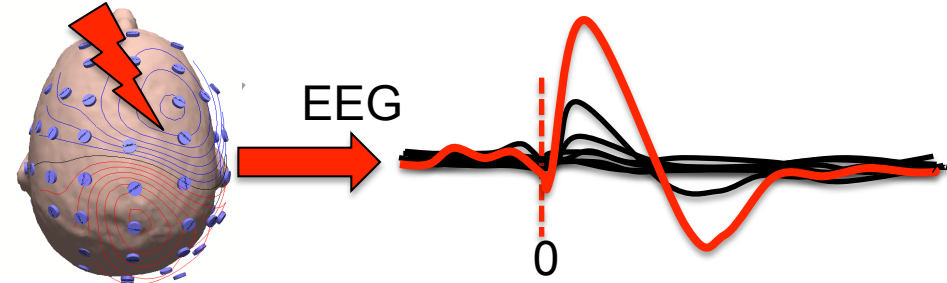
## Wakefulness

TMS

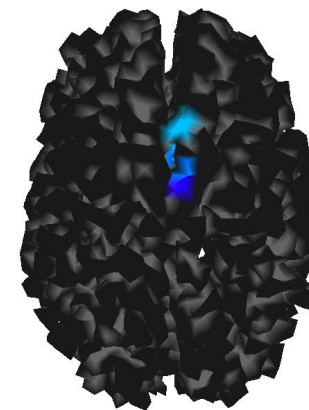
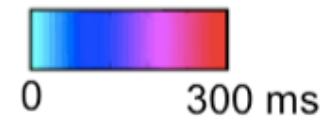
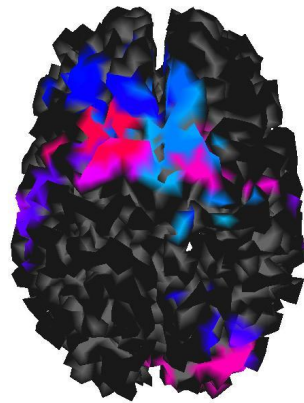
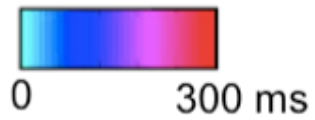


## Sleep

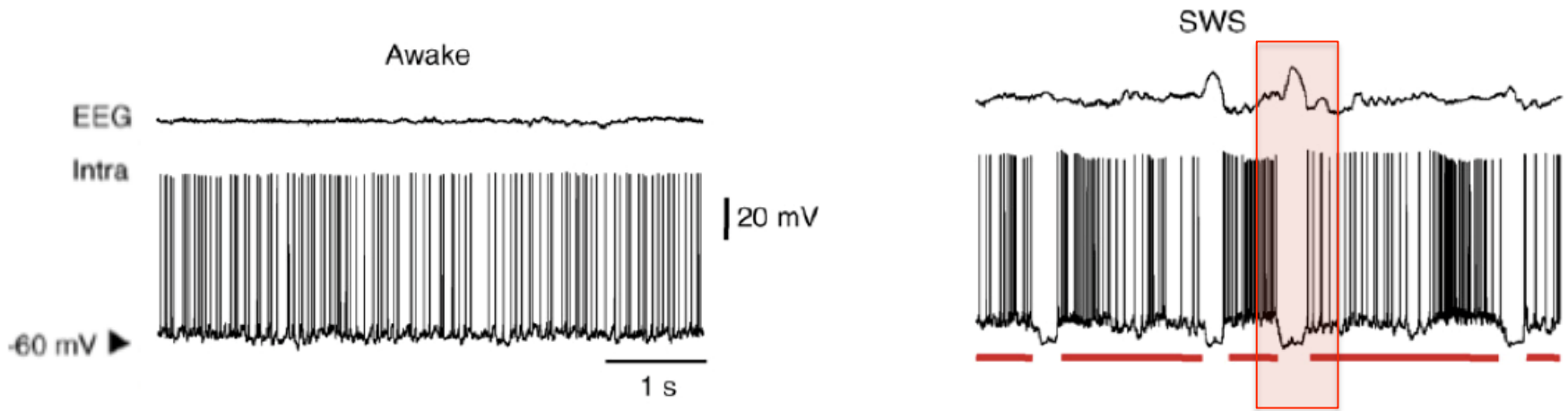
TMS



Massimini et al *Science*, 2005

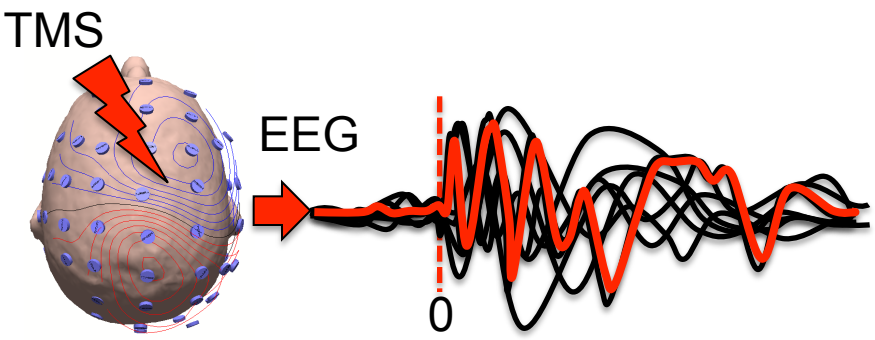


# Cortical Bistability

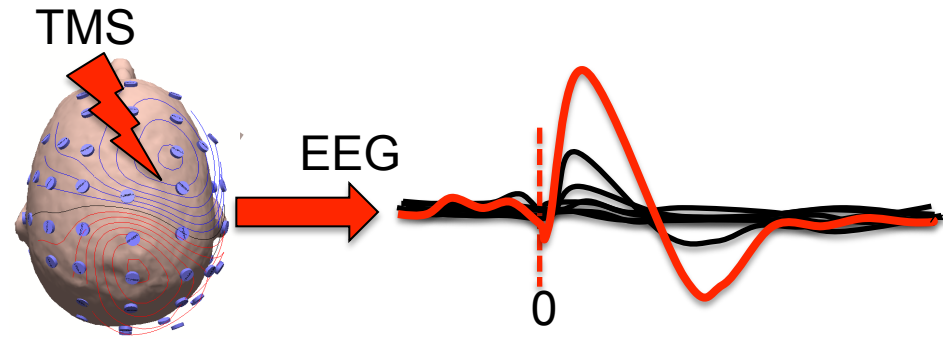


Steriade et al., *J. Neurophysiol.* 2001  
Chauvette et al., *J. Neurosci.* 2011

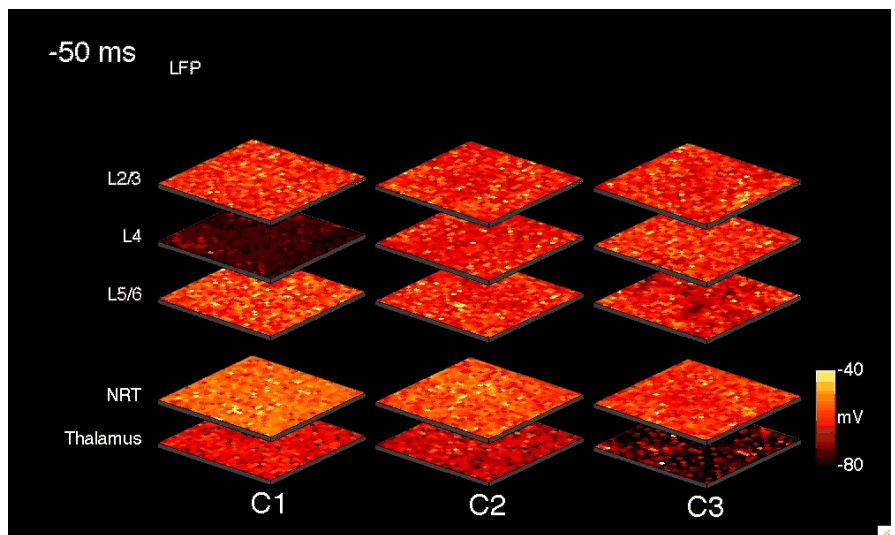
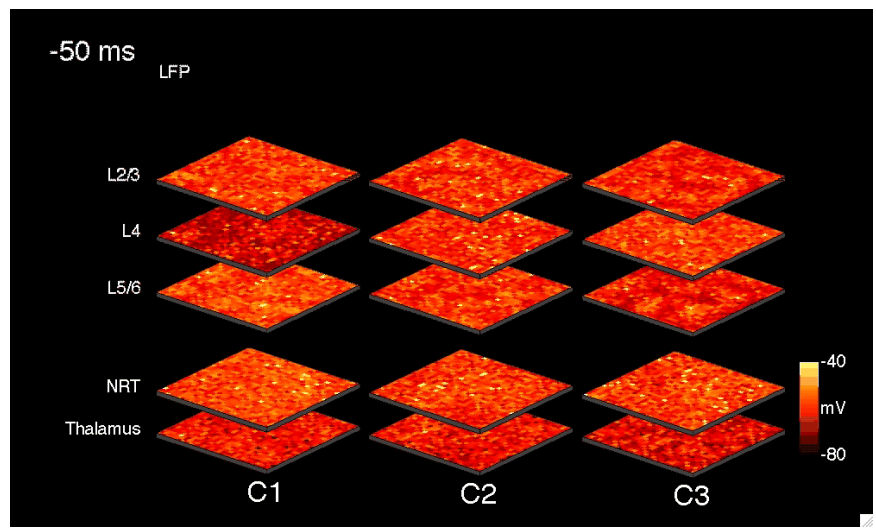
# Wakefulness



# Sleep

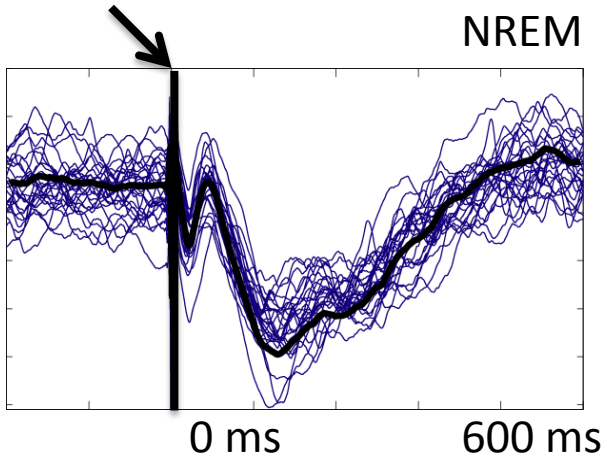
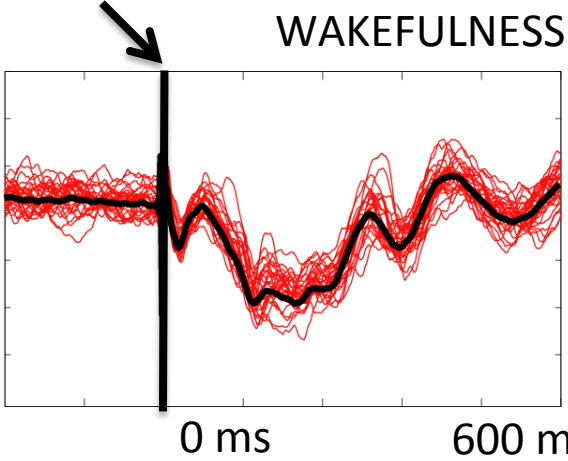
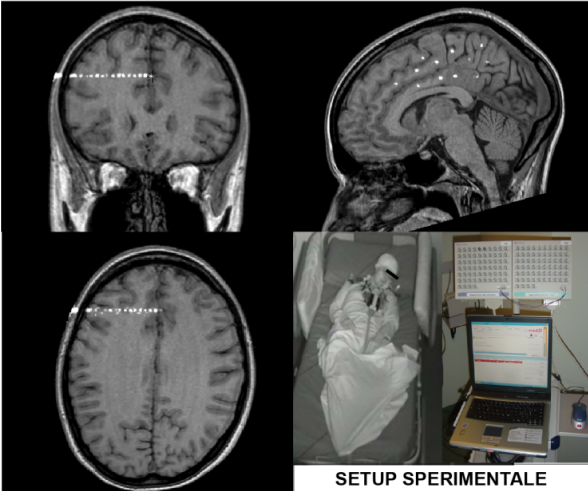


Massimini et al *Science*, 2005

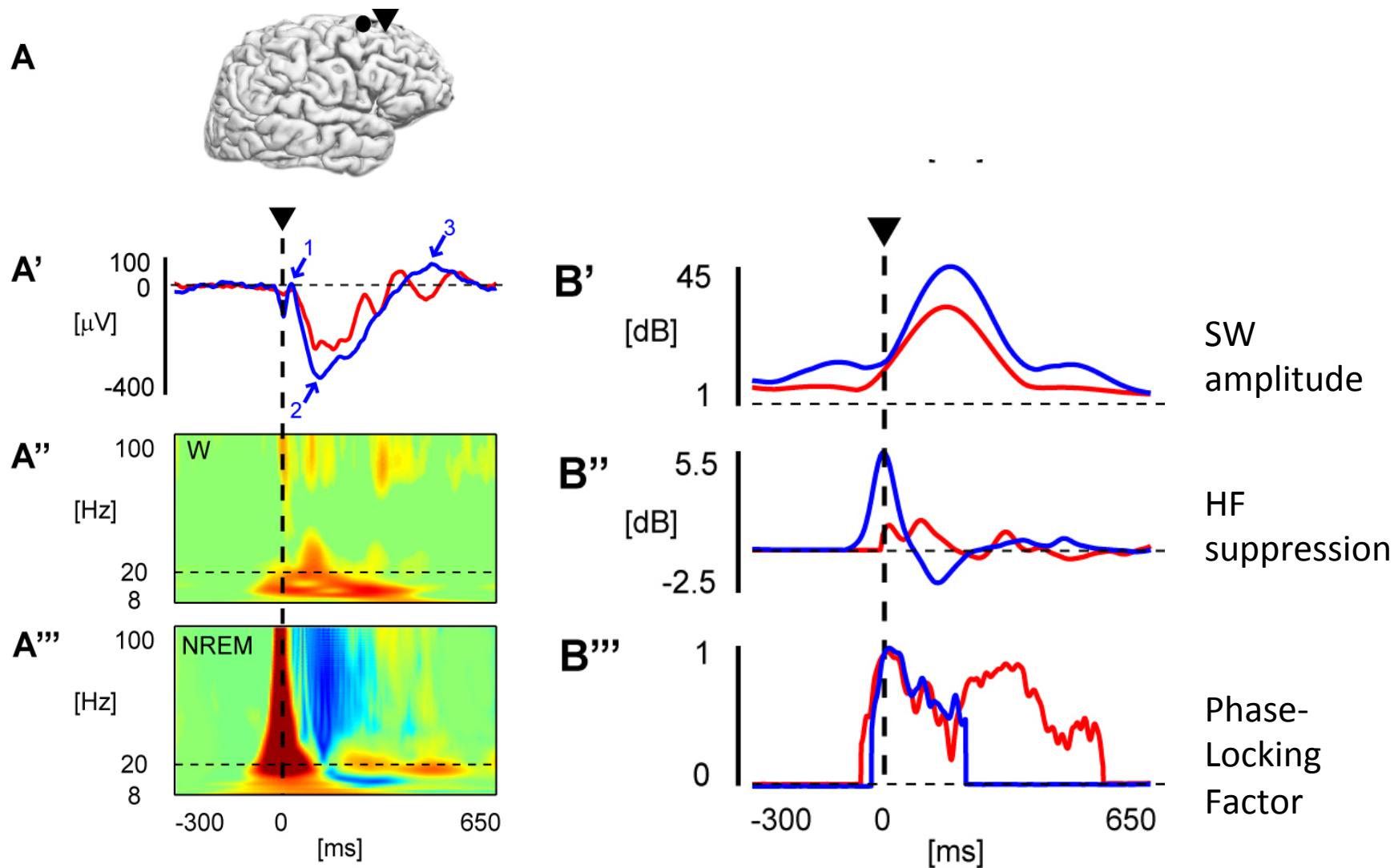


Esser et al., *J. Neurophys.* 2009

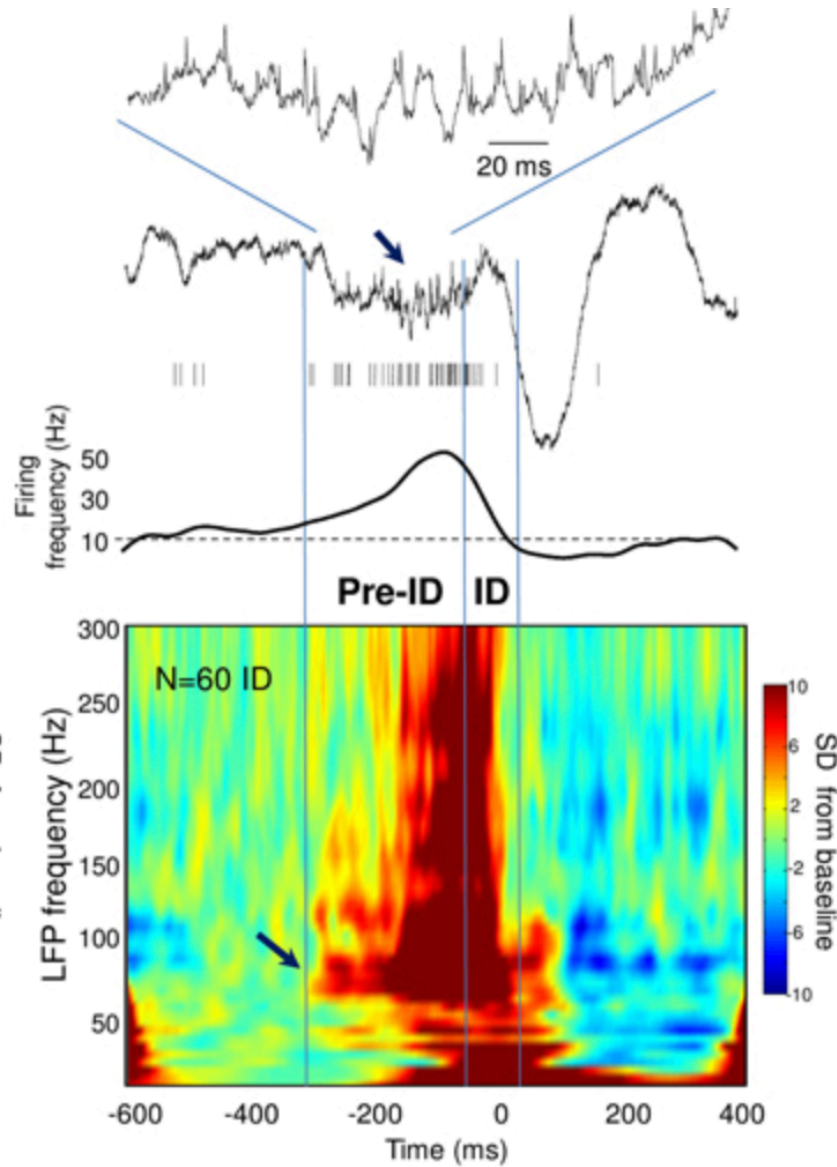
# INTRACRANIAL STIMULATION/RECORDING

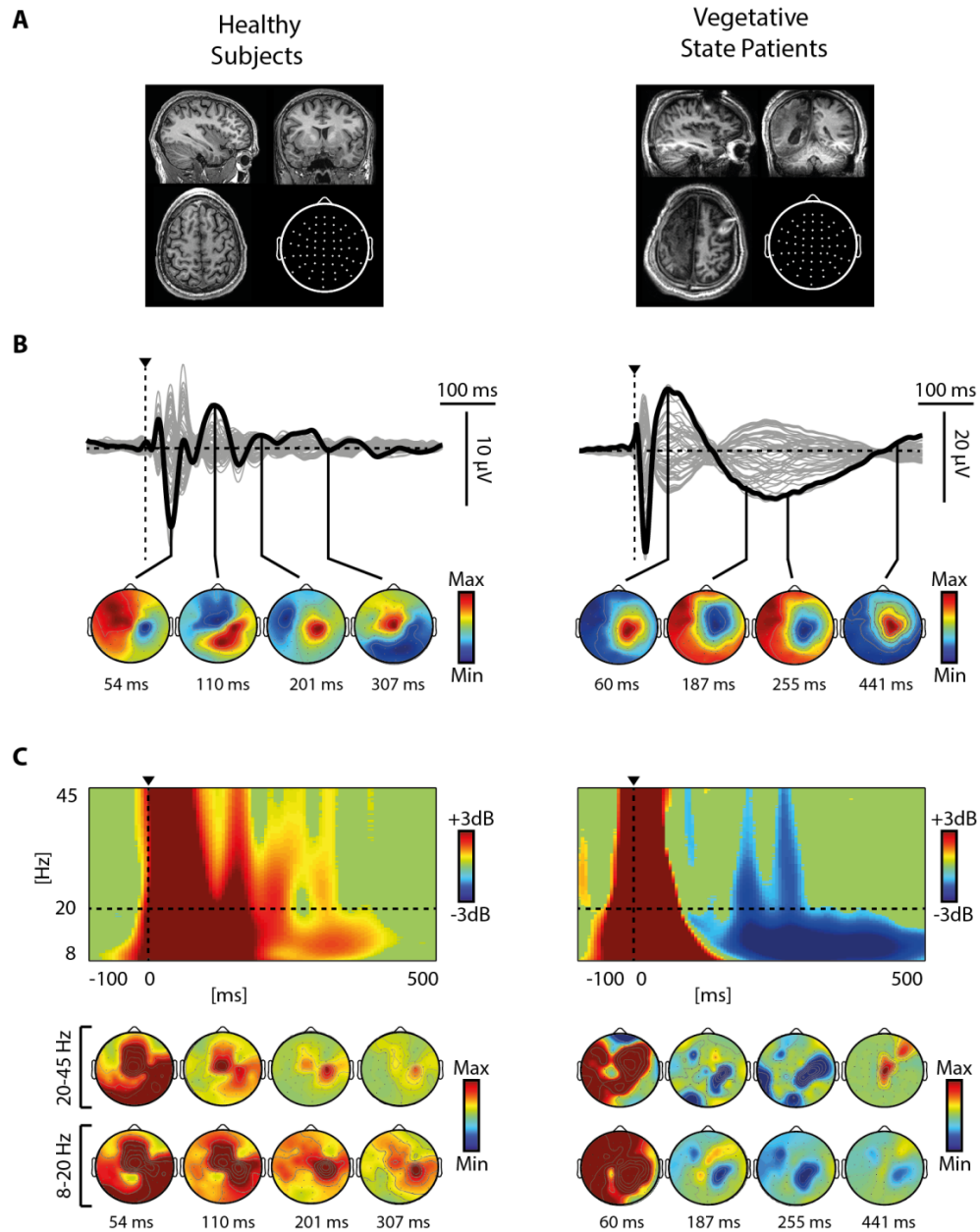


## 2 – Empirical evidences



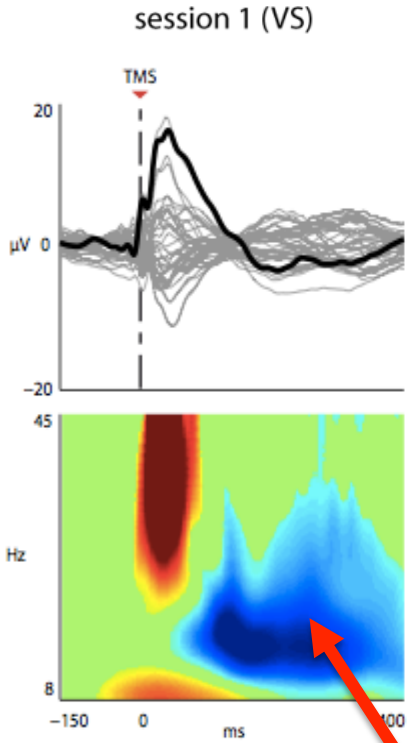
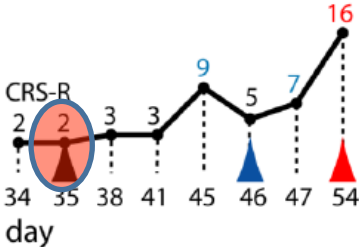
# Drug resistant temporal lobe epilepsy







# RECOVERY

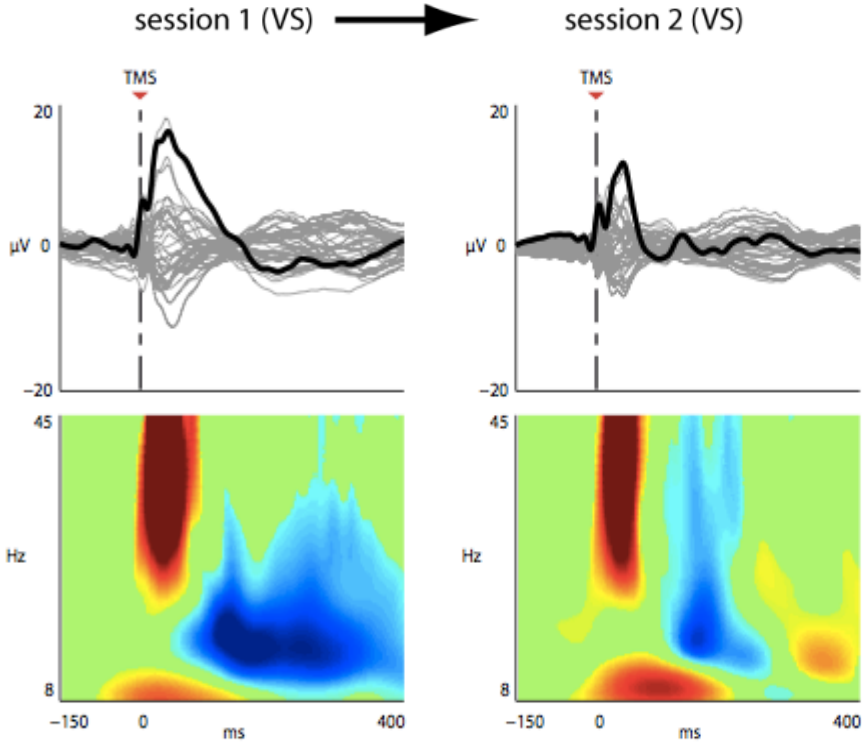
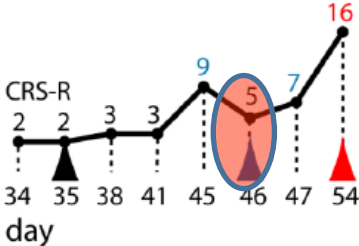


**DOWN STATE**

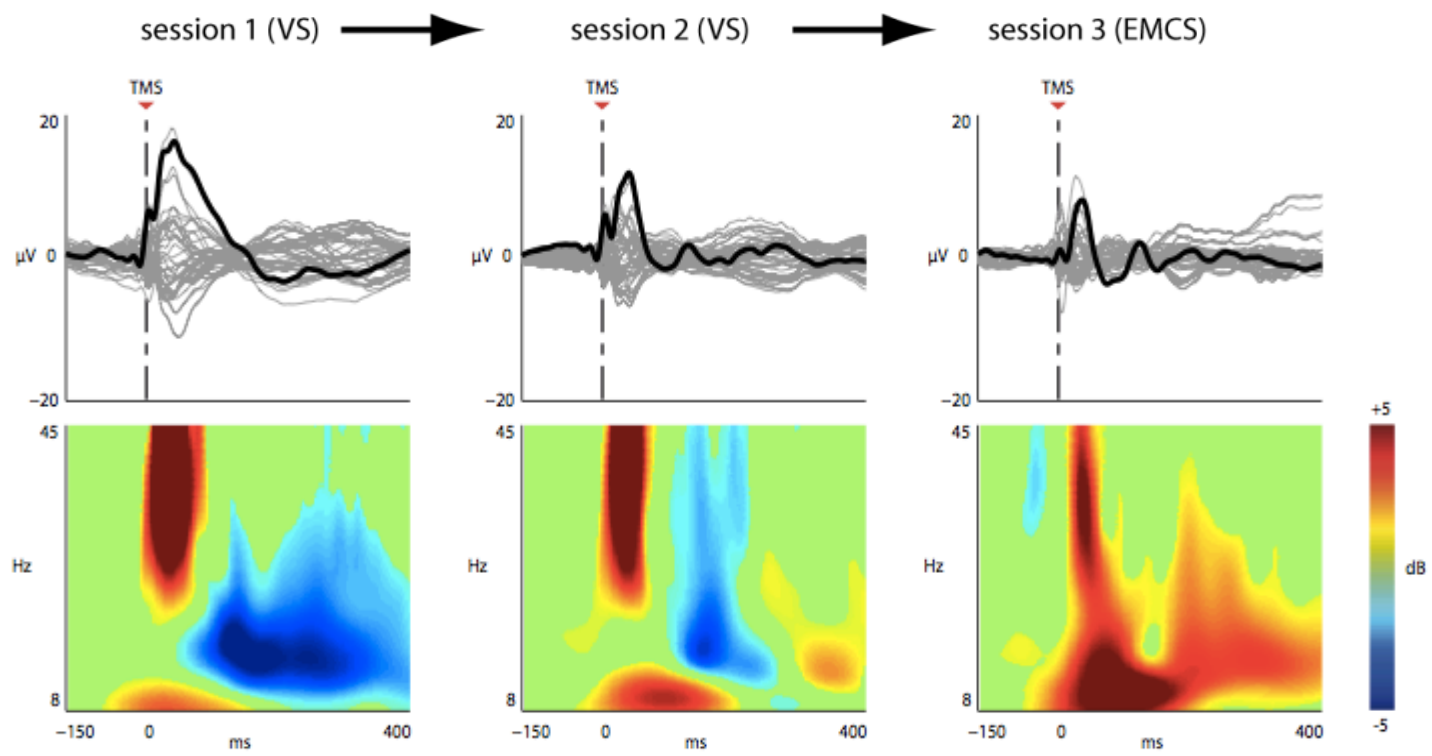
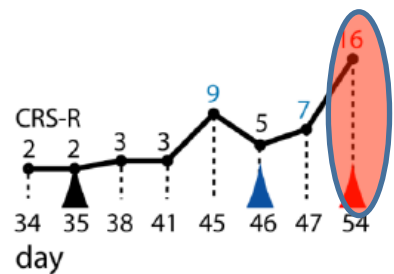
Rosanova, Fecchio et al., *in preparation*



# RECOVERY



# RECOVERY



Rosanova, Fecchio et al., *in preparation*

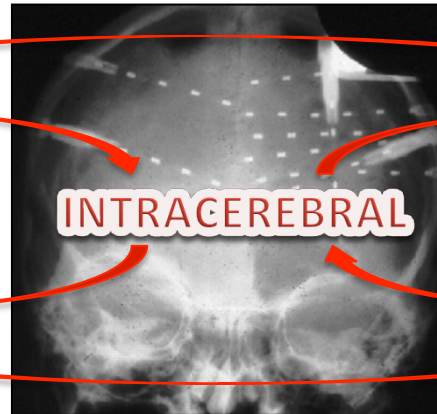
# Exploring the mechanisms of loss and recovery of complexity

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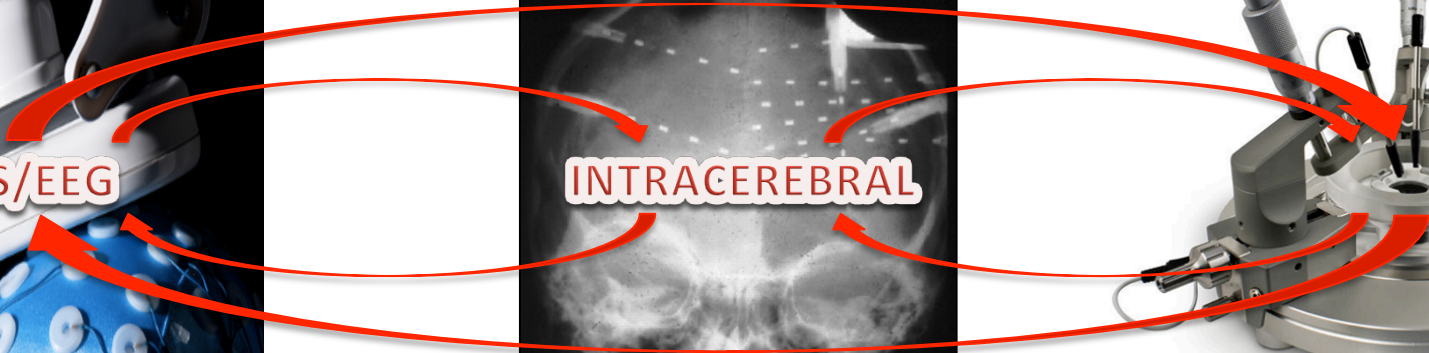
macroscale/bedside



mesoscale



microscale



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