41° CONGRESSO NAZIONALE
LEGA ITALIANA CONTRO L'EPILESSIA
ROMA, 6 / 8 GIUGNO 2018

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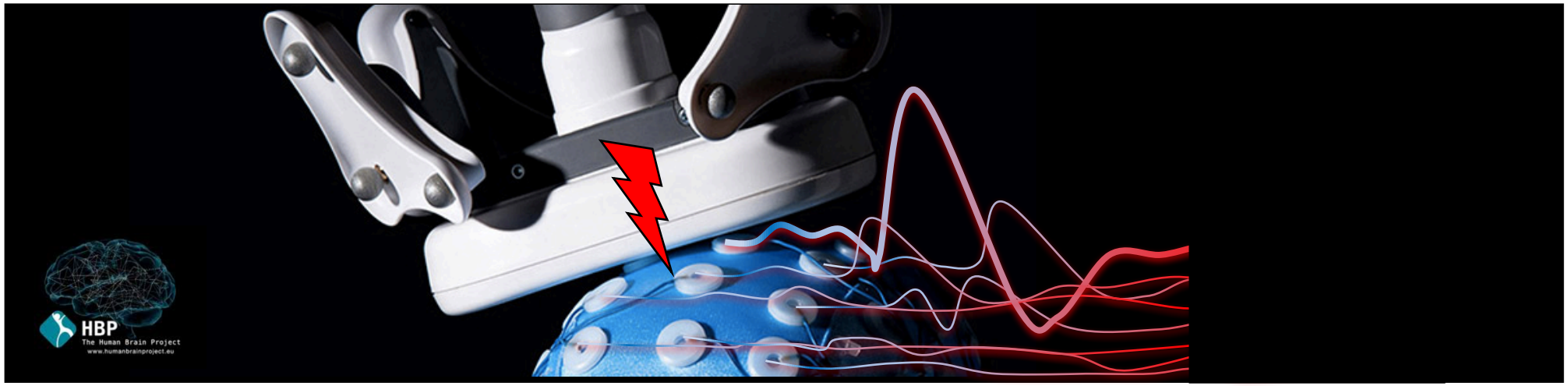
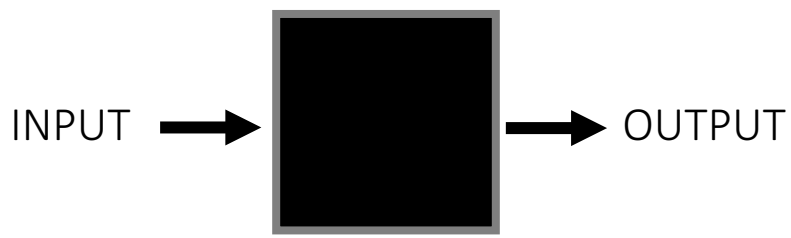
Cortical mechanisms of Loss and Recovery of Consciousness

Marcello Massimini MD, PhD

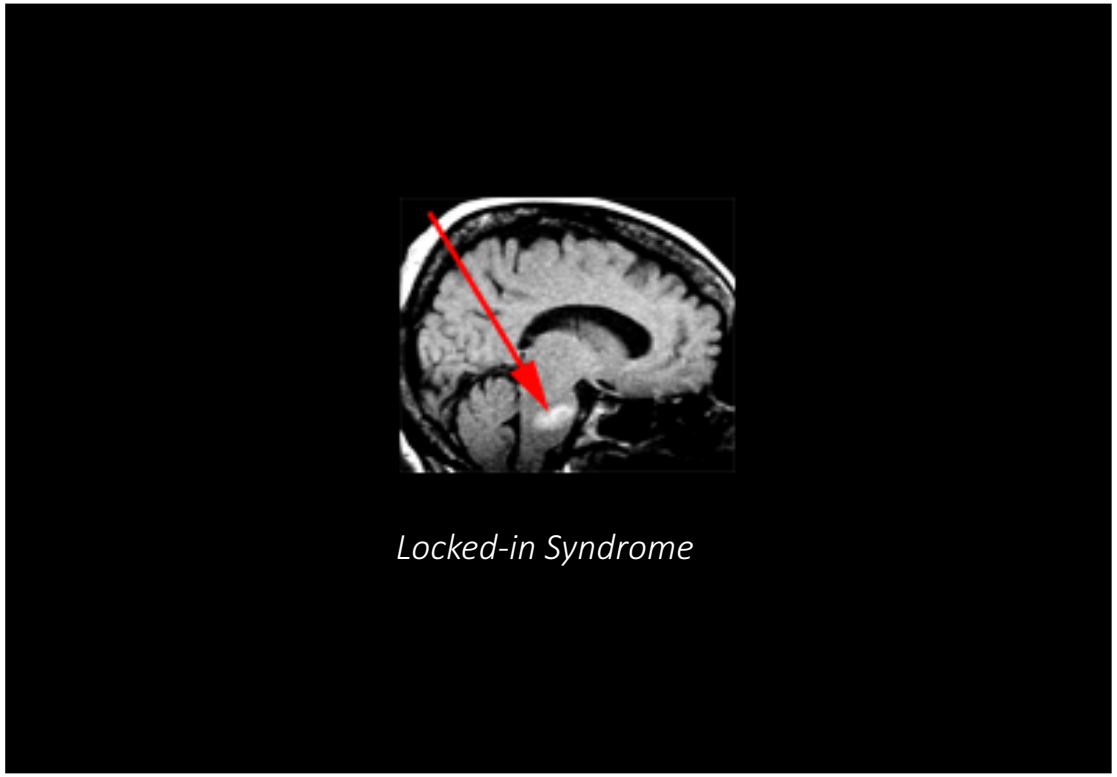


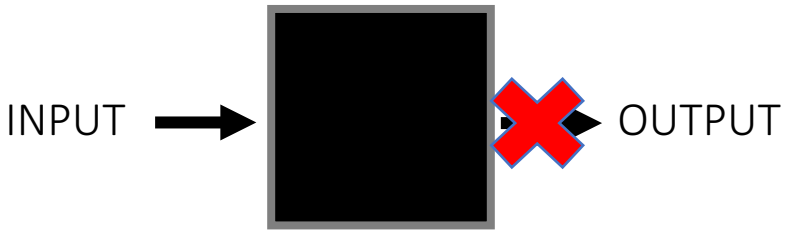
UNIVERSITÀ DEGLI STUDI
DI MILANO

detecting consciousness currently relies on probing sensory processing and motor ouputs

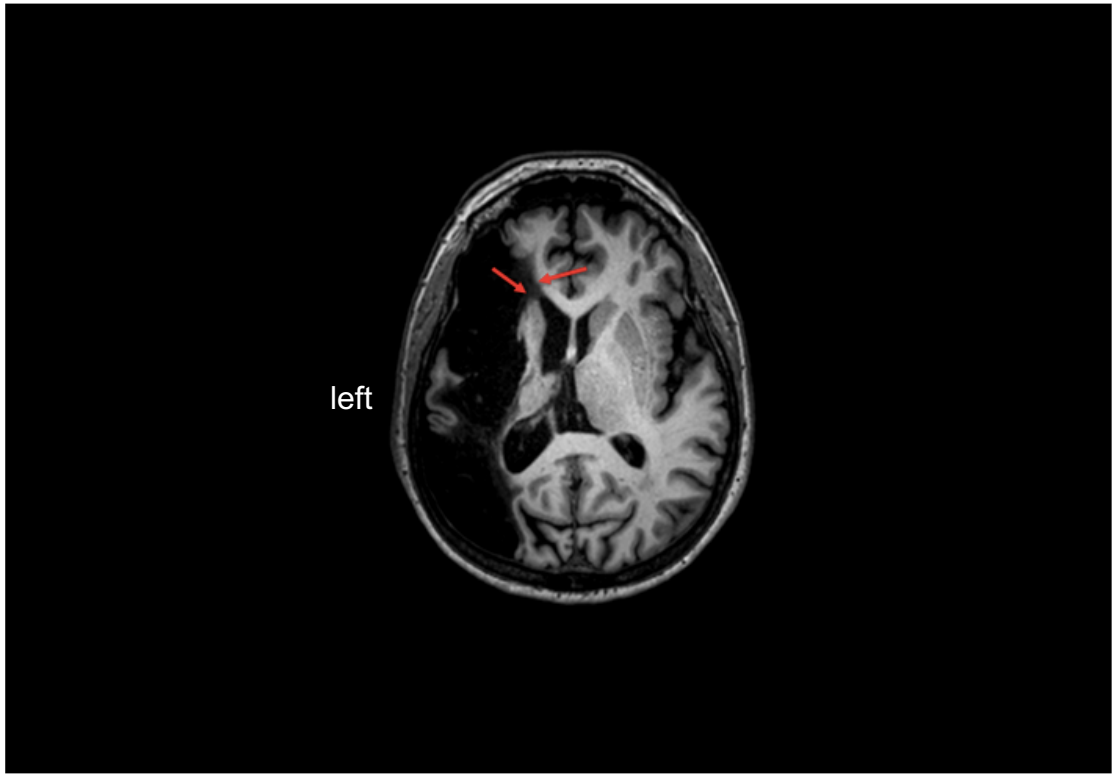


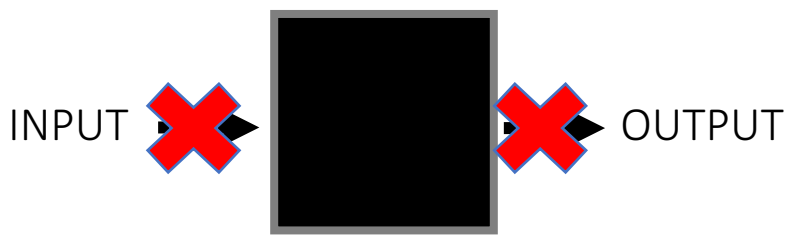
executive functions and motor outputs can be impaired in conscious patients…



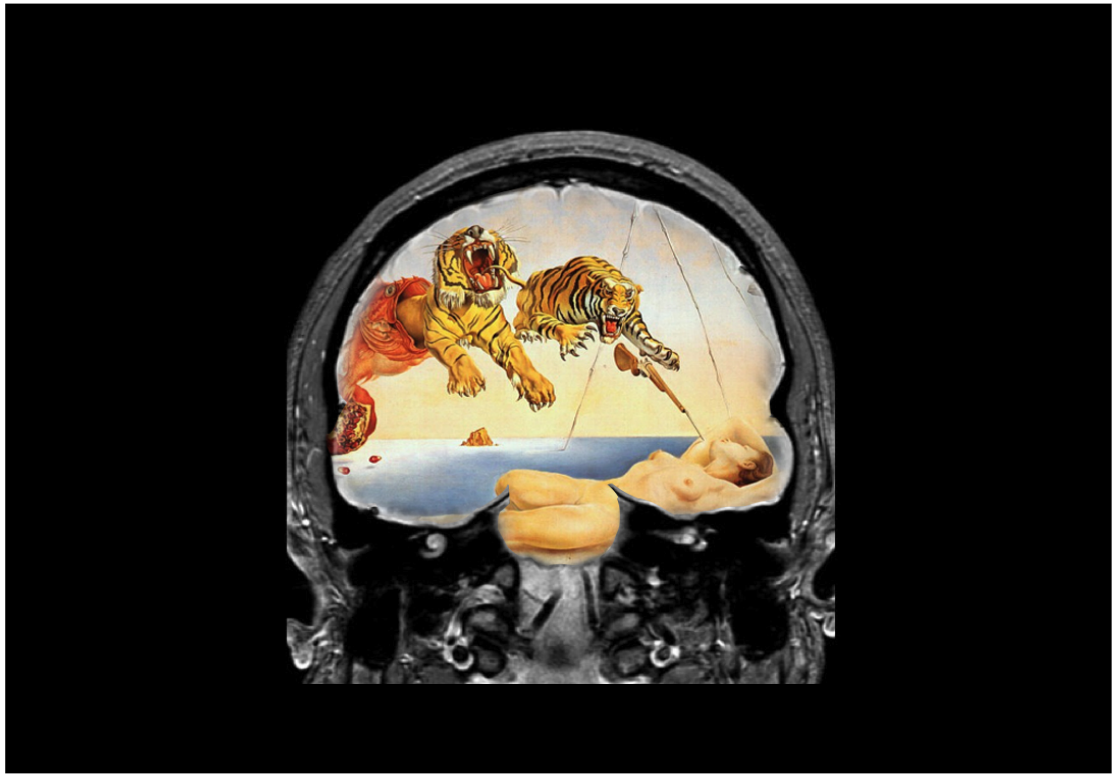


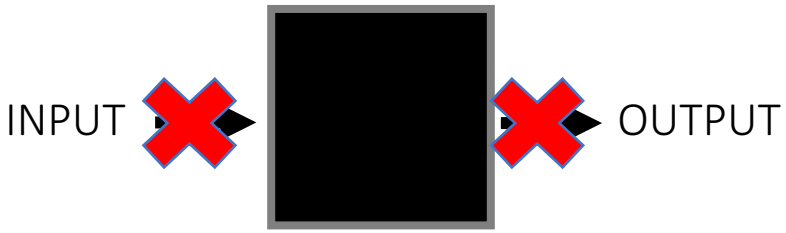
…as well as sensory processing





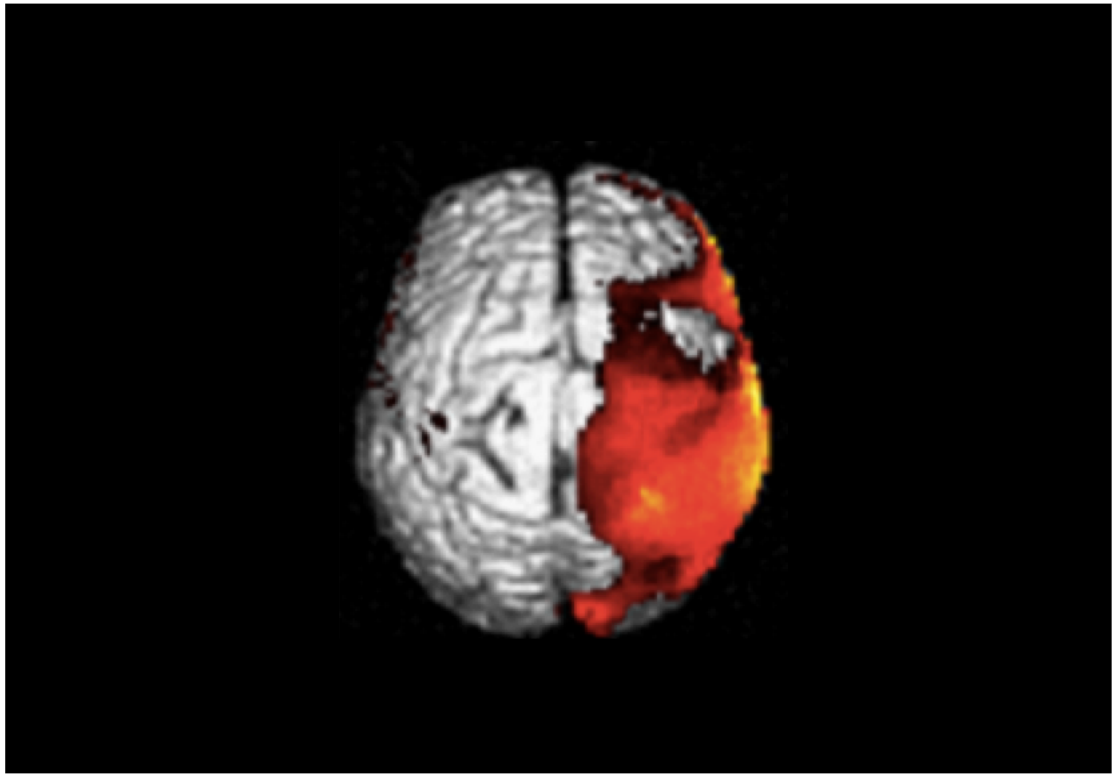
consciousness can be entirely generated within the brain…





Modified from S. D'Alì "The dream"

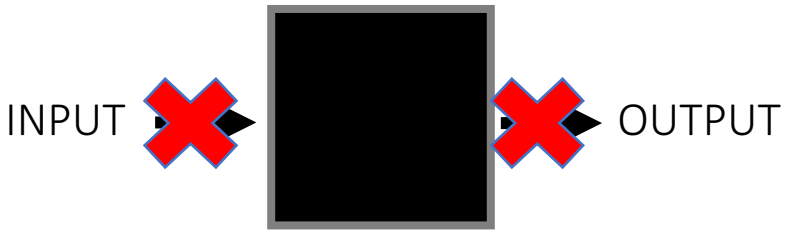
…and we are saving many patients who retain large islands of cortex



In the US:

50,000 unresponsive patients (VS)
300,000 minimally responsive (MCS)

All at risk of misdiagnosis!



Majerus et al., 2005
Laureys and Schiff 2012

A brain-based index independent of sensory processing, executive and motor functions

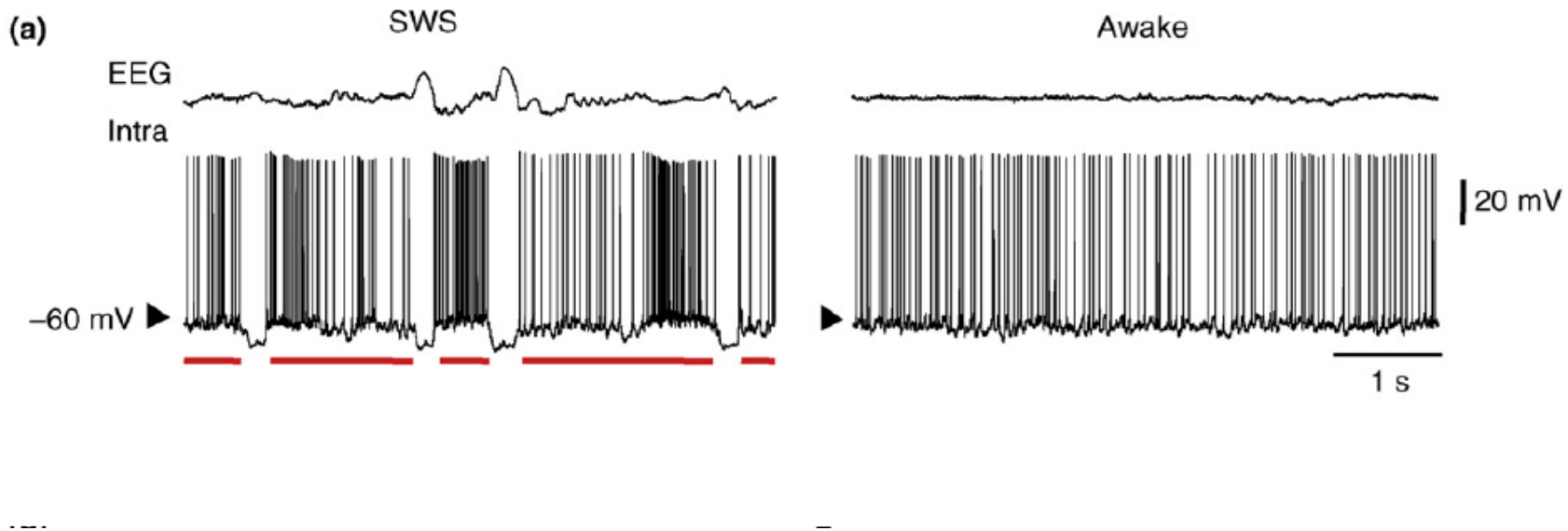
nature REVIEWS NEUROSCIENCE

Neural correlates of consciousness: progress and problems

Christof Koch[1], Marcello Massimini[2,3], Melanie Boly[4,5] and Giulio Tononi[5]

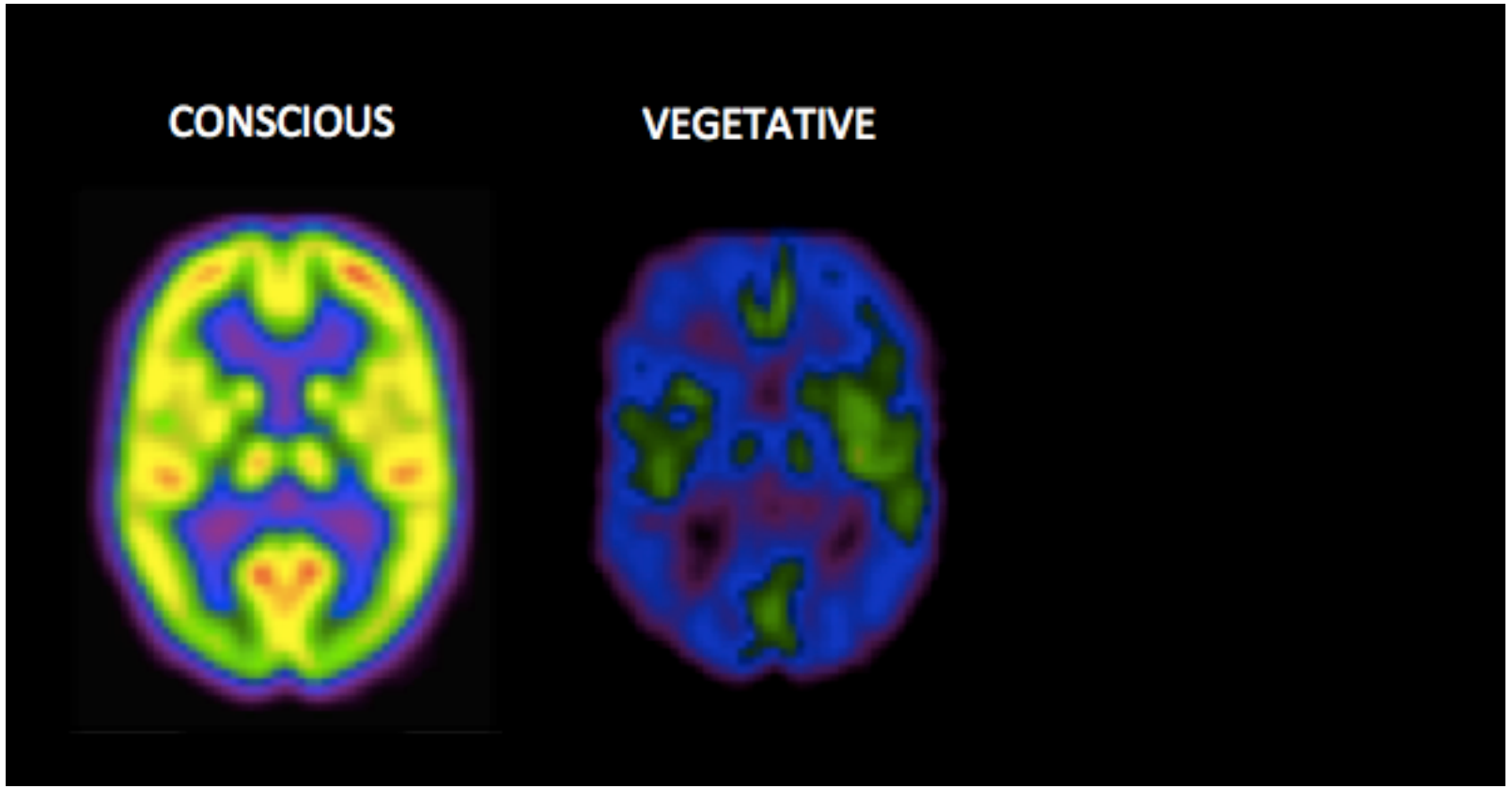
level of neural activity?

level of neural activity?



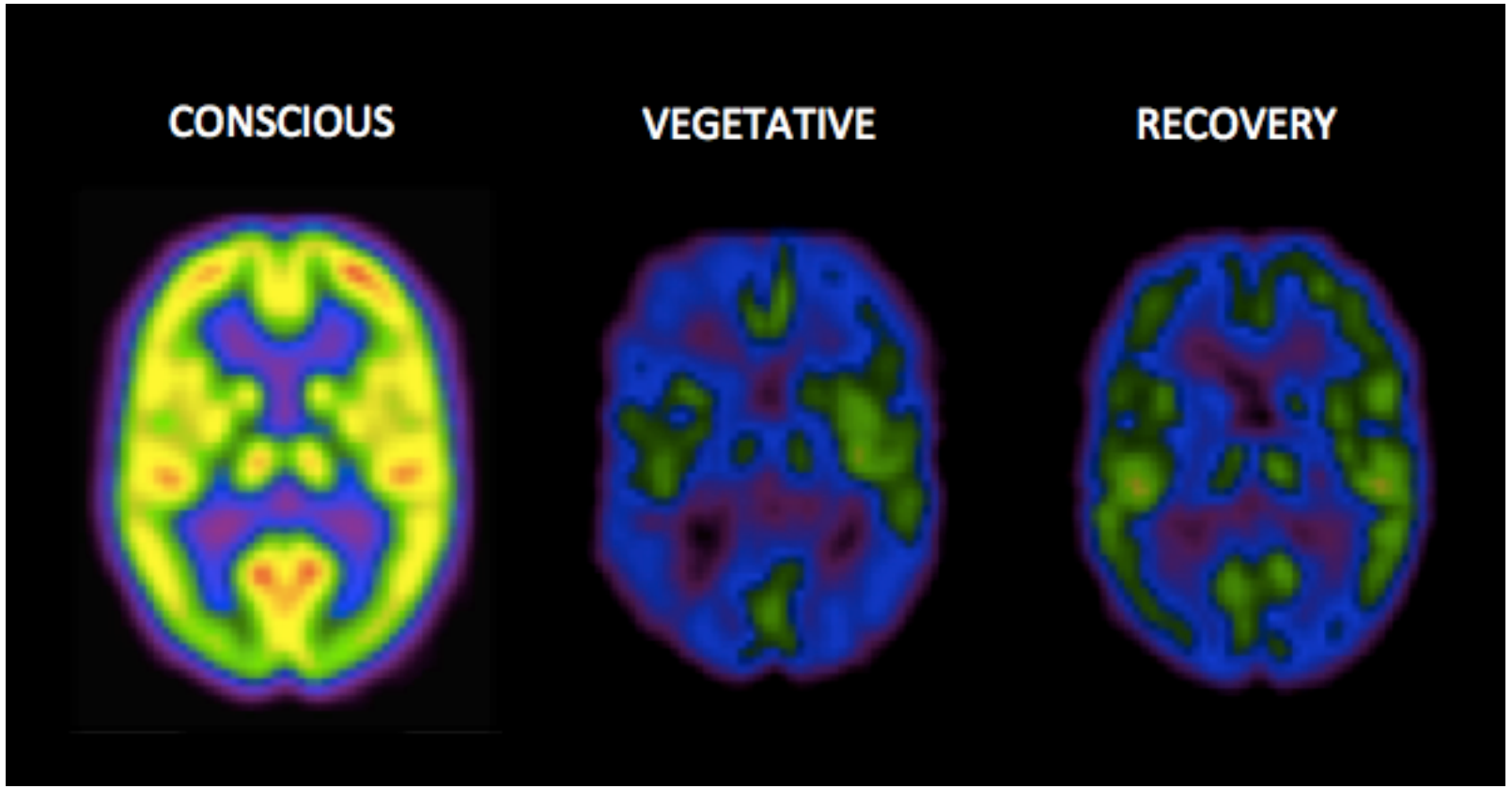
Steriade et al., *J. Neurophysiol.* 2001

level of neural activity?



Laureys et al., Neurology 2002

level of neural activity?



Laureys et al., Neurology 2002

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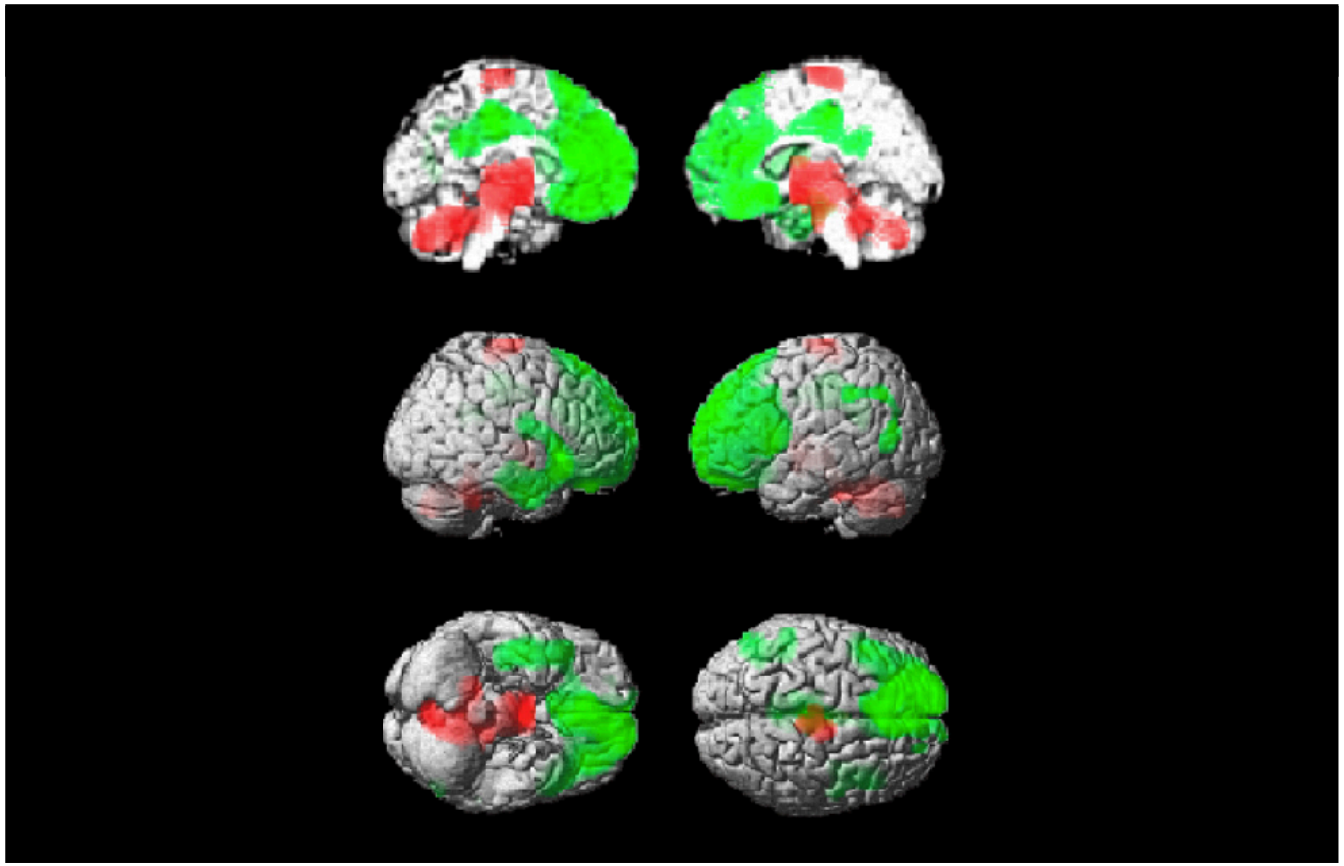

Bai et al., *J Neurosci* 2010; Blumenfeld et al., *Neuroimage* 2003; Engel et al., *Science* 1982

synchrony of neural activity?

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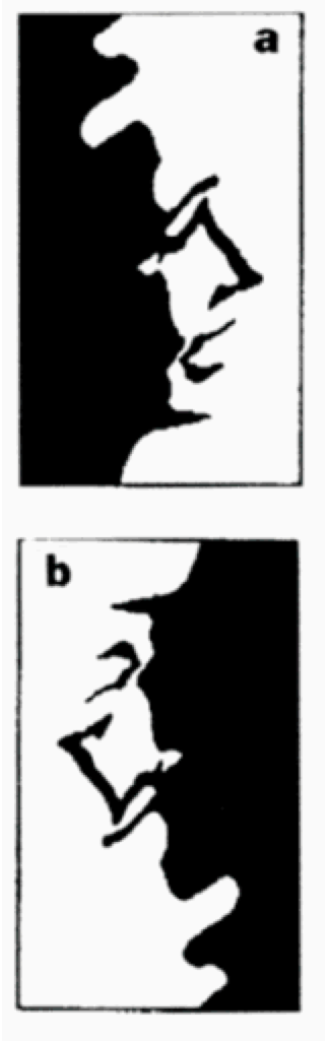
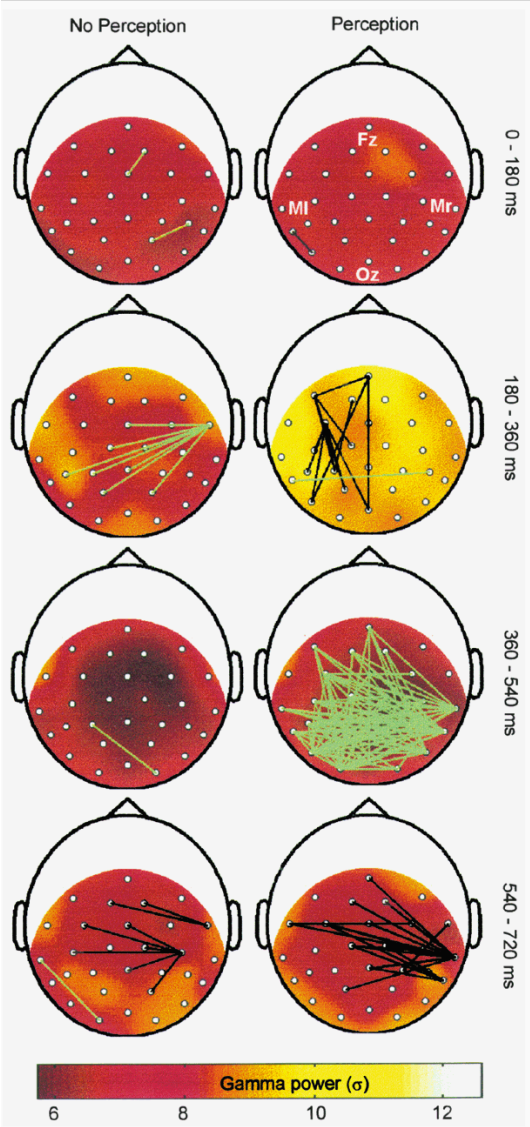
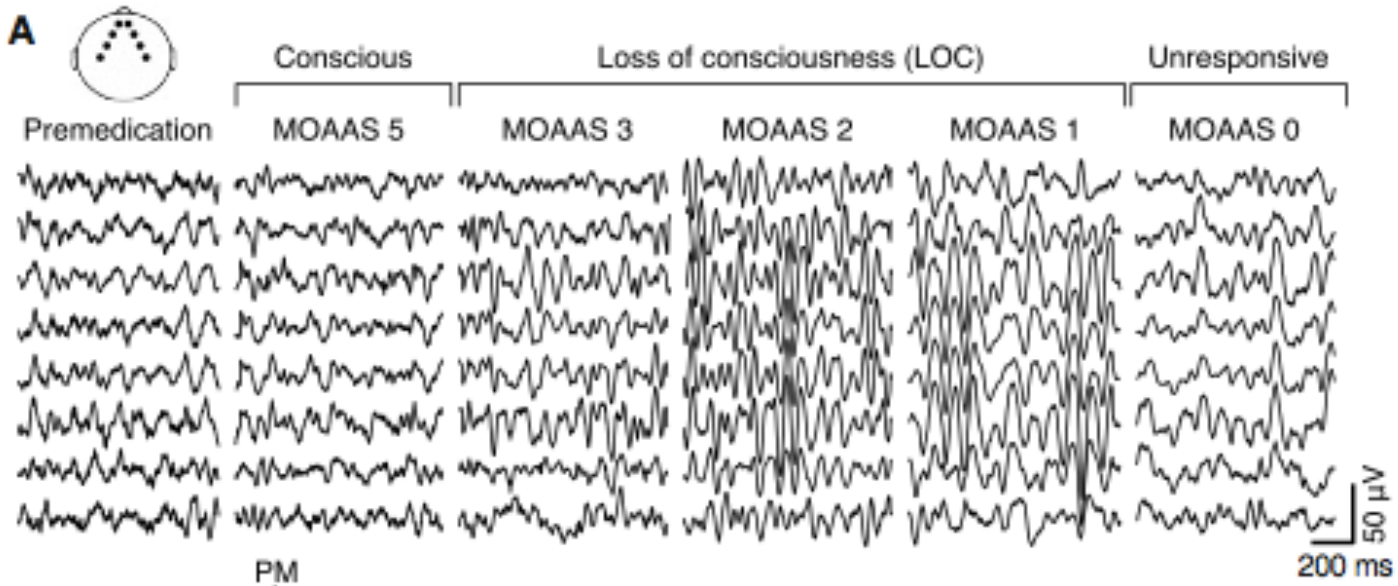




Rodriguez et al, *Nature 1998*

<u>synchrony</u> of neural activity?



Supp et al., *Curr Biol* 2011

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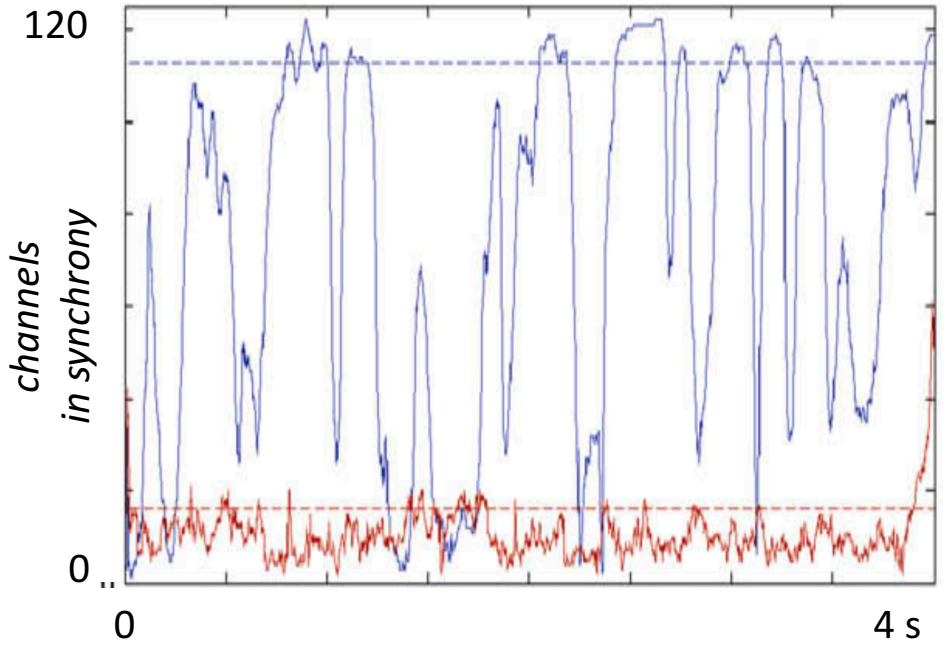

Pockett et al 2009

spectral features, entropy?

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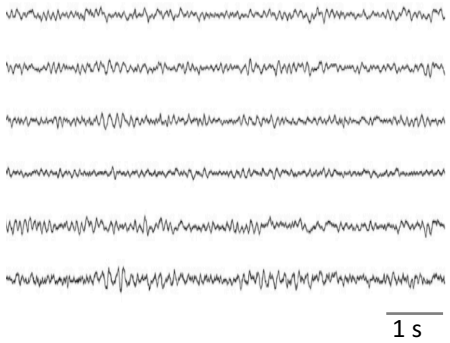
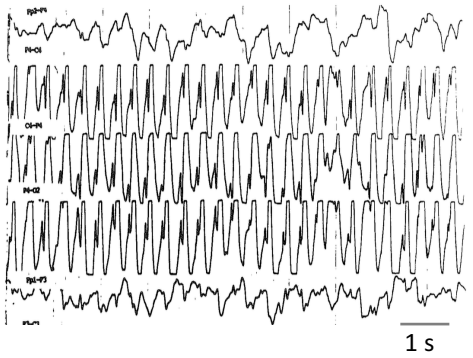
Kaskinoro et al. *British Journal of Anesthesia*, 2010

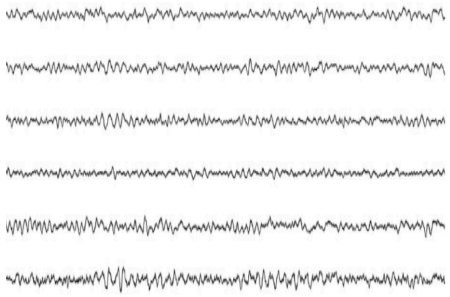
spectral features, entropy?





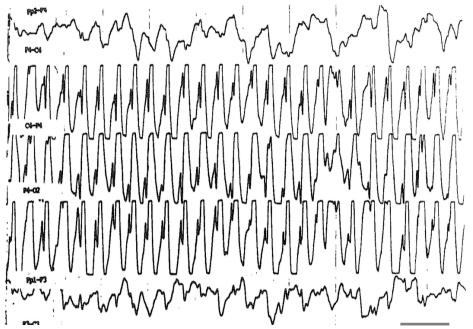
spectral features, entropy?

Alpha Coma



Bremer et al 2005

1 s



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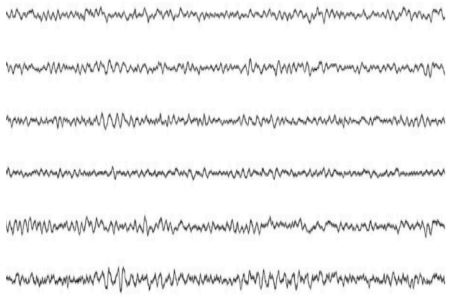
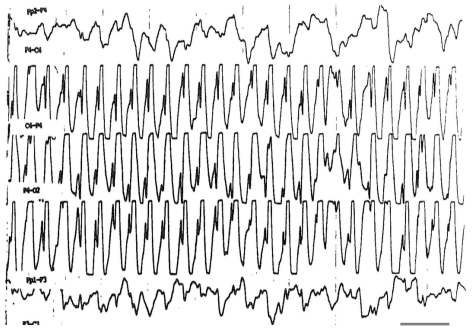


Bremer et al 2005

1 s

Status Epilepticus



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Gokygit et al 1995

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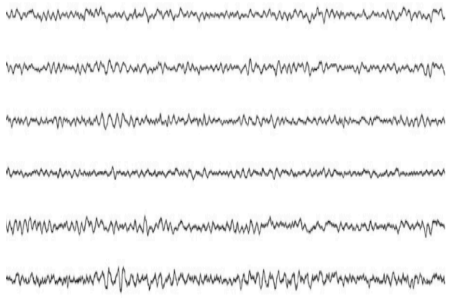
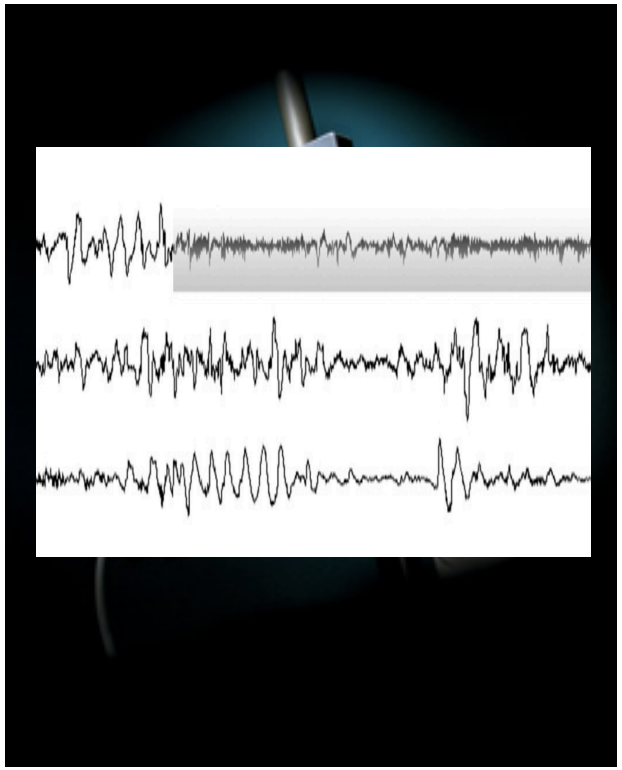
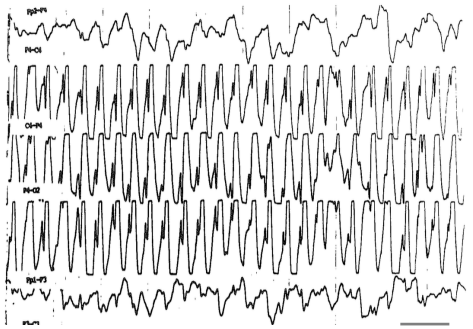


Bremer et al 2005



Nobili et a 2011

Status Epilepticus



Gokygit et al 1995

IIT

INTEGRATED INFORMATION THEORY OF CONSCIOUSNESS

IIT

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

 integration & differentiation = complexity

Tononi, 2004; 2005; Tononi and Koch, 2008; Oizumi et al., 2014

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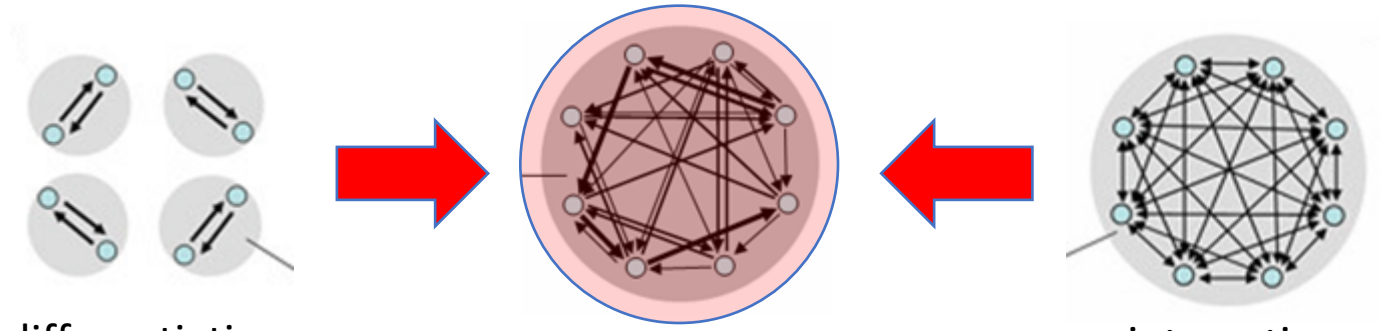

Tononi, 2004; 2005; Tononi and Koch, 2008; Oizumi et al., 2014

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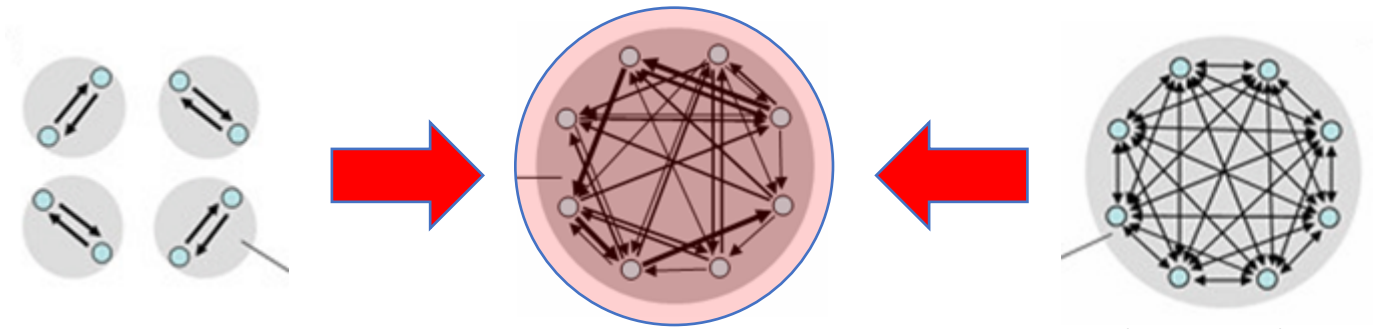
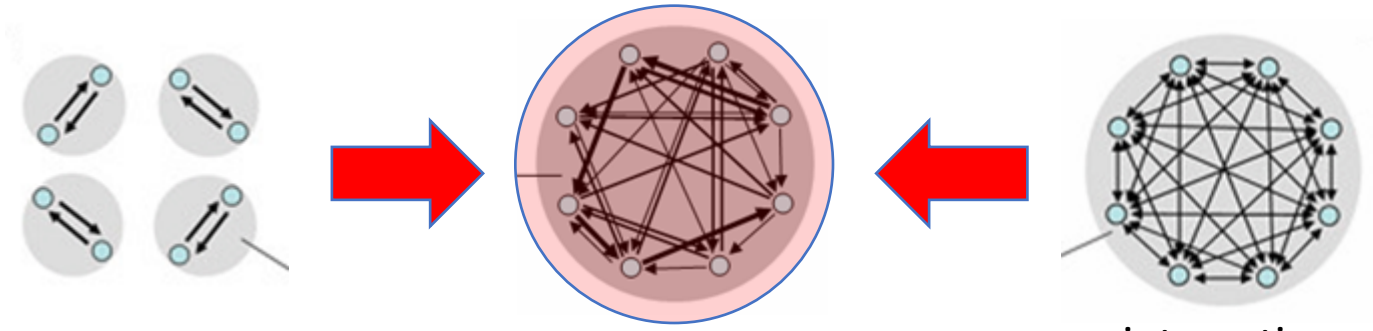
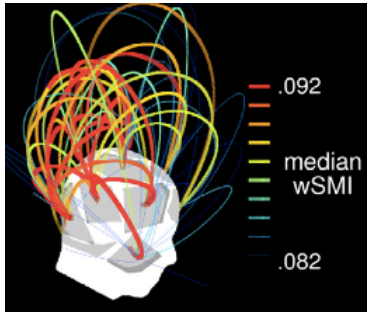


integration

integration & differentiation = complexity

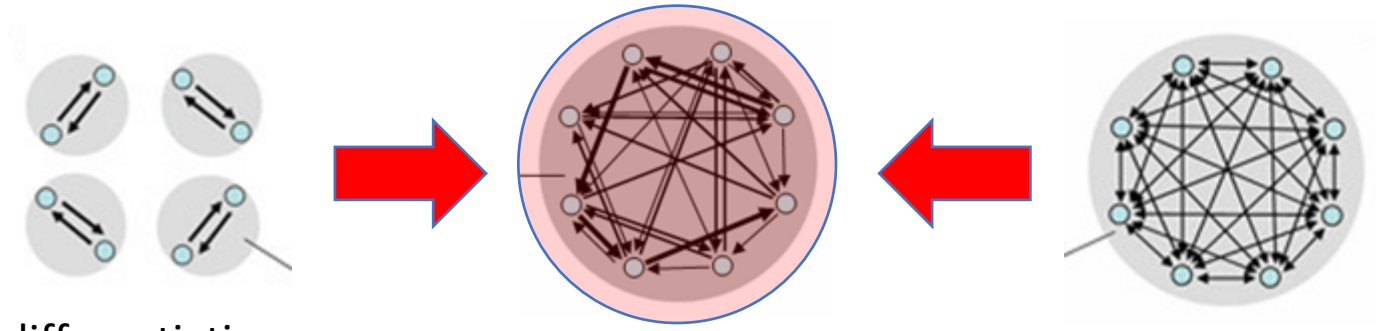


integration



King et al, 2013

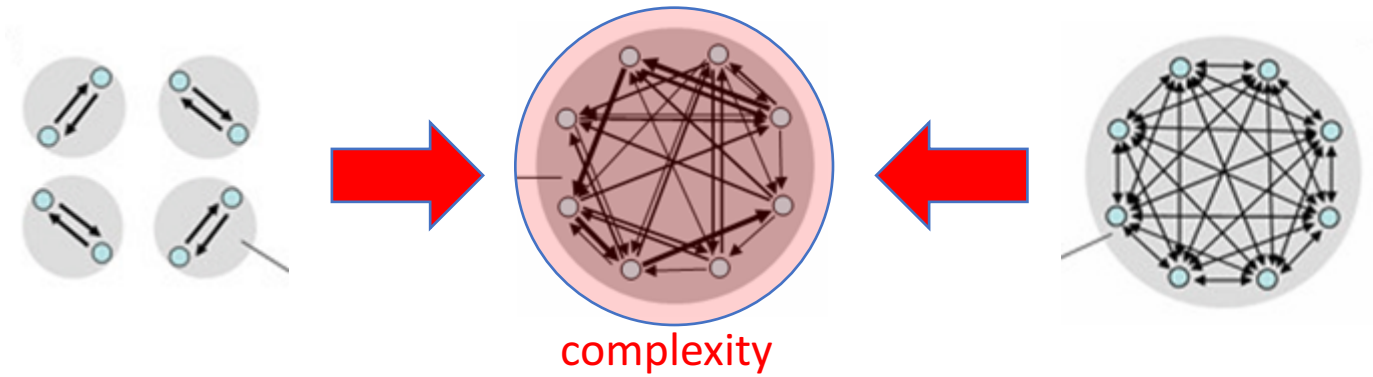
integration & differentiation = complexity



differentiation

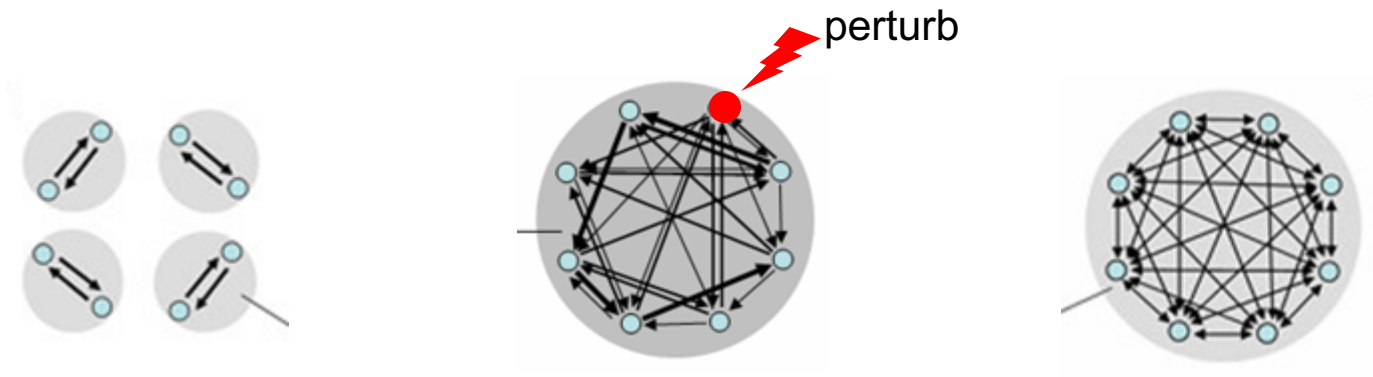
Kaskinoro et al. *British Journal of Anesthesia*, 2010

A Perturbational Approach



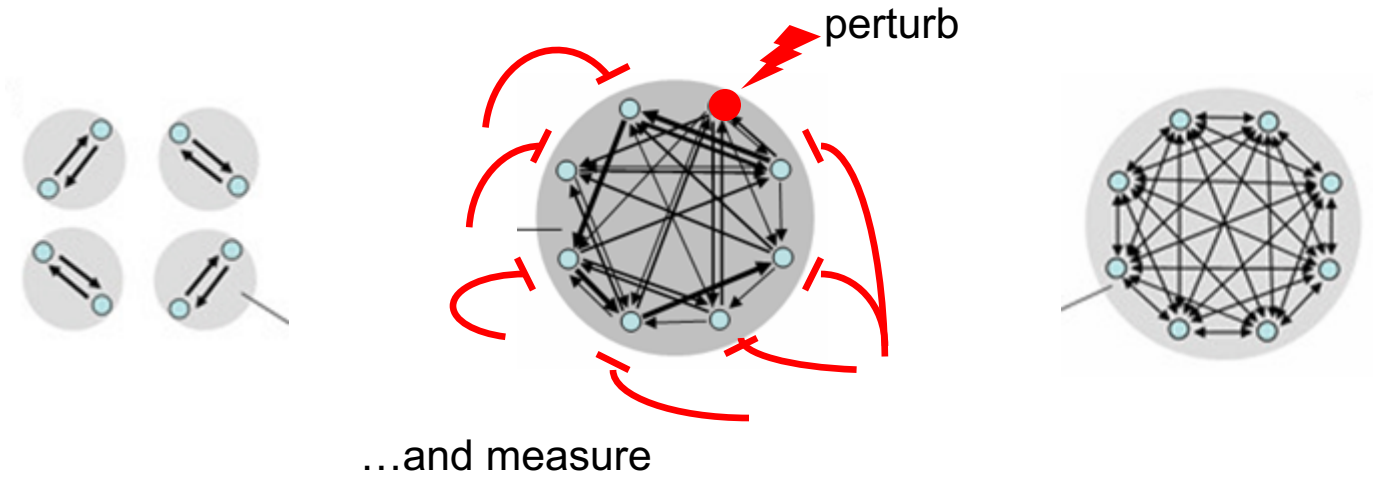
Massimini et al., *PBR* 2009

A Perturbational Approach



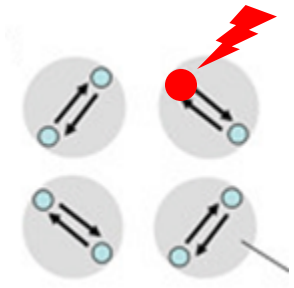
Massimini et al., *PBR* 2009

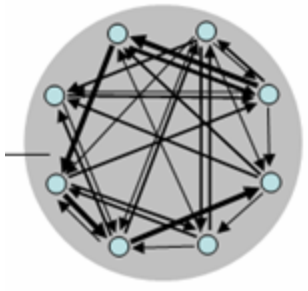
A Perturbational Approach

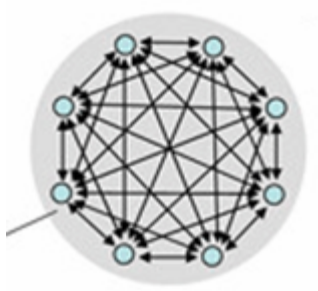


Massimini et al., *PBR* 2009

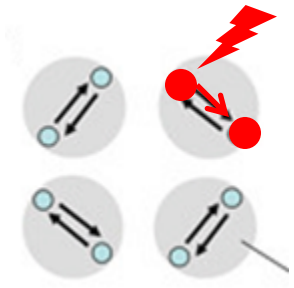
A Perturbational Approach

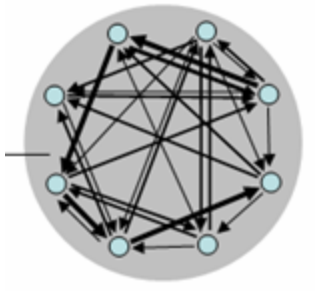


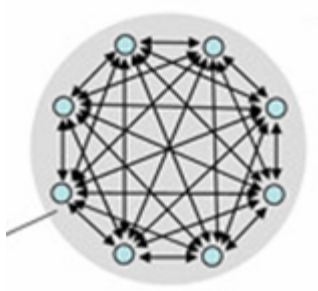




A Perturbational Approach







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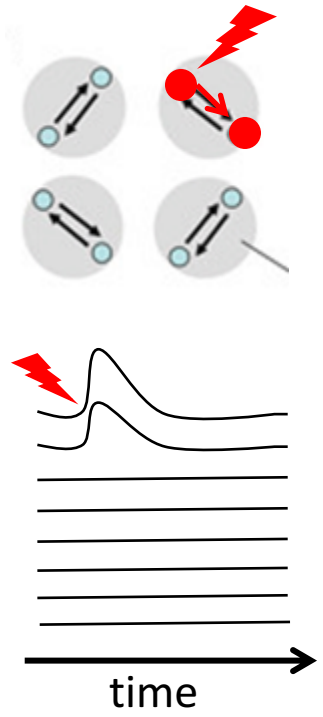

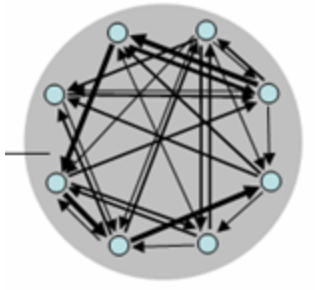

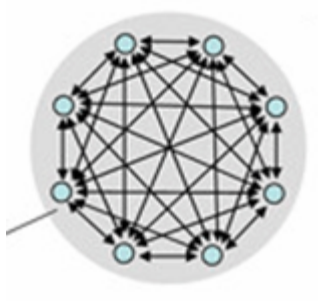

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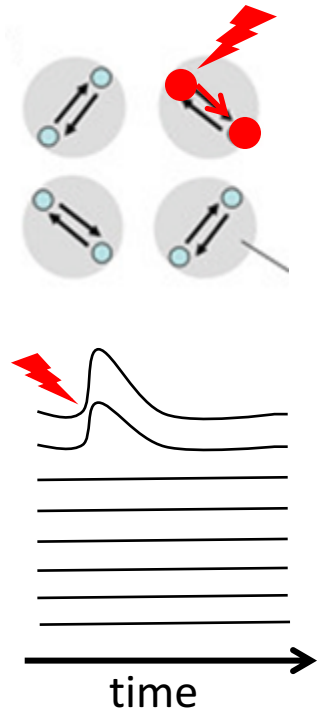

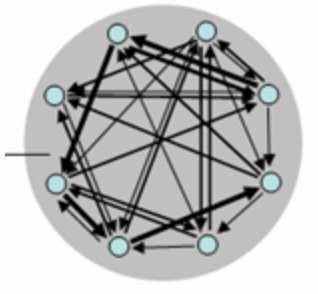

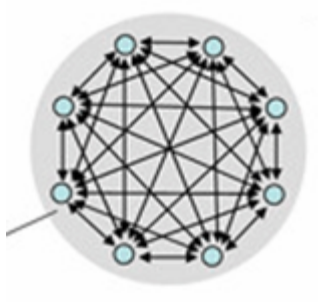

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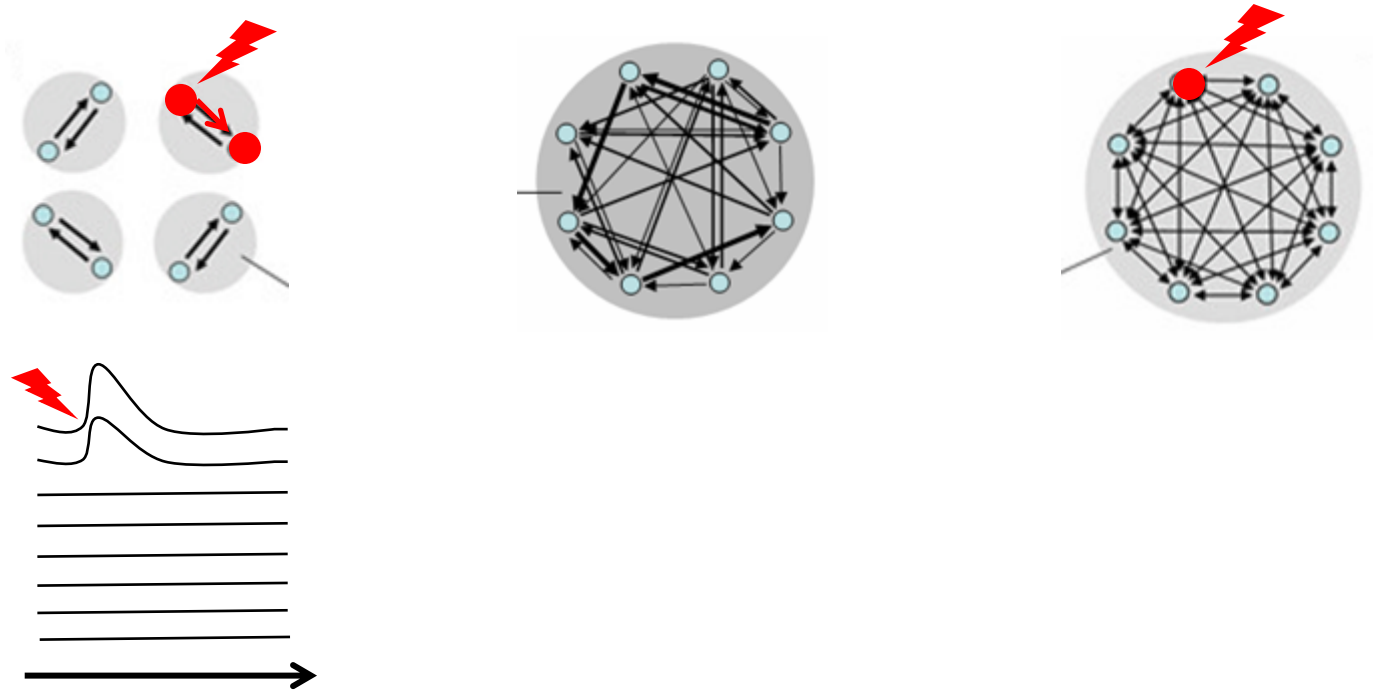

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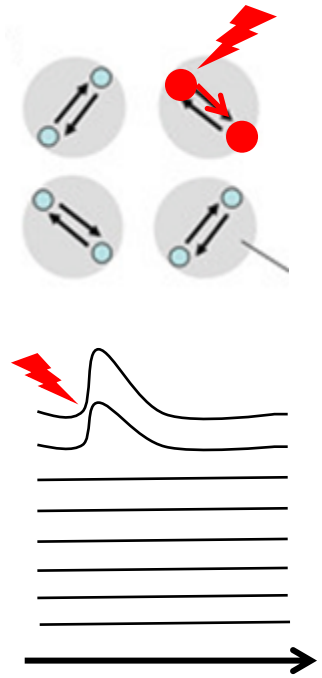

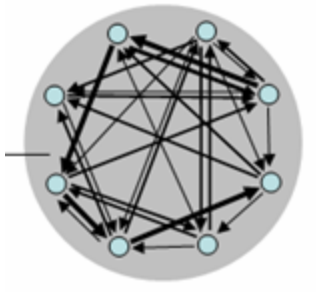

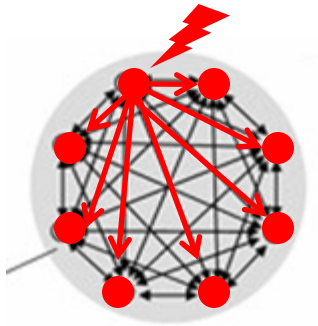

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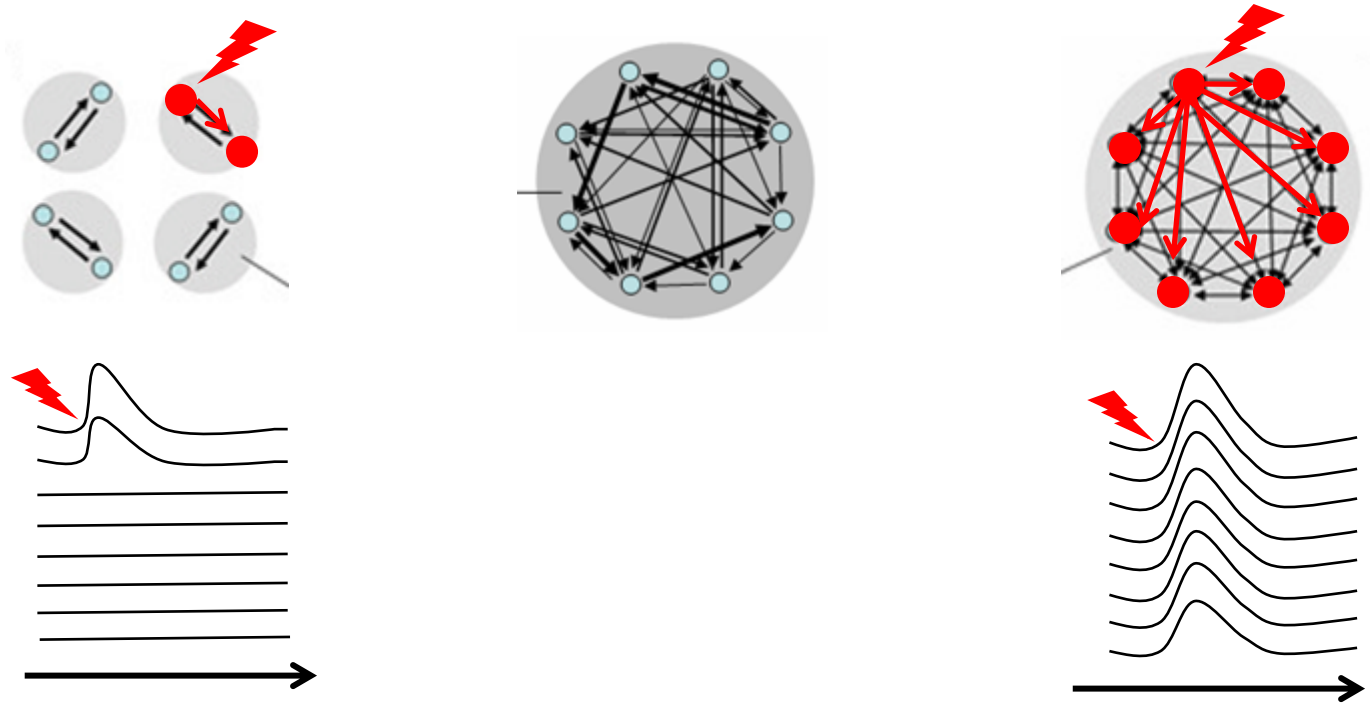

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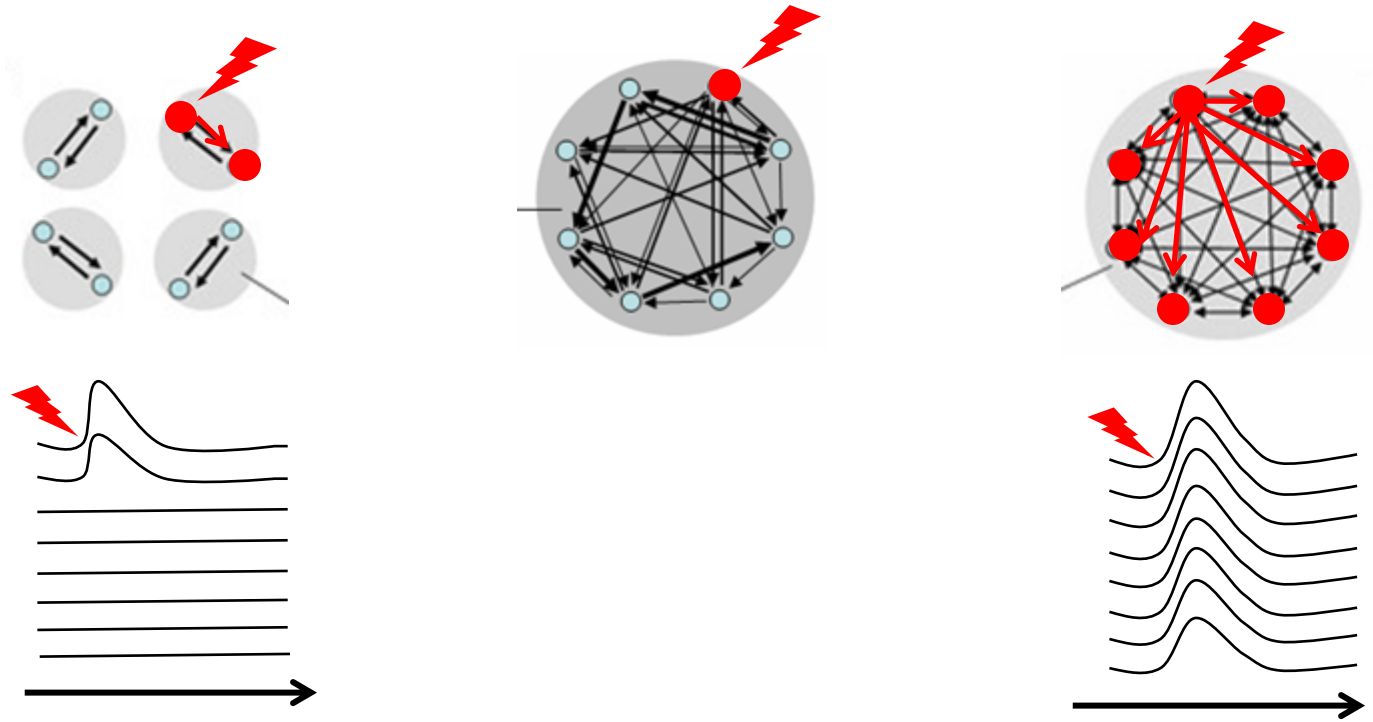

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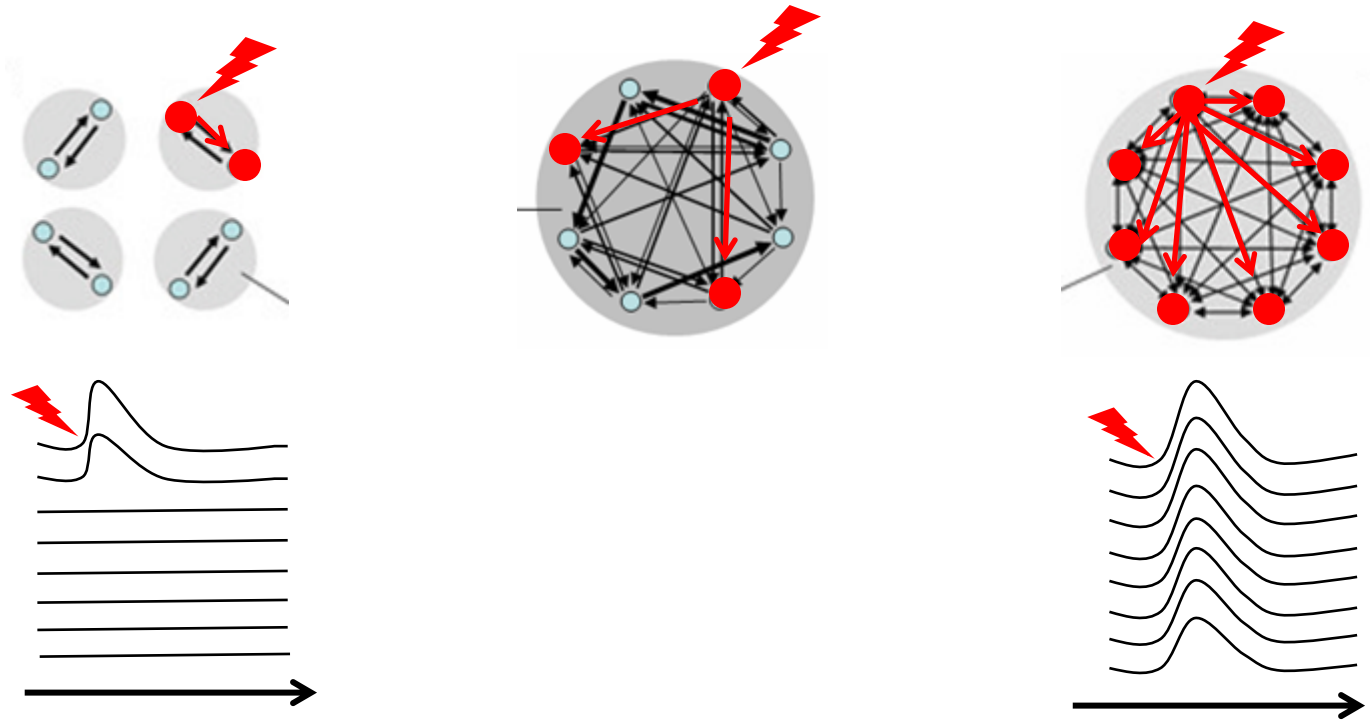

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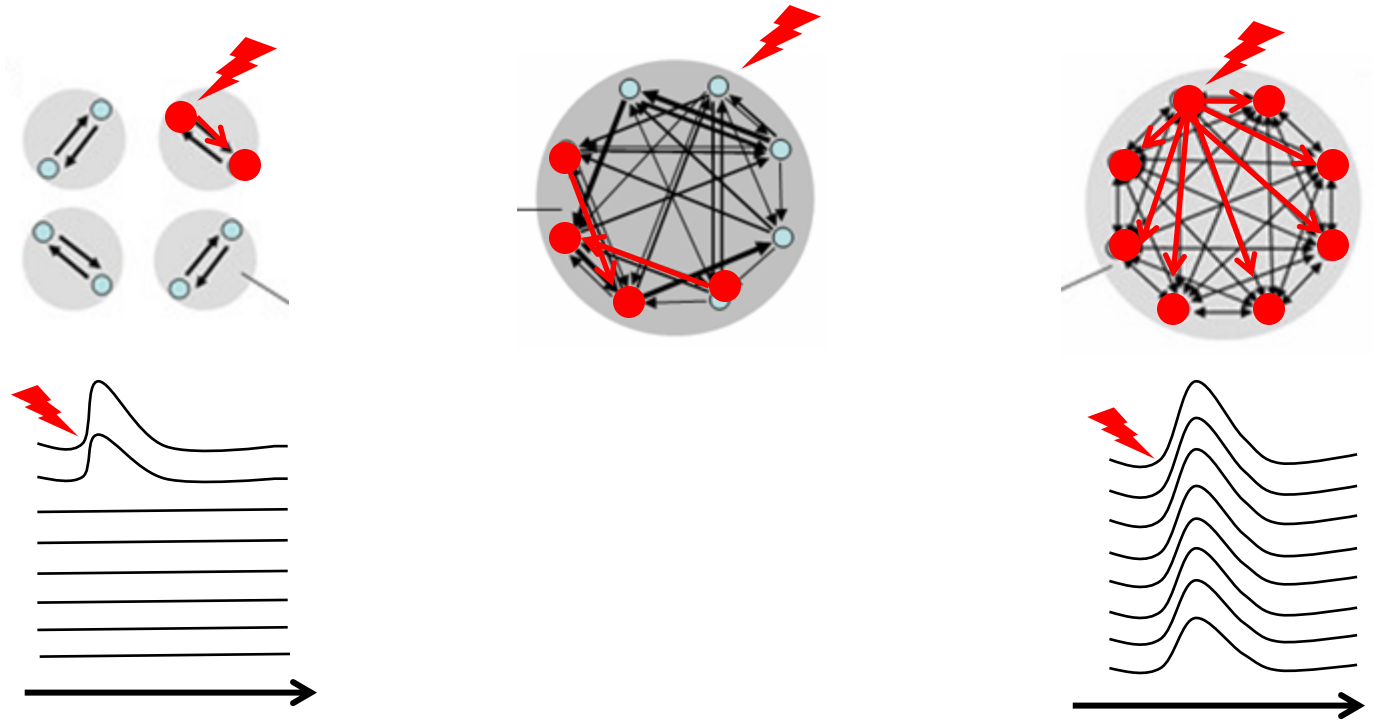

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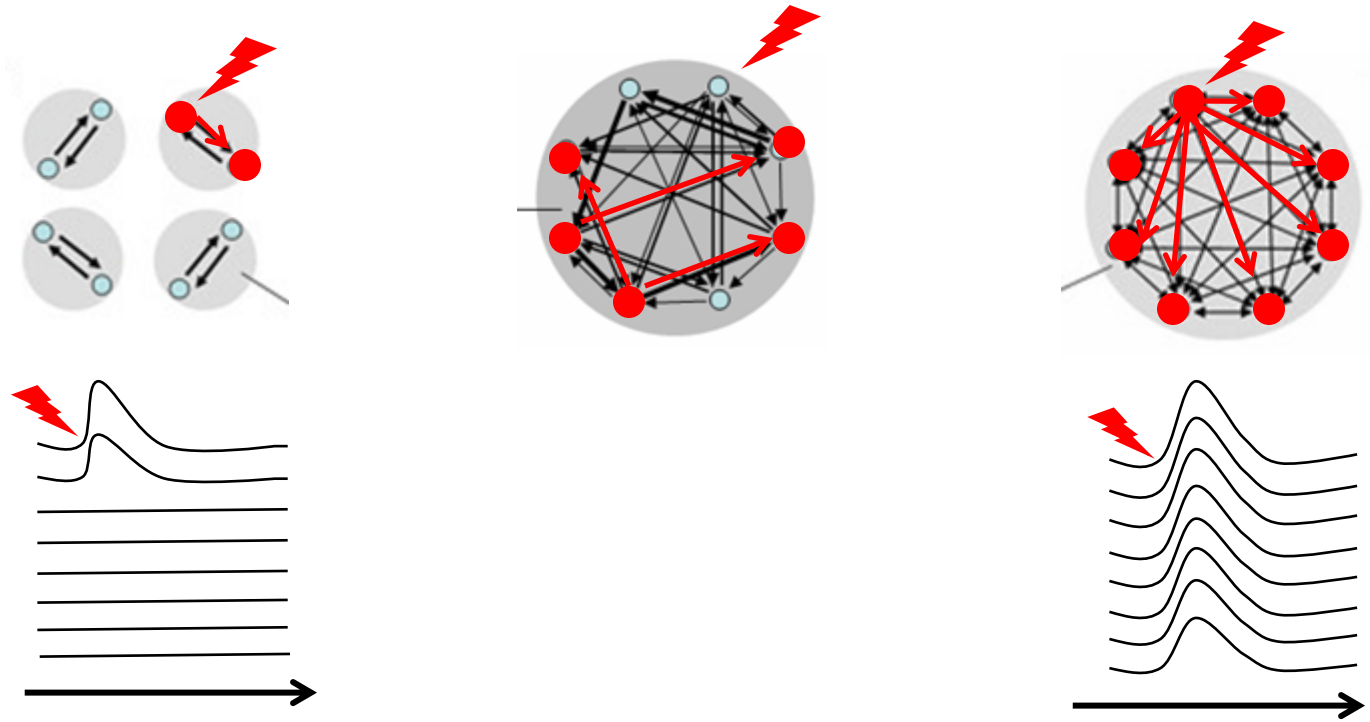

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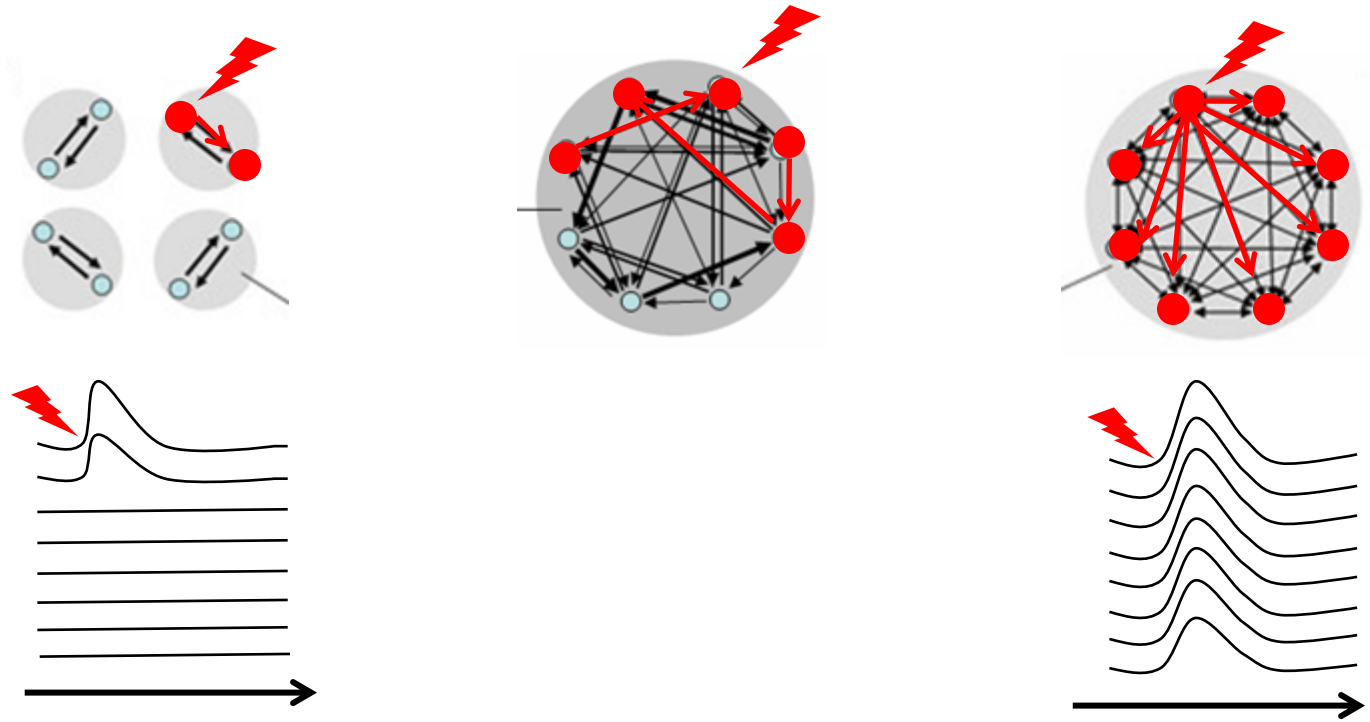
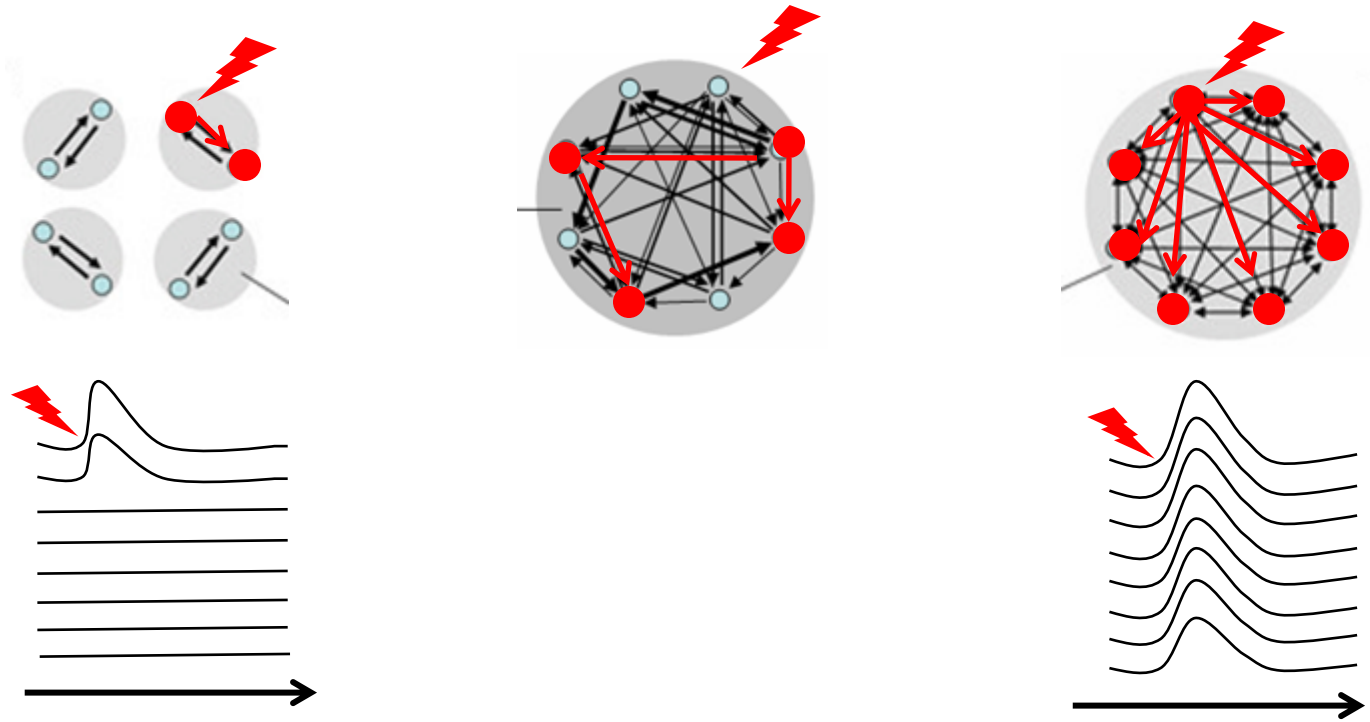


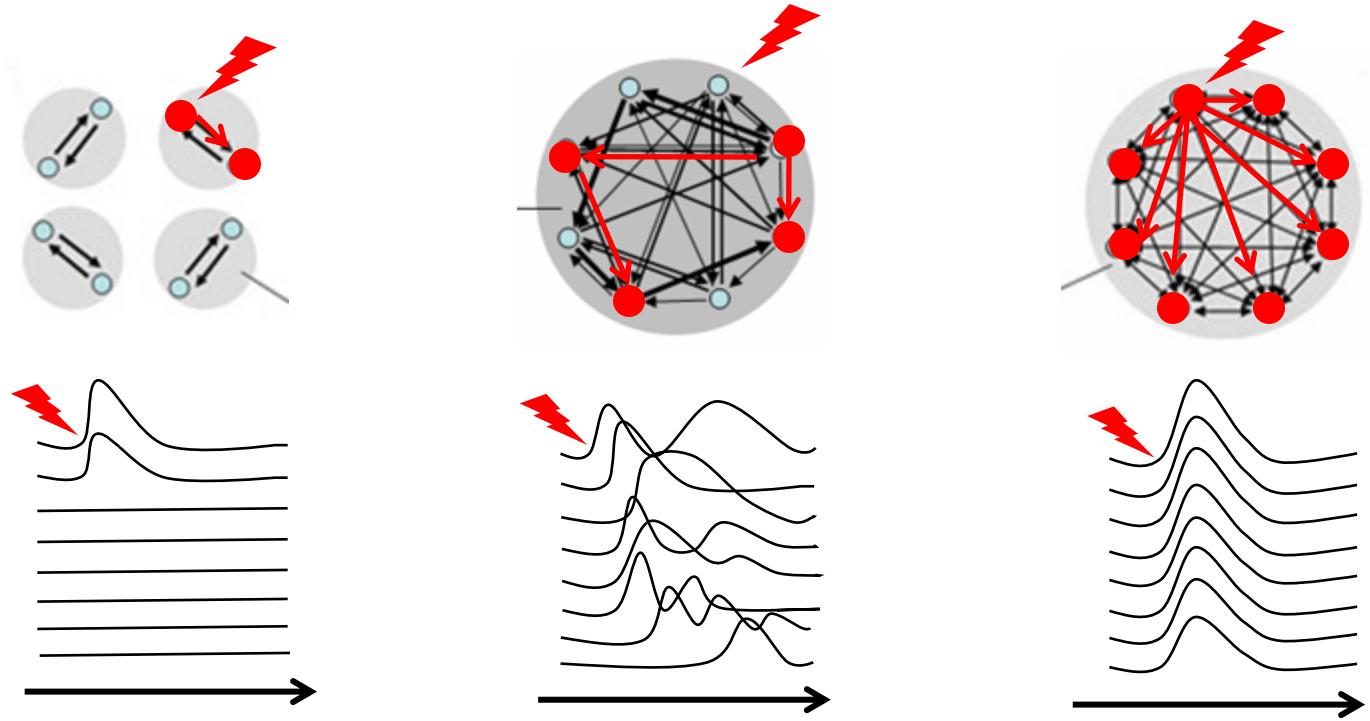
A Perturbational Approach



Causal Interactions vs. Temporal Correlations

Integration + differentiation

A Perturbational Approach

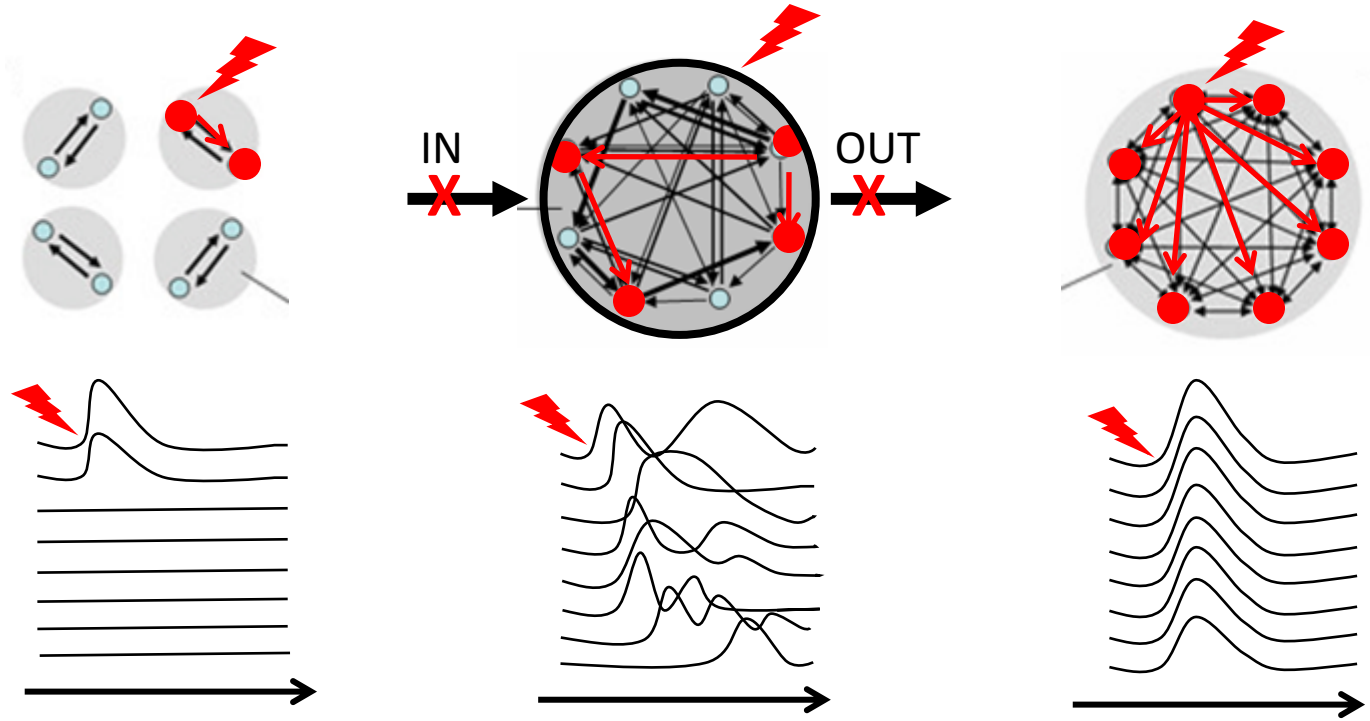


Causal Interactions vs. Temporal Correlations

Integration + differentiation

Independent of inputs & outputs

A Perturbational Approach



Causal Interactions vs. Temporal Correlations

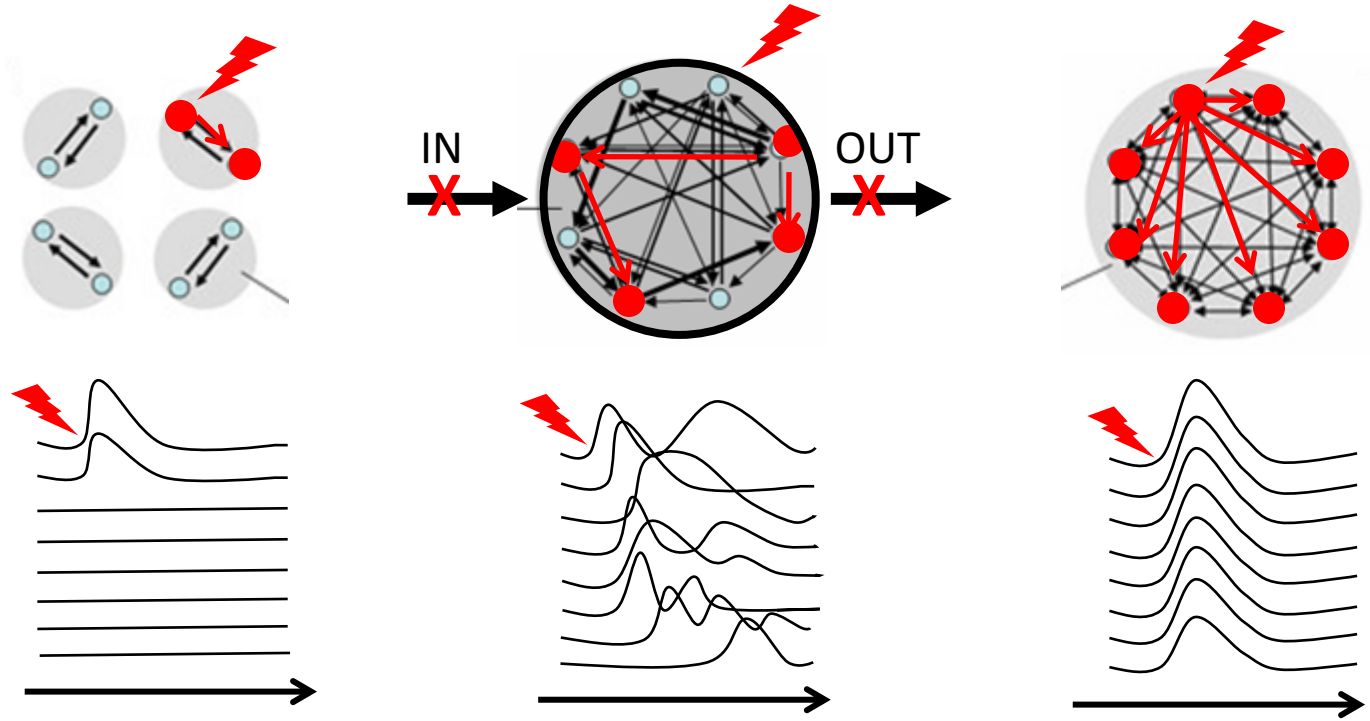
Integration + differentiation

Independent of inputs & outputs

≠

Levels of activity
Synchrony
Spread of activity
Entropy
ERPs

A Perturbational Approach



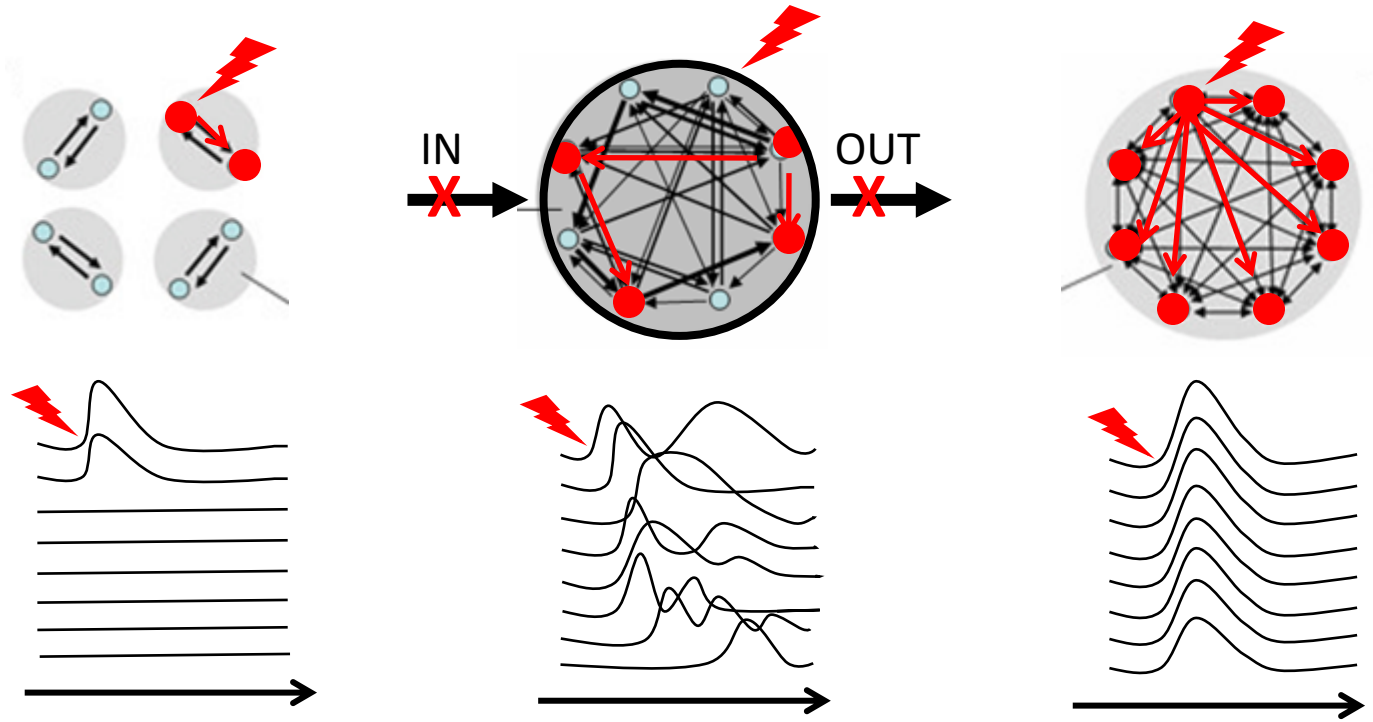
Causal Interactions vs. Temporal Correlations

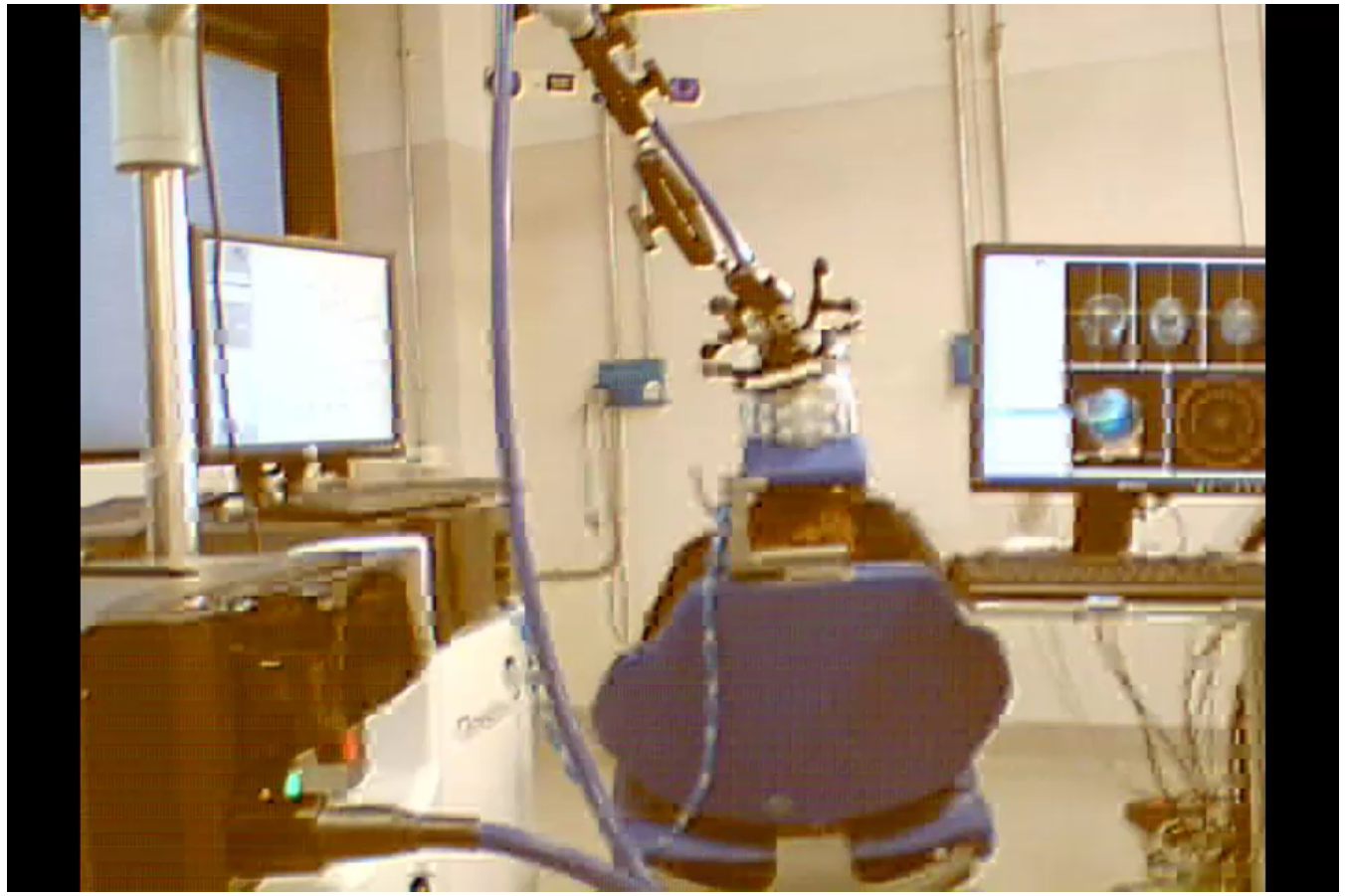
Integration + differentiation

Independent of inputs & outputs

$=$ *the amount of information that is generated by causal interactions within an integrated system* $\cong \Phi$

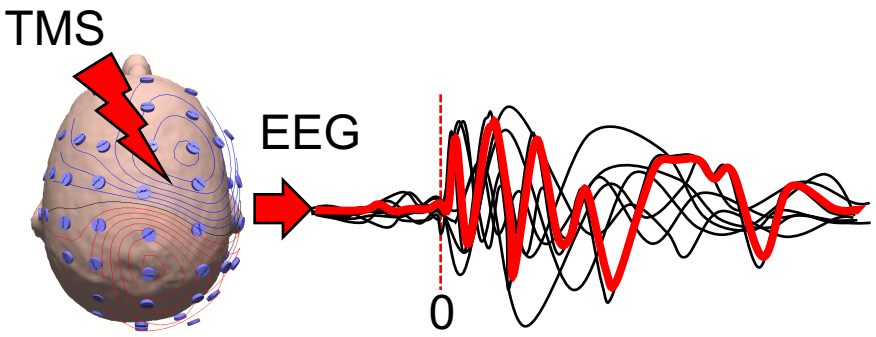
A Perturbational Approach





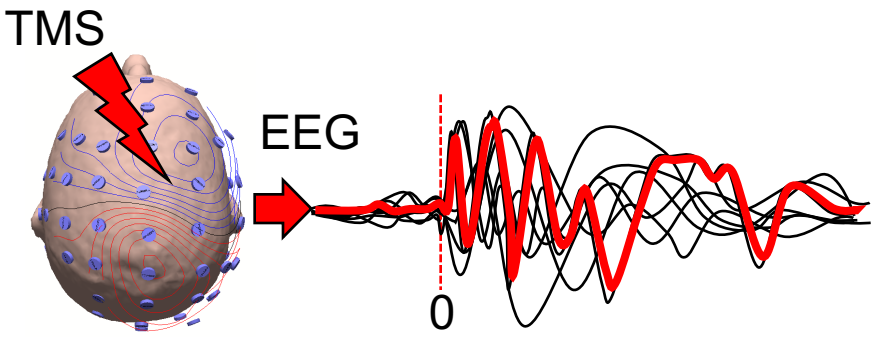
TMS/EEG: A set-up for non-invasive cortical stimulation and recording

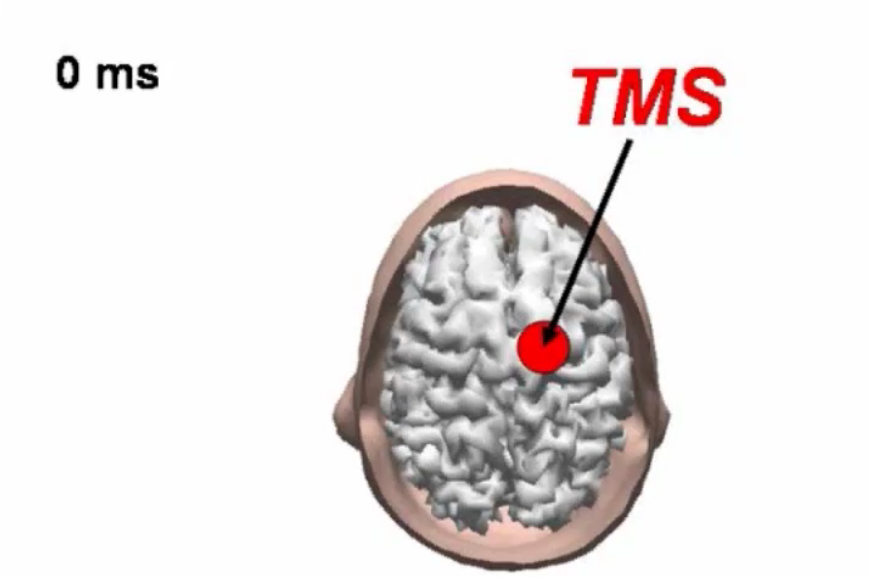
Wakefulness



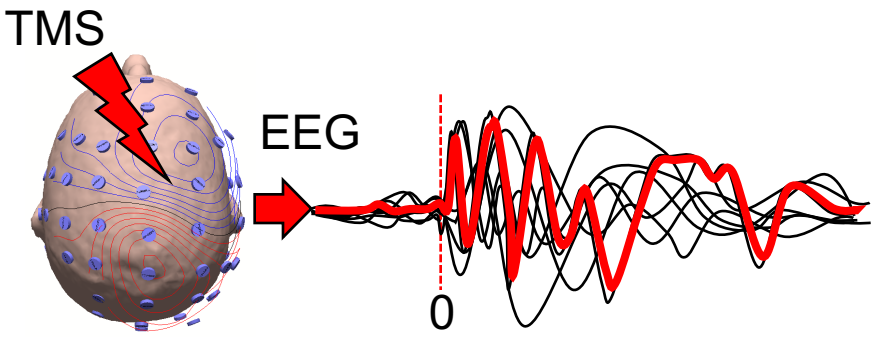
Massimini et al *Science*, 2005

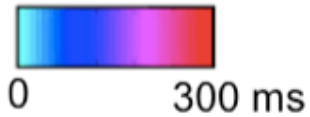
Wakefulness

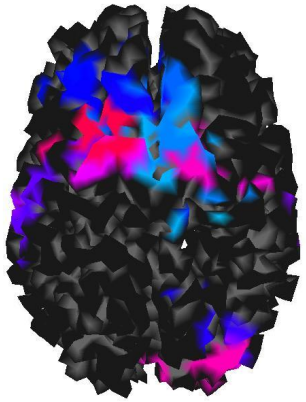




Wakefulness

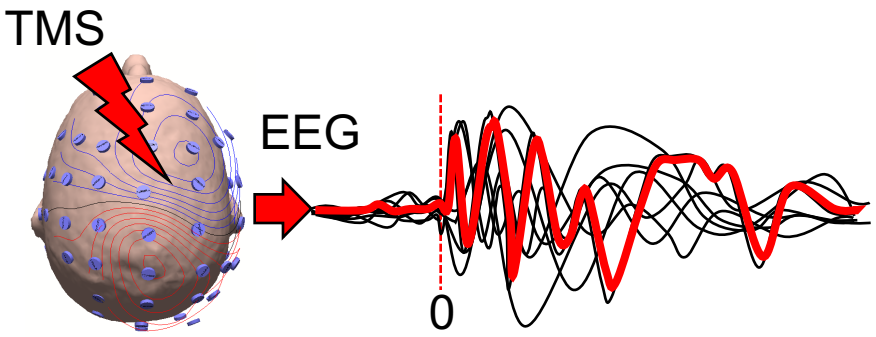






Massimini et al *Science*, 2005

Wakefulness



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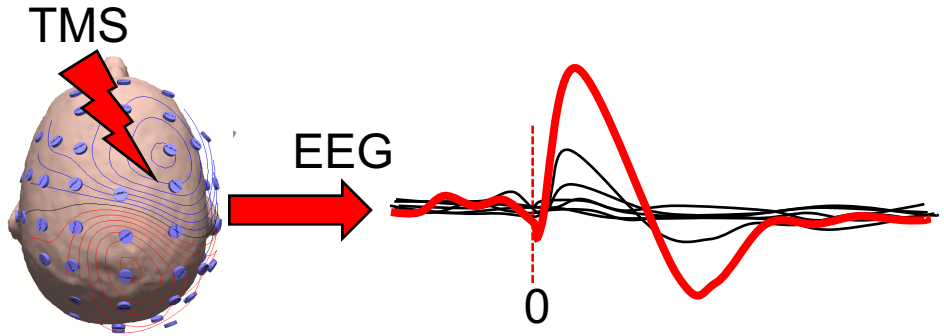

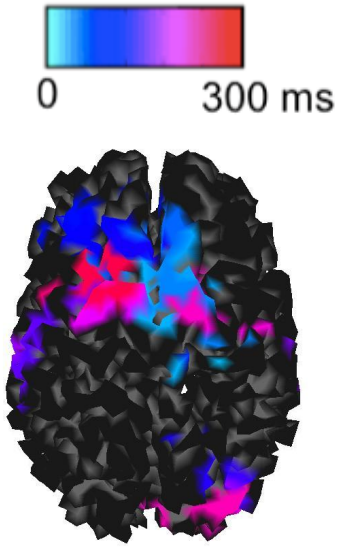

Massimini et al *Science*, 2005

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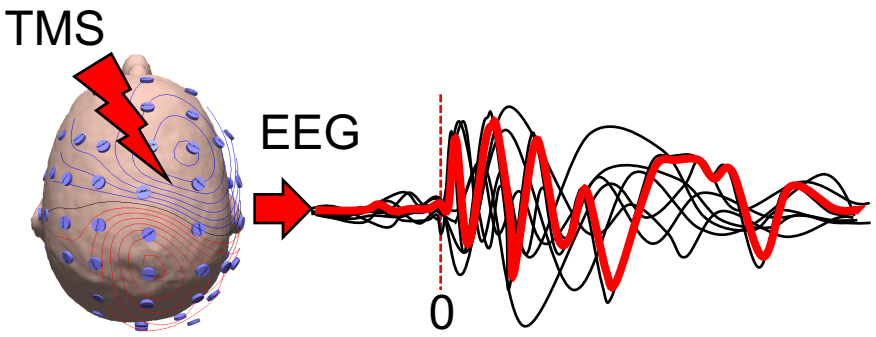

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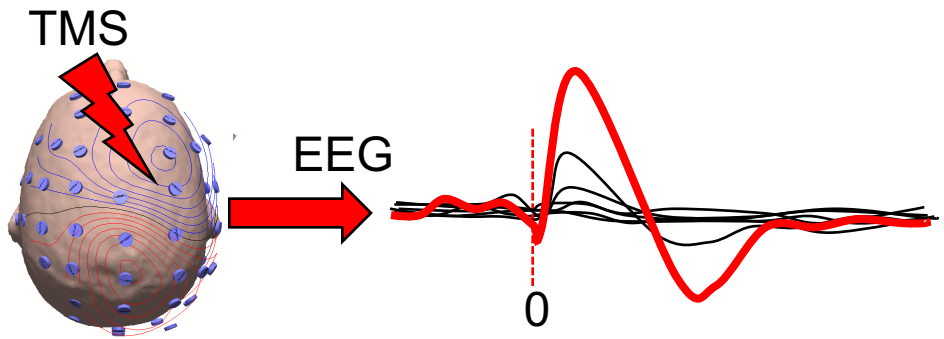
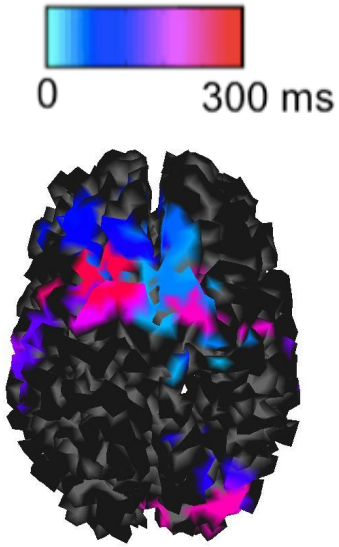
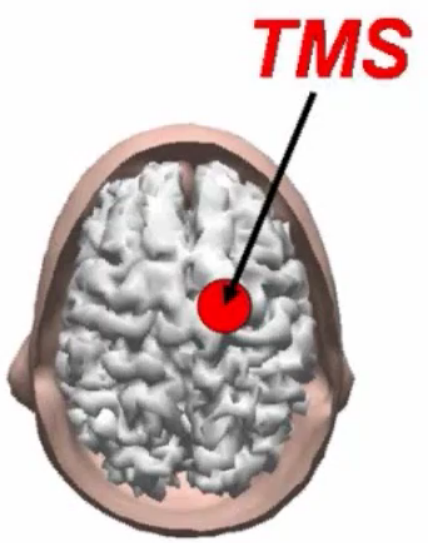
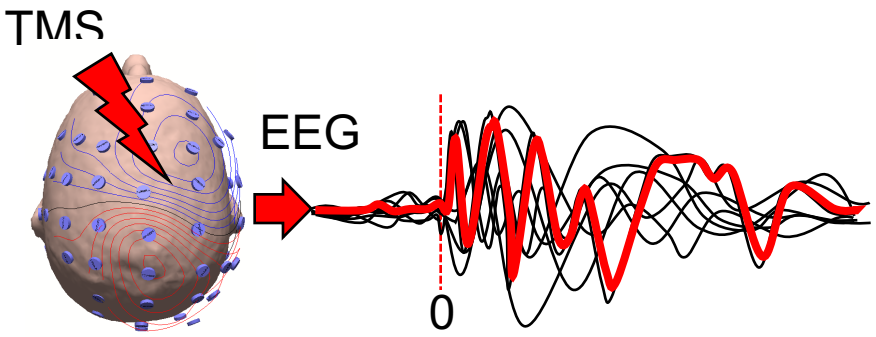






Massimini et al *Science*, 2005

Wakefulness



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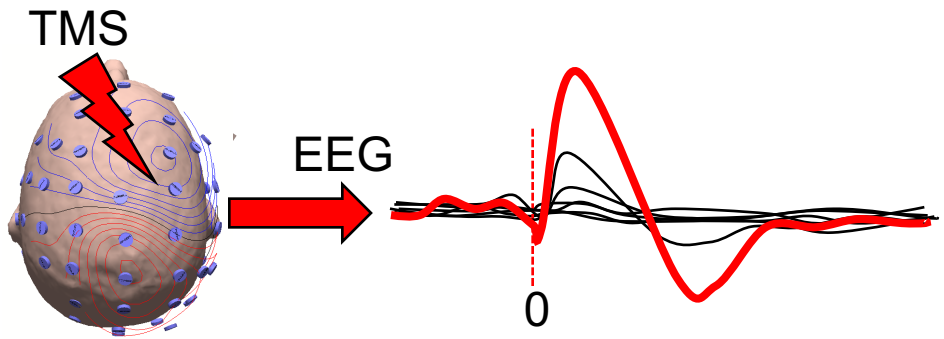
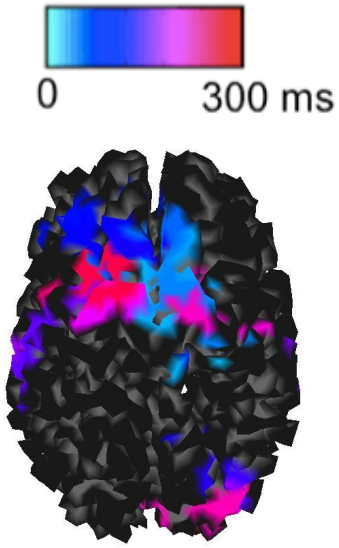
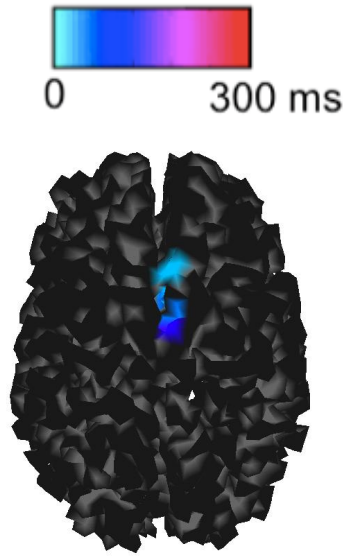
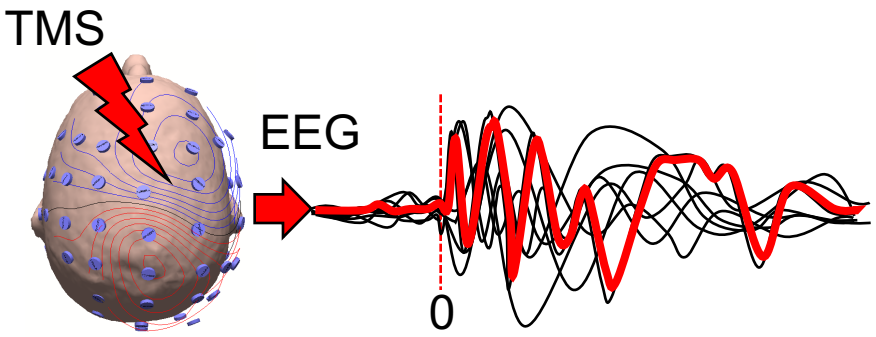






Massimini et al *Science*, 2005

Wakefulness



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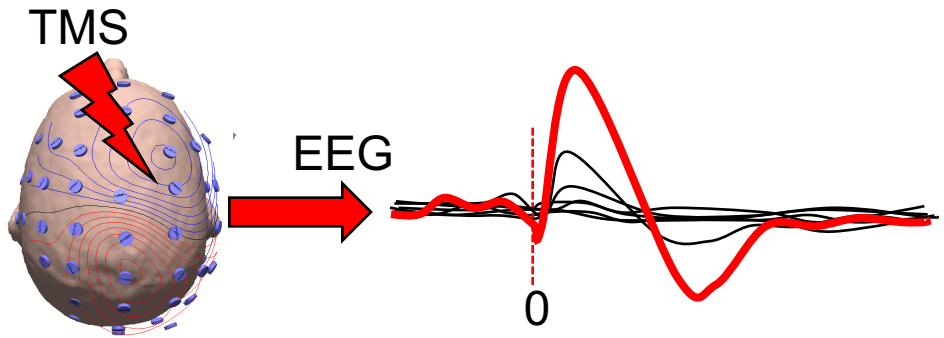
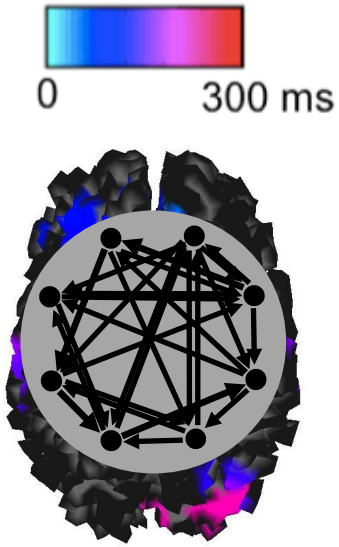
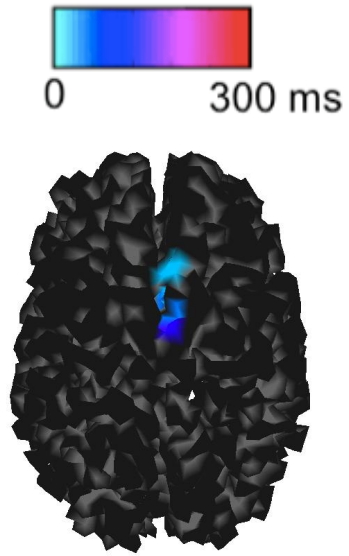
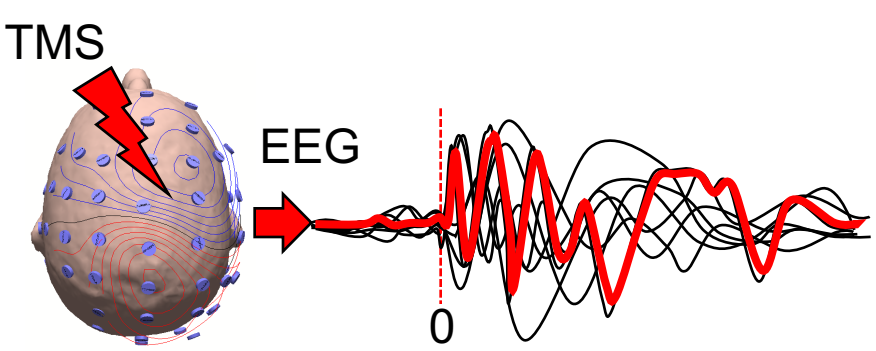






Massimini et al *Science*, 2005

Wakefulness



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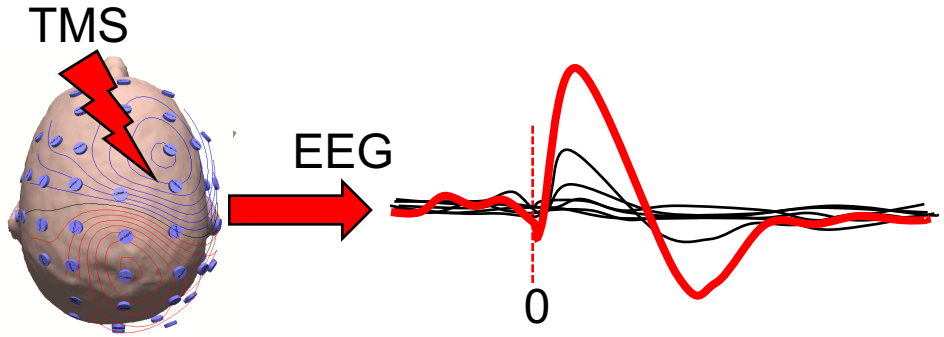
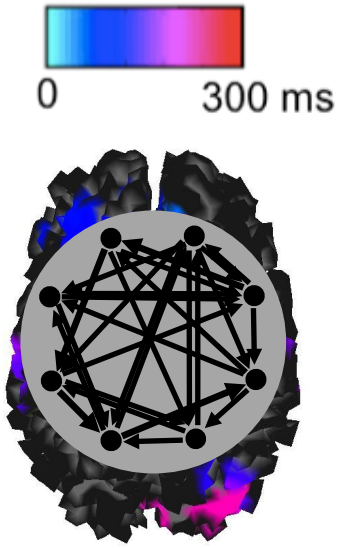
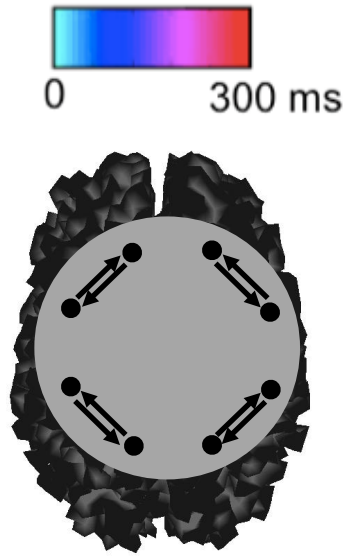
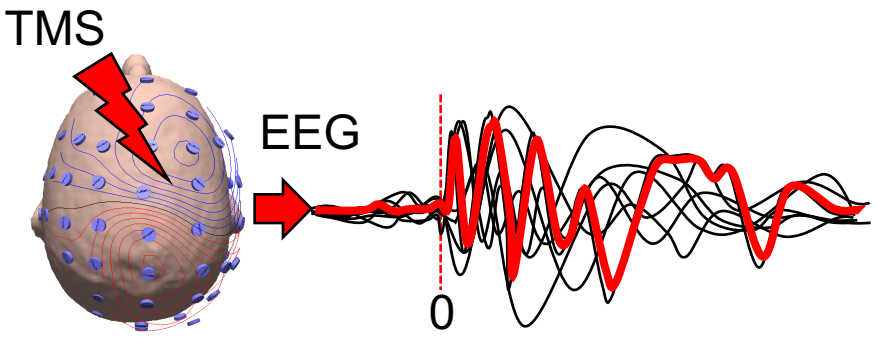






Massimini et al *Science*, 2005

Wakefulness



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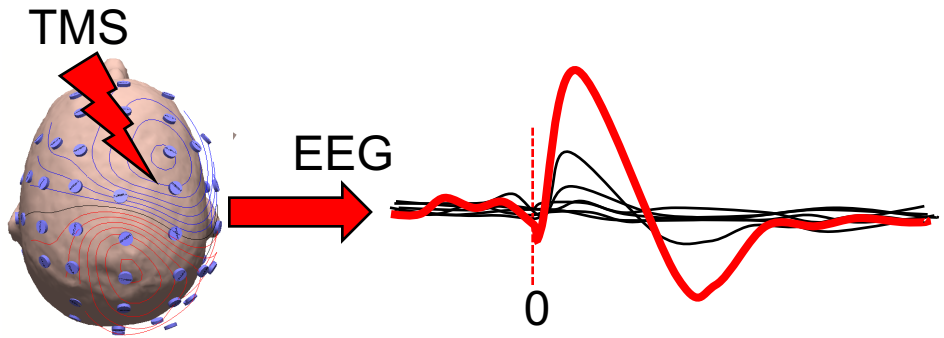
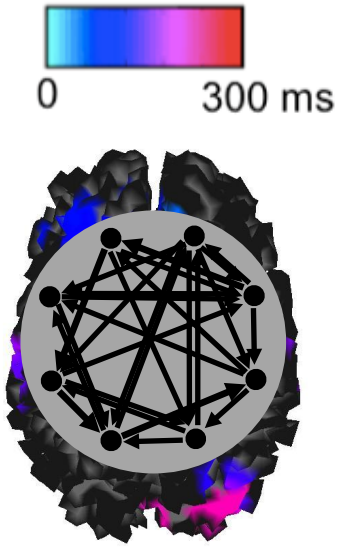
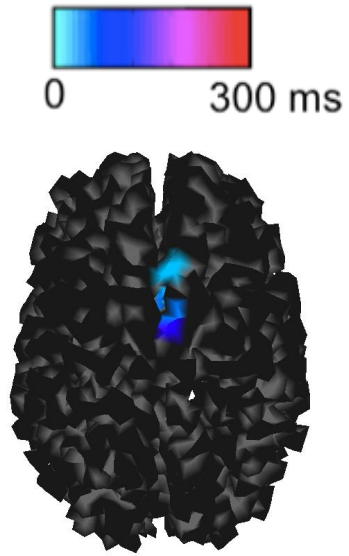
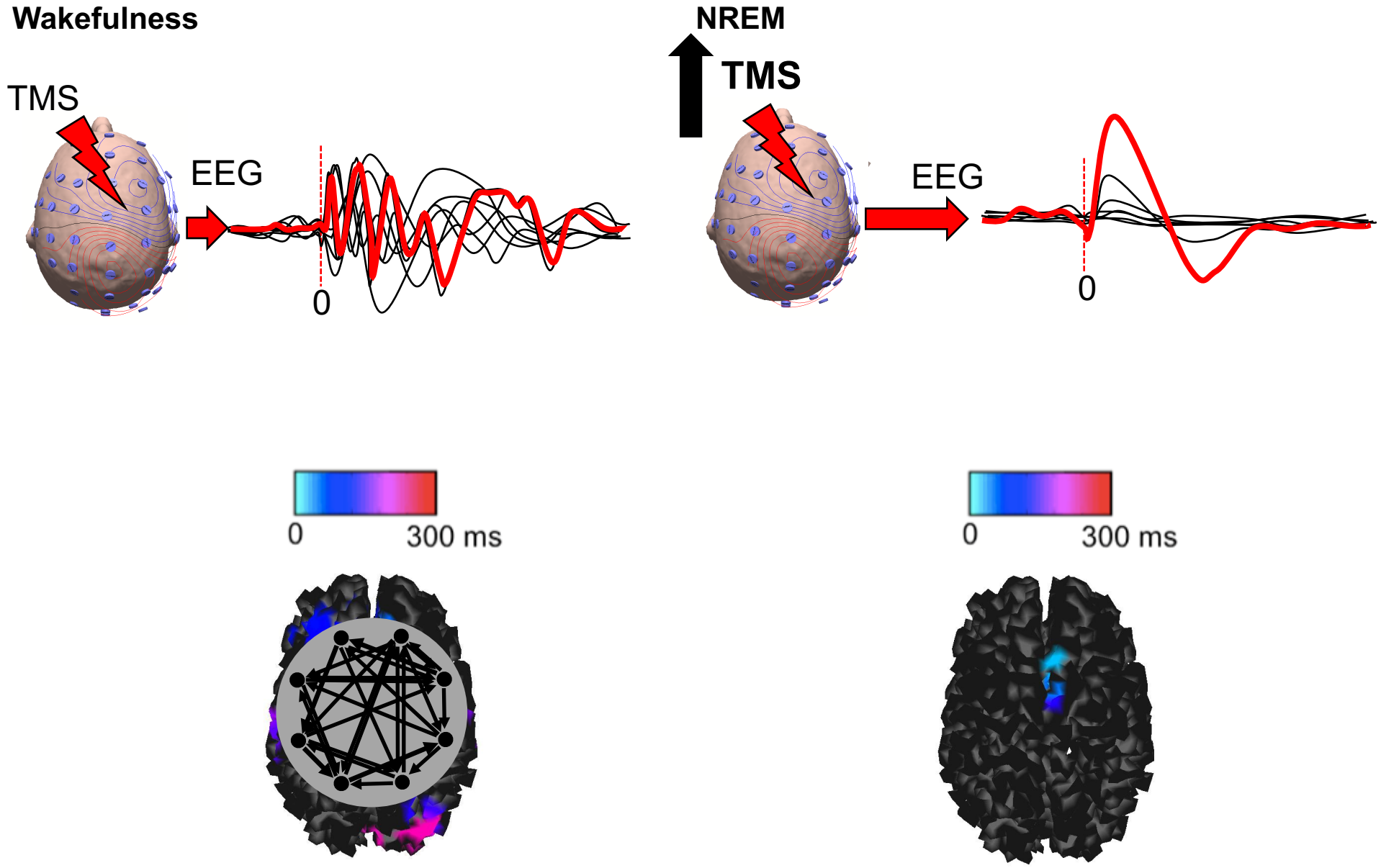


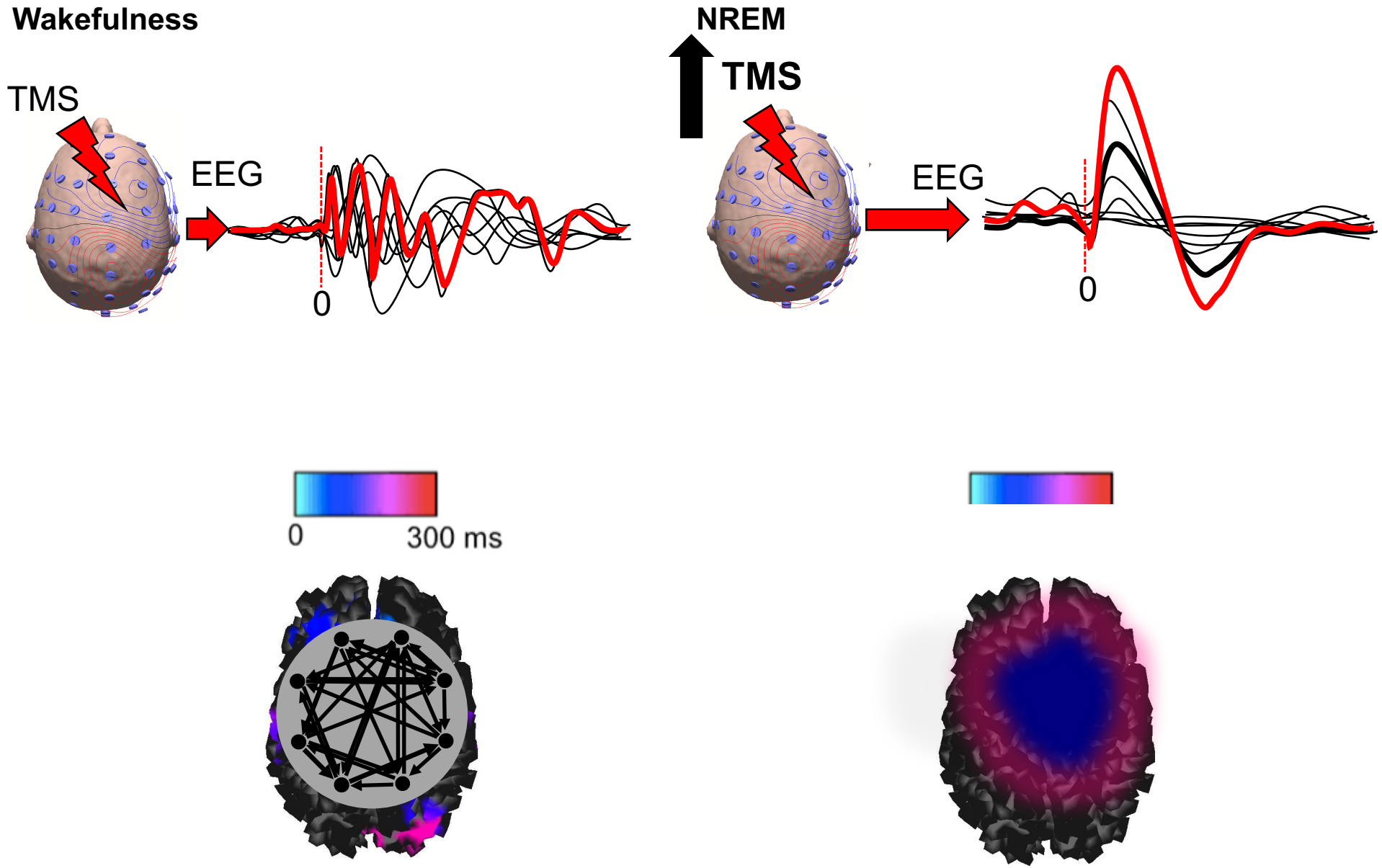




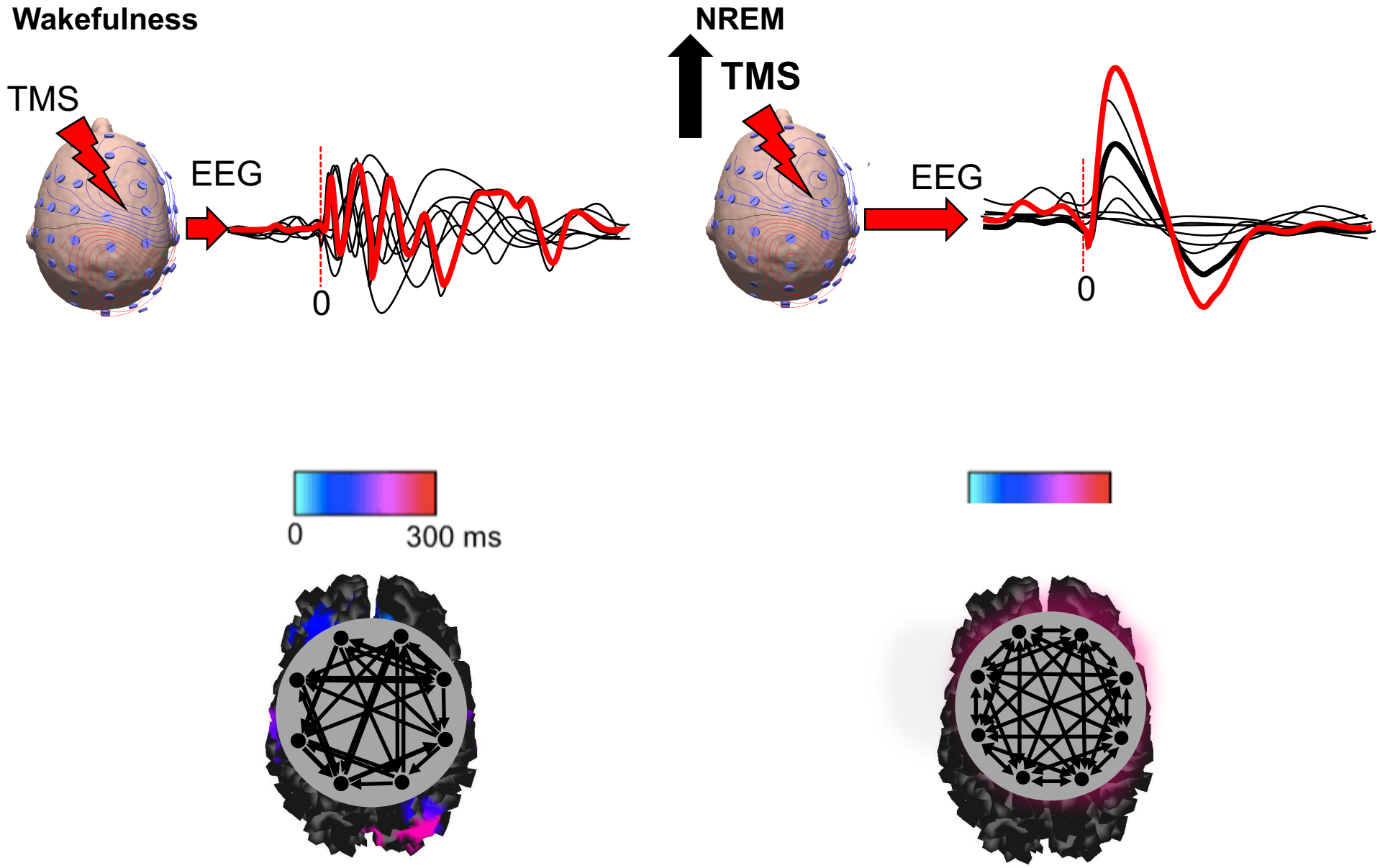
Massimini et al *Science*, 2005



Massimini et al *Science*, 2005



Massimini et al *Science*, 2005; Massimini et al., PNAS 2007

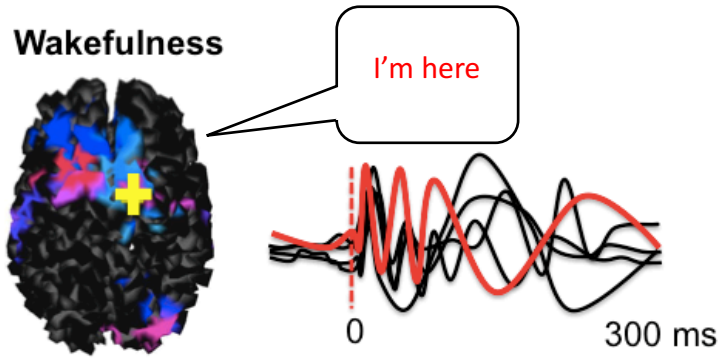


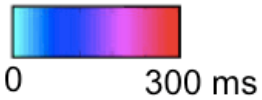
Massimini et al *Science*, 2005; Massimini et al., PNAS 2007

Dreaming

Massimini et al., Cogn. Neurosci., 2010

Dreaming





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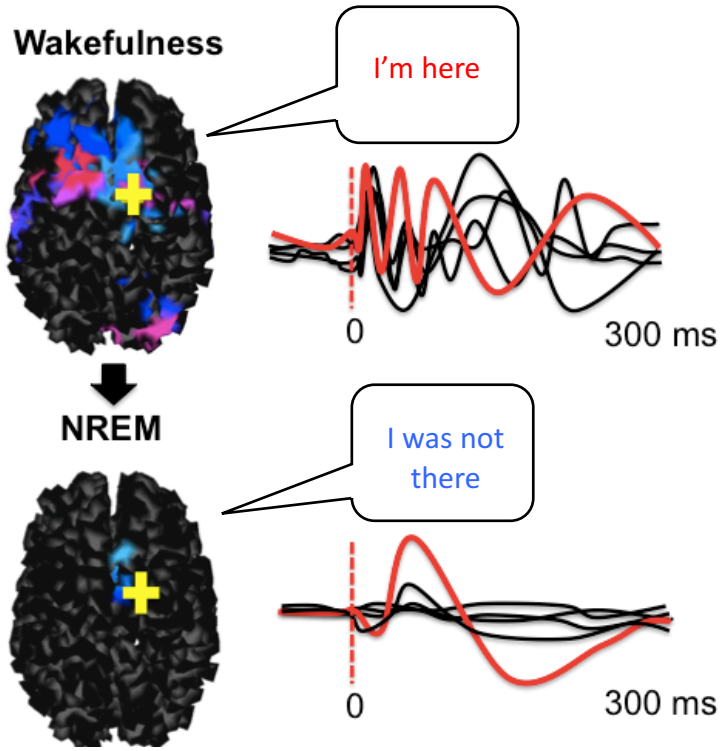
Dreaming



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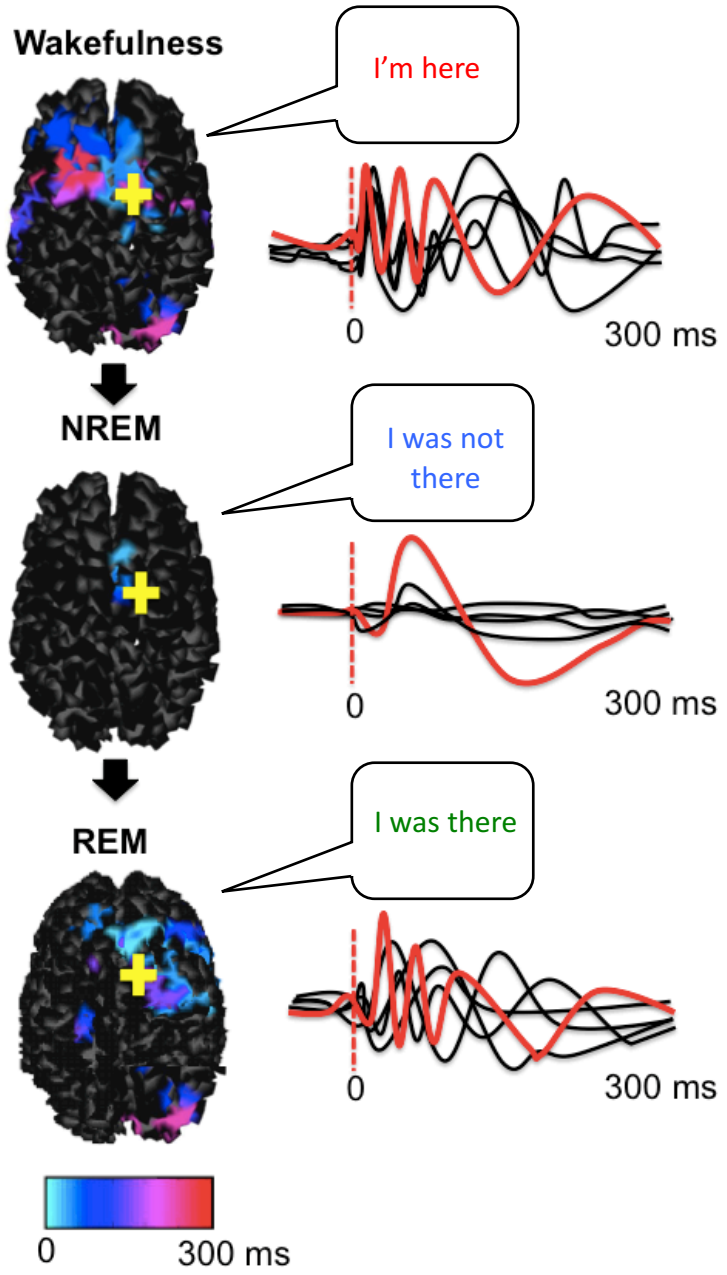
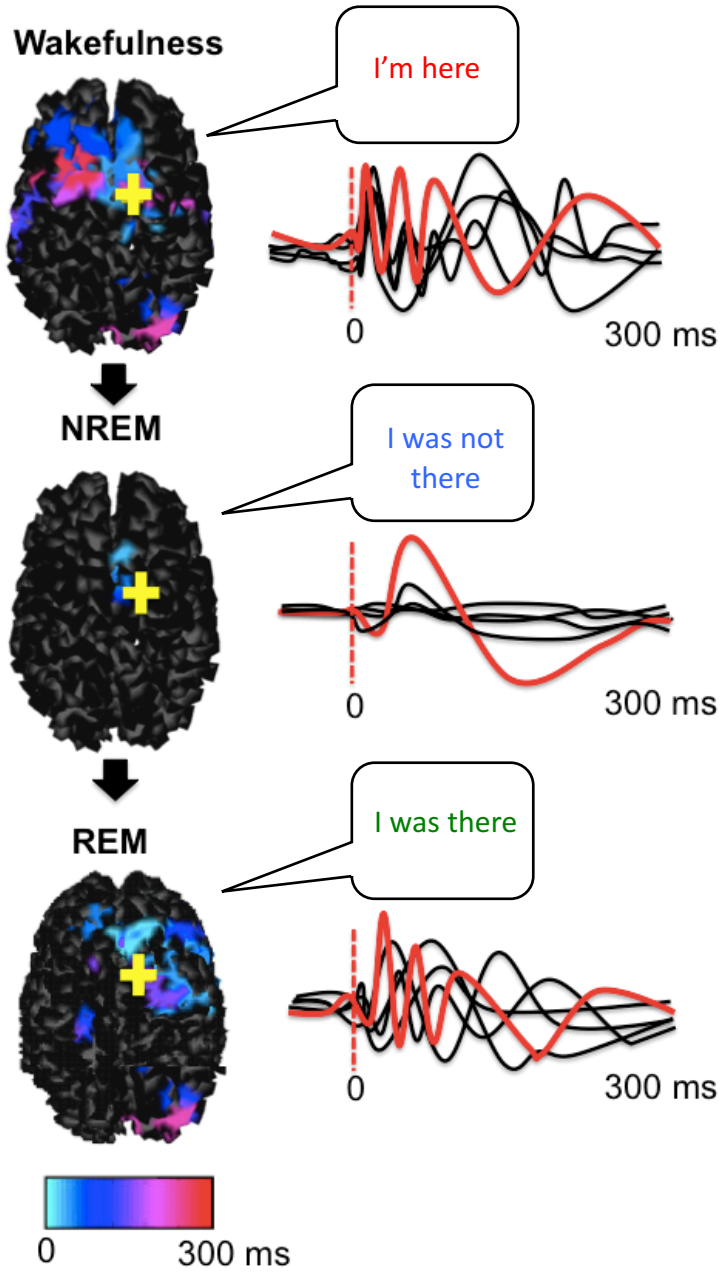


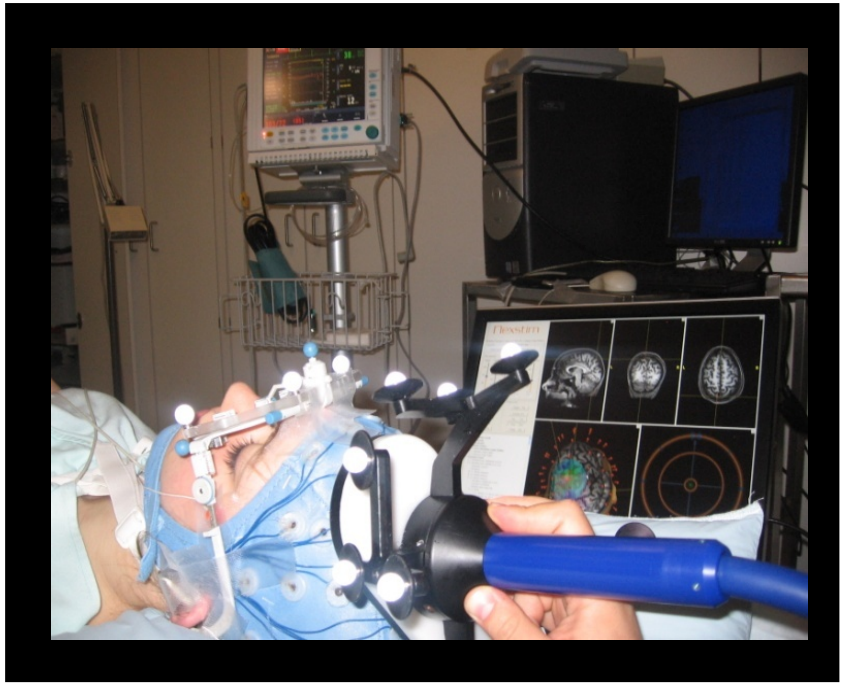
Massimini et al., Cogn. Neurosci., 2010;

Dreaming

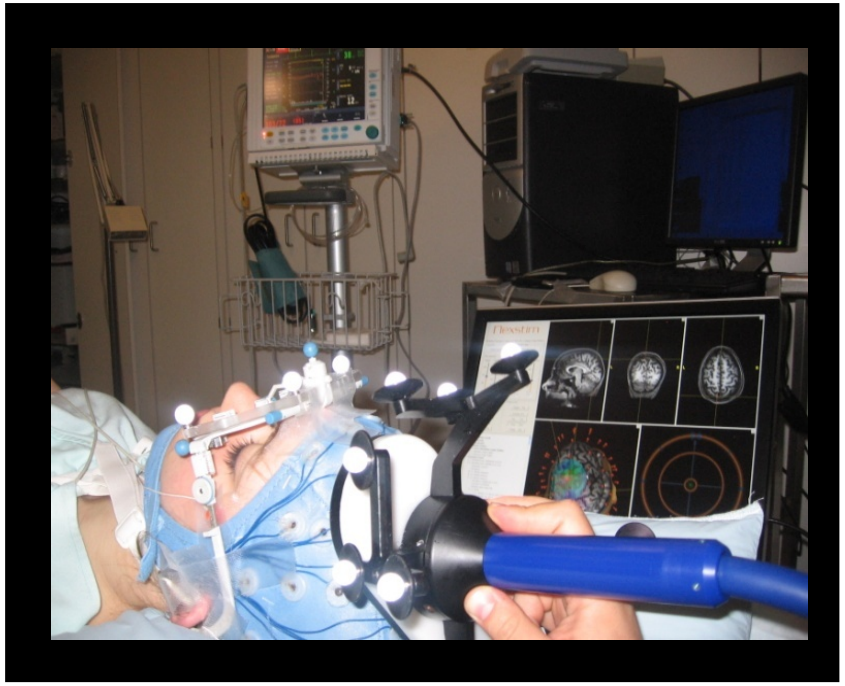


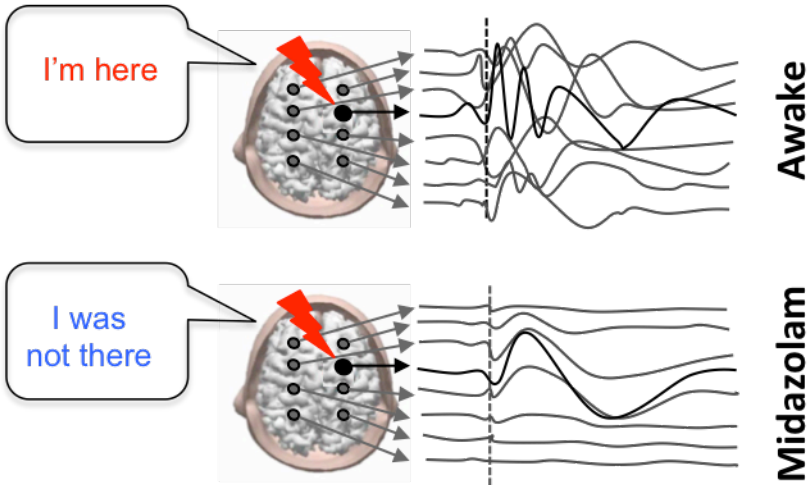
Massimini et al., Cogn. Neurosci., 2010; Nieminen, Gosseries et al., Sci Rep 2016

Anesthesia



Anesthesia





Ferrarelli et al *PNAS*, 2010

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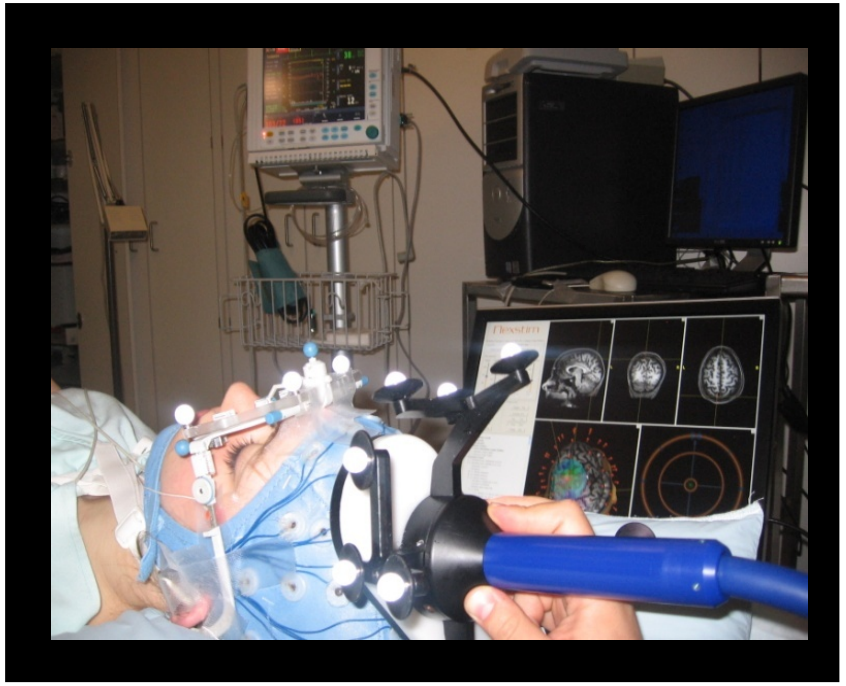
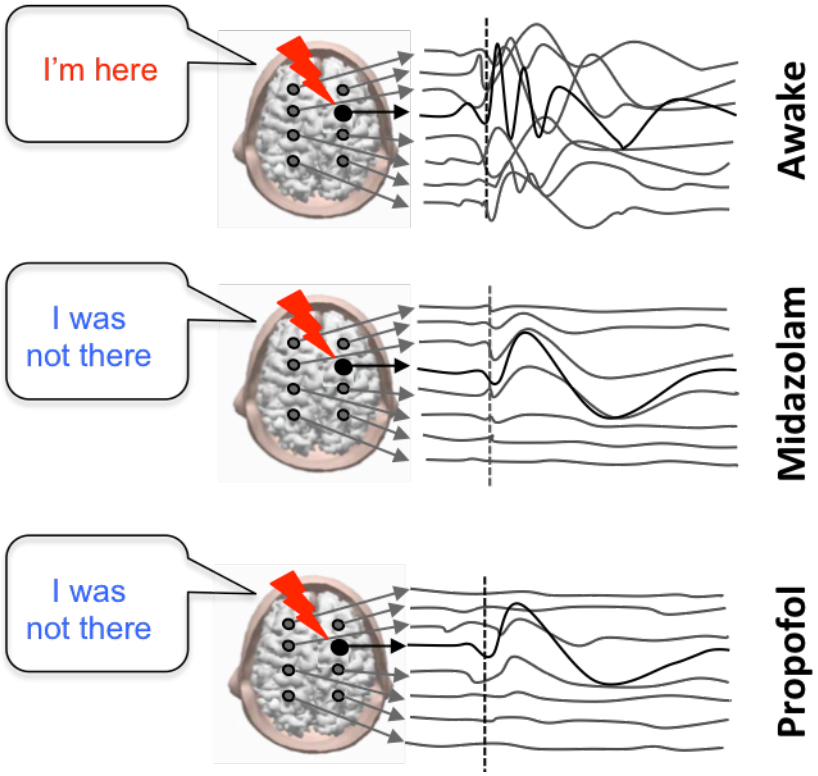
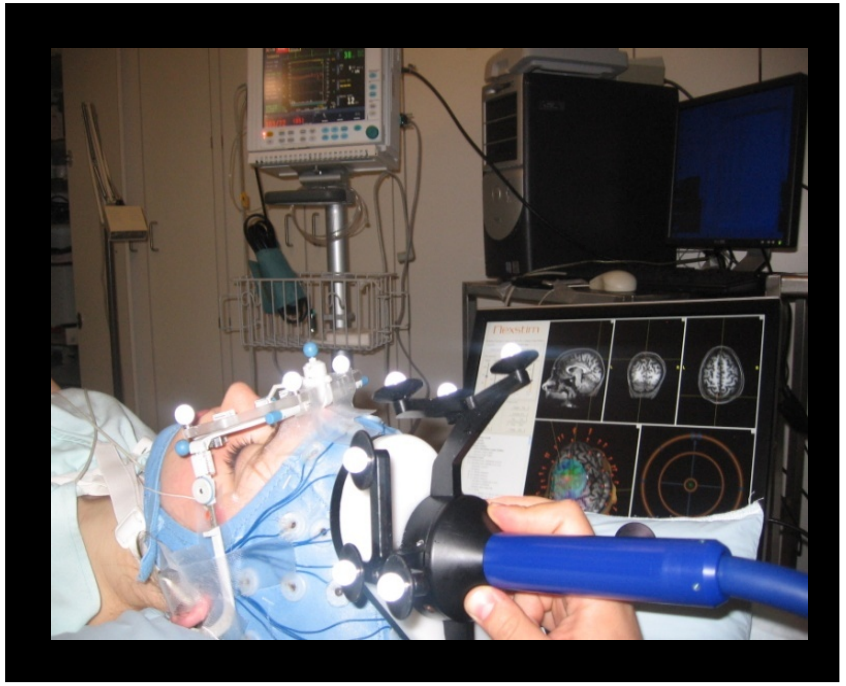
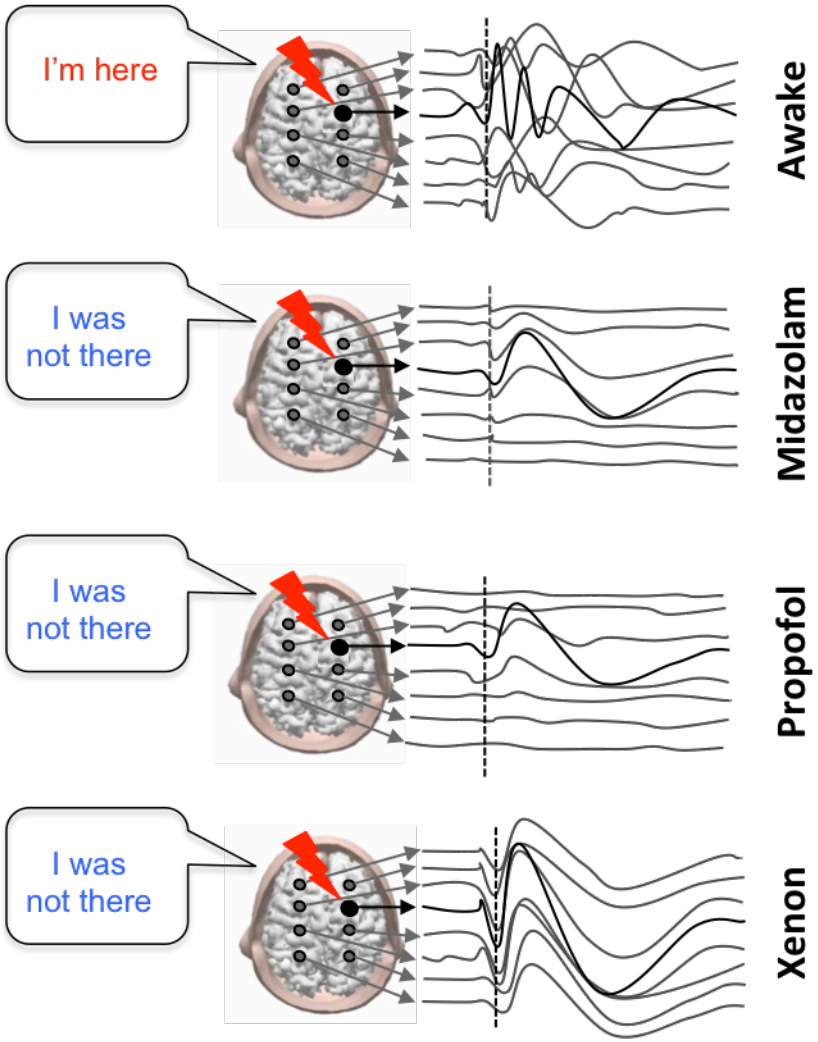




Ferrarelli et al *PNAS*, 2010; Sarasso, Boly et al., *Current Biology* 2015

Anesthesia





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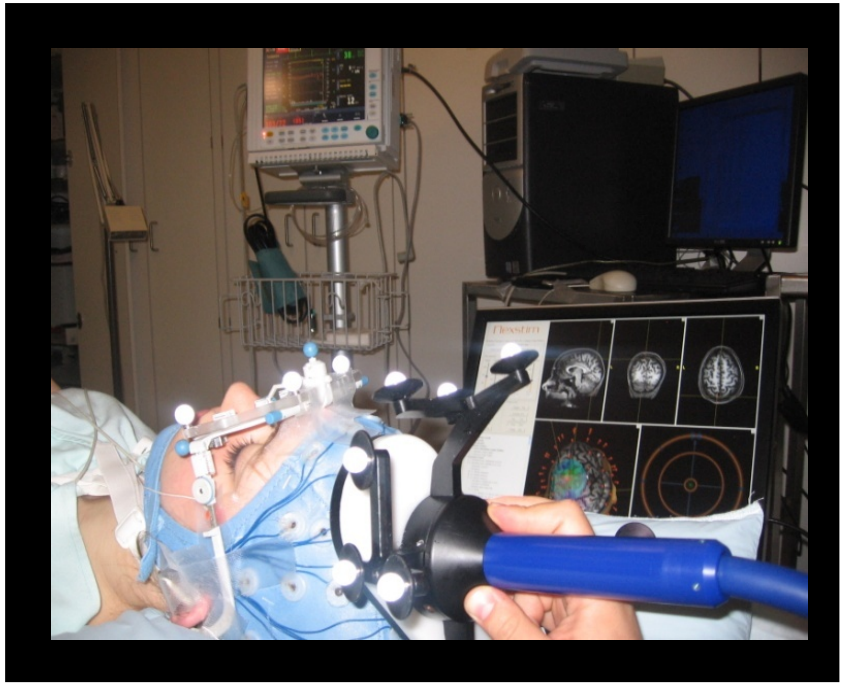

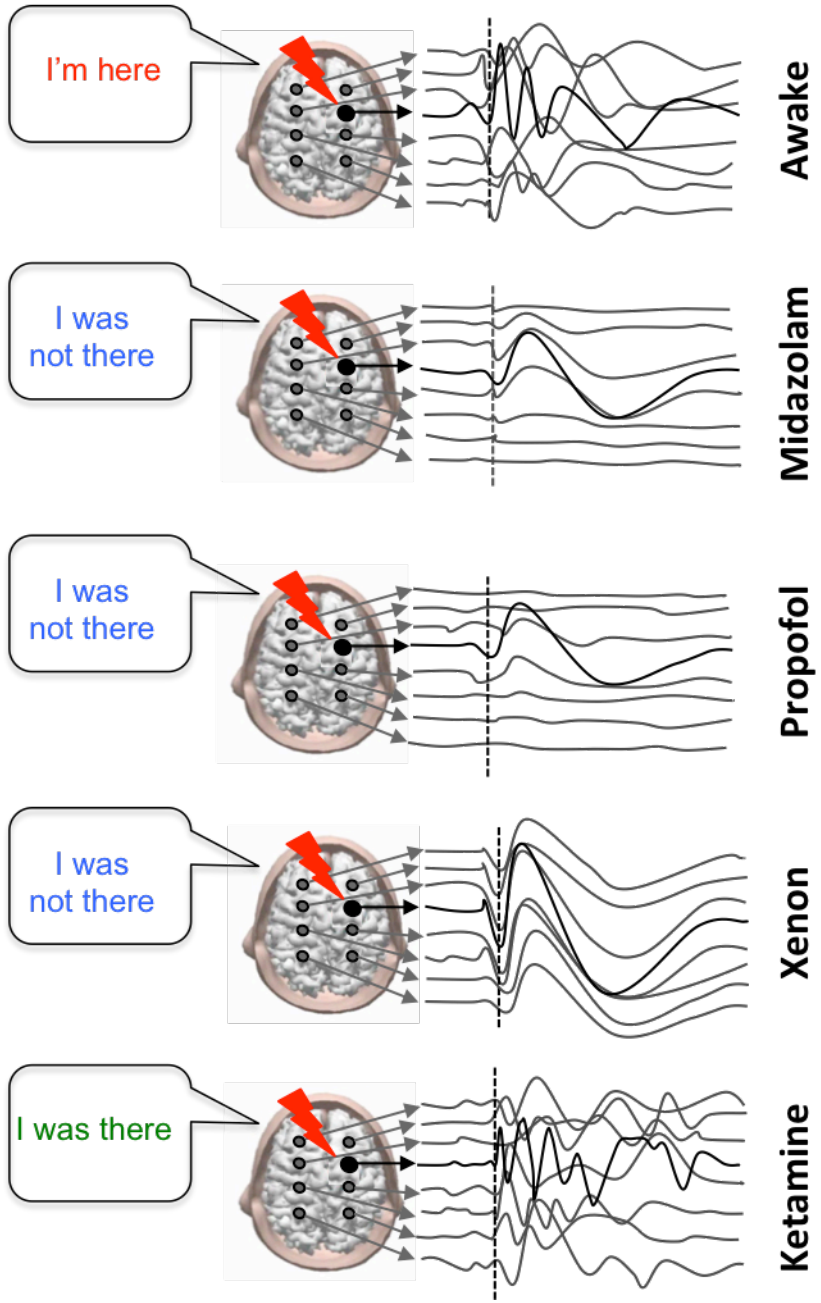

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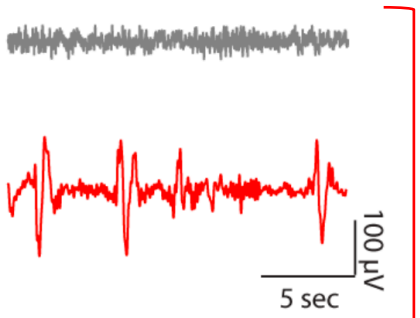
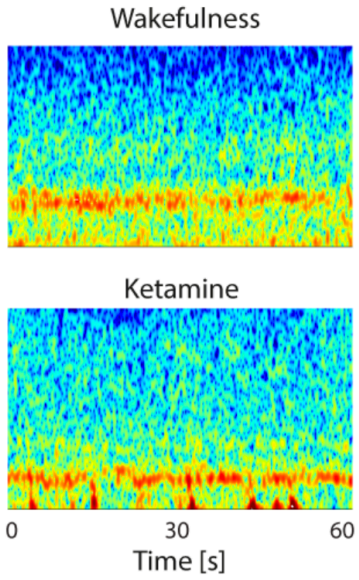
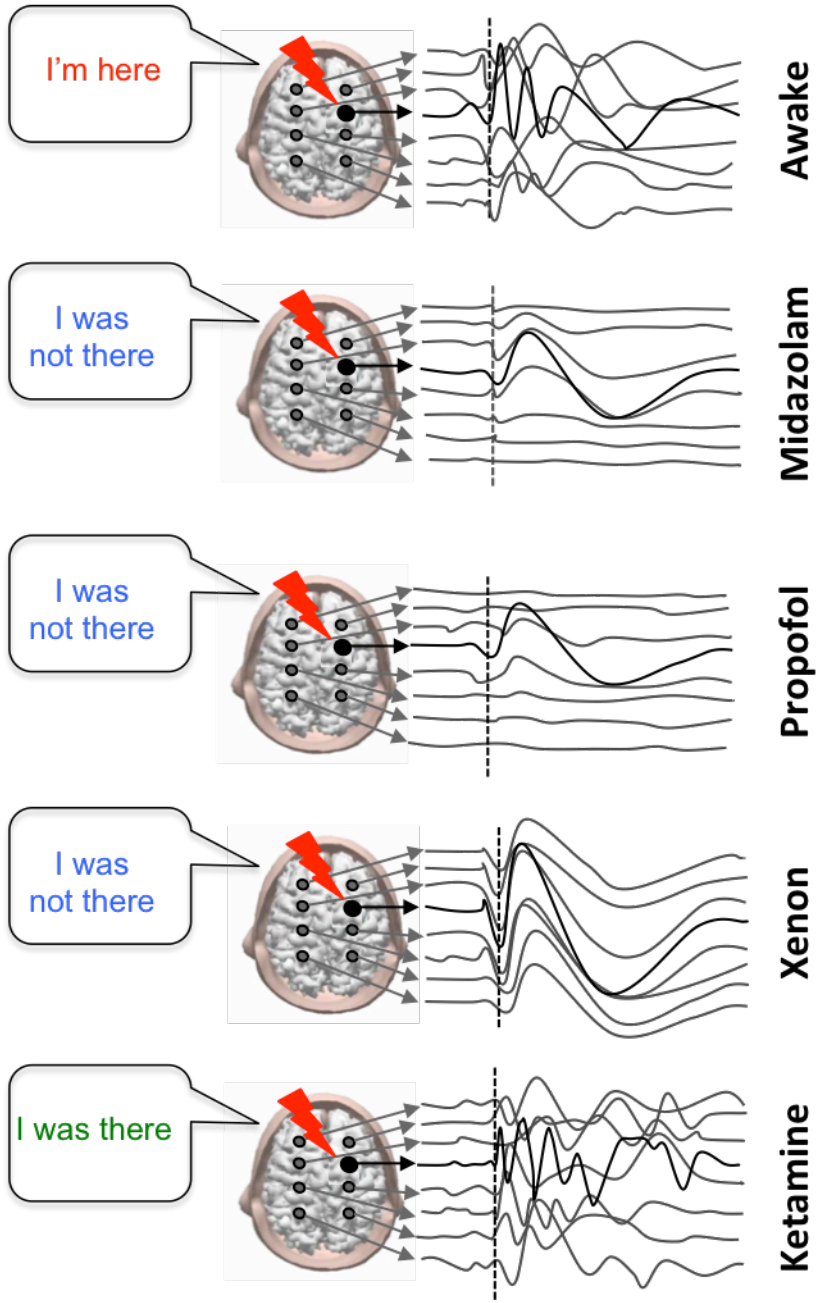
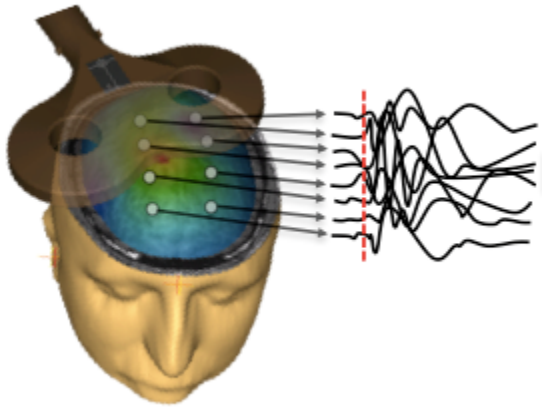






Ferrarelli et al *PNAS*, 2010; Sarasso, Boly et al., *Current Biology* 2015

A quantification: the Perturbational Complexity Index (PCI)



Casali et al., *Science Translational Medicine* 2013;

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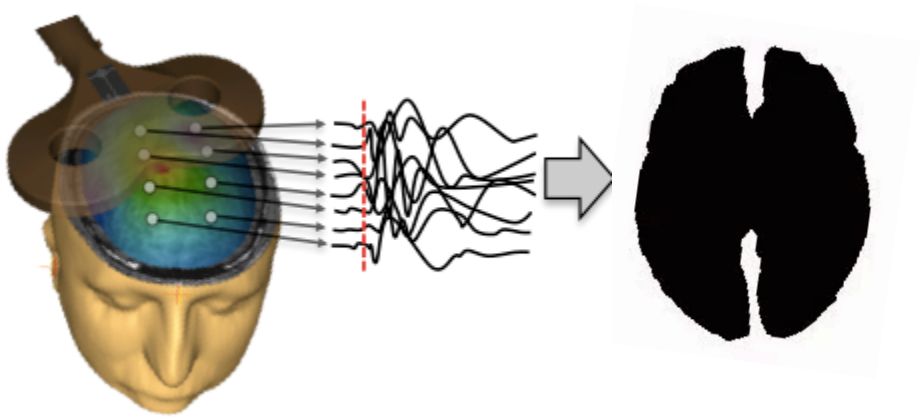

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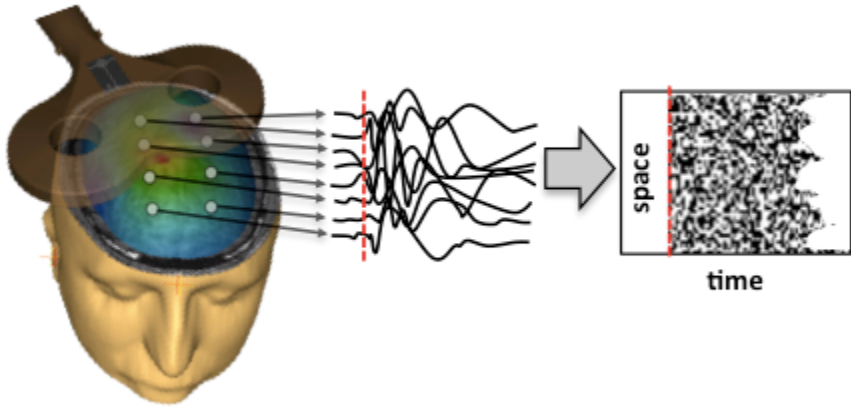
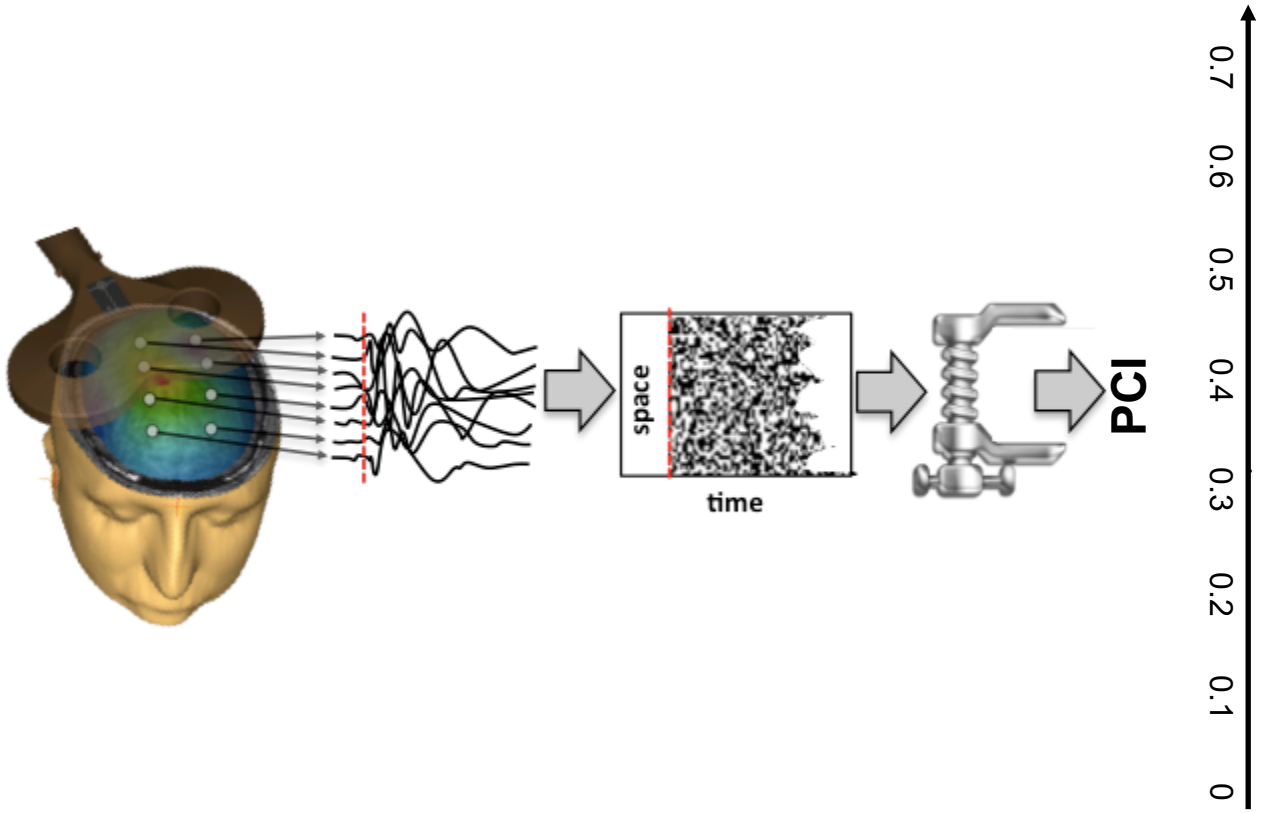


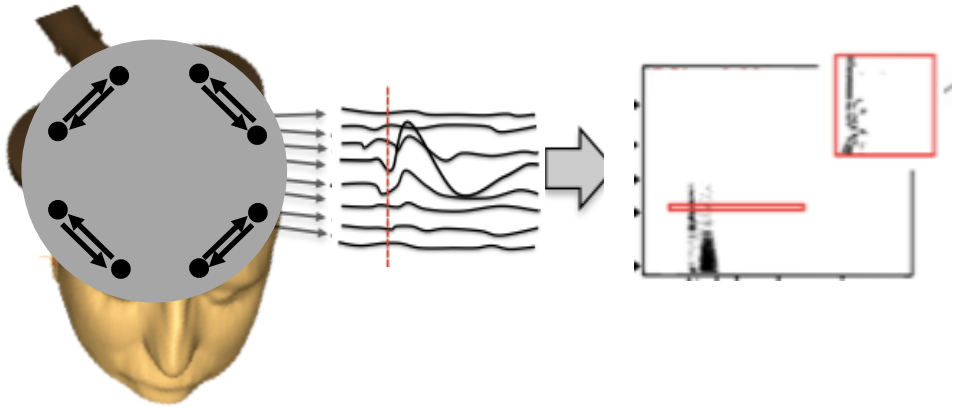
Casali et al., *Science Translational Medicine* 2013;

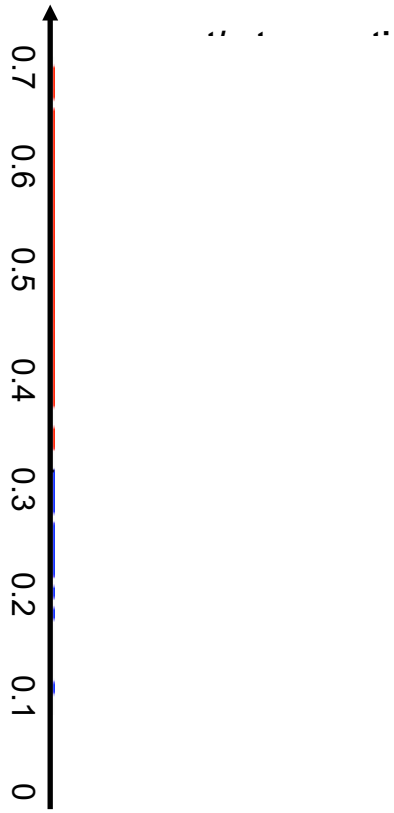
A quantification: the Perturbational Complexity Index (PCI)



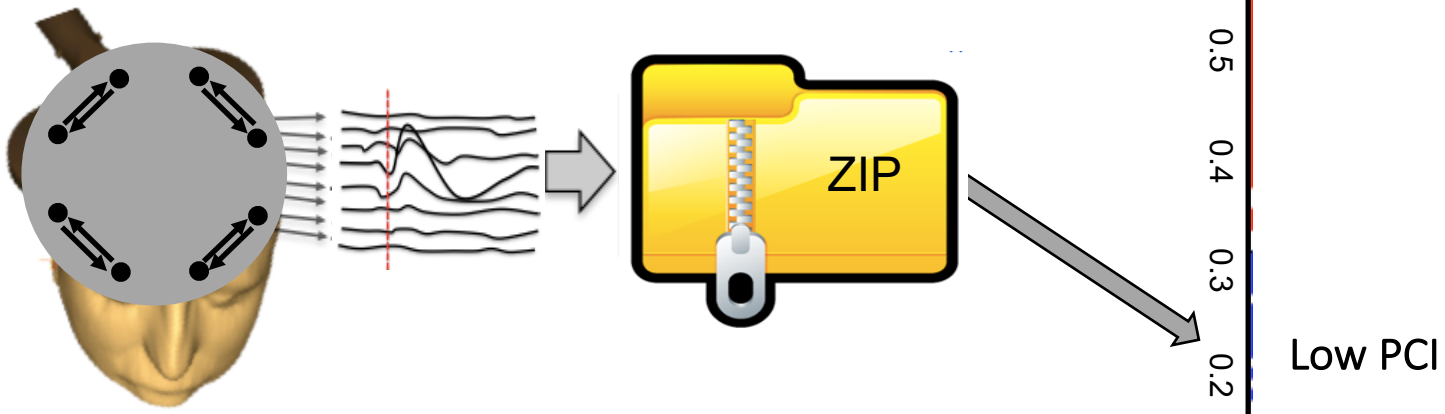
Casali et al., *Science Translational Medicine* 2013;

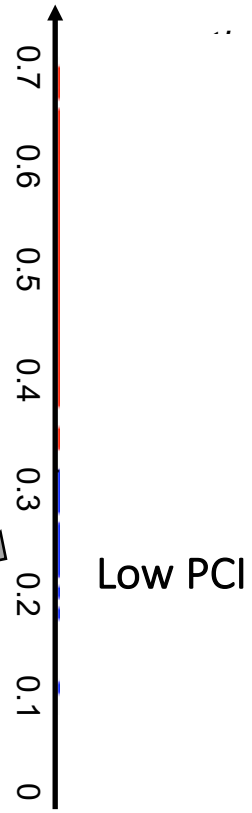
No Integration





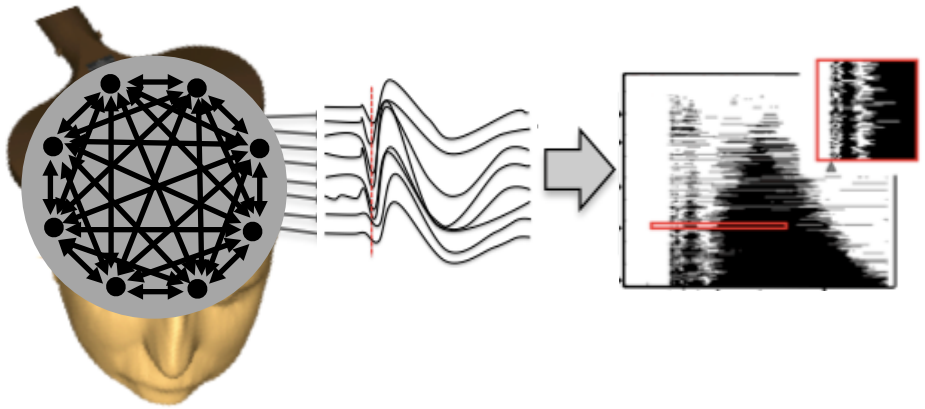
No Integration

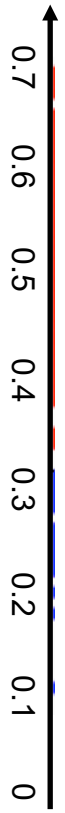




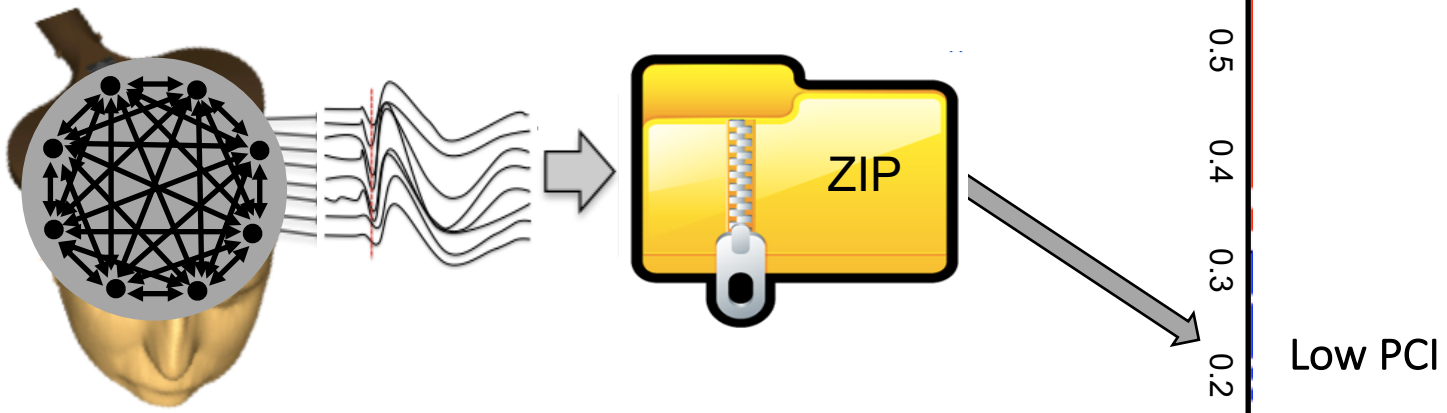
Low PCI

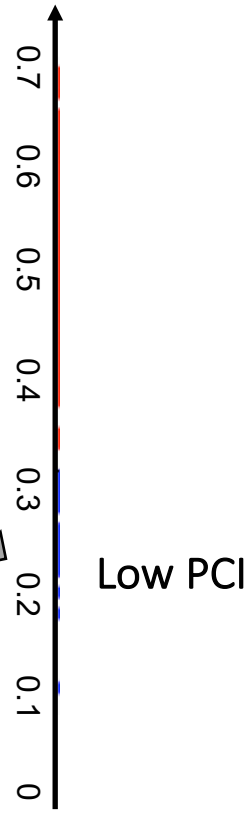
No Differentiation





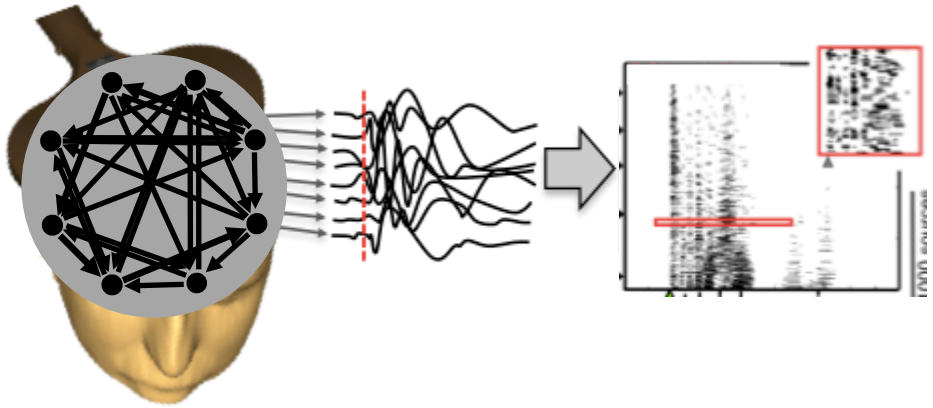
No Differentiation

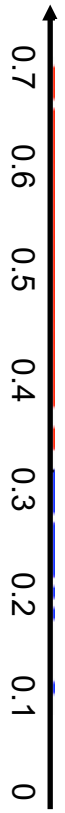


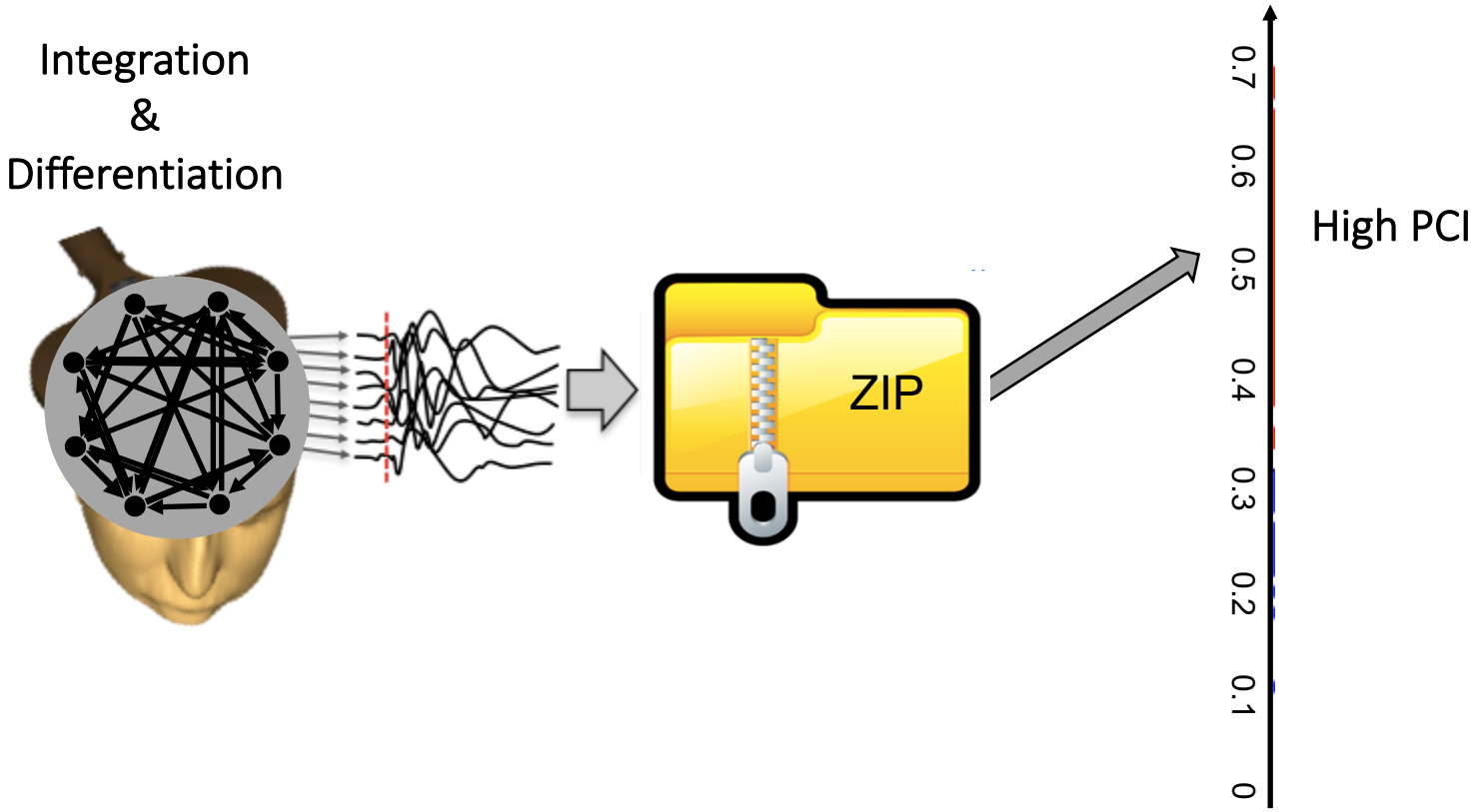


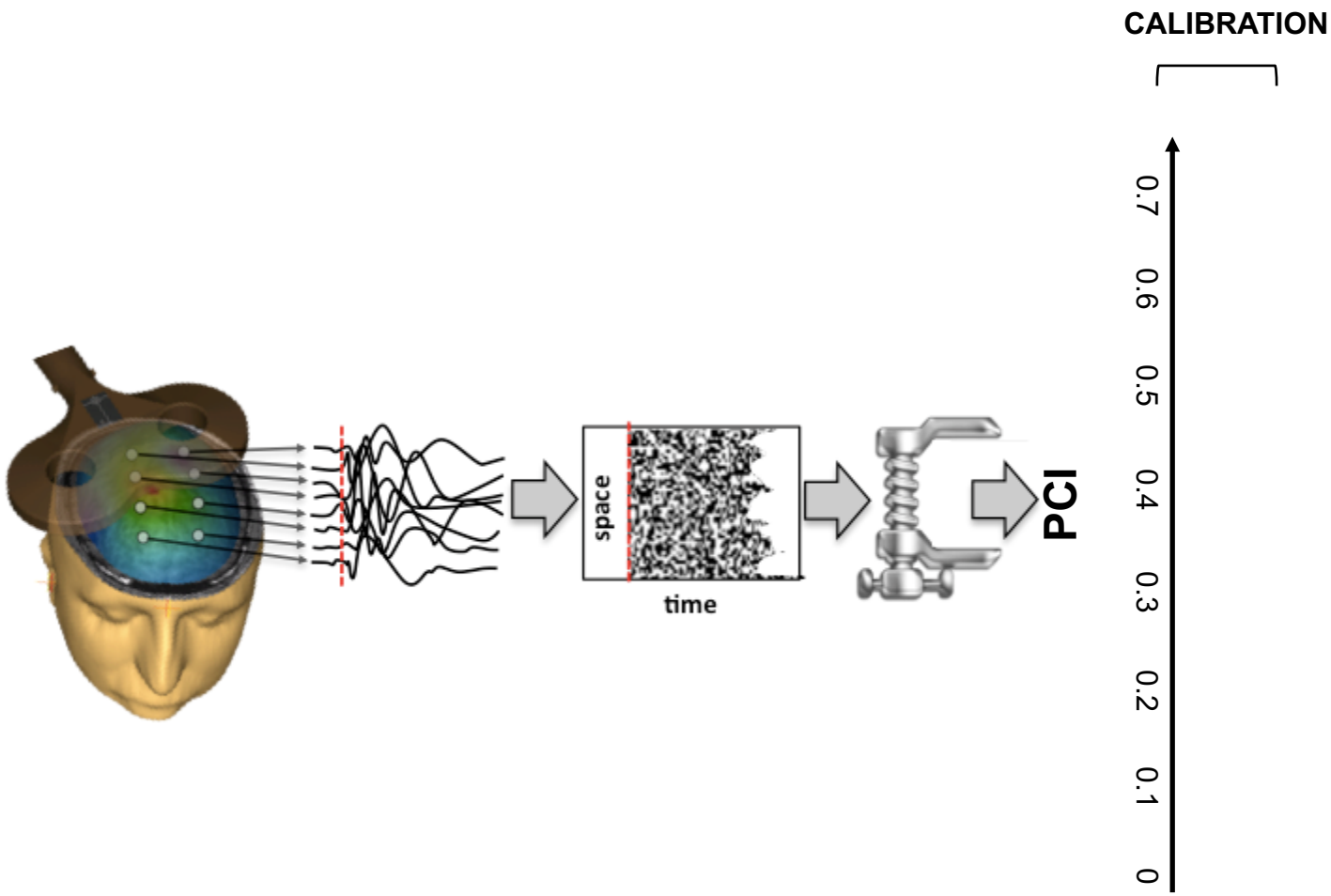
Low PCI

Integration
&
Differentiation

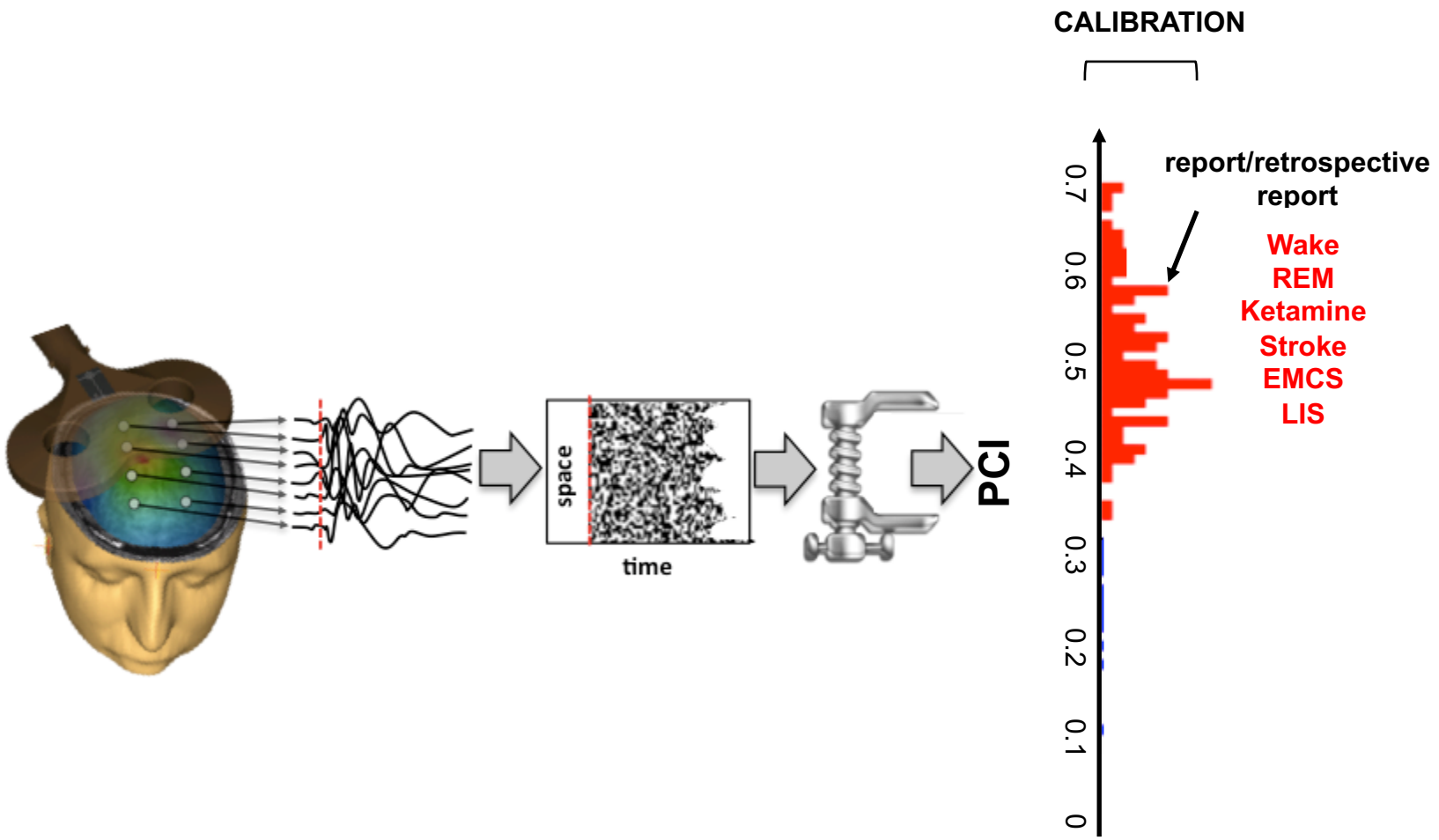




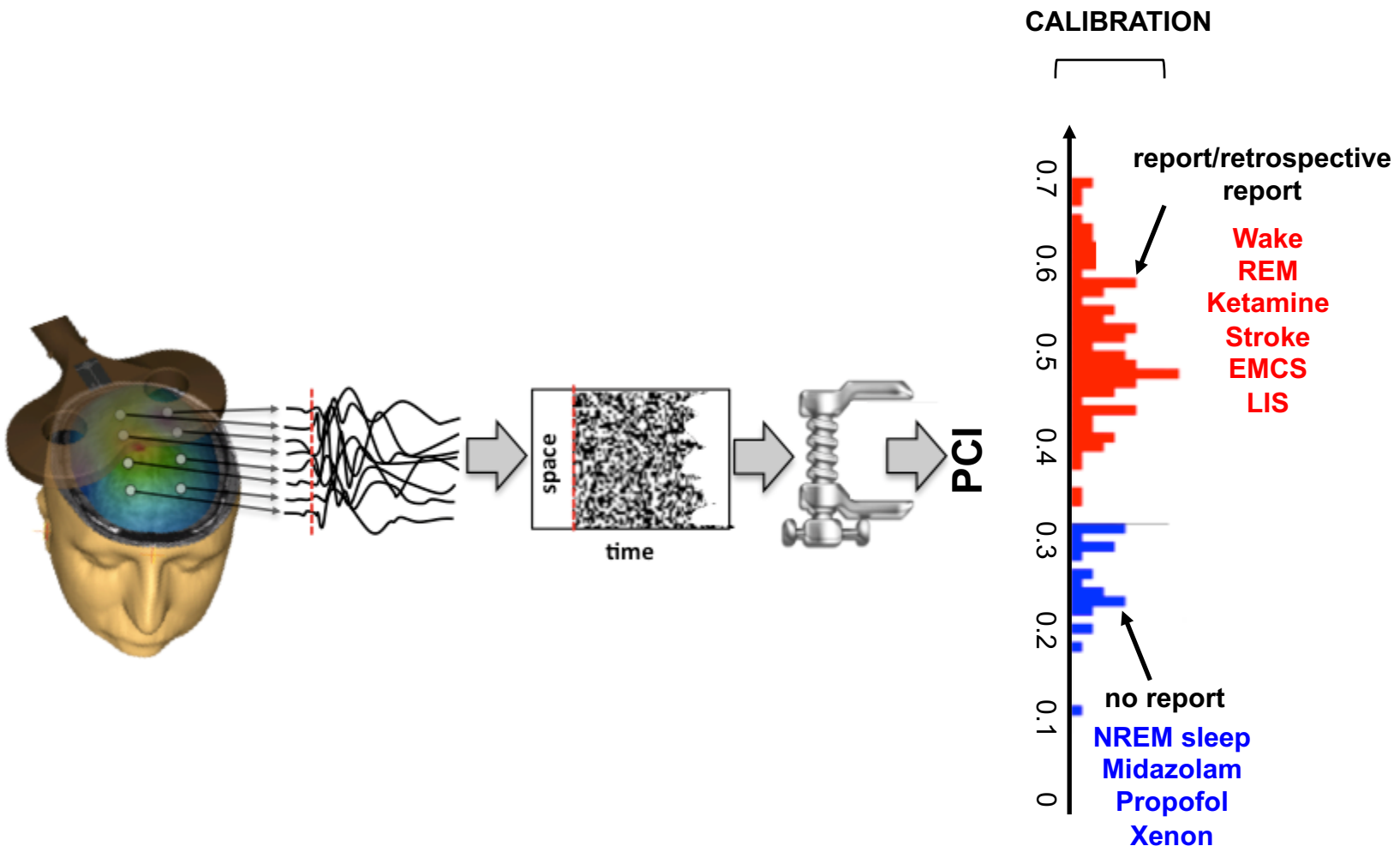

Integration
&
Differentiation
ZIP
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
High PCI



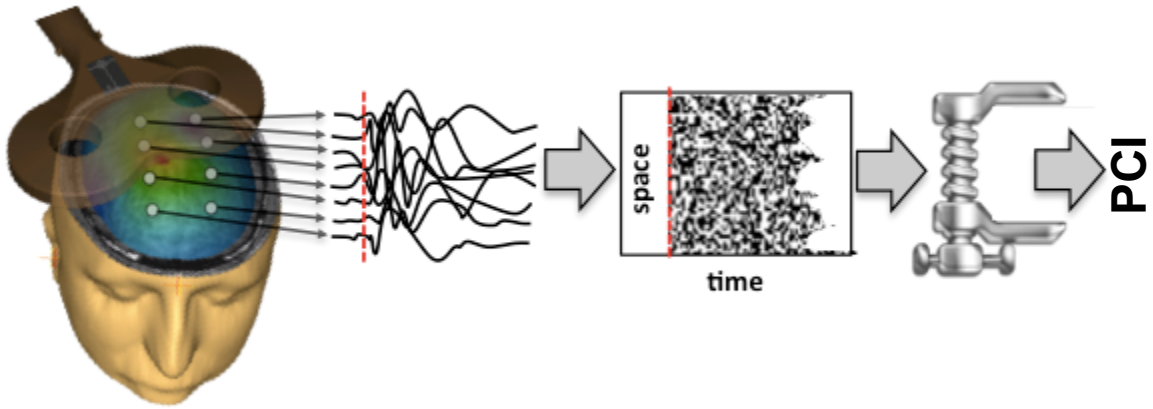
Casarotto et al *Annals of Neurology 2016*

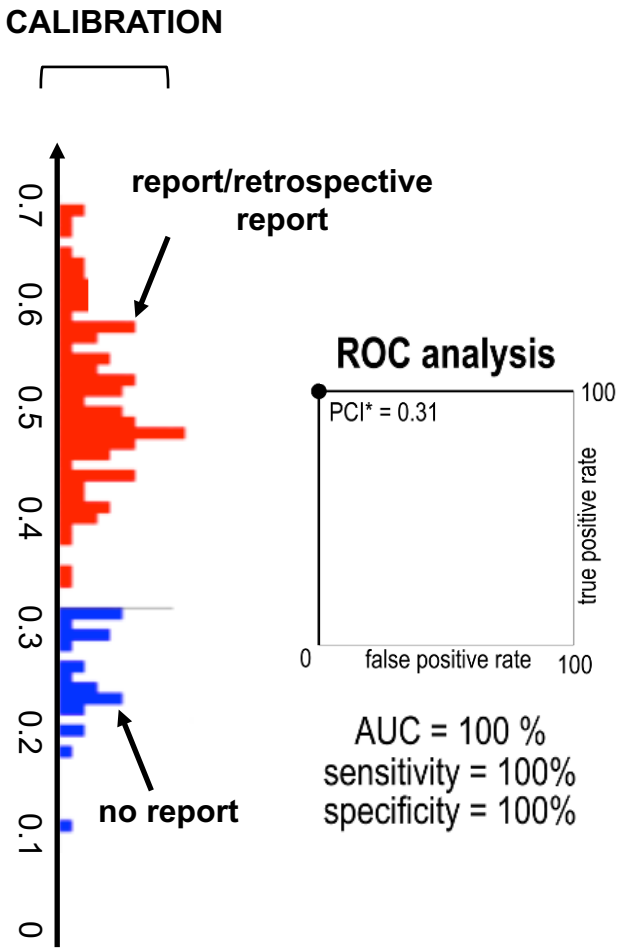


Casarotto et al *Annals of Neurology 2016*

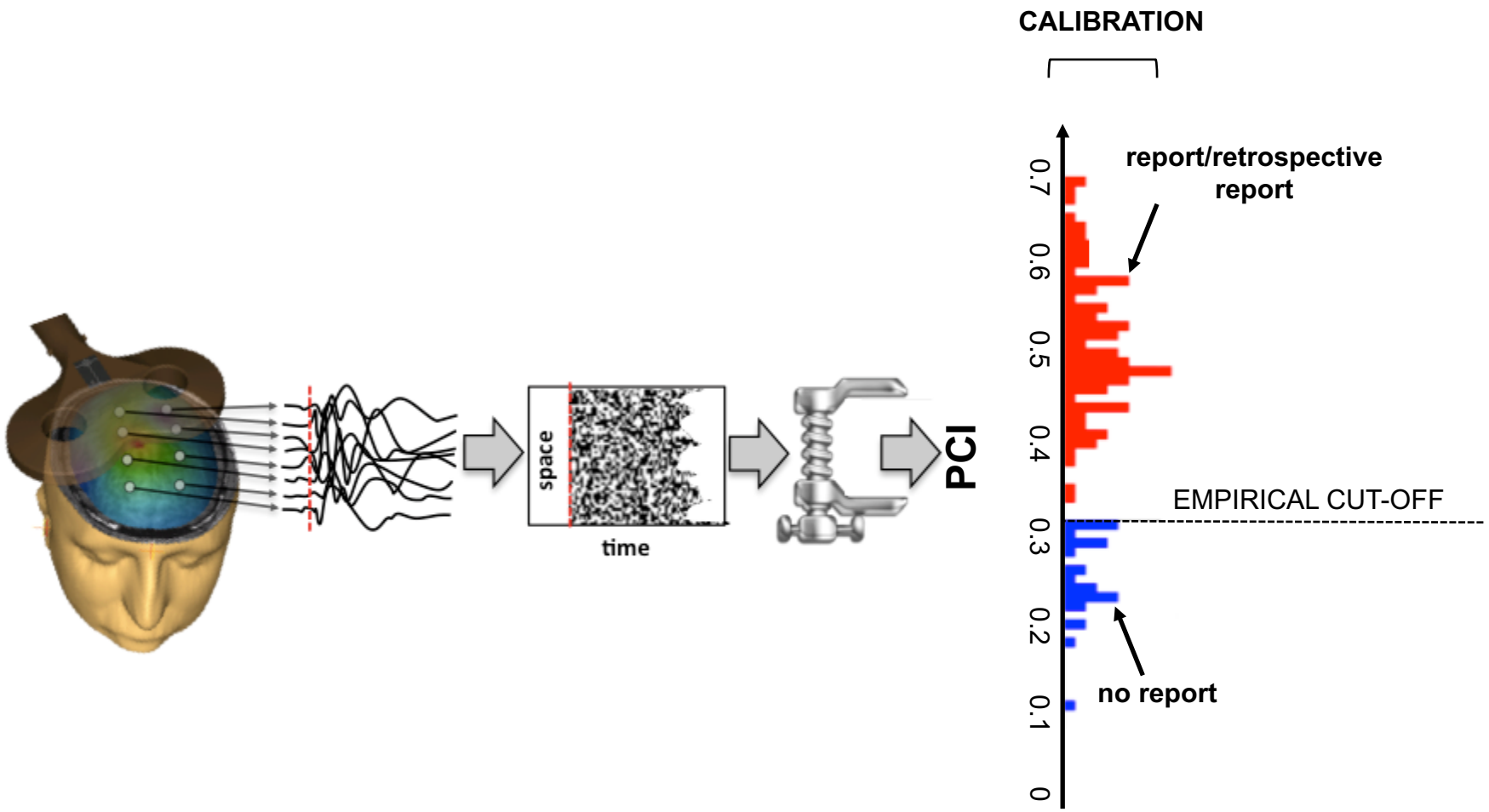


Casarotto et al *Annals of Neurology 2016*

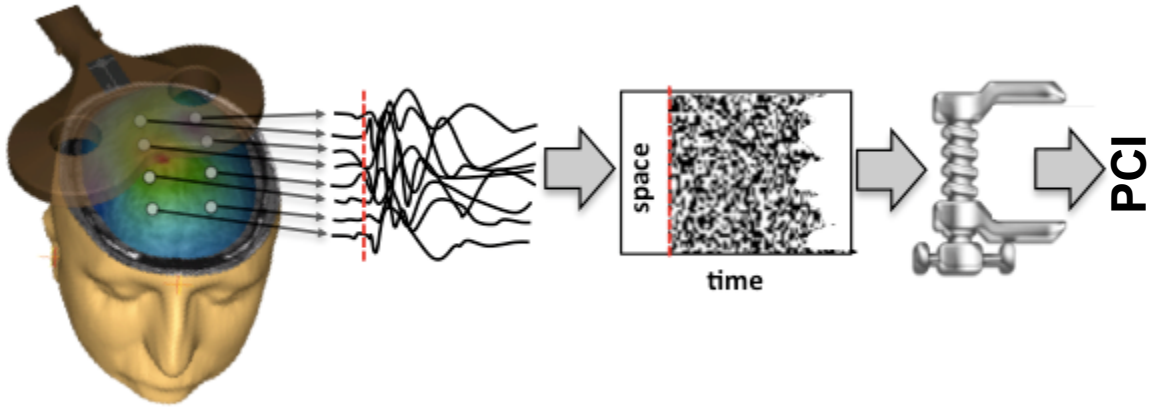


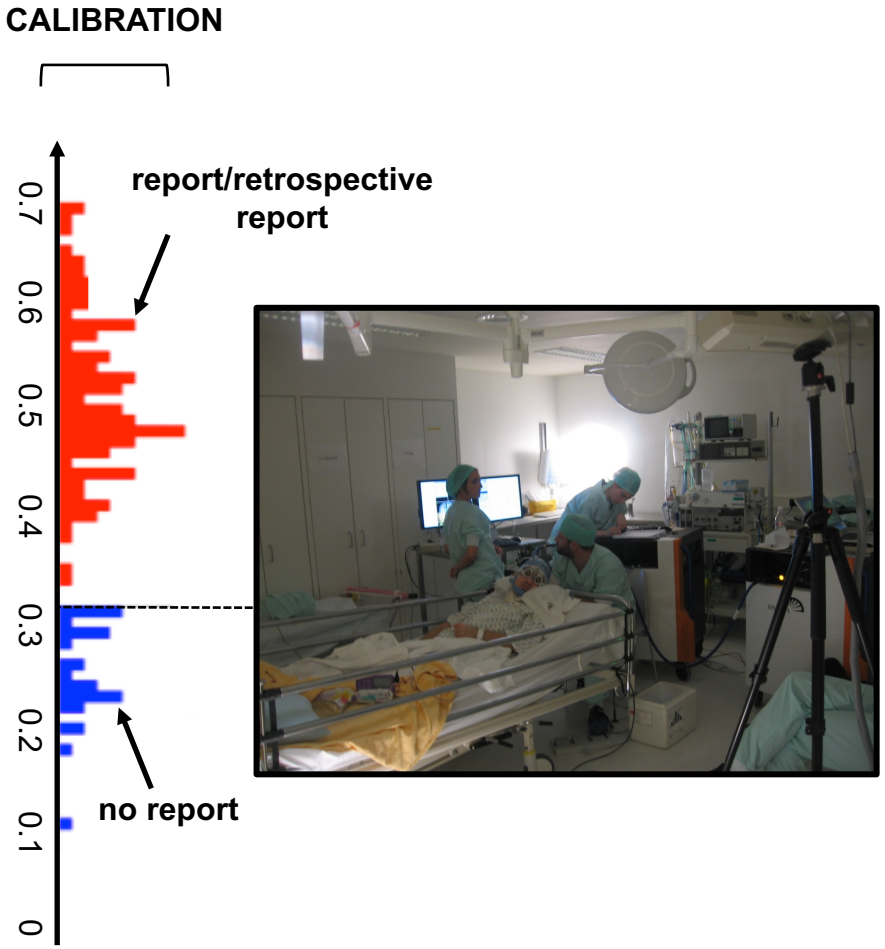


Casarotto et al *Annals of Neurology 2016*

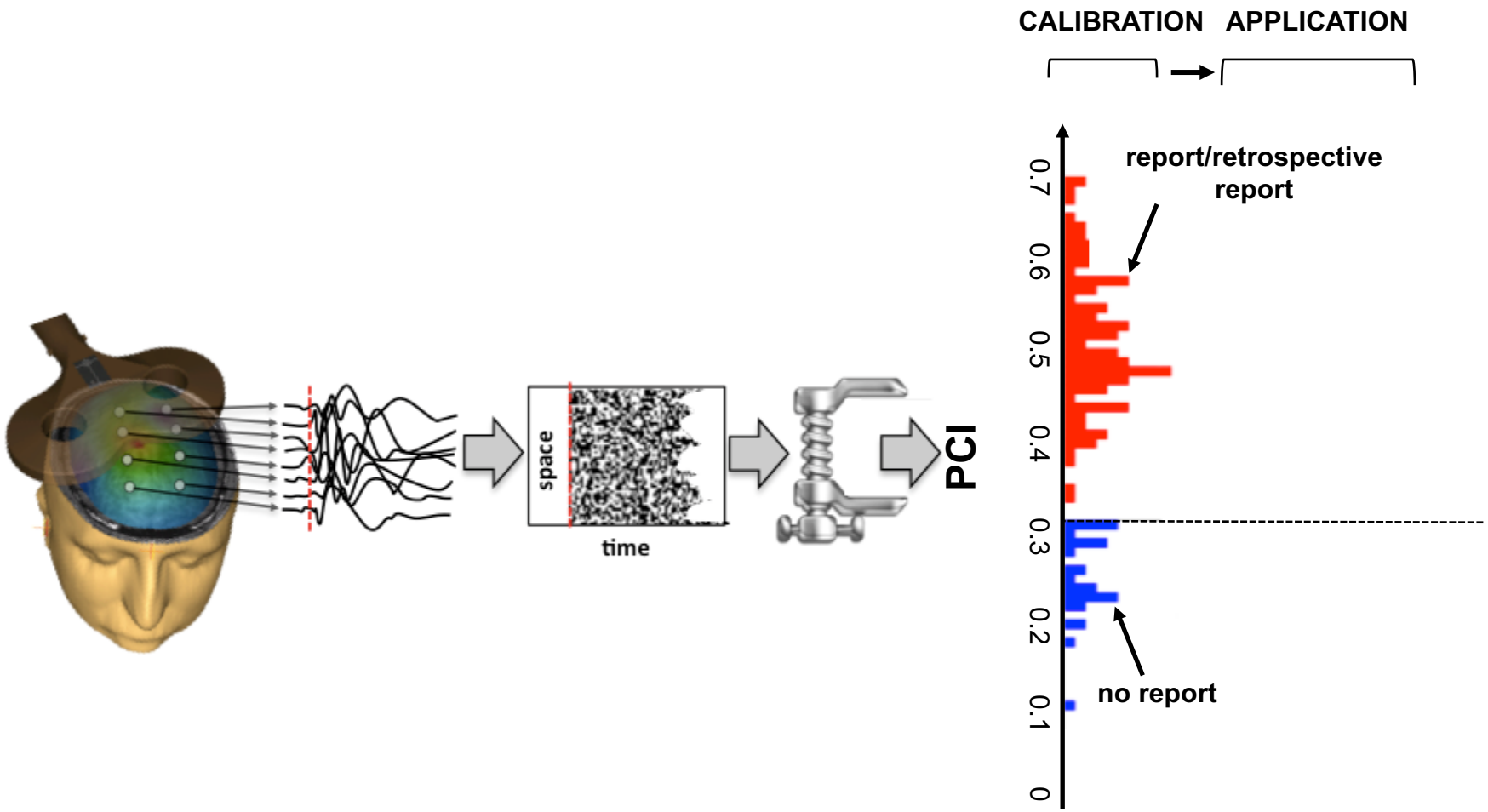


Casarotto et al *Annals of Neurology 2016*

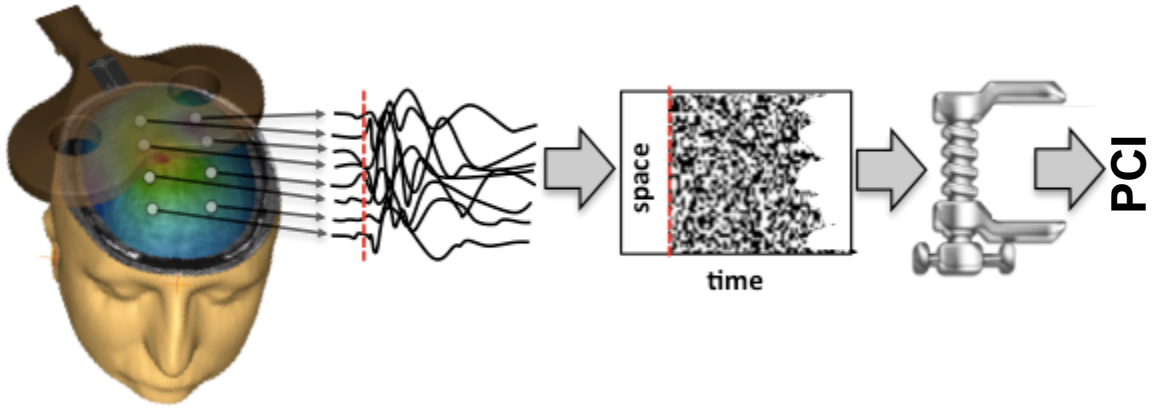


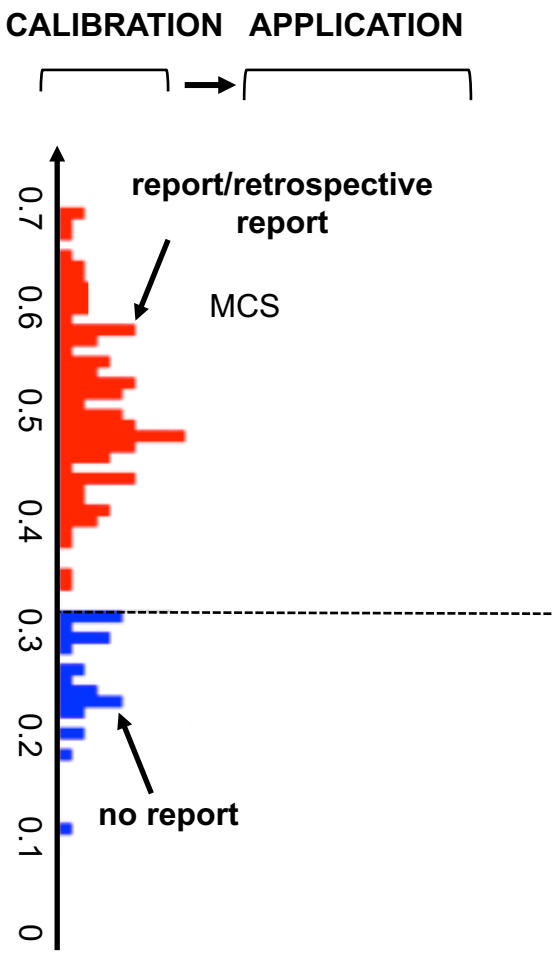


Casarotto et al *Annals of Neurology 2016*

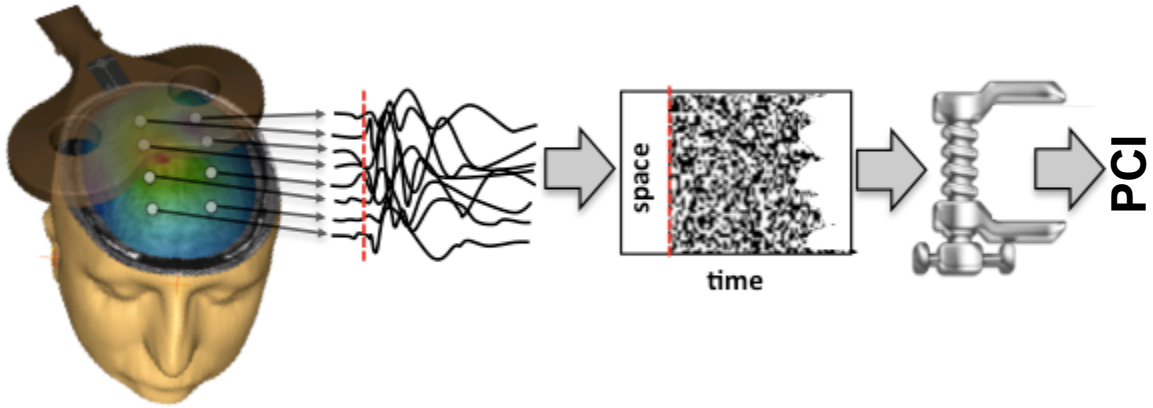


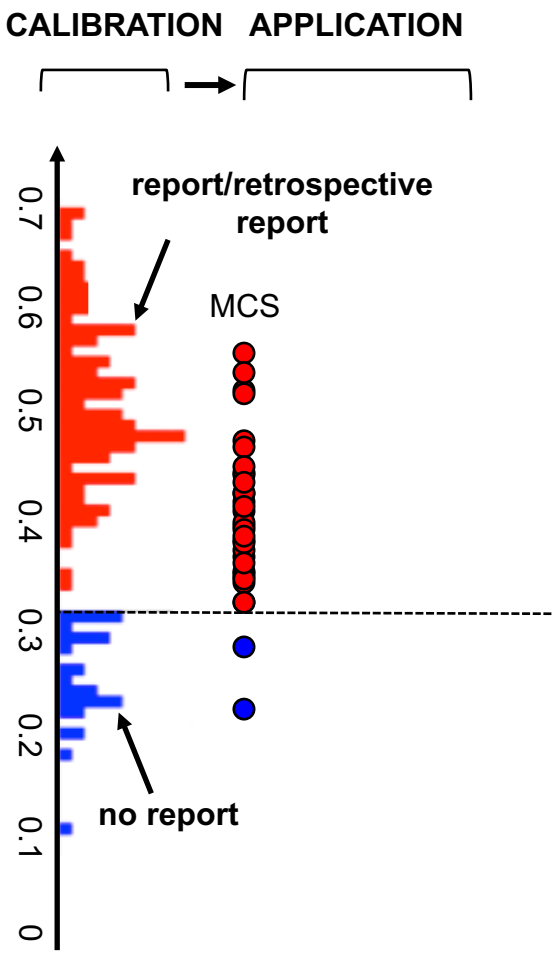
Casarotto et al *Annals of Neurology 2016*





Casarotto et al *Annals of Neurology 2016*





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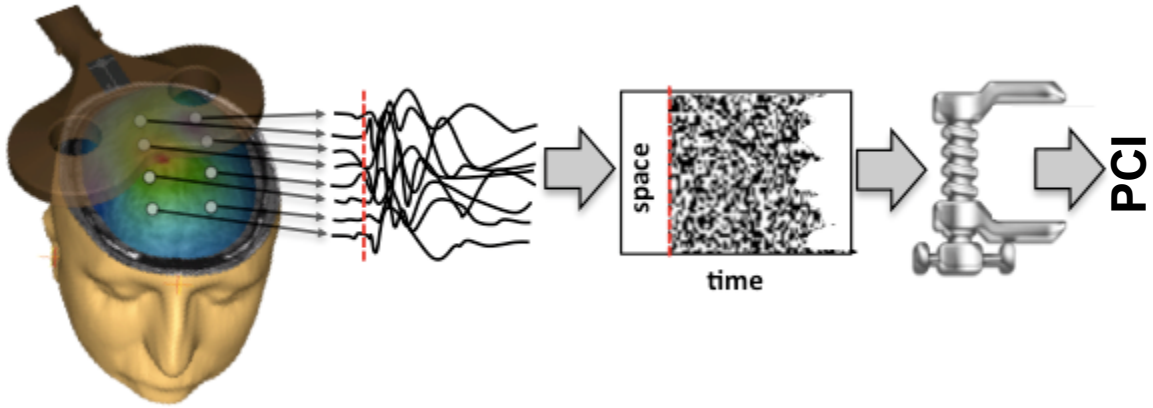

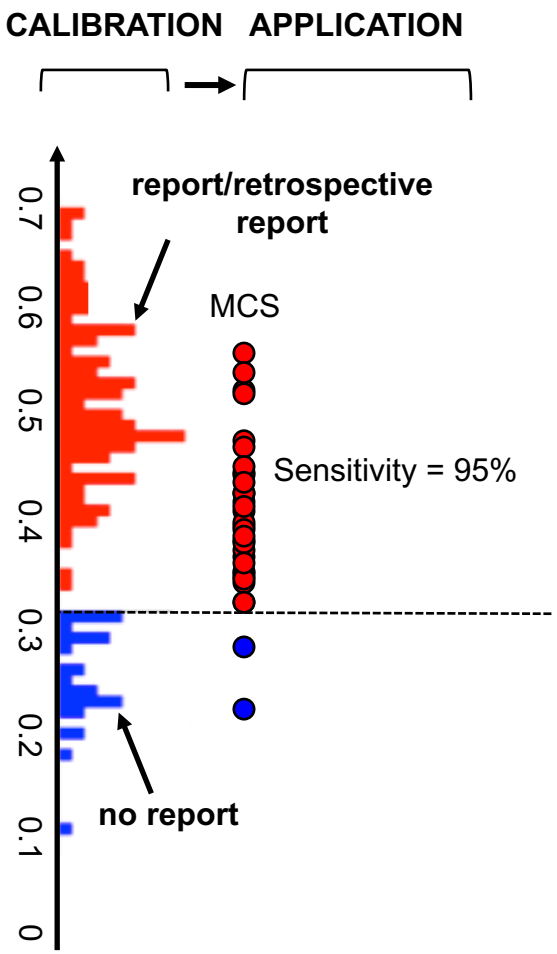

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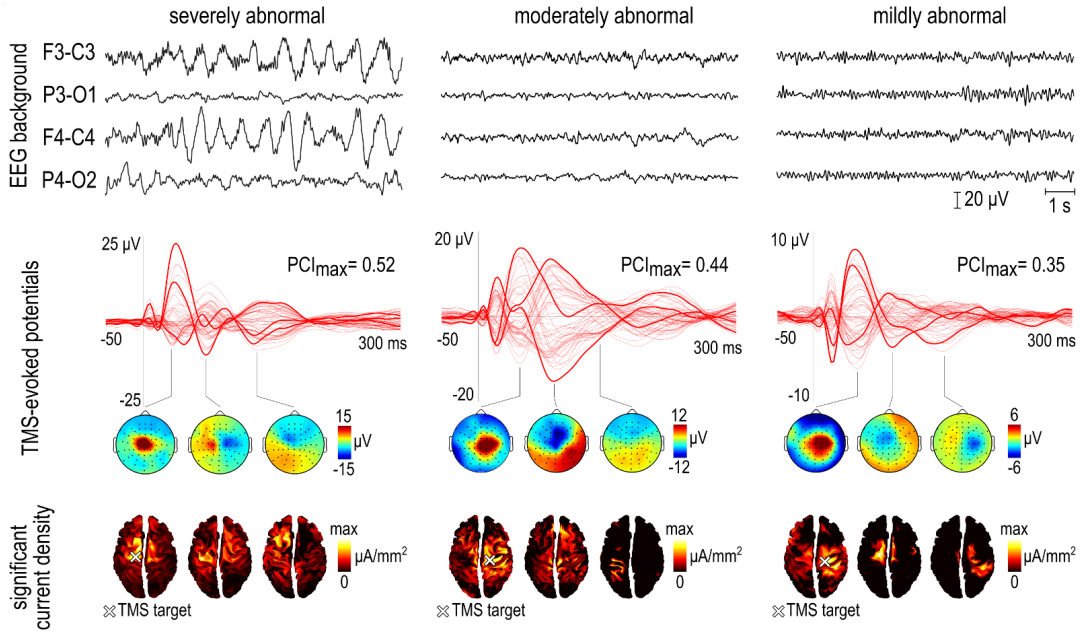
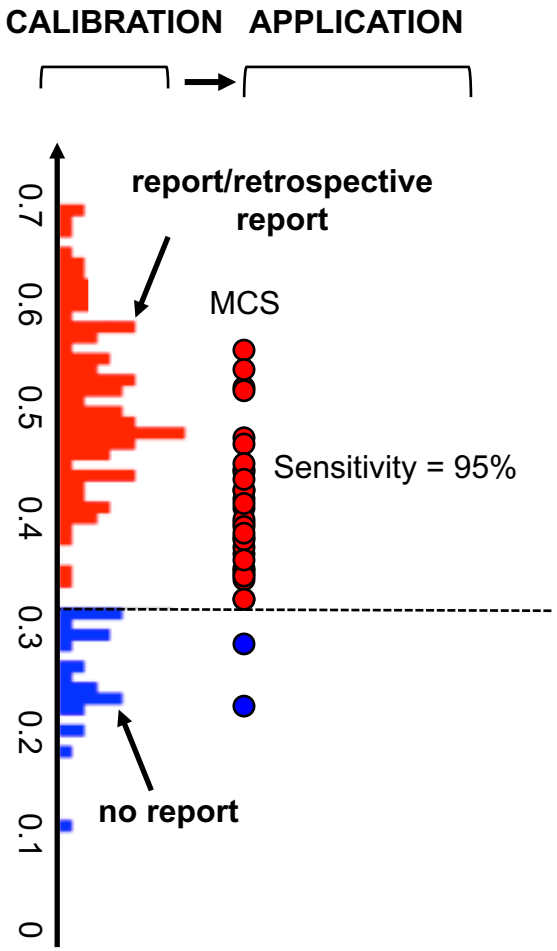
Spont. EEG





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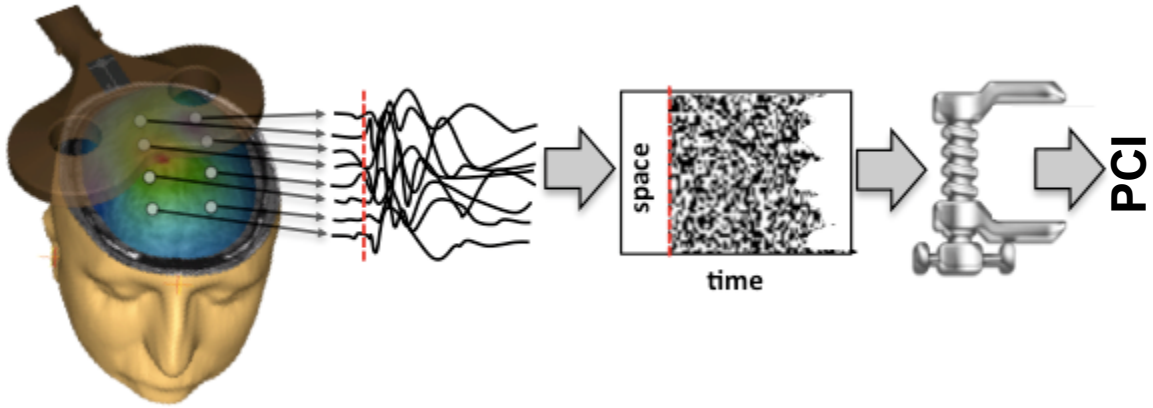
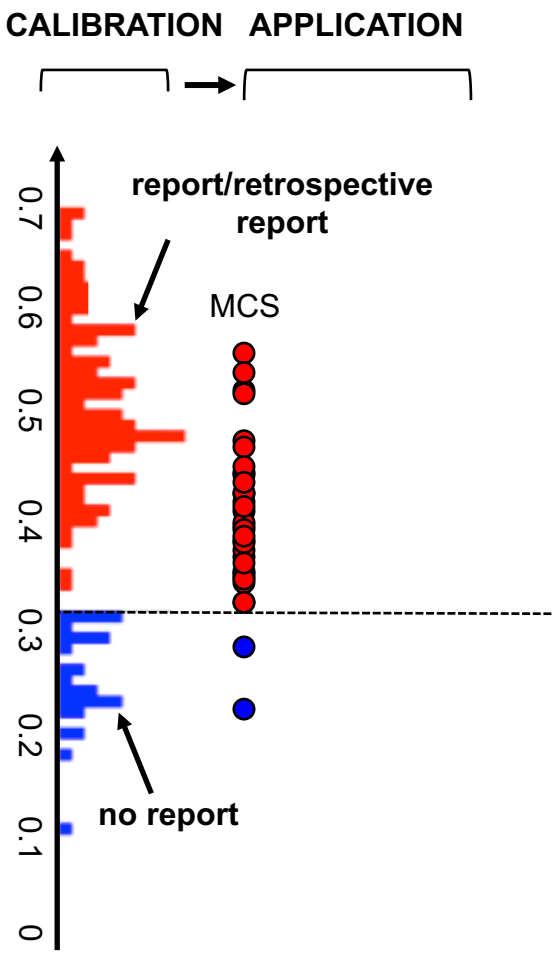
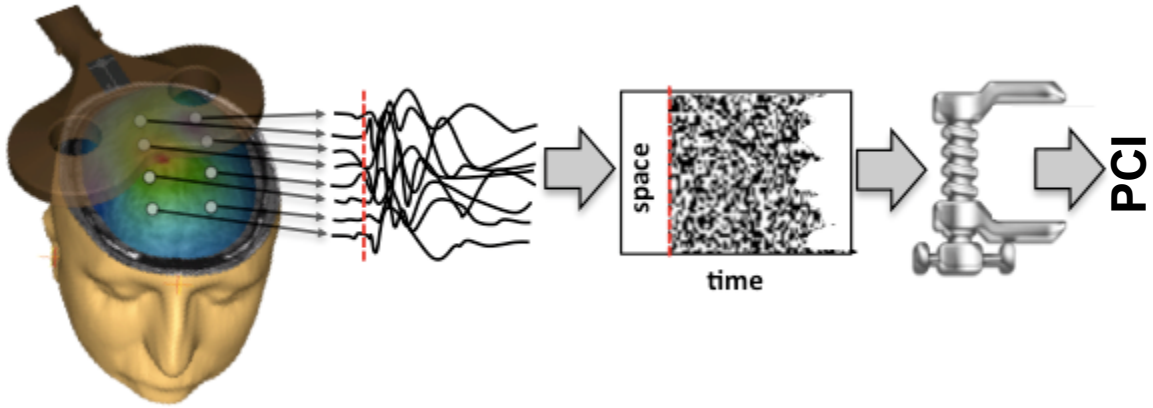
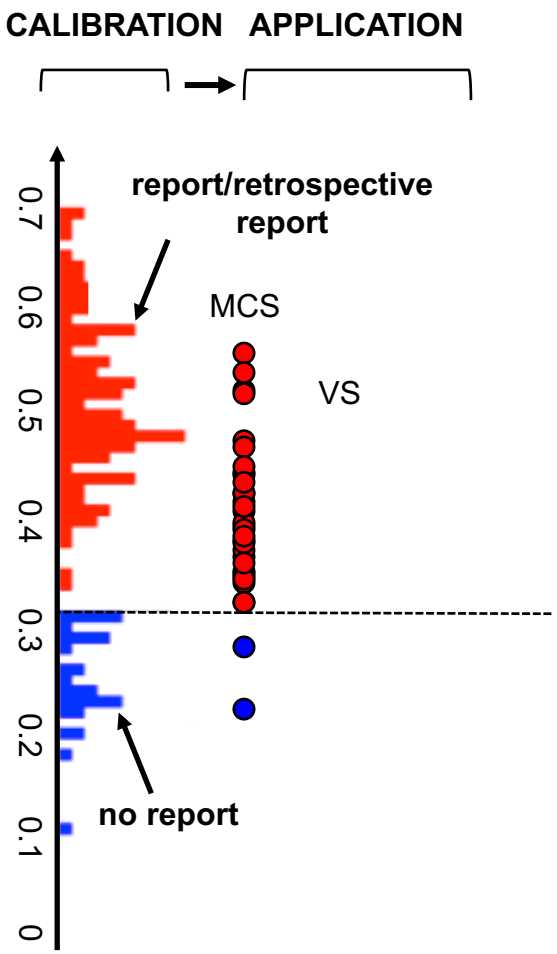


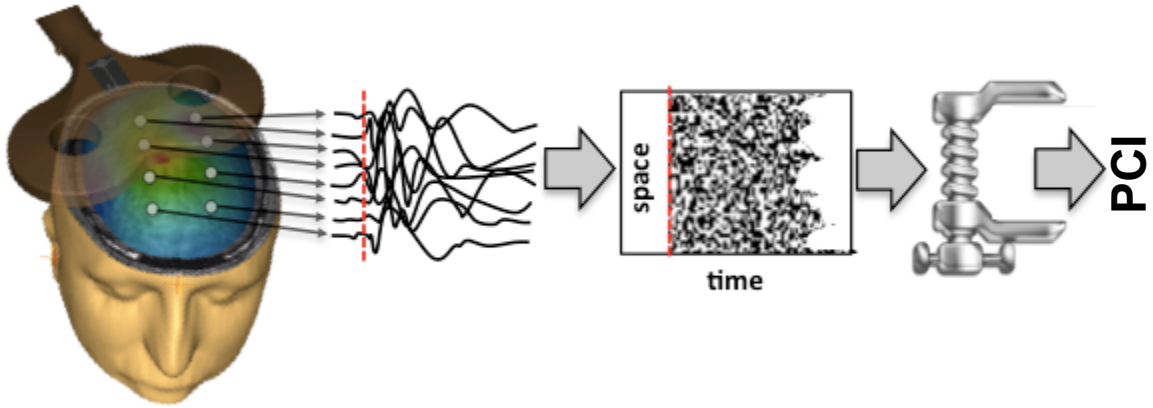


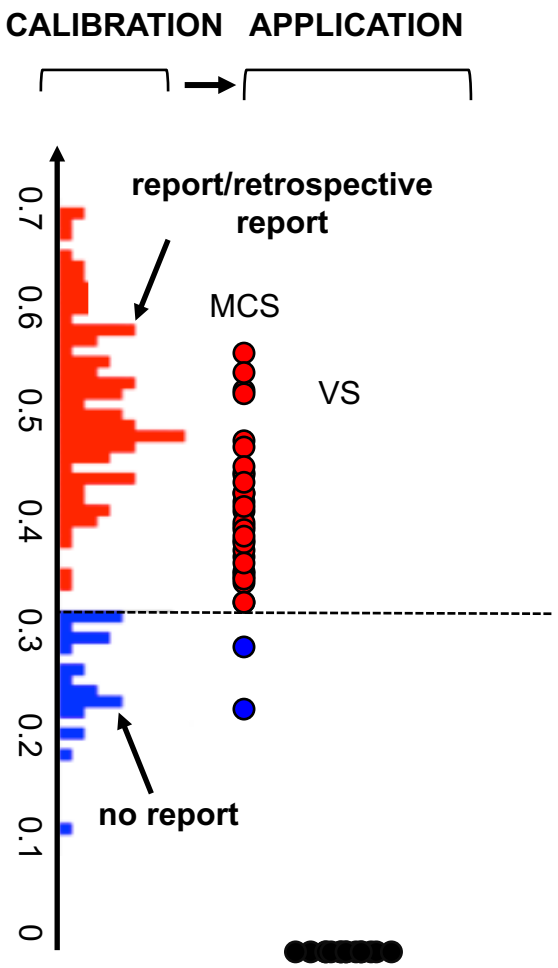
Casarotto et al *Annals of Neurology 2016*



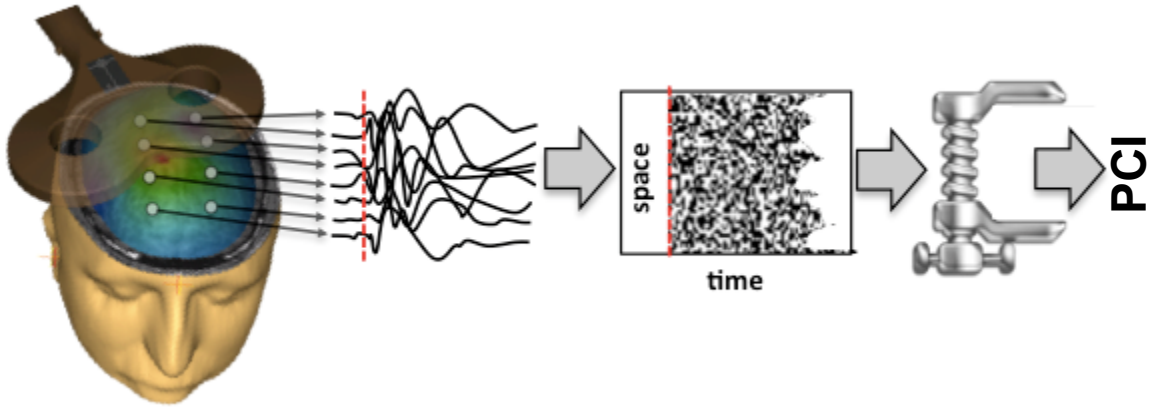


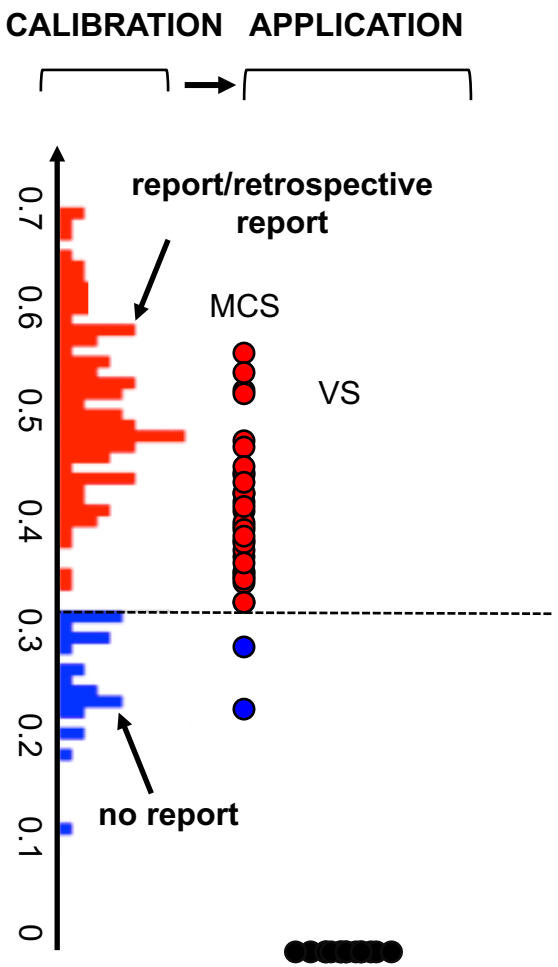
Casarotto et al *Annals of Neurology 2016*



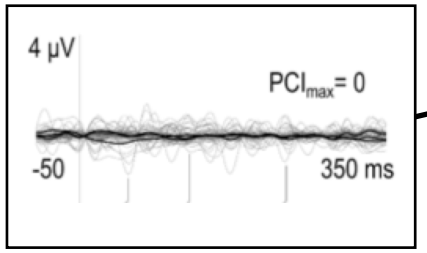


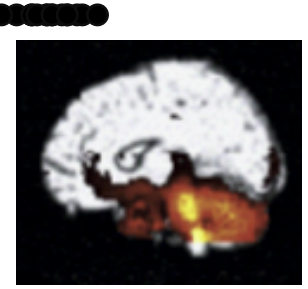
Casarotto et al *Annals of Neurology 2016*

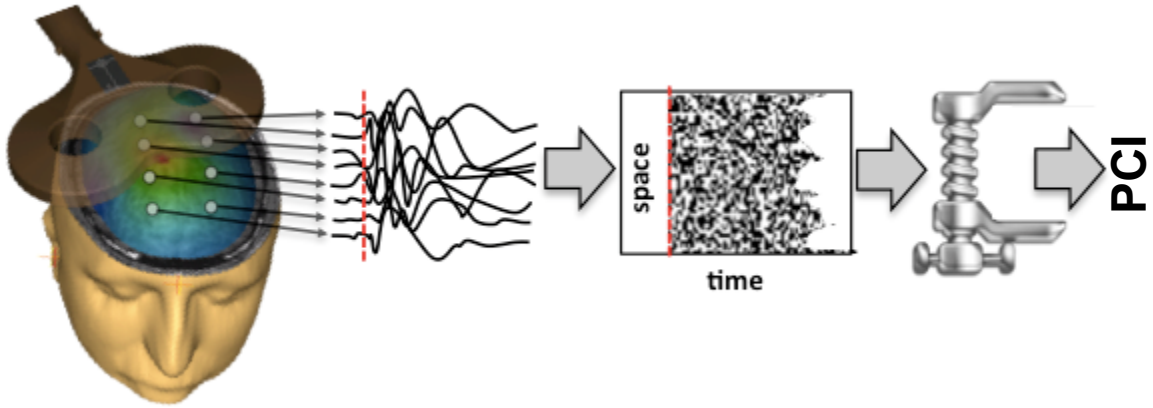

space
time
PCI

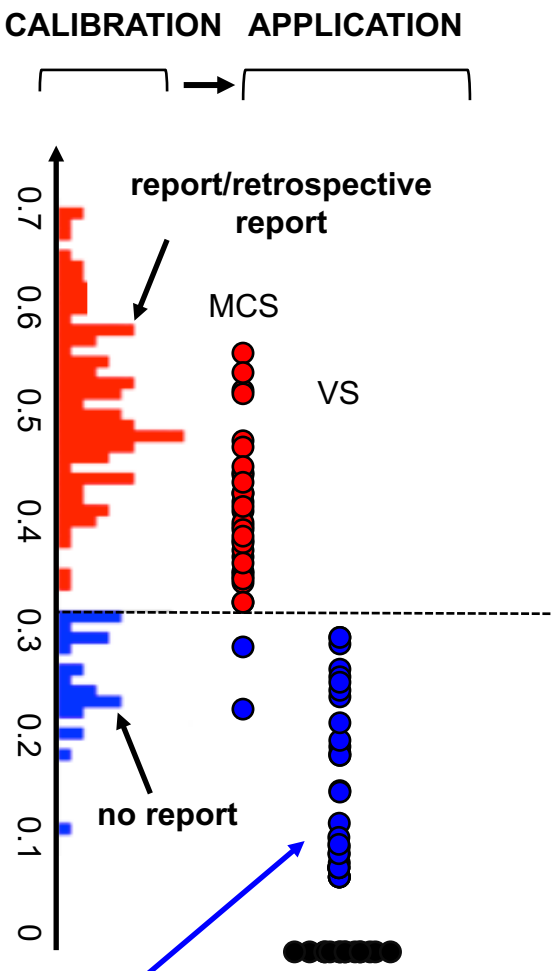

CALIBRATION
APPLICATION
report/retrospective report
MCS
VS
no report
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0

no response

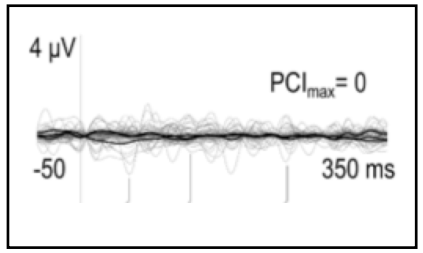

4 µV
PCI$_{max}$= 0
-50
350 ms



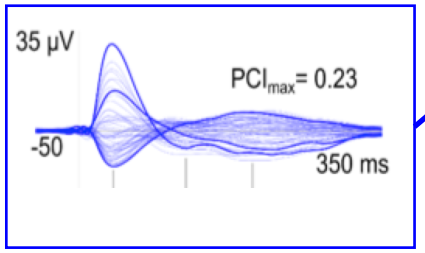


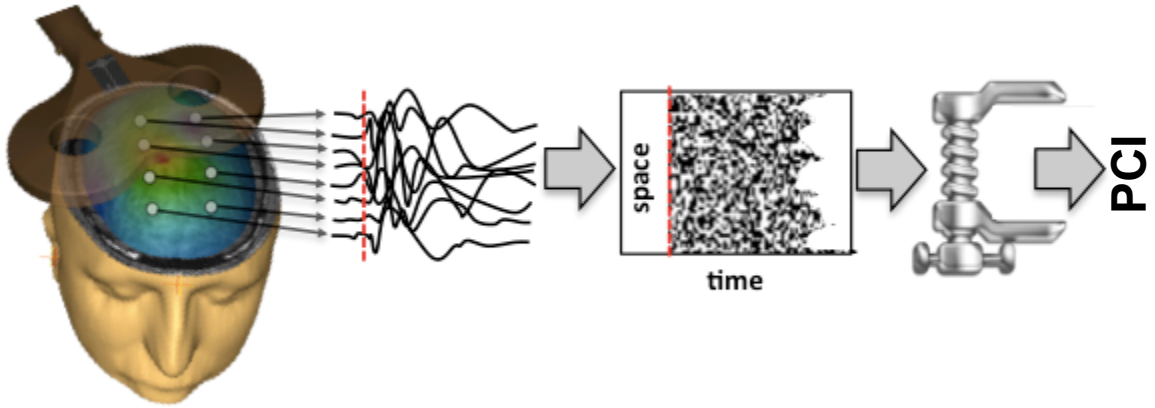


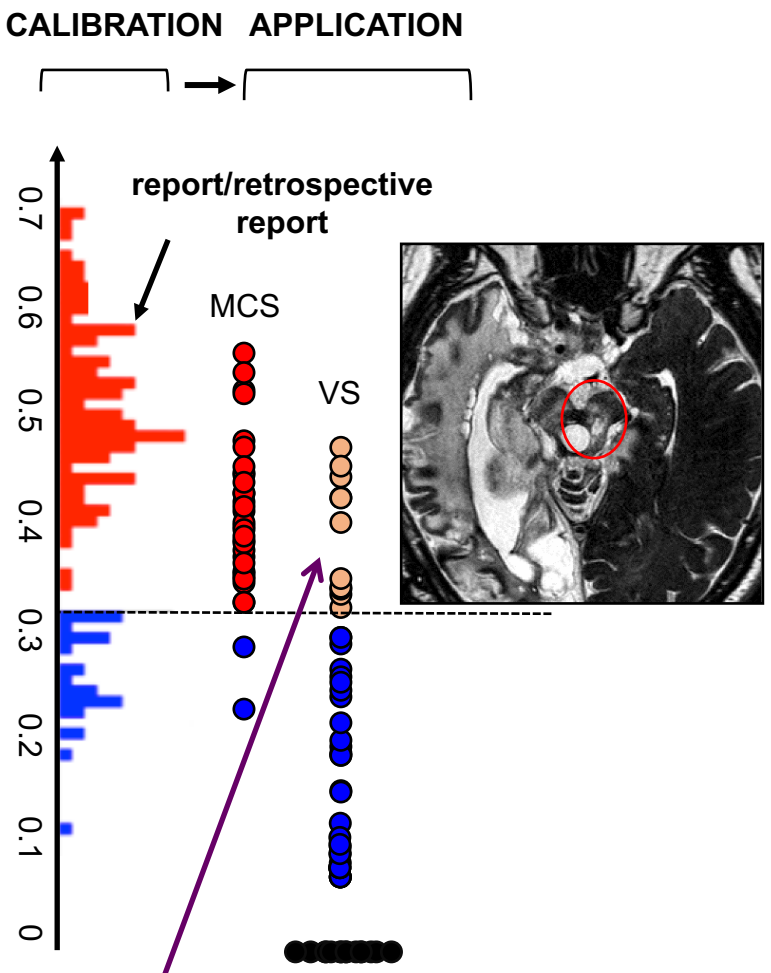
no response

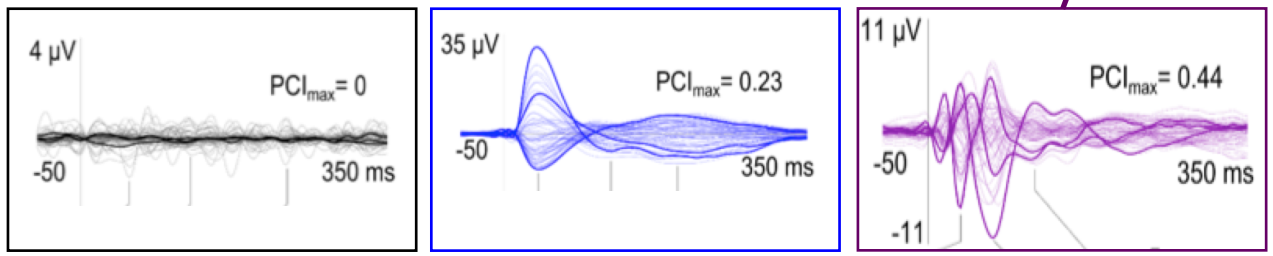


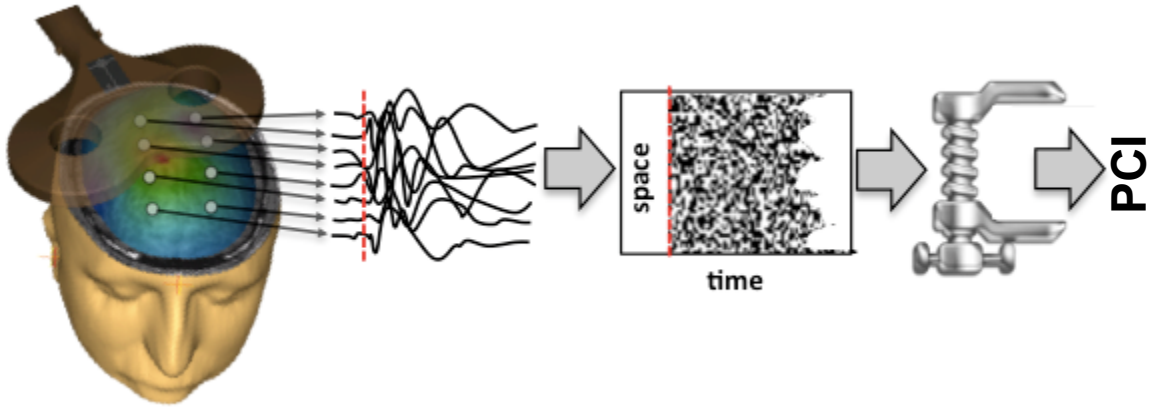
low-complexity

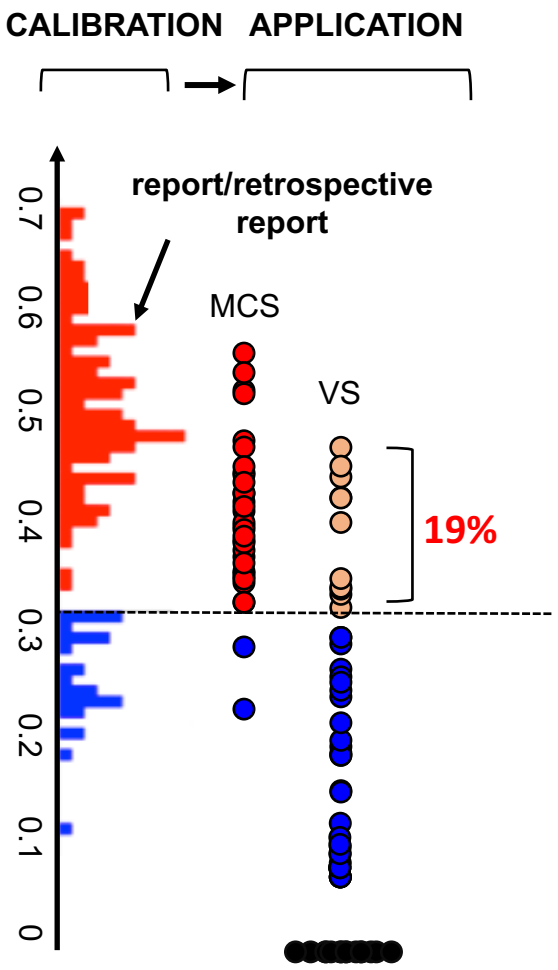



space
time
PCI

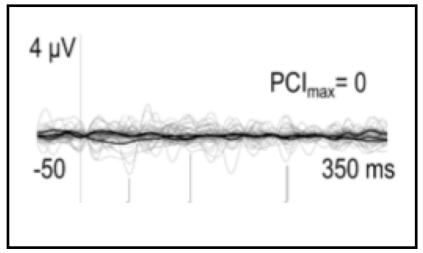

CALIBRATION
APPLICATION
report/retrospective report
MCS
VS
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0


no response
low-complexity
4 µV
PCI$_{max}$= 0
-50
350 ms
35 µV
PCI$_{max}$= 0.23
-50
350 ms
11 µV
PCI$_{max}$= 0.44
-50
350 ms
-11

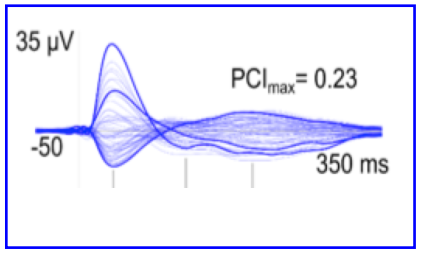




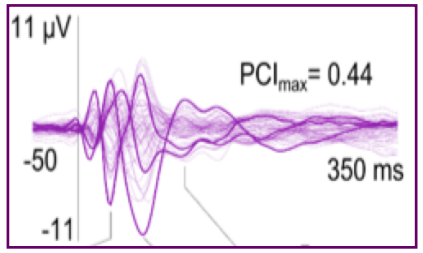
no response

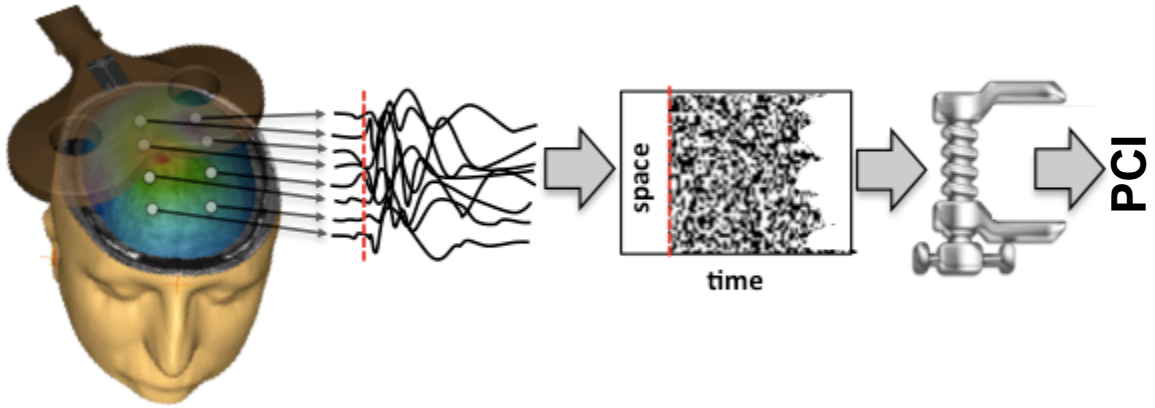


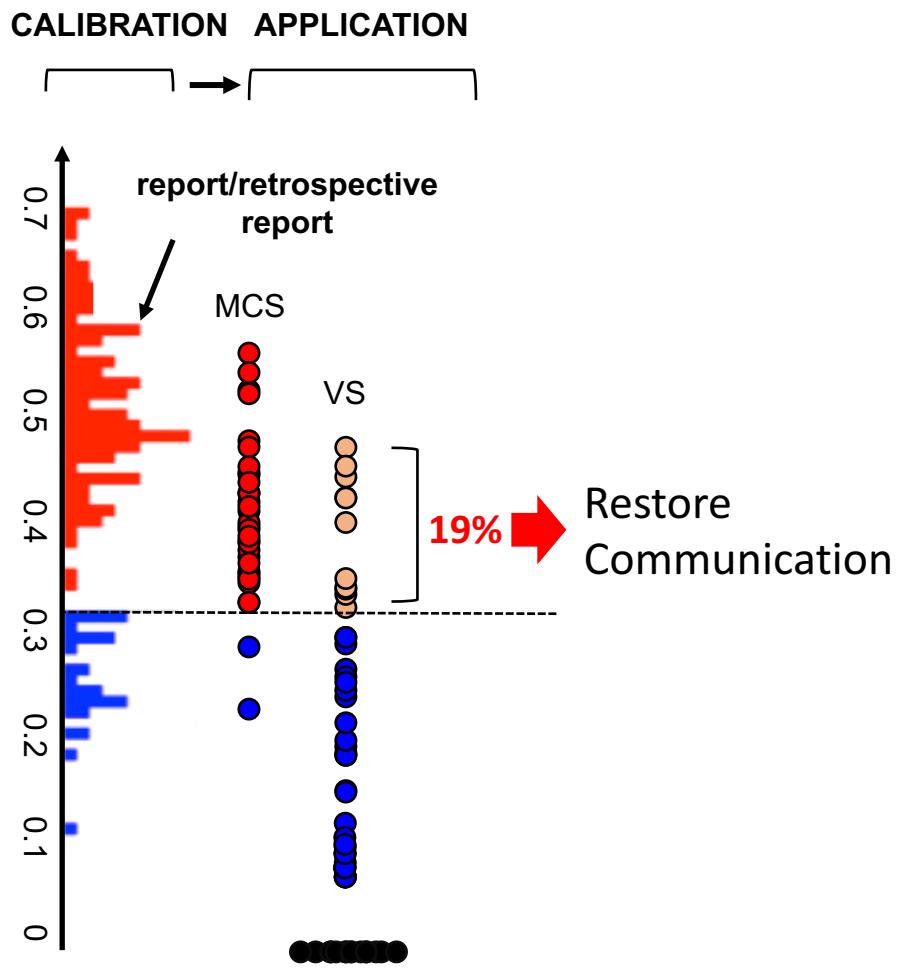
low-complexity

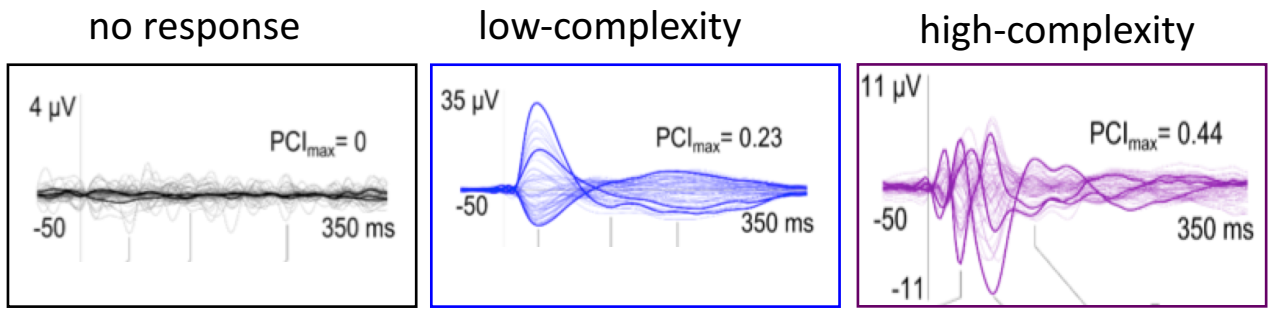


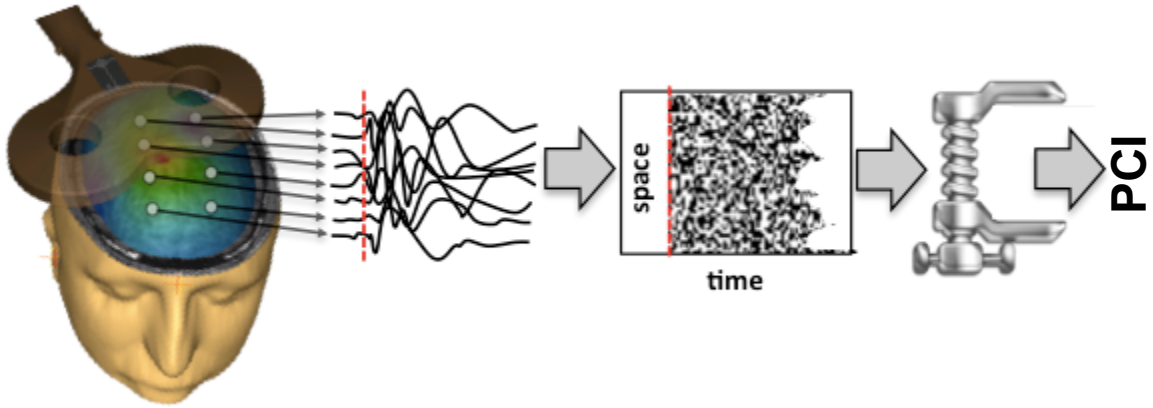
high-complexity

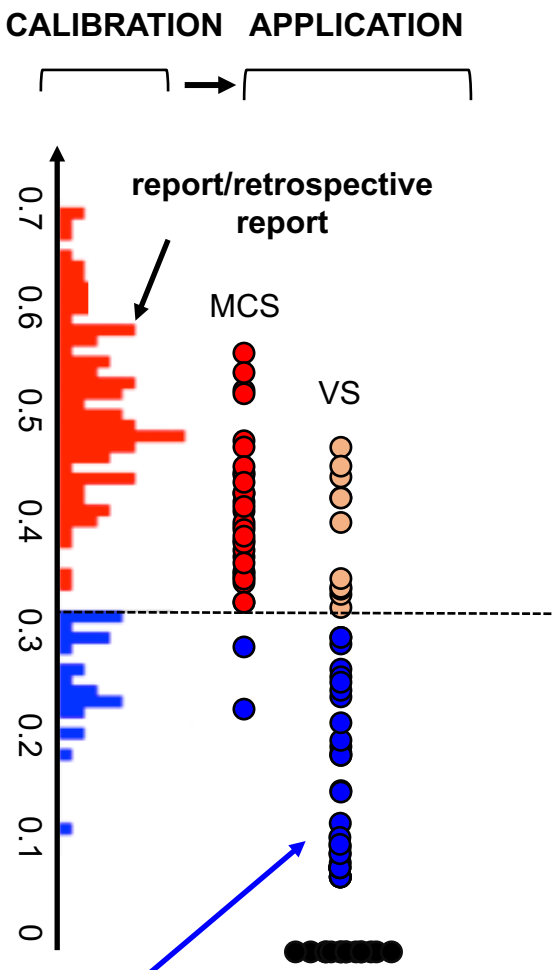



space
time
PCI

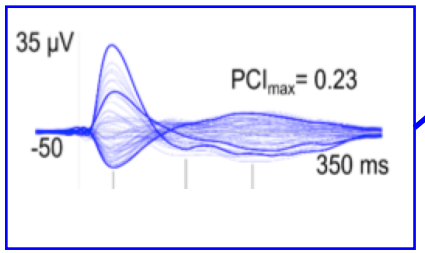

CALIBRATION
APPLICATION
report/retrospective report
MCS
VS
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
19%
Restore Communication


no response
low-complexity
high-complexity
4 µV
PCImax= 0
-50
350 ms
35 µV
PCImax= 0.23
-50
350 ms
11 µV
PCImax= 0.44
-50
-11
350 ms

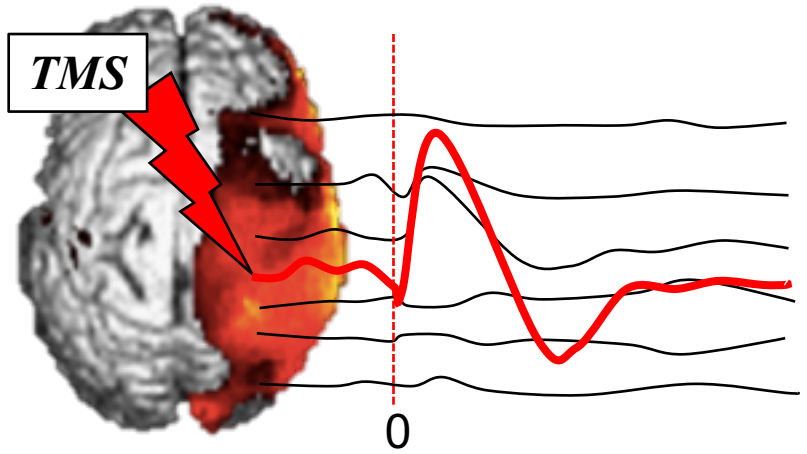




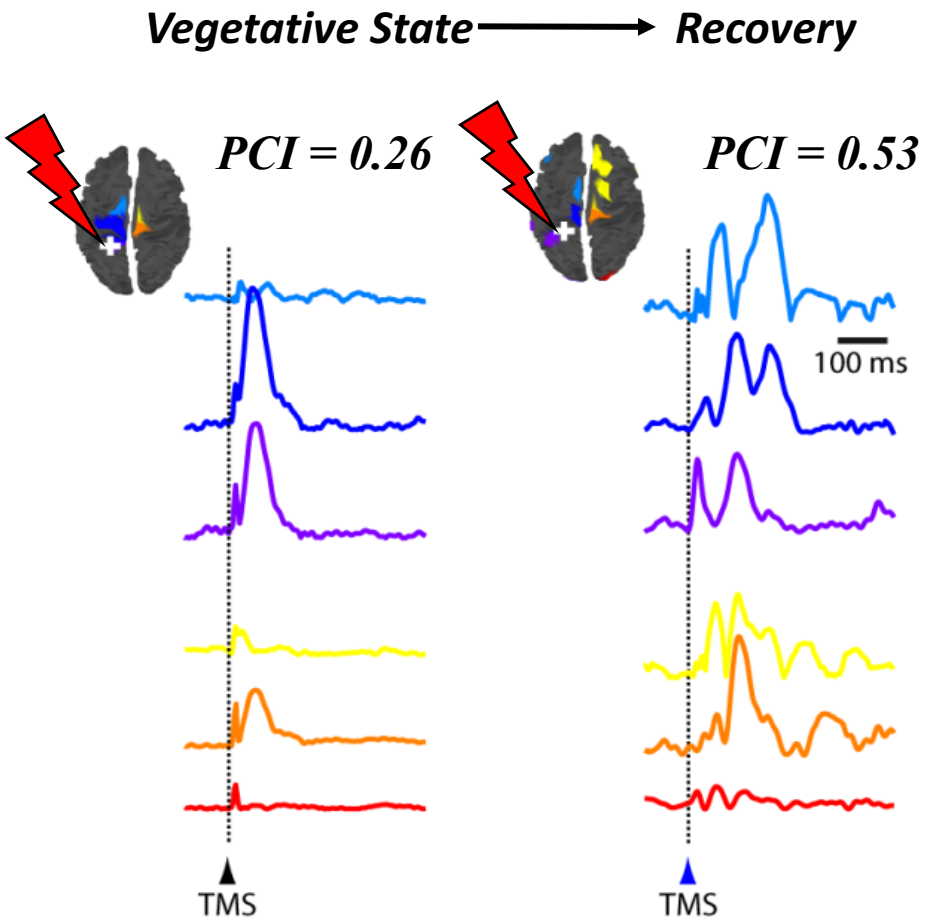
low-complexity



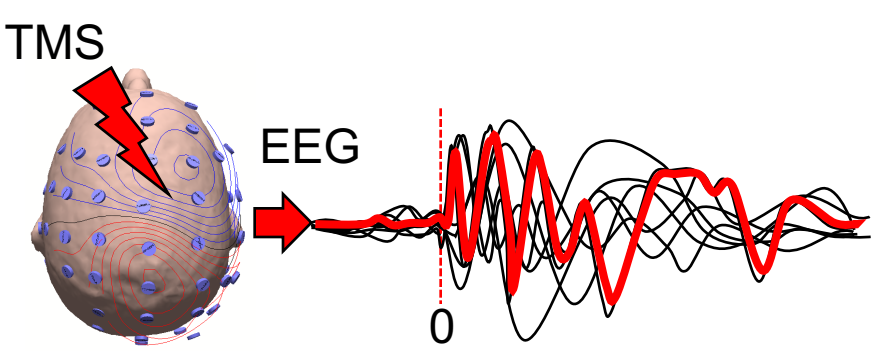
Structurally intact, metabolically active,…



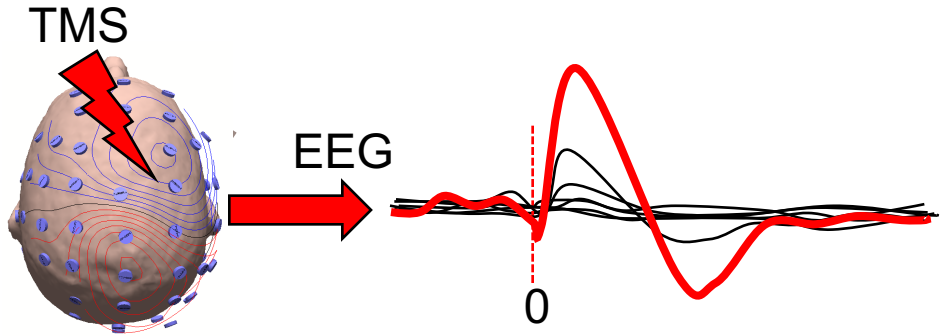
…but stuck in low-complexity



Wakefulness

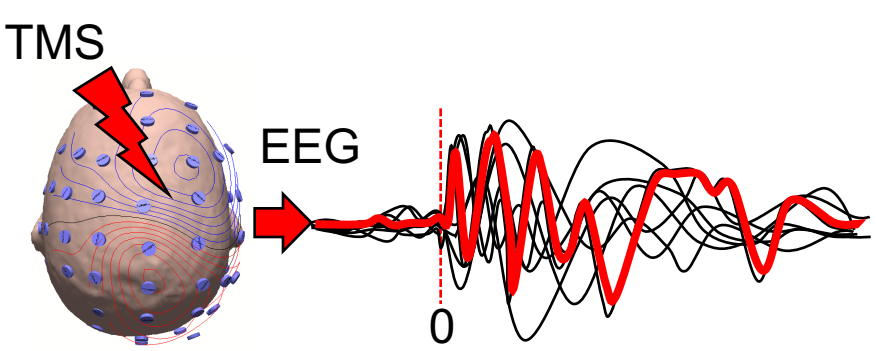


Sleep

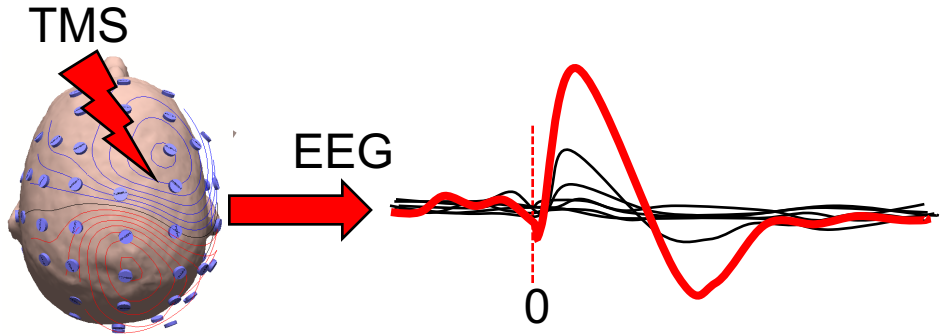


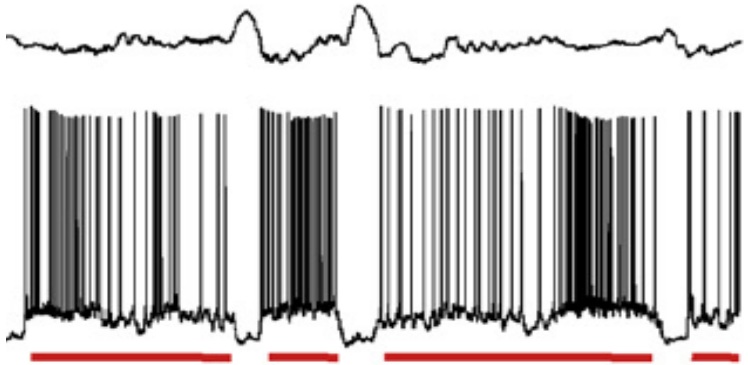
Steriade et al., *J. Neurophys*. 1993

Wakefulness

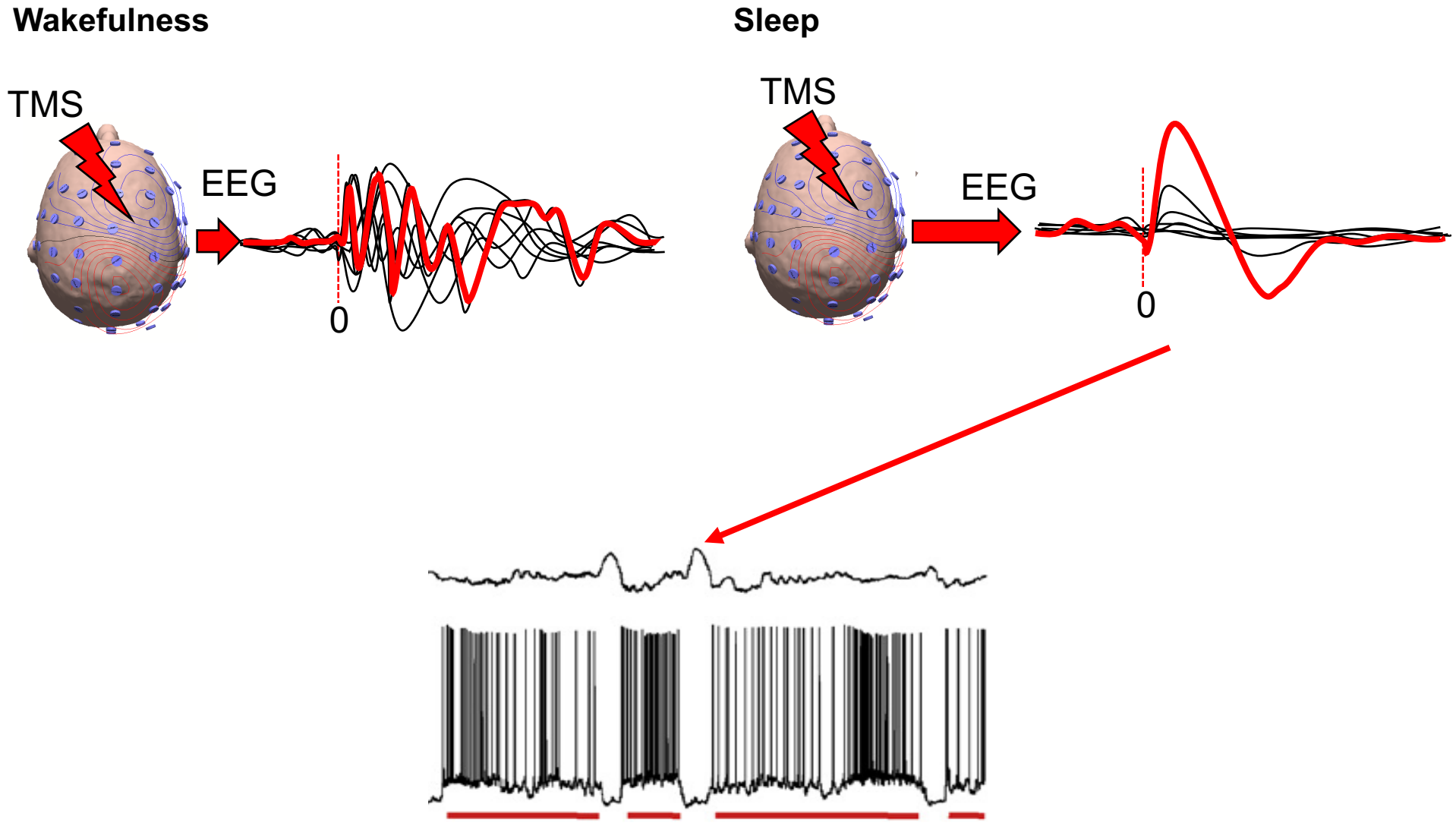


Sleep



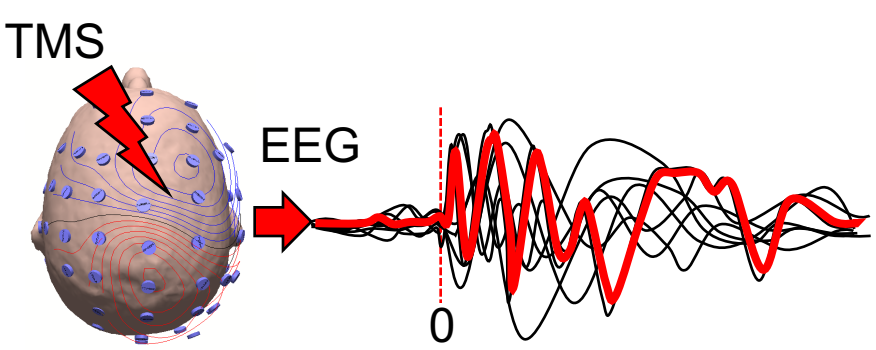


Steriade et al., *J. Neurophys*. 1993

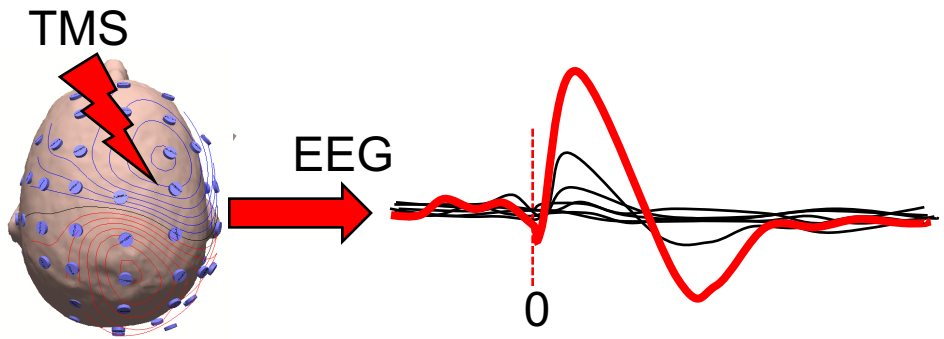


Steriade et al., *J. Neurophys*. 1993

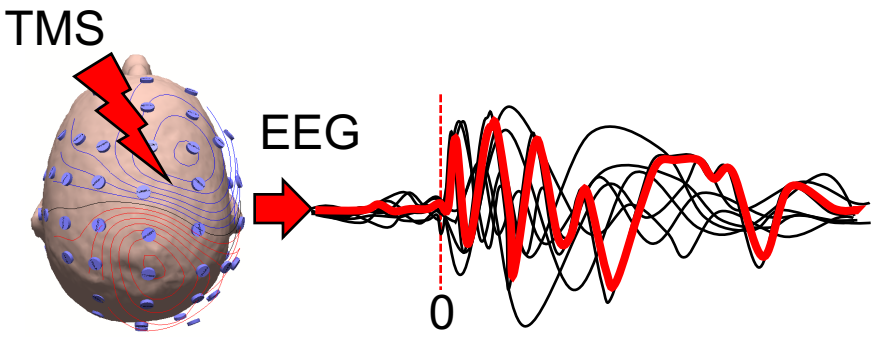
Wakefulness



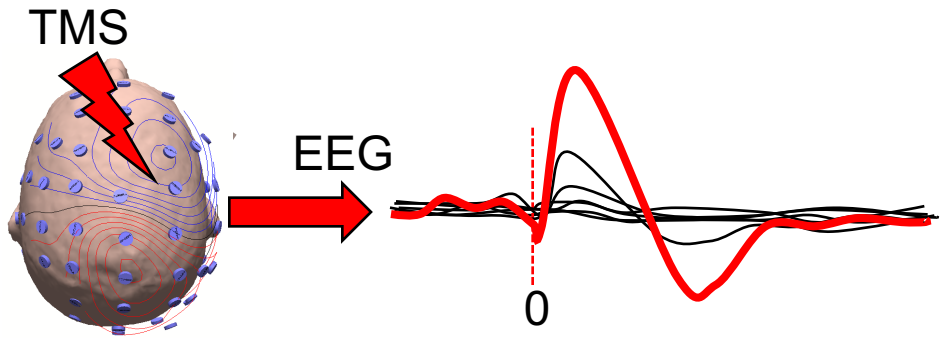
Sleep

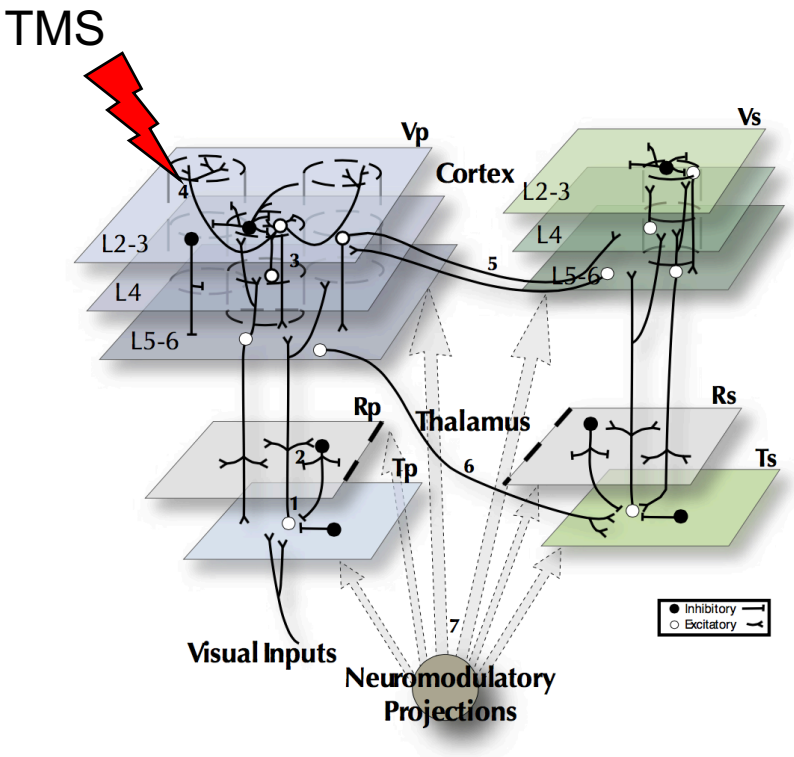


Wakefulness



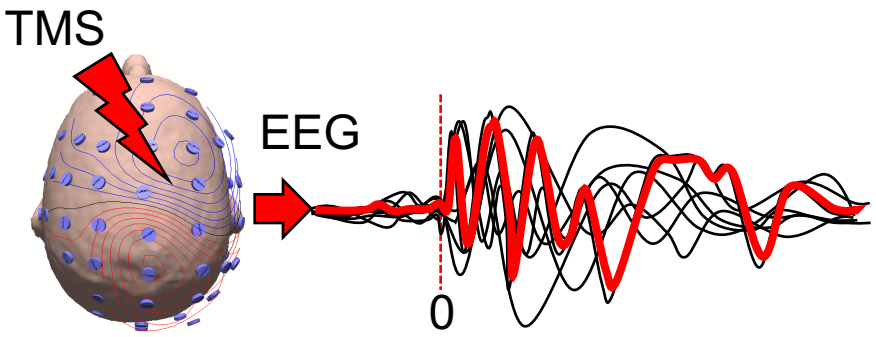
Sleep



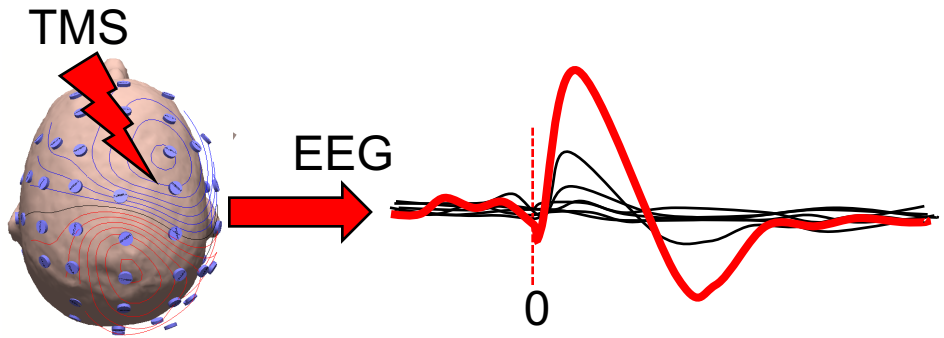


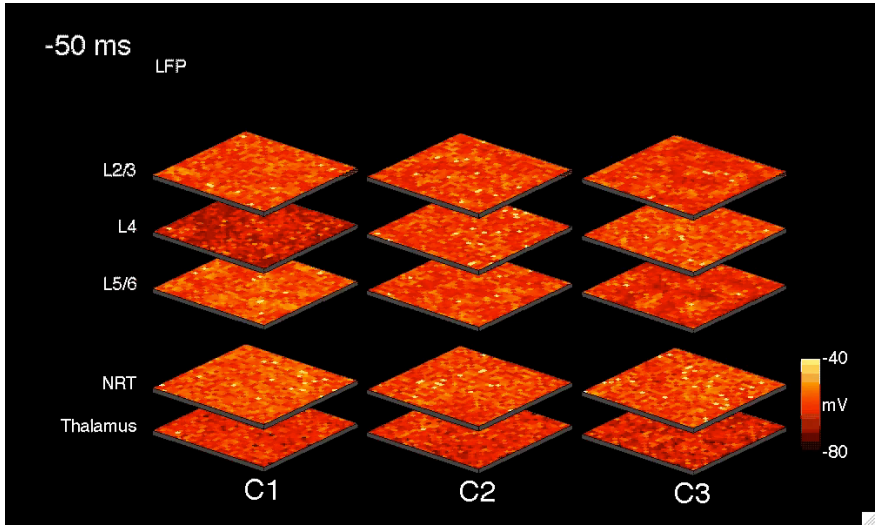
Esser et al., *J. Neurophys*. 2009

Wakefulness



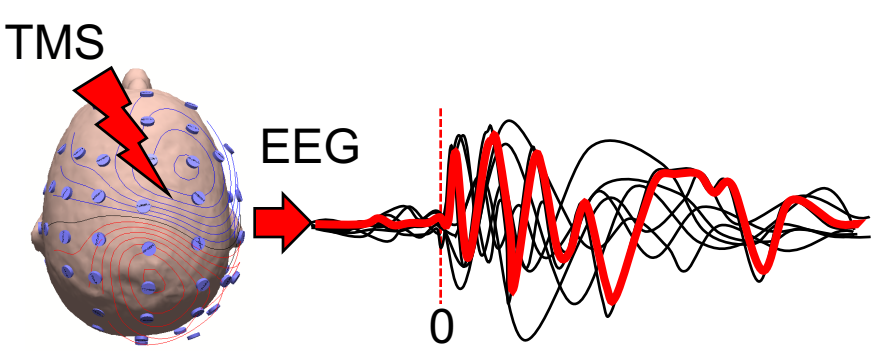
Sleep



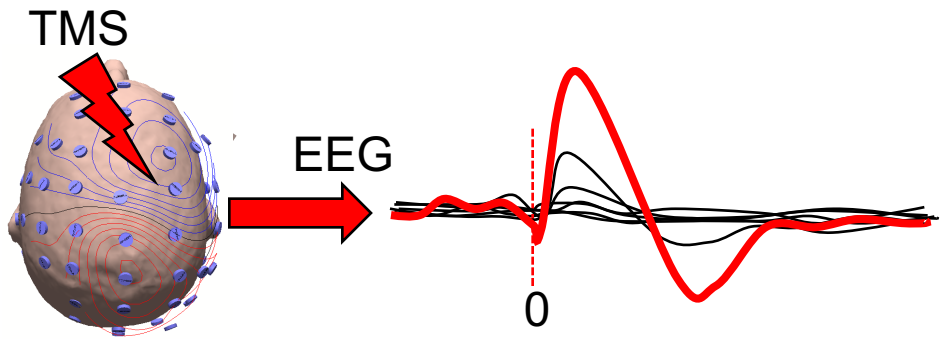


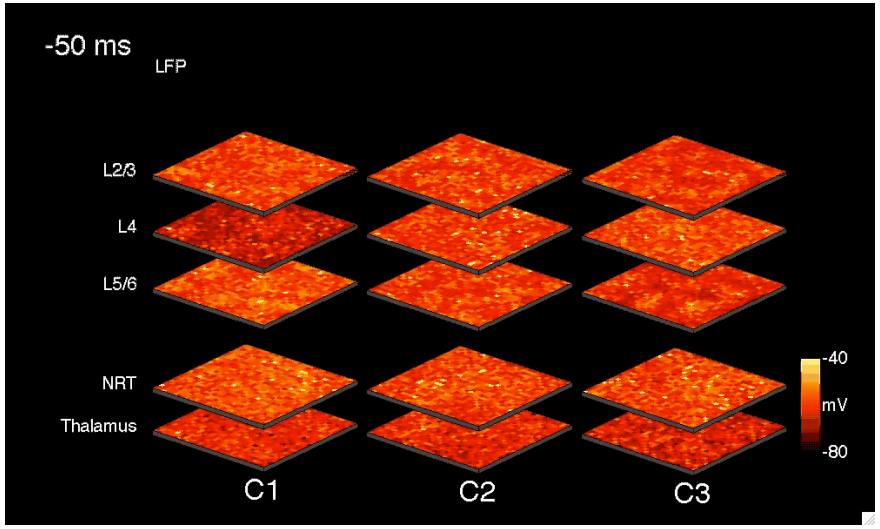
Esser et al., *J. Neurophys*. 2009

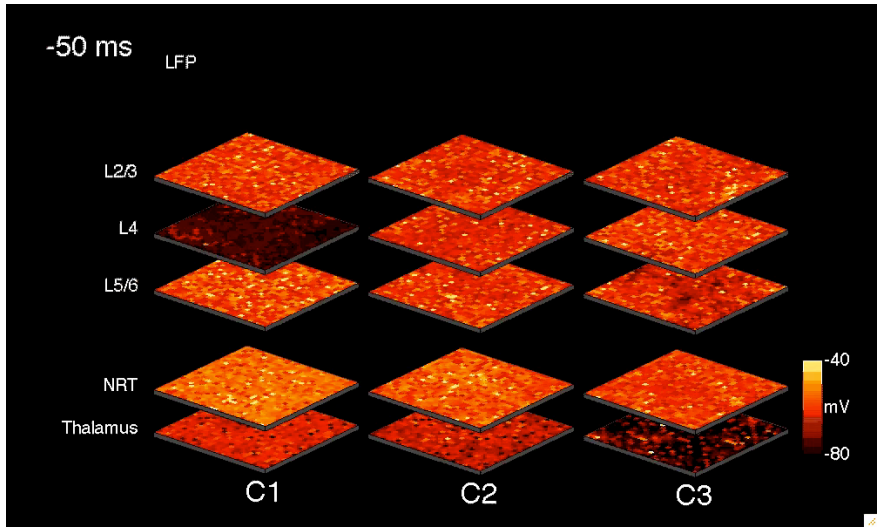
Wakefulness



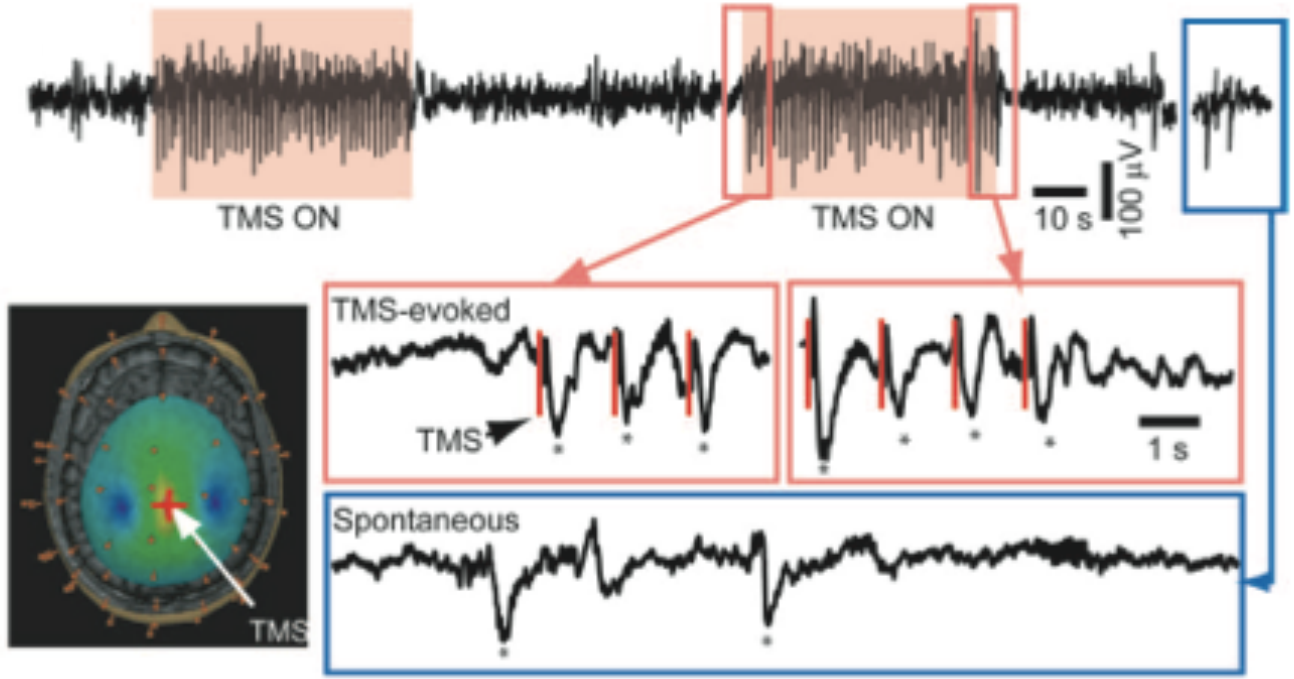
Sleep



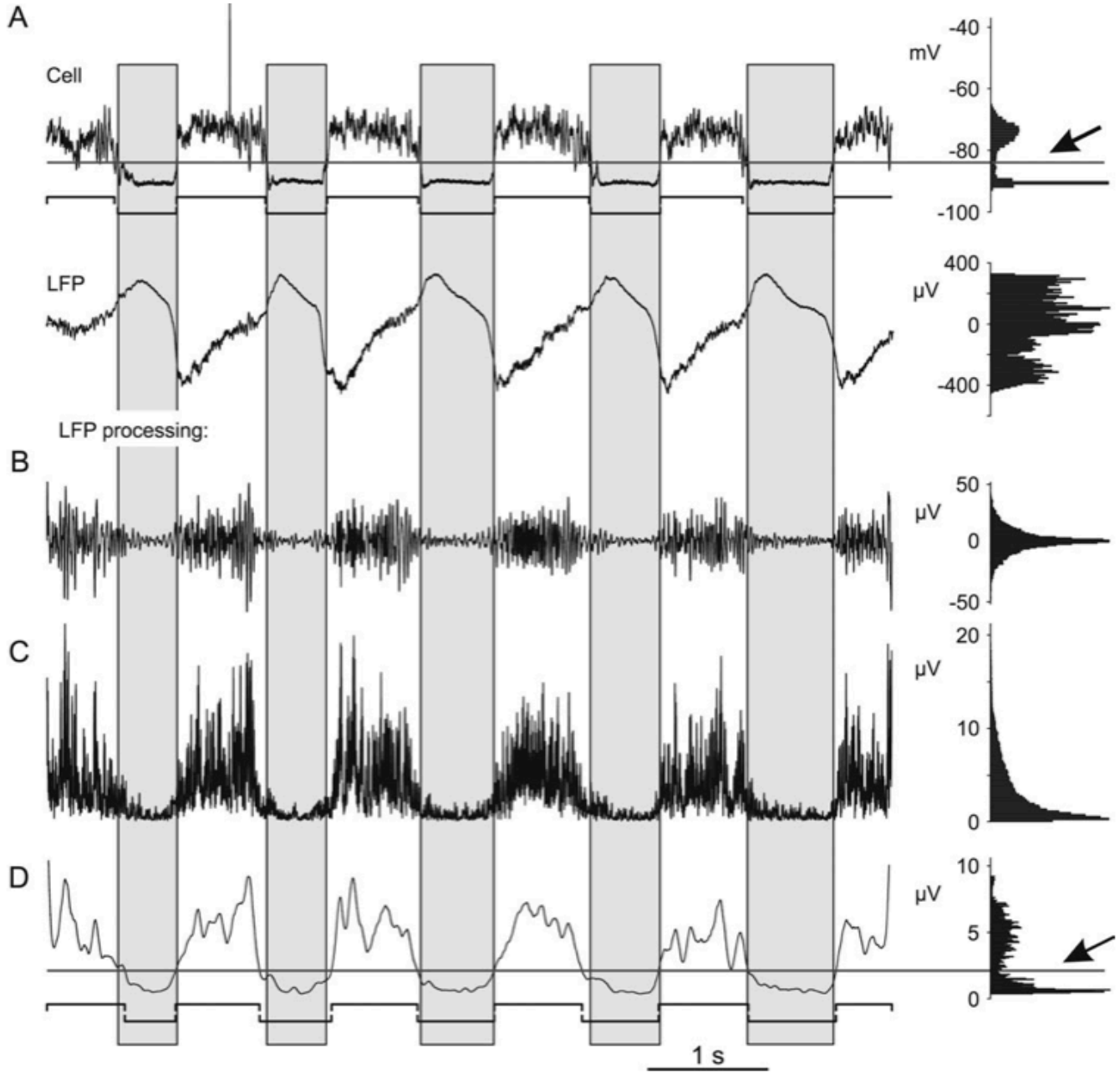




Esser et al., *J. Neurophys*. 2009



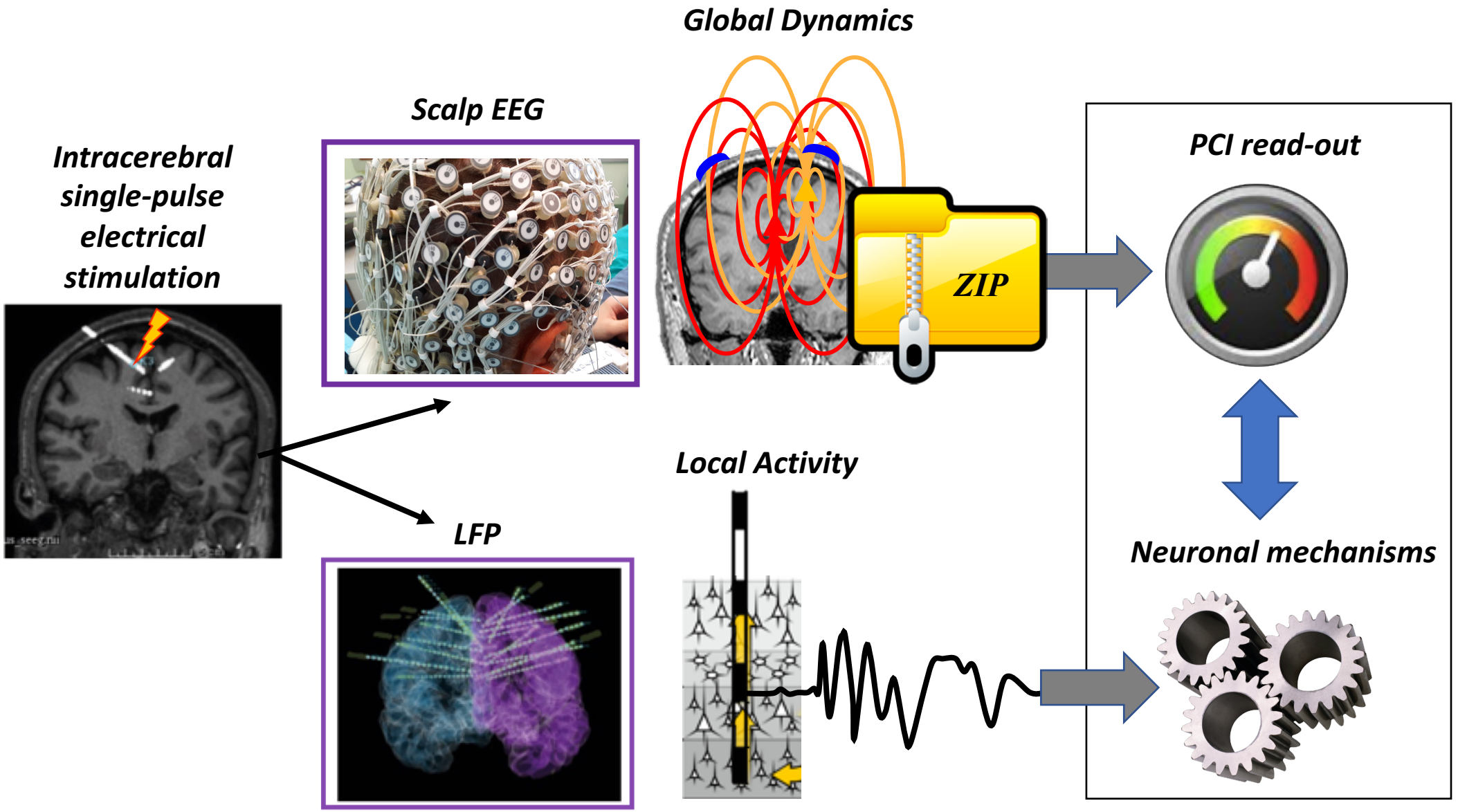
Massimini et al., *PNAS* 2007; Massimini et al., *Eur J. Neurosci*. 2010

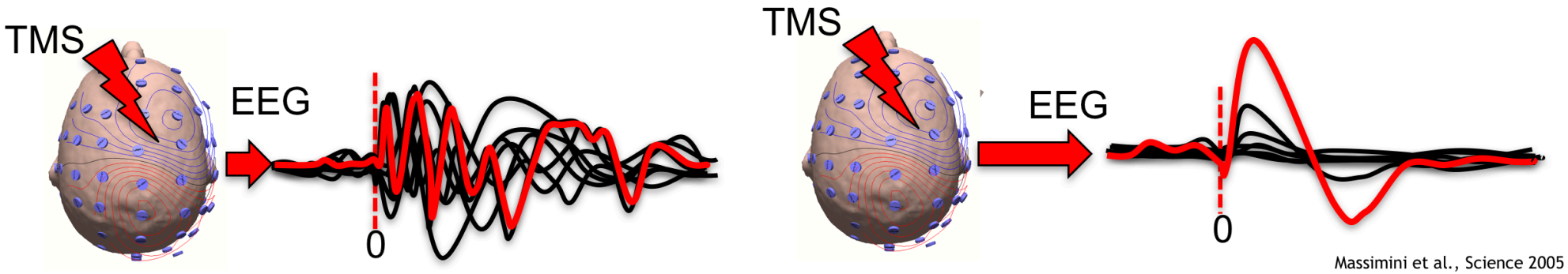


Mukowsky et al., Cereb Cortex, 2007

Understanding the mechanismsm of loss and recovery of complexity

Understanding the mechanismsm of loss and recovery of complexity



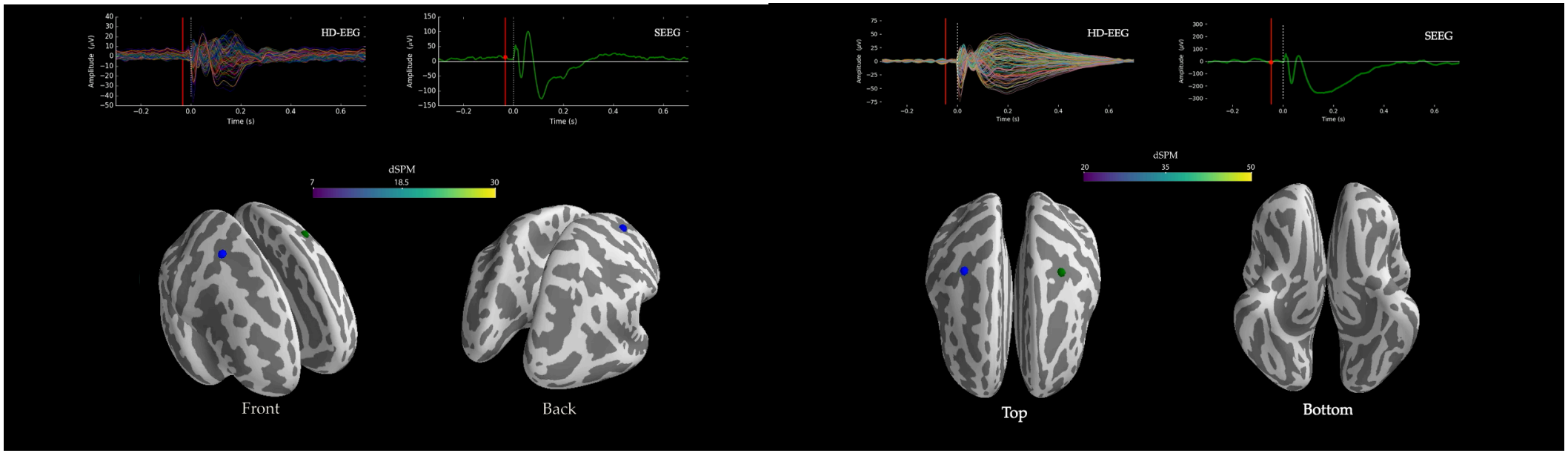


Massimini et al., Science 2005

INTRACRANIAL

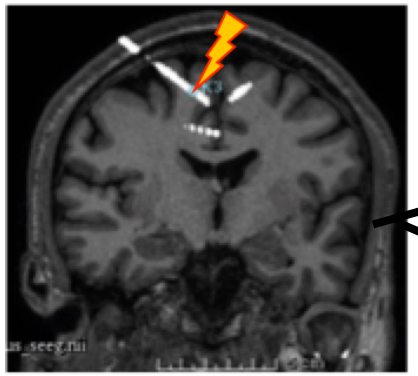
Wakefulness

Sleep



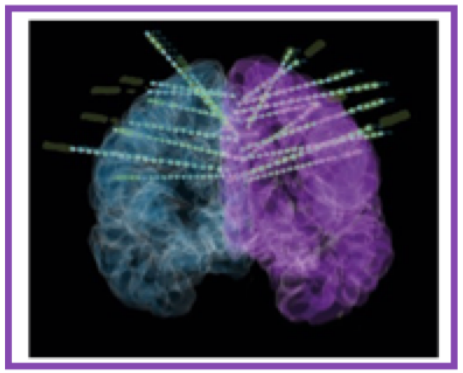
Understanding the mechanismsm of loss and recovery of complexity: a multi-scale approach

Intracerebral single-pulse electrical stimulation

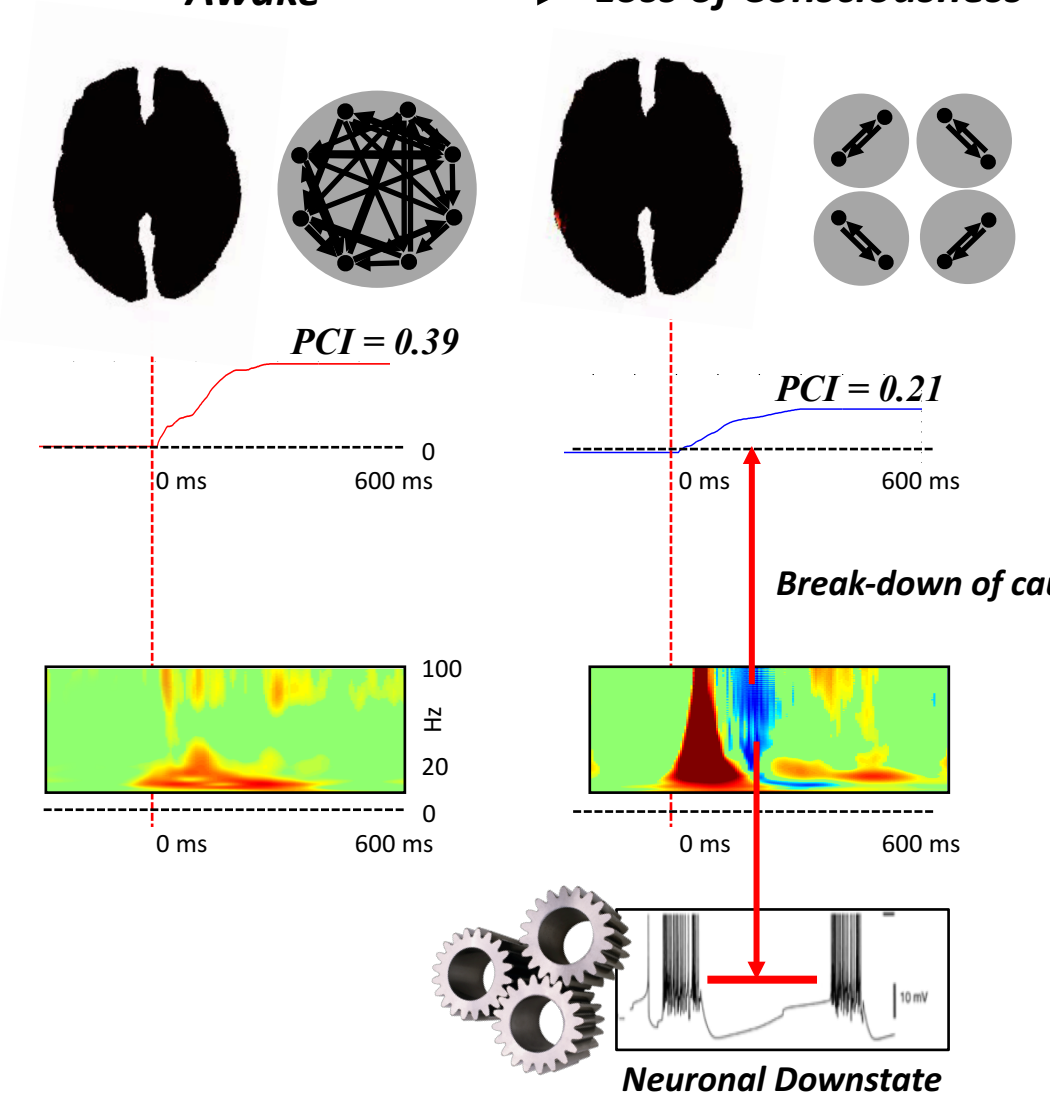


Scalp EEG

LFP

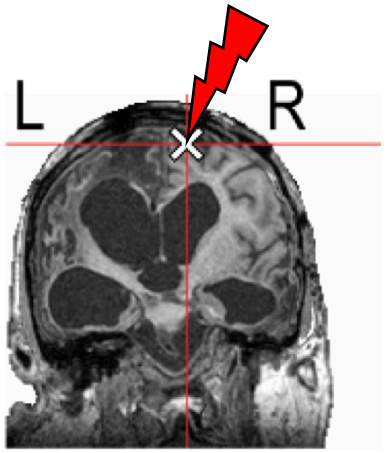


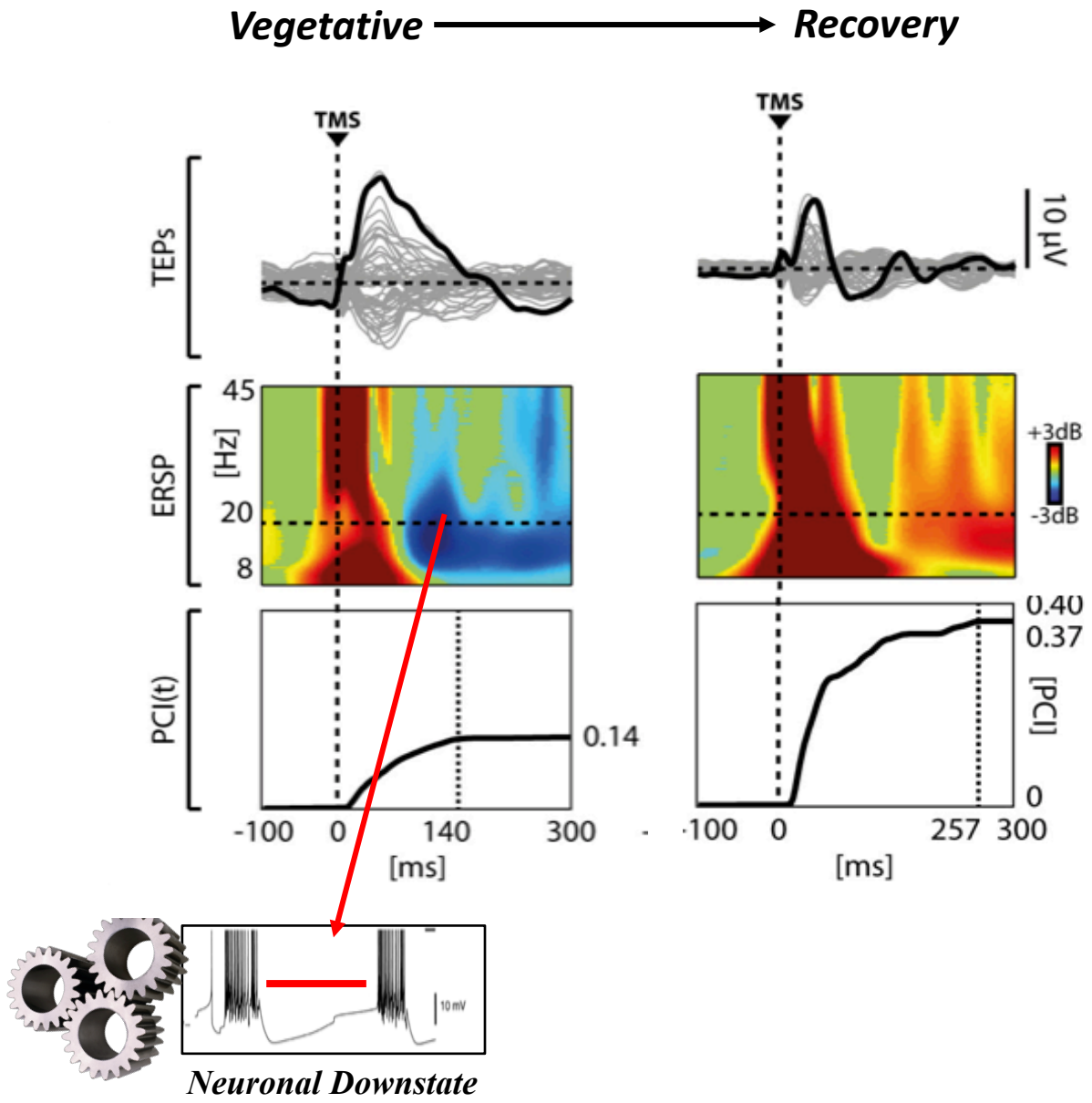
Awake → ***Loss of Consciousness***



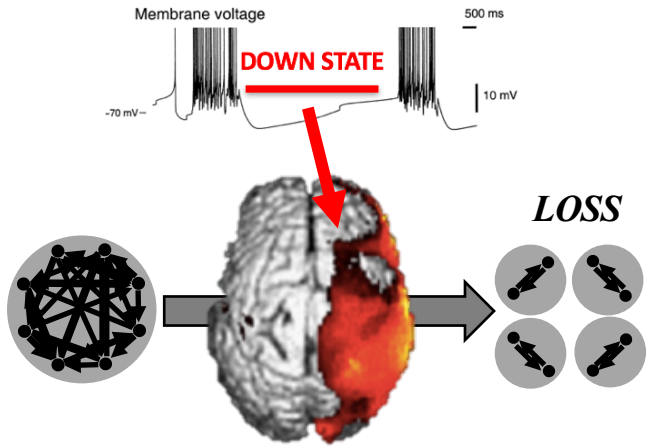
Neuronal Downstate

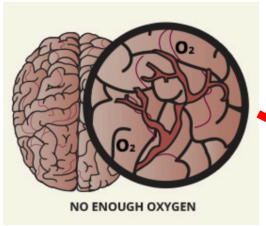
Pigorini et al., Neuroimage 2015



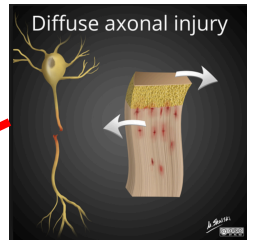


Rosanova et al, *in preparation*


Membrane voltage
500 ms
DOWN STATE
10 mV
-70 mV
LOSS

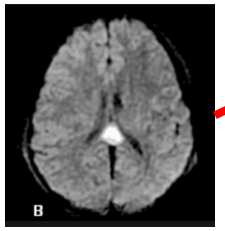


hypoxia

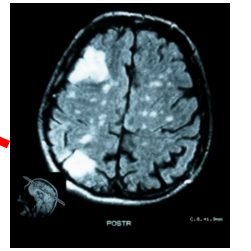


axonal Injury

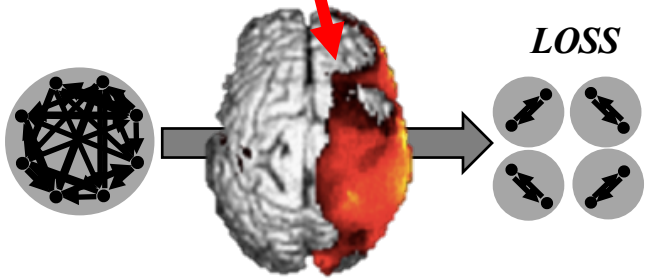
1. ↑ *activity dependent K+ currents*
2. ↑ *ADP dependent K+ currents*
3. *Shift to bursting mode*
4. ↑ *Inhibition/excitation*



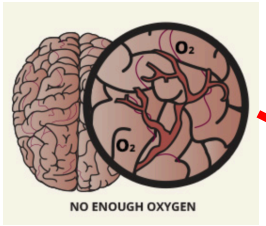
brainstem lesion



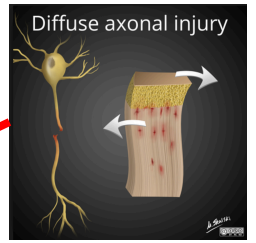
multifocal Injury



McCormick 1992
Steriade et al., 1993
Compte et al., 2003
Sanchez-Vives et al 2000
Timofeev et al., 2000
Destexhe et al, 2007
Funck et al, 2017
Zucca et al., 2017



hypoxia



axonal Injury

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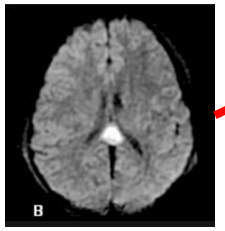
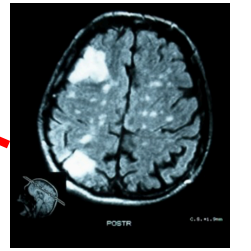


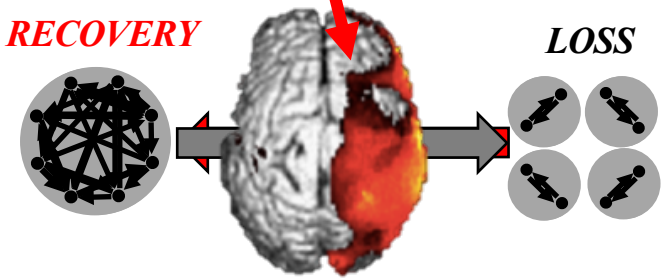
brainstem lesion



multifocal Injury

RECOVERY

LOSS



While structural lesions and disconnections cannot be reversed, it may still be possible to restore complexity by acting pharmacologically on neuronal bistability

OXFORD

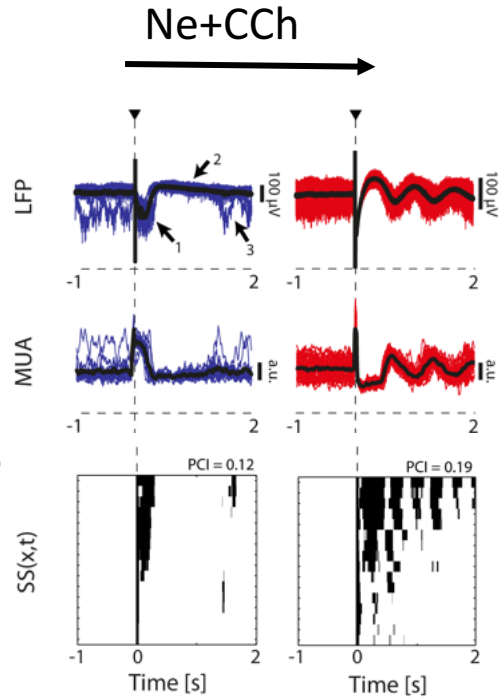
Cerebral Cortex, 2017; 1–10

doi: 10.1093/cercor/bhx122
Original Article

ORIGINAL ARTICLE

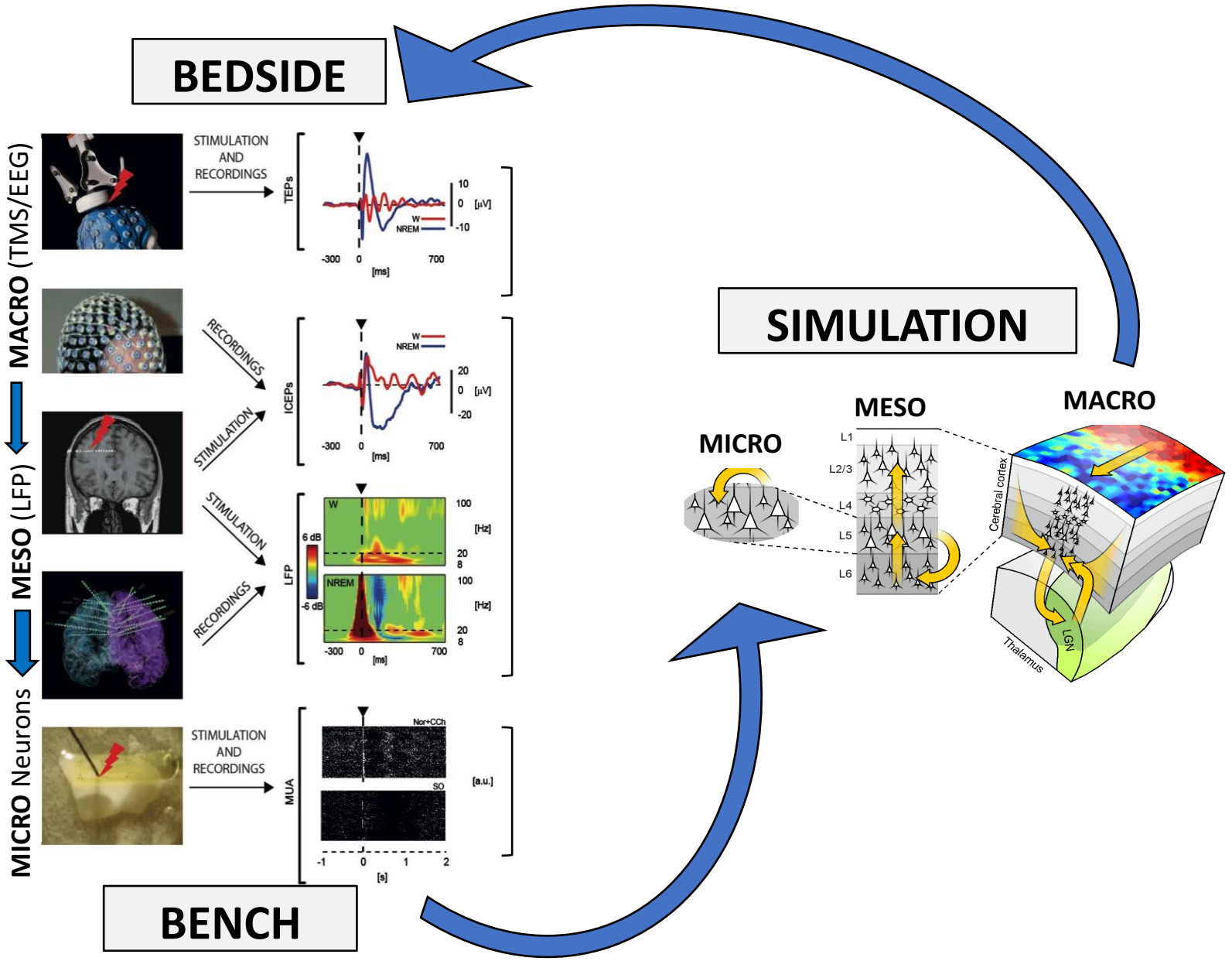
Bistability, Causality, and Complexity in Cortical Networks: An In Vitro Perturbational Study

Mattia D'Andola[1], Beatriz Rebollo[1], Adenauer G. Casali[2], Julia F. Weinert[1], Andrea Pigorini[3], Rosa Villa[4,5], Marcello Massimini[3,6] and Maria V. Sanchez-Vives[1,7]



Mechanisms of Loss and Recovery of Brain Complexity: across scales, species and models

Human Brain Project



Thank you!

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