Opportunities and Challenges in EEG-based Assessment of Cognitive Status in Severe Brain Injury

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Statistical Challenges in Neuroscience

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Outline

- Overview
  - Severe brain injury and global disorders of consciousness: importance and challenges
  - Assessing brain function: why EEG?
- Biophysical principles underlying EEG
  - Space
  - Time
  - Rationale for spectral methods
- Application: assessment of cognitive capacity in severely brain-injured patients
- Conclusion: critical importance of meeting the statistical challenges

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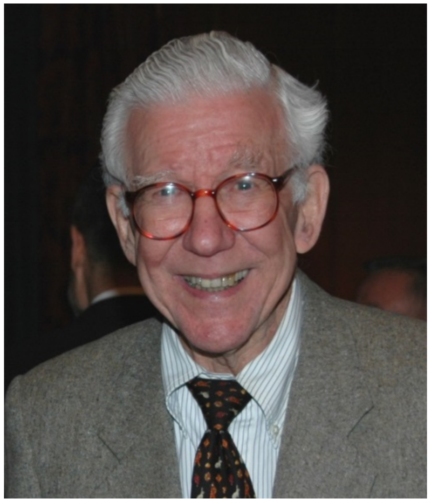

Fred Plum 1924 - 2010

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IntElect Medical, Inc.

The Challenge

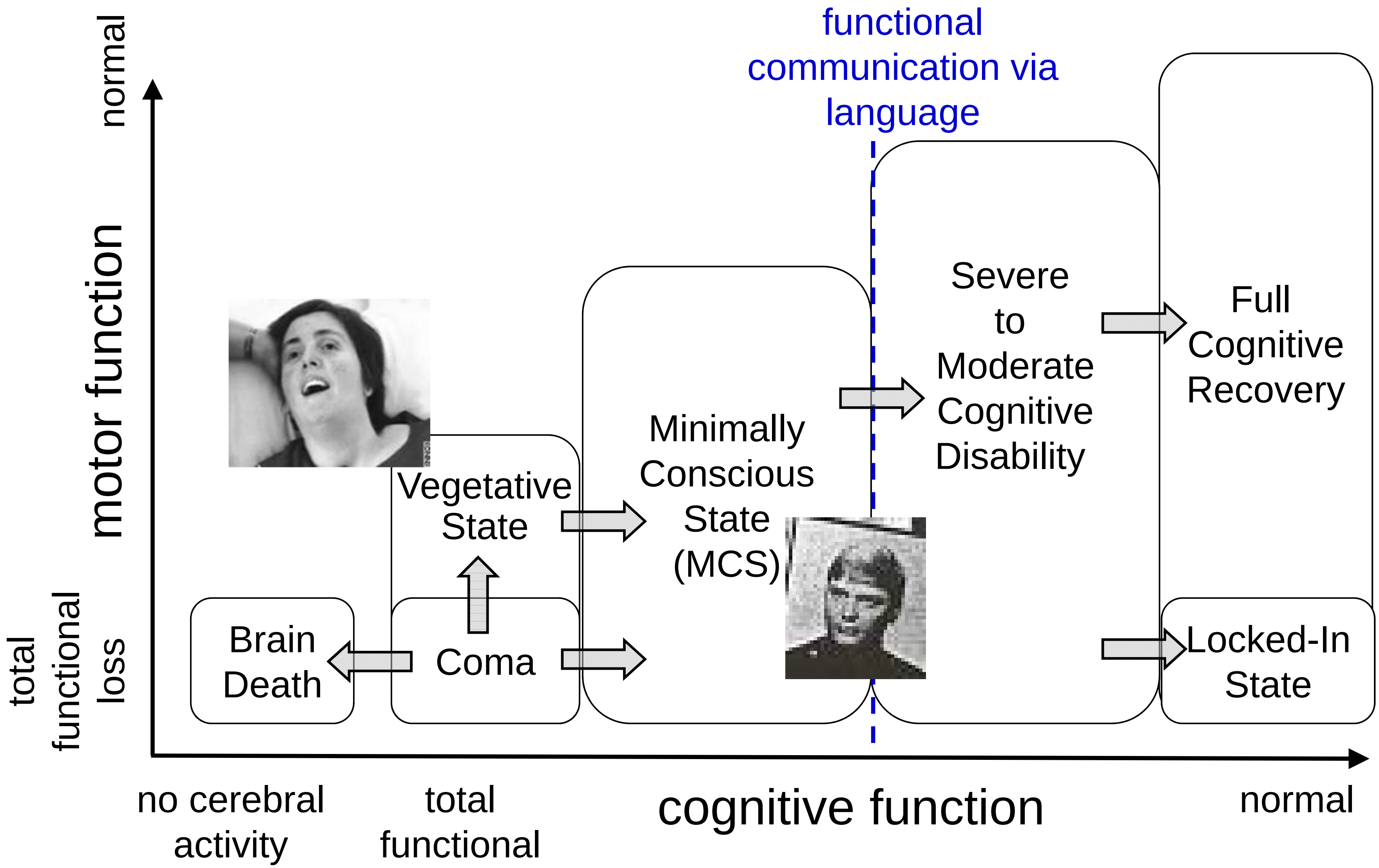
- Severe brain injury leads to marked and prolonged impairment of consciousness
  - More than 300,000 affected individuals in the US, millions worldwide
  - Multiple causes: trauma, cardiac arrest, stroke
  - Many patients recover, but recovery can take years
  - Social and economic costs are enormous

- Barriers to study are significant
  - Historically, a sense of futility
  - Causative injuries are typically multifocal and heterogeneous: each patient is different
  - Determining whether prognosis was correct may take years
  - Ethical issues

A neurological perspective

- “Consciousness” is not binary, and has many components
- Arousal
  - a range from coma to delirium
  - necessary but not sufficient for organized behavior
- Attention
  - spatial and temporal selectivity
  - Maintenance and regulation over time (e.g., working memory)
- Non-reflexive behavior
  - stimulus-response relationships that can be modified by context
  - communication: following commands, answering questions
- State changes over time
  - slow timescales (months and years): recovery following devastating injuries -- well-recognized but not so well understood
  - rapid timescales (seconds): episodic fragments of behavior -- less well-recognized, and even less-well understood

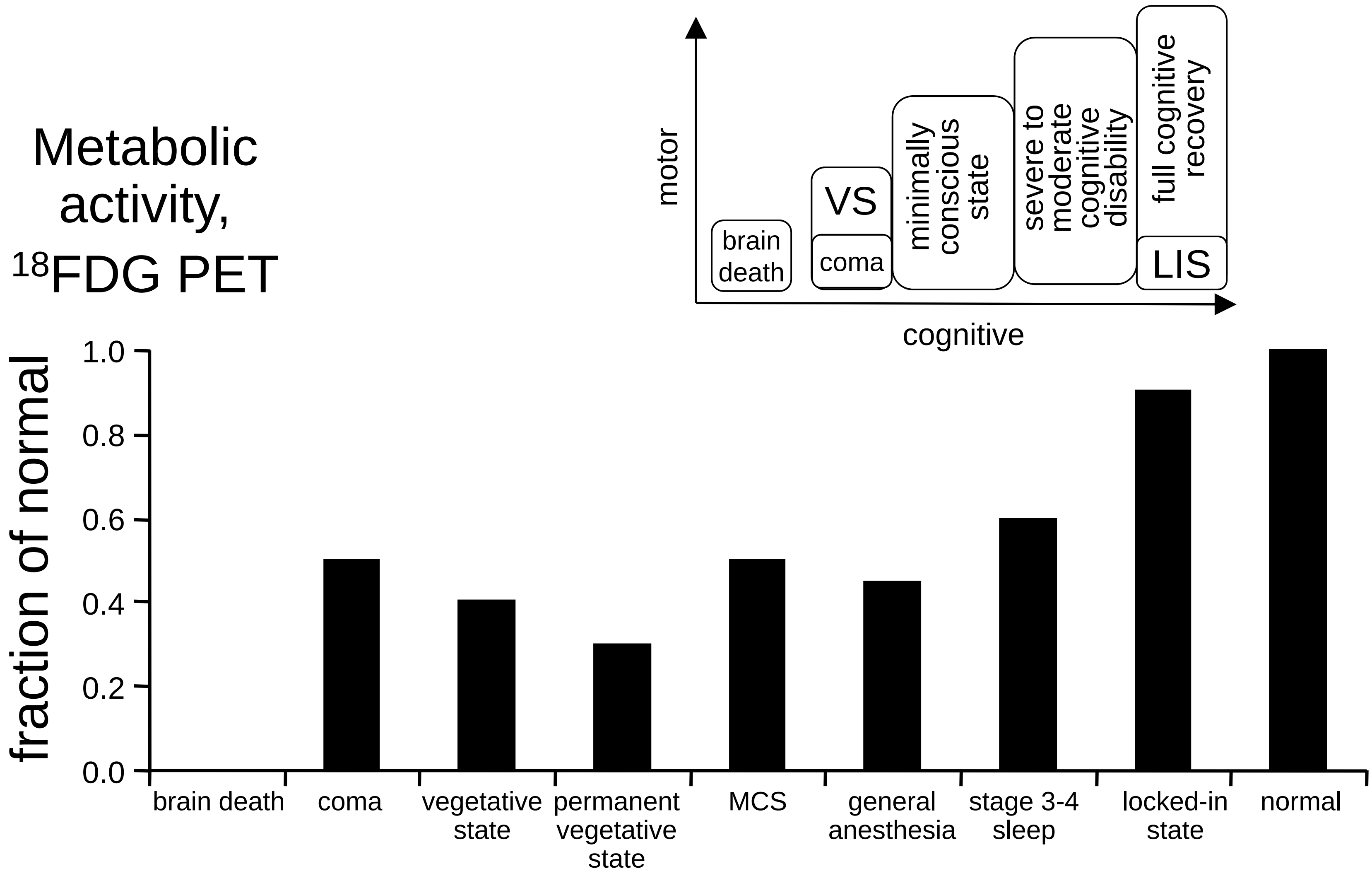
A conceptual scheme



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

Resting cerebral metabolism correlates with global level of function

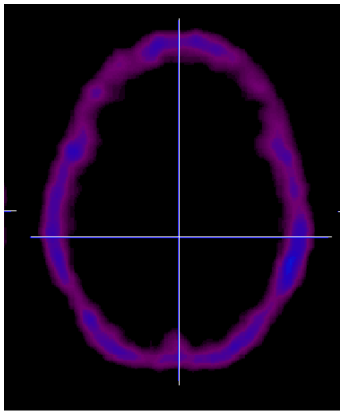
Metabolic activity, ^{18}FDG PET



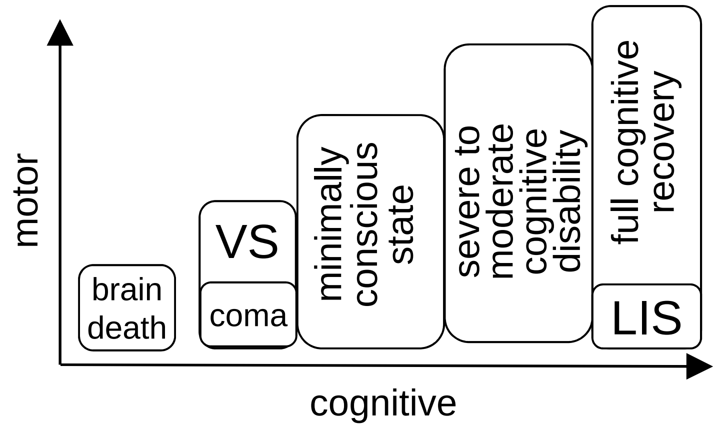
Laureys, Owen, and Schiff (2004)

Resting cerebral metabolism: localization

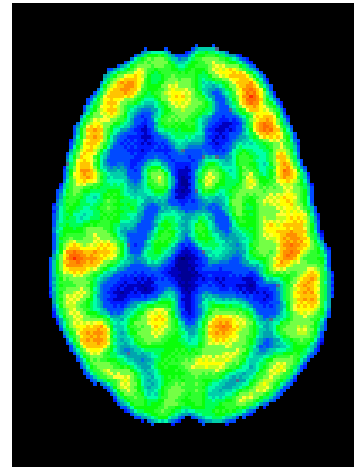
brain death



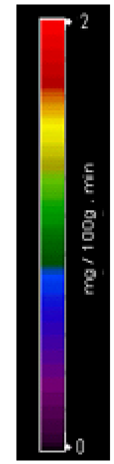
localization



normal

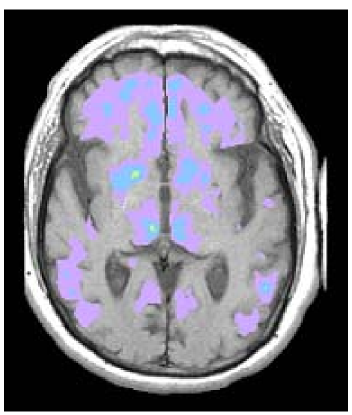


^{18}FDG-PET



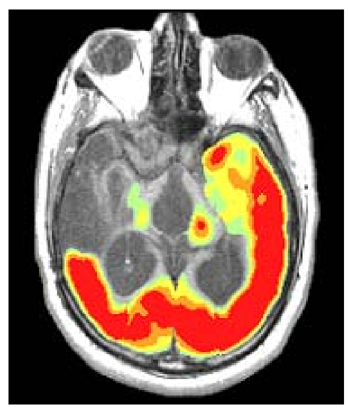
2 mg/ 100g-min

vegetative state



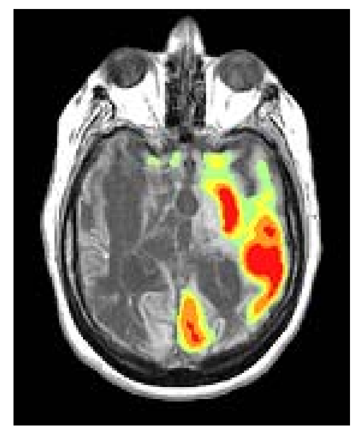
minimal cortical activity

OR



near-normal cortical activity but damaged brainstem core

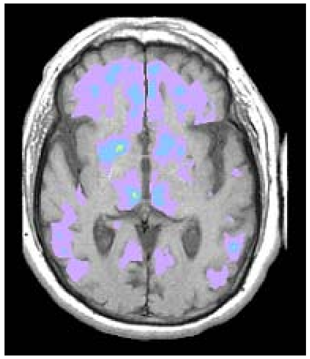
VS near emergence



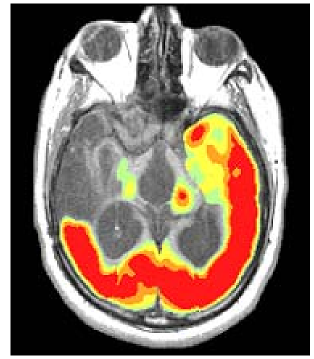
islands of near-normal cortical activity

Cortical OR subcortical injuries can eliminate organized behavior

minimal cortical activity

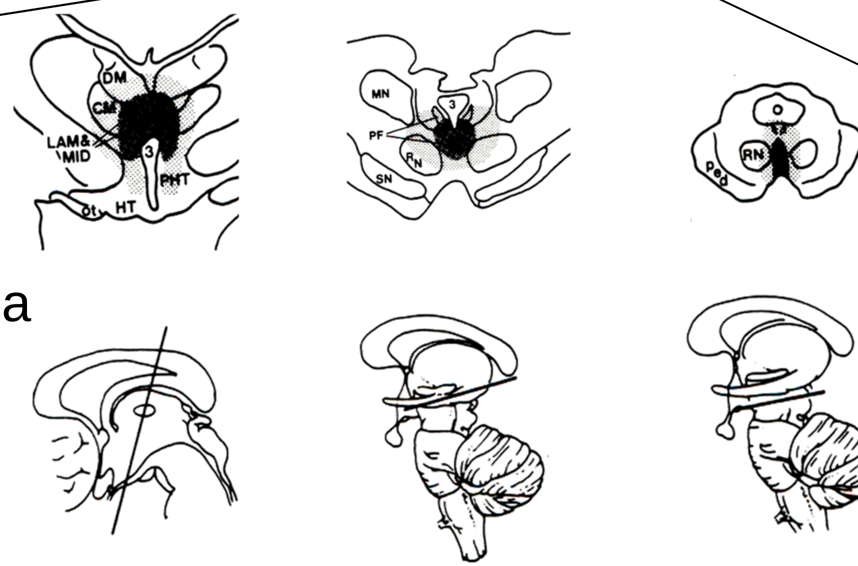


OR



near-normal cortical activity but damaged brainstem

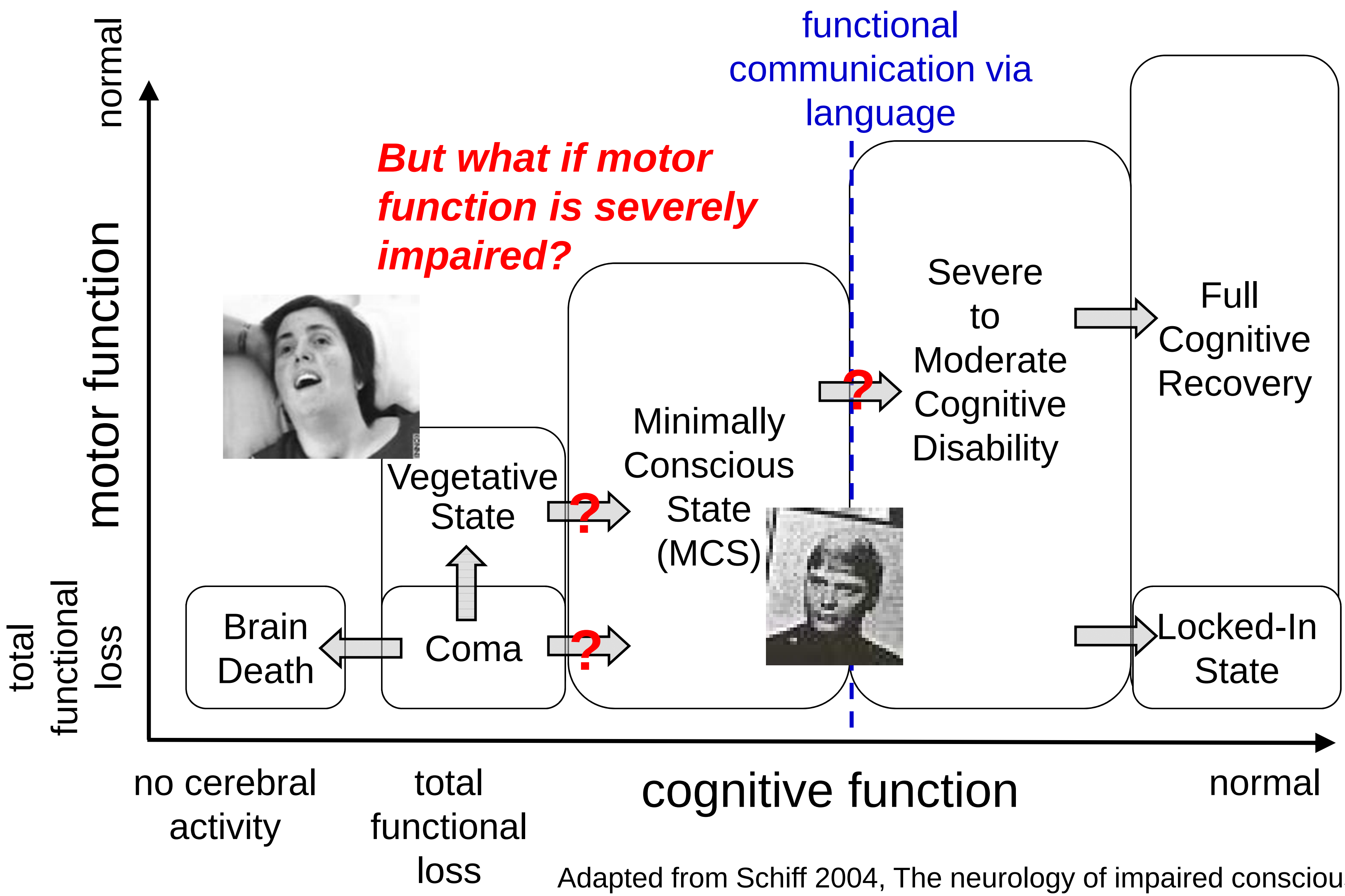
Injuries affecting the midbrain and central thalamus can cause coma



Plum, 1991
(and previous)

- *Changing levels of subcortical dysfunction may account for fluctuations and recovery in less severely injured patients.*
- *Modulating subcortical activity is a viable therapeutic strategy.*

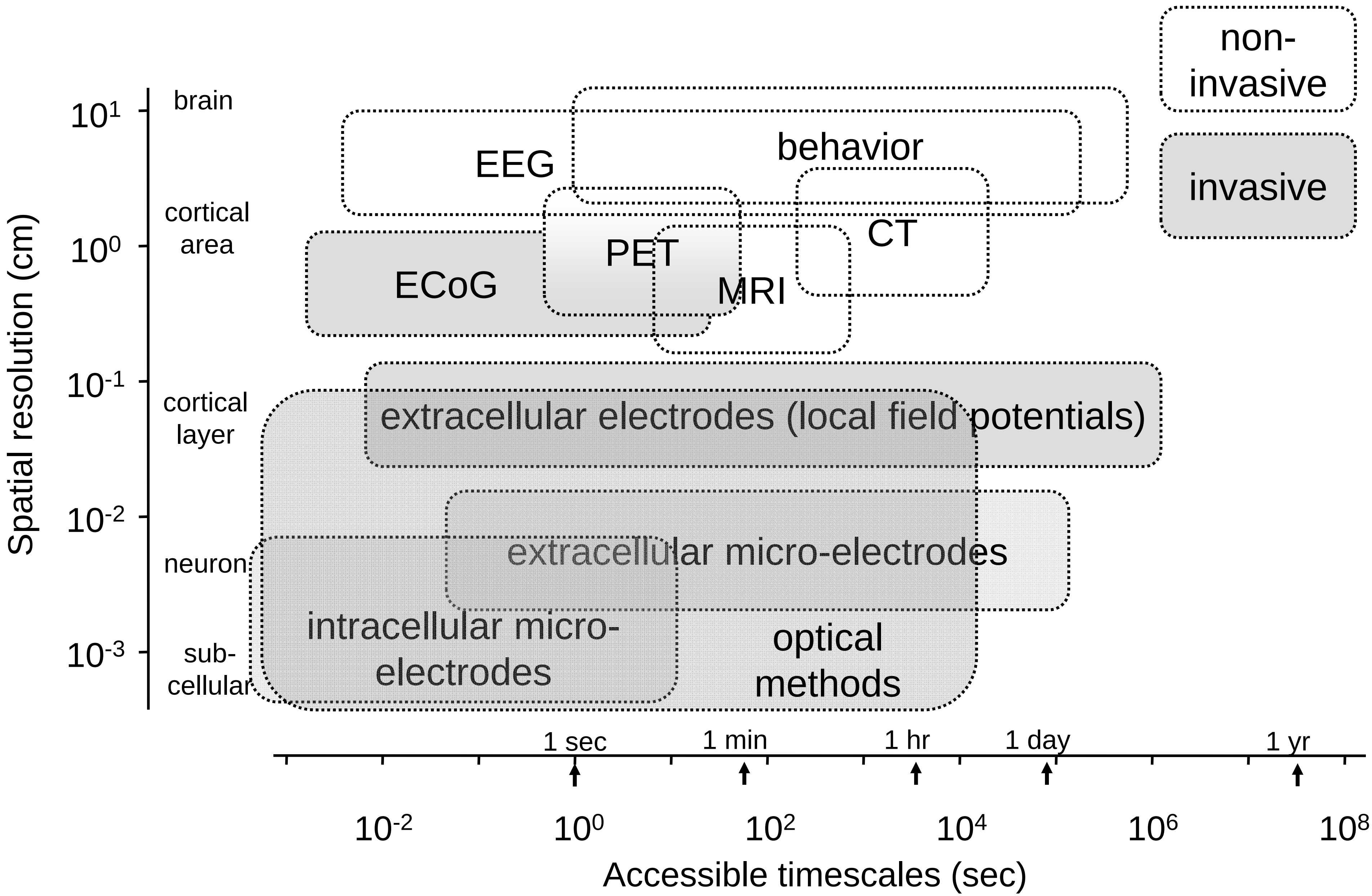
A conceptual scheme



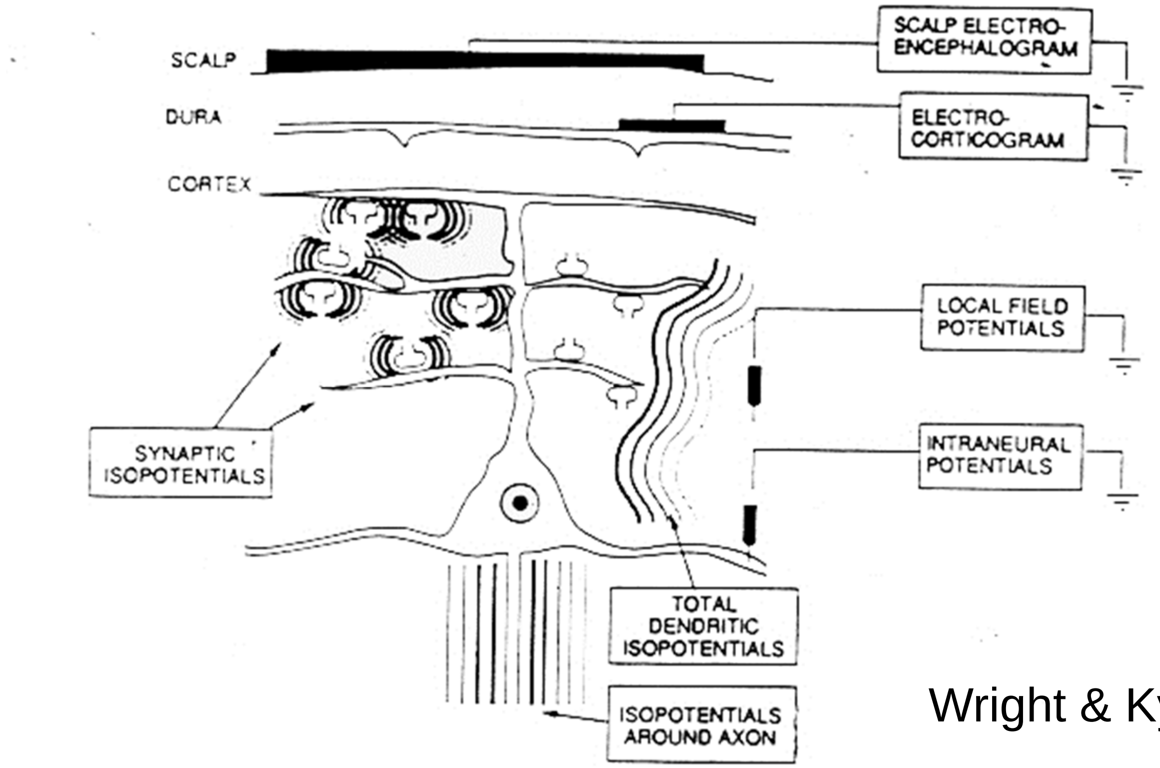
Adapted from Schiff 2004, The neurology of impaired consciousness.
In: The Cognitive Neurosciences III, MIT Press

So there’s a critical need for methods of assessment of brain function that do not rely on motor output.

Assessing brain function: overview



How can we interpret mass recordings? Basic problem: many scales



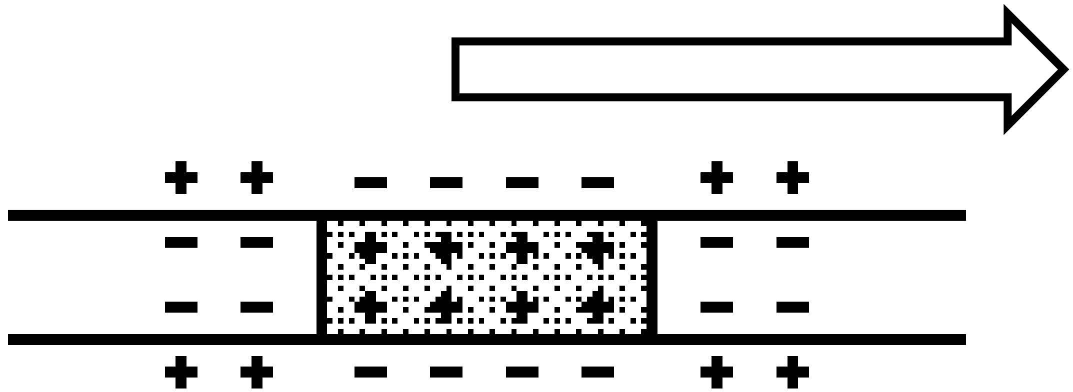
Wright & Kydd

- Detailed modeling is hopeless
- But can get surprisingly far by considering
  - Spatial factors
  - Temporal factors

Spatial factors: Principles

- The generation of bioelectric signals is nonlinear (Hodgkin-Huxley equation, etc.)
- But the bulk electrical properties of the brain are linear
  - Sources can be considered to be a set of dipoles
  - Net contribution can be analyzed by superposition
- This allows us to make some useful statements about what generates the EEG
  - Action potentials: Not usually
  - Synaptic potentials: Yes, specific cell types

Action potentials ("spikes") propagating along fibers do not contribute to the EEG

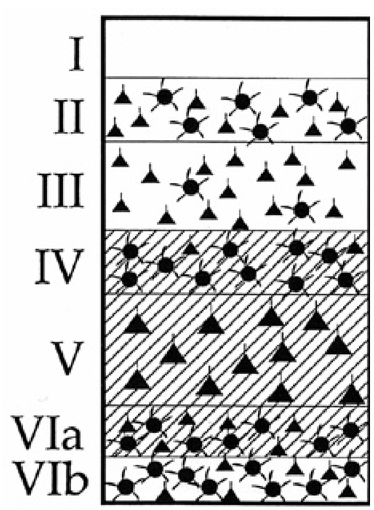


dipoles at leading and trailing edges cancel

(the dipole approximation is valid at a distance of 1-3 cm or more)

Neocortical circuitry is stereotyped

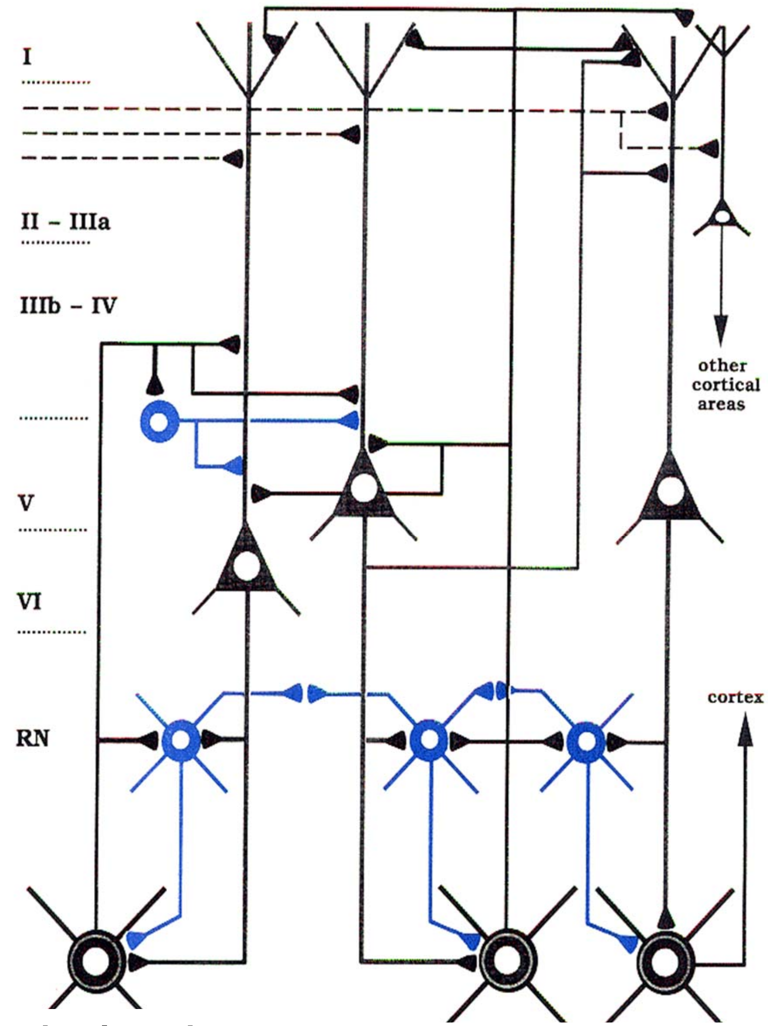
cellular composition



Humphreys et al.,
J. Neuropath. Exp.
Neurol. (1991)

Layer V is dominated by pyramidal cells

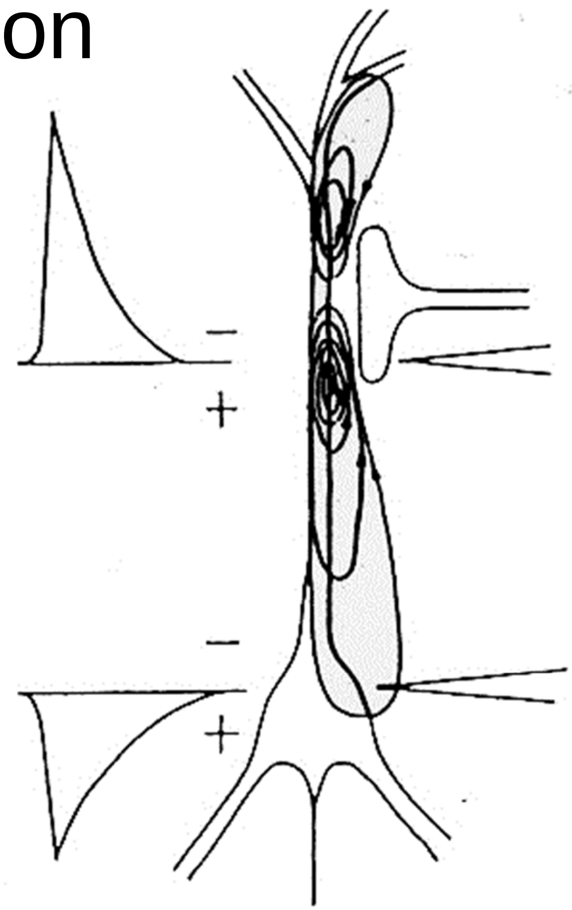
connectivity



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

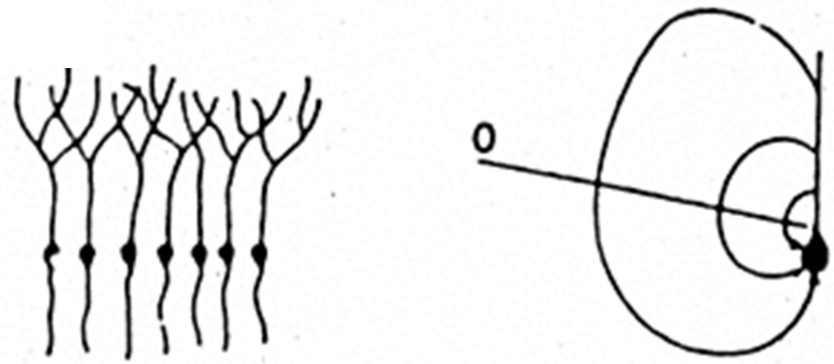
Synaptic inputs produce non-cancelling dipoles

Excitation



Neuronal geometry matters

stellate neurons:
dipoles cancel



pyramidal neurons:
dipoles reinforce, but only if
the neurons are aligned

The main generators of the EEG are the synaptic potentials impinging on pyramidal cells that form aligned layers in cortex

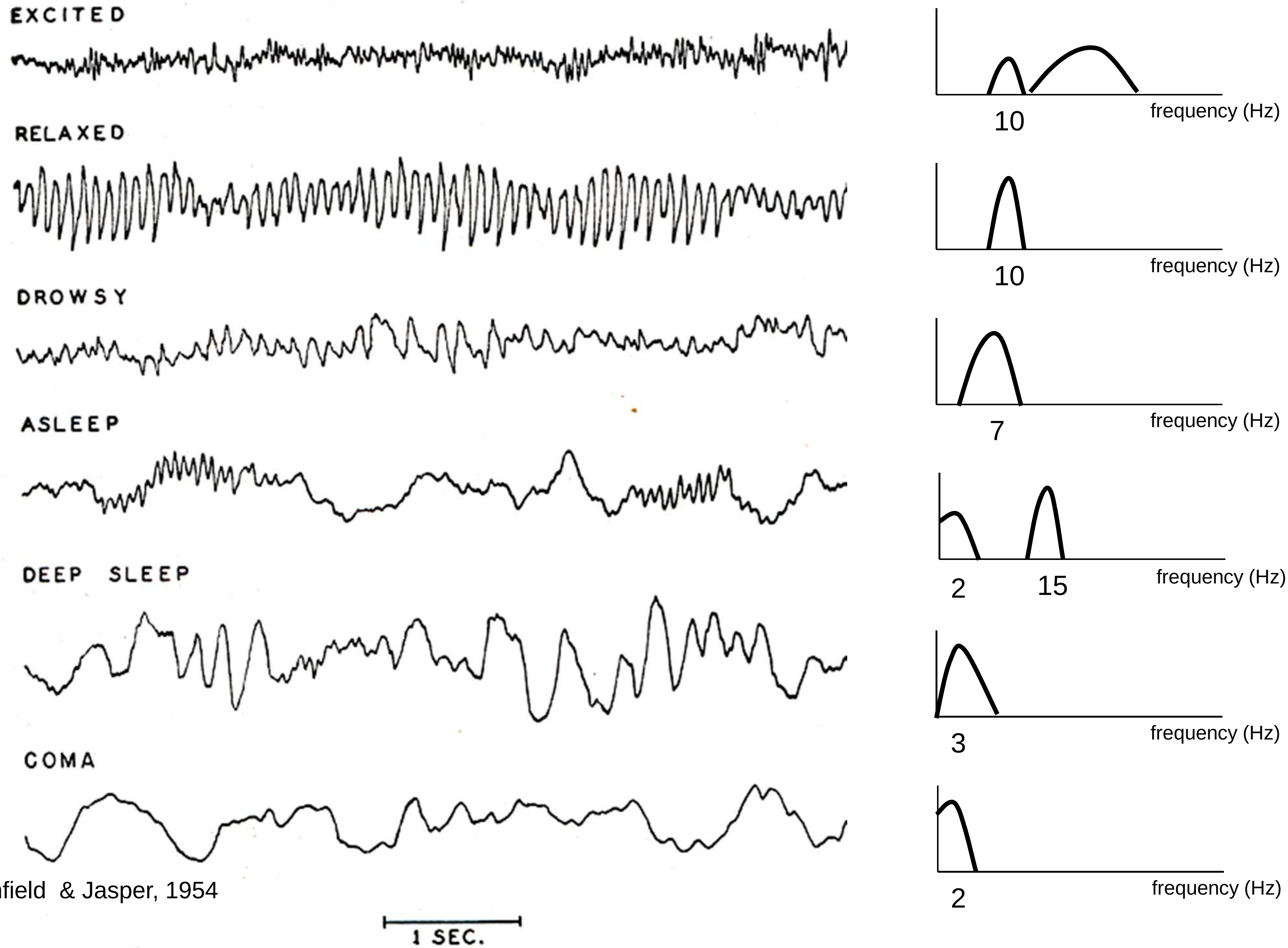
Temporal factors: A simple statistical principle

- *N* uncorrelated sources contribute proportionally to $N^{1/2}$, while *N* correlated sources contribute proportionally to *N*
- *N* is large (10^6-10^8)
- So small (e.g., 1%) correlations dominate random activity
- Conclusion: the EEG is generated by small subpopulations of weakly-correlated cortical pyramidal cells

Biology: these correlations are established by primarily by thalamocortical connections, and secondarily by corticocortical connections.

So the EEG is well-positioned to assay the large-scale brain dynamics that are relevant to consciousness.

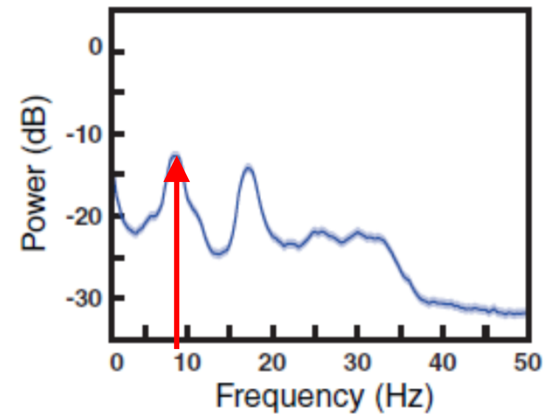
The spectrum provides a useful summary



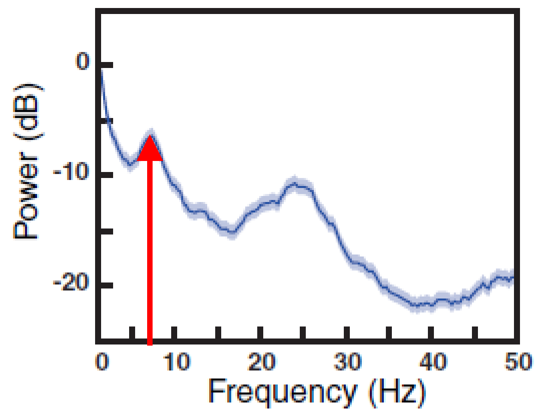
Penfield & Jasper, 1954

In clinical application:

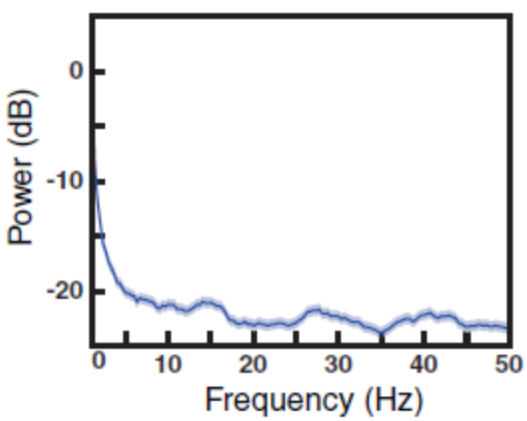
normal wakefulness



minimally conscious state



vegetative state

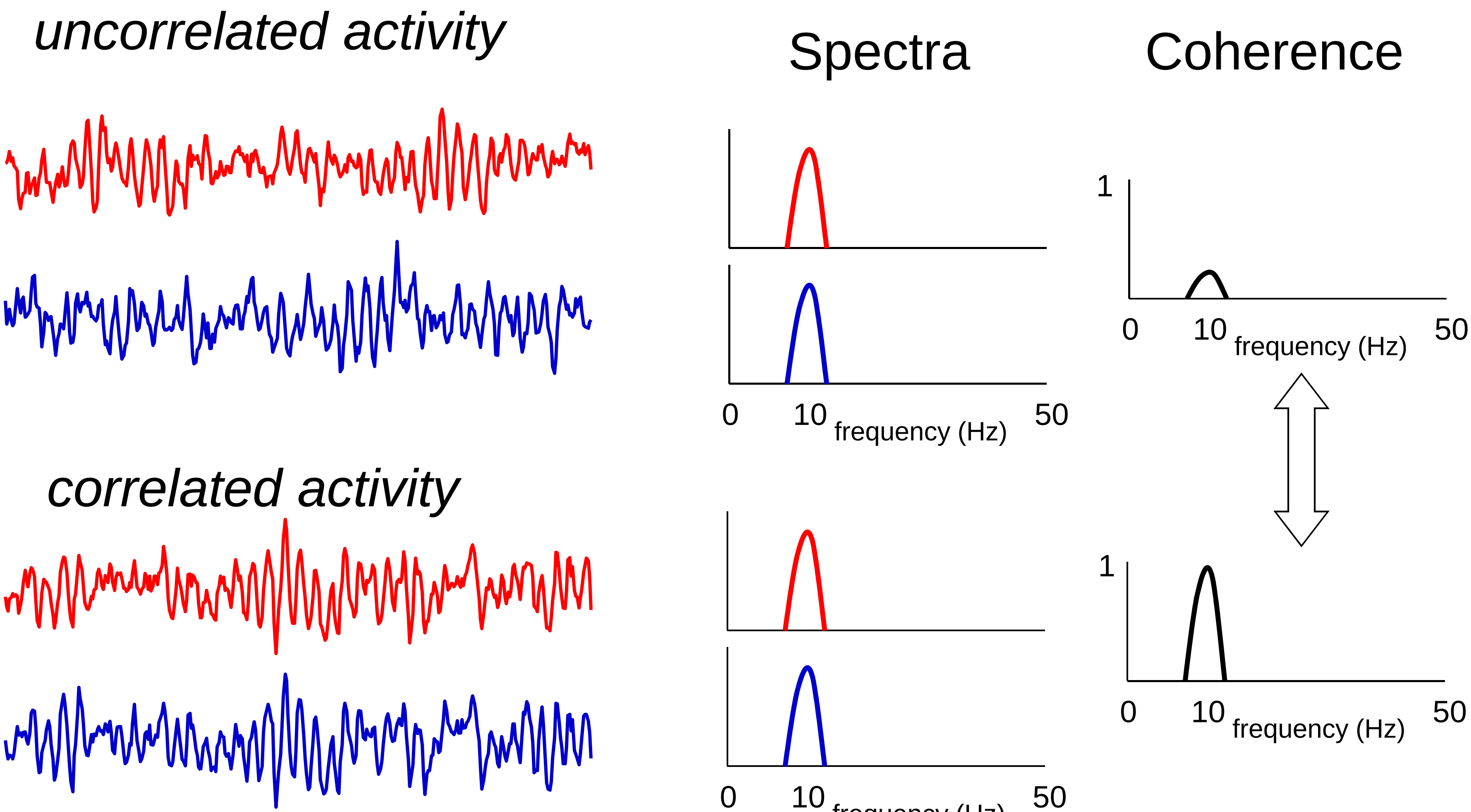


A shift from 6 Hz to 9-11 Hz

The emergence of a dominant rhythm

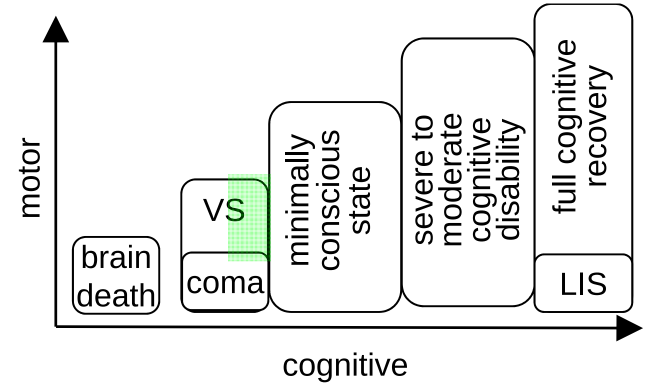
Schiff, Nauvel, Victor, 2013

Relationship between EEG signals: coherence

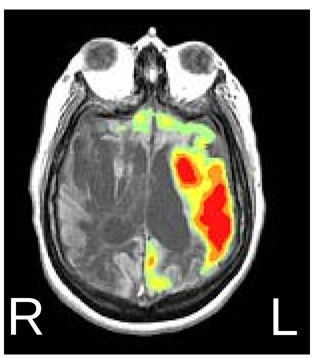


- We can also look at phase relationships, and how spectra and coherence change in time.

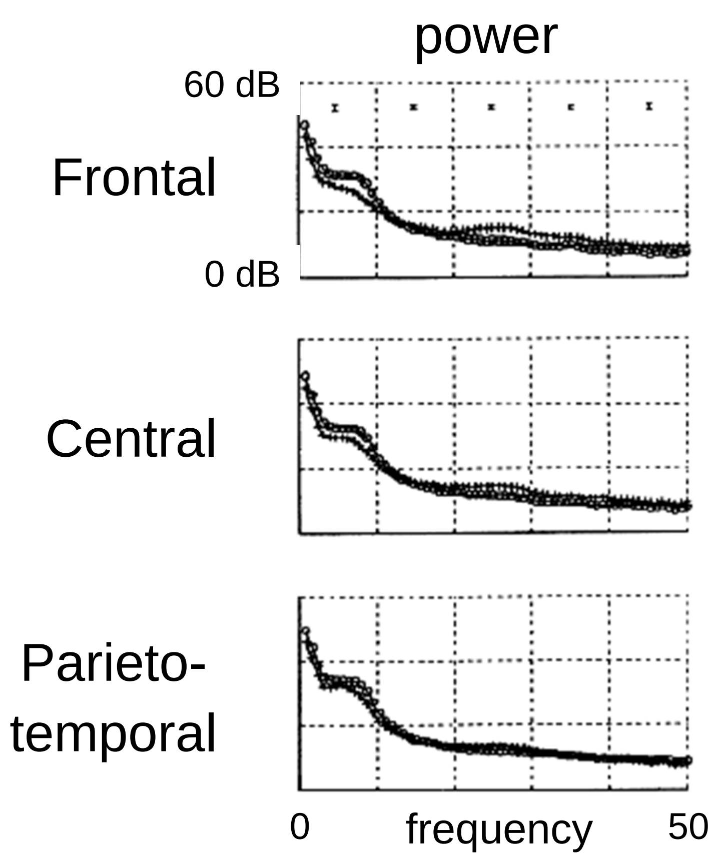
Hemispheric dysfunction: coherence provides additional information



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



^{18}FDG-PET

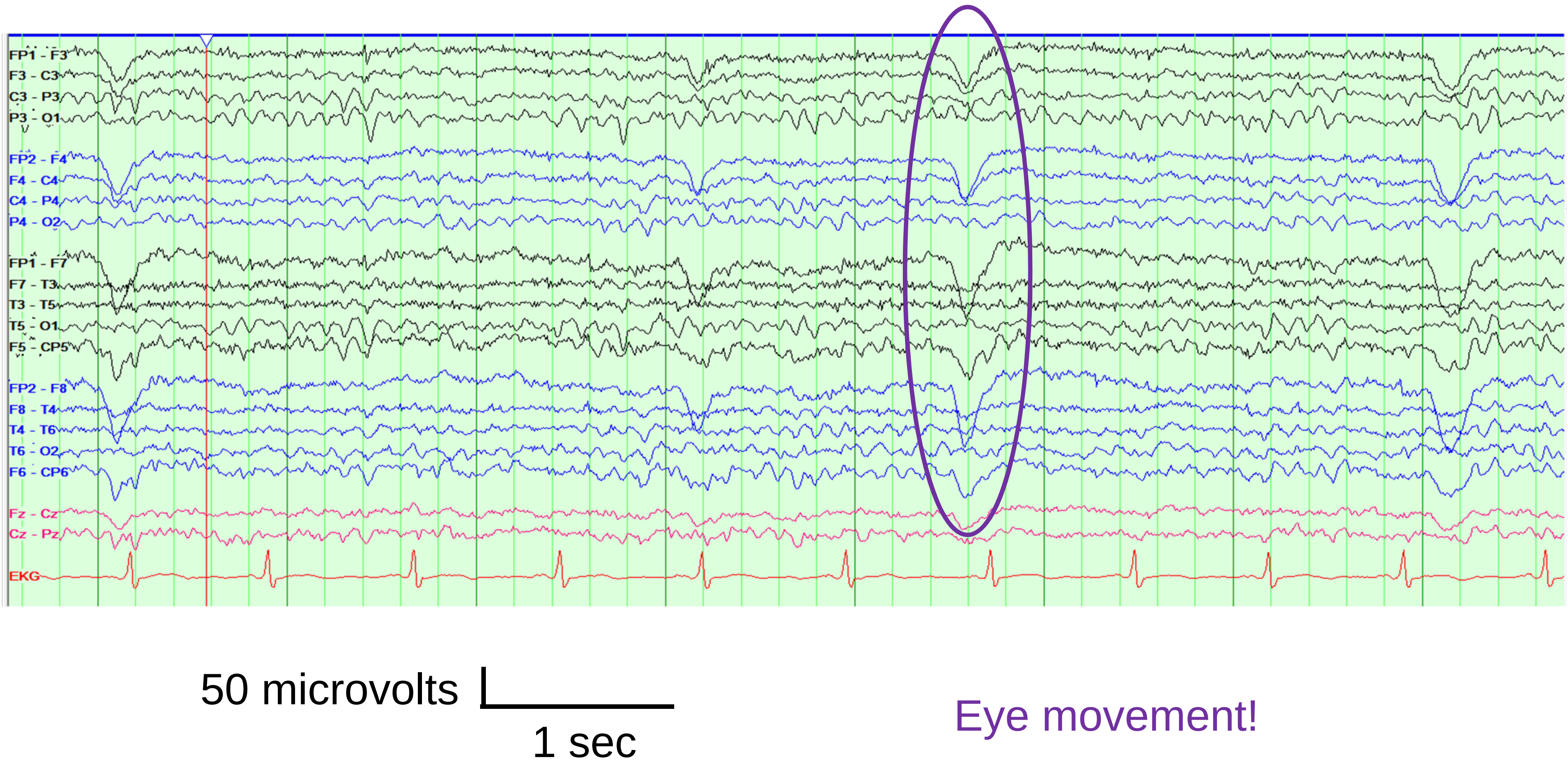


Davey, Victor, Schiff, 2000

So the EEG looks very promising

- Resting EEG spectra reflect global level of function
- Coherence reflects integrity of corticocortical interactions
- Task-induced changes in EEG may be a way of assaying cognitive function, independent of motor output

But there's a problem:



Artifact is a BIG problem

- Scalp bioelectric signals have many sources
  - The brain
  - Eye movements
  - Muscle activity
  - Sweat
- And many environmental contaminants
  - Patient movement
  - Line noise
  - IV’s, monitors, ventilators
  - Anything with a transformer
- Artifacts are
  - Intermittent
  - State-dependent
  - Often overlapping brain signals in frequency
  - Not the same in patients and healthy control subjects

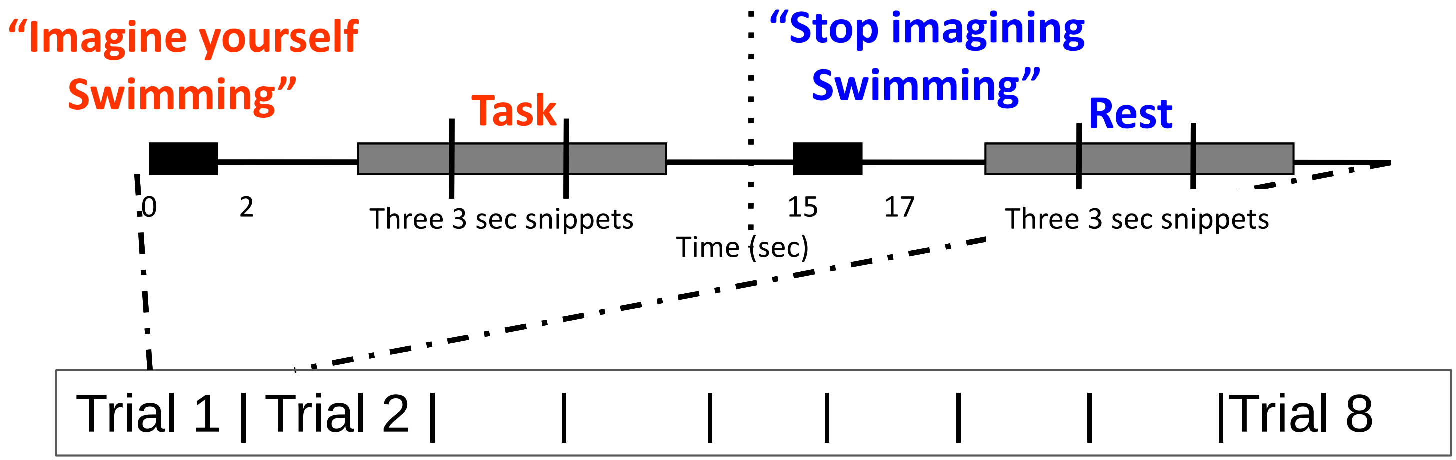
Application

Can EEG changes demonstrate motor imagery -- an element of cognitive function?

Goldfine, A.M., Victor, J.D., Conte, M.M., Bardin, J.C., and Schiff, N.D. (2011) Determination of awareness in patients with severe brain injury using EEG power spectral analysis. Clinical Neurophysiology 122, 2157-2168.

Protocol design and data flow

Separate runs on separate days. One run is 8 trials of EEG recording during:



<u>Pre-processing</u>

1. Manual rejection of snippets with visible motion artifact
2. Removal of line noise
3. Removal of EMG and eye movement artifact with ICA

<u>Dimensional Reduction</u>

1. Application of Laplacian montage
2. Fourier analysis of each channel in each snippet

<u>Univariate (Frequency-by-Frequency) Analysis</u>

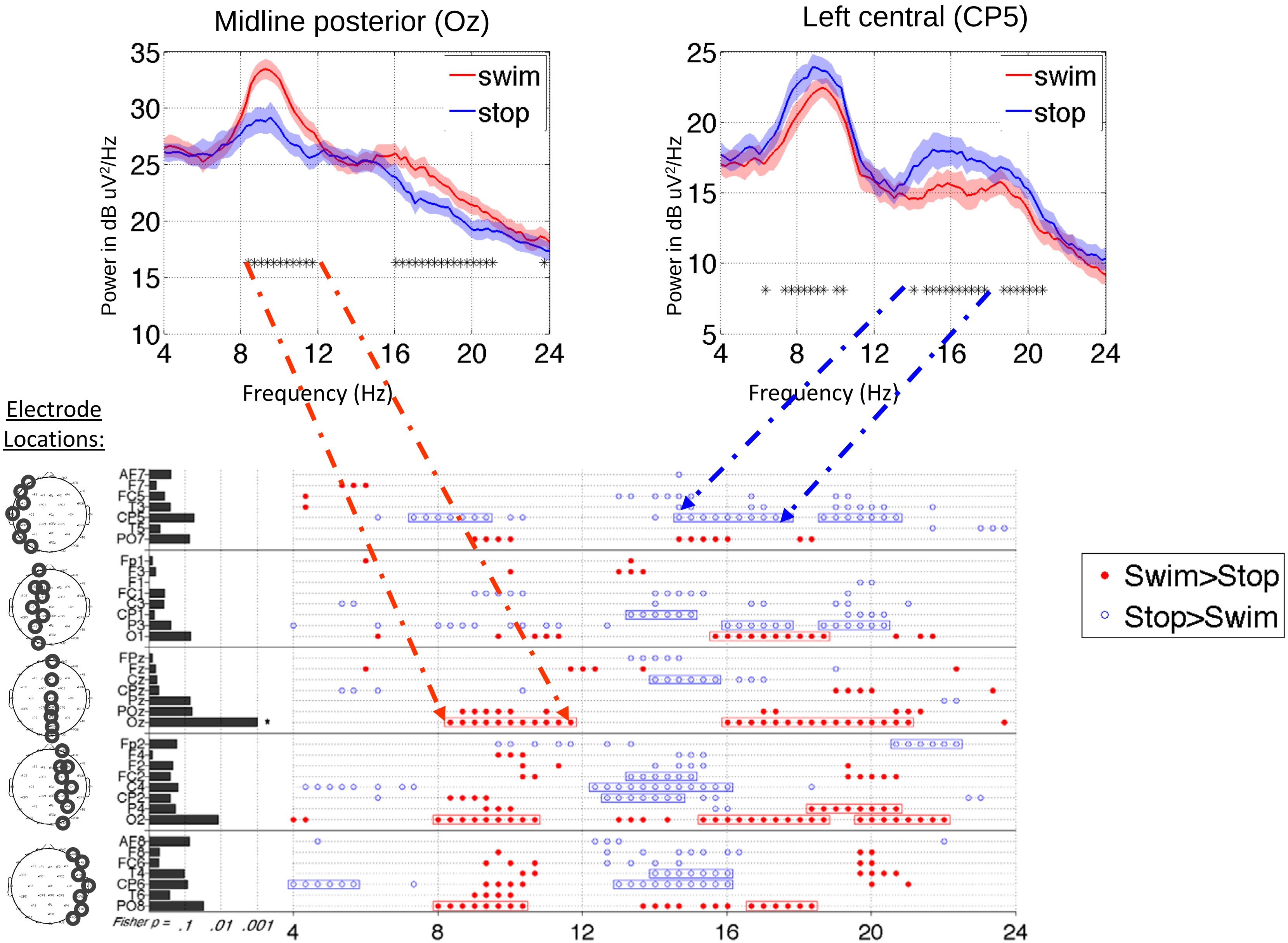
1. Two Group Test (TGT) on each channel, 4 to 24Hz
2. FDR applied to TGT results to correct for multiple comparisons (channels and frequencies)

<u>Mujltivariate Analysis</u>

1. Fisher Discriminant (FD), 2Hz-wide bins from 4 to 24 Hz
2. Significance determined by shuffle test
3. FDR applied to correct for multiple comparisons (channels)

Goldfine et al., 2011

Healthy control subject, one run

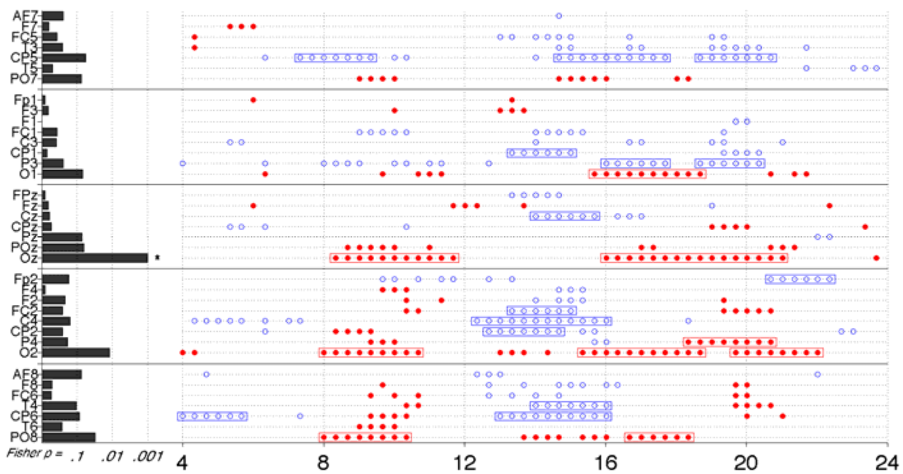


Fisher discriminant results

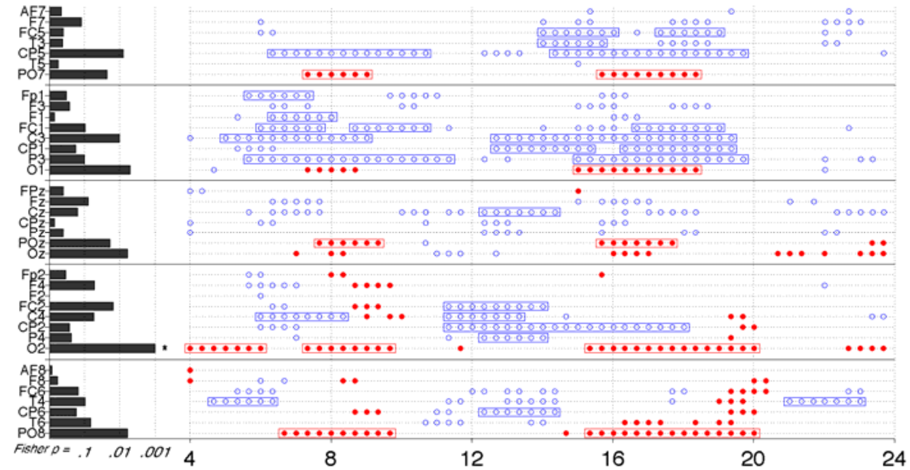
Goldfine et al., 2011

Healthy control subject, consistency across runs

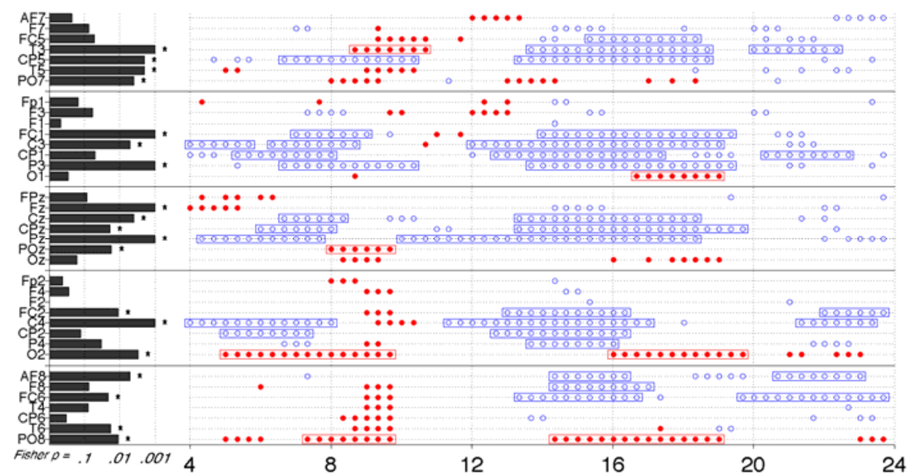
Run 1

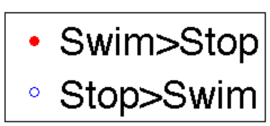


Run 2



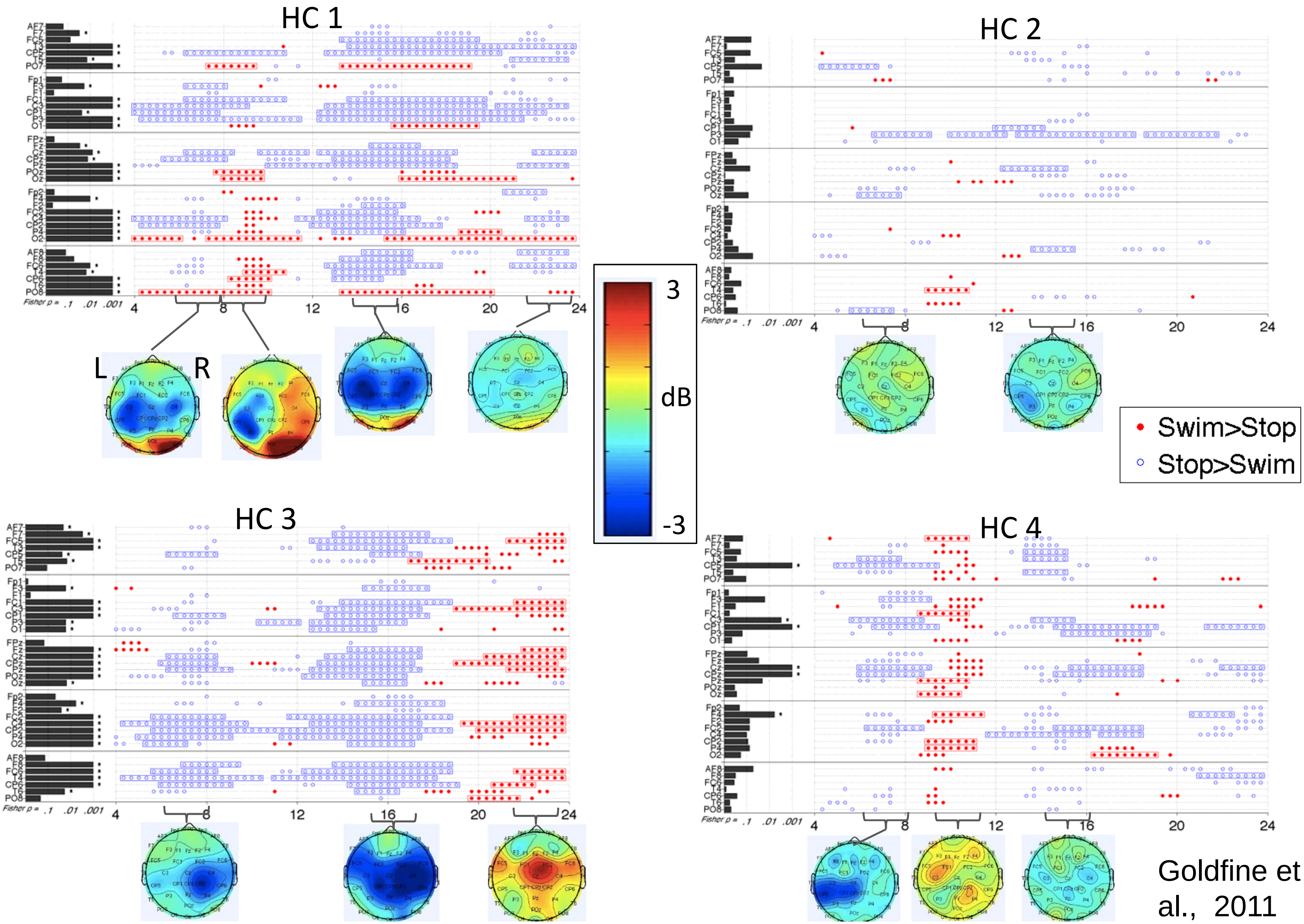
Run 3





Goldfine et al., 2011

Healthy controls, runs pooled for each subject



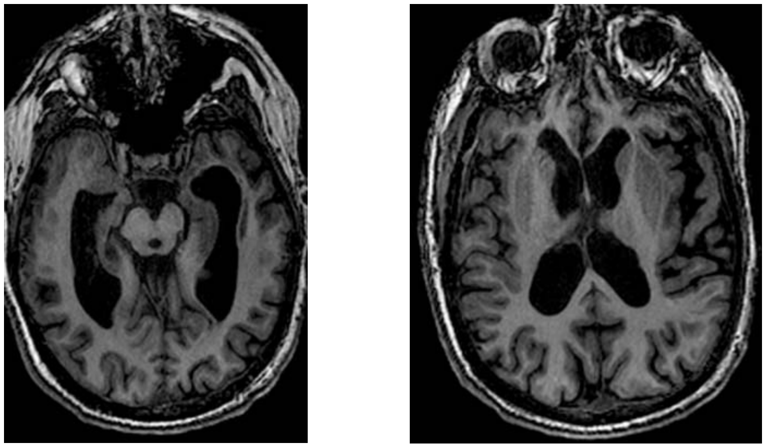
Goldfine et al., 2011

Results from healthy controls

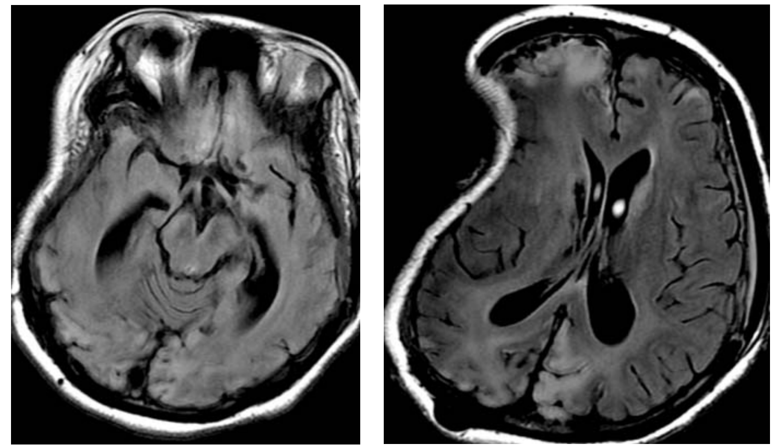
- The EEG identifies task performance
- But there is only modest consistency across subjects

Brain structure (MRI) in patient subjects

subject 1



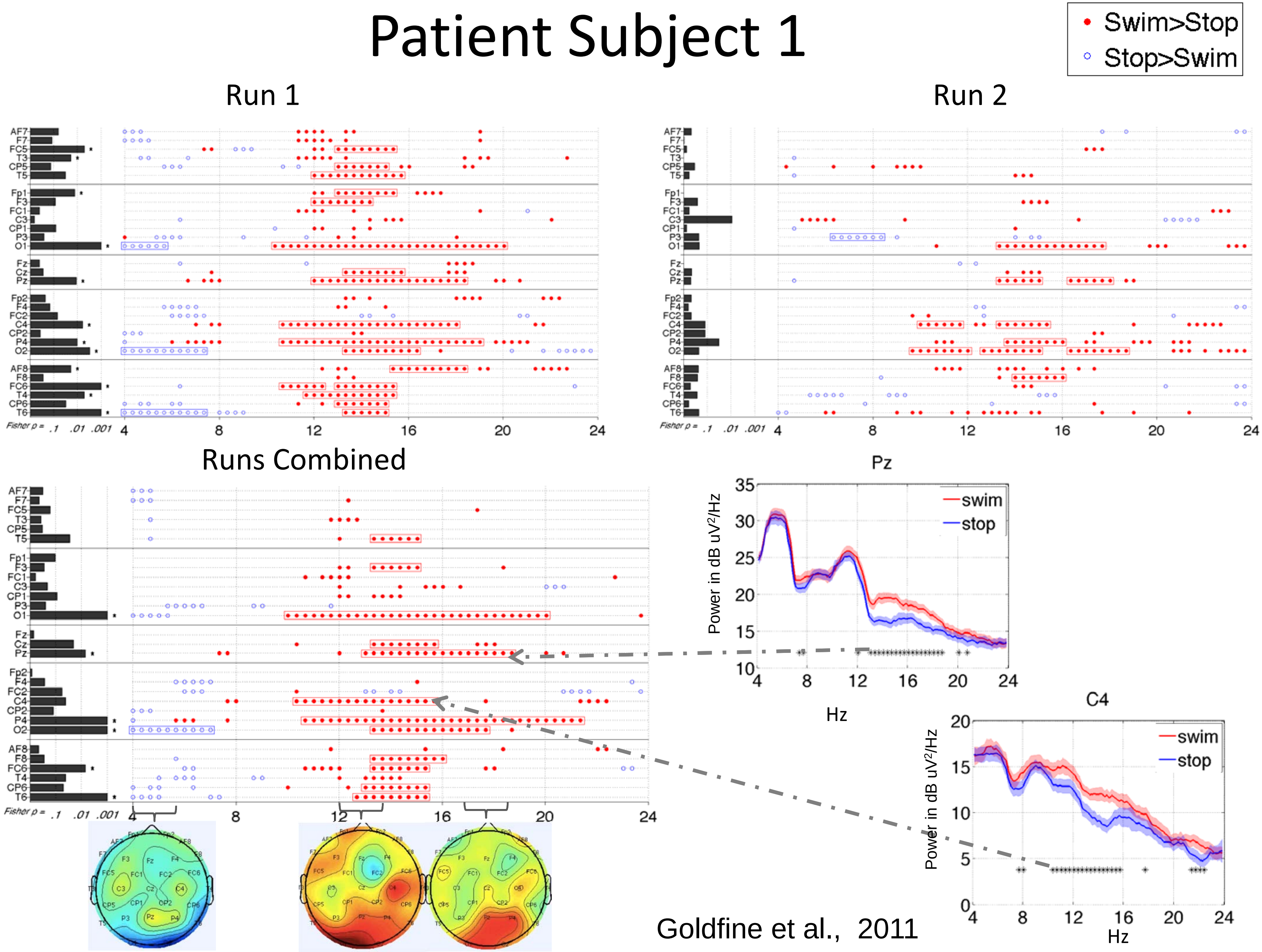
subject 2



subject 3

Goldfine et al., 2011

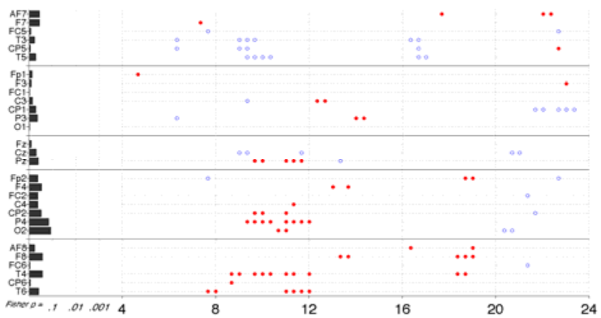
Patient Subject 1



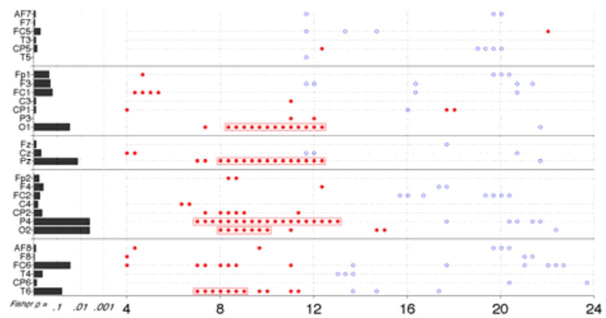
Goldfine et al., 2011

Patient Subject 2

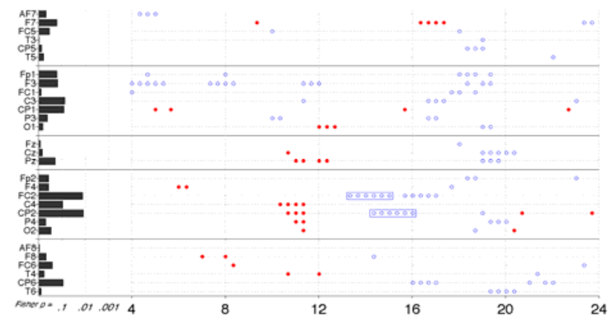
Run 1



Run 2



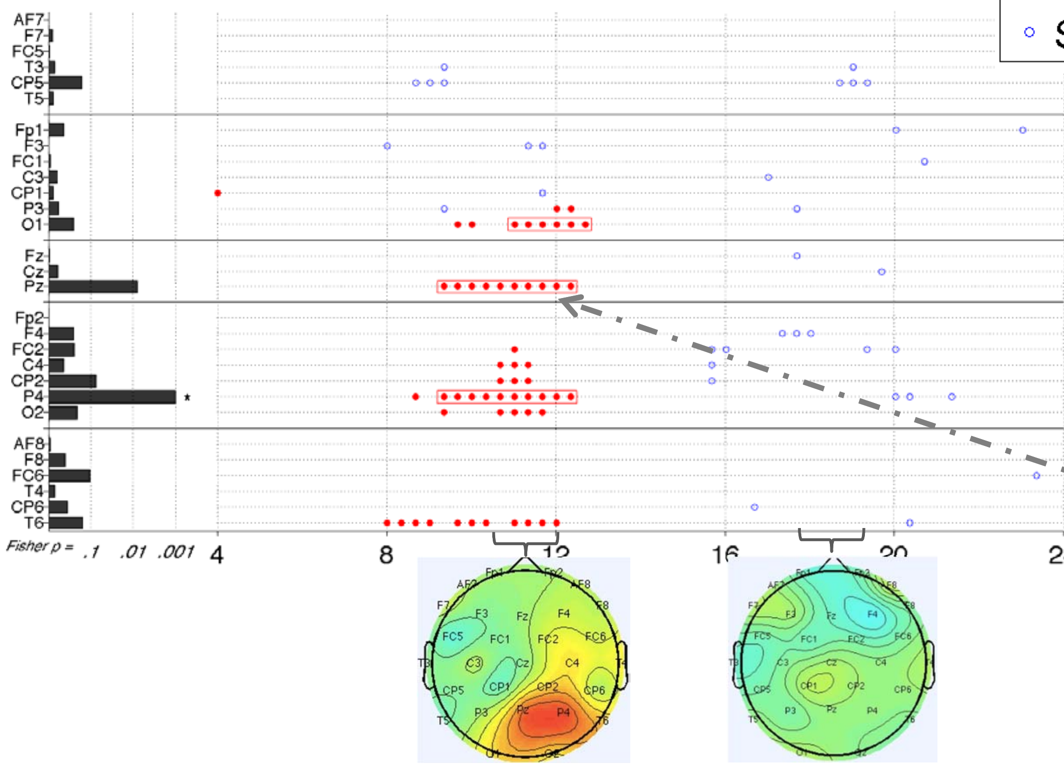
Run 3

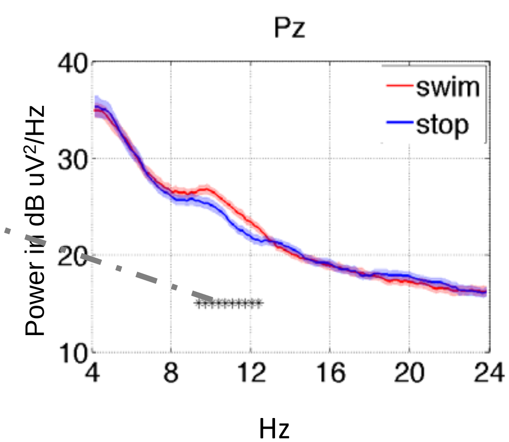


Swim>Stop
Stop>Swim

Visit 1 command following
Swim performed:
2/24/2009
Run 1 12:23:23
Run 2 12:31:12
Run 3 12:44:40

Runs
Combined

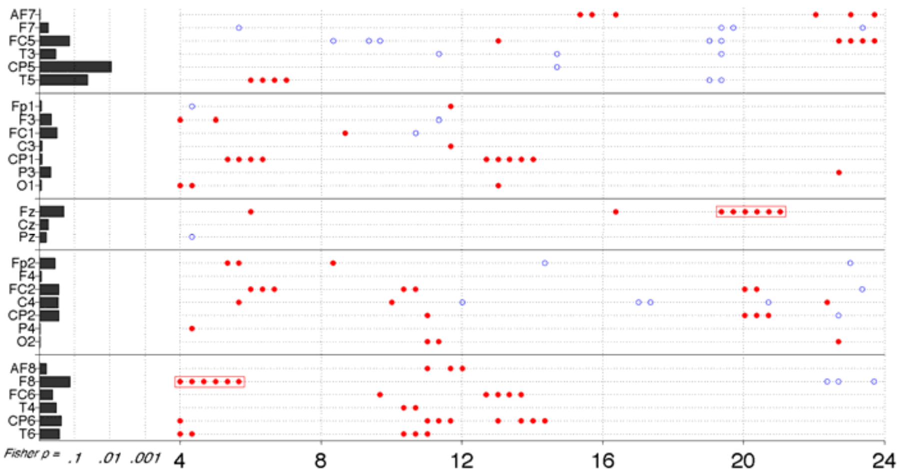




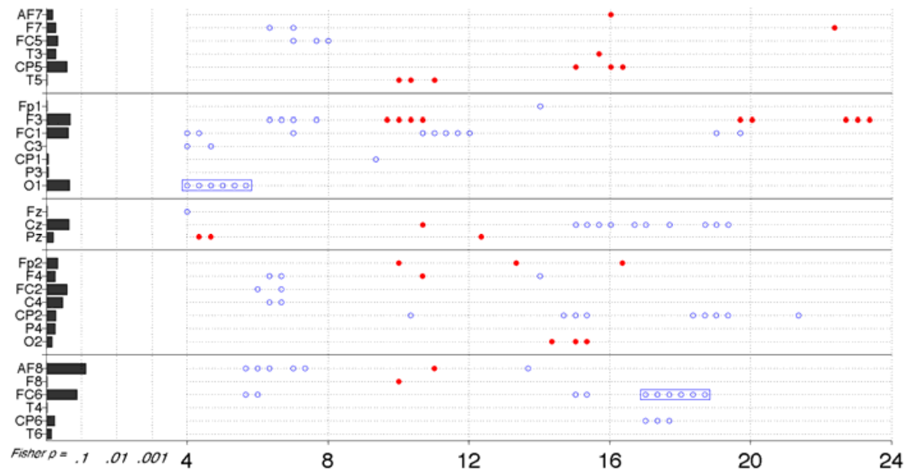
Goldfine et al., 2011

Patient Subject 3

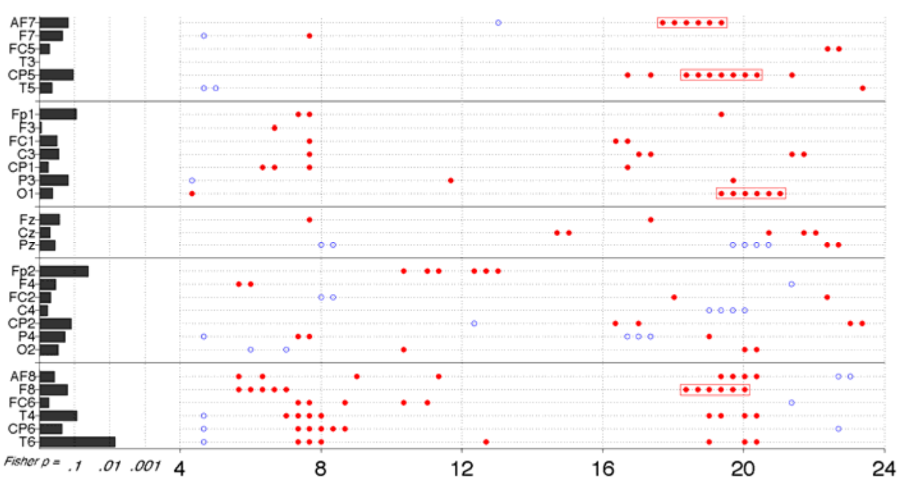
Run 1



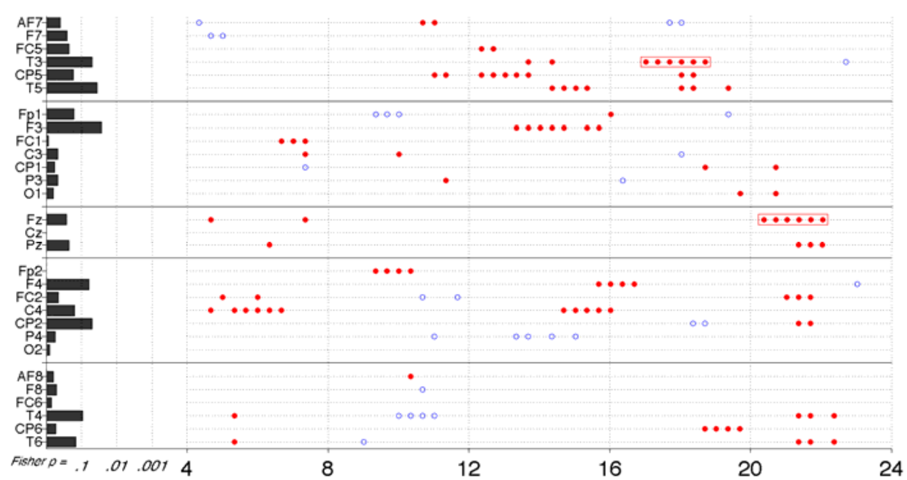
Run 2



Run 3



Run 4



Runs combined: Nothing consistent

Goldfine et al., 2011

Summary from three MCS patient subjects

- Results
  - S1 and S2 showed task-related changes in each run, consistent across runs: “positive”
  - S3 showed task-related changes in some runs, but inconsistent across runs: “indeterminate”

- Observations
  - Response pattern did not match healthy controls
  - Univariate analysis (each frequency, each channel, with multiple comparisons correction) yields more positives than multivariate analysis (Fisher discriminant at each channel)

Another study

Can EEG changes demonstrate motor imagery -- an element of cognitive function?

Cruse, D., Chennu, S., Chatelle, C., Bekinschtein, T.A., Fernández-Espejo, D., Pickard, J.D., Laureys, S., and Owen, A.M. (2011) Bedside detection of awareness in the vegetative state: a cohort study. The Lancet 378, 2088-2094.

Task-dependent changes reported in 3 of 16 patients *that had been considered vegetative*

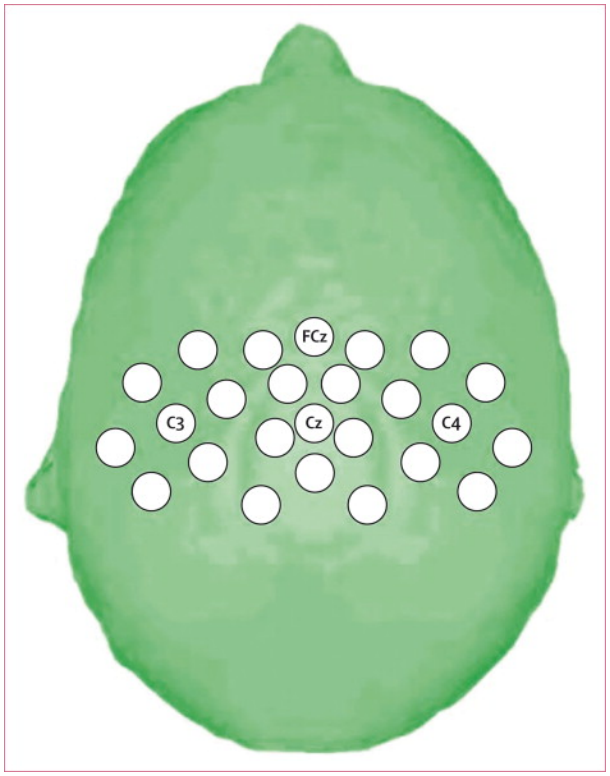
Main findings, I

	Sex	Age at assessment (years)	Interval postictus (months)	Cause (TBI/non-TBI)	CRS-R	Number of tasks contributing to analyses	EEG classification accuracy (%)	p value for EEG command following
Patient 1	Male	35	9	Anoxia	7	202	61·38%	<0·01
Patient 2	Male	63	39	Anoxia	5	113	61·90%	NS
Patient 3	Male	55	21	Anoxia	4	160	47·50%	NS
Patient 4	Male	35	32	Anoxia	6	69	43·47%	NS
Patient 5	Male	30	24	Anoxia	6	102	51·96%	NS
Patient 6	Female	41	56	Anoxia	5	132	53·78%	NS
Patient 7	Male	63	32	Anoxia	7	76	56·58%	NS
Patient 8	Female	44	1	Anoxia	3	86	48·83%	NS
Patient 9	Male	48	94	Anoxia	6	116	58·62%	NS
Patient 10	Female	36	77	Stroke	3	114	39·47%	NS
Patient 11	Male	62	1	Stroke	6	142	48·59%	NS
Patient 12	Male	45	23	Trauma	6	146	71·23%	<0·001
Patient 13	Male	29	3	Trauma	6	96	78·13%	<0·001
Patient 14	Male	29	16	Trauma	6	150	40·70%	NS
Patient 15	Male	14	18	Trauma	6	60	41·66%	NS
Patient 16	Male	21	7	Trauma	7	98	47·95%	NS

Of 16 patients who appeared vegetative by bedside exam, three had signifiicant ($p<0.01$) evidence of command-following on EEG.

Cruse et al., 2011

Main findings, II



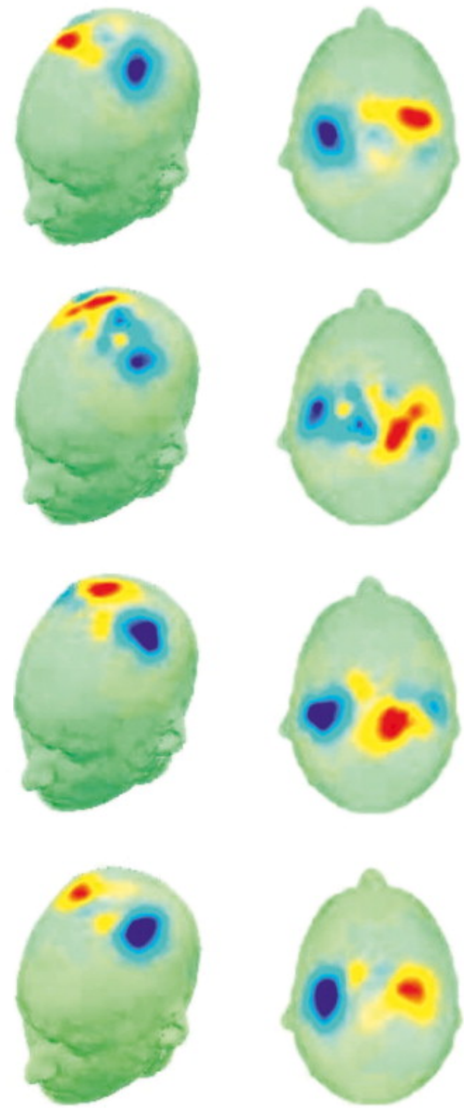
Inferred topography of features that distinguished periods of motor imagery: “formally identical” in patients and controls

healthy control

patient 1

patient 12

patient 13



Cruse et al., 2011

This is news!

Bedside detection of awareness in the vegetative state: a cohort study. Lancet, 2011.

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

abc NEWS

Test Shows Awareness, Consciousness for Brain-Damaged Patients

- New research using a portable electrode test suggests nearly 20 percent of those previously determined to be vegetative state may be consciously aware of their surroundings and even able to communicate through easily detectable brain signals.

The New York Times

Study Finds Signs of Awareness in 3 'Vegetative' Patients

- Three severely brain-injured people thought to be in an irreversible "vegetative" state showed signs of full consciousness...

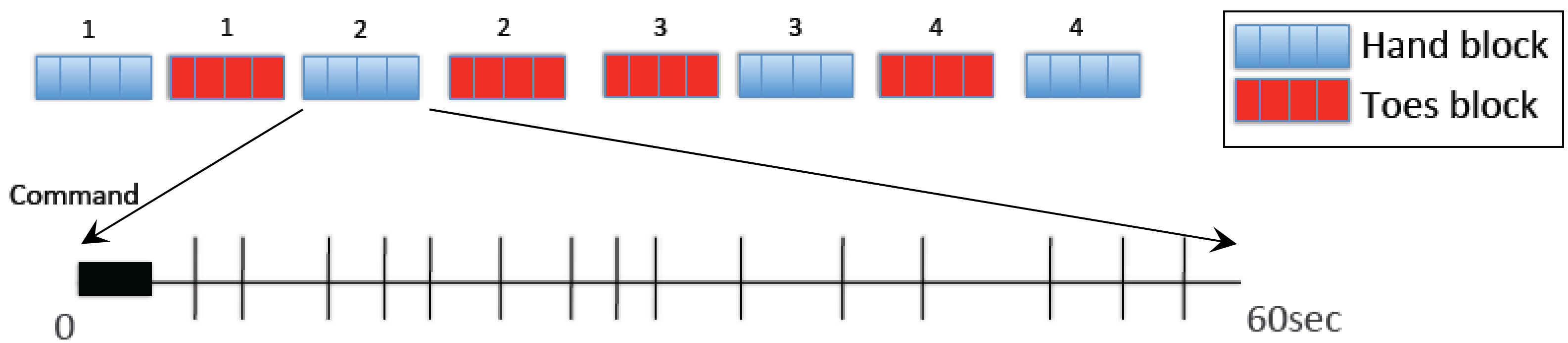
What's going on here?

- Similar behavioral paradigm as in Goldfine et al. 2011: motor imagery

- Different analytical approach: massive multivariate analysis

- Surprising and potentially very important finding: command-following in patients thought to be vegetative

Cruse et al. (2011) procedure



Protocol

- Command given at start of block
- Tones spaced randomly, 3 to 6.5 sec
- 10 to 16 commands per block
- Block order pseudorandomized, never more than two hand or two blocks consecutively

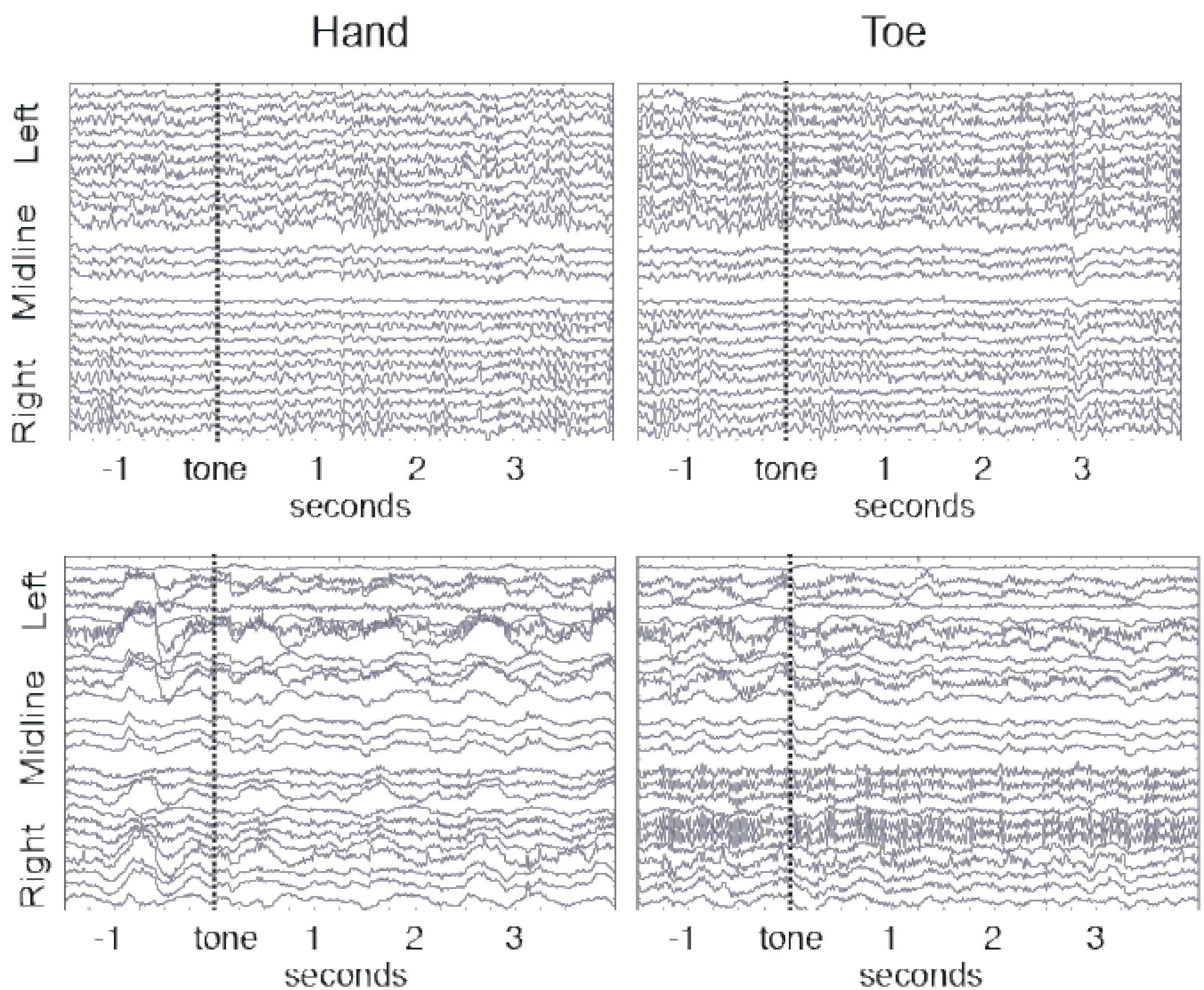
Pre-processing

- Data epoched into trials 1.5 sec pre-tone to 4 sec post-tone
- Trials with “significant artifact” removed

Example data

healthy control

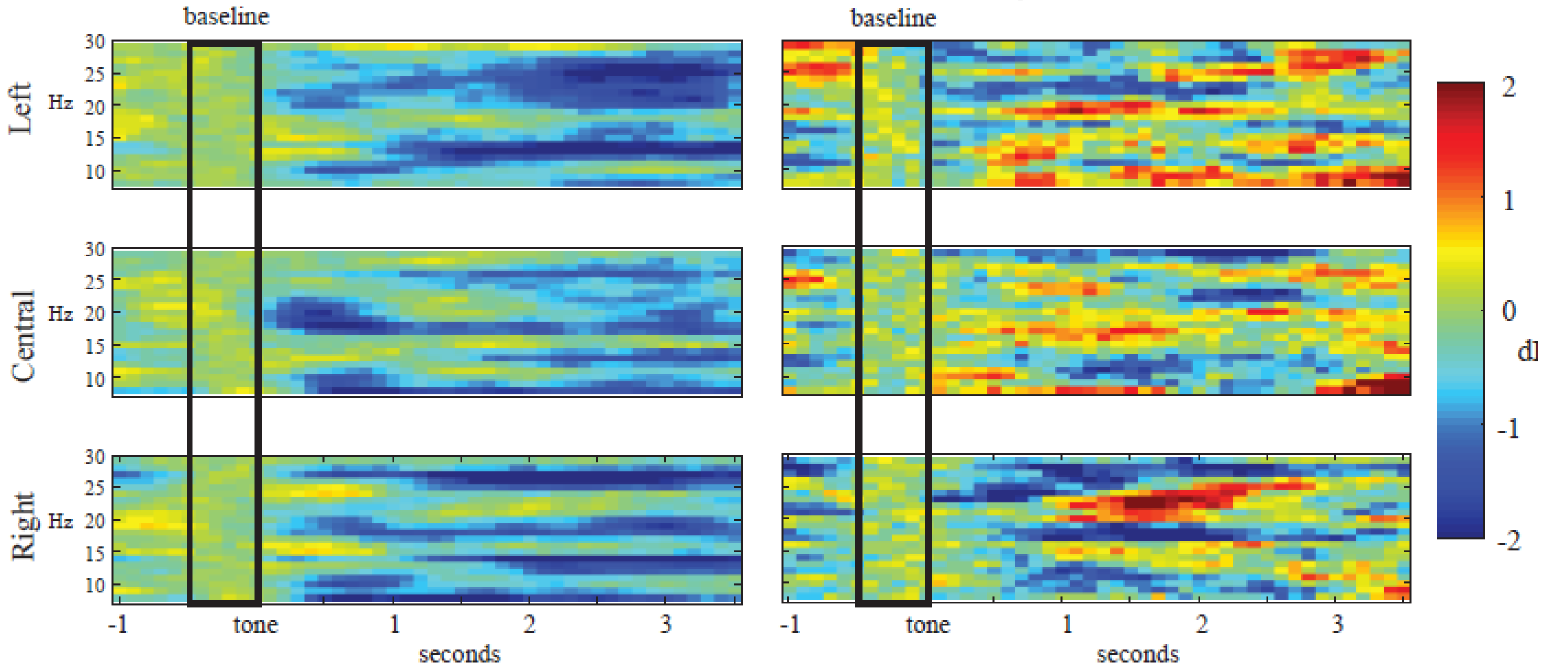
patient 13



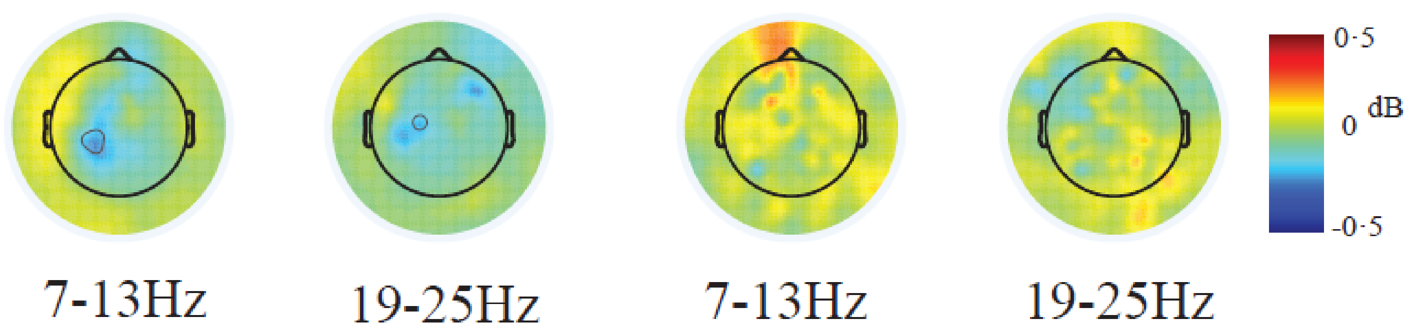
Courtesy of Cruse, Owen, et al.,

What do variations in power look like?

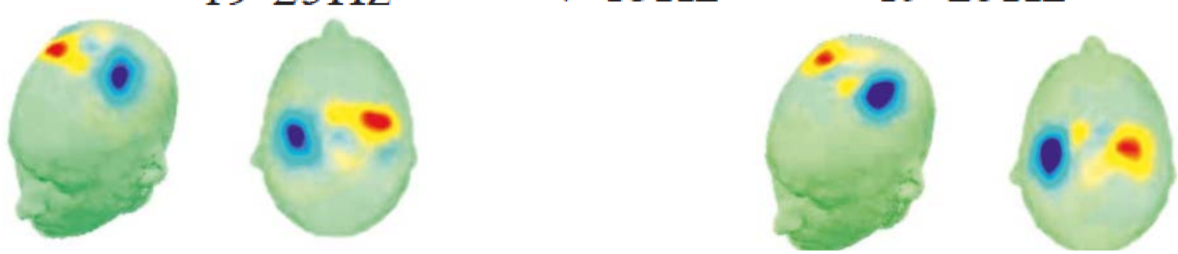
healthy control | patient 13



hand and foot trials pooled

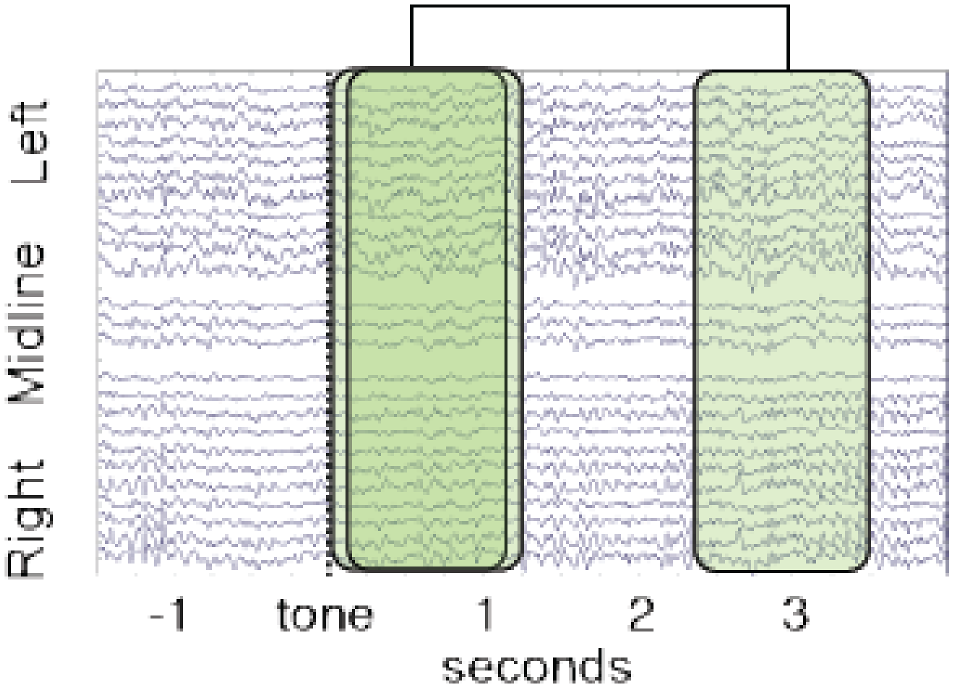


Topography, full dataset



Cruse et al., 2011

Cruse et al. (2011) analysis

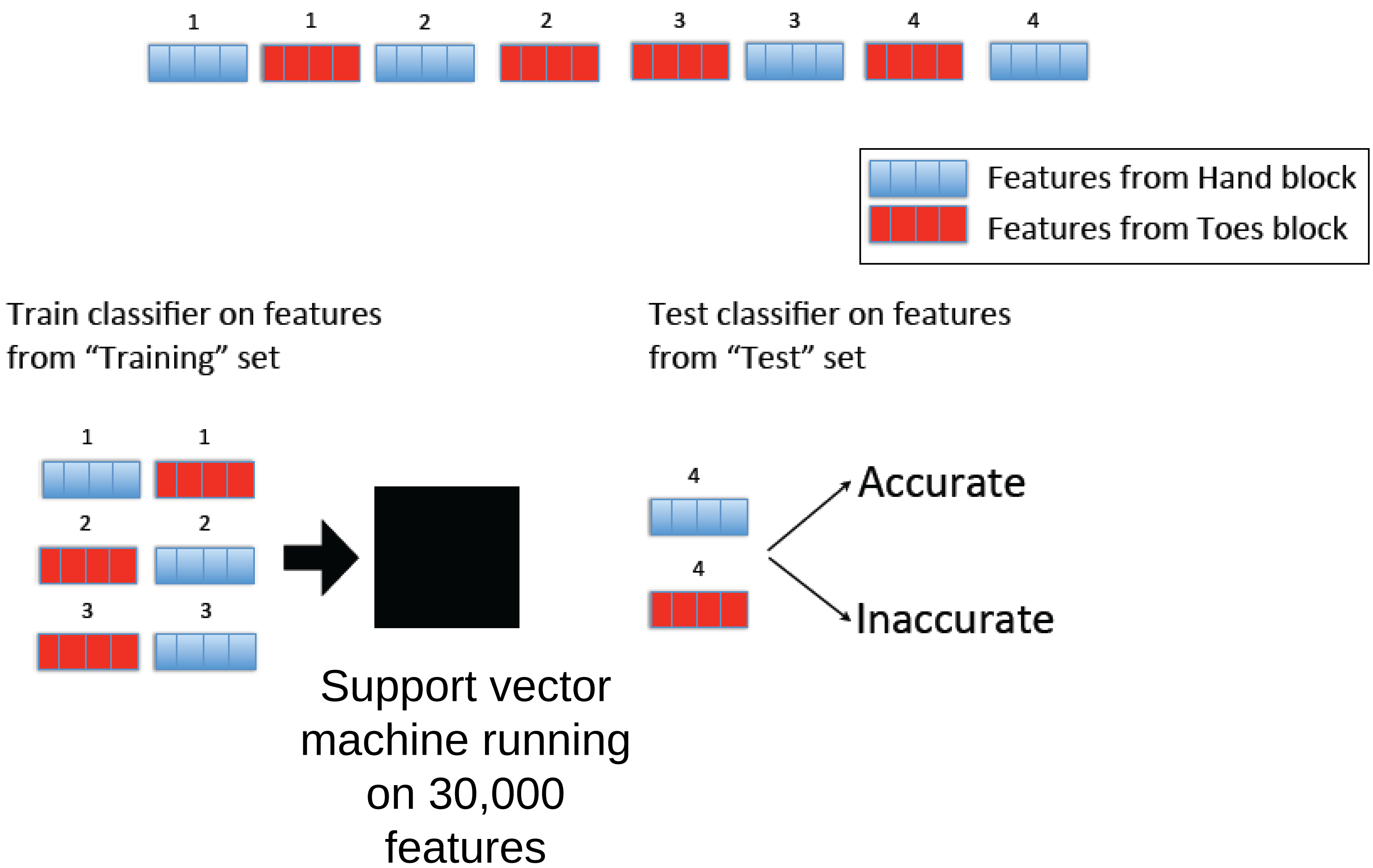


EEG converted to features based on spectral power:
4 frequency ranges (7-13, 13-19, 19-25, 25-30)
25 channels
300 sliding windows across the period of interest

4 x 25 x 300 = 30,000 features!

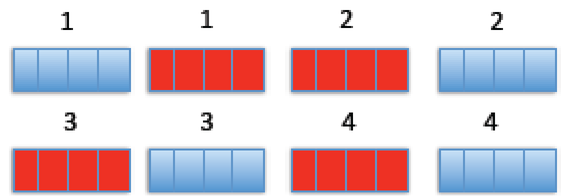
Classify as hand vs. foot via support vector machine, with cross-validation

Cross-validation



Cross-validation details

- Blocks used as test datasets to account for possibility of state changes between blocks. But…

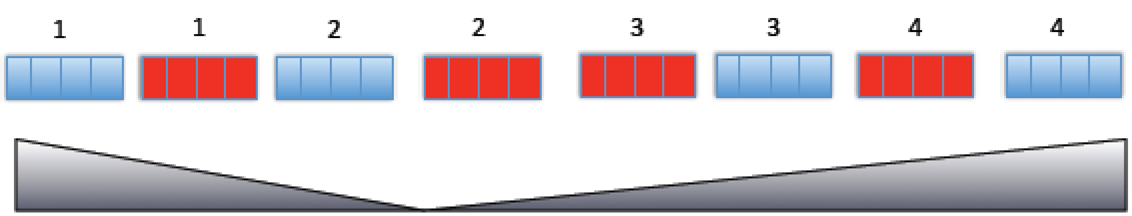


- Test datasets were always matched pairs.
- Pairs nearby in time may have correlations not present in further apart pairs.

Training	Test
223344	11
113344	22
112244	33
112233	44

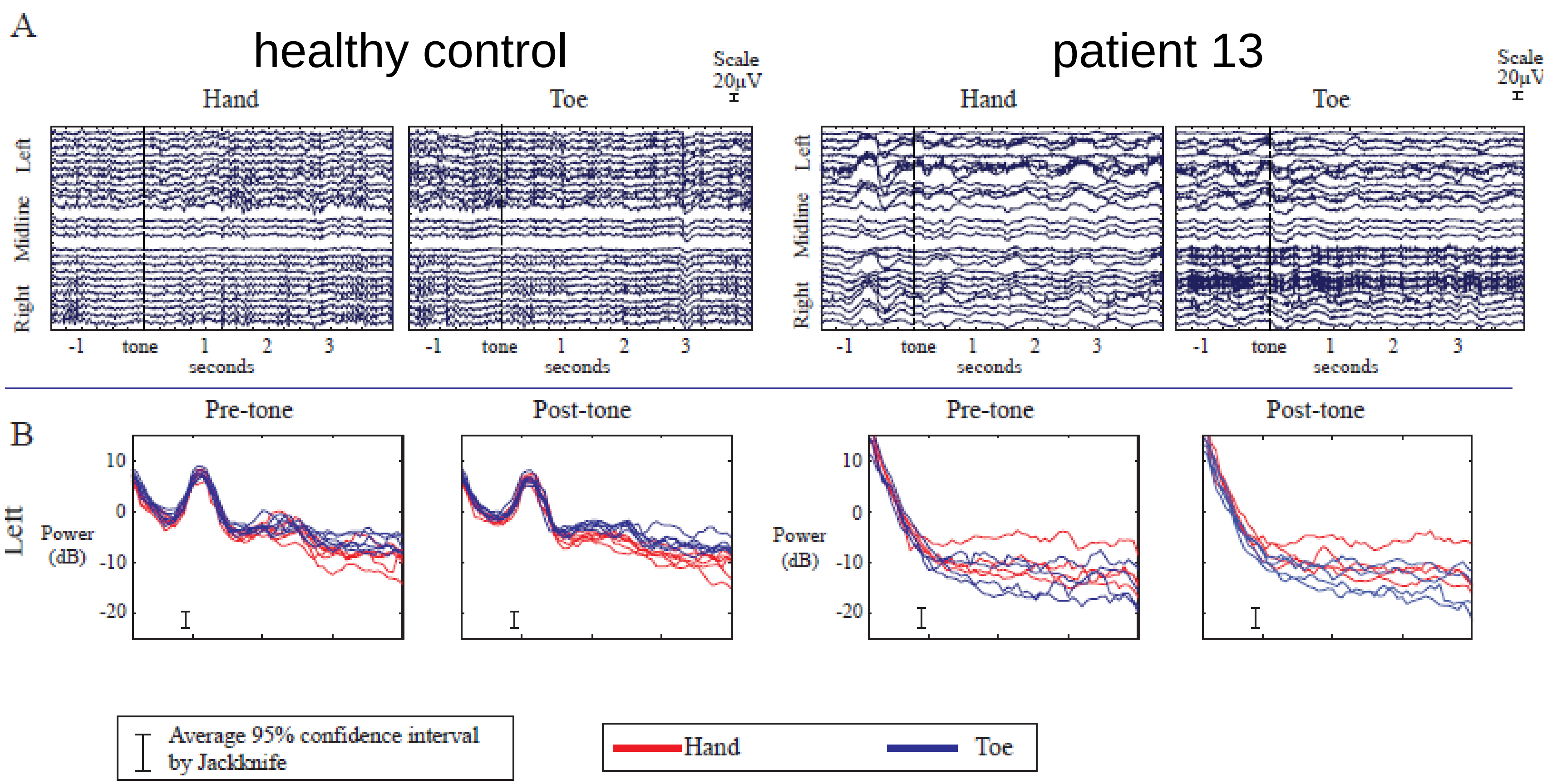
Slow correlations have two consequences:

Trials within blocks are not independent assays.
Correlations between blocks may not be task-related.



- Muscle tension
- Level of arousal
- Overt movement

Evidence for slow variations across blocks

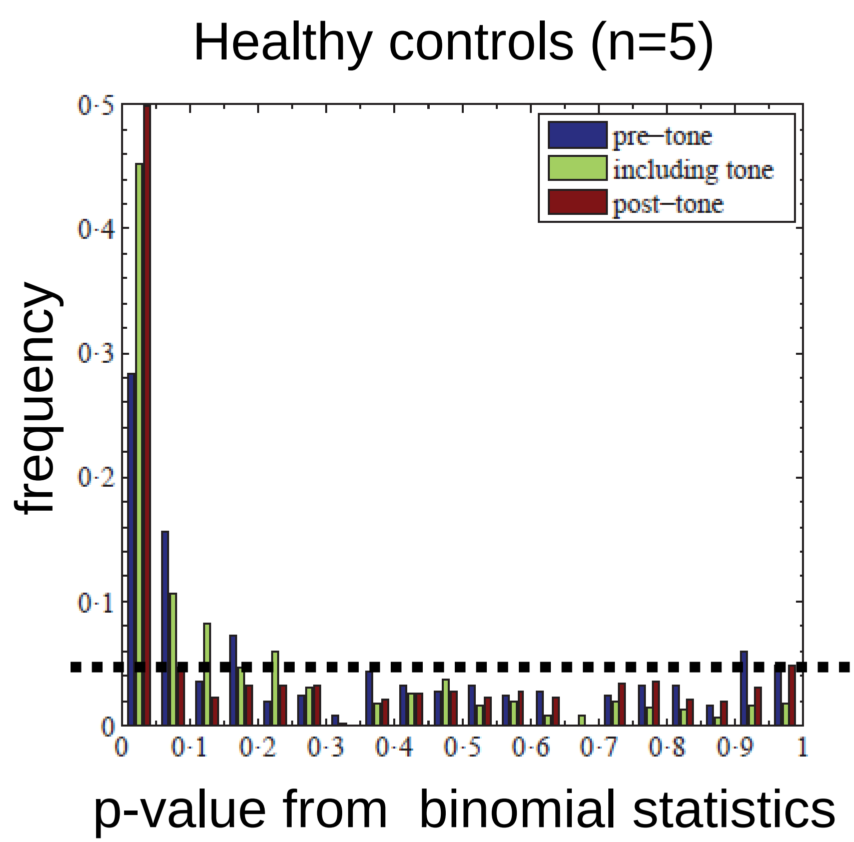


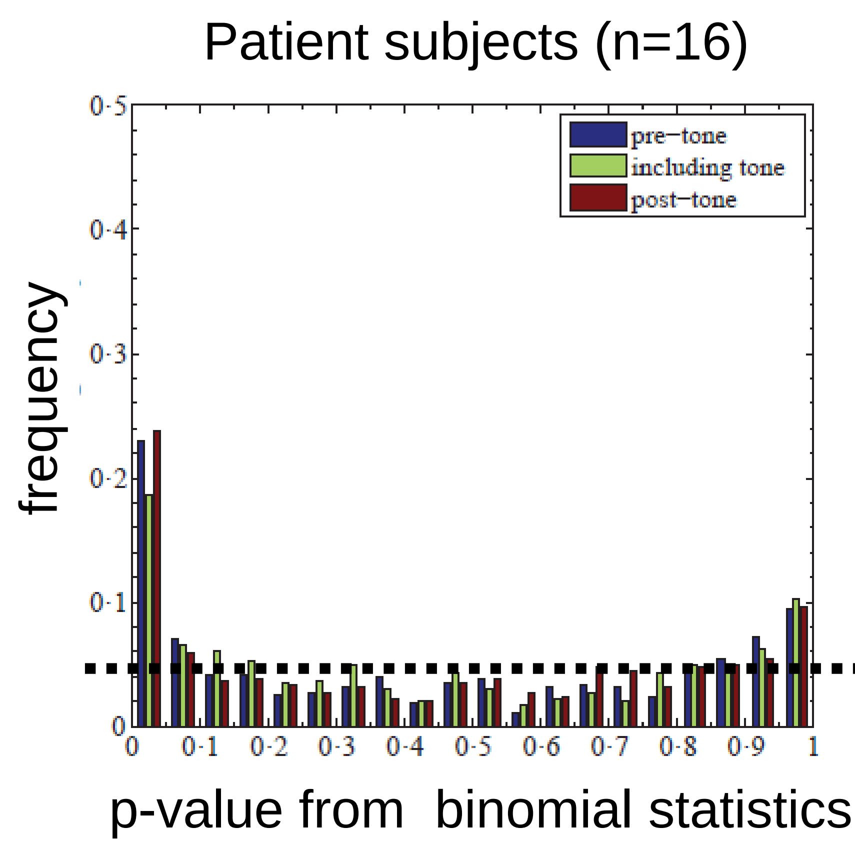
There is a greater change between blocks than expected from the estimates within blocks.

These changes are larger than the differences between hand and toe.

Goldfine et al., 2013

Do slow variations affect the binomial significance test?

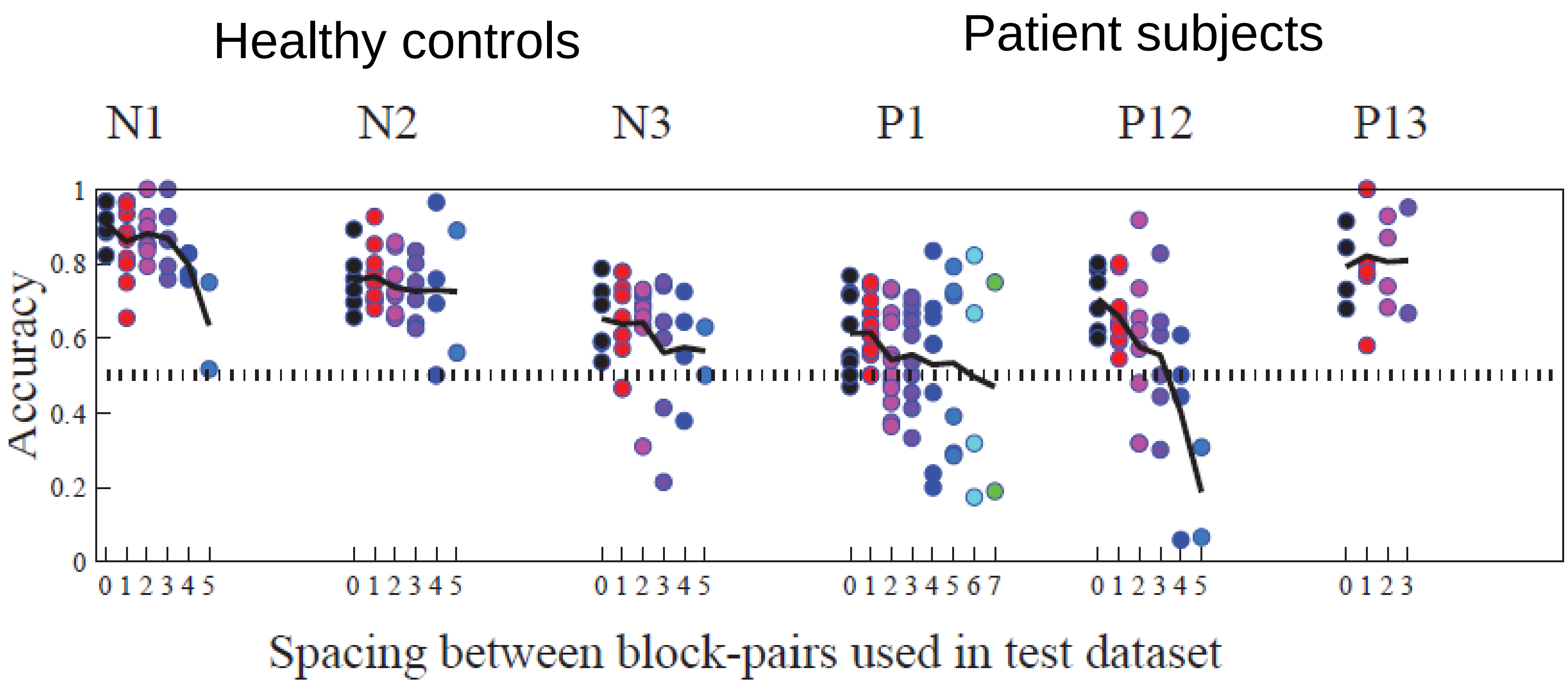




Yes: in patients, there is an excess of “significant” anti-prediction.

Goldfine et al., 2013

Do slow variations across blocks affect out-of-sample testing?



Yes: out-of-sample accuracy falls as spacing between block pairs increases.

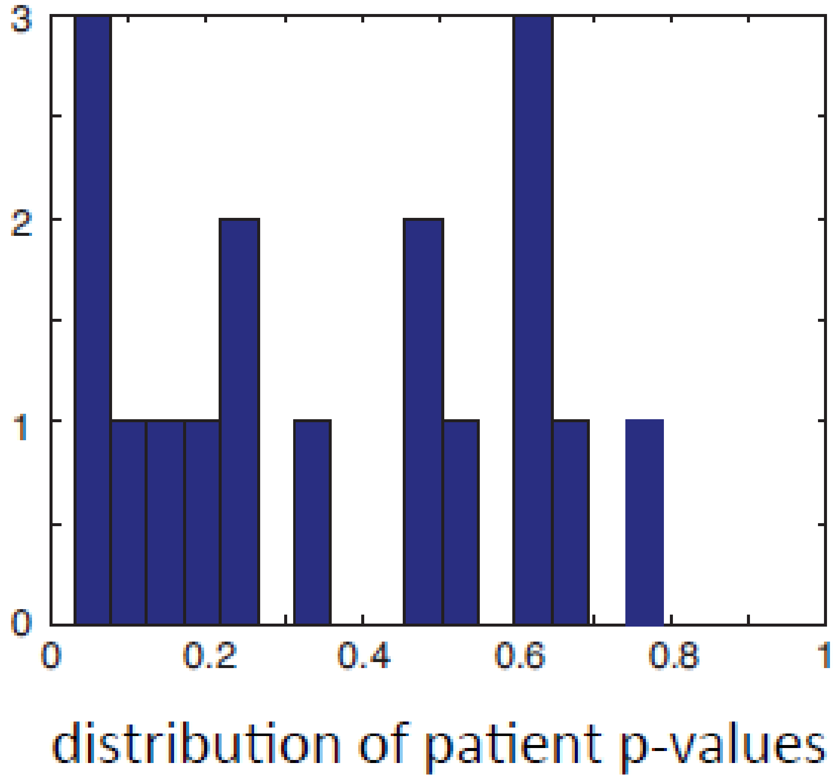
Goldfine et al., 2013

Reanalysis: permutation test on all blocks

	Positive Subjects	# of blocks	Accuracy (original SVM)	Binomial two-sided p-value	Permutation p-value
Healthy controls	N1	6	0·9096	$9x10^{-30}$	0·0022
	N2	6	0·7561	$3x10^{-11}$	0·0022
	N3	6	0·6529	$8x10^{-5}$	0·0498
Patient subjects	P1	8	0·6139	0·0015	0·0930
	P12	6	0·7123	$3x10^{-7}$	0·0649
	P13	4	0·7812	$3x10^{-8}$	0·0286

Goldfine et al., 2013

But there is no a priori reason to think that any patient is positive.



0 of 16 patients' p-values remain significant after correction for multiple comparisons (FDR or Bonferroni).

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(3 of 5 controls remain significant)

Goldfine et al., 2013

Conclusions

- EEG plays a crucial role in objective assessment of brain function and cognitive capacity
- Genesis of EEG signals is well-understood, but their analysis is fraught with challenges
  - Wealth of candidate features
  - Complex dynamics of signal and artifact
- Meeting the challenges requires statistical approaches tailored to the biology

Thank you.