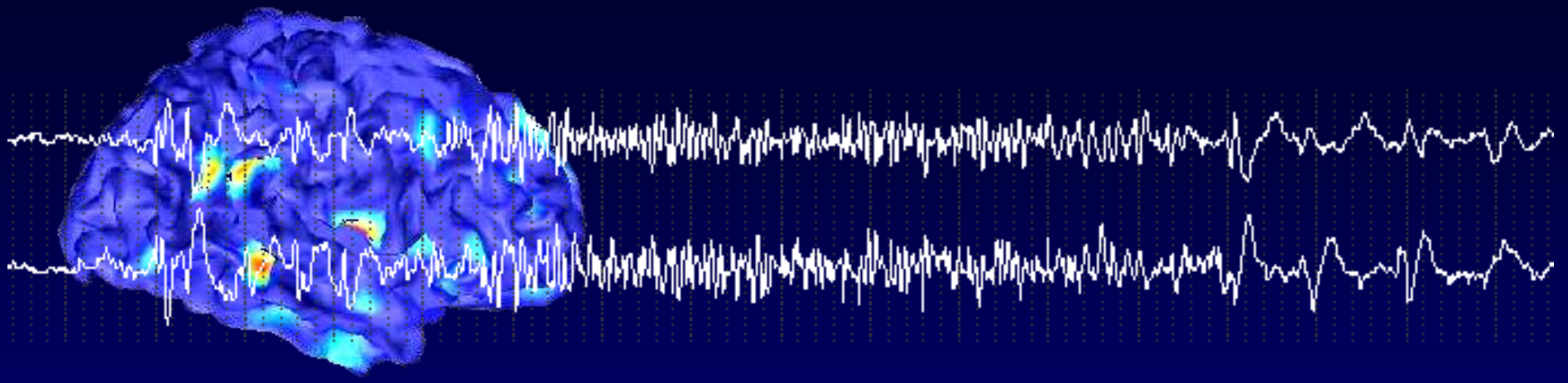


Resting state and neural networks in epilepsy

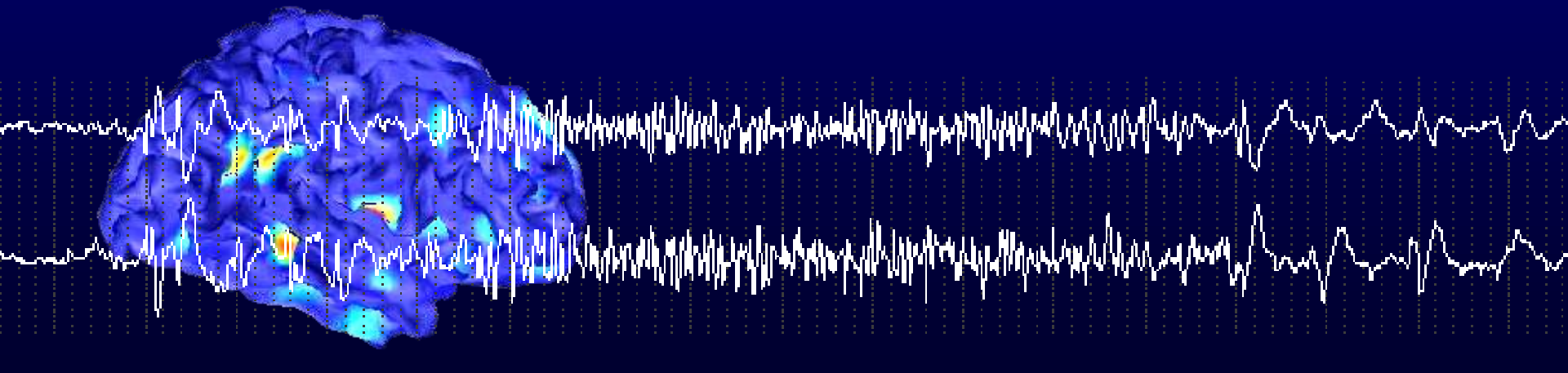
Scuola Superiore di Neurologia. CORSO RESIDENZIALE SIN
Update su diagnosi e monitoraggio delle epilessie
Genova, 24 - 25 febbraio 2015

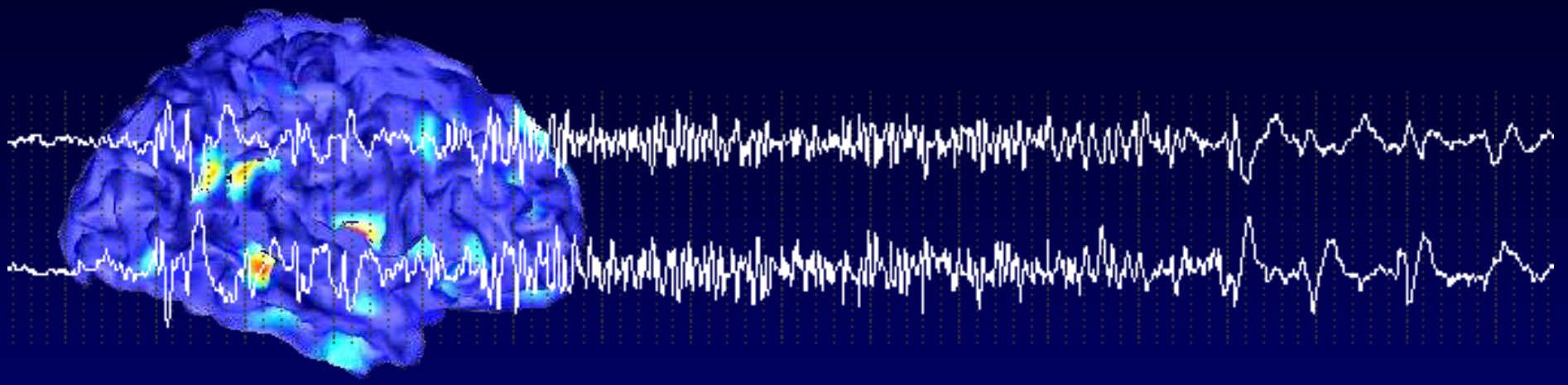
SOMMARIO

√ Epilepsy in the era of "modern network science": the contribution of EEG/fMRI

√ Resting state networks: brain never rests

√ From "phrenologic" to holistic dimension: functional and structural connectivity





Epilepsy in the era of “modern network science”: the contribution of EEG/fMRI

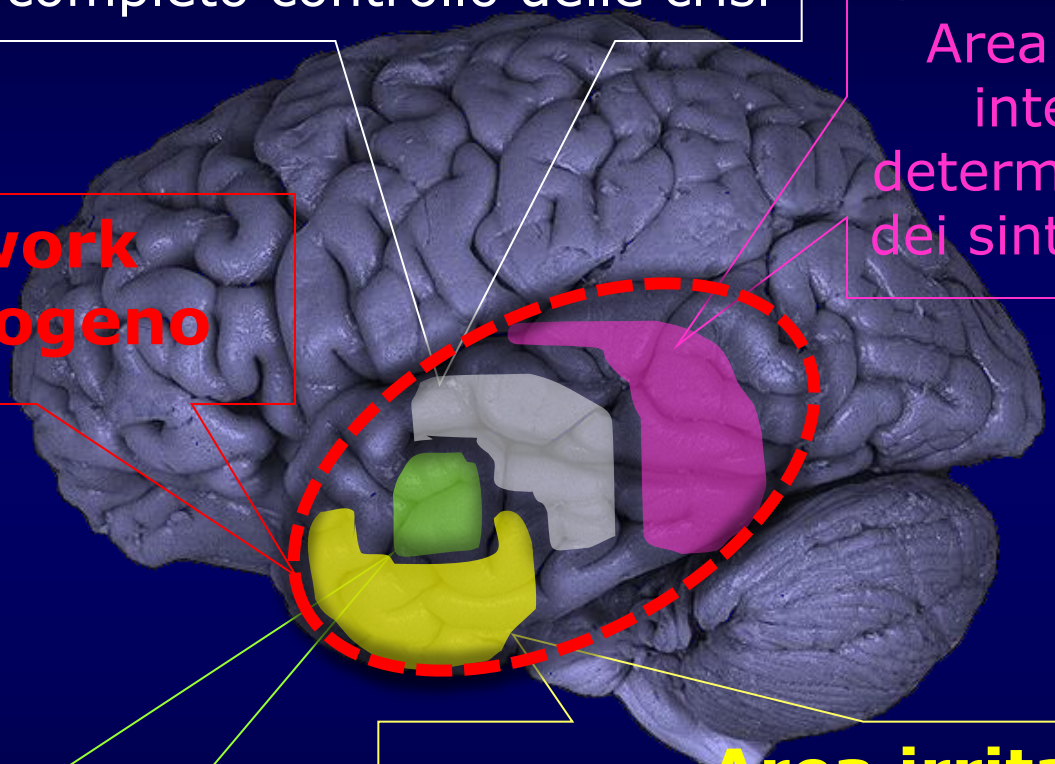
Area epilettogena

Area corticale da cui origina la scarica critica; è necessario rimuoverla per ottenere il completo controllo delle crisi

Area sintomatogenica

Area corticale il cui interessamento determina la comparsa dei sintomi/segni critici

Network epilettogeno



Area lesionale

Lesione sottostante ai processi epilettici

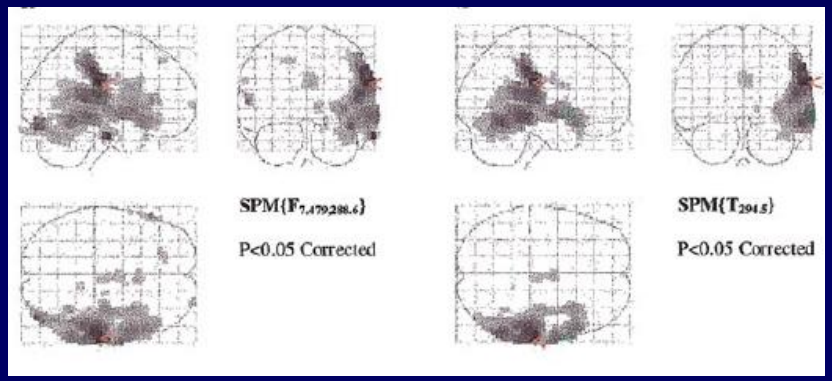
Area irritativa

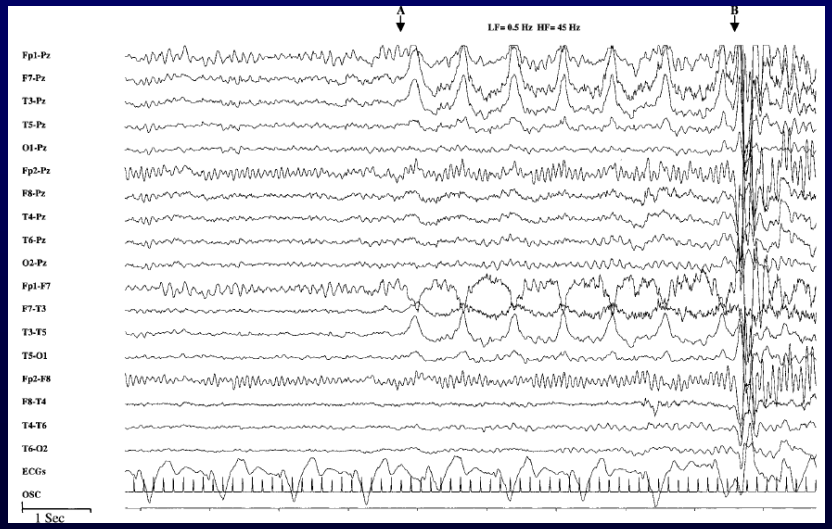
Area corticale coinvolta nella generazione delle anomalie intercritiche; non è necessario rimuoverla per ottenere il completo controllo delle per il crisi

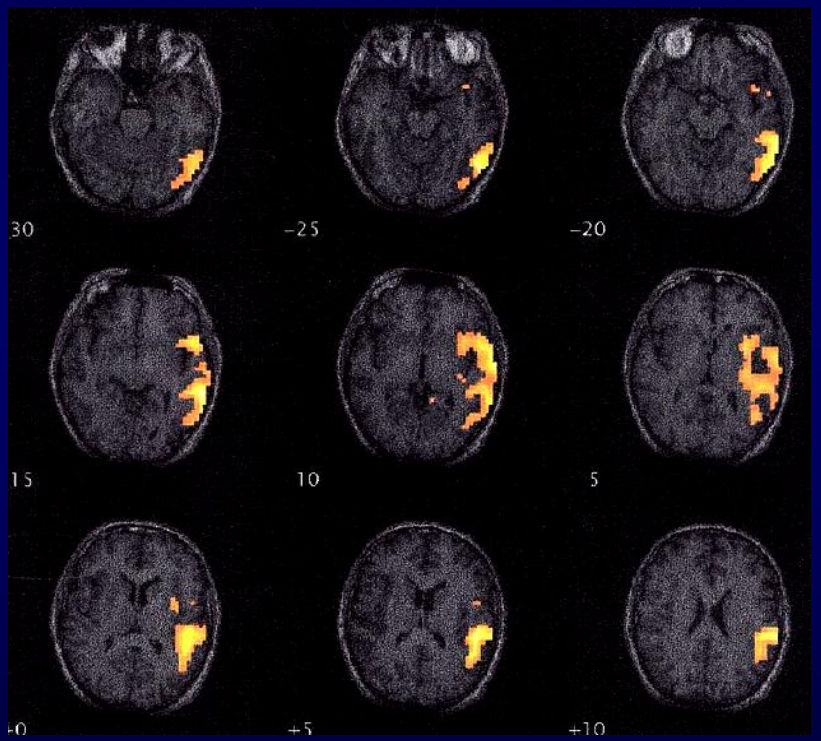
NeuroImage **16**, 32–40 (2002)
doi:10.1006/nimg.2002.1073, available online at http://www.idealibrary.com on IDEAL®

Simultaneous EEG-Correlated Ictal fMRI

Afraim Salek-Haddadi, Martin Merschhemke, Louis Lemieux, and David R. Fish*

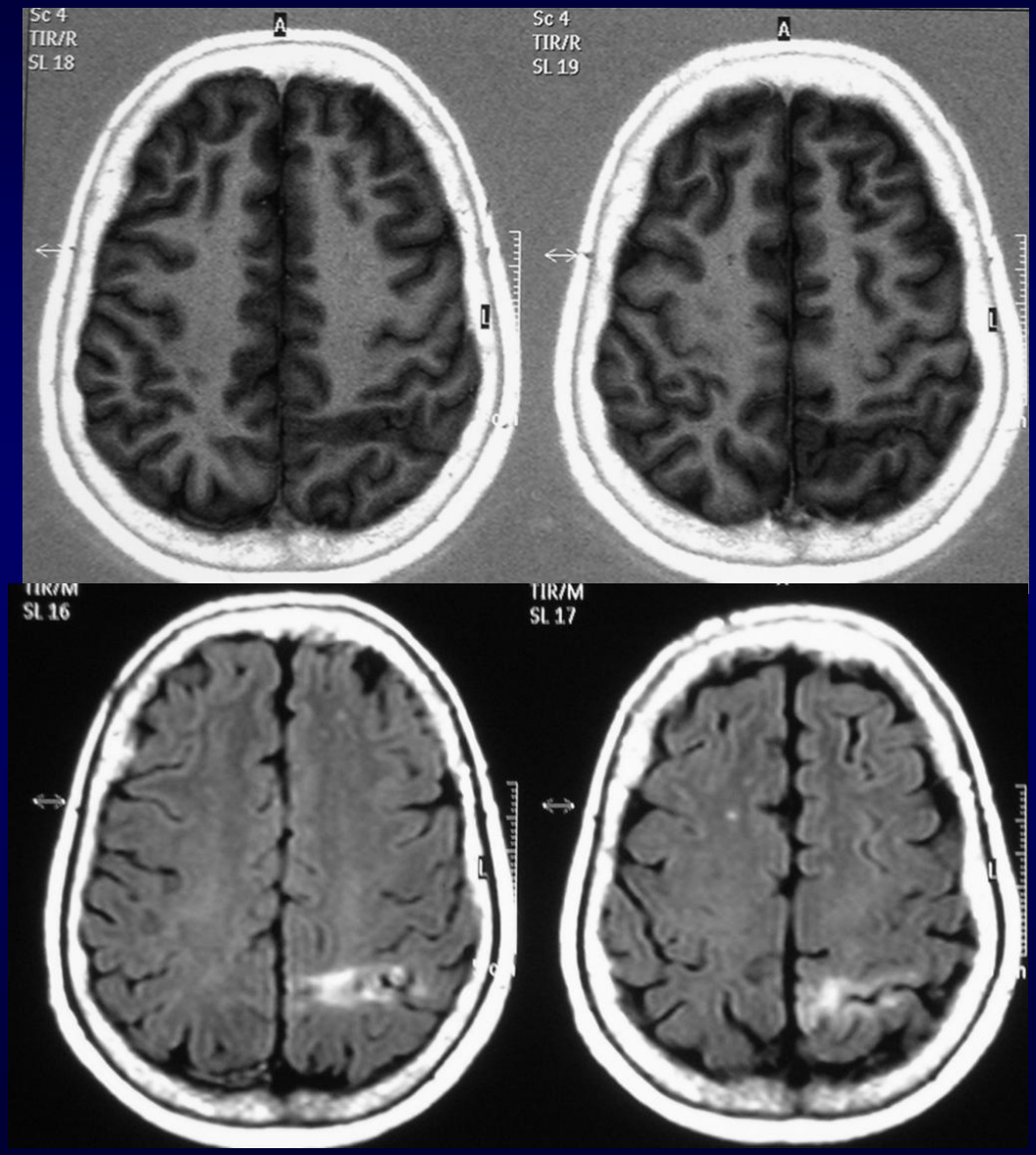




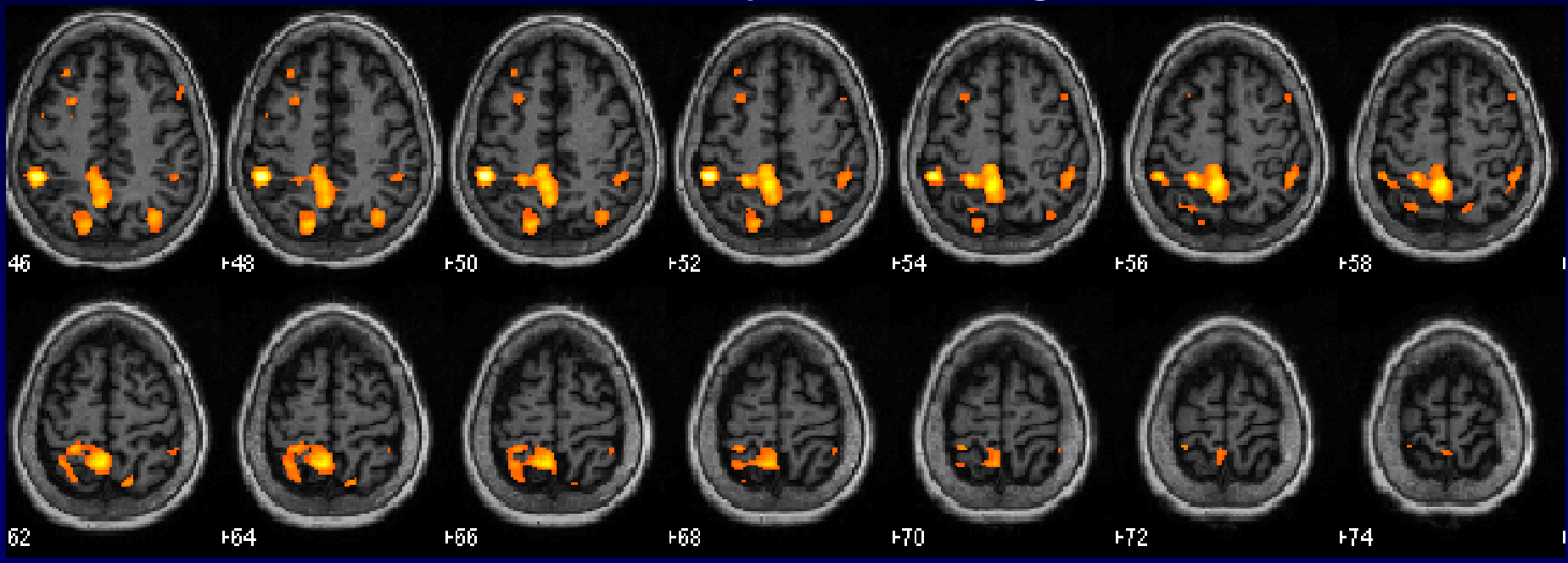


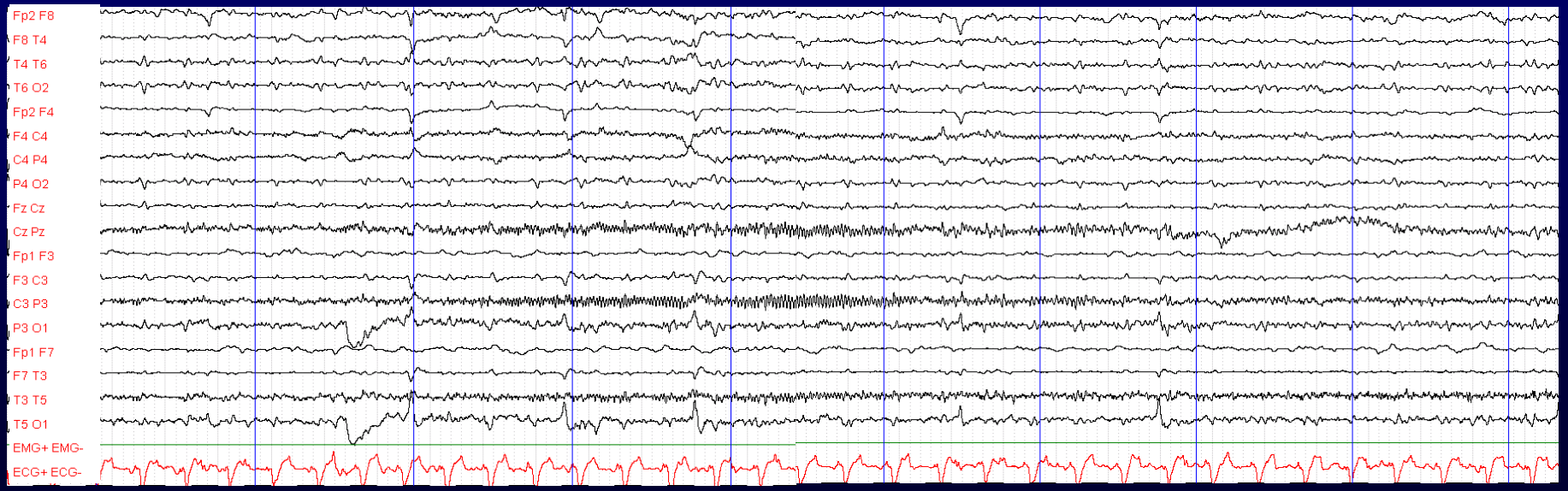
Salek-Haddadi et al, *Neuroimage* 2002

Symptomatic partial epilepsy (MCD)
Vertiginous seizures arising from left parietal region



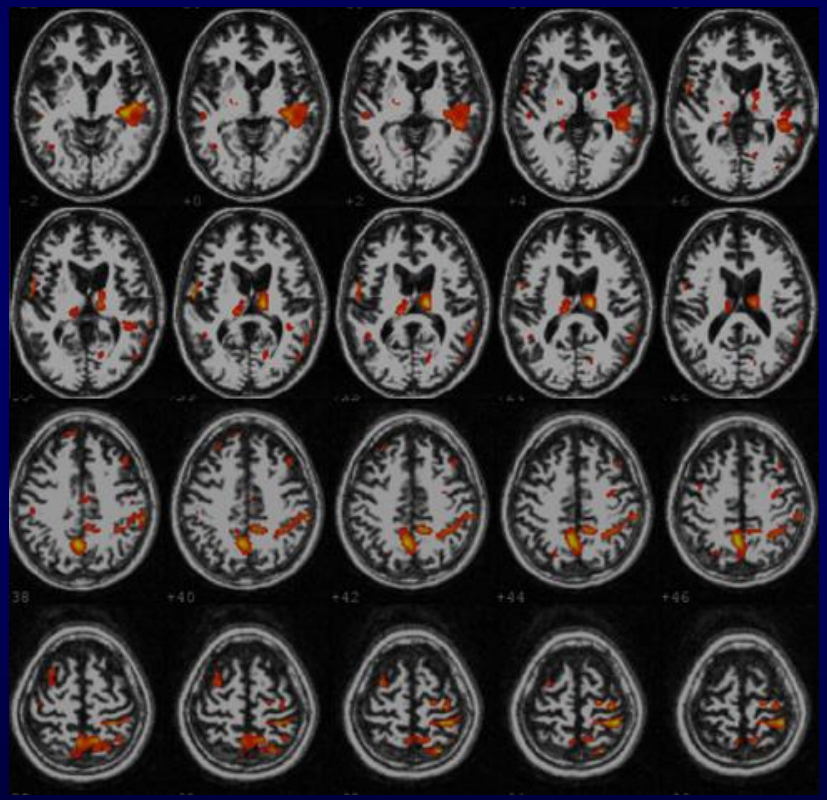
Vertiginous seizures arising from left parietal region
Ictal hemodynamic changes



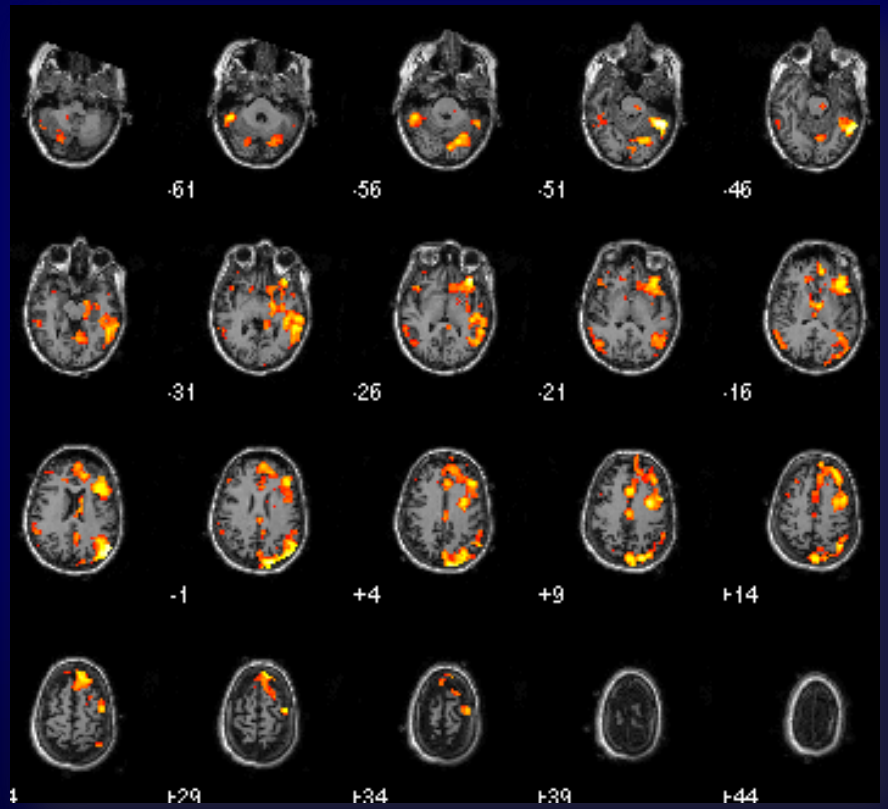


Network and subcortical involvement in partial seizures

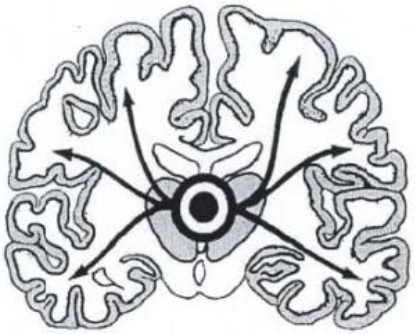
Rasmussen Encephalitis
Perisilvian seizures



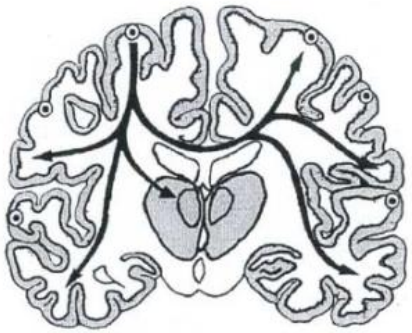
Cryptogenic partial epilepsy
Seziures with loss of contatct



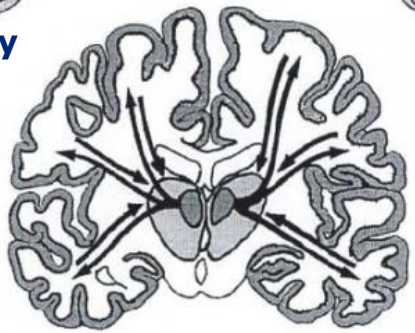
Physiopathology of GSWDs in IGE



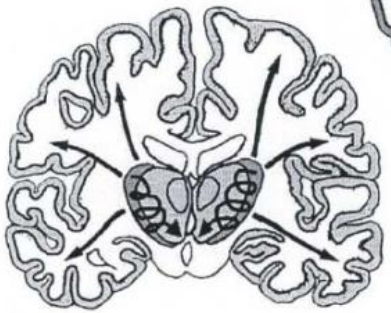
Centrencephalic Theory



Cortical Theory

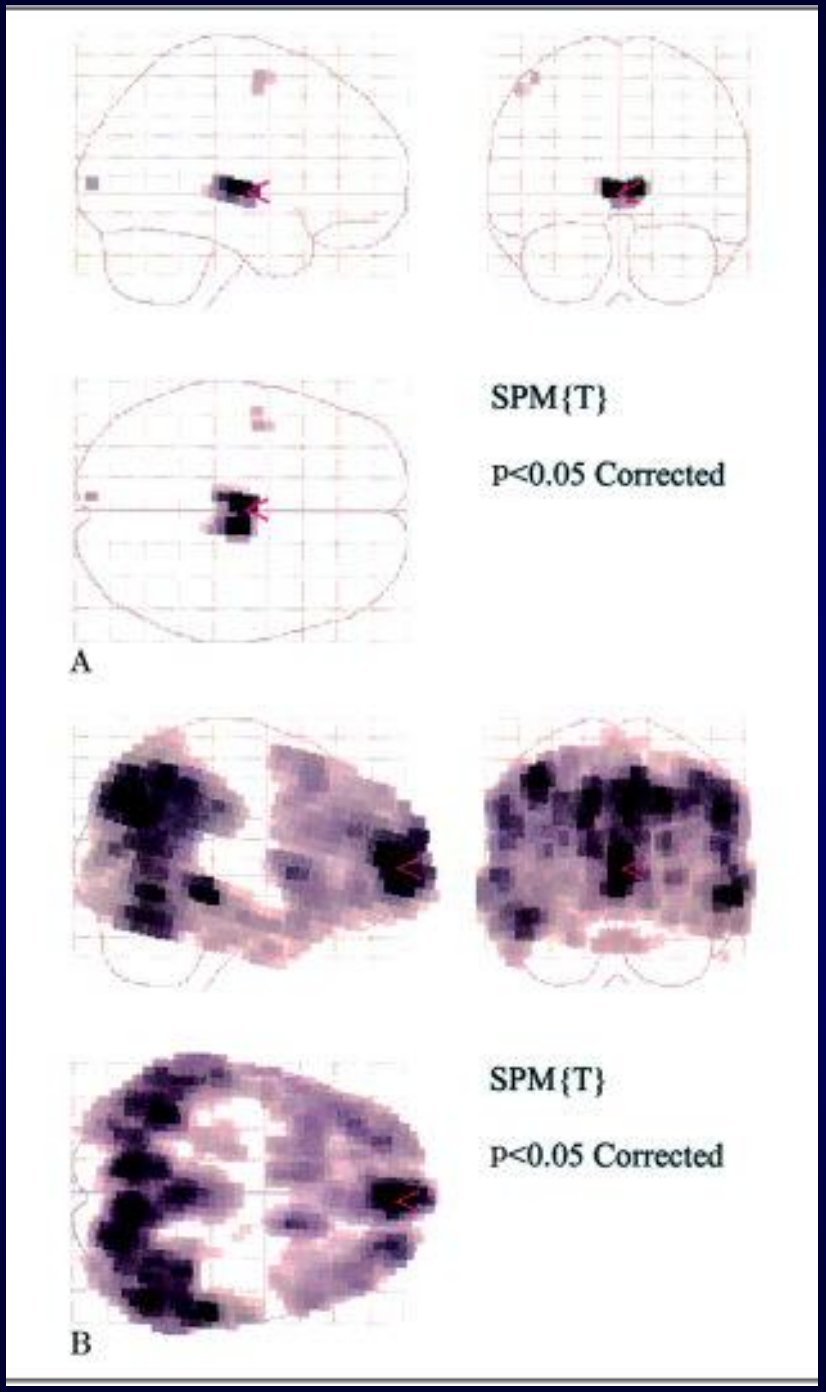


Corticoreticular Theory



Thalamic clock theory

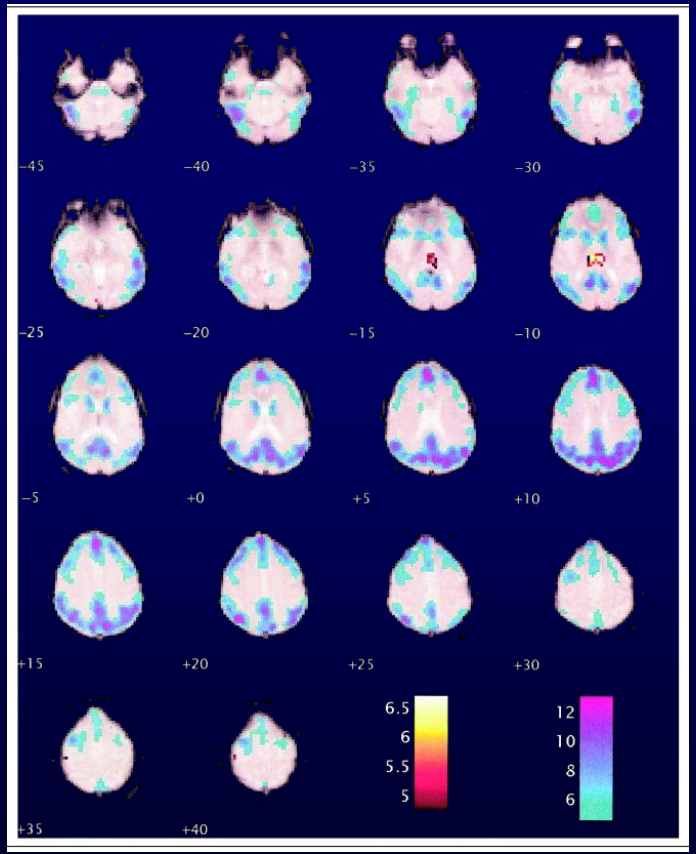
Cortical Focus Theory

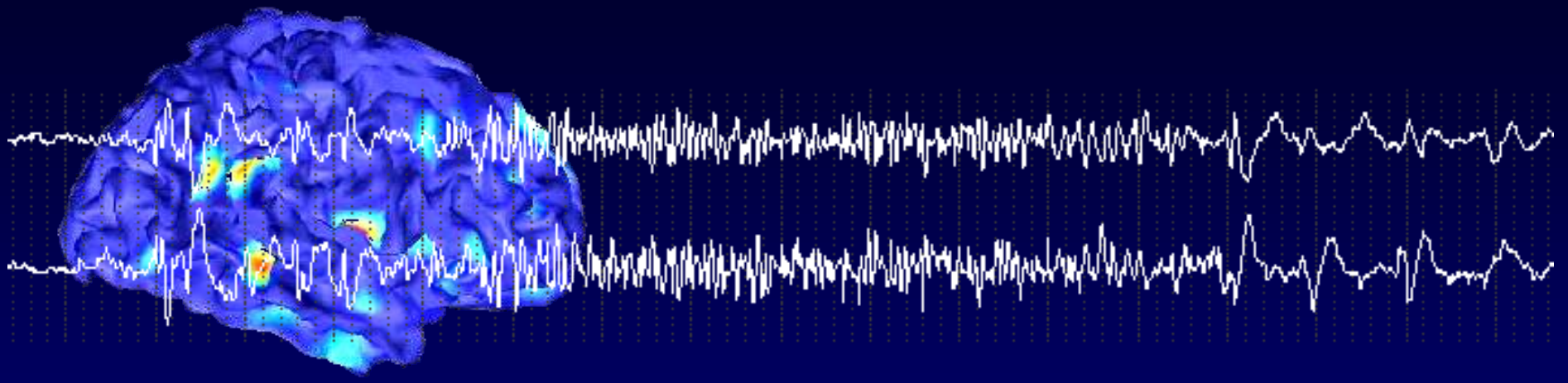


Functional Magnetic Resonance Imaging of Human Absence Seizures

Afraim Salek-Haddadi, MRCP,[1,2] Louis Lemieux, PhD,[1,2] Martin Merschhemke, MD,[1,2] Karl J. Friston, FMedSci,[3] John S. Duncan, DM,[1,2] and David R. Fish, FRCP[1,2,4]

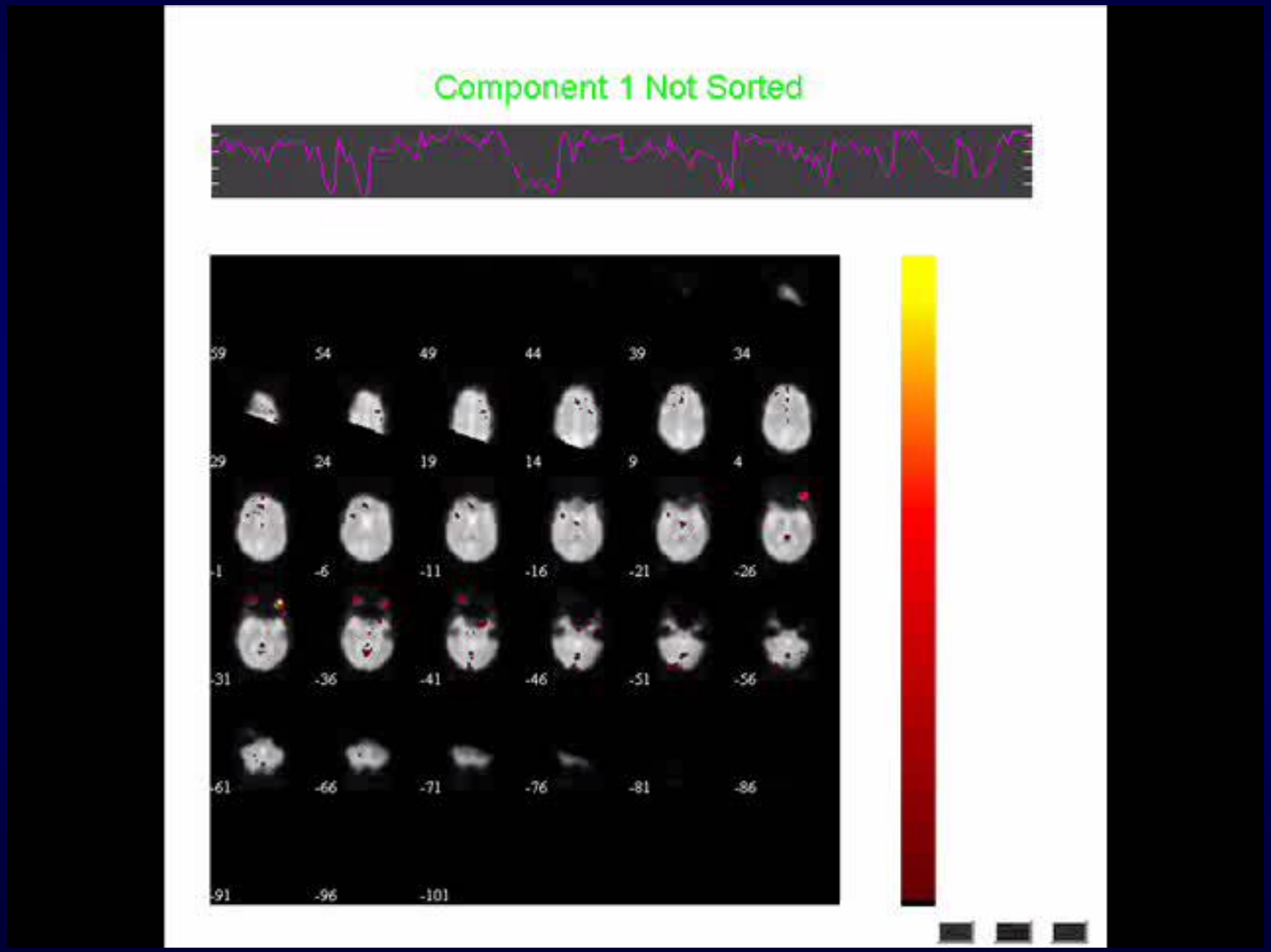
Ann Neurol 2003;53:663–667



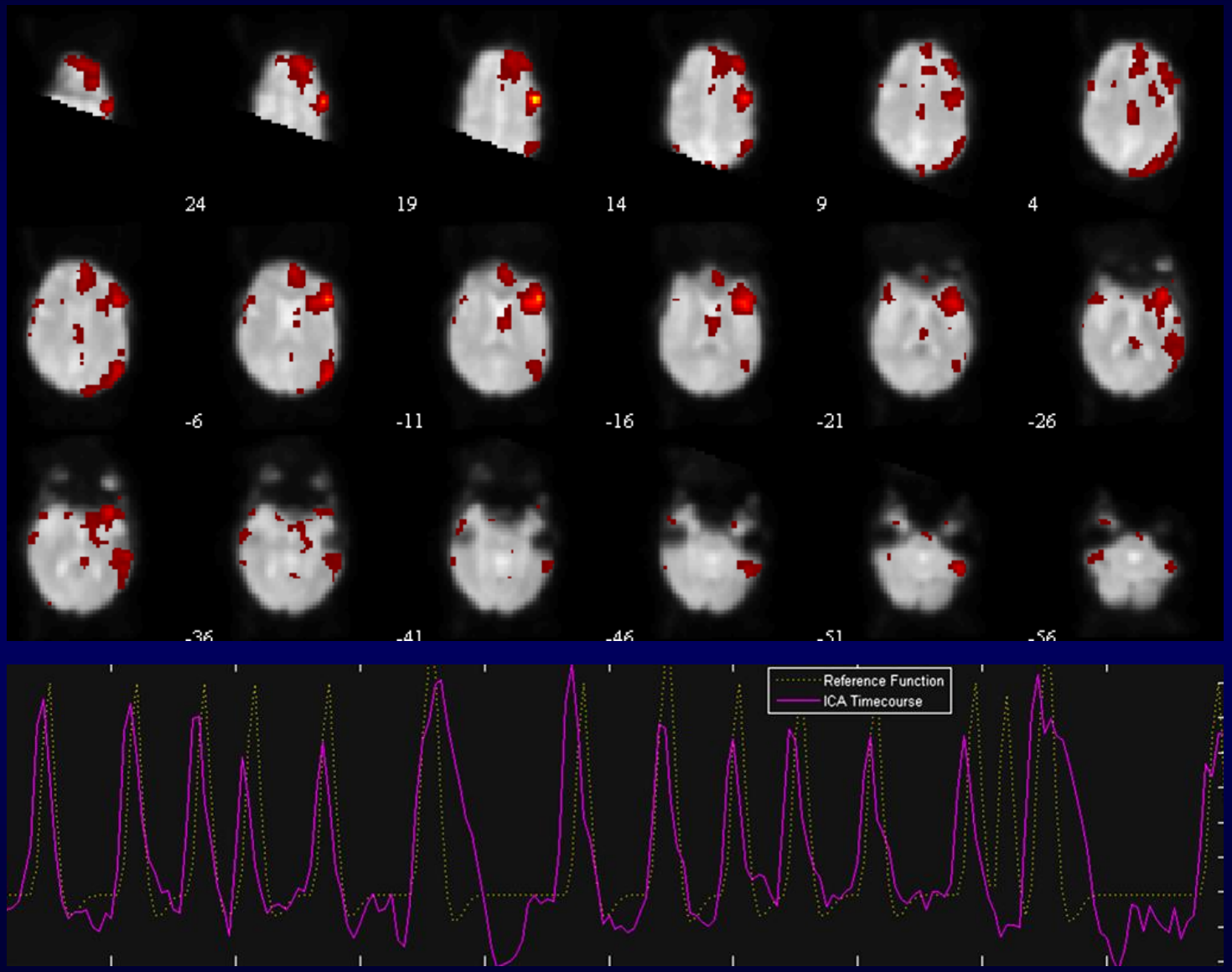


Resting state networks: brain never rests

Independent component analysis (ICA)
The brain cocktail party

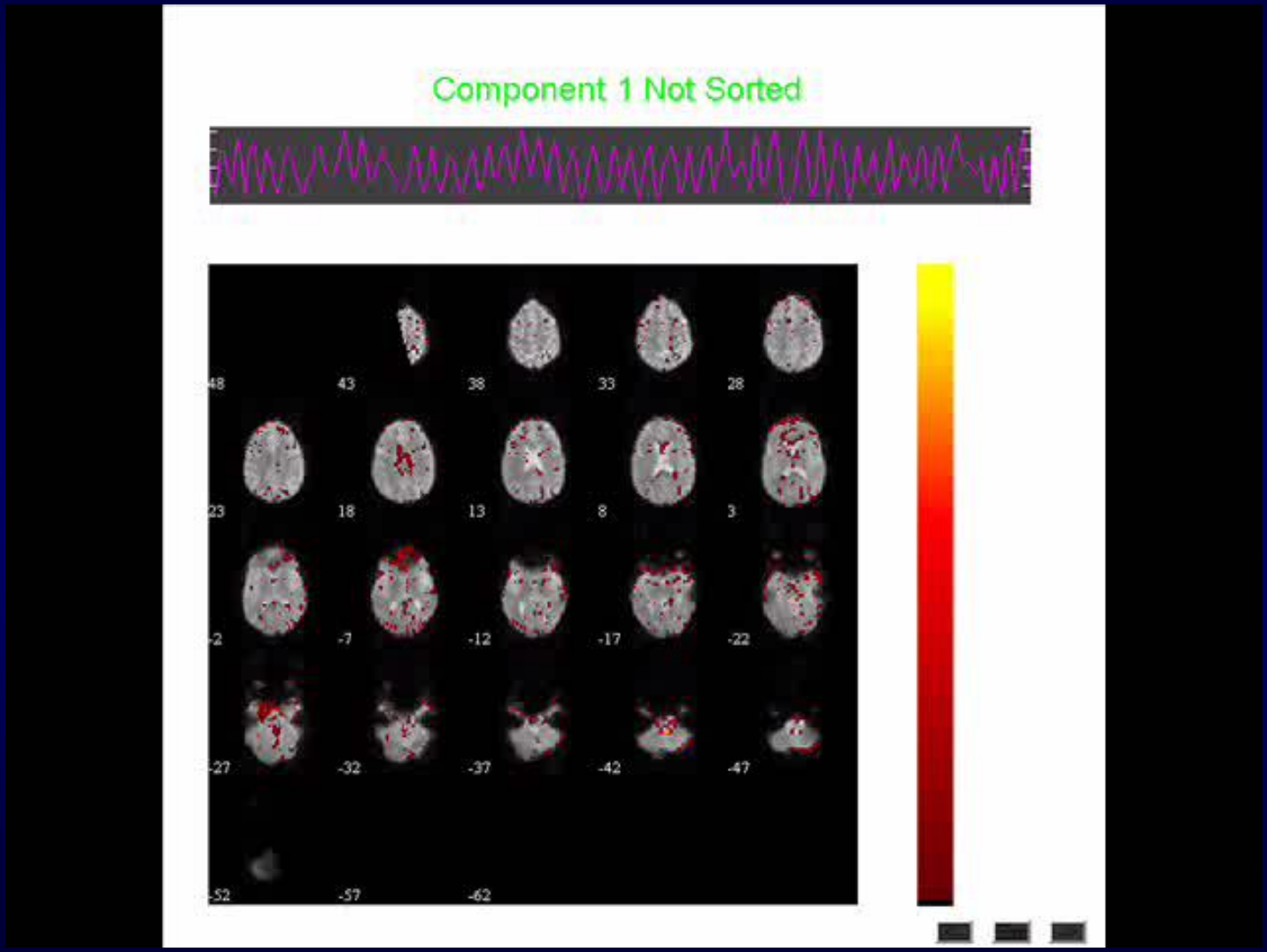


Cryptogenic partial epilepsy.
Seizures with loss of contact involving right fronto-temporal regions

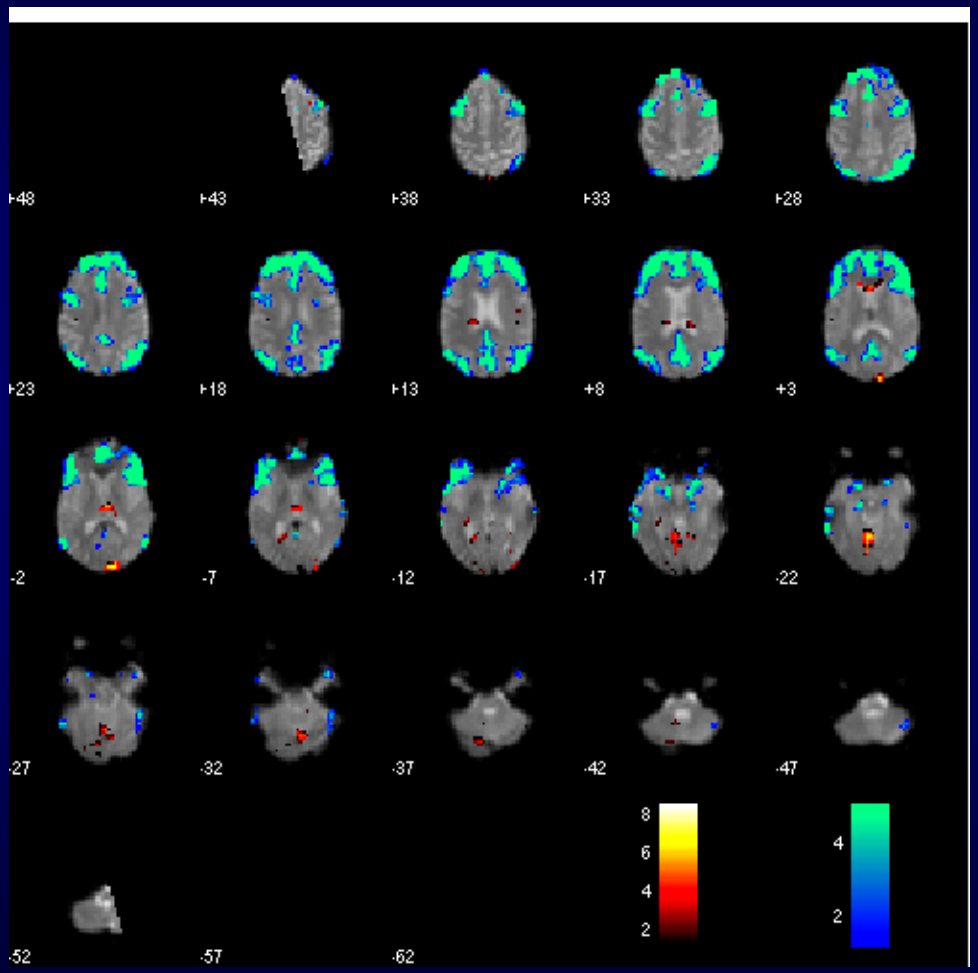


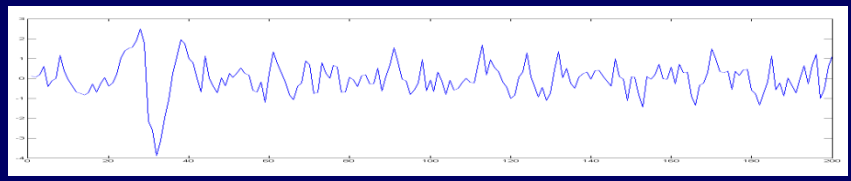
ICA – software GIFT, FastICA algorithm

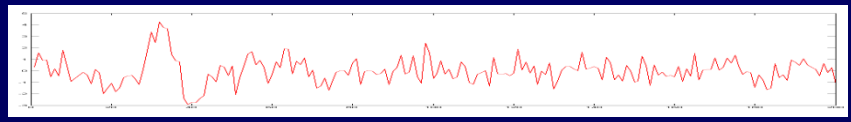
Independent component analysis (ICA)
The brain cocktail party



Idiopathic generalized epilepsy (JAE).
Typical absence seizure







Idiopathic generalized epilepsy (JAE)
Typical absence eizure

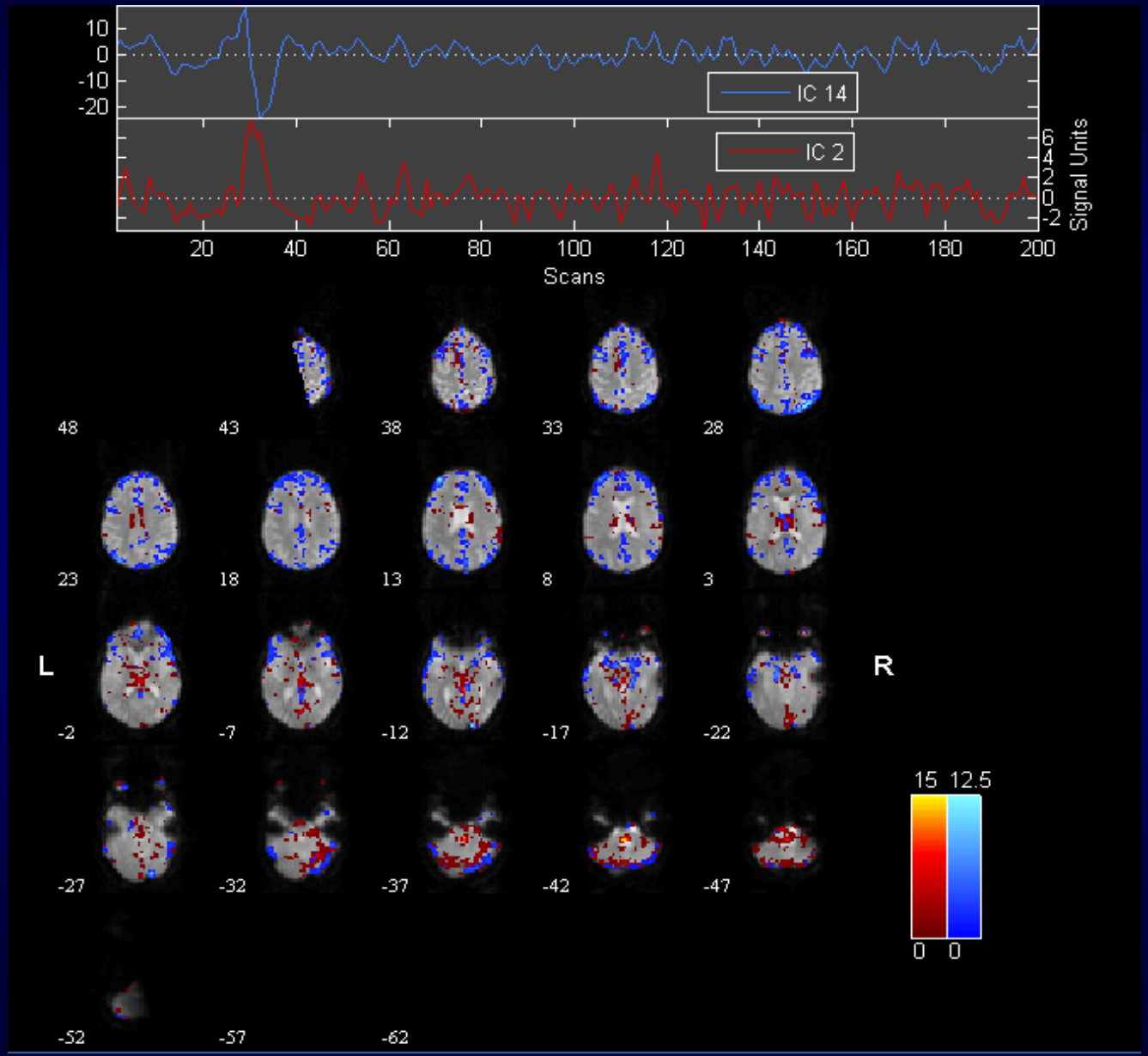


Table 2. The main resting state networks of the human brain

- Motor and sensory networks
  - Visual network
  - Auditory network
  - Sensorimotor network
- Networks mediating higher brain functions
  - Default mode network
  - Attention networks
    - Dorsal attention network
    - Ventral attention network
    - Alertness network
  - Salience network
  - Executive control network
  - Reward emotion network
  - Language networks

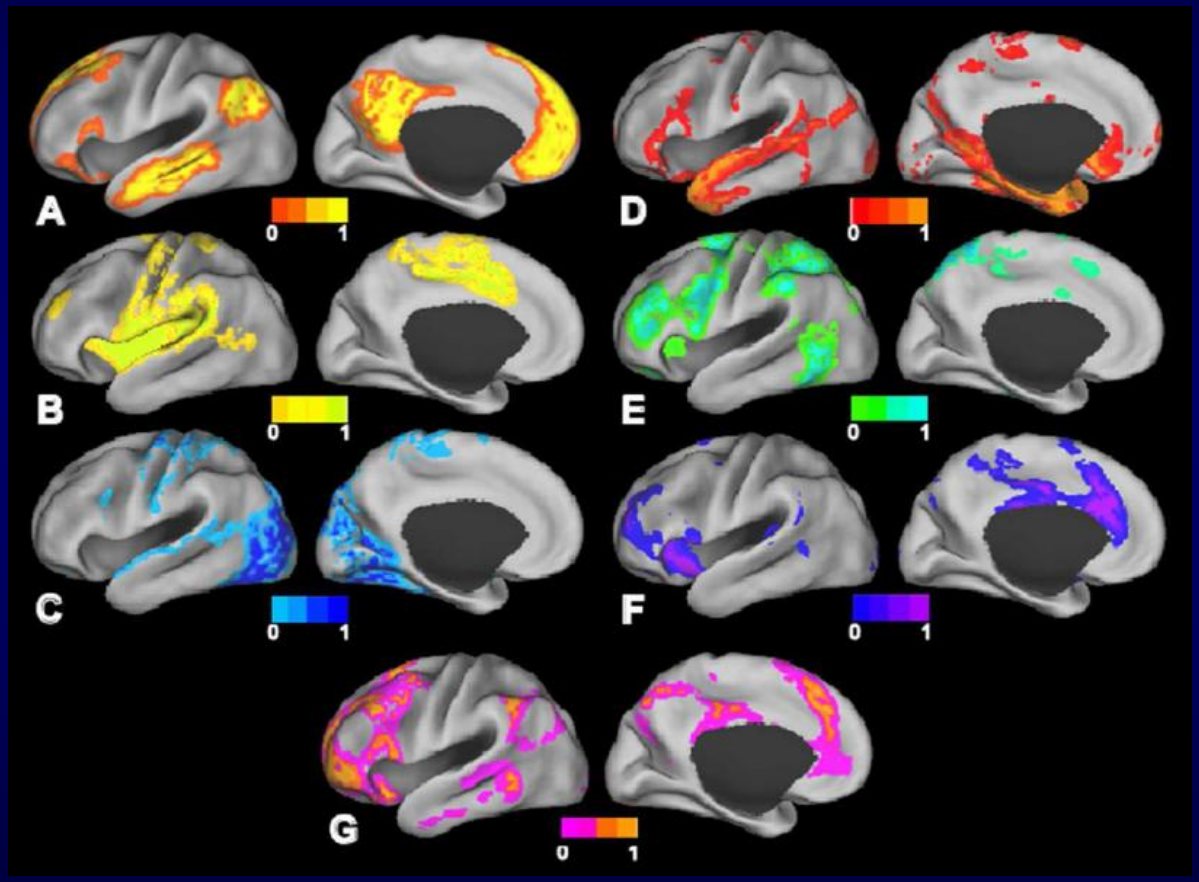
Cataldi M et al., Epilepsia 2013

Resting state networks in normal brain

A) default mode

B) somatomotor

C) visual



D) language

E) dorsal attention

F) ventral attention

G) frontoparietal control

Lee MH et al., AJNR 2013

Default brain network

- ✓ The first RSN to be identified by using PET study
- ✓ It comprises:
  - ✓posterior cingulate/precuneus cortex (PCC)
  - ✓bilateral inferior parietal lobule (IPL)
  - ✓mesial prefrontal cortex (mPFC), sometimes with the inclusion of other regions such as the lateral and medial temporal lobes

Bagshaw AP, Cavanna AE. Epilepsy & Behavior 2013

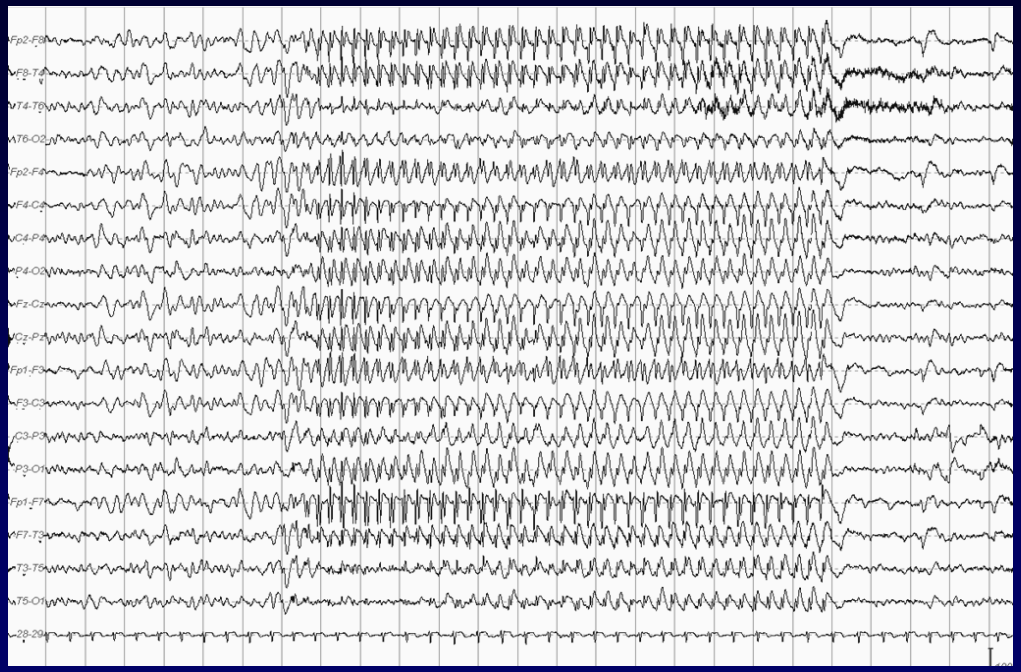
Default brain network

✓ The PCC seems to play a particularly important role within the DMN, having the highest level of metabolic activity at rest

✓ Implication in the maintenance of the conscious state

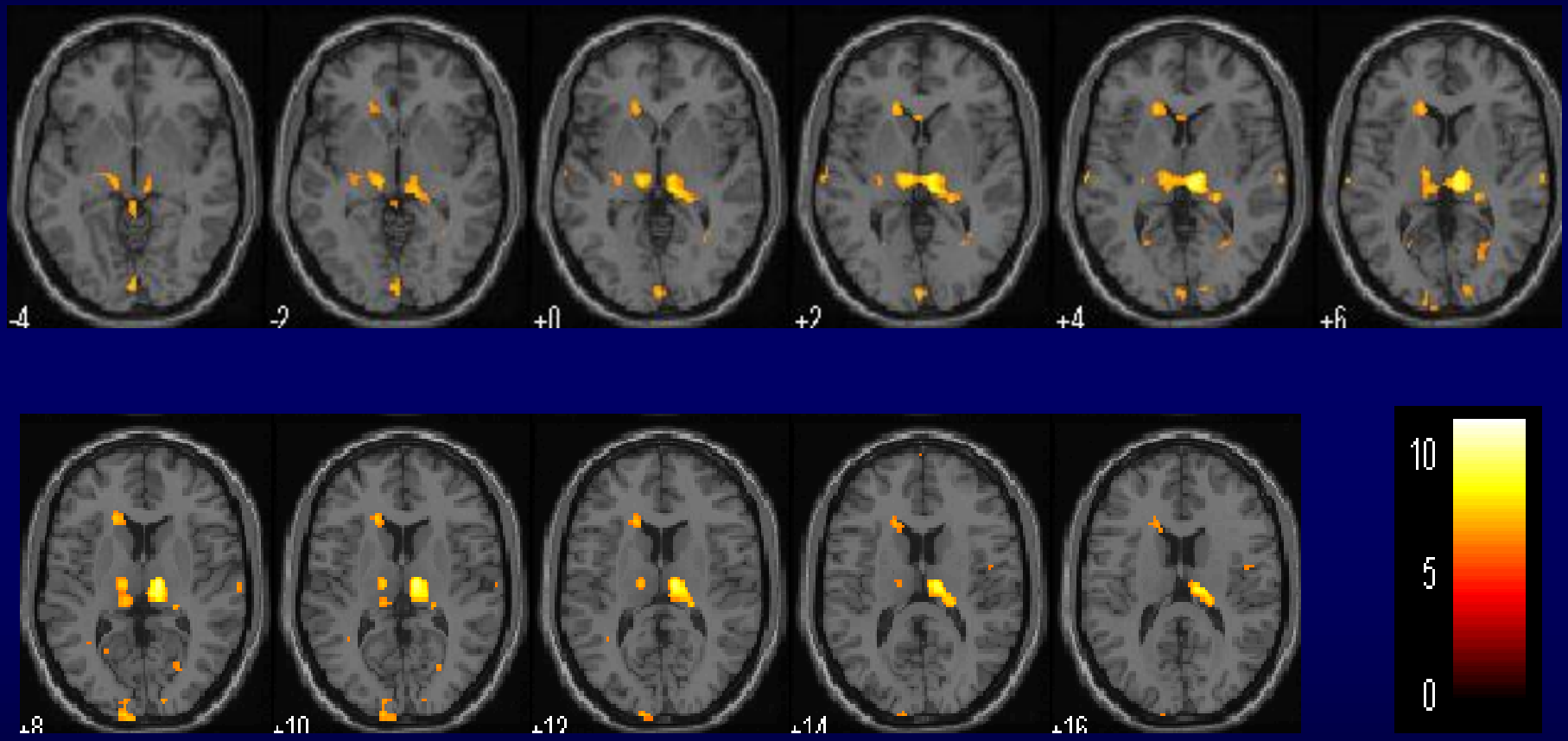
✓ DMN is preferentially engaged during rest, modified in altered states of consciousness, and that its task-induced reductions in activity are dependent upon the level of cognitive engagement

Bagshaw AP, Cavanna AE. Epilepsy & Behavior 2013

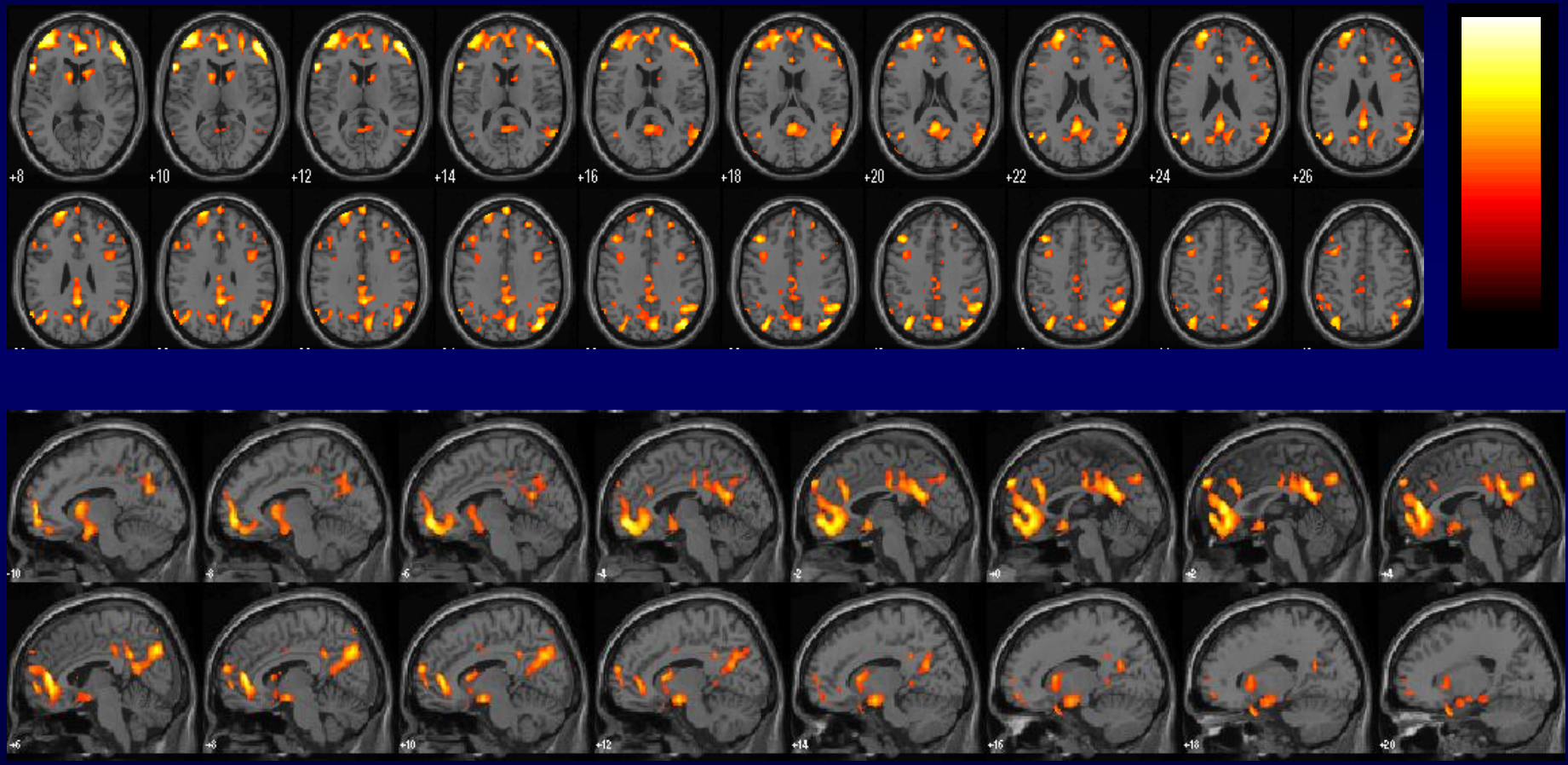

Fp2-F8
F8-T4
T4-T6
T6-O2
Fp2-F4
F4-C4
C4-P4
P4-O2
Fz-Cz
Cz-Pz
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
T5-O1
28-29


Fp2-F8
F8-T4
T4-T6
T6-O2
Fp2-F4
F4-C4
C4-P4
P4-O2
Fz-Cz
Cz-Pz
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
T5-O1
28-29

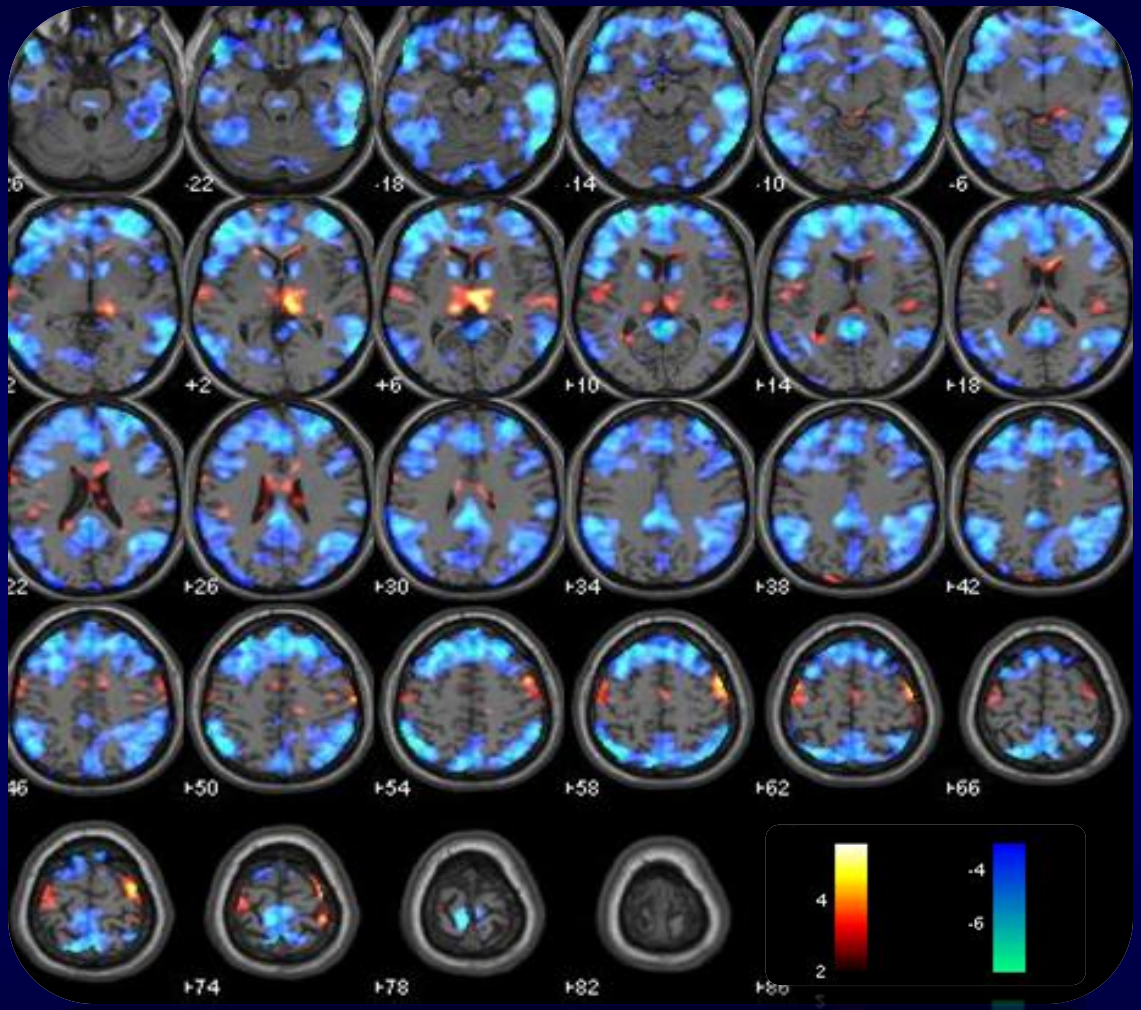
Typical absence
ACTIVATION



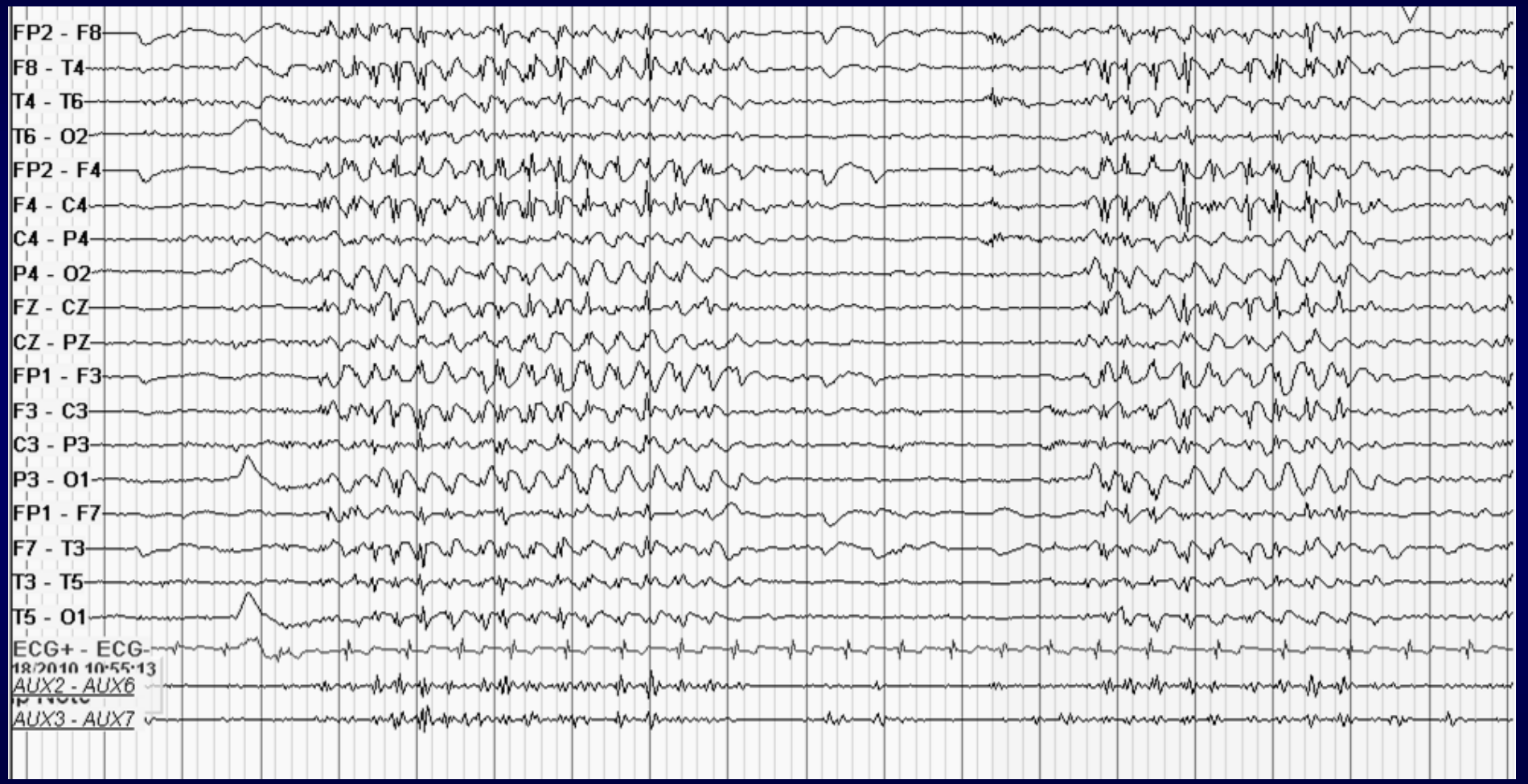
Typical absence
DEACTIVATION



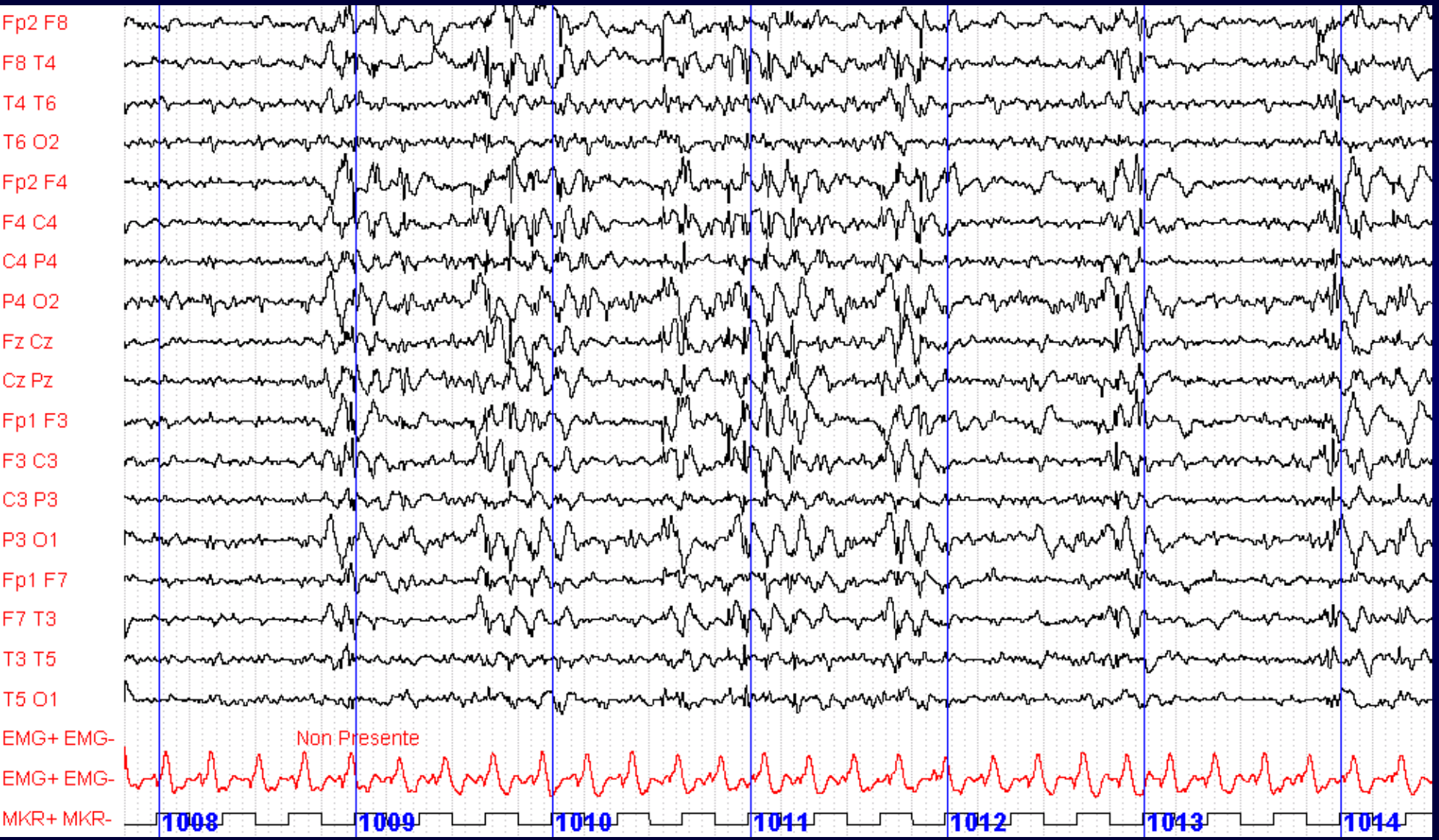
activation vs deactivation



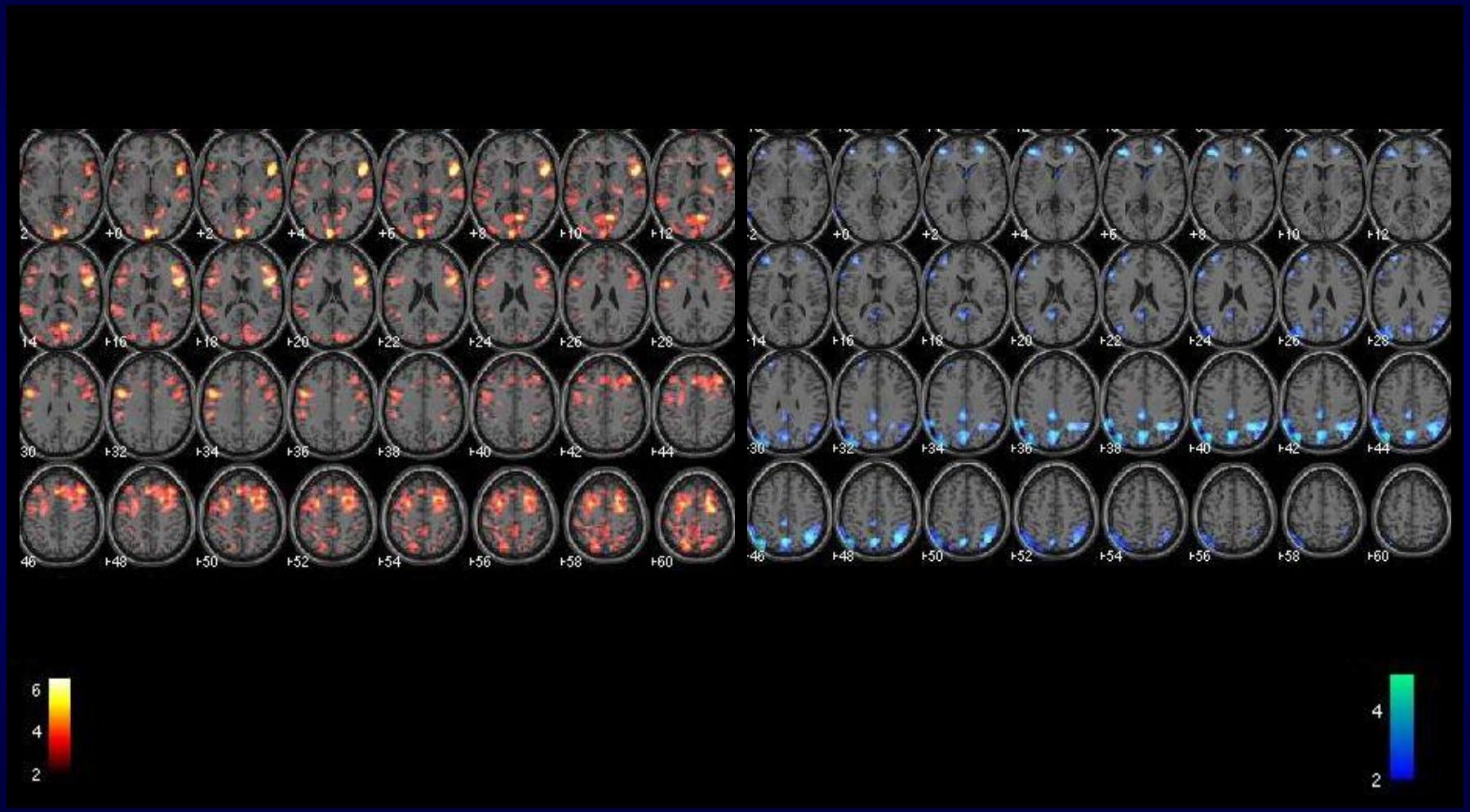
Myoclonic SE in JME misdiagnosed as ADHD



EEG/fMRI study



Intrascanner EEG recording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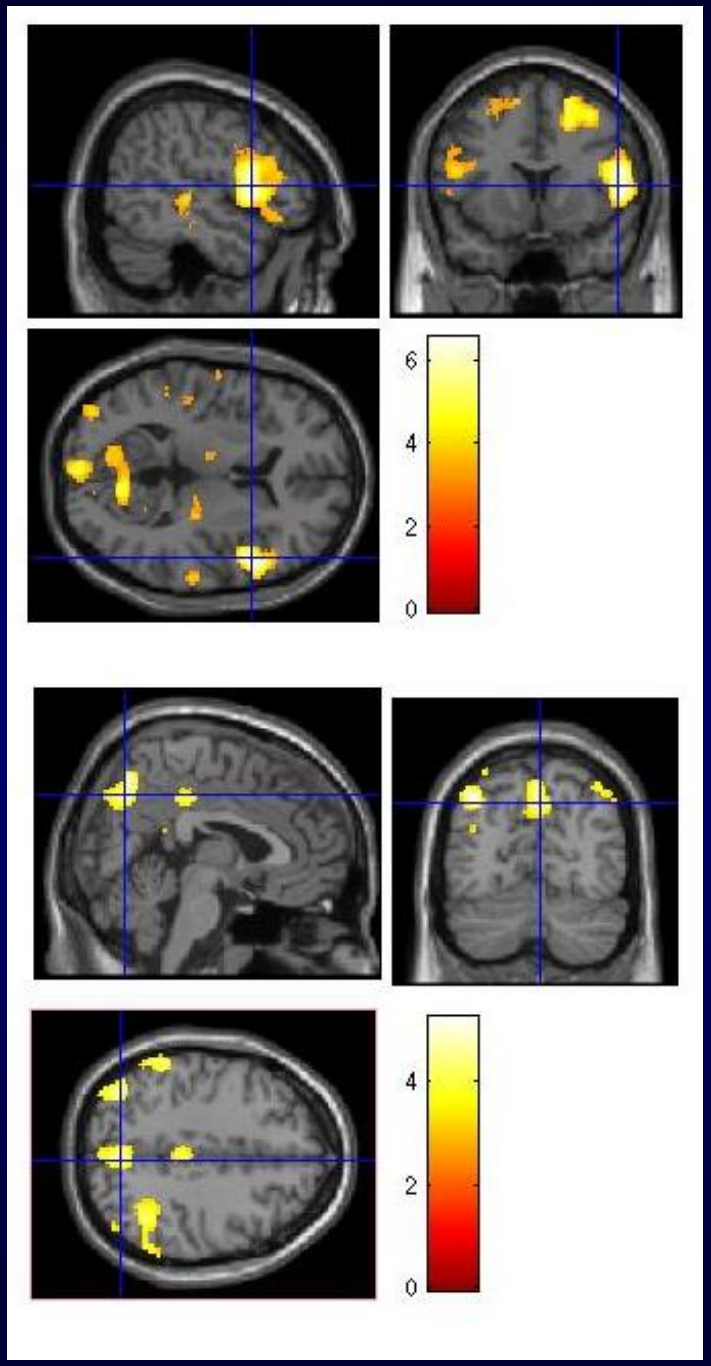
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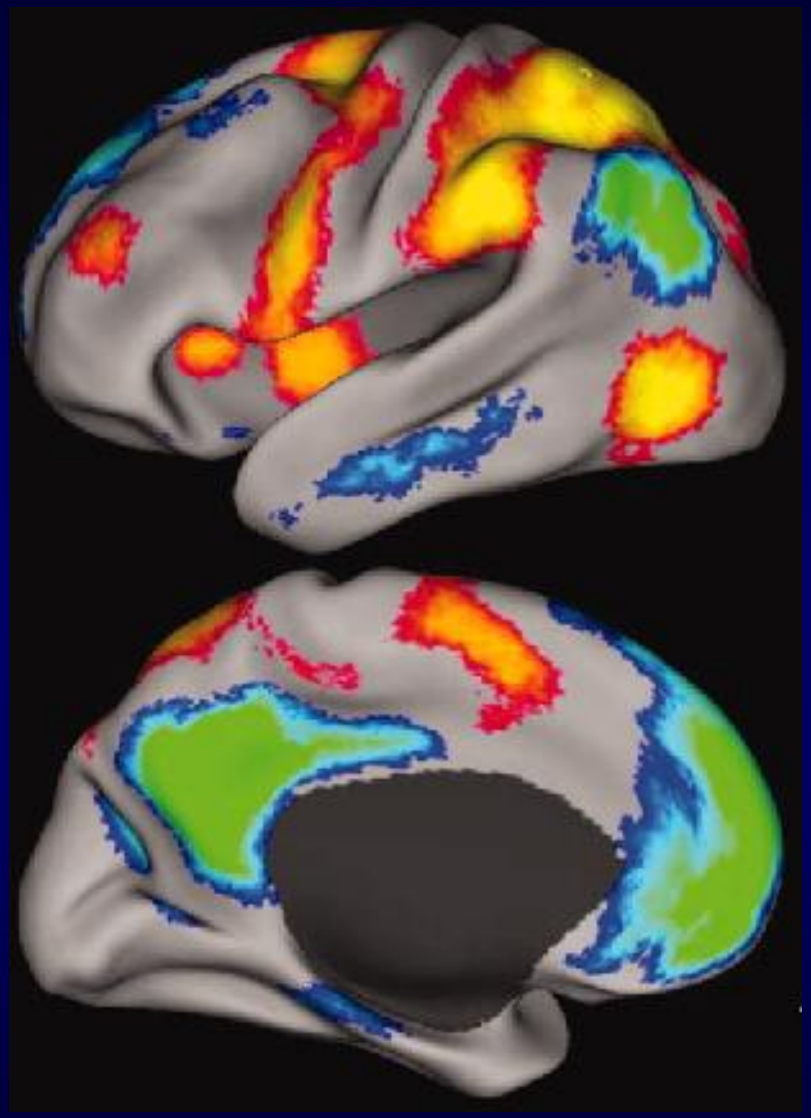


"default brain network"

Interconnected and anatomically well connected system activated during internal tasks (daydreaming, imaging the future, retrieving from memory, etc.)

Mesial temporal structures → memory

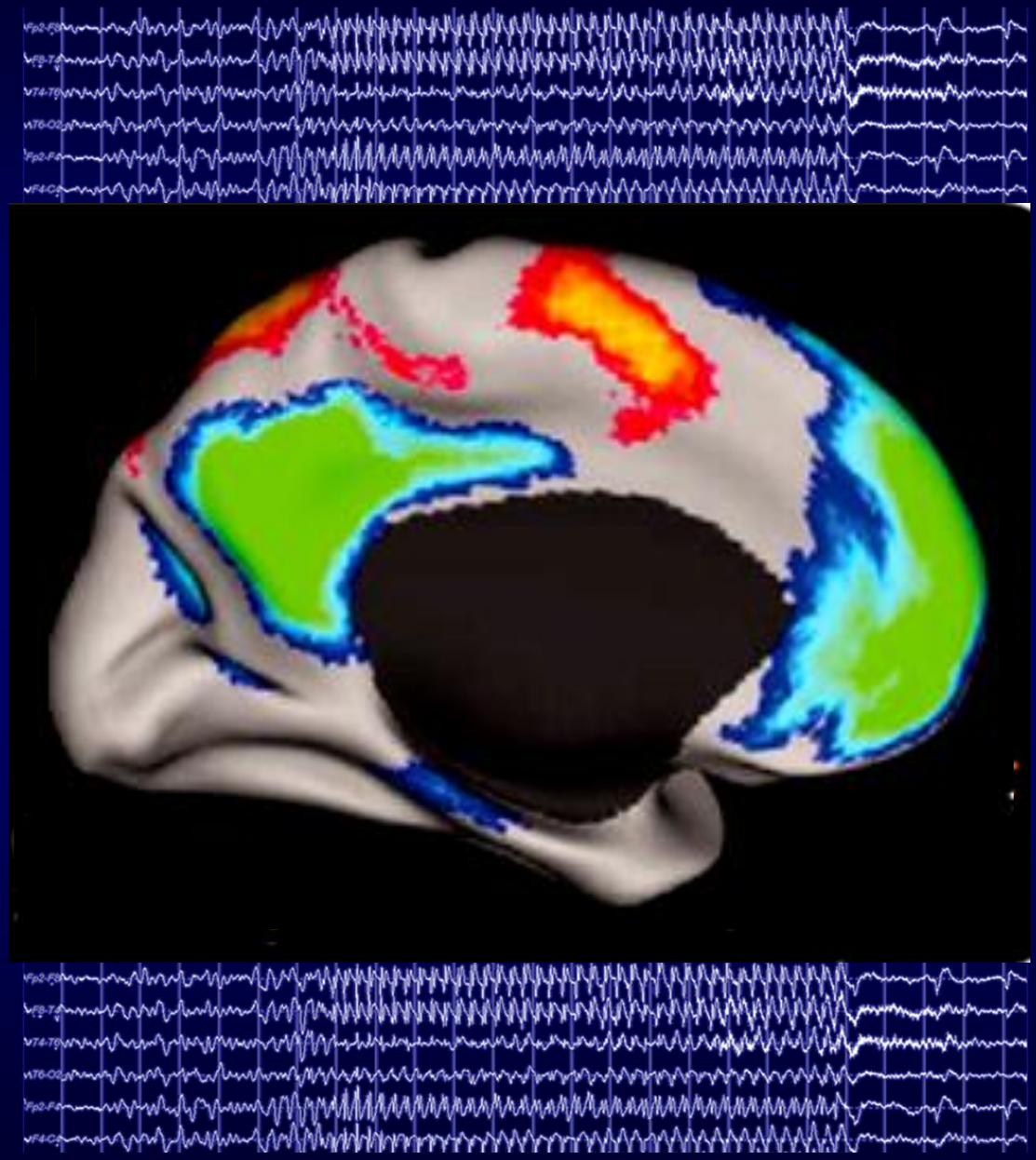
Mesial prefrontal cortex → mental simulation

Posterior cingulate cortex, precuneus, parietal cortex → integration

task-positive network

Fox MD et al. PNAS 2005

DMN deactivation during absence seizure



The spectrum of consciousness disorders

State	Coma*	PVS	ASZ	AKM	HKM	CPS	DEL
Arousal	−	+	+	+	+	+	+
Attention	−	−	−	+	+/−	+/−	+/−
Intention	−	−	−	−	+	+/−	+/−
Memory	−	−	−	−	−	−	+/−
Awareness	−	−	−	−/?	−/?	+/−	+/−

PVS = Persistent vegetative state
ASZ = Absence seizure
AKM = Akinetic mutism
HKM = Hyperkinetic mutism
CPS = Complex partial seizure
DEL = Delirium

Schiff and Plum, J Clin Neurophysiol 2000

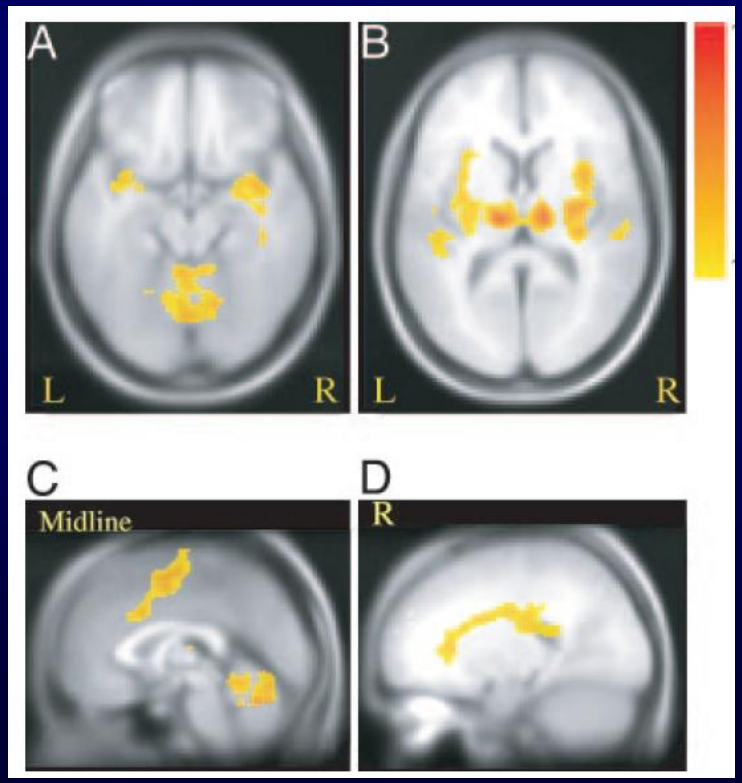
PNAS

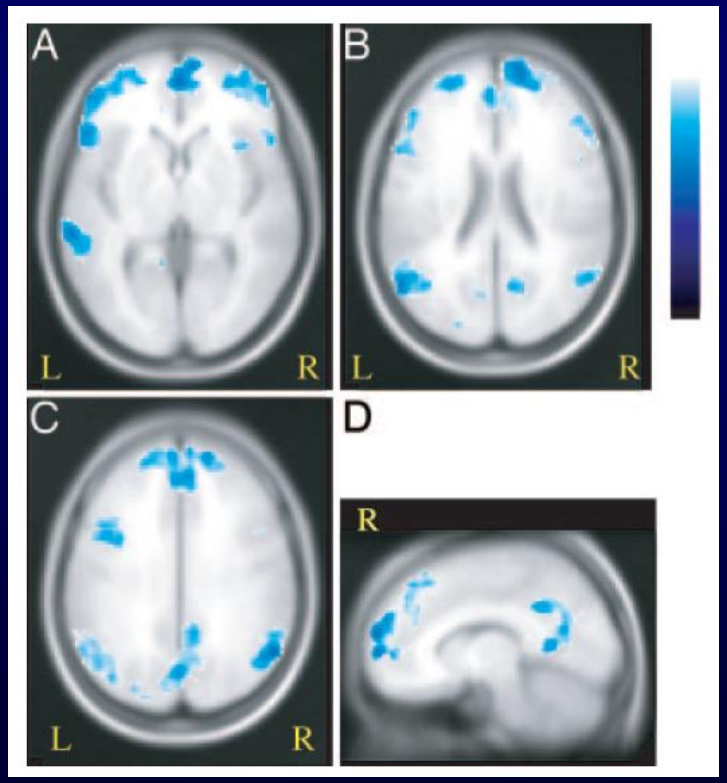
Generalized epileptic discharges show thalamocortical activation and suspension of the default state of the brain

J. Gotman*, C. Grova, A. Bagshaw, E. Kobayashi, Y. Aghakhani, and F. Dubeau

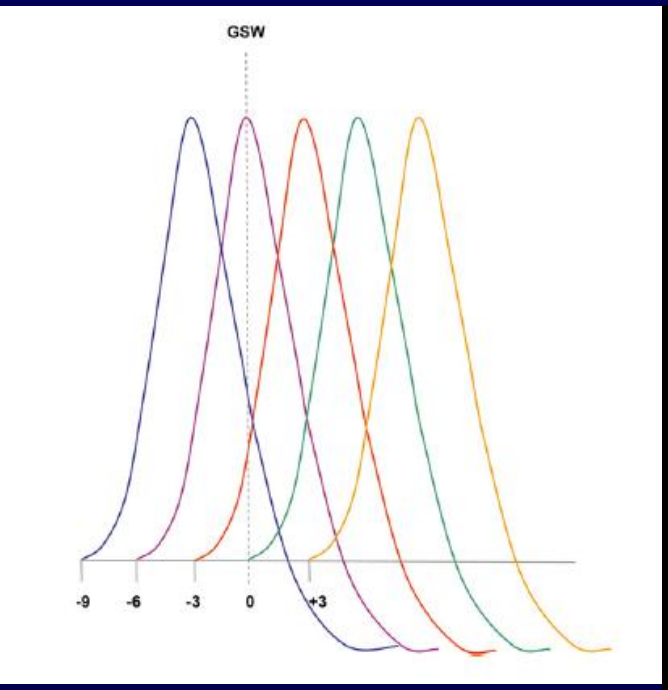
Montreal Neurological Institute and Department of Neurology and Neurosurgery, McGill University, 3801 University Street, Montréal, QC, Canada H3A 2B4

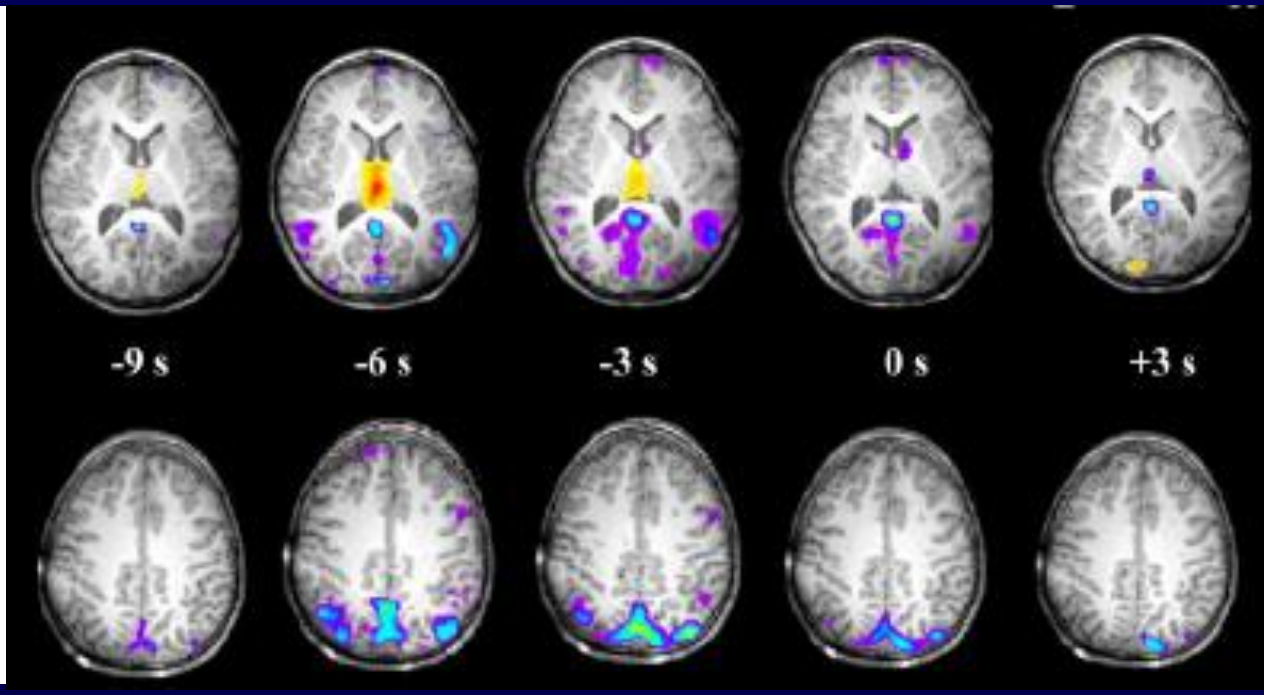
Edited by Marcus E. Raichle, Washington University School of Medicine, St. Louis, MO, and approved August 26, 2005 (received for review June 13, 2005)





Changes in activity of striato–thalamo–cortical network precede generalized spike wave discharges





Moeller et al., Neuroimage 2008

PCC and consciousness

✓These 'neural correlates of consciousness' (NCC) include bilateral subcortical midline structures

✓Medial thalamus, basal ganglia and upper brainstem, bilateral orbitofrontal cortex, anterior and posterior cingulate regions, and frontal and parietal association cortices

✓Precise link between the NCC and the DMN remains to be clarified, but there is a clear overlap between the two

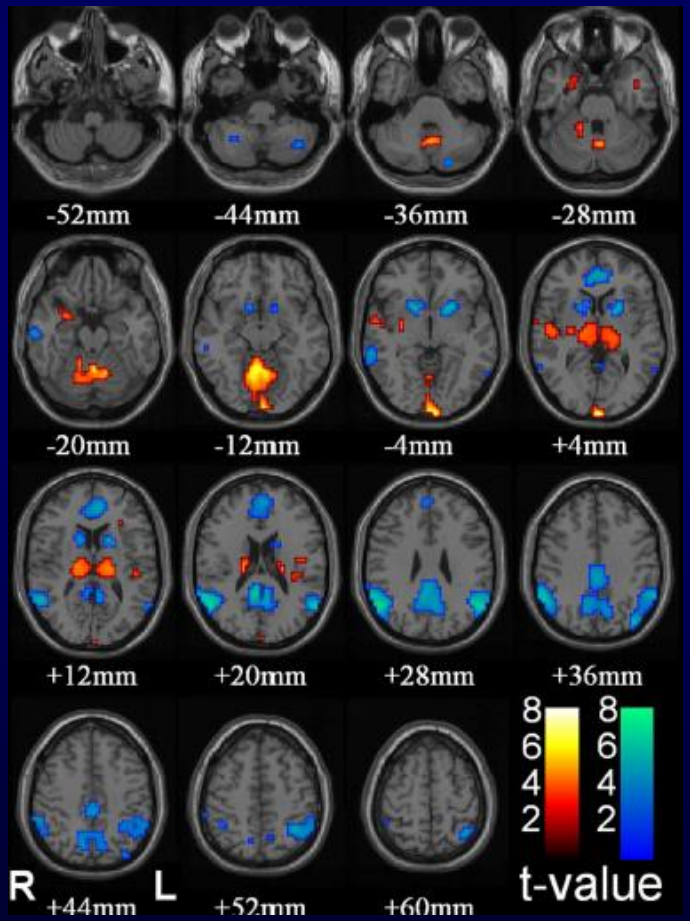
✓Central role of PCC in maintaining a state of consciousness

frontiers in NEUROLOGY

REVIEW ARTICLE
published: 01 September 2014
doi: 10.3389/fneur.2014.00162

Insights into the mechanisms of absence seizure generation provided by EEG with functional MRI

Patrick W. Carney[1,2,3] *and Graeme D. Jackson*[1,2,3] *



The DMN time course shows that BOLD changes occur before an absence occurs and awareness becomes impaired

DMN as a core network with changed activity central to AS and interictal epileptiform discharges.

Its BOLD change is a consequence of an absence or, perhaps more likely, facilitating its occurrence.

Resting state networks

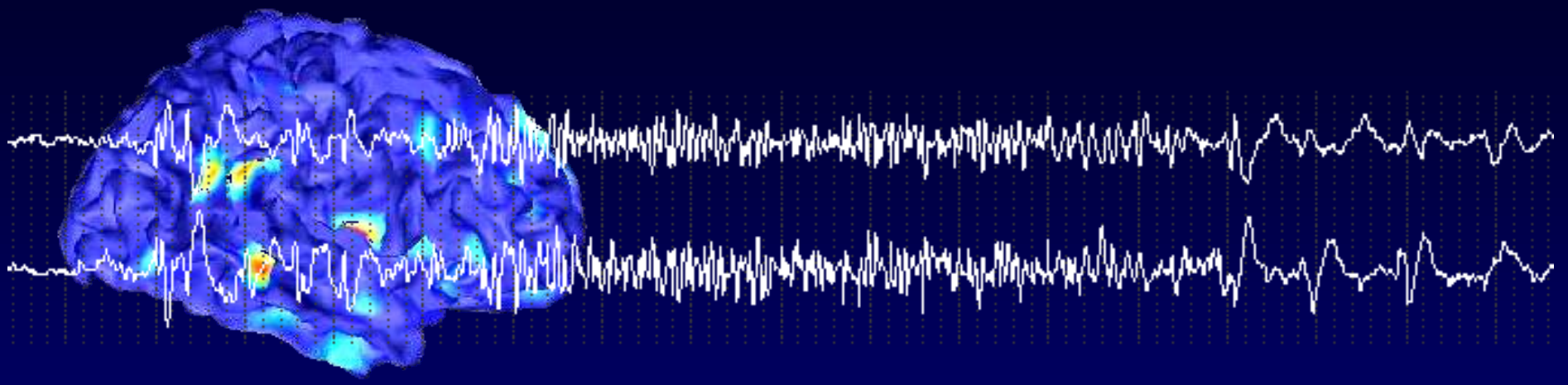
✓The concept of resting state network originated from the seminal work of Biswal et al. (1995)

✓Alternating finger tapping/rest, evidence of low frequency fluctuations of fMRI signal in motor cortex at rest with a high degree of correlation, with similar fluctuations in contralateral motor cortex

✓Similar coherent fluctuations in other functionally connected brain regions (language and visual cortices)

✓Fluctuations as expression of ***fc*** among distant brain regions active also at rest

✓The fluctuations are caused by spontaneous changes in BOLD signal



From “phrenologic” to holistic dimension: functional and structural connectivity

Concepts in Functional and Structural Networks

- ✓ **Functional connectivity**
- ✓ Statistical associations between physiologic recordings of different brain areas
- ✓ The extent to of functional connection of different brain areas depends on the level of synchronous temporal activity (synchronization)
- ✓ Functional connectivity can be studied in a task-related paradigm or in a so-called resting-state condition

- ✓ This condition allows the detection of intrinsic activity of the brain

van Diessen E et al., Epilepsia 2013

Concepts in Functional and Structural Networks

- ✓ **Structural connectivity**
- ✓ Where functional connectivity is considered as an on-going physiologic process of "communication" between different brain areas, structural networks can be considered as the supporting hardwire

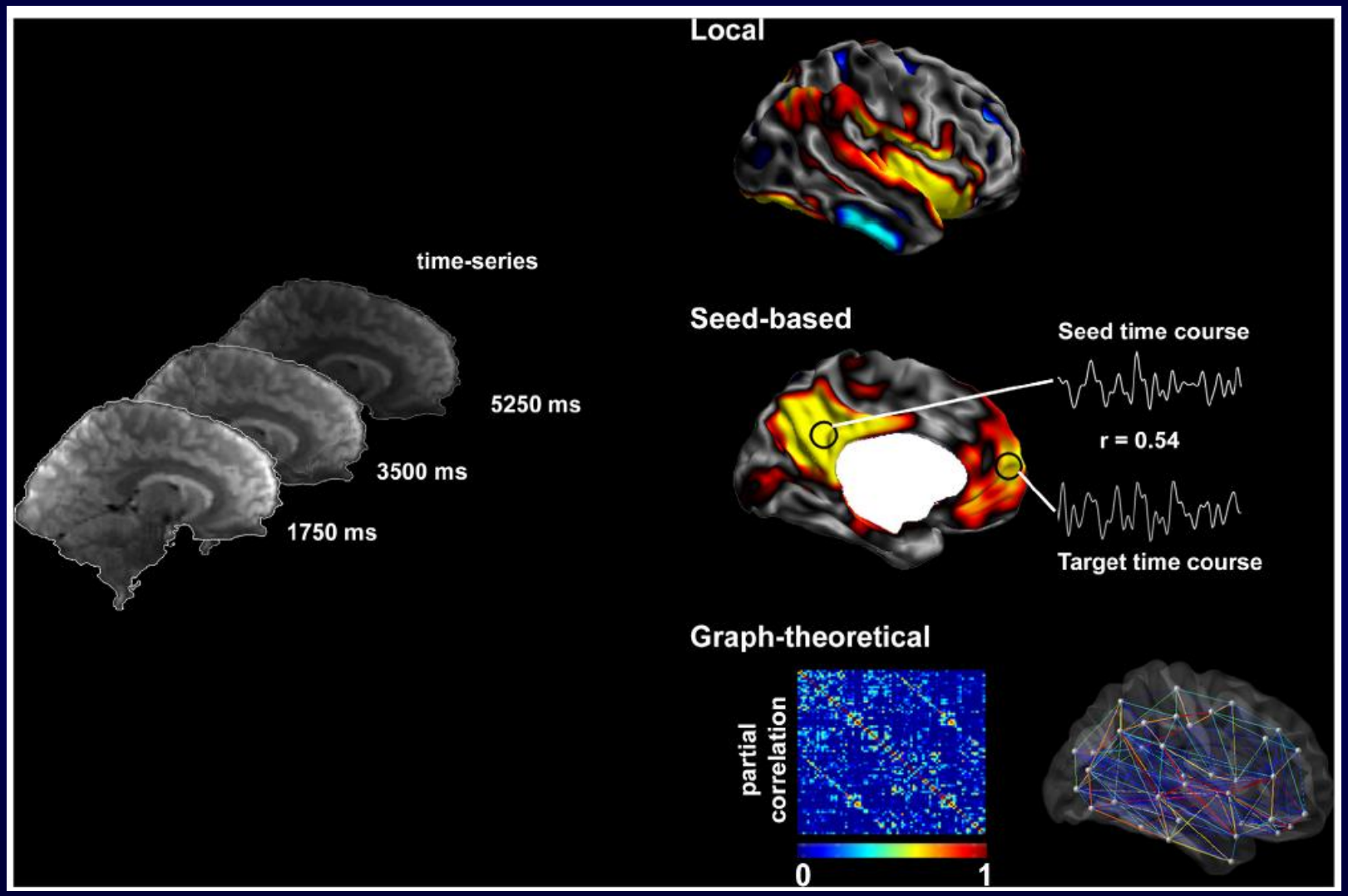
- ✓ There is a positive correlation between structural and functional connectivity although their exact relation is complex

- ✓ Most commonly, structural connectivity is inferred from DTI

van Diessen E et al., Epilepsia 2013

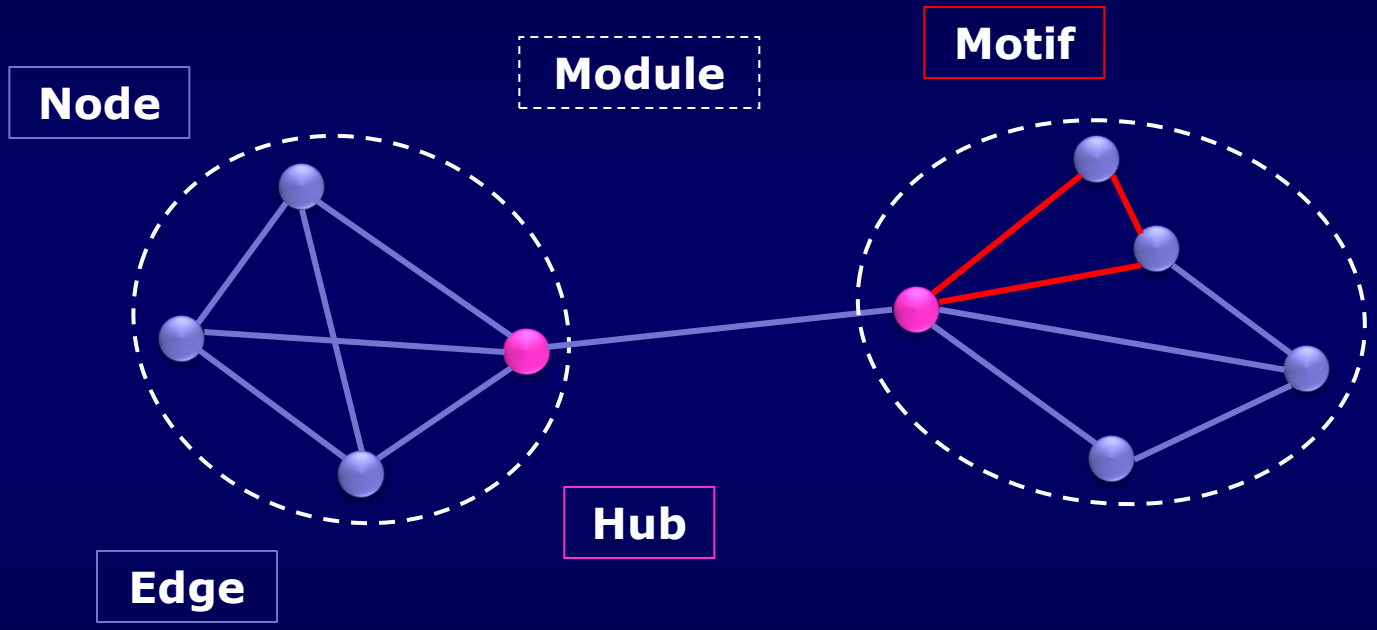
Resting state fMRI (*rs*fMRI)

Methods to assess resting state brain function



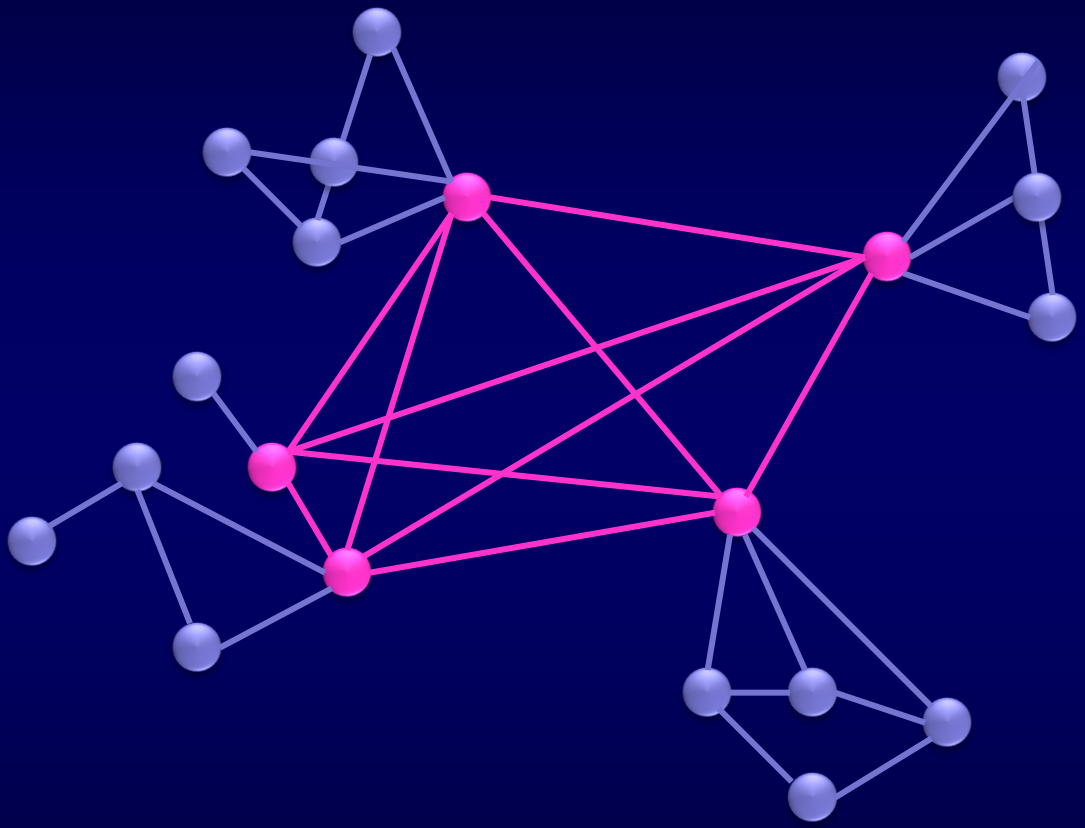
Caciagli L et al., **Frontiers in Neuroscience 2014**

Graph theory: the mathematics of networks



Modifidied from Stam CJ. Nat Rev Neurosci 2014

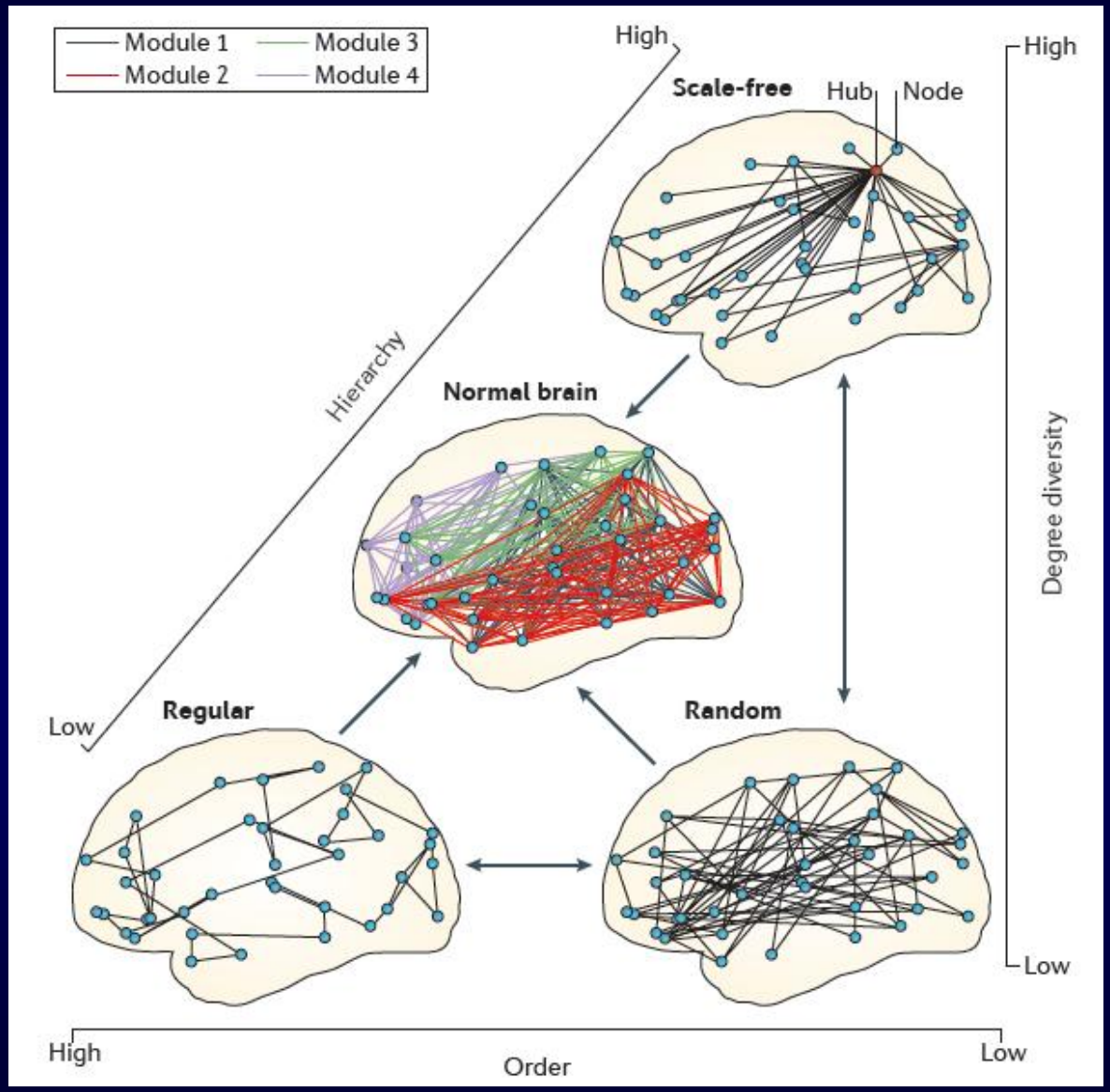
Graph theory: the mathematics of networks



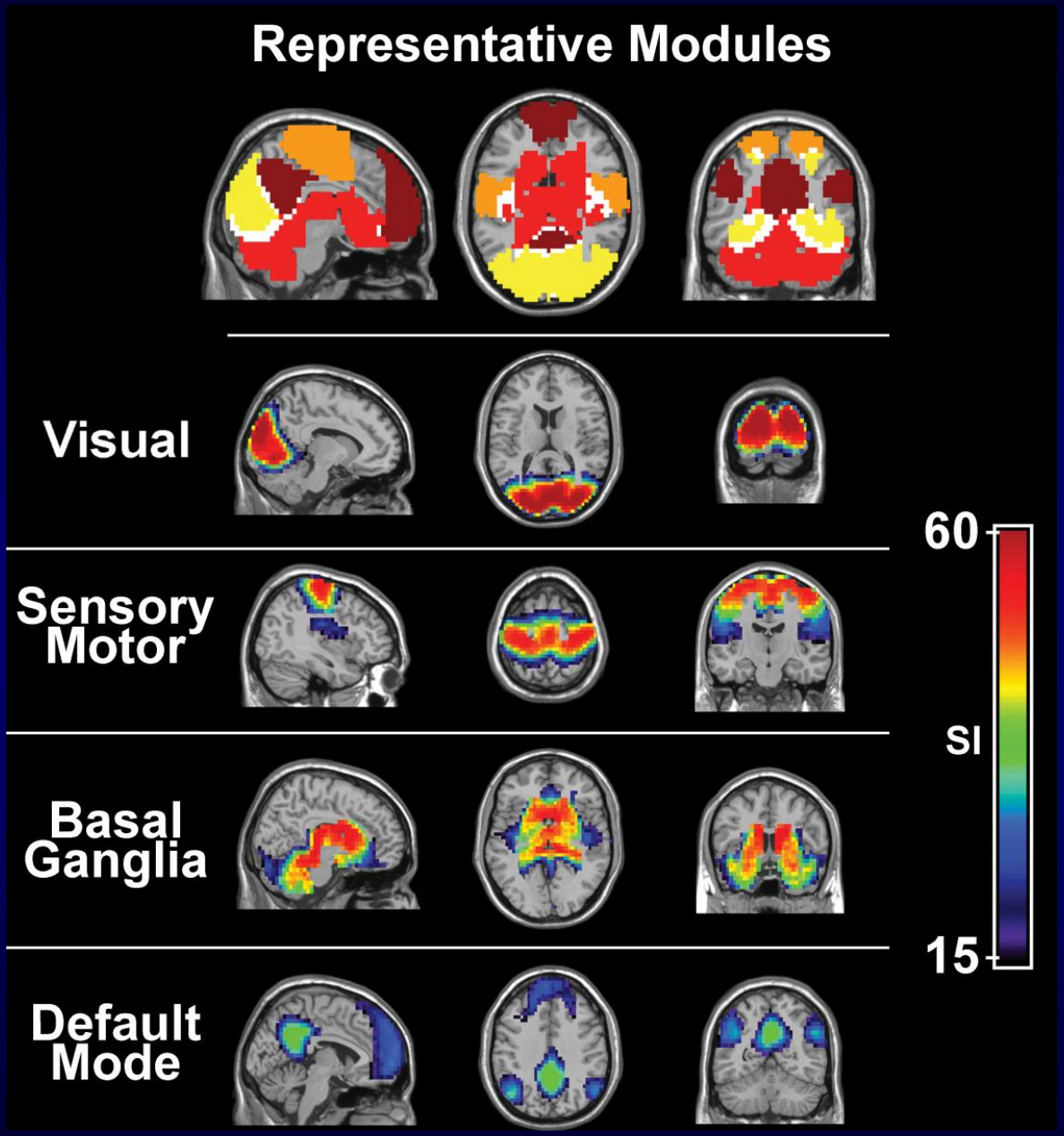
Rich club

Modified from Stam CJ. Nat Rev Neurosci 2014

Graph theory: the mathematics of networks



Stam CJ. Nat Rev Neurosci 2014



Moussa MK et al., Plos One 2012

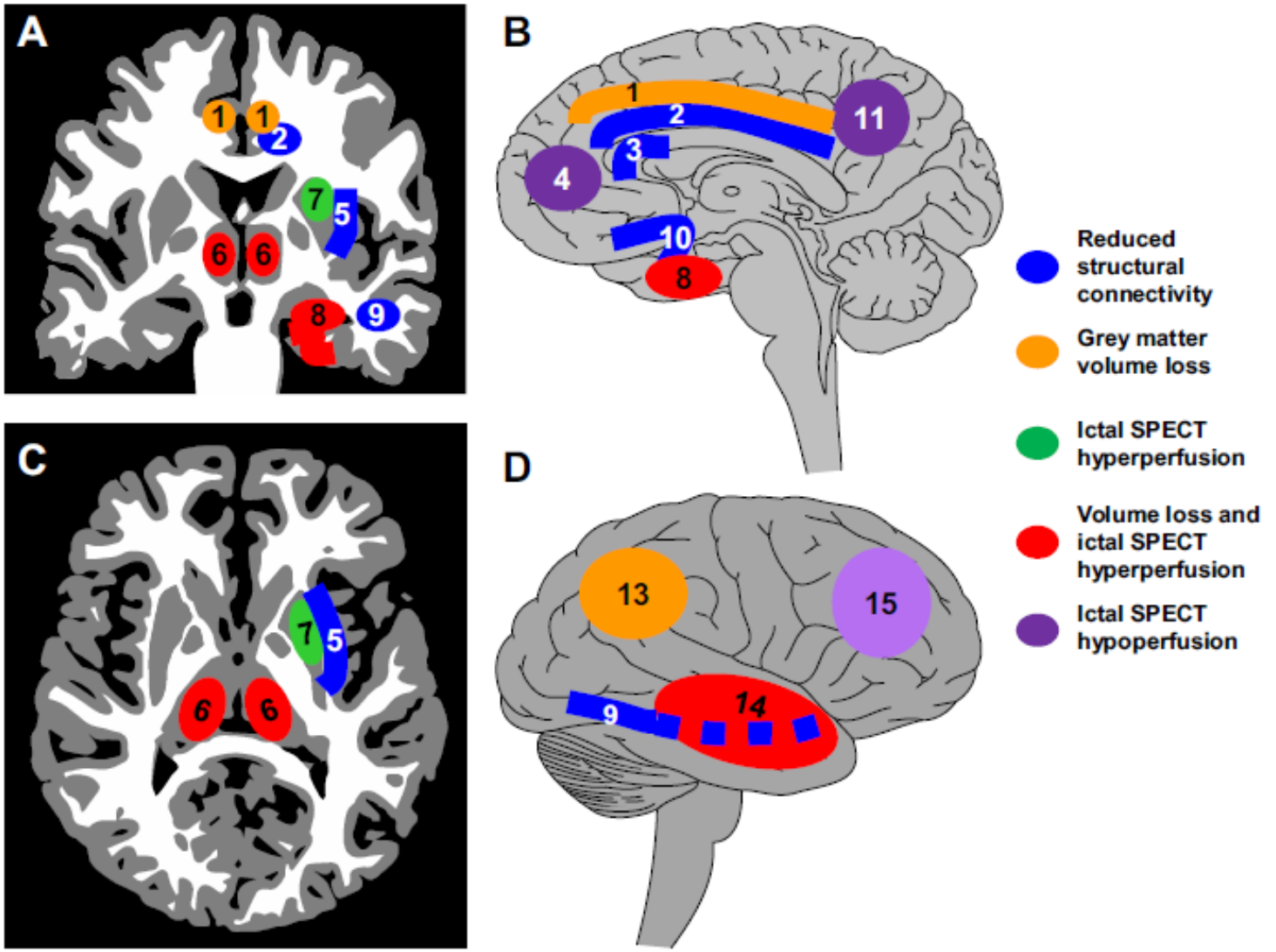
Functional and structural connectivity

Table 1. Overview on strengths and weaknesses of different modalities used in network analytic studies

Modality	Strengths	Weaknesses
Functional networks		
EEG	Widely used in clinical practice High temporal resolution Suitable to study ictal networks	Low spatial resolution (less for high-definition EEG) Sensitive to volume conduction artifacts
Intracranial recordings	Direct electrical recordings of neuronal activity High temporal and spatial resolution No myogenic artifacts	Only available in a surgical setting No whole brain network analysis possible
MEG	High temporal and spatial resolution Source space analysis allows identification of anatomic network specification	Sensitive to movement artifacts Not widely available
fMRI	High spatial resolution Allows the study of subcortical networks separately Widely available	Low temporal resolution Assumption of BOLD changes in respect to electrophysiologic changes in the epileptic brain
Structural networks		
Cortical thickness	Inferred from standard MRI sequences High spatial resolution	Analysis of individual networks complicated Analysis of subcortical structures not possible
DTI	Physical network connections can be studied Both cortical and subcortical structures and their interconnectedness can be studied	Several technical pitfalls when analyzing DTI data Many arbitrary choices in the process of data extraction

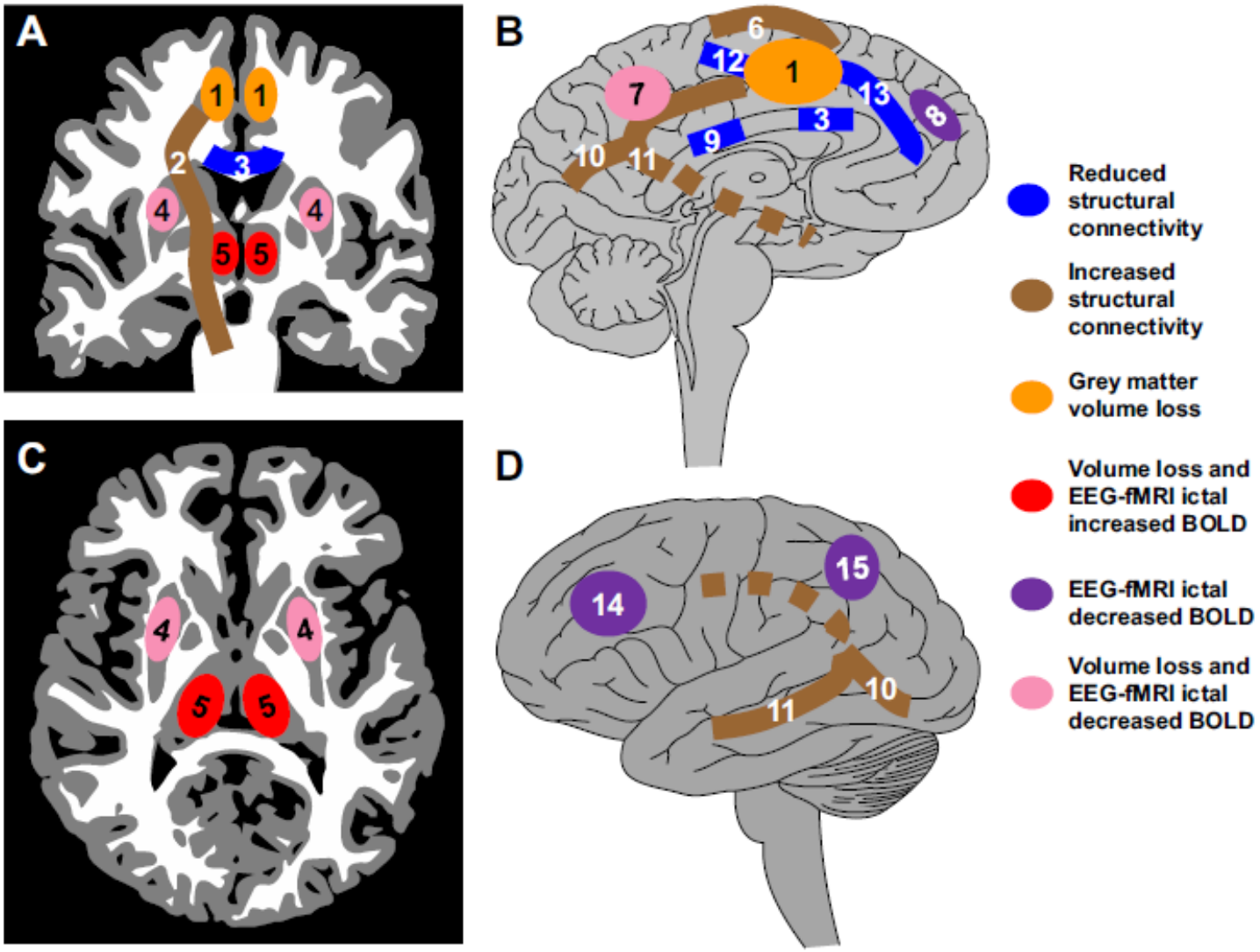
van Diessen E et al., Epilepsia 2013

Brain network abnormalities seen in neuroimaging in MTLE



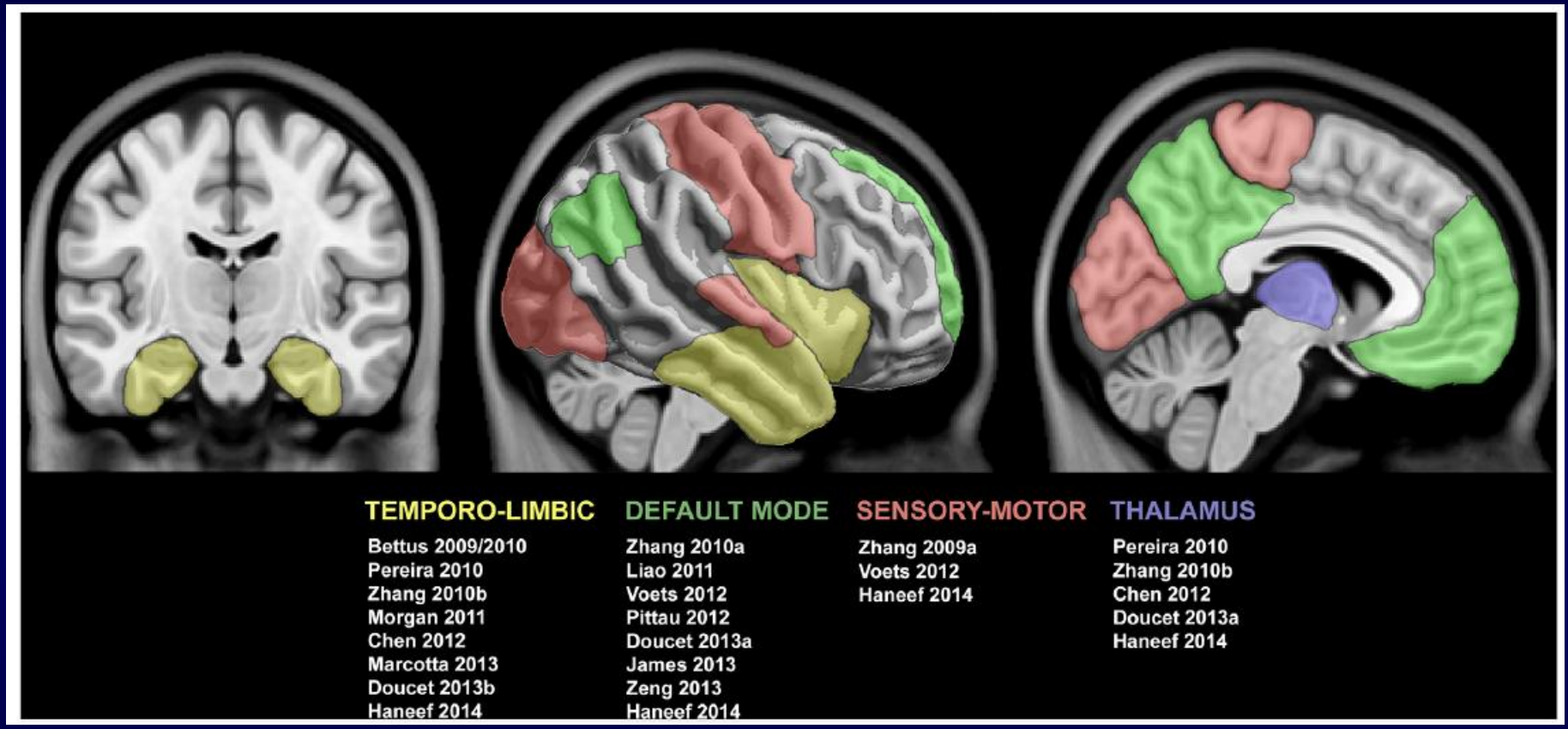
Richardson MP. JNNP 2012

Brain network abnormalities in neuroimaging in JME



Richardson MP. JNNP 2012

Summary of studies reporting functional connectivity anomalies in TLE



Caciagli L et al., Frontiers in Neuroscience 2014

Resting state networks in TLE

- ✓ Epilepsy determines abnormalities in
  - ✓ Default-Mode Network
  - ✓ Activity of Attention Networks
  - ✓ Executive Control Network
  - ✓ Reward/Emotion Network

Cataldi M et al., Epilepsia 2013

Clinical implications of Functional and Structural Networks in Epilepsy

- ✓ Investigation of the mechanisms underlying comorbid cognitive decline (loss of network efficiency)
- ✓ Potential identification of patients at risk for developing cognitive impairment.
- ✓ First seizure and prediction of epilepsy: fc as useful diagnostic tool (>sensitivity and >specificity compared to EEG)
- ✓ Network studies more reliable than epileptiform transients in predictioon of diagnosis of epilepsy

van Diessen E et al., Epilepsia 2013

Clinical implications of Functional and Structural Networks in Epilepsy

- ✓ Functional network biomarkers to predict the risk of seizure recurrence
- ✓ Network properties may improve prediction of outcome (seizure recurrence) after epilepsy surgery
- ✓ Network analysis to improve the outcome of epilepsy surgery:
  - ✓ In patients with TLE with resection of cortical areas with clusters of highly synchronized activity was related to an increased seizure control
  - ✓ Resection of hub nodes that were active during a seizure was associated with seizure freedom in patients with neocortical epilepsy

van Diessen E et al., Epilepsia 2013

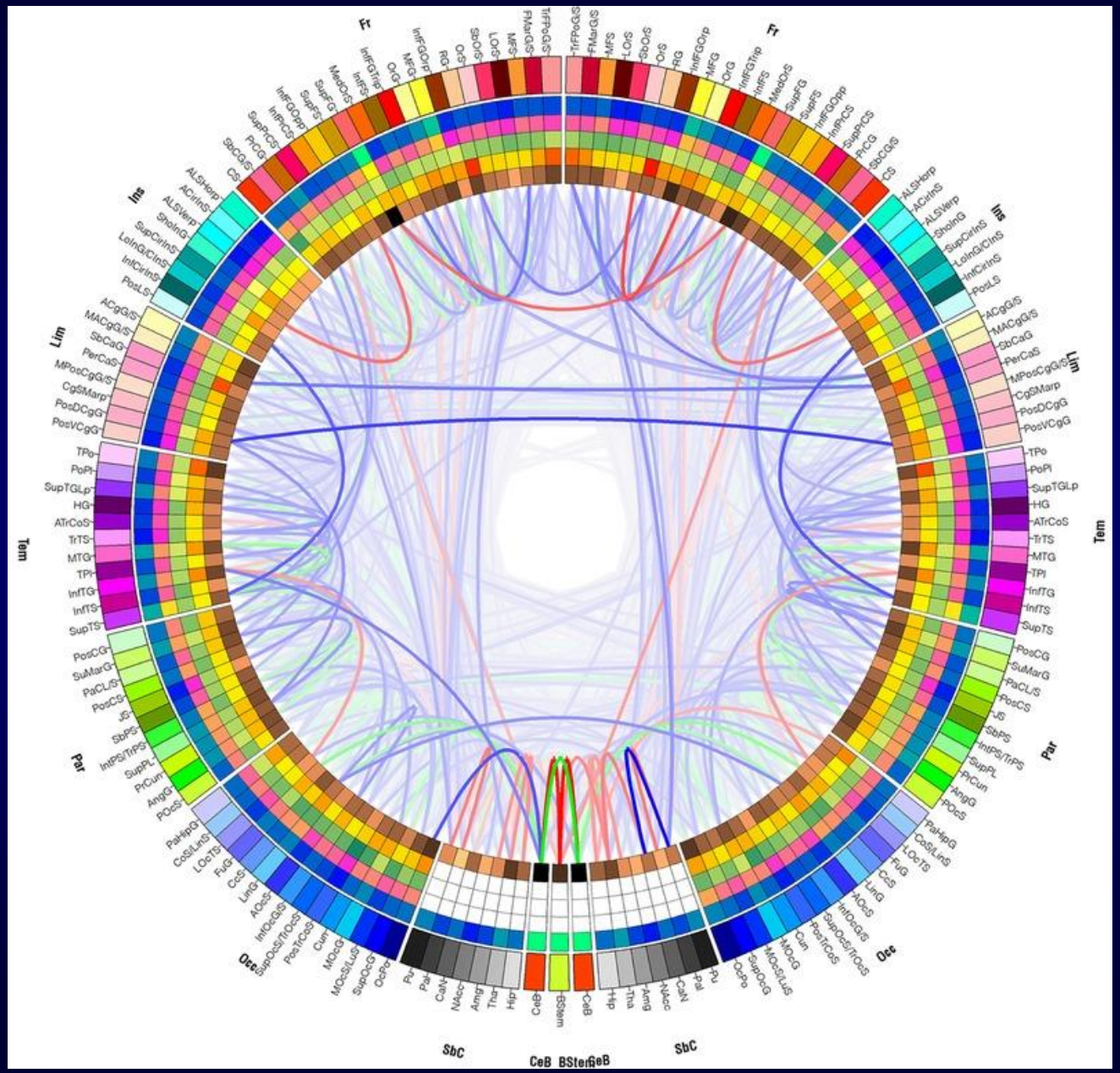
Limitations of *fc* measures

✓ Susceptibility to motion-induced artefacts and physiological noise (i.e., respiration and pulse-related artifacts)
✓ Heterogenous approach in "cleaning" and filtering resting-state fMRI data
✓ Scanner-to-scanner variability, lack of acquisition standards.
✓ Small sample sizes of the studies (typically < 30 patients with epilepsy)

✓ Heterogeneous and polymorphic nature of epilepsy

Abela E et al., Clin Neuroradiol 2014

Perspectives and future directions



Conclusions

✓In both focal and generalized epileptiform discharges functional activation and deactivation in specific large-scale networks

✓Circumscribed epileptogenic process can have extended effects on many brain systems

✓Possible explanation of different epilepsy related aspects (cognitive impairment, pharmacoresistance, seizure propagation pathways or the effect of resective operations)

✓Better understanding of altered network as a way for development of biomarkers for epilepsy and its pathophysiology


NEUROLOGIST
PHYSICIST
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