Large-scale brain dynamics and neurologic disturbances of consciousness

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Sloan-Swartz Summer Meeting
July 2007
San Diego, CA

Overview

- Summary: humans with severe structural brain damage present an important opportunity to test models of large-scale brain dynamics and their functional roles
- Plan
  - A neurological view of consciousness
  - Neural substrates
  - Evidence from animal studies
  - A minimal model
  - Opportunities to study large scale brain dynamics in man

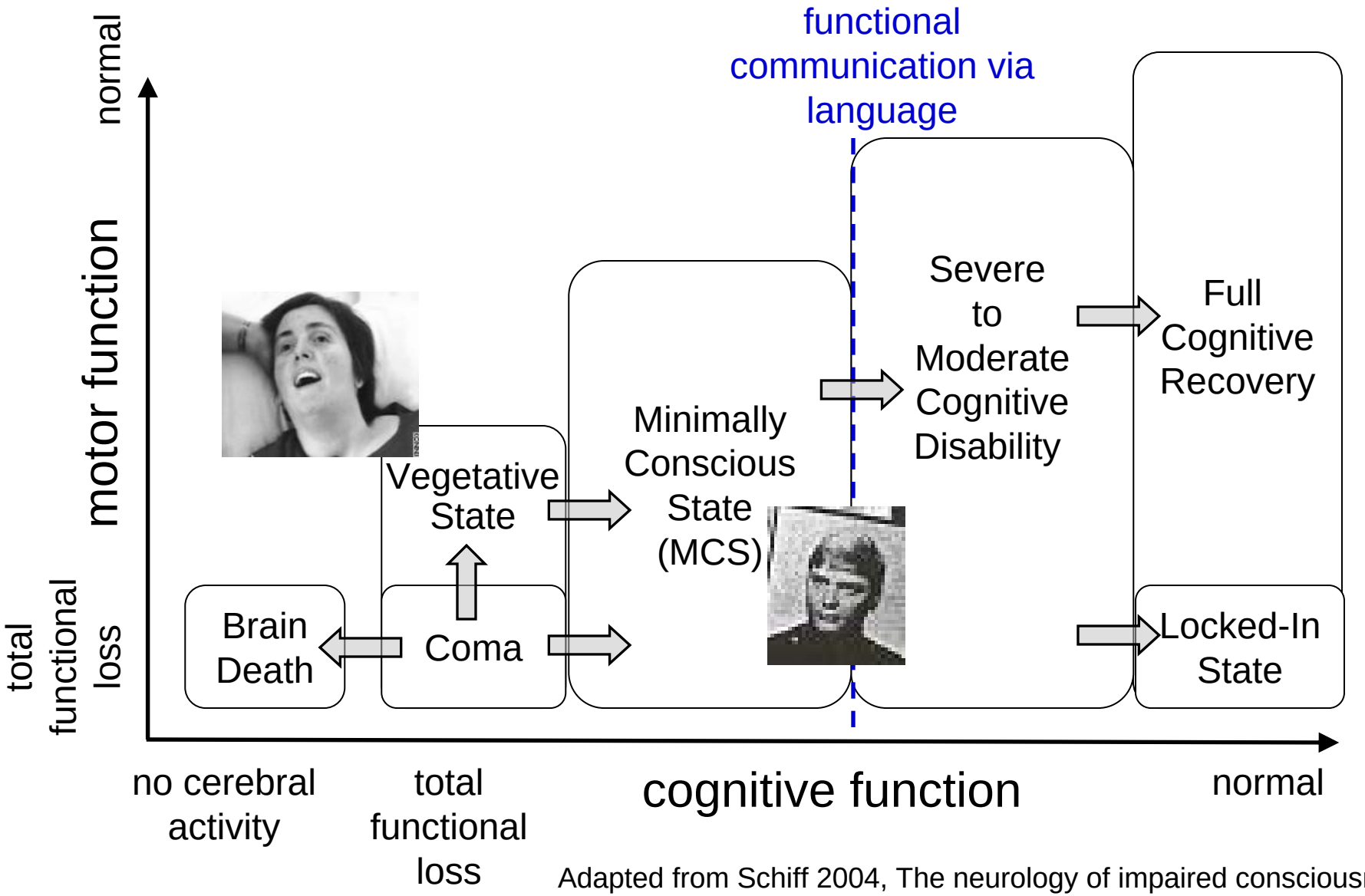
A Neurological View

- Arousal
  - coma to delirium
  - arousal necessary but not sufficient for organized behavior
- Attention
  - spatial and/or temporal selectivity
  - maintenance over time
- A conceptual scheme for global disorders of consciousness
  - Operational definition of reflexive vs. conscious behavior
  - “Hard Data”: metabolic imaging at rest and with activation
- State changes over time
  - Slow timescales: well-recognized in survival following devastating injuries
  - Rapid timescales: not so well recognized or understood

Some Definitions

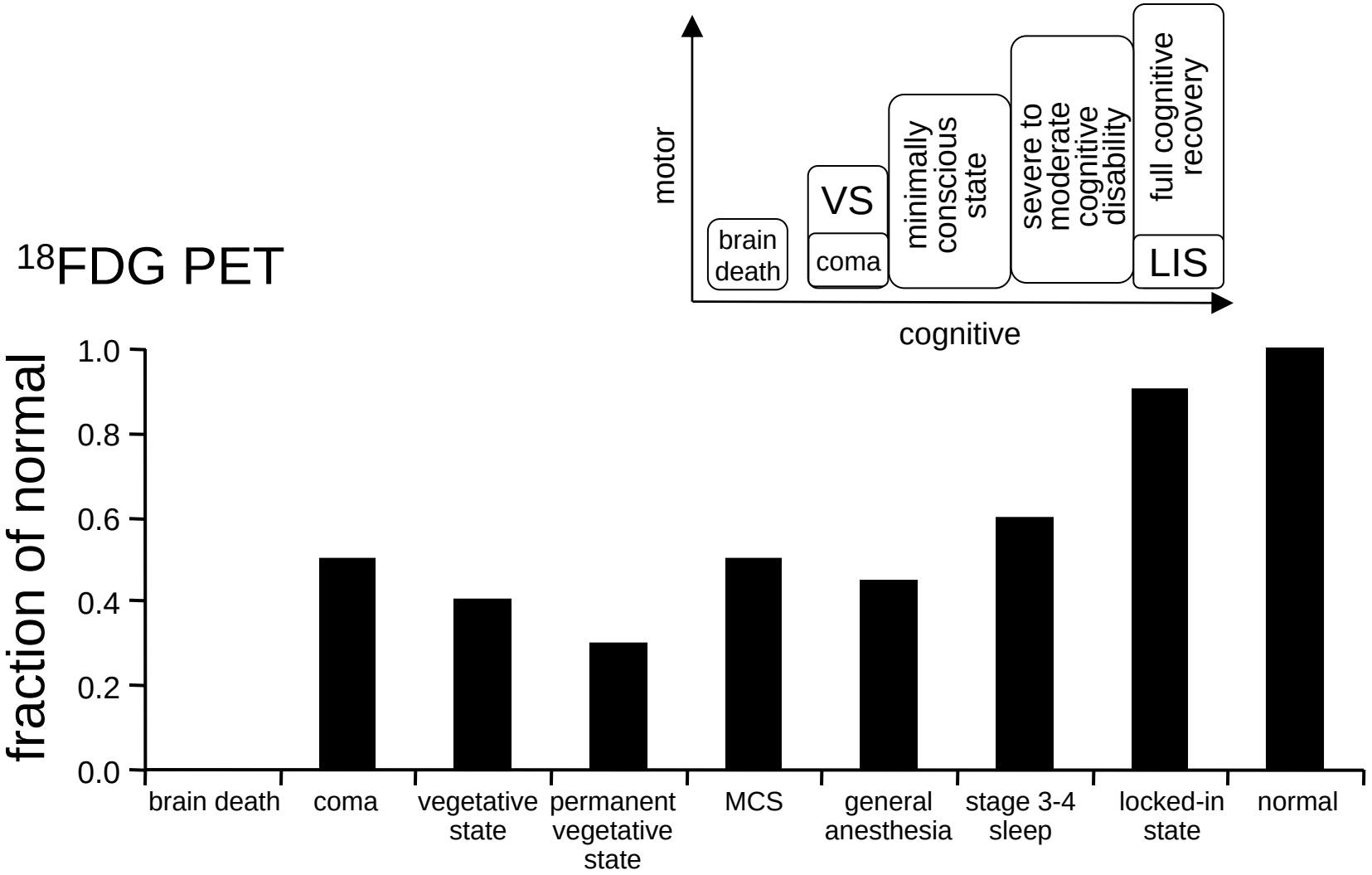
- Coma
  - unarousable unresponsiveness with eyes closed
  - brainstem and spinal reflexes may be present
  - *always* transient
- Vegetative State (Jennett and Plum, 1972)
  - unresponsiveness with cyclic periods of “asleep” and “awake” states manifest by spontaneous eye opening
  - arousal to stimulation and conjugate eye movements typically present
- Minimally Conscious State (Giacino et al., 2002)
  - severely altered consciousness with intermittent but definite behavioral evidence of self or environmental awareness
  - non-stereotyped motor responses, fragments of speech
- Locked-in State (Plum and Posner, 1966)
  - Apparent unresponsiveness due to complete de-efferentation
  - Eyes may be open or closed
  - *Not* a disorder of consciousness

Global Disorders of Consciousness



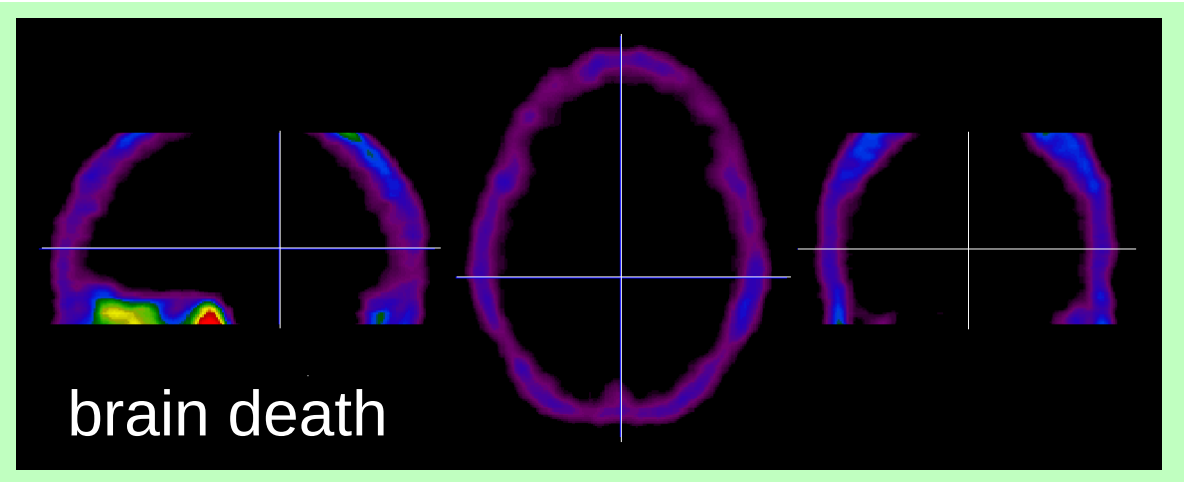
Adapted from Schiff 2004, The neurology of impaired consciousness. In: The Cognitive Neurosciences III, MIT Press

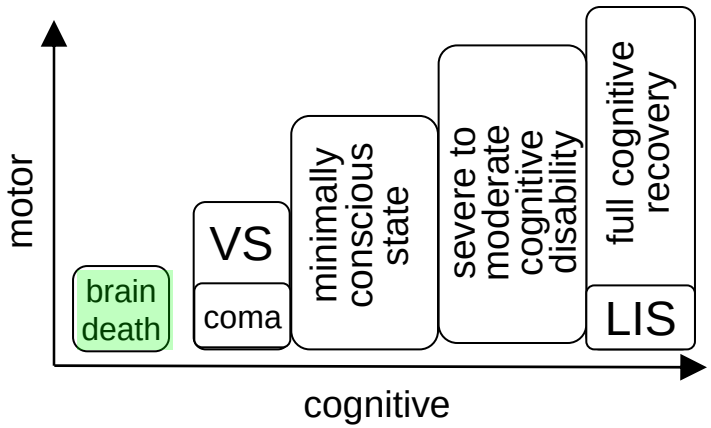
Resting Cerebral Metabolism Across States

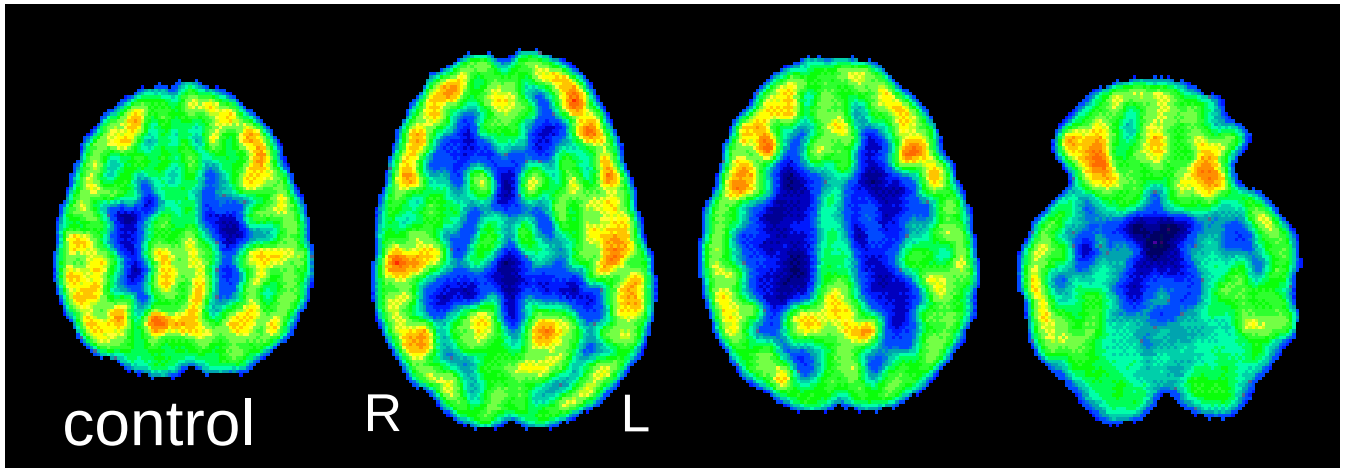


Laureys, Owen, and Schiff (2004)

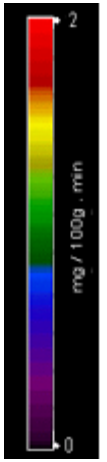
Cerebral Metabolism is Absent in Brain Death







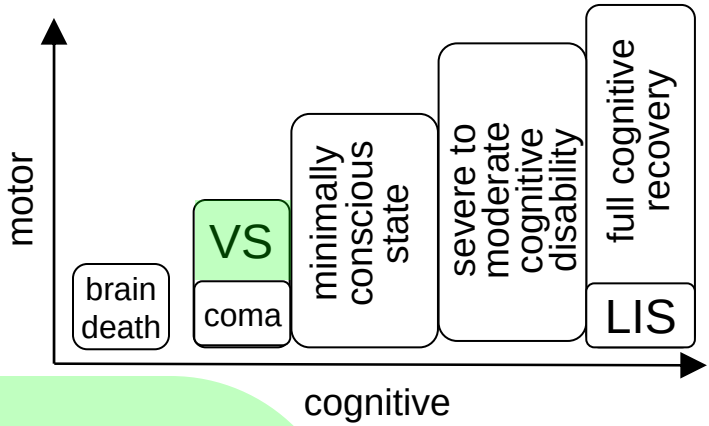
^{18}FDG-PET



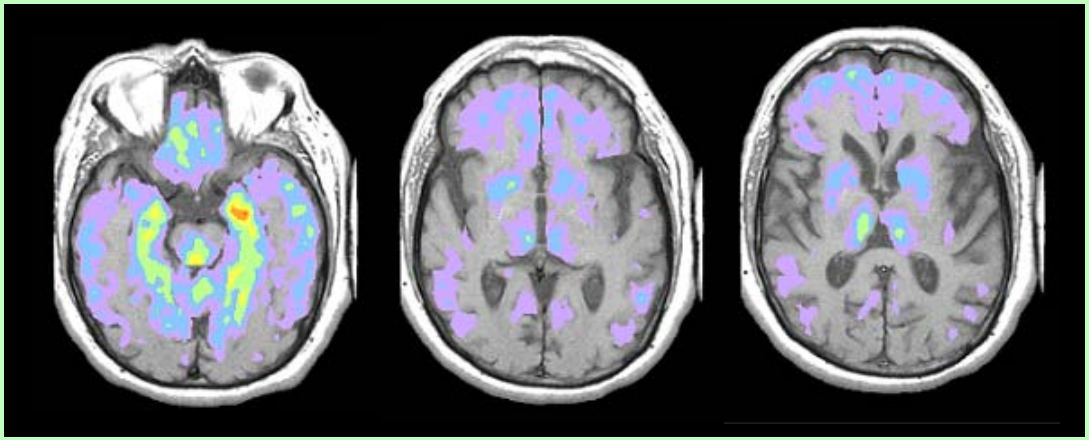
2 mg/100g-min

Laureys, Owen, and Schiff (2004)

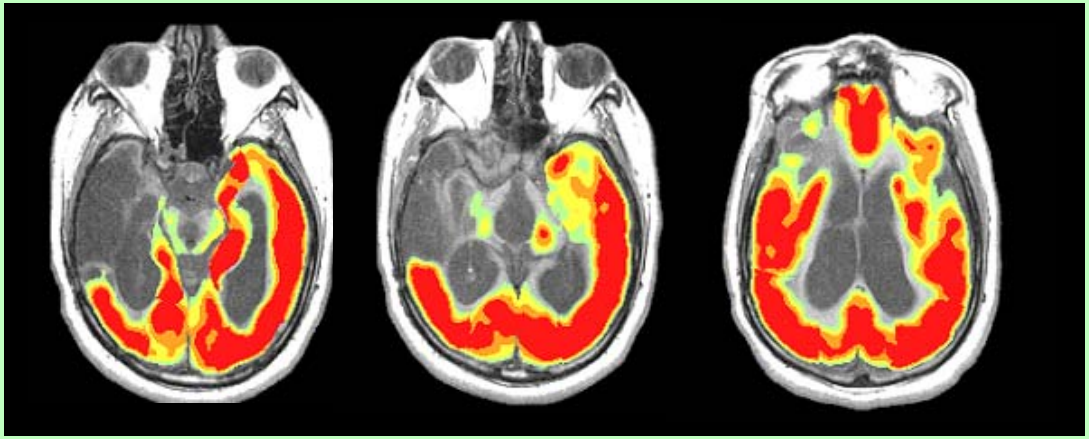
Resting Cerebral Metabolism is Markedly Reduced in Persistent Vegetative State



minimal cortical activity (4/5 patients)



near-normal cortical activity but minimal core brainstem activity



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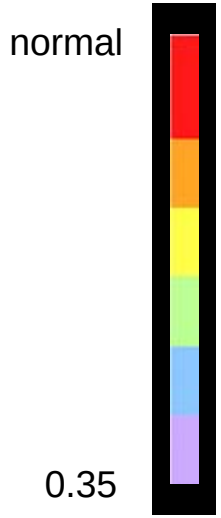
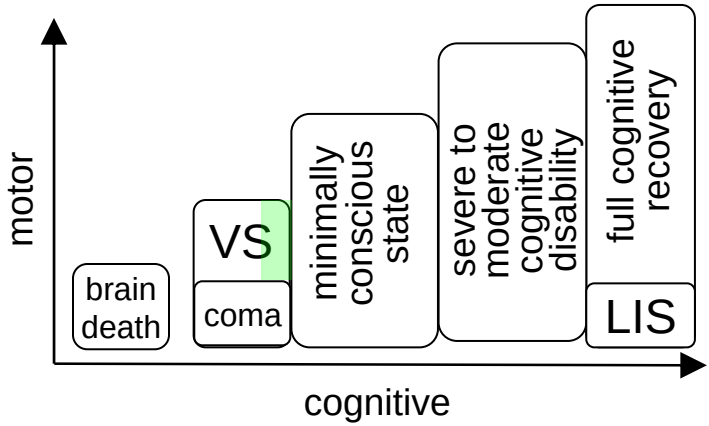
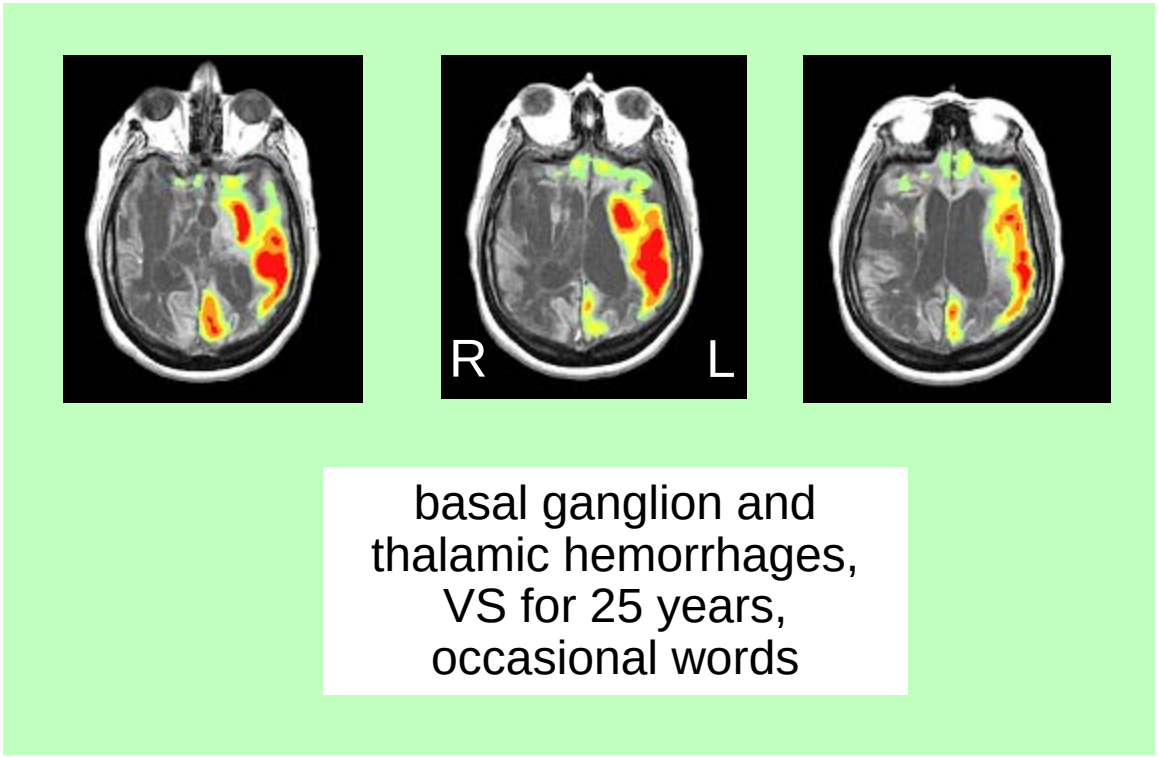


Schiff, Ribary et al., 2002

Near-Normal Islands of Cerebral Metabolism in VS with Behavioral Fragments





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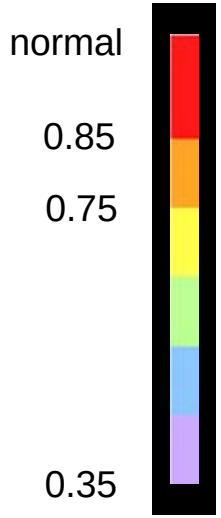


Islands of high metabolic activity, brain average is < 50% of normal

Schiff, Ribary et al., 1999

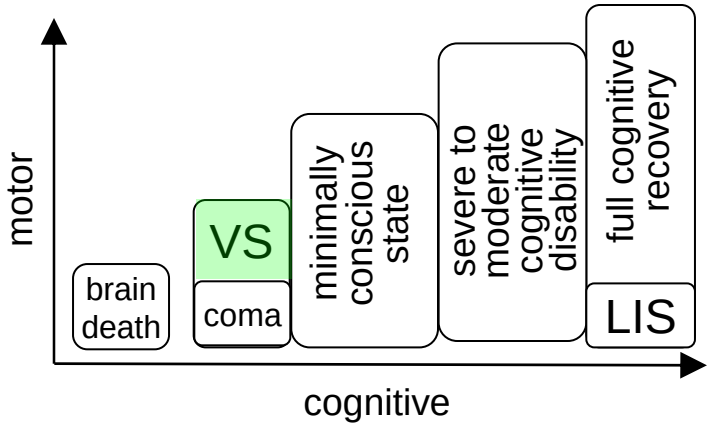
Activation by Noxious Stimuli in Vegetative State: Disconnection

electrical stimulation of median nerve

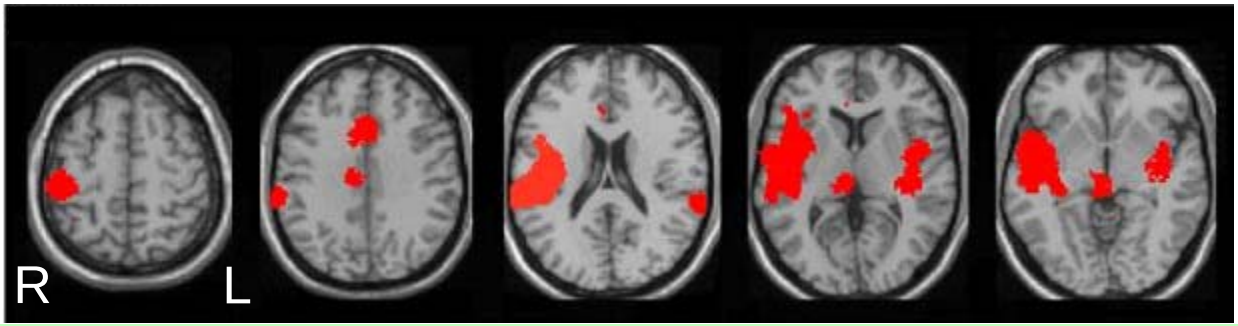
^{18}FDG PET

normal activation

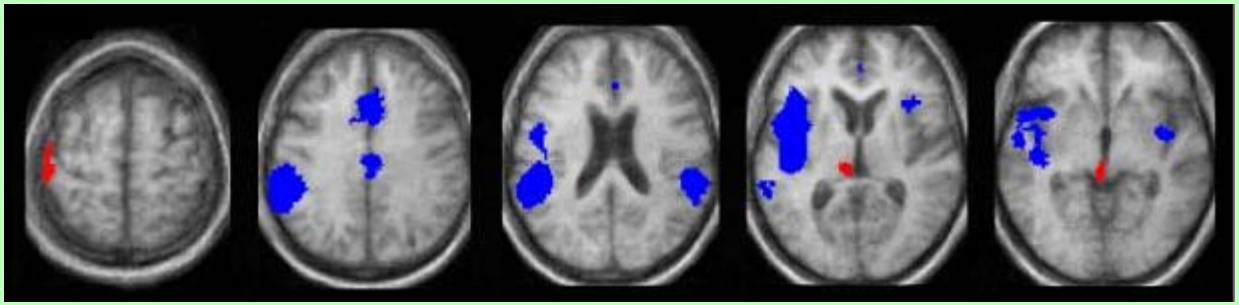
no activation AND significantly different from normal activation



controls (N=15)



persistent VS (N=15)

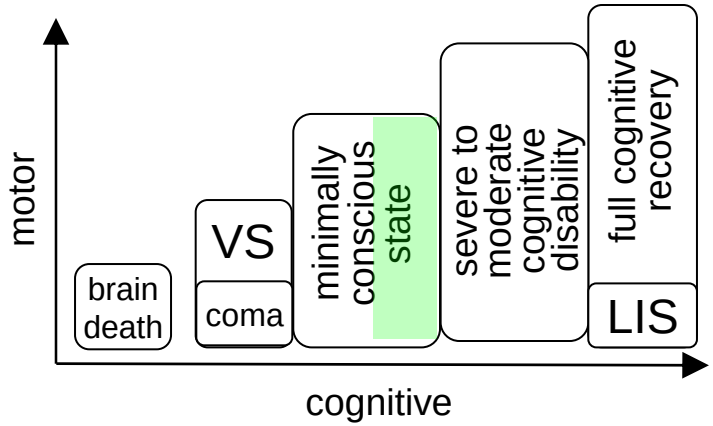


Normal activation of primary cortex and thalamus, but no activation of association cortices or contralateral areas

Laureys, Faymonville et al. 2002

Activation by Speech in MCS: Present but Abnormal

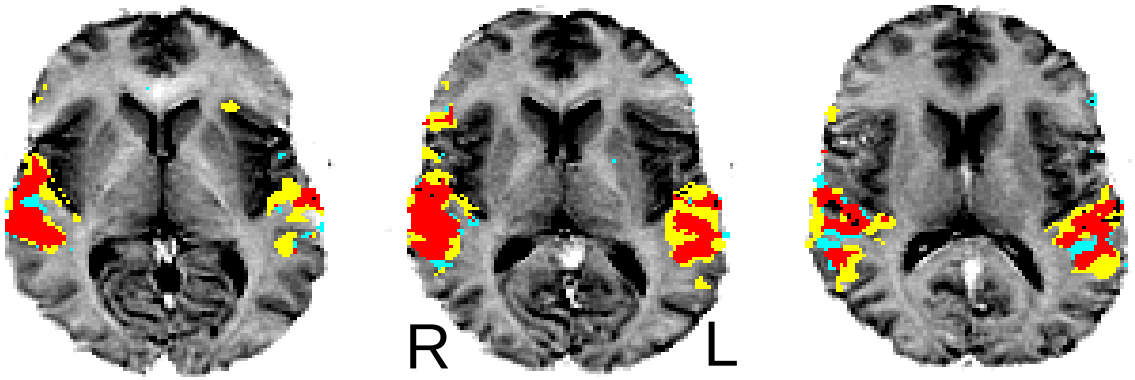
passive presentation of speech, familiar voice



fMRI activations

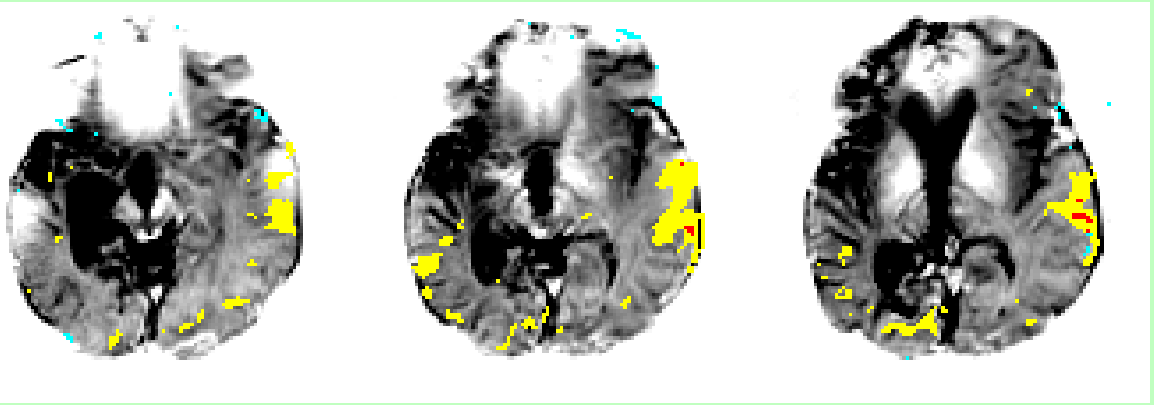
- Forward Speech
- Reversed Speech
- Overlap

control



MCS

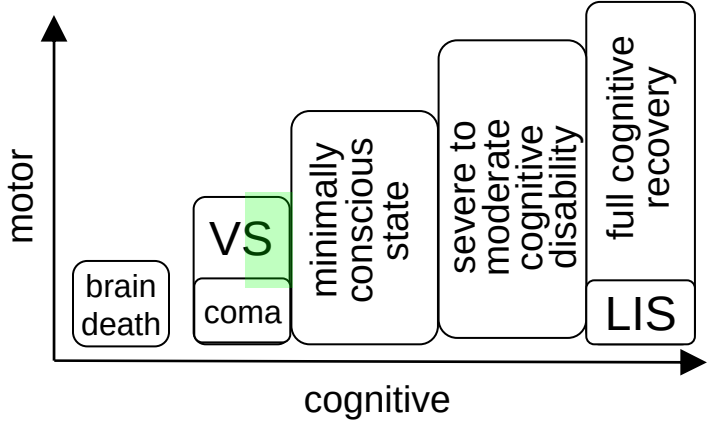
Hemorrhage -> VS
VS -> MCS at 1 yr
studied at yr 2.5
^{18}FDG: 41% of normal



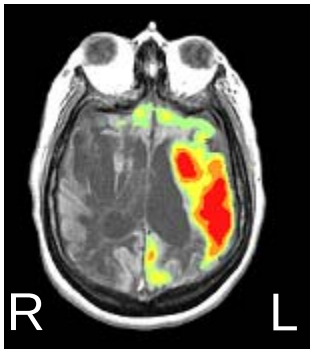
Schiff, Rodriguez-Moreno, et al., 2005

EEG Correlates of State

EEG Correlates of Hemispheric Dysfunction in VS: Coherence, not Power

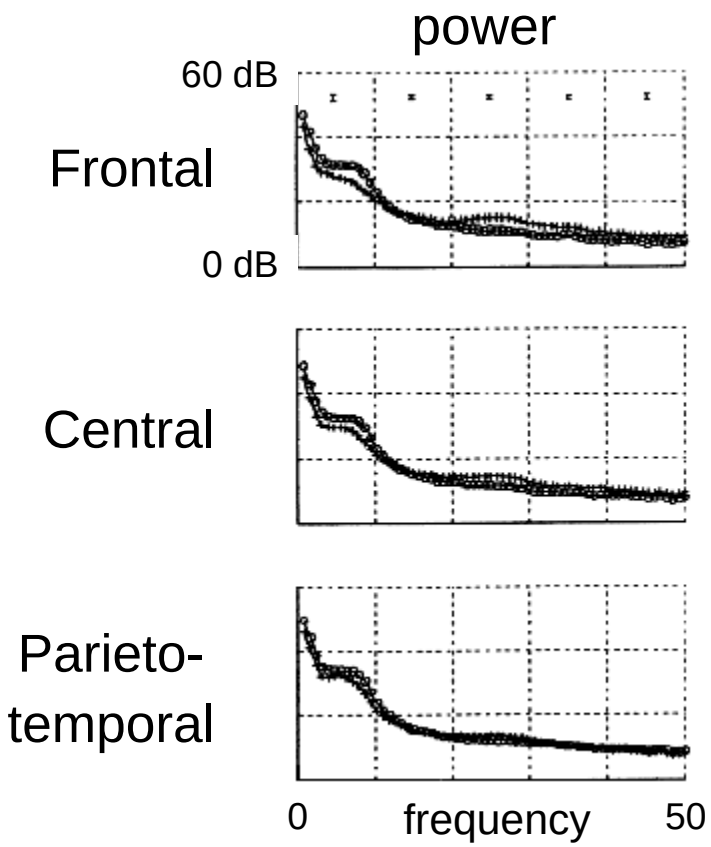


basal ganglion and thalamic hemorrhages, VS for 25 years, occasional words



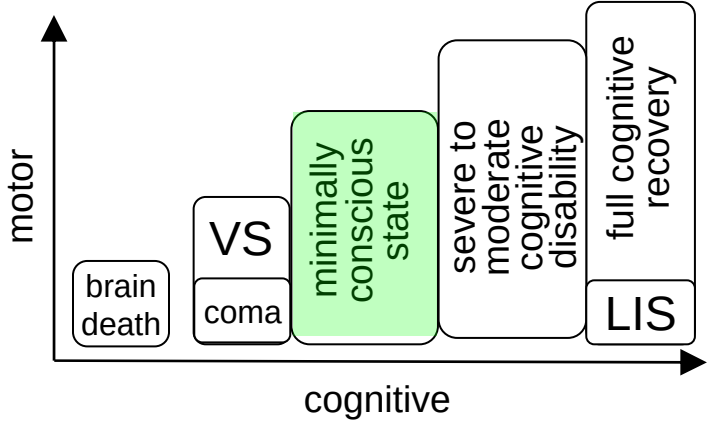
^{18}FDG-PET

0.35 0.85 normal

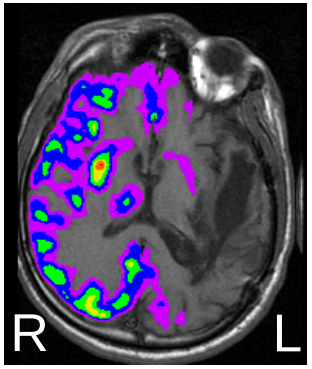


Davey, Victor, Schiff, 2000

EEG Correlates of Hemispheric Dysfunction in MCS: Coherence, not Power



MCS, 18 mos



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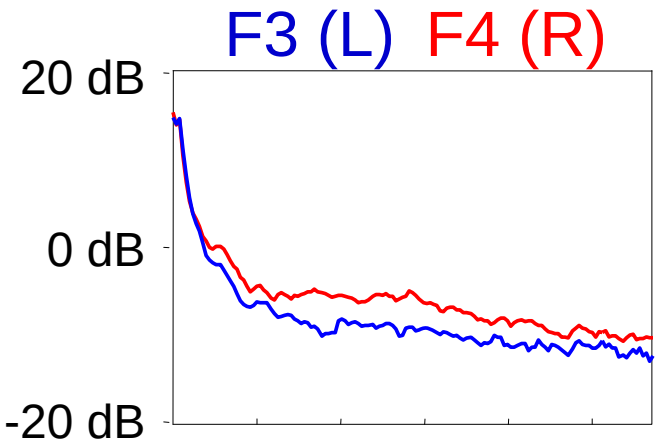
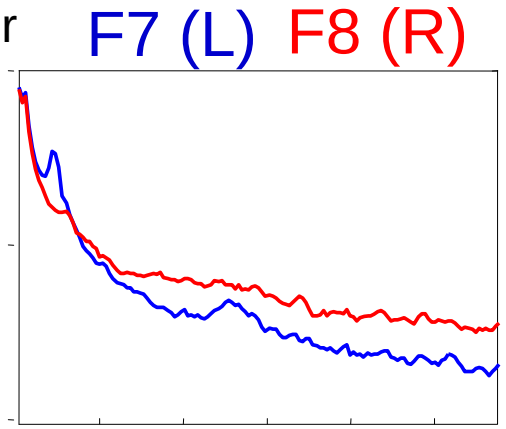
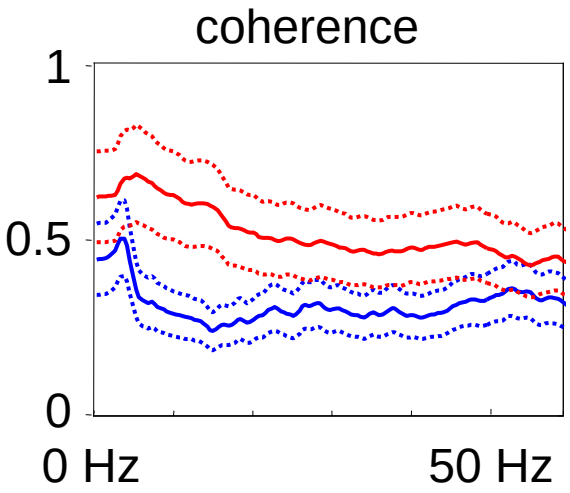
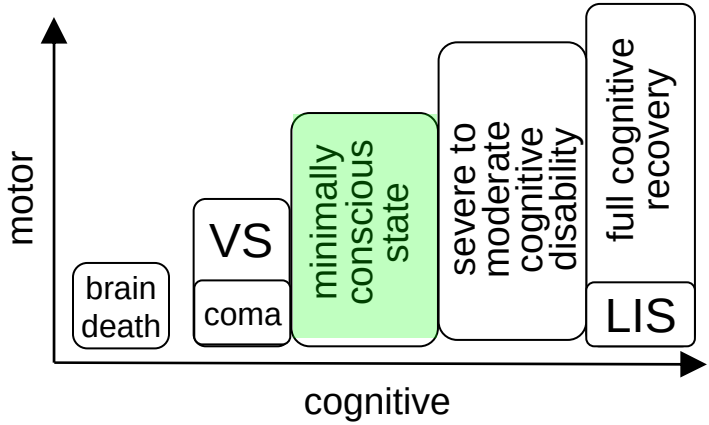


power

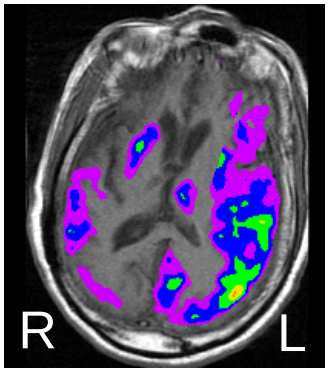




EEG Correlates of Hemispheric Dysfunction in MCS: Sleep-Wake Dependence

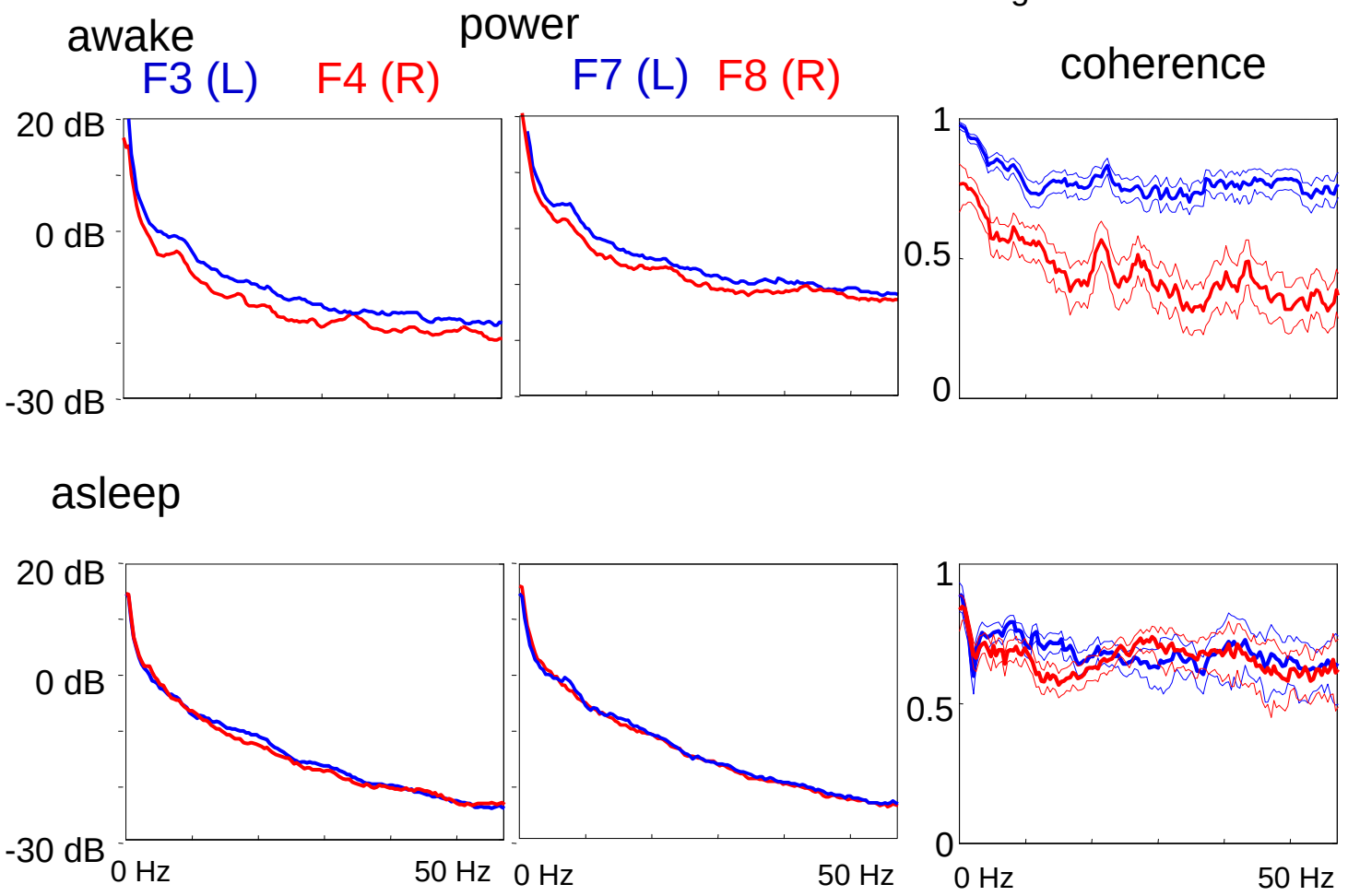


blunt head trauma,
VS for < 1 yr,
MCS for 2.5 yrs,
follows commands

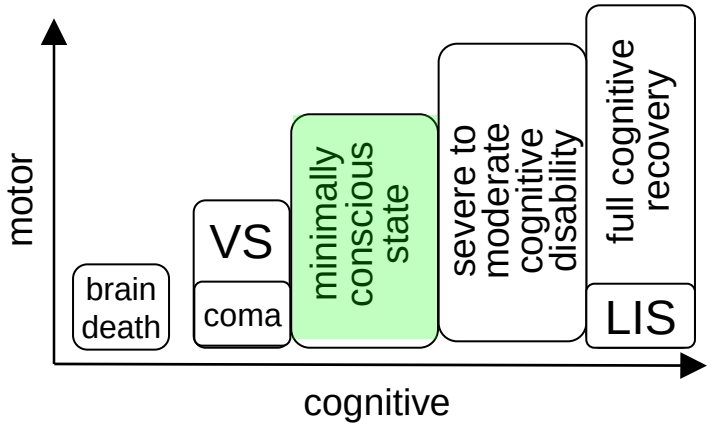


^{18}FDG-PET

0.35 0.85 normal

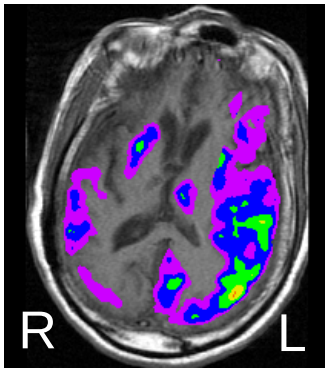


EEG Correlates of Hemispheric Dysfunction in MCS: Harmonic Structure



awake

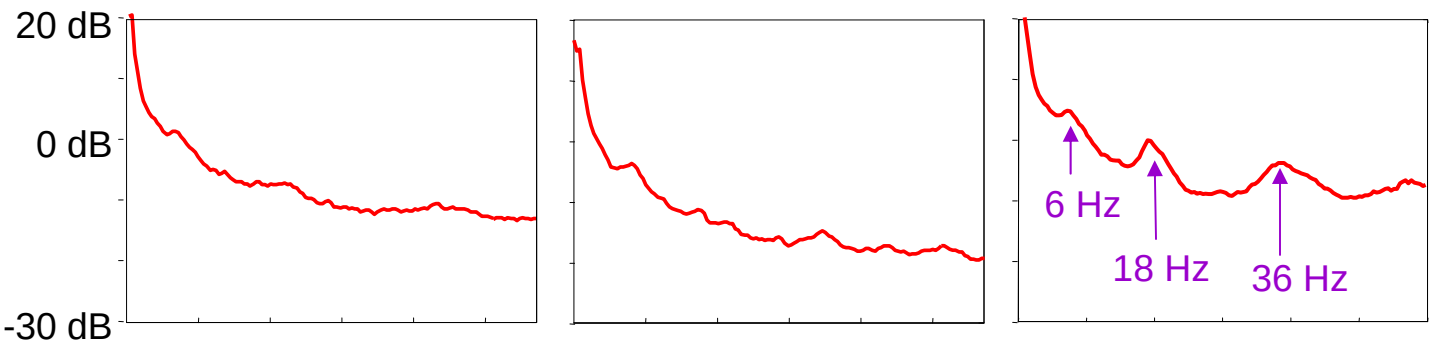
blunt head trauma,
VS for < 1 yr,
MCS for 2.5 yrs,
follows commands



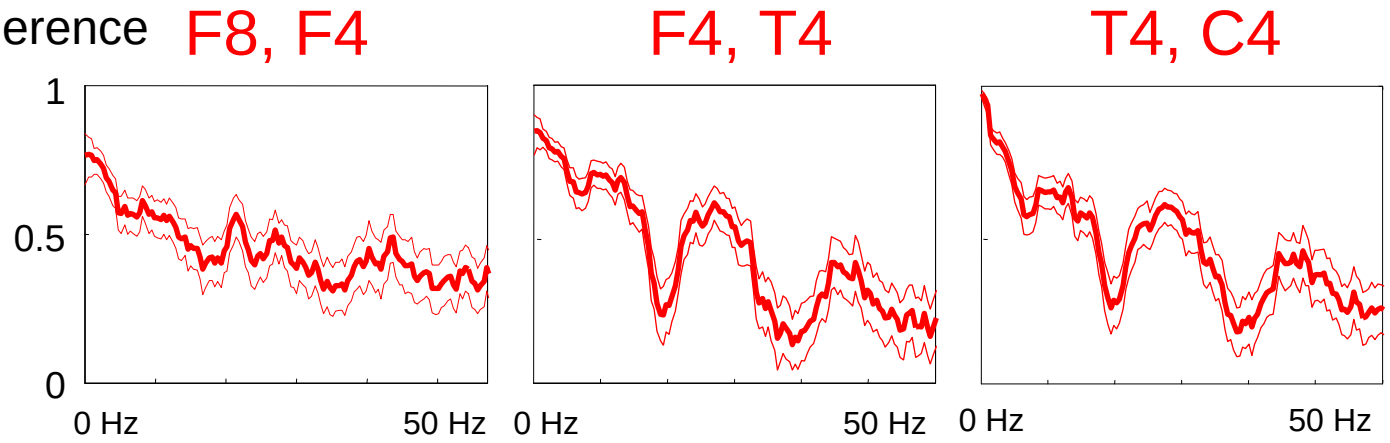
^{18}FDG-PET

0.35 0.85 normal

power



coherence



Neural Substrates

- Neurologic abnormalities producing disturbances of consciousness
  - Diffuse cortical
  - Reticular activating system (Moruzzi and Magoun, 1949)
- Arousal and gating systems
  - Midbrain glutamatergic neurons: excitation of thalamic intralaminar nuclei (Steriade and Glenn, 1982)
  - Pontine cholinergic neurons: inhibition of thalamic reticular nucleus and excitation of thalamic relay nuclei (Steriade et al., 1997, et al.)
  - Thalamic reticular nucleus inhibits relay neurons (Skinner and Yingling, 1977)
- Thalamic relay nuclei
  - Excitation to cortical granular layers
    - LGN, etc: primary cortices
    - Pulvinar: association cortices
  - Reciprocal inhibition (via interneurons) from cortical output layers
- Thalamic intralaminar nuclei
  - Project to superficial and infragranular layers in specific combinations of cortices
  - Project to basal ganglia
  - Hypothesis: supports inter-regional coactivations that enable organized behavior

First demonstrations of control of arousal regulation through electrical stimulation of the central thalamus

COMMUNICATIONS

BRAIN STEM RETICULAR FORMATION AND ACTIVATION OF THE EEG [1]

G. Moruzzi, M.D. [2] and H. W. Magoun, M.D.
Department of Anatomy, Northwestern University Medical School

Transitions from sleep to wakefulness, or from the less extreme states of relaxation and drowsiness to alertness and attention, are all characterized by an apparent breaking up of the synchronization of discharge of elements of the cerebral cortex, an alteration marked in the EEG by the replacement of high-voltage slow waves with low-voltage fast activity. The magnitude of the electrical change parallels the degree of transition, and that most commonly observed in clinical electroencephalography is a minimal one, consisting of an alpha-wave blockade during attention to visual stimulation. Such activation of the EEG may be produced by any type of afferent stimulus that arouses the subject to alertness, or it may be centrally generated, but the basic processes underlying it, like those involved in waking from sleep, have remained obscure.

Recent experimental findings which may contribute to this subject have stemmed from the observation that EEG changes seemingly identical with those in the physiological arousal reactions can be produced by direct stimulation of the reticular formation of the brain stem. The following account describes such features of the response and its excitable substrate as have been determined, provides an analysis of changes in cortical and thalamic activity associated with it, and explores the relations of this reticular activating system to the arousal reaction to natural stimuli. Alterations produced by acute lesions in this system are presented in a succeeding paper. The effects of chronic lesions within it are under investigation.

METHODS

The experiments were performed in cats under chloralosane anesthesia (35-50 mgm./K, intraperitoneally) or in the "encéphale isolé" of Bremer, prepared under ether, with exposure margins infiltrated with procaine. Ephedrine was administered intravenously immediately after transection of the cord at C 1. At least an hour elapsed after ether was discontinued before work was begun.

Concentric bipolar electrodes, oriented with the Horsley-Clarke technique, were used for stimulation of, or pickup from, the brain stem. Condenser discharges from a Goodwin stimulator were employed routinely. Lesions were made surgically or electrolytically, and their positions, together with those of electrode placements, were verified histologically.

Potentials were recorded with a Grass model III amplifier and inkwriter. Some cortical records were taken directly from the pial surface, but usually as much of the brain case as possible was left intact, and most cortical pickups were between two screw electrodes, 5-10 mm. apart, inserted through burr holes in the calvarium until their tips rested on the dura overlying functional areas. With bipolar leads and by grounding the scalp, stimulus artifacts were negligible. Other technical details are given in the legends.

[1] Aided by a grant from the National Institute of Dental Health, U. S. Public Health Service.
[2] University of Pisa, Italy. Visiting Professor of Neurology, supported by the Rockefeller Foundation.

Moruzzi and Magoun et al. 1949

B. Effect of Excitatory State or Levels of Consciousness

The spontaneous electrical rhythms of the brain are most sensitive to functional states best described under the heading of alterations in the level of consciousness or attention. The alpha and beta rhythms

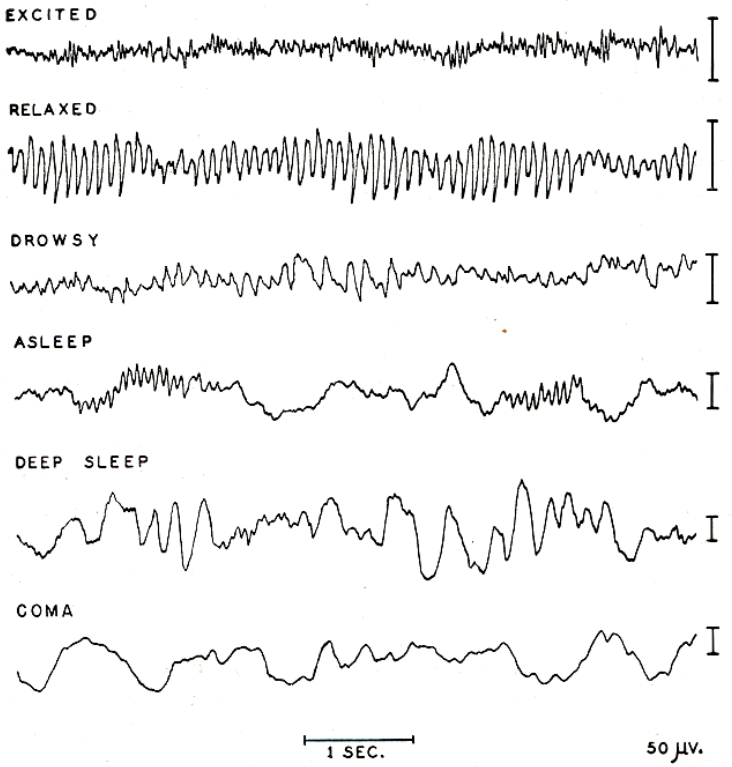


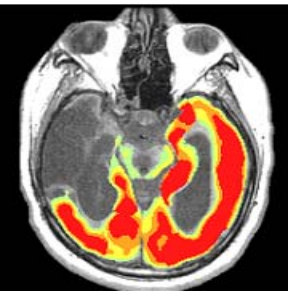
Fig. V-2.

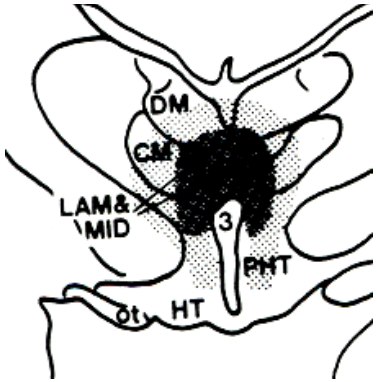
Fig. V-2. Characteristic electroencephalograms during variations in states of consciousness.

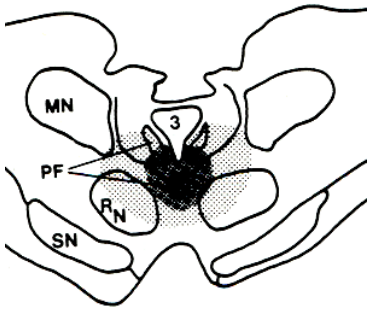
Penfield, WG, Jasper, HH, (1954) *Epilepsy and the functional anatomy of the human brain*

Localization of focal subcortical injuries producing acute coma

80% of cases include dark regions

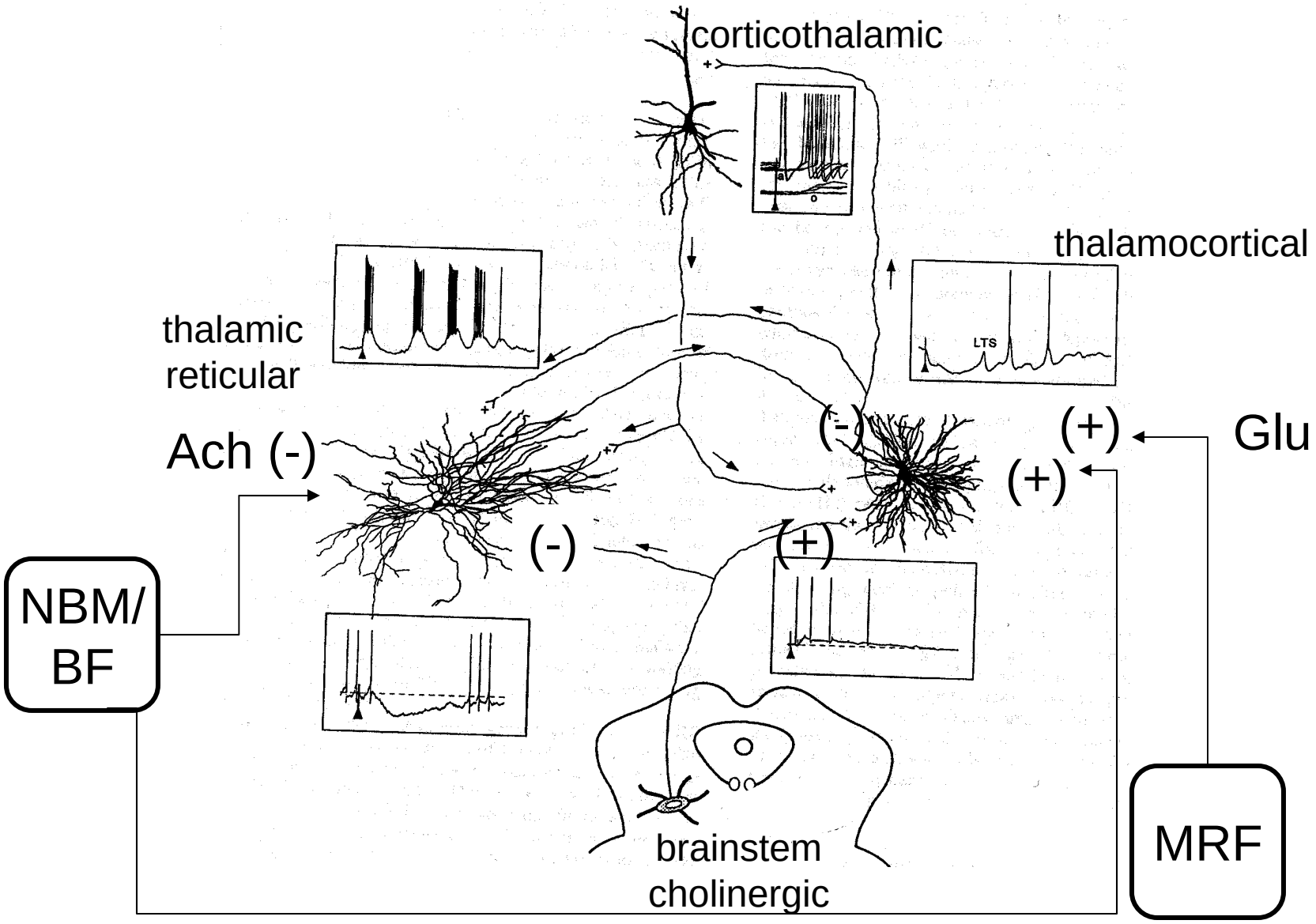






Plum, 1991 (and previous)

Excitation and dis-inhibition of thalamocortical neurons by midbrain and pontine nuclei



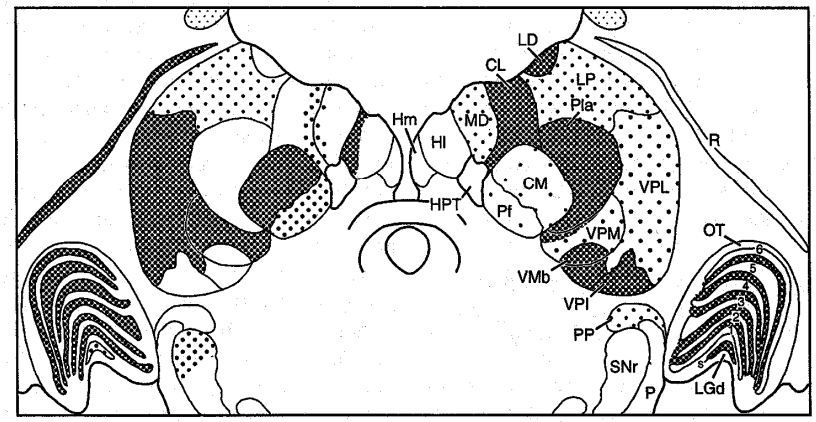
Core and matrix of the primate thalamus

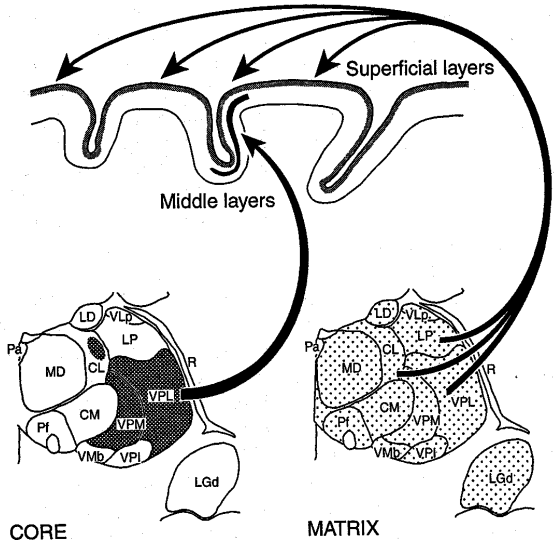
core

matrix

Parvalbumin

Calbindin



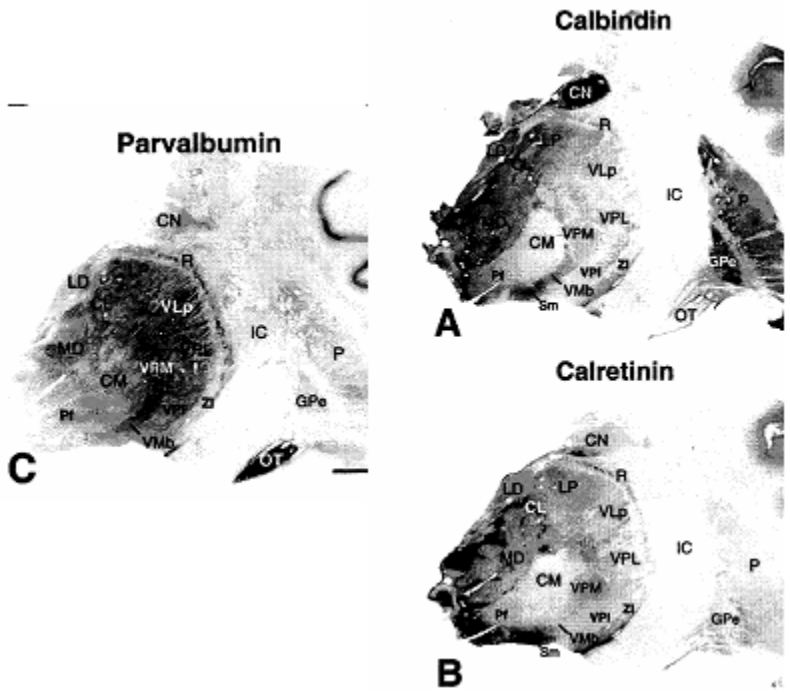


Jones, 1998

staining for three calcium binding proteins in human thalamus

core

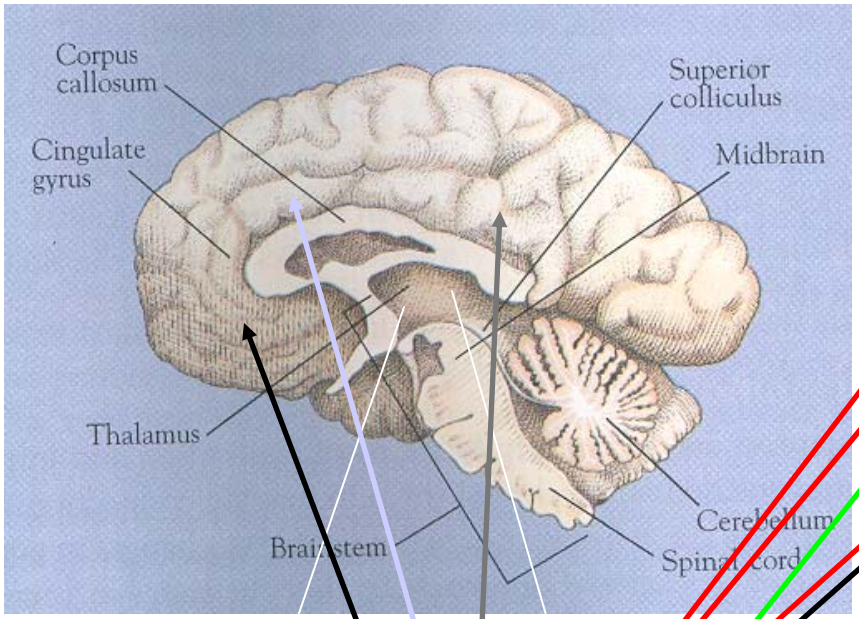
matrix

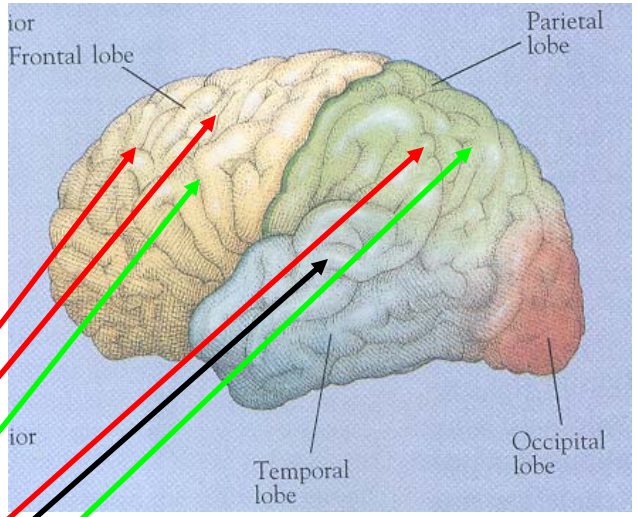


Staining for calbindin and calretinin subdivide the “matrix” component.

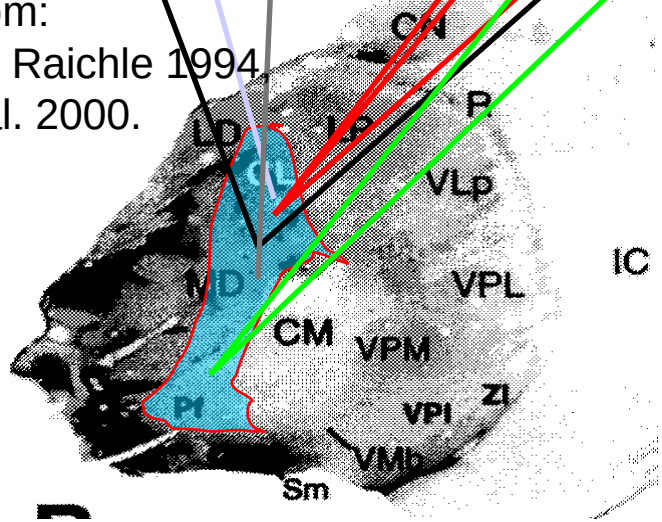
Munkle et al. 1999, 2000

Projections from intralaminar nuclei

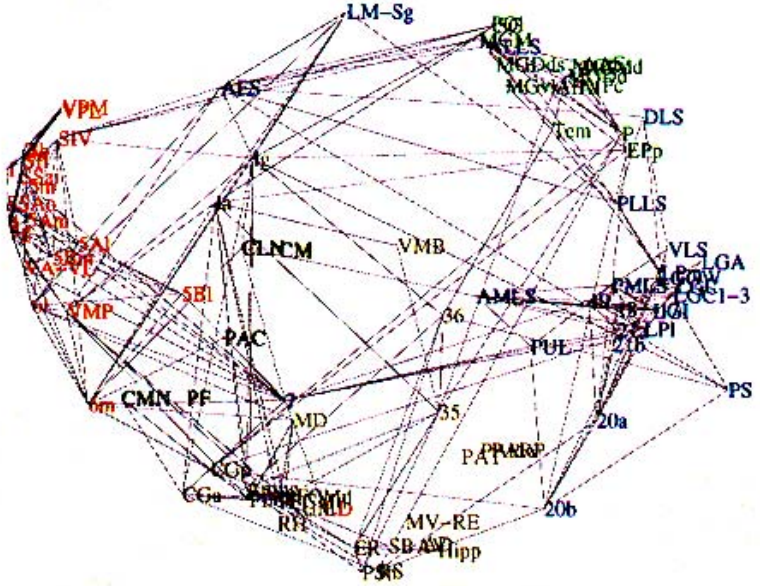




Adapted from:
Posner and Raichle 1994
Munkle et al. 2000.

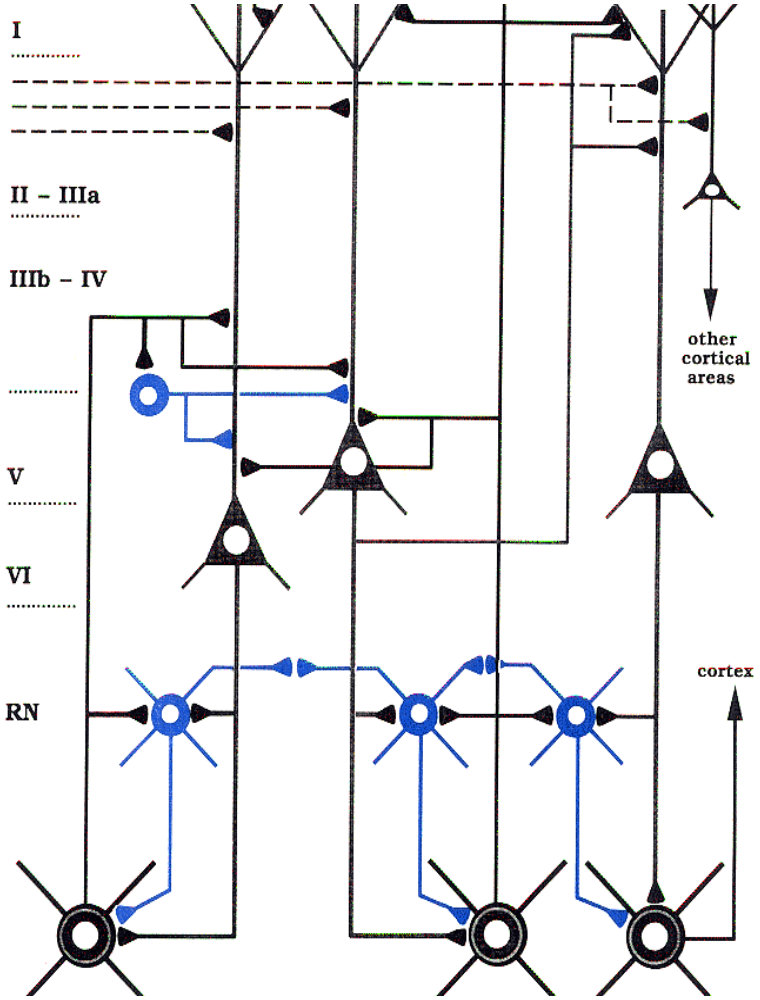


Multidimensional scaling of thalamocortical connectivities



Scannell et al. 1999

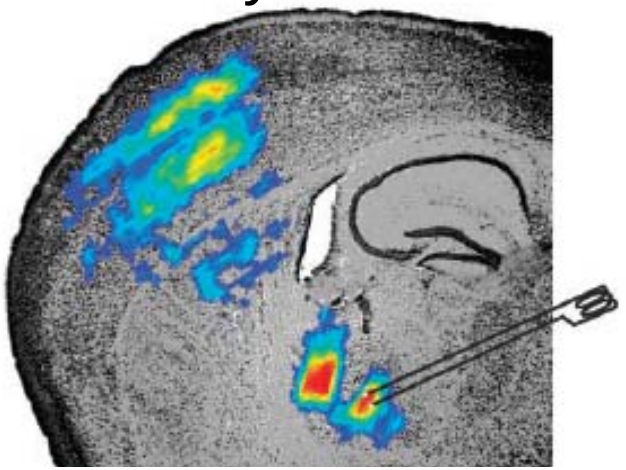
Relationship Between Thalamic Specific and Intralaminar Projections



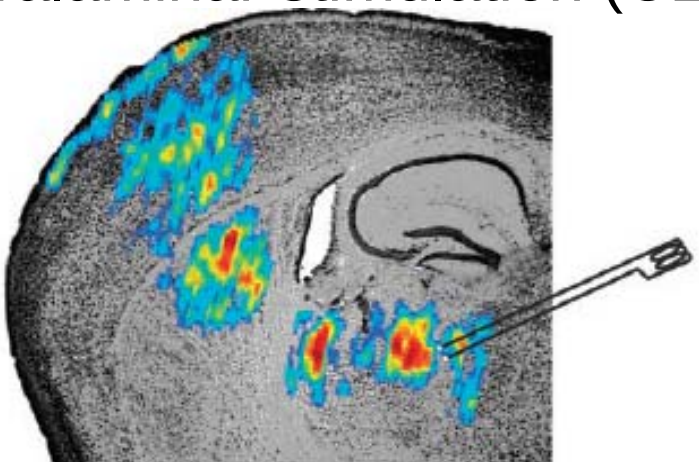
specific relay nuclei

intralaminar nuclei

Specific Relay Stimulation (VB)



Intralaminar stimulation (CL)



Llinás, Leznik, and Urbano (2002)

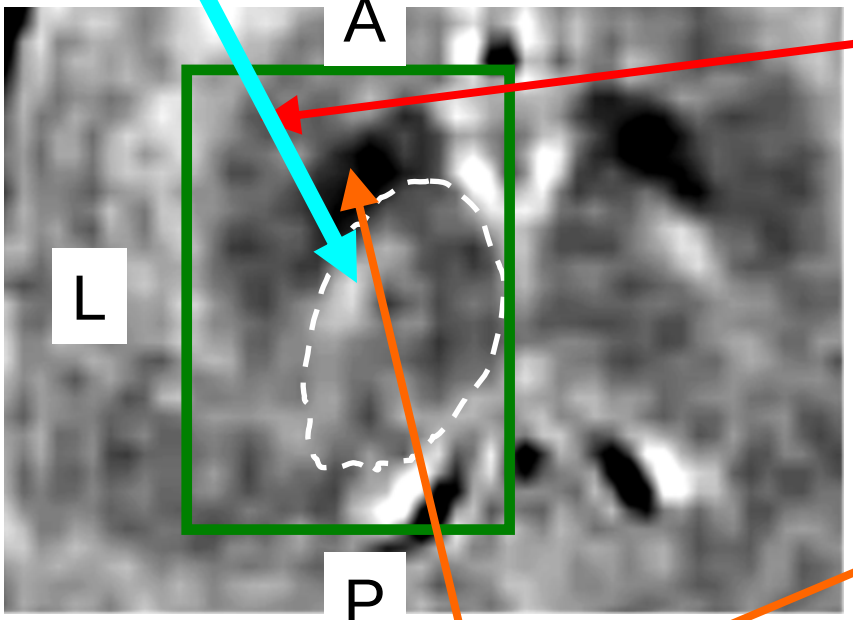
Adapted from Llinas et al. 1994, by Purpura and Schiff 1997

Central Thalamic Activity and Stimulation in a Reaction Time Task (macaque)

with Keith Purpura

MRI Localization of Recording Site

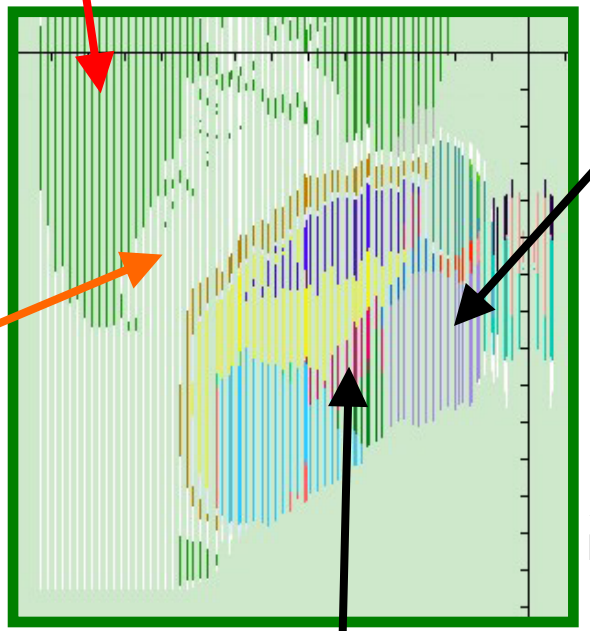
susceptibility artifact at electrode tip



Axial MRI image

caudate/ putamen

internal capsule



median dorsalis nucleus

2 mm

Atlas section from Ilinsky and Kultas-Ilinsky, 2002

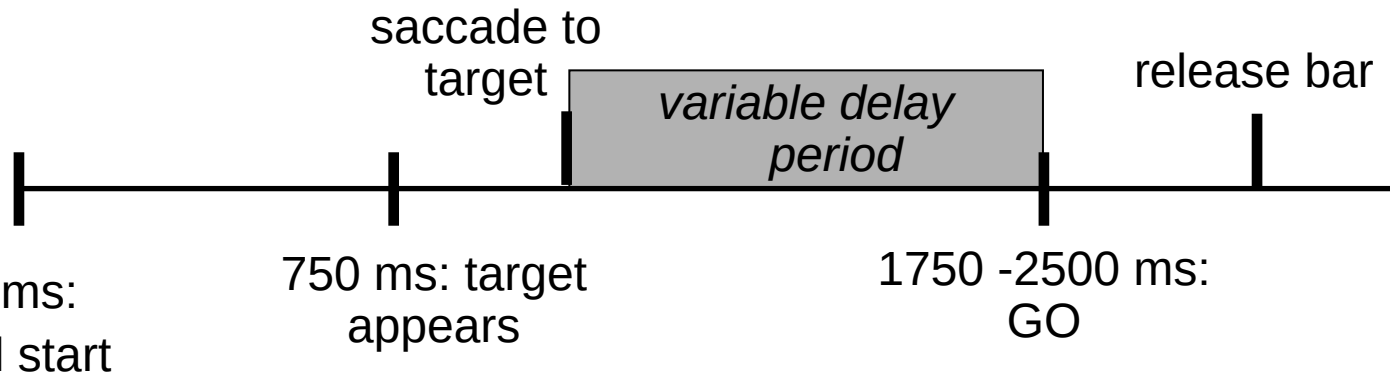
central lateral nucleus

saccade-related field potentials in 24/26 sites, consistent with this localization (Schlag and Schlag-Rey 1984)

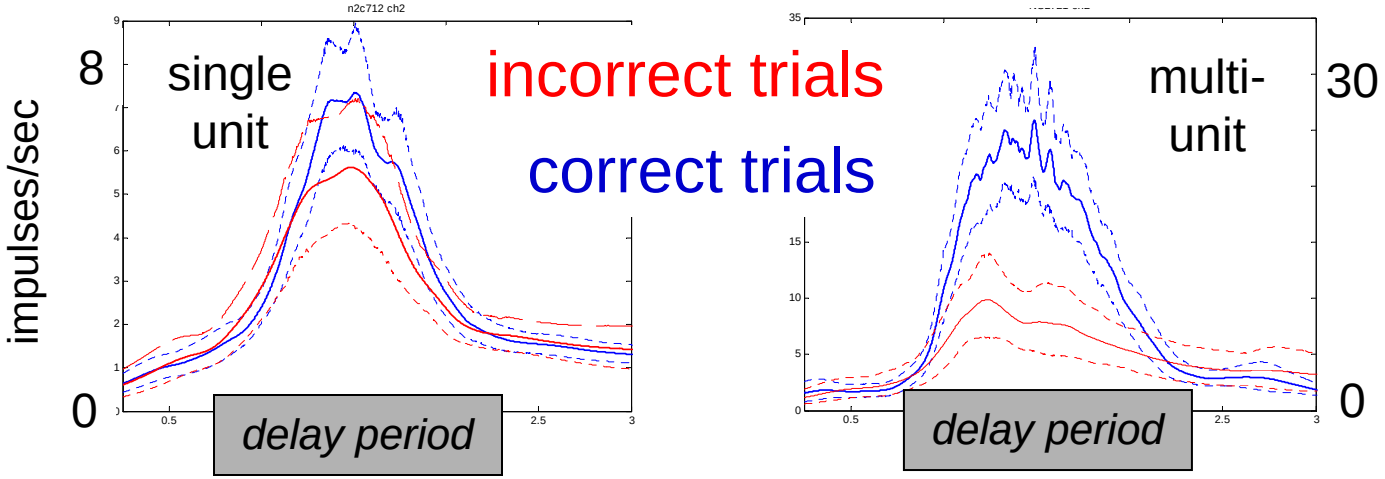
Schiff and Purpura

Single- and Multi-Unit Responses

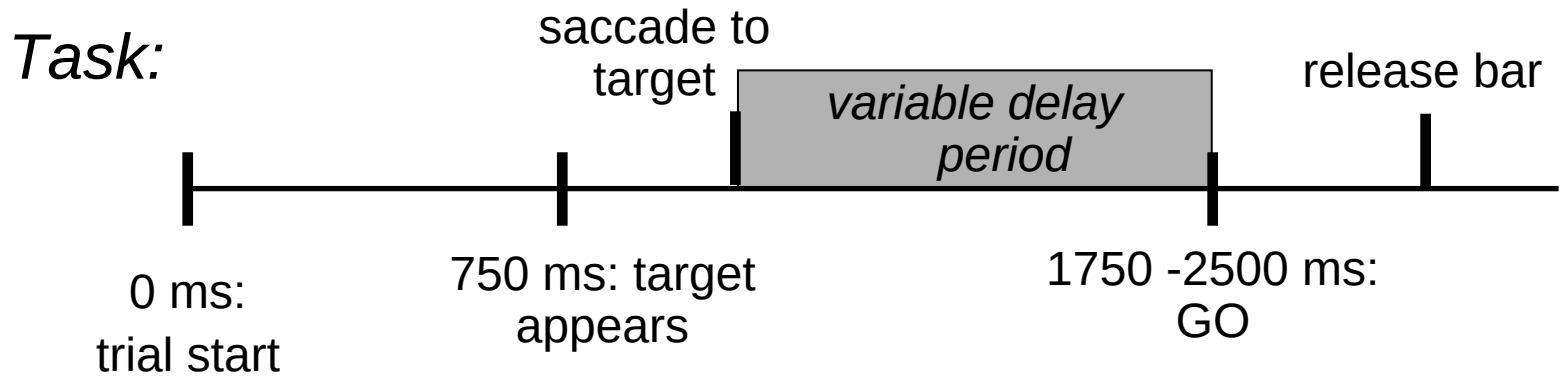
Task:



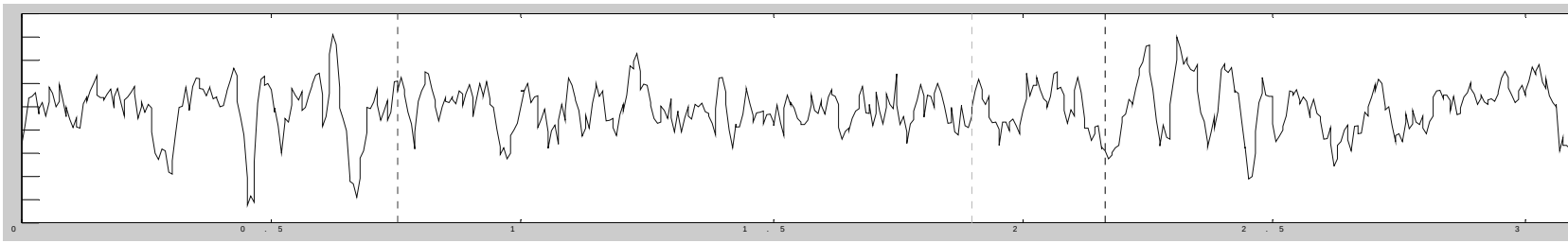
Responses



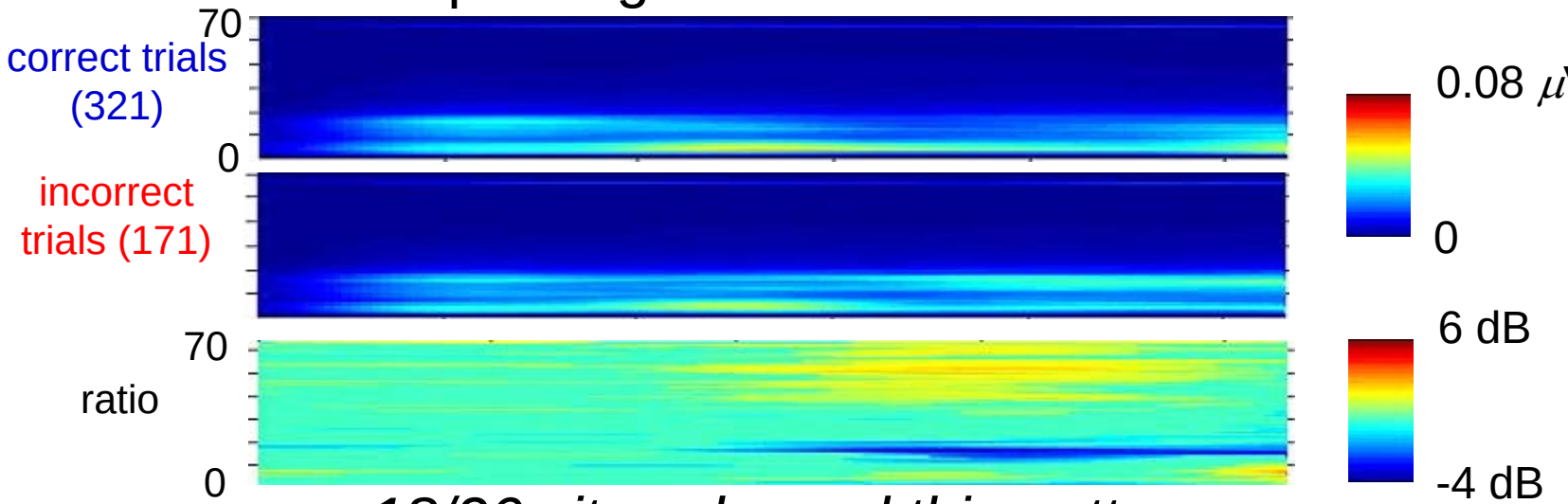
Local Field Potential Responses



LFP

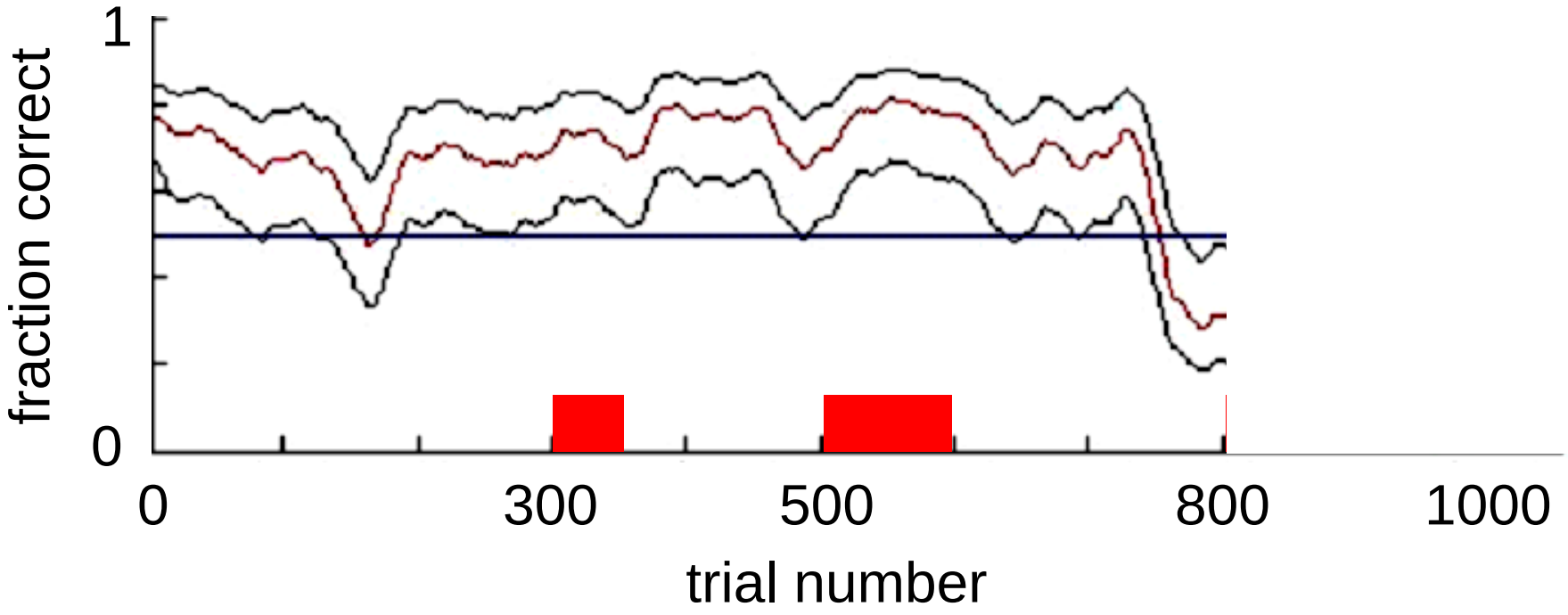


spectrograms



18/26 sites showed this pattern

Performance degrades over time, but recovers with central thalamic stimulation



Continuous stimulation: 500 μA bipolar, 50 Hz
(50 μs per phase, interphase 10 μs)

Analysis: thanks to Emery Brown and Anne Smith

Towards a More Rigorous Link Between Circuitry, EEG, and Behavior

- The Robinson model as a starting point
  - What it explains
  - What it may not explain
- Where we are headed

Thalamocortical Population Model (Robinson)

General Formulation

A population-based continuum model

For each neuronal population *a:*

Firing rate Q is an instantaneous sigmoidal function of cell body potential V_a:

$$Q(V_a(t)) = \frac{Q_0}{1+\exp(-\frac{V_a(t)-\theta}{\sigma})}$$

Cell body potential V_a is a filtered sum of (delayed) input signals ϕ_b:

$$V_a(t) = \int_{-\infty}^{t} L(t-t') \sum_b \nu_{ab}\phi_b(t'-\delta_{ab})dt' \quad \text{with} \quad L(u) = \frac{\alpha\beta}{\beta-\alpha}(e^{-\alpha u} - e^{-\beta u})$$

differential form

$$DV_a(t) = \sum_b \nu_{ab}\phi_b(t-\delta_{ab}) \qquad \text{with} \qquad D = \frac{1}{\alpha\beta}\frac{d^2}{dt^2} + (\frac{1}{\alpha}+\frac{1}{\beta})\frac{d}{dt} + 1$$

Damped wave equation (typical axonal range r_a and axonal velocity c_a):

$$\left(\frac{r_a^2}{{c_a}^2}\frac{d^2}{dt^2} + \frac{2r_a}{c_a}\frac{d}{dt} + 1 - r_a^2\nabla^2\right)\phi_a(x,t) = Q(V_a(x,t))$$

Robinson, Rennie, Rowe 2002

Thalamocortical Population Model (Robinson)

Special Features

Four populations (*a*=e, i, s, r):

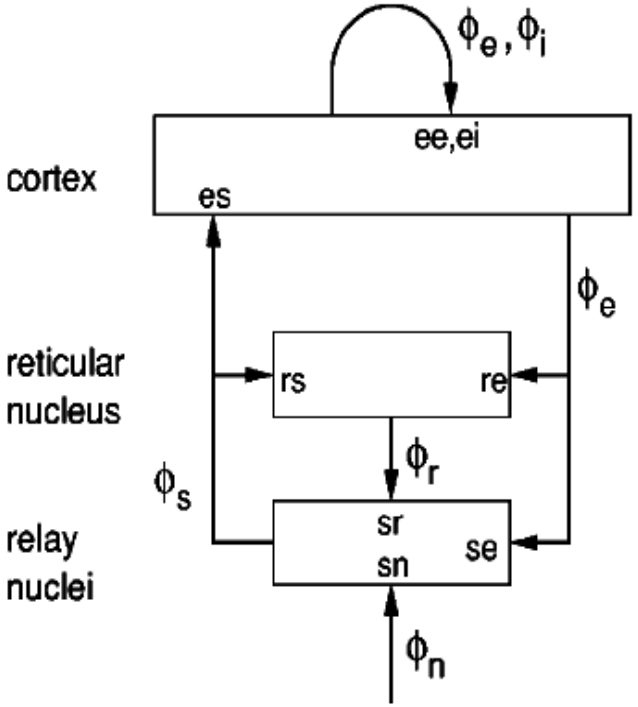
cortical excitatory and inhibitory, thalamic specific (relay) and reticular

Partial connectivity

Only thalamocortical and corticothalamic delays are nonzero; these are $t_0/2$.

All axonal lengths are negligible except for cortical excitatory.

Filtering from synaptic input to cell body potential is universal, with $\beta=4\alpha$.



$\nu_{ei}<0$, $\nu_{sr}<0$, others positive

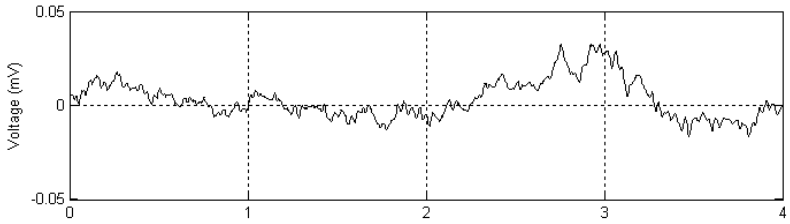
Robinson, Rennie, Rowe 2002

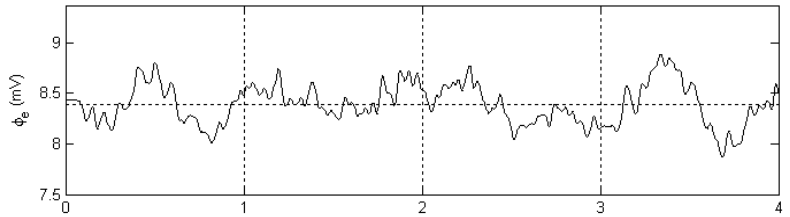
Comparison with Real EEG

Human EEG

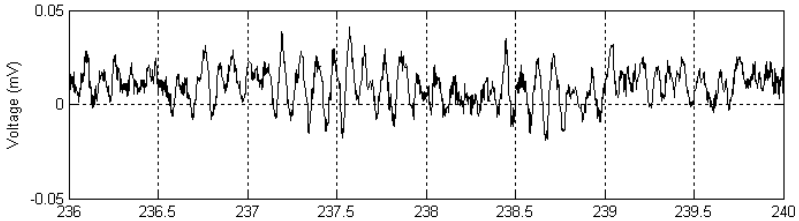
Model ϕ_e

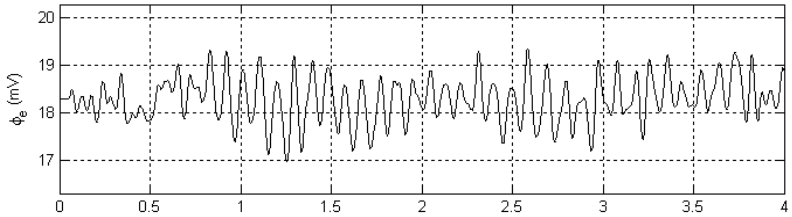
eyes open



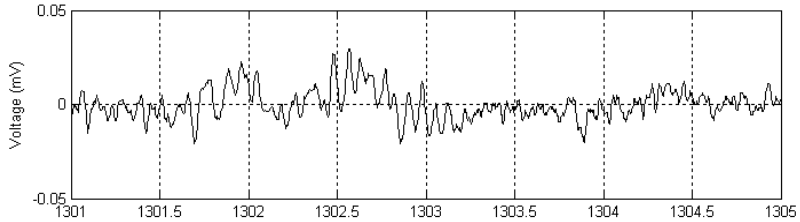


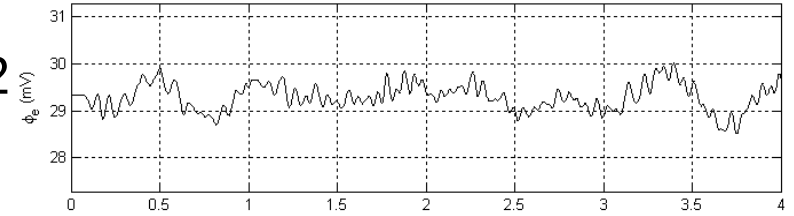
eyes closed



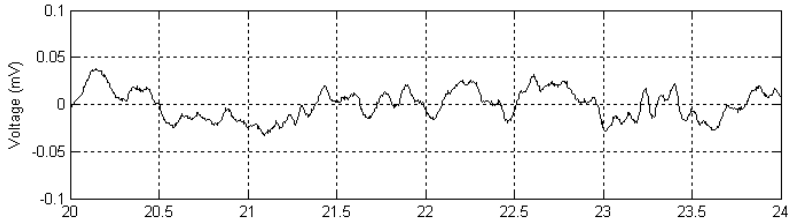


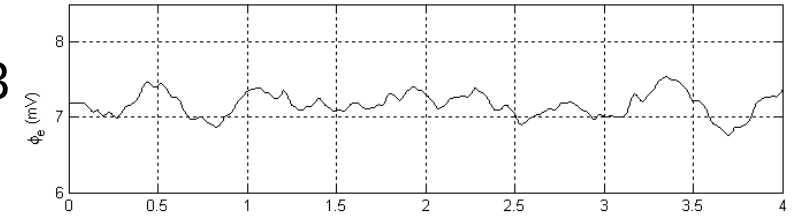
Stage 2 sleep





Stage 3 sleep





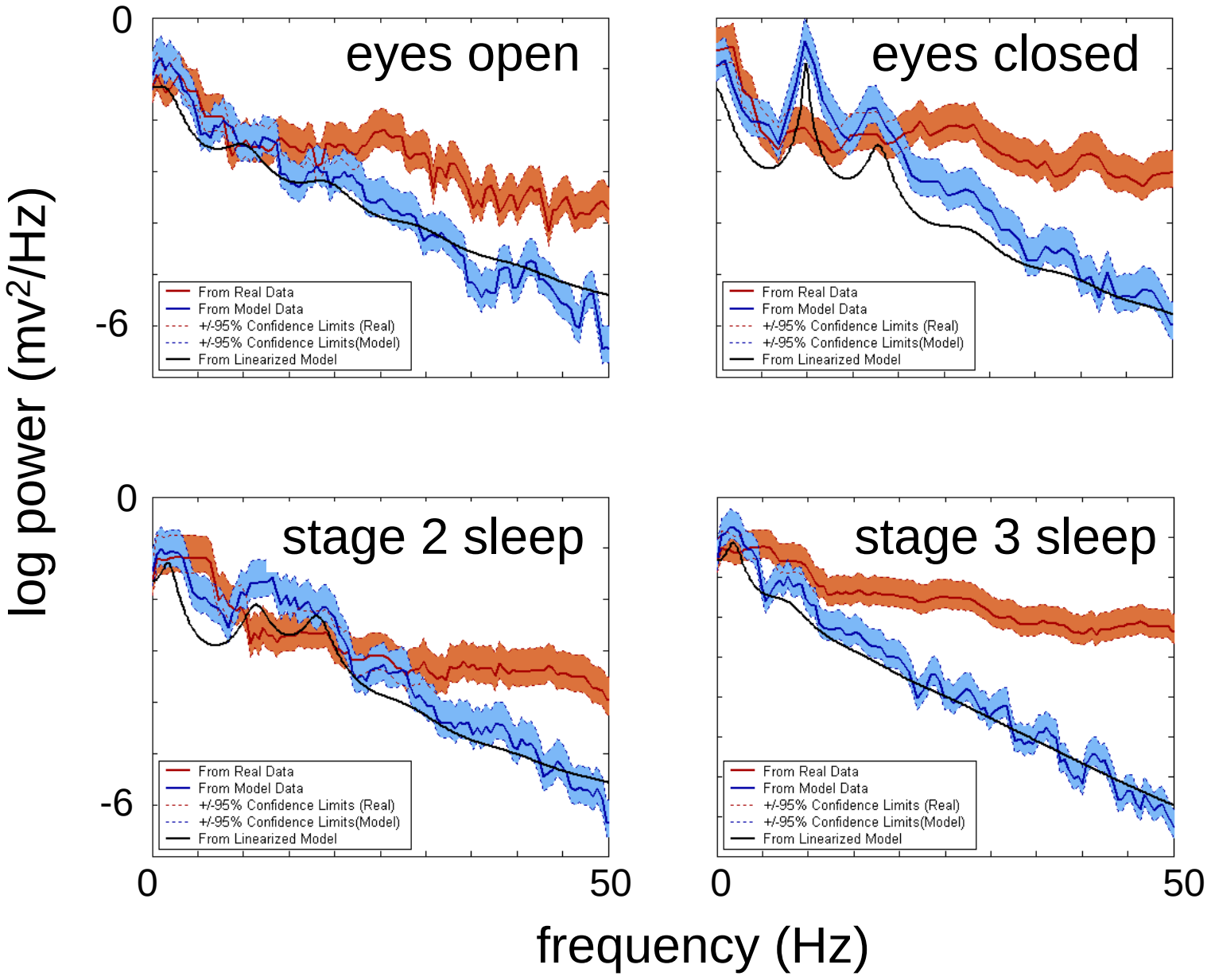
1s

DeBellis 2005

Qualitative Analysis

- Strategy
  - 8 coupled nonlinear delay differential equations (variables: ϕ_a, ϕ_a')
  - Identify the fixed points
  - Linearize
  - Find eigenmodes: $(\lambda I - A - Be^{-\lambda t})v = 0$
- Results
  - One fixed point in physiological range for each state
  - Each fixed point is stable
  - Linearized spectrum very close to that of numerical solutions

Comparison with Real EEG: Spectra



Human EEG

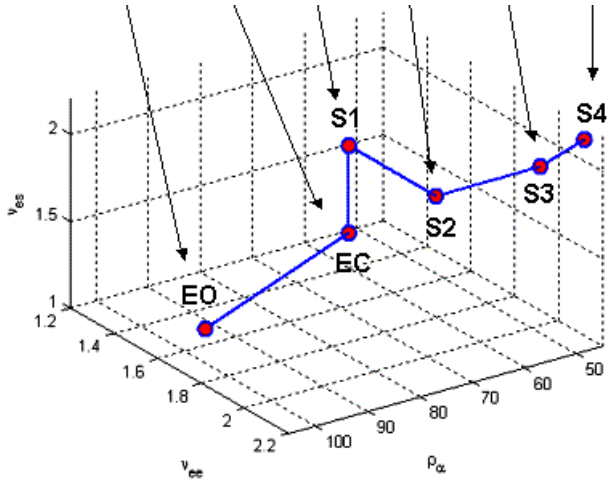
Numerical model

Linearized model

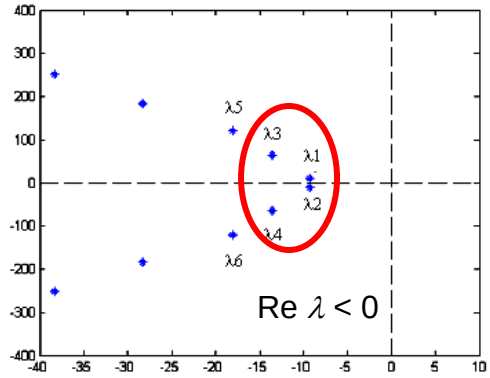
DeBellis 2005

State Transitions

Sequence of states corresponds to an orderly change of model parameters

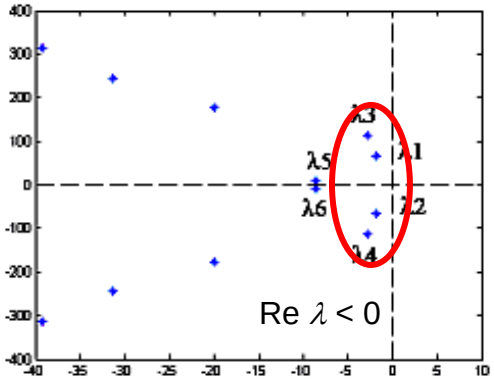


Appearance of new dominant frequencies corresponds to shifts in position of dominant eigenvalues

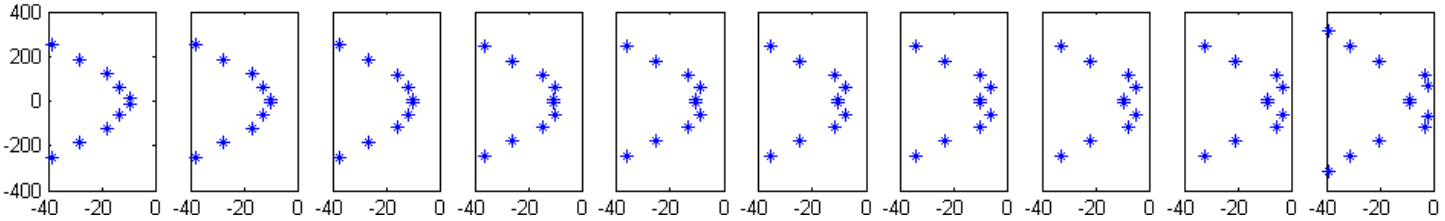


Solutions of

$\det(\lambda I - A - Be^{-\lambda t}) = 0$



Eyes open



Eyes closed

DeBellis 2005

Robinson Model: Reasons for Enthusiasm

- With above simplifications, there are 15 parameters (including 2 dimensional constants)
- With reasonable physiological choices for the parameters, space-clamped behavior accounts for EEG spectra in
  - Wakefulness (eyes open, eyes closed)
  - The four sleep stages
  - Spike/wave epilepsy
- It also accounts for the *sequence* of state transitions

What is Missing

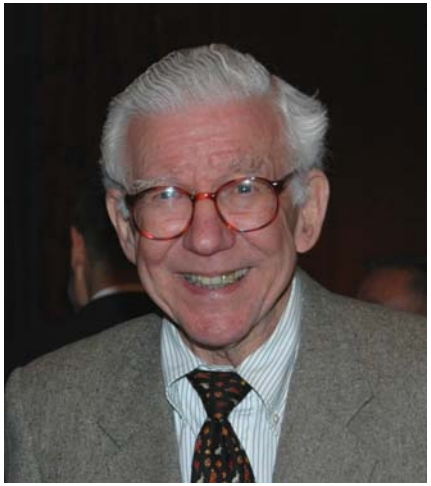
- In each state, the linearized Robinson model is as good as the full model. That is, model does not account for aspects of the EEG beyond the power spectrum
  - Lengths and shapes of envelopes of narrowband activity
  - Correlations across frequency bands
    - Vertex waves and K complexes
    - Harmonic stacks
  - Any other nonlinear phenomenon
- No distinction between specific and nonspecific thalamic nuclei, cortical laminae, …
- Spatial aspects entirely unexplored
  - Coherence
  - Role of the details of thalamocortical connectivity
- Unclear whether large-scale activity is a just a correlate or a “cause” of behavioral state

Studying Brain Dynamics in Humans with Severe Damage

- Ethical Considerations
  - A large, mostly young population, typically marginalized and considered hopeless
  - No ability to consent
  - Denied possibility of benefit from medical advances (Fins & Schiff)
- Scientific and Medical Considerations
  - No control over lesion, each is different (maybe an advantage?)
  - Anatomic imaging, metabolic imaging, and long-term EEG monitoring are becoming available (significant logistical barriers)
  - It *is* the system of interest, not merely a model
    - language
    - rich behavioral repertoire
  - Technology for safe perturbation exists: deep brain stimulation
  - Major up-side

The Team

- Human Behavior: Joe Giacino (JFK) , Erik Kobylarz (WMC)
- Human Imaging: Joy Hirsch, Henning Voss, Aziz Ulug (Columbia, WMC)
- Human EEG: Matt Davey, Erik Kobylarz (WMC)
- Primate Physiology and Behavior: Keith Purpura (WMC)
- Primate Imaging: Doug Ballon, Linda Heier (WMC/Citigroup Imaging)
- Rodent Studies: Daniel Herrera, Prasad Shirvalkar (WMC)
- Robinson Model: Bob De Bellis (WMC, Swartz)
- Ethics: Joe Fins (WMC)
- Human DBS: Ali Rezai (Cleveland Clinic)



Fred Plum

- Weill Medical College and The New York Presbyterian Hospital (New York City, NY)
- Columbia University Functional Imaging Laboratory (New York City, NY)
- JFK Johnson Rehabilitation Center (Edison, NJ)
- The Cleveland Clinic Foundation (Cleveland, OH)

- NINDS, NIMH, NIDRR
- The Dana Foundation
- McDonnell Foundation
- The Swartz Foundation