Intro to pharmacological (ph)MRI and EEG-fMRI

Jennifer Evans

26Jul17

FMRIF Summer Course

Outline

- Pharmacological MRI
  - Role of fMRI in drug discovery
  - Types (study design)
    - examples
  - Confounding factors & how to mitigate them
- Basics of EEG-fMRI
  - Nuts and bolts
  - Example study
- Summary

Pharmacological fMRI

- An fMRI experiment + drug administration

- Pharmacological modulation of
  - ‘activity’ over pharmacokinetic timescales
  - task-related `activity`
  - ‘resting state activity’

- Recall that BOLD (Blood Oxygenation Level Dependent Imaging) signals are a function of changes in
  - Metabolic oxygen consumption
  - Cerebral blood flow
  - Cerebral blood volume

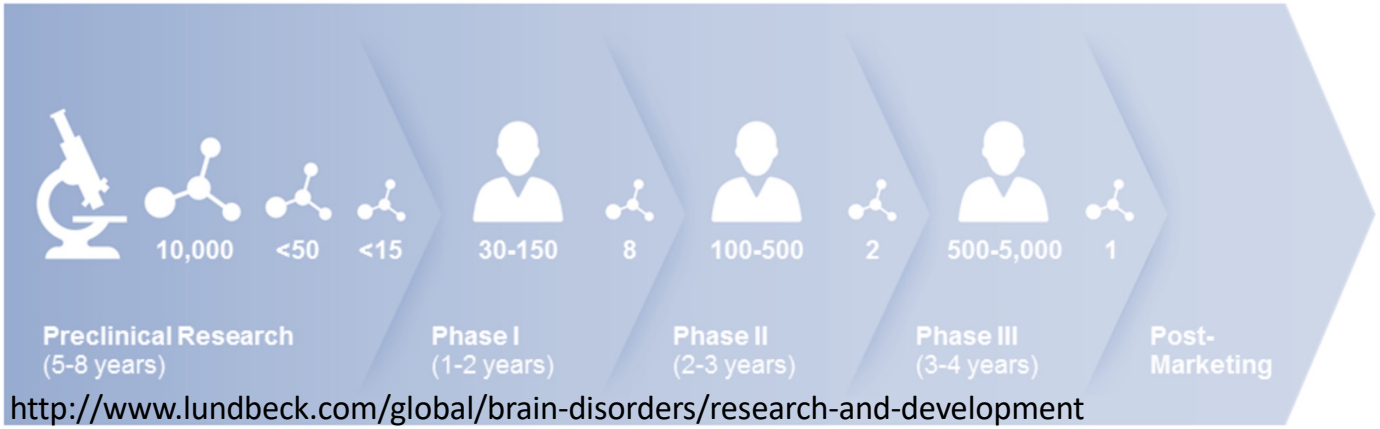
Pharmacological imaging

- Demonstrate a drug effect on central activity
  - Central penetration?
  - Choosing a dose
- Provide confidence for go/no-go decisions in drug development
- Objectively identify target targets for drug action
- Suggest / confirm a mechanism of action at brain systems level
  - Comparing compounds with different mechanisms
- A neuroscientific tool for modulating brain systems

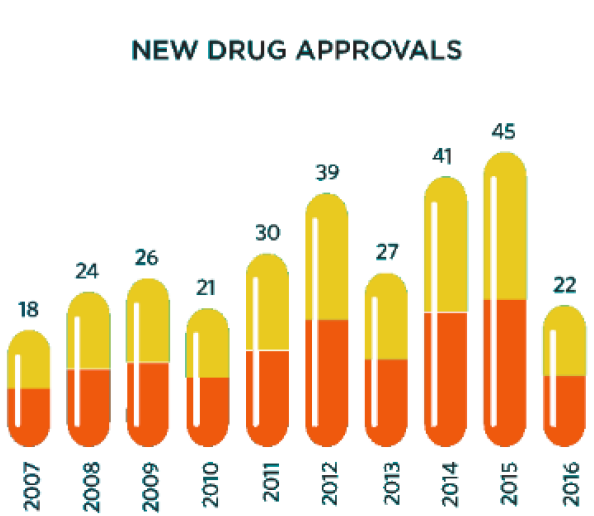
Wise R.G.

Drug development process …

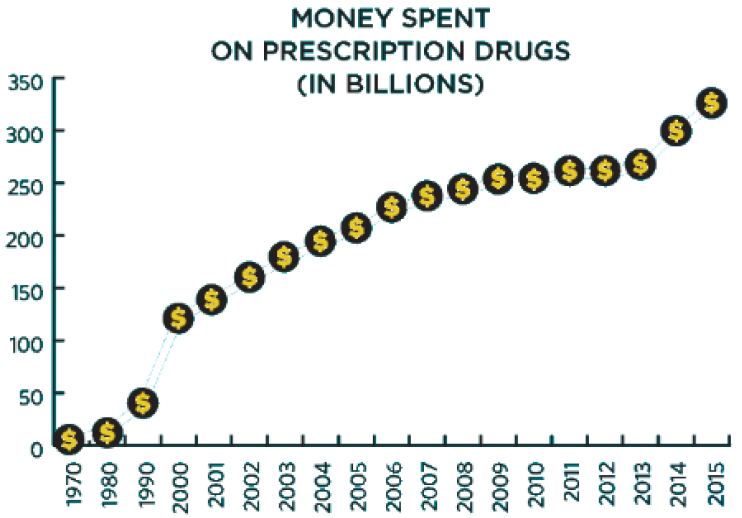
- Long and costly



http://www.lundbeck.com/global/brain-disorders/research-and-development



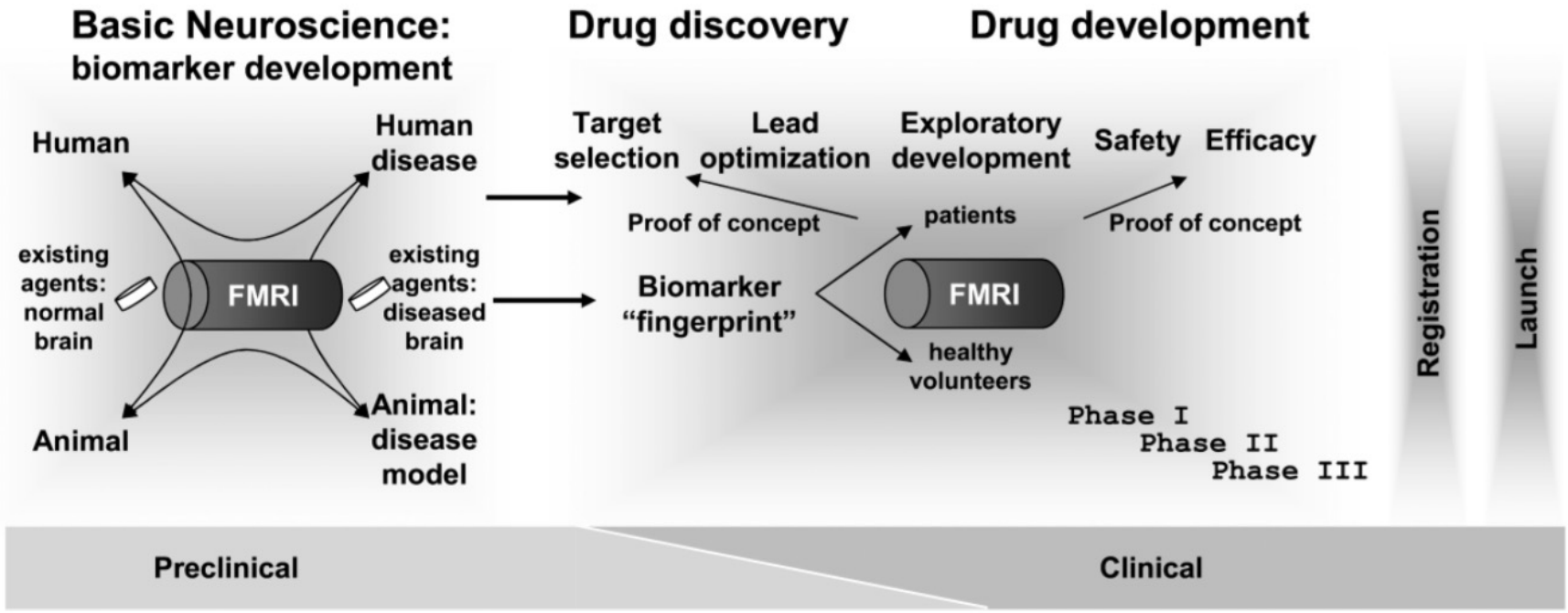
Only 22 novel drugs were approved last year—
a 57 percent drop from approvals in 2015.



Americans spent $324.6 billion on prescription drugs in 2015.
This amount represents almost 20 percent of
US health-care costs per capita.

John D. Loike and Jennifer Mille ,The Scientist, Feb, 2017, Opinion--Improving-FDA-Evaluations-Without-Jeopardizing-Safety-and-Efficacy

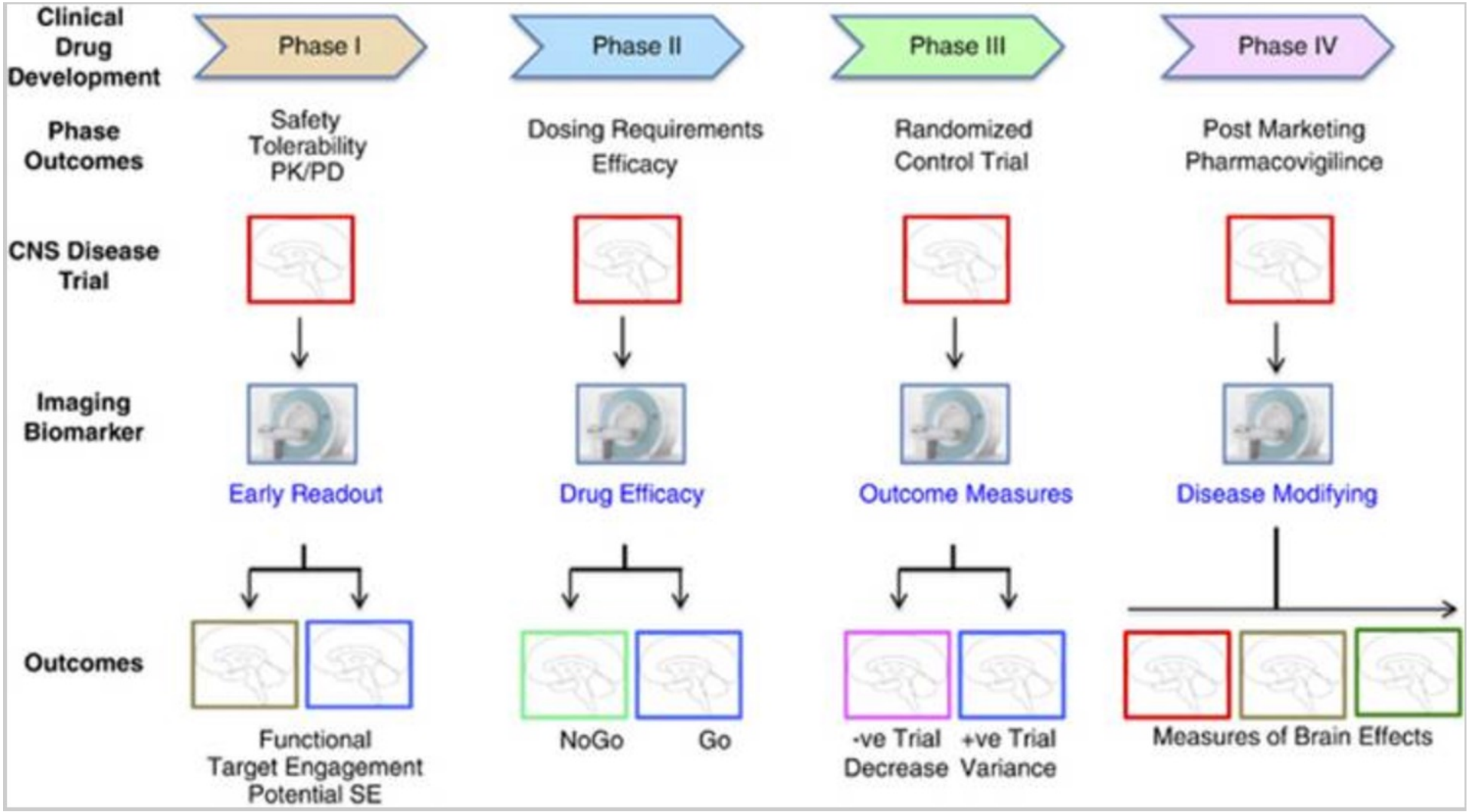
(CNS) Drug development



- majority of clinical trials have failed to translate into measurable clinical benefit
- integrate imaging early in drug development
  - to identify direct neural targets
  - determine subgroups (responders, non-responders)
  - dosing

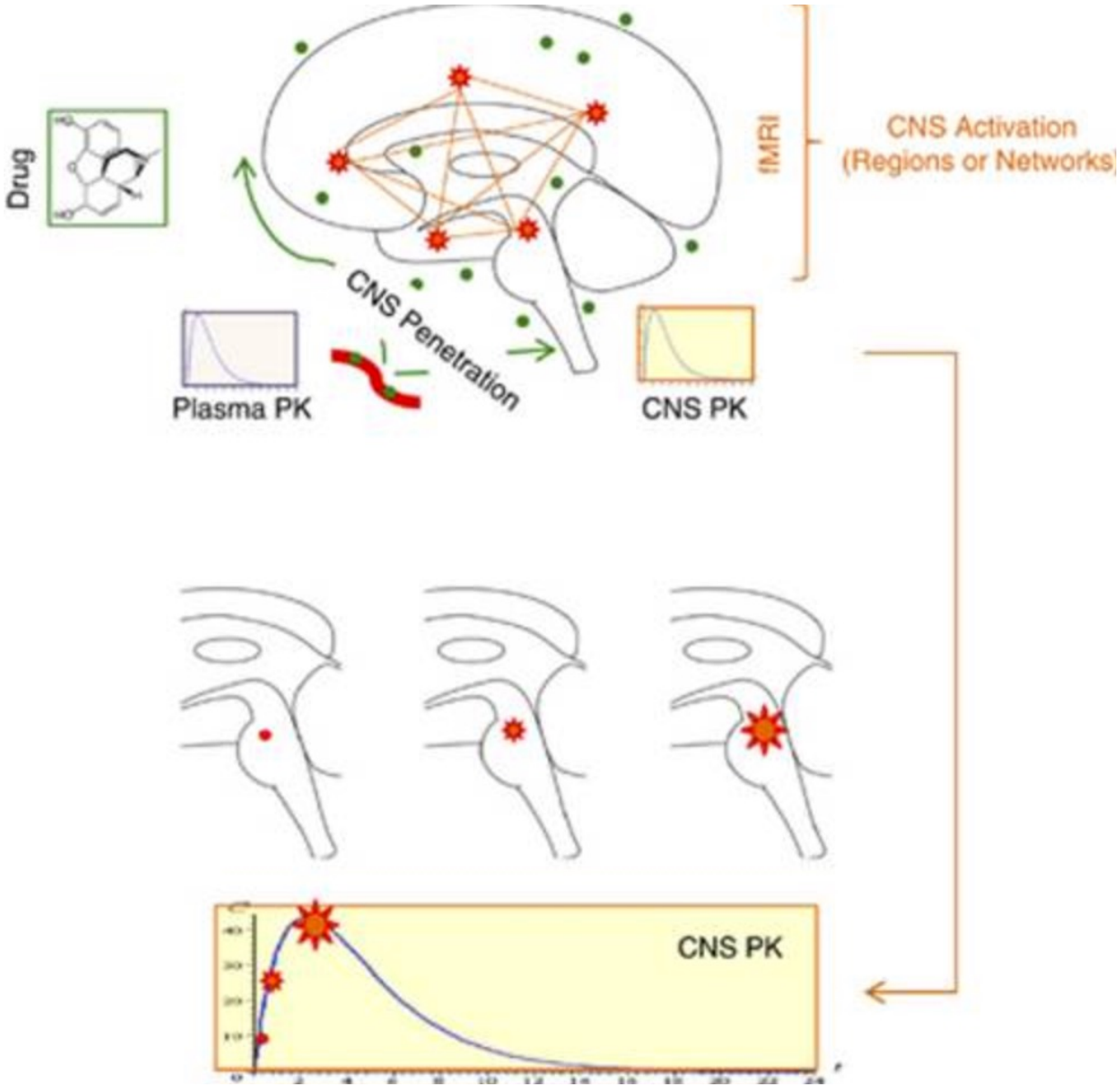
Wise, RG, et al, JMRI, 23:862–876 (2006)

Role of imaging in clinical trials



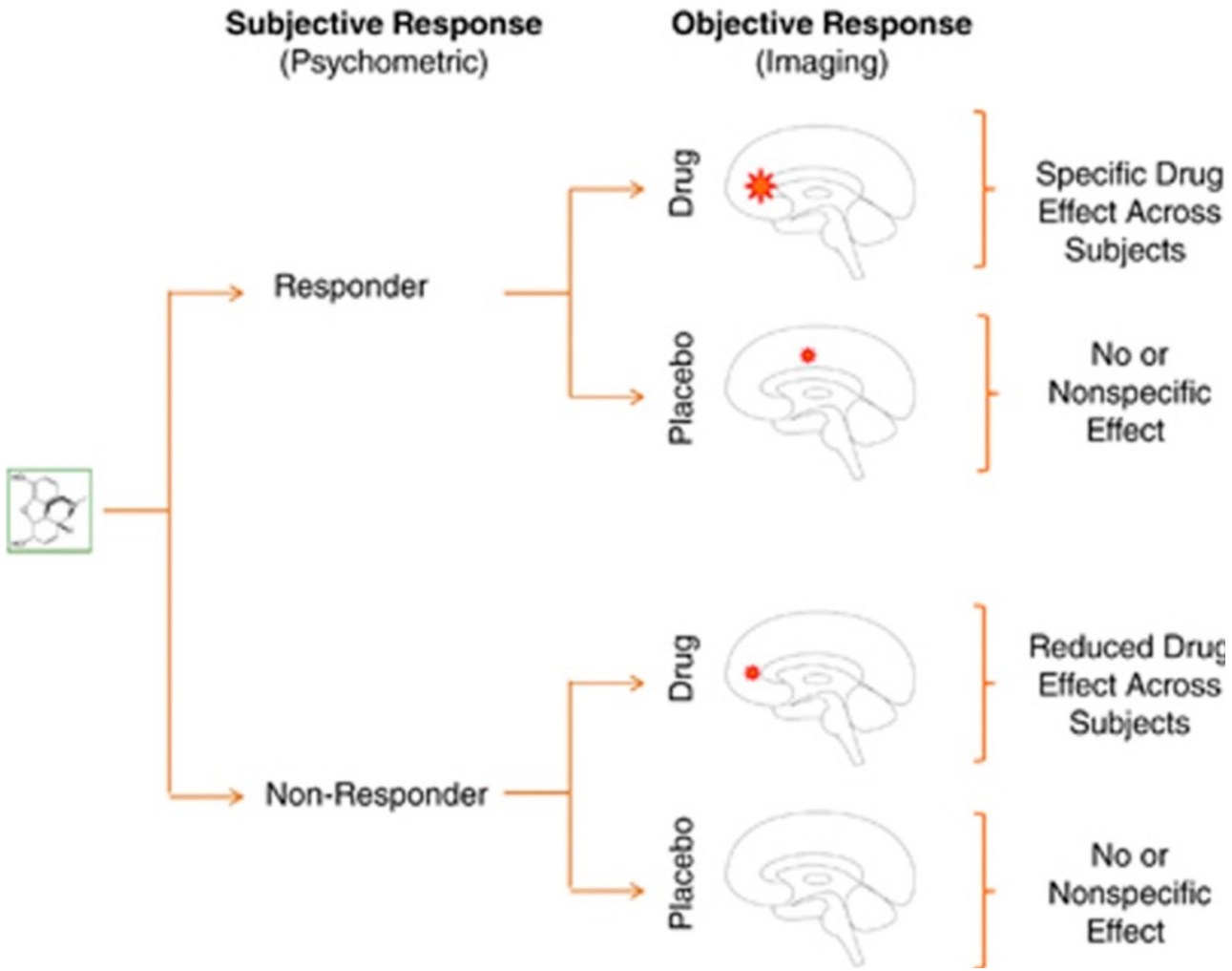
Borsook, D. et al, Transl Psychiatry. 2013 Jul 16;3:e282

Drug penetration into the brain



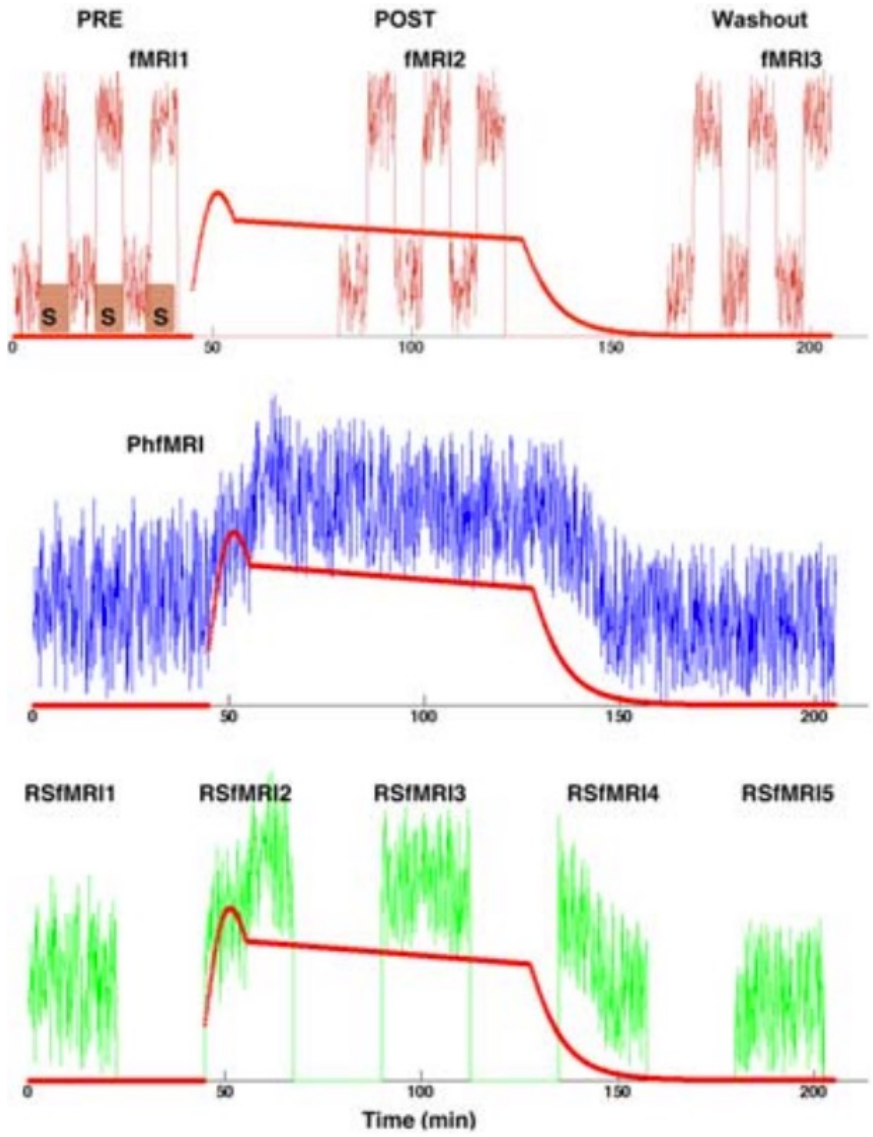
Borsook, D. et al, Transl Psychiatry. 2013 Jul 16;3:e282

Adjunct to subjective response



Borsook, D. et al, Transl Psychiatry. 2013 Jul 16;3:e282

Study design

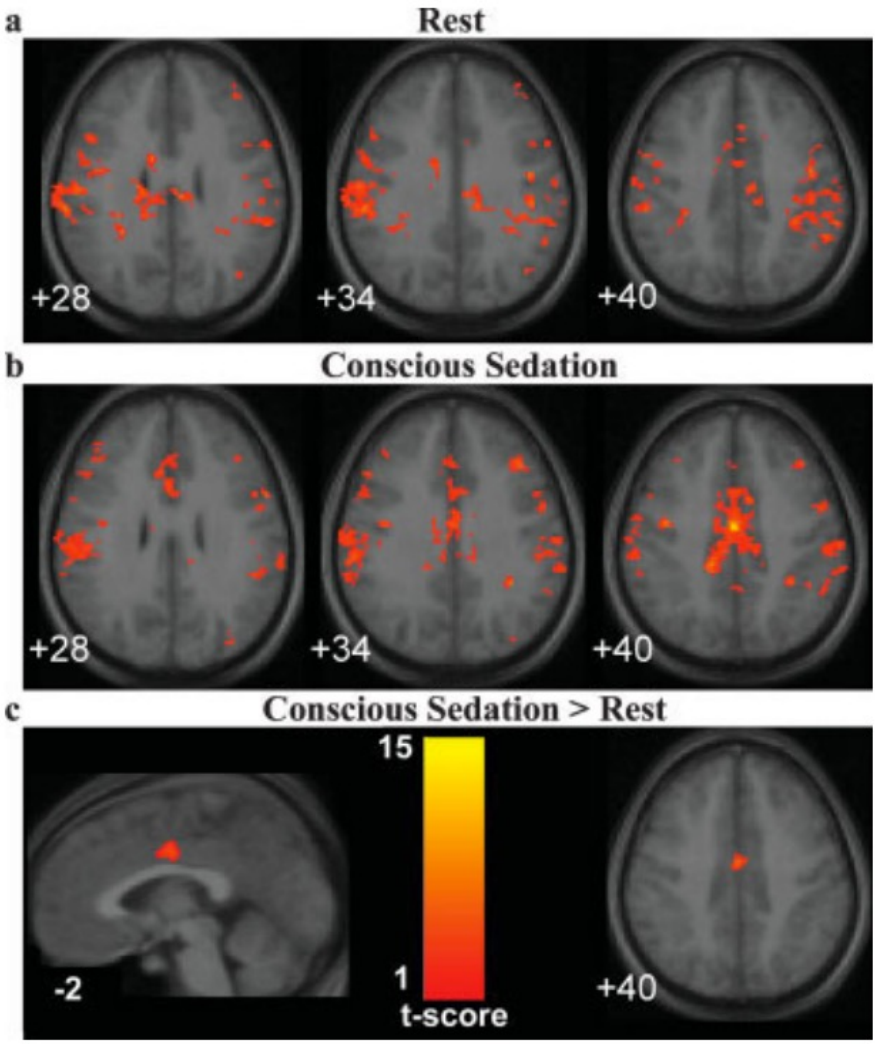


Khalili-Mahani N et al Human Brain Mapping. 2017.

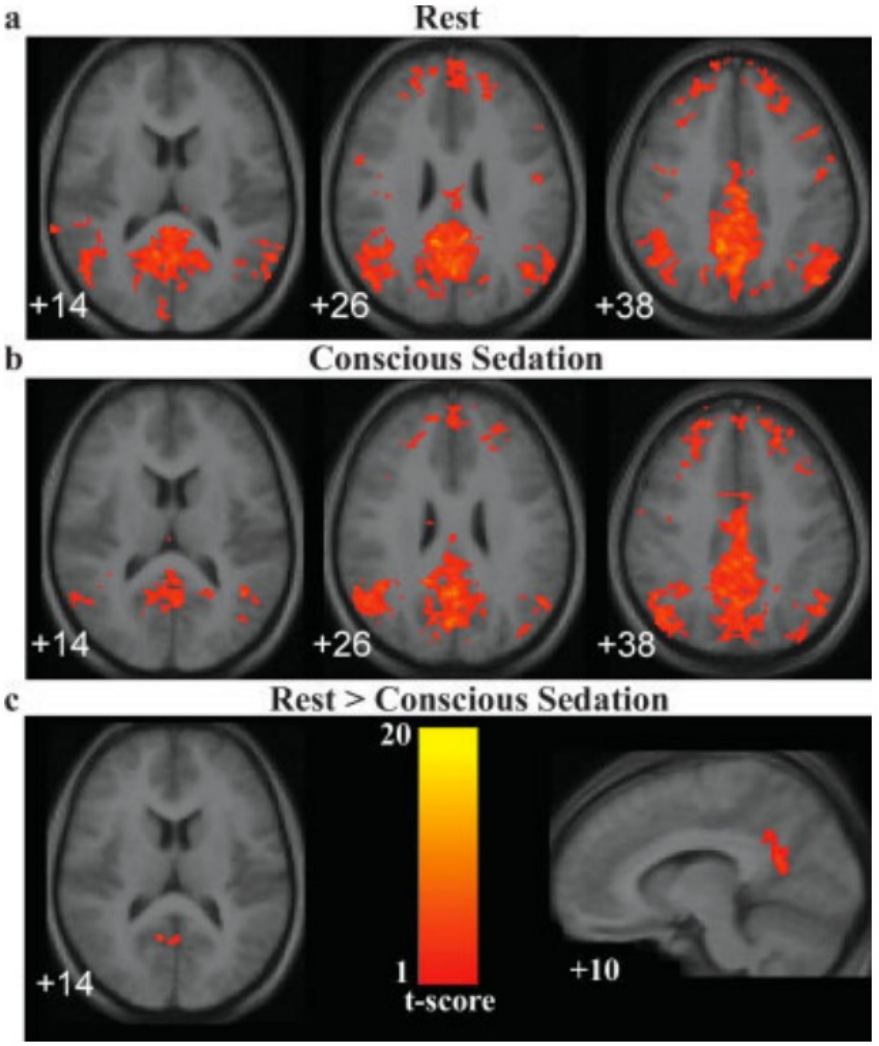
Resting state changes

- Midazolam sedation

Sensory motor

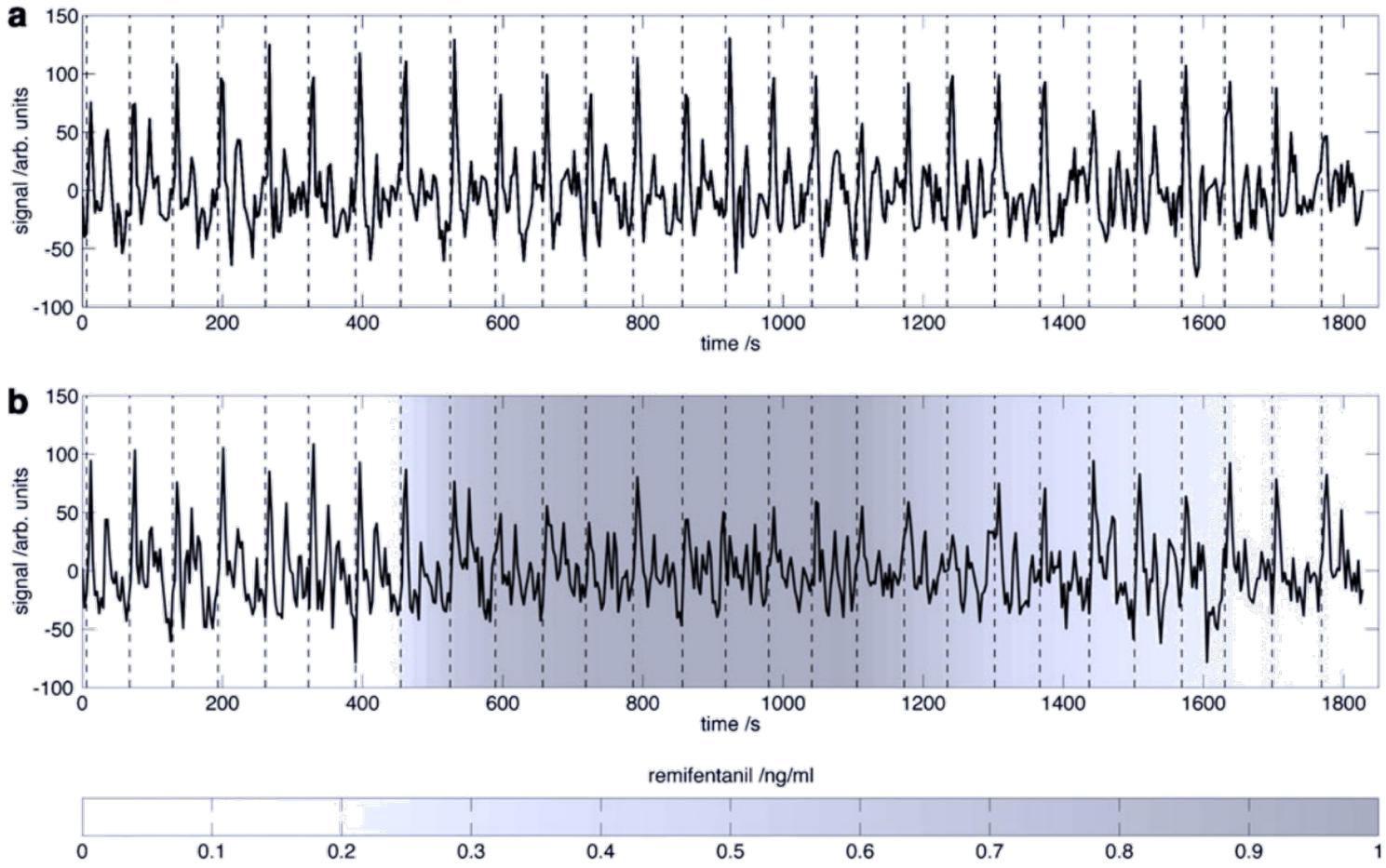


Default mode



Greicius, M et al., Human Brain Mapping 29:839–847 (2008)

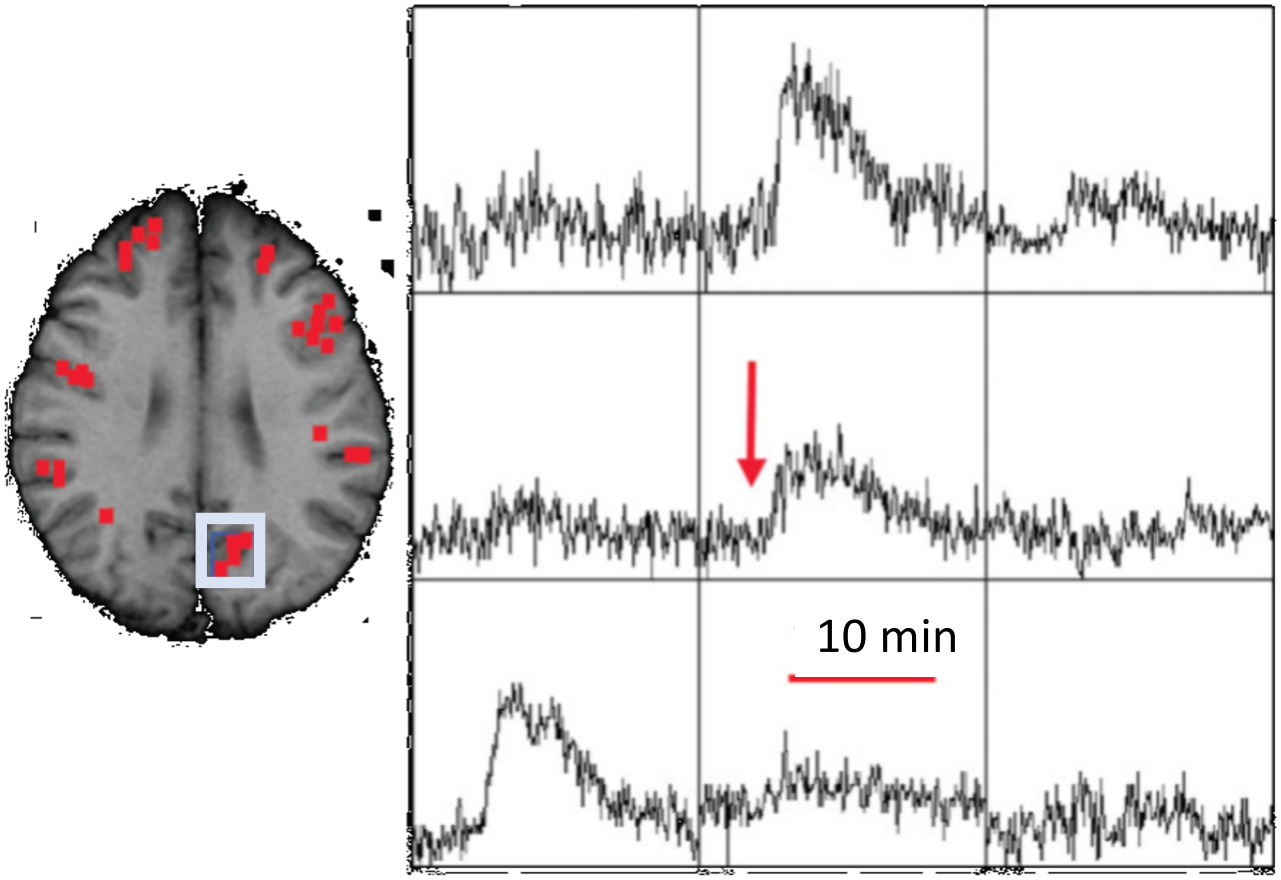
Response changes

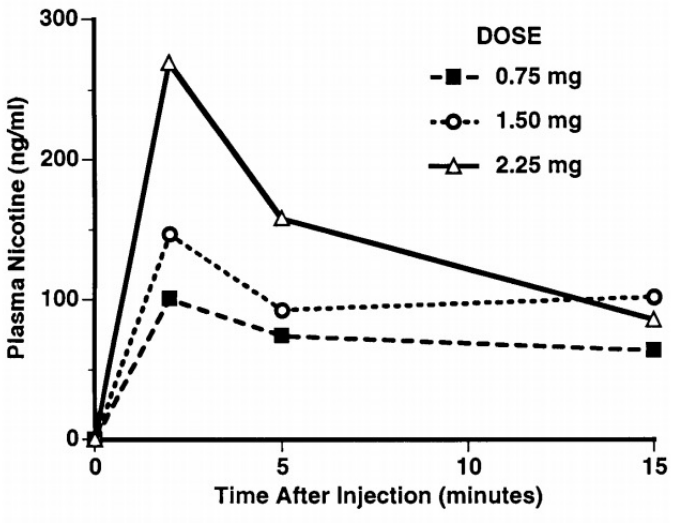


- Decrease in the response to painful stimulus (dashed lines) during drug administration

Wise RG et al NeuroImage 16, 999–1014 (2002).

Acute drug response

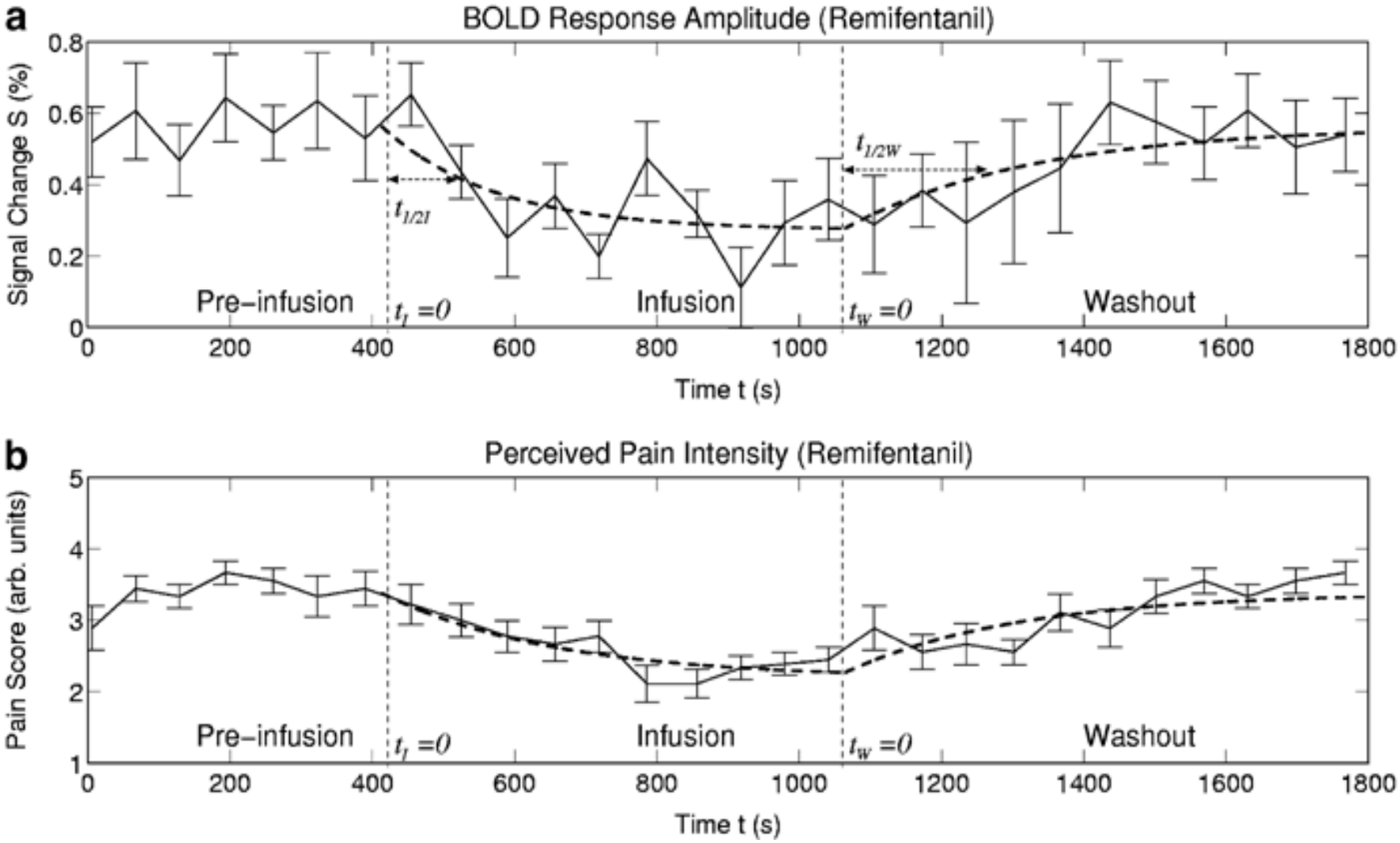




- 1 min injection of nicotine

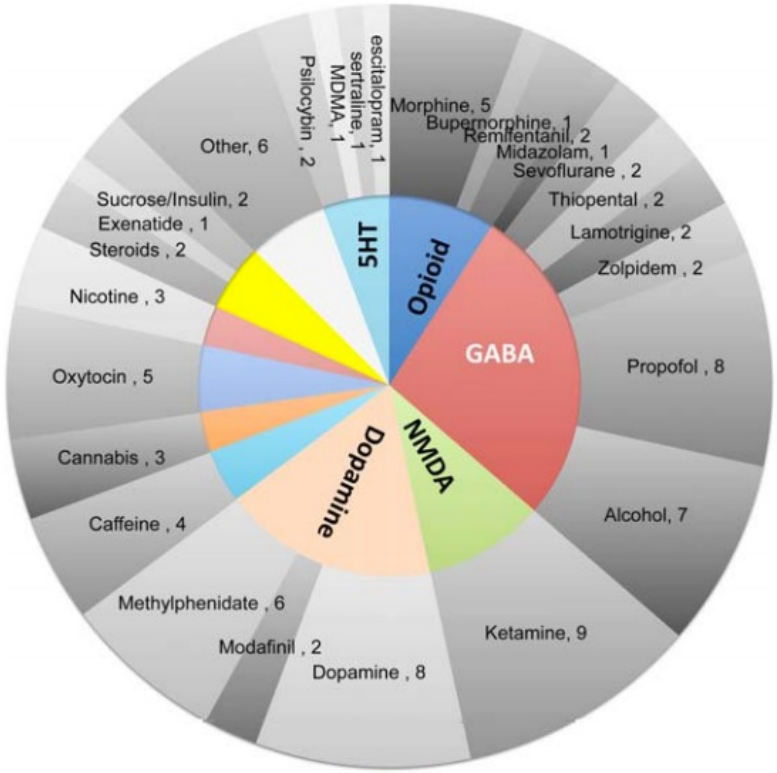
Stein E et al. Am J Psychiatry. 1998 Aug;155(8):1009-15.

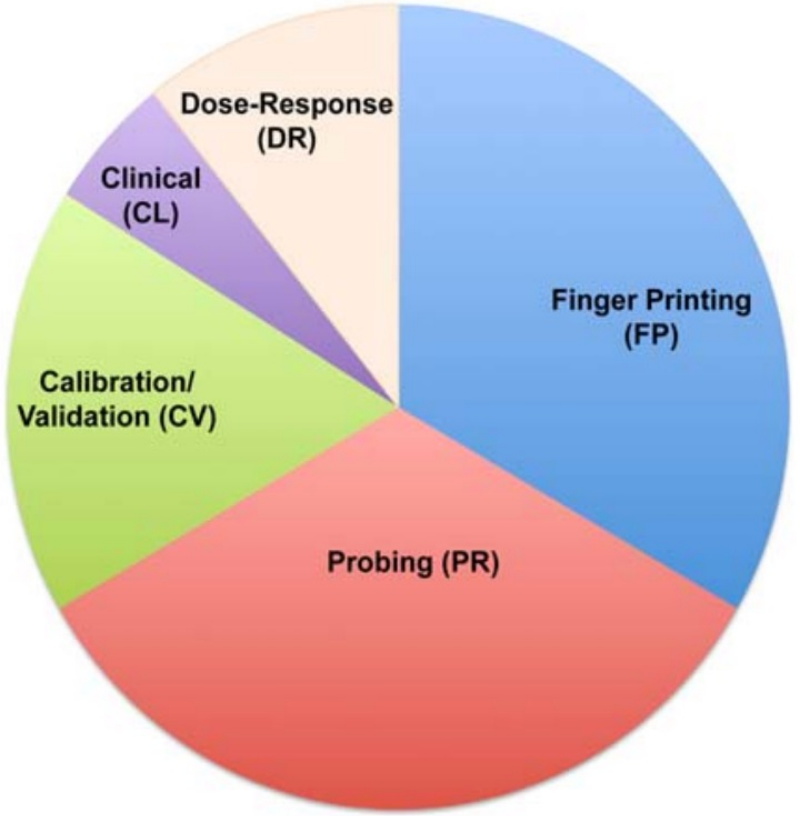
Pharmacokinetic response



Wise et al. Neuropsychopharmacology. 2004

Drugs tested





Khalili-Mahani N et al Human Brain Mapping. 2017.

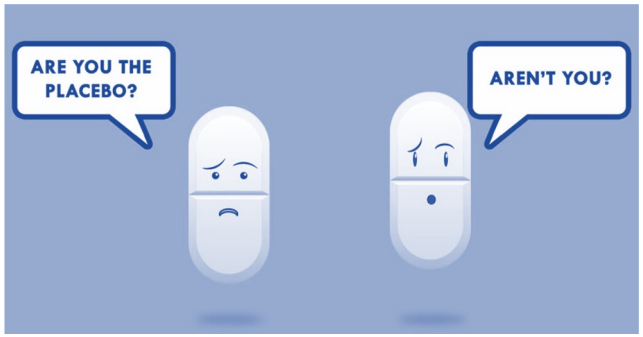
Possible confounding factors…. and solutions

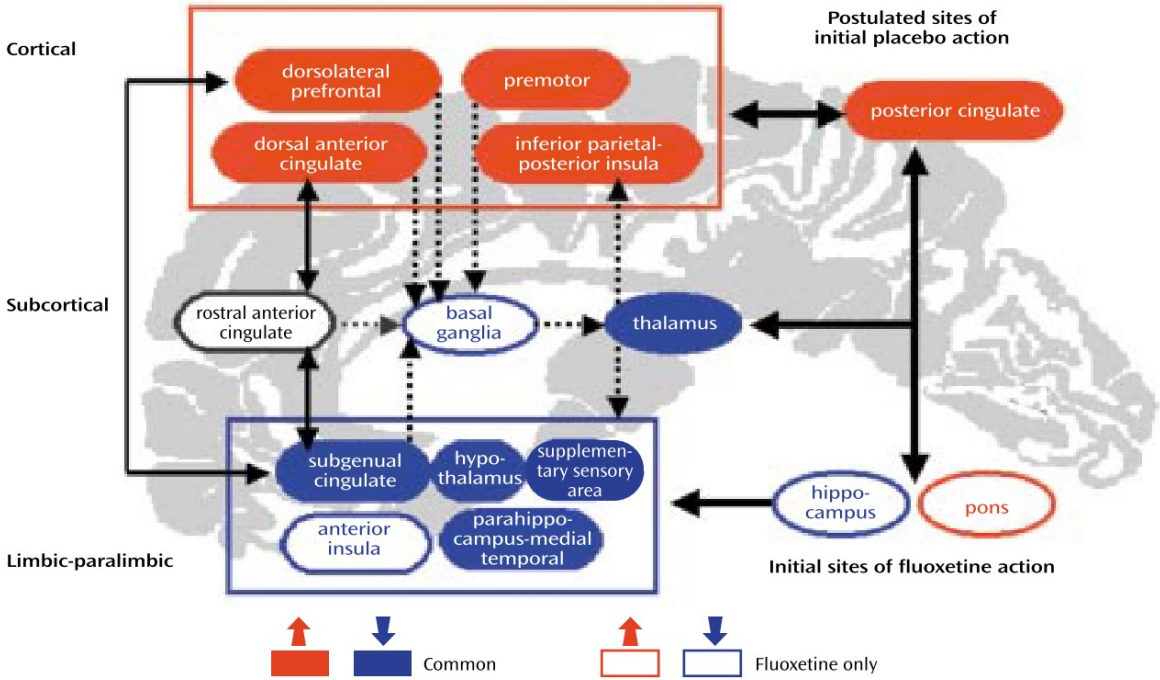
- Cognitive:
  - Placebo effect
    - Study design
- Acquisition:
  - These changes are slow (minutes) and on the same scale as drift artifacts
    - Use multi-echo fMRI?
- Signal:
  - BOLD signal is affected by changes in blood flow/volume
    - Use EEG-fMRI?

Wise, RG. JMRI(2006)

Placebo effect

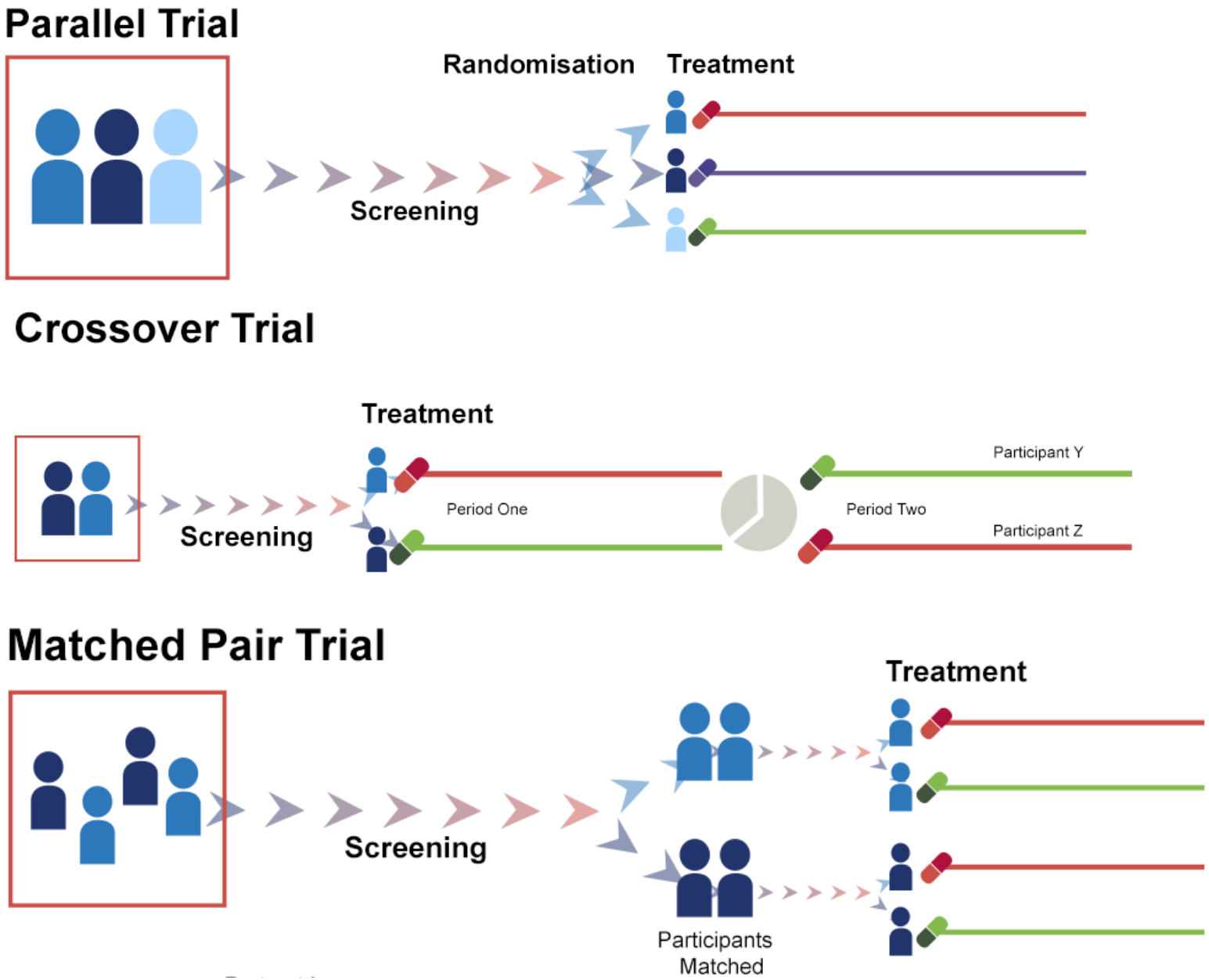
- Driven by the expectation that the treatment will bring relief
- Has been shown to have significant overlap with brain regions that are associated with drug response





Mayberg HS et al. *Am J Psychiatry*. 2002;1595.

Study design



https://www.eupati.eu/clinical-development-and-trials/clinical-trial-designs/

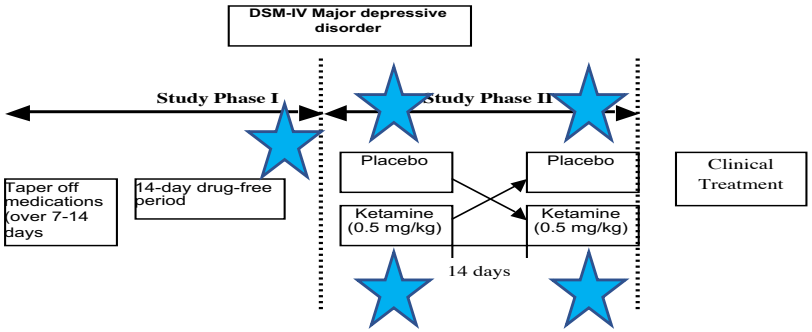
Study design considerations

- Open-label / randomized
- Single/ double-blind
- Placebo controlled
- ‘Healthy’ volunteers and patient population(s)

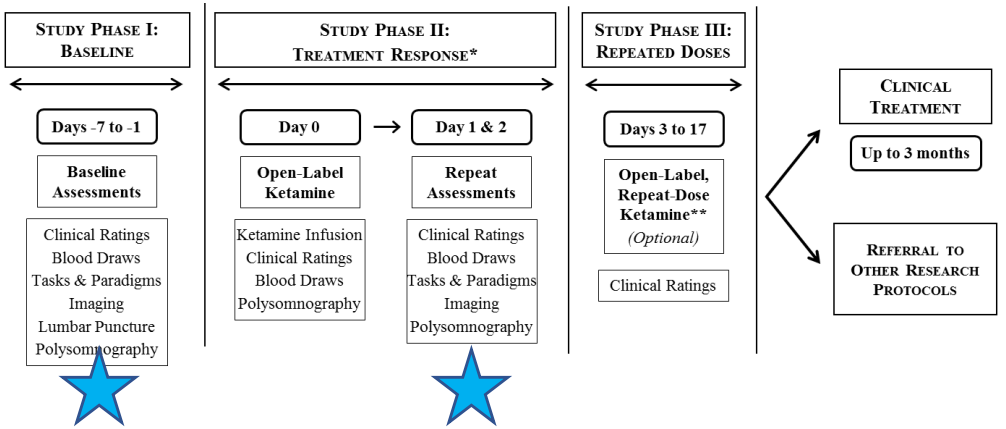
- Considerations
  - Number of subjects
  - Baseline?
  - Speed of drug action / duration / crossover effects
  - Reliability/repeatability of measurement

ETPB examples

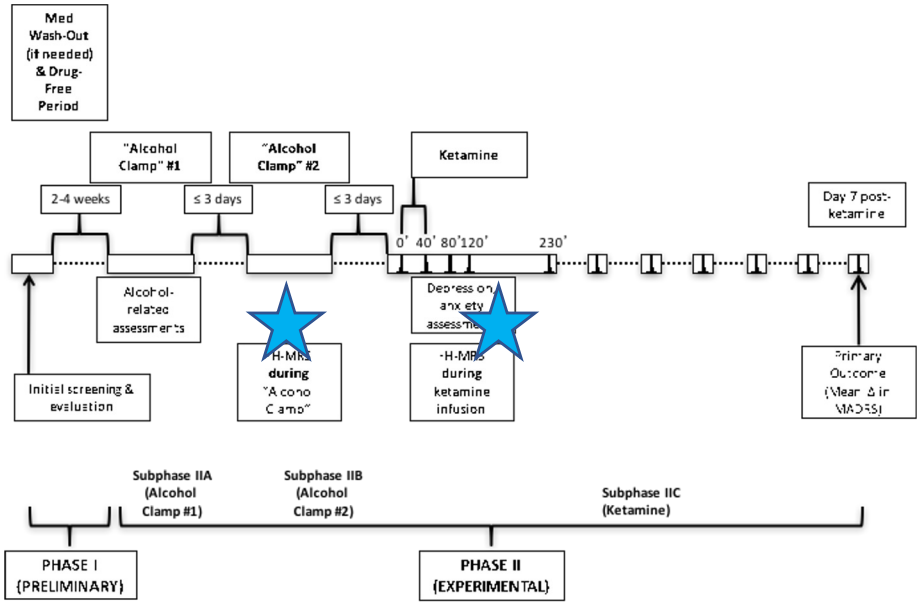
04-M-0222 – Ket-MOA



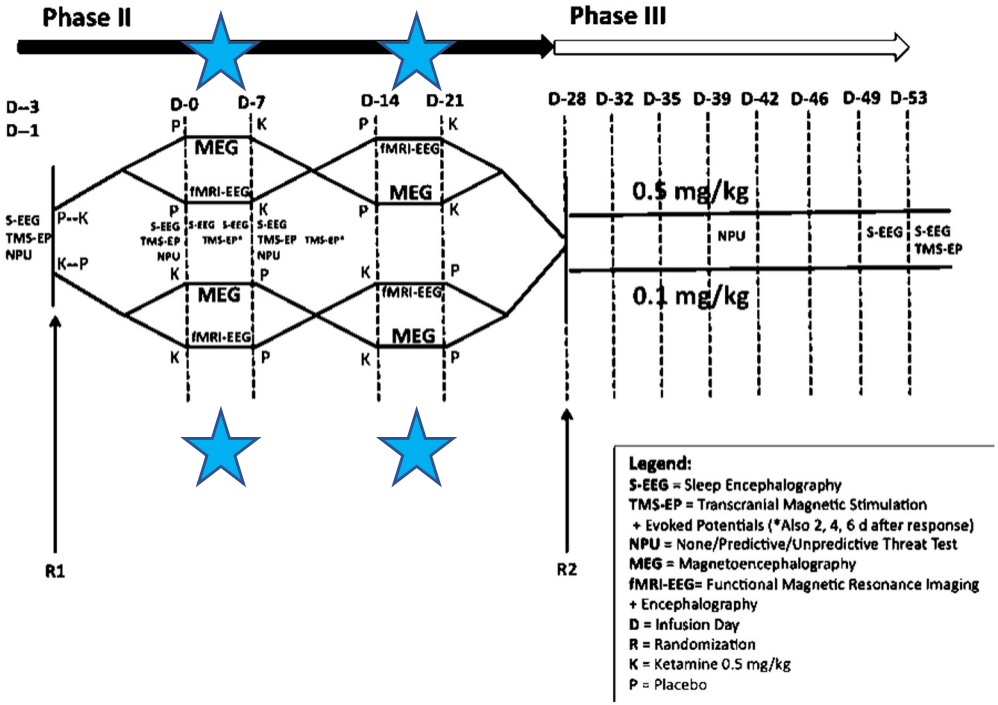
15-M-0188 - RISC



14-M-0085 – Ket-Alc



17-M-0060 – Repeat Dose



Schematics courtesy of Alex Noury

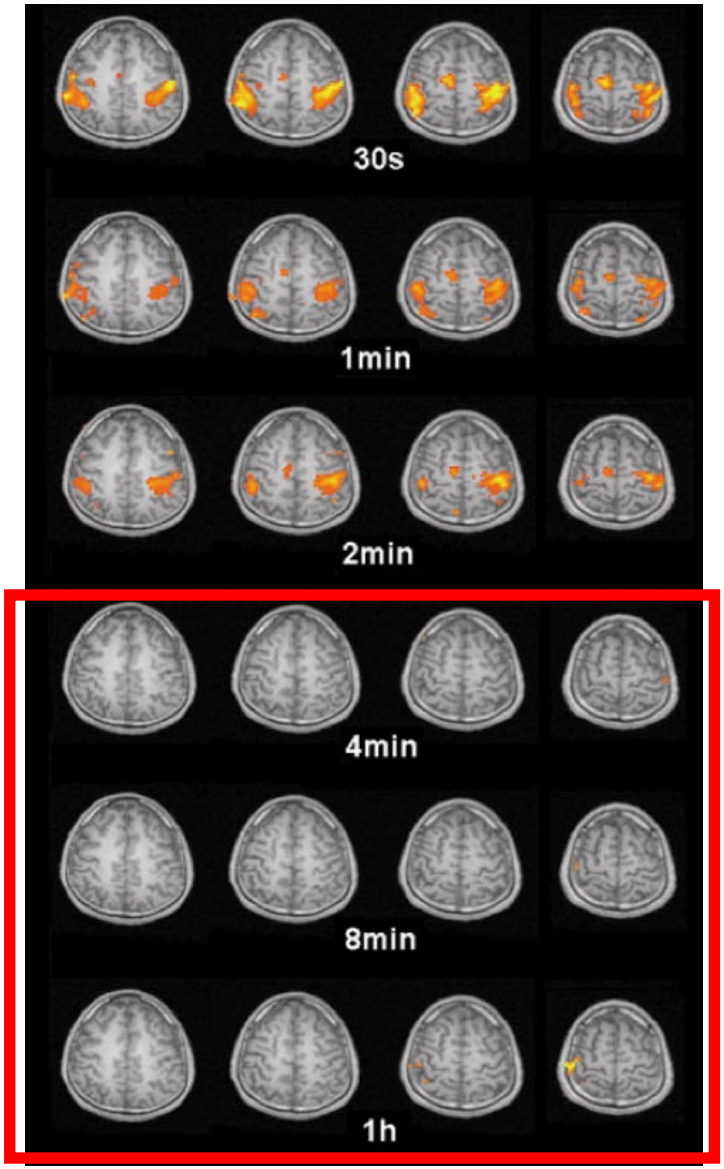
Possible confounding factors…. and solutions

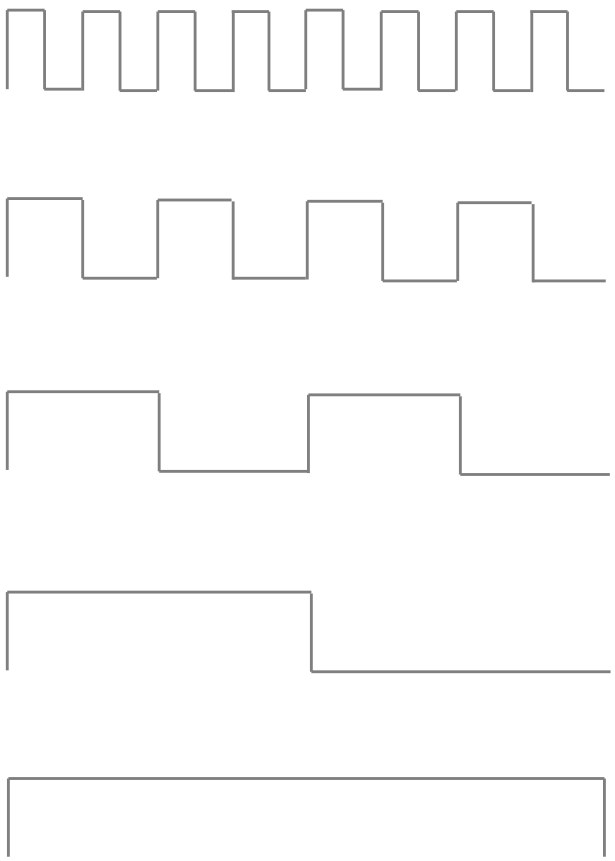
- Cognitive:
  - Placebo effect
    - Study design
- Acquisition:
  - These changes are slow (minutes) and on the same scale as drift artifacts
    - Use multi-echo fMRI?
- Signal:
  - BOLD signal is affected by changes in blood flow/volume
    - Use EEG-fMRI?

Wise, RG. JMRI(2006)

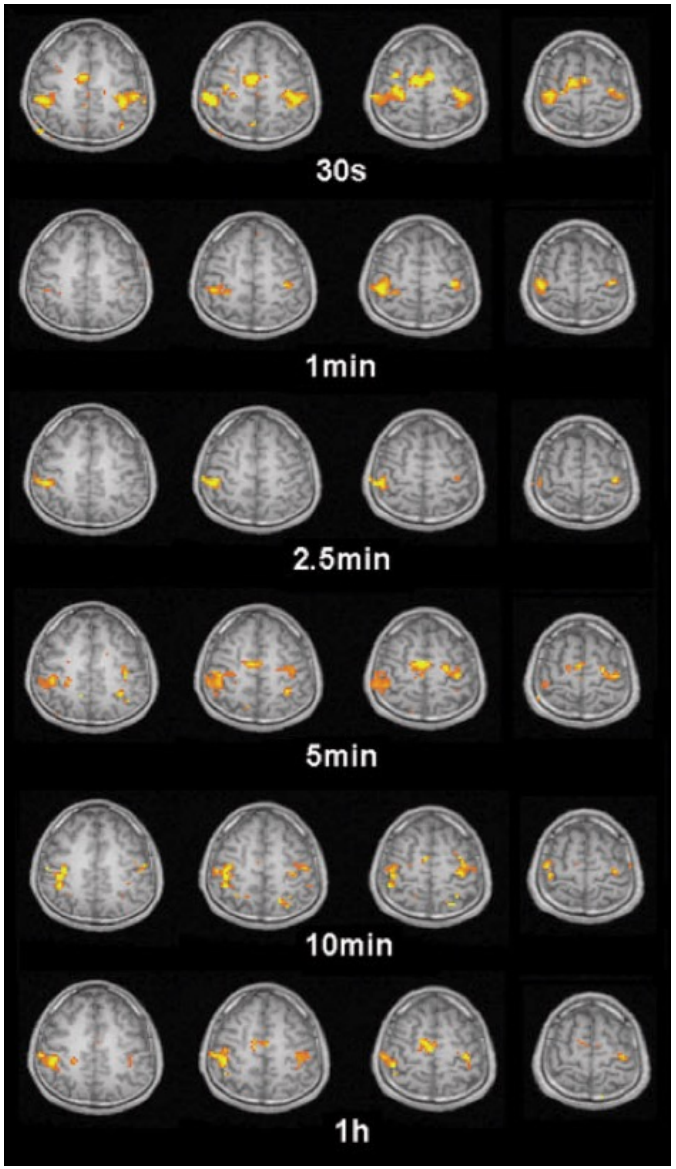
Imaging slow stimuli doesn't work well

BOLD





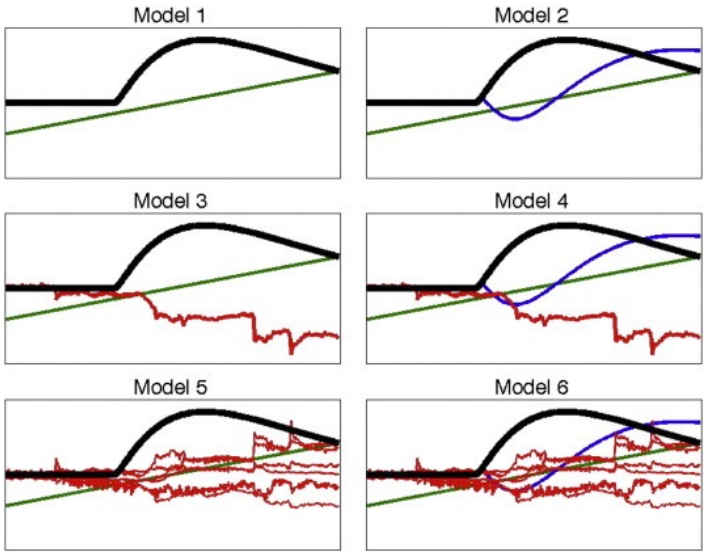
ASL

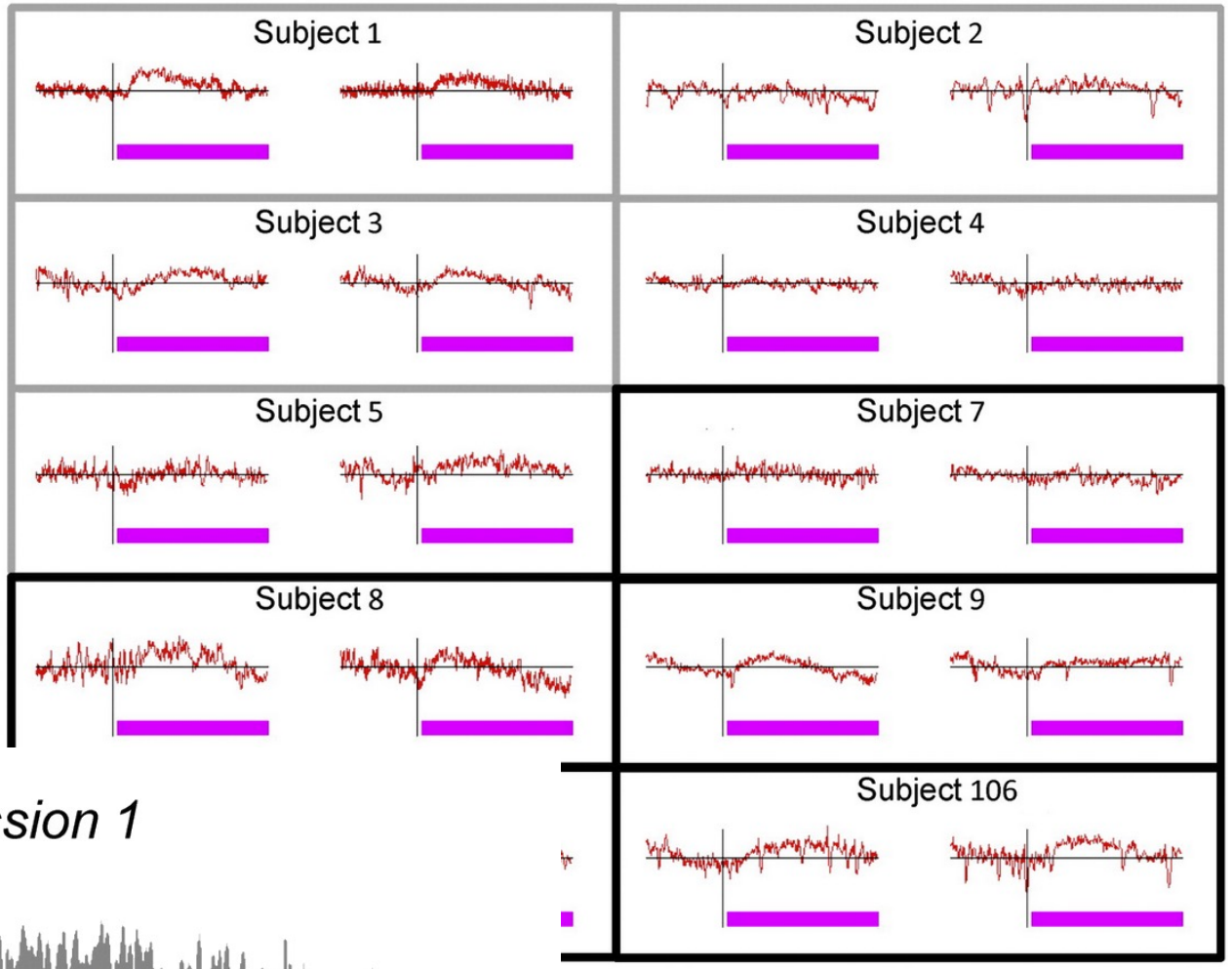


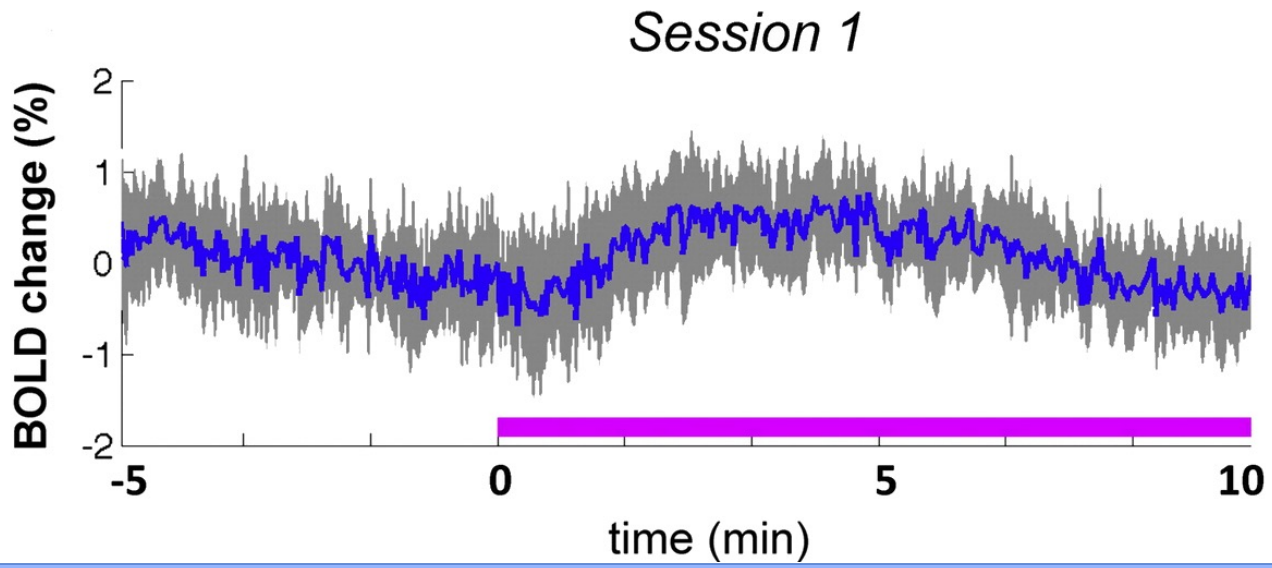
- BOLD has greater signal strength
- ASL has greater sensitivity for long duration stimuli

Wang et al, MRM (2003)

Response to ketamine infusion



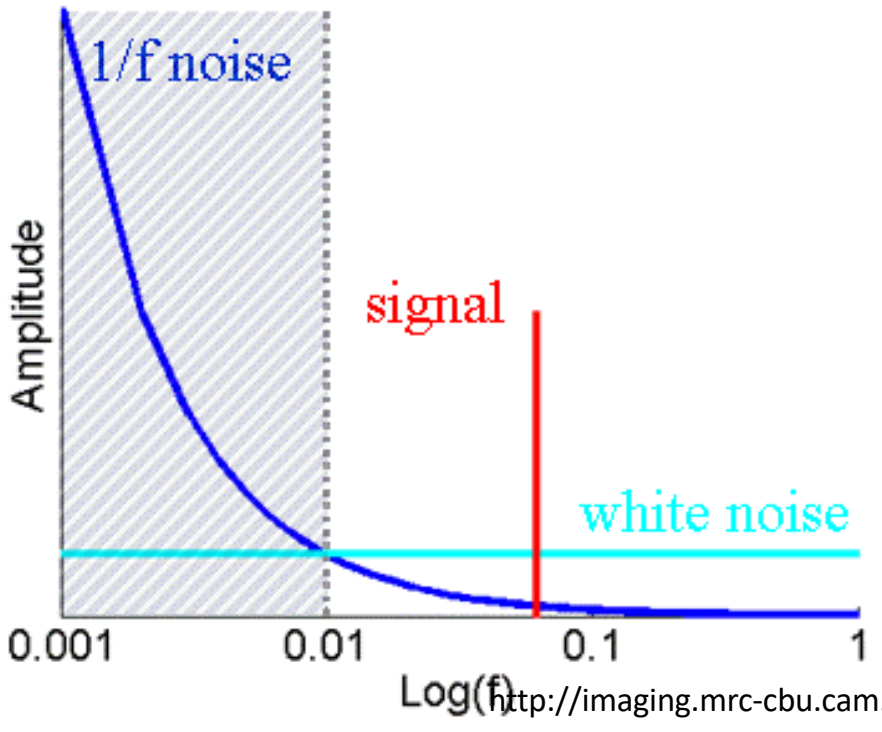




De Simoni et al, Neuroimage (2013)

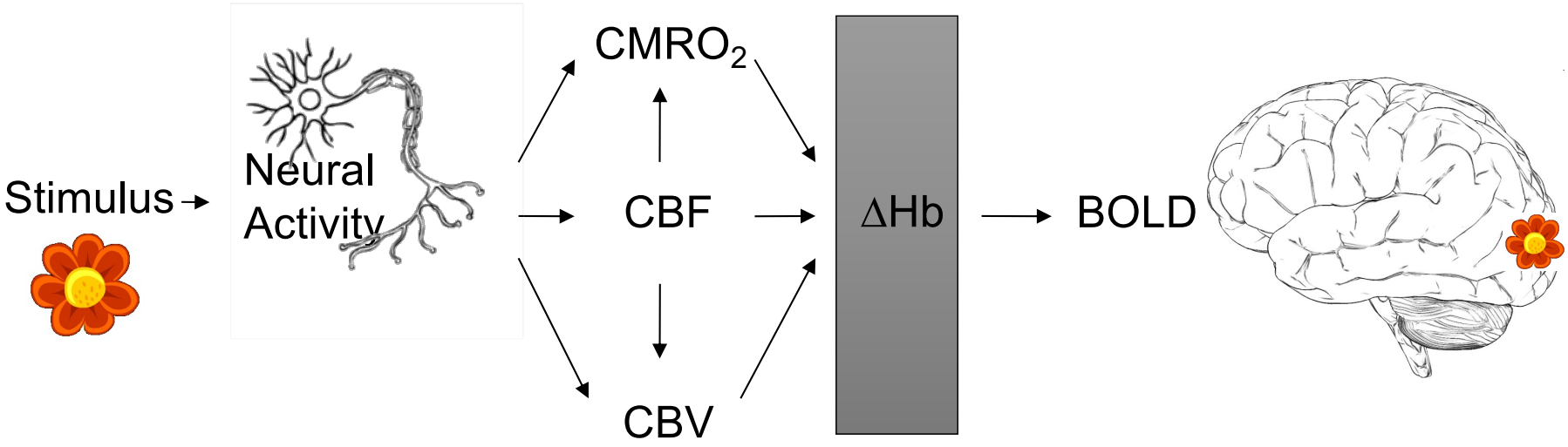
The problem

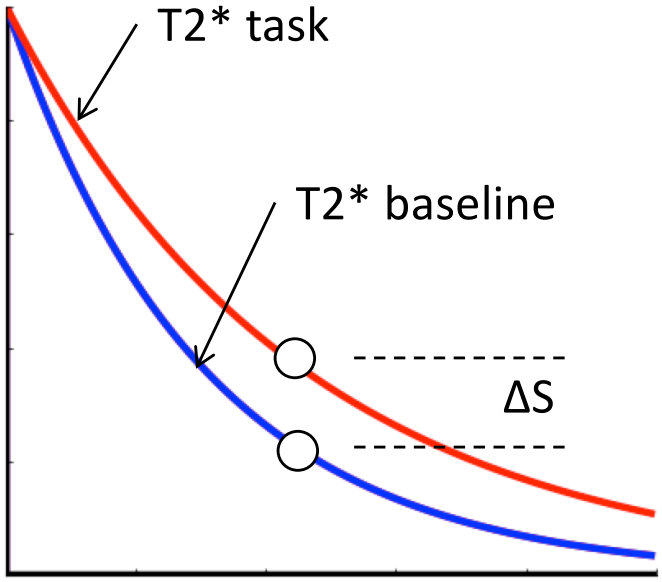
- With single echo data artifactual drifts are indistinguishable from BOLD signal
  - High pass filter, model
  - set the task frequency higher
  - remove ICA components…



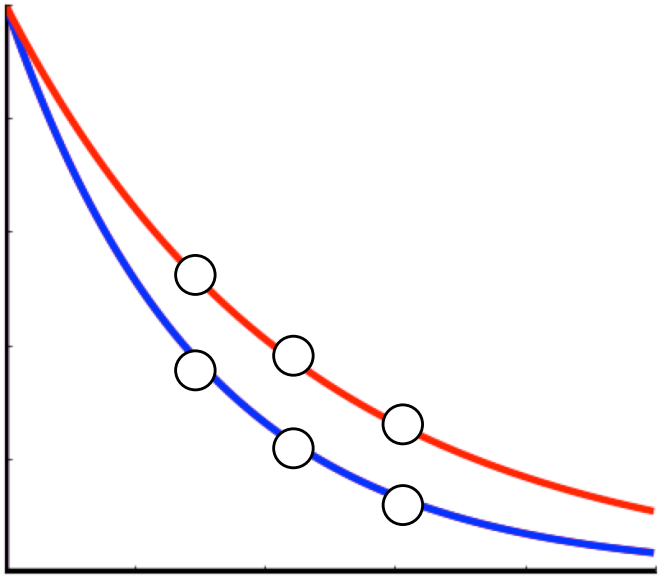
http://imaging.mrc-cbu.cam.ac.uk/imaging/DesignEfficiency#A_fig8

What does fMRI measure?





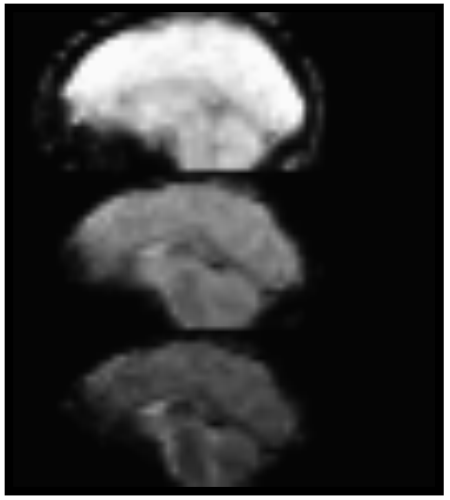
Multi-echo (ME) fMRI.

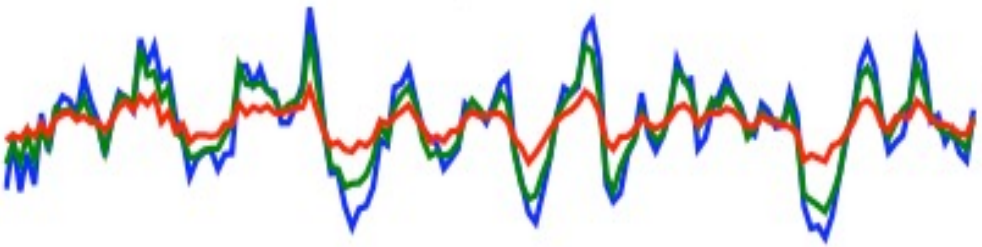


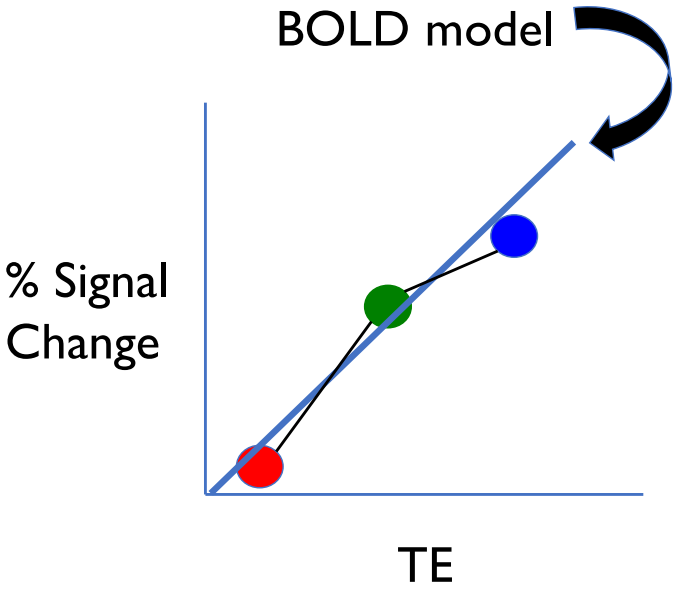
TE 1

TE 2

TE 3



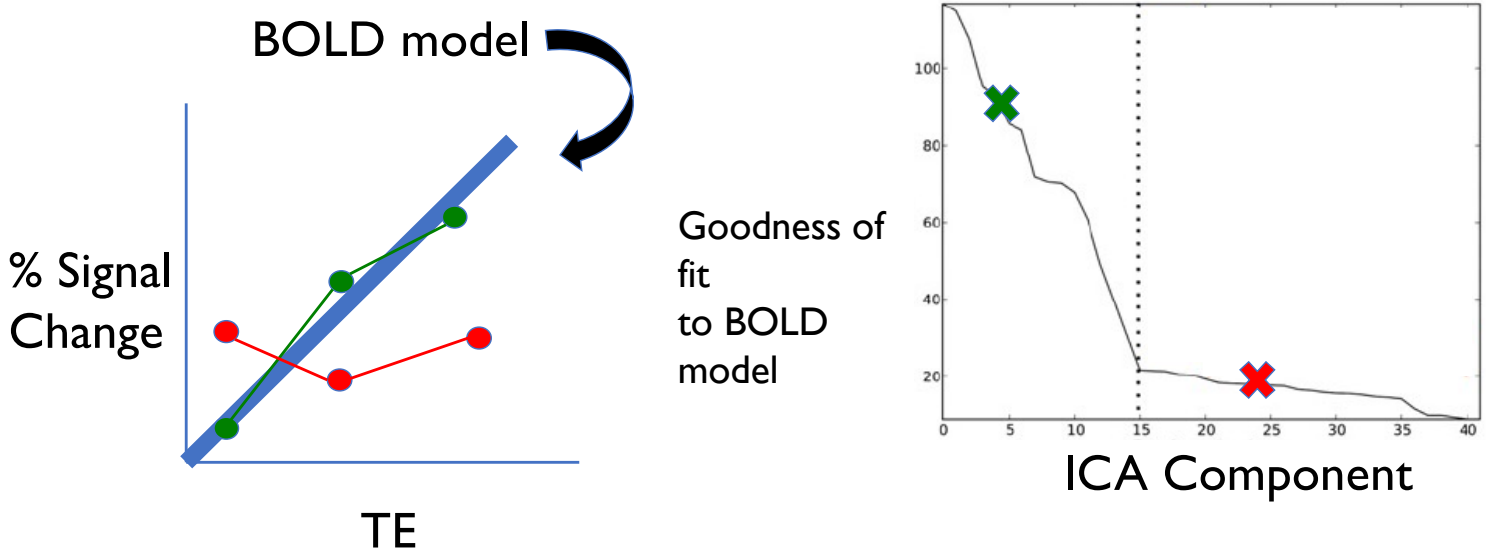


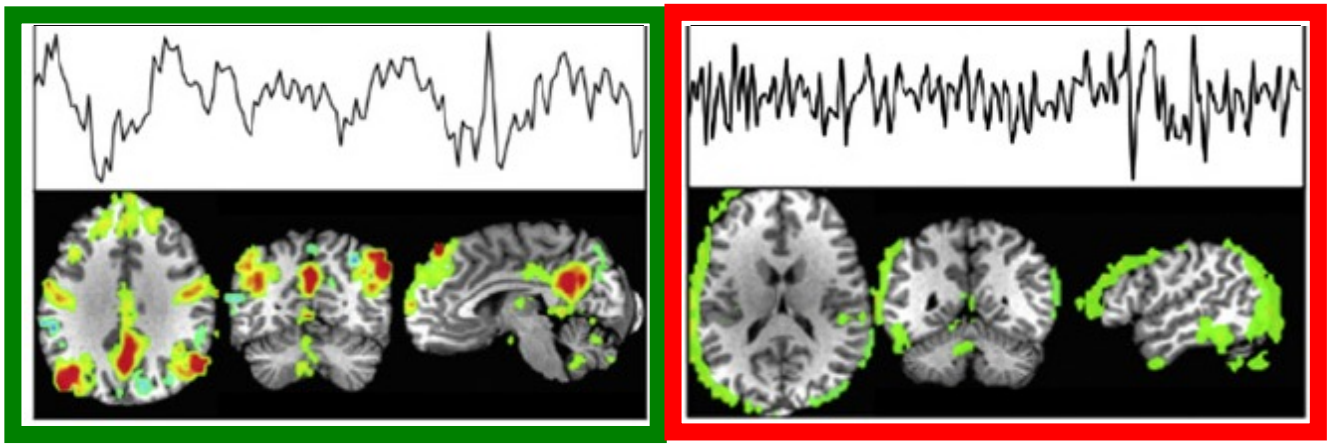


Kundu, P, Inati, S, Evans, JW et al (2012) NeuroImage Vol 60, Iss 3 2012 1759 - 1770

Multi-echo denoising

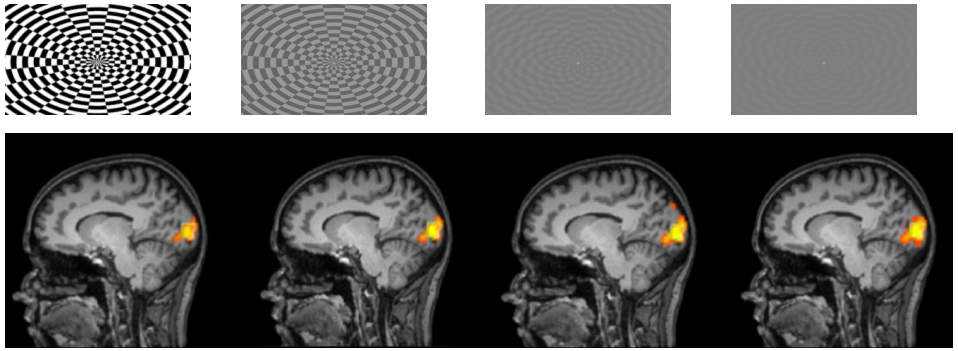
- Enables the identification of signals that scale with measured TEs

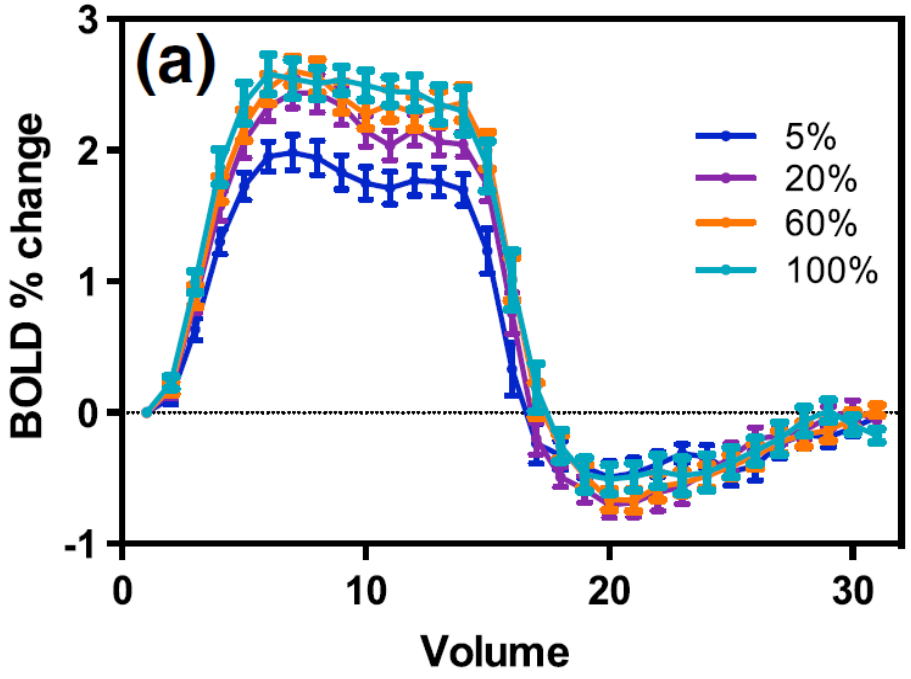


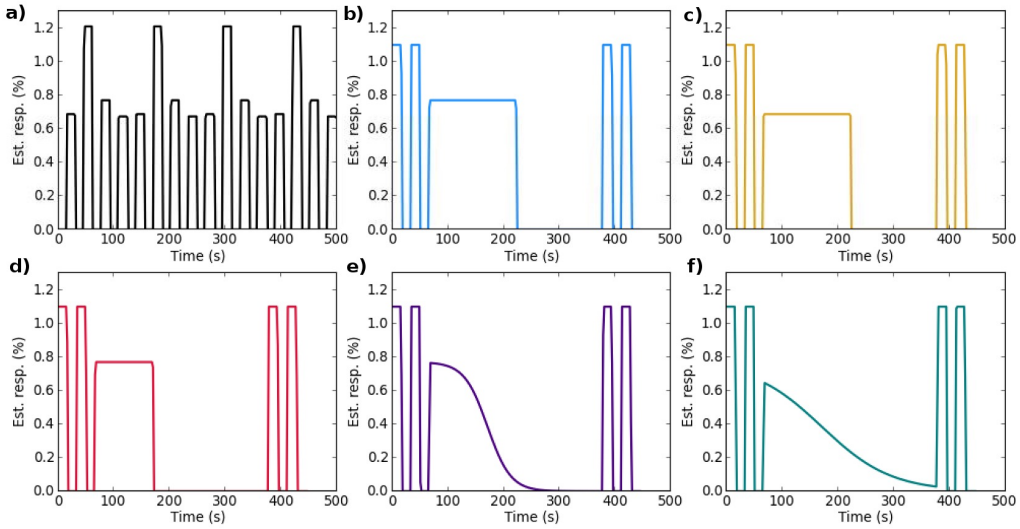


BOLD, EEG signals and visual contrast change.

- BOLD intensity varies as a function of stimulus contrast
- Contrast sensitivity is not linear

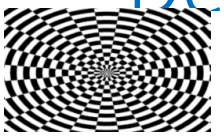


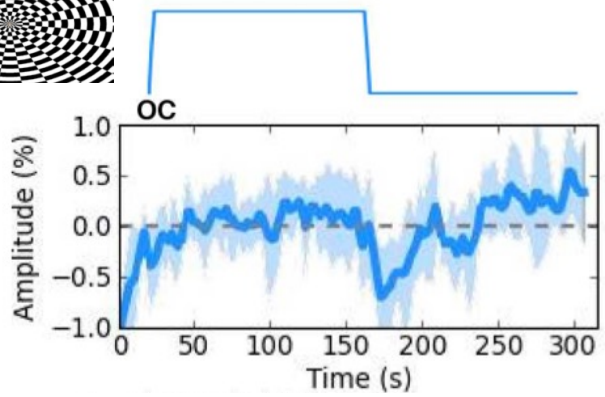


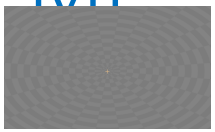


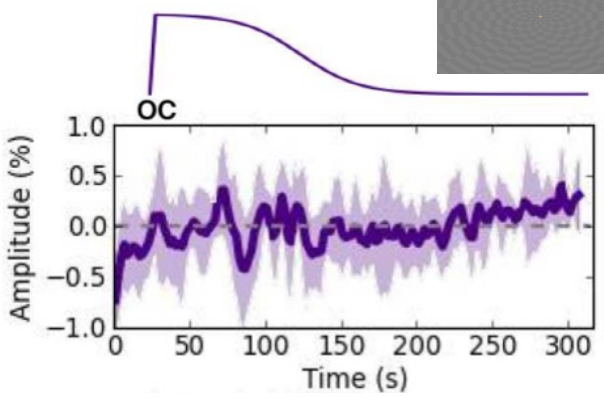
Chiachiaretta et al, Neuroimage (2013)

Detection of slow BOLD with ME









- Group average timeseries taken over voxels in V1 for a visual block and ramp contrast task
- The thick line is the mean and the shading is the standard error.

- Slope task is not visible in OC or detrended data

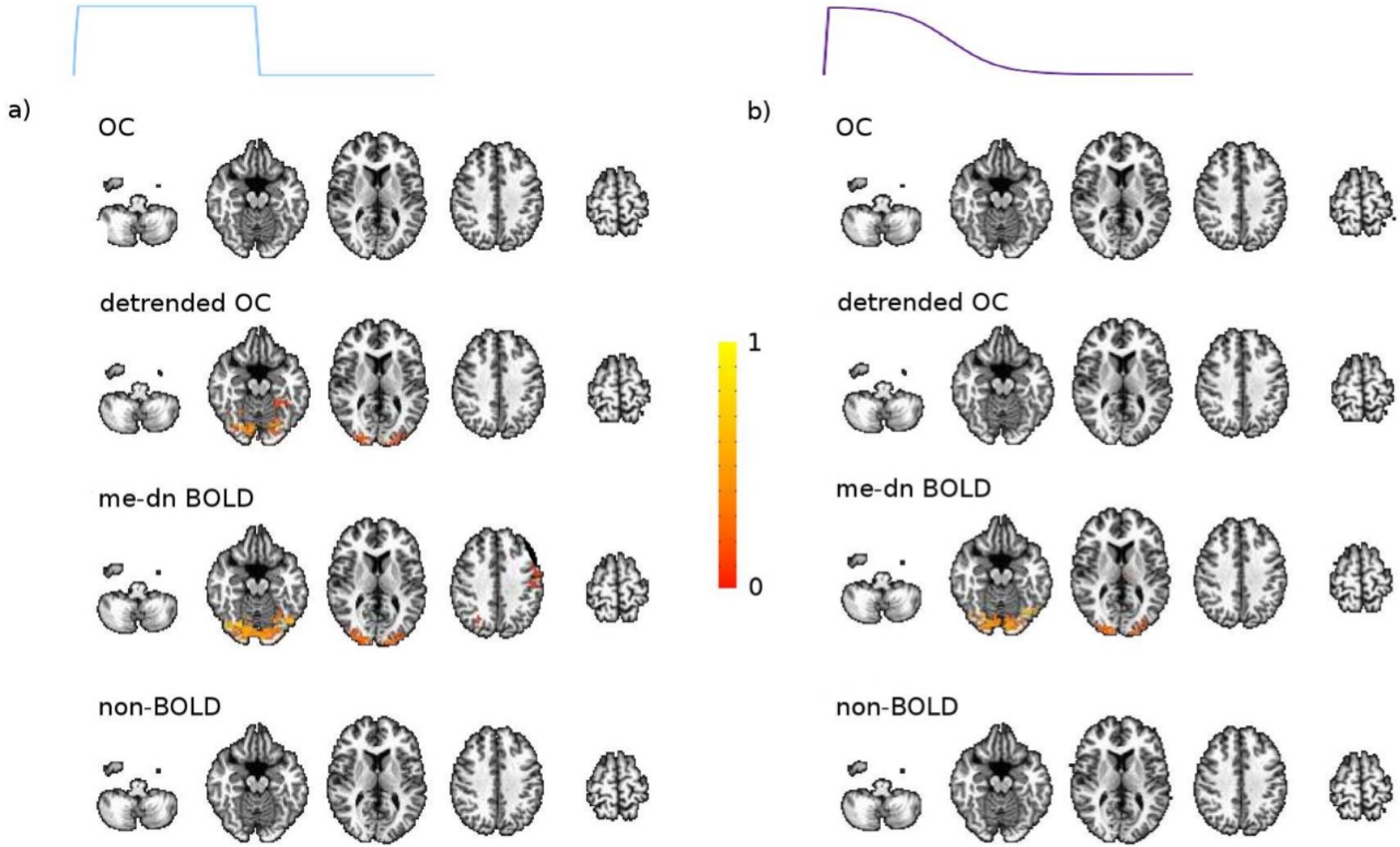
- Both tasks are clear in the me-dn BOLD data

- The scanner specific drift is visible in the non-BOLD data
- It effectively cancels the ramp in the OC data

Evans, J.W., et al. NeuroImage 105, 189–197.

Group spatial correlation maps

- Task positive correlation spatial extent group maps for a) block and b) ramp tasks for the medn BOLD, OC, detrended and non-BOLD timeseries.



- The block response is resolved in the detrended data and in the medn
- The ramp task is only seen in the medn data
- No positive task correlation is seen in the OC or non-BOLD data

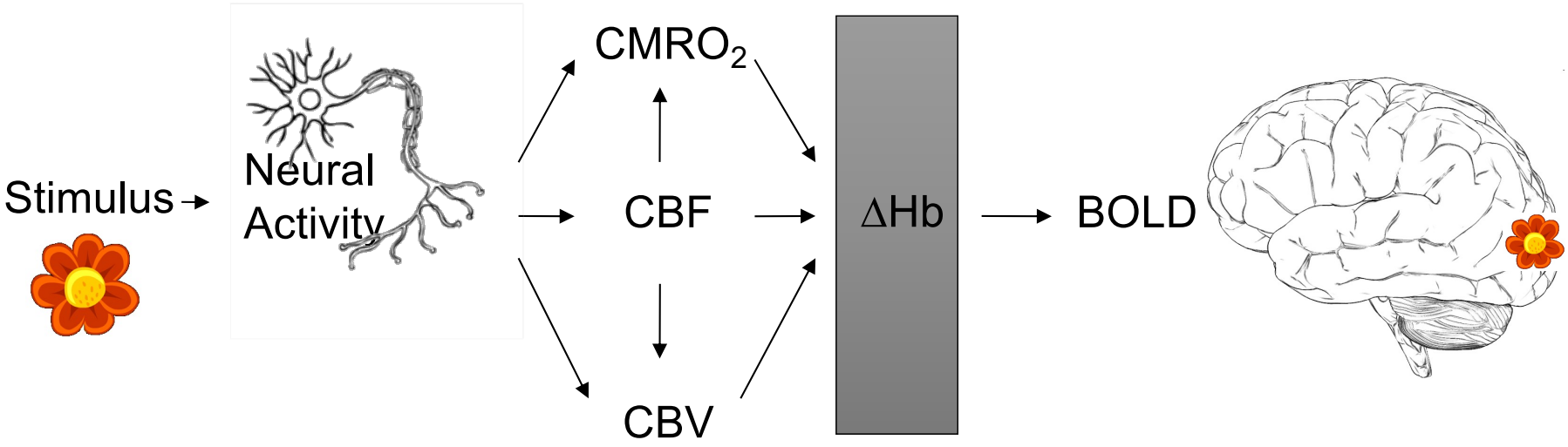
Evans, J.W., et al. NeuroImage 105, 189–197.

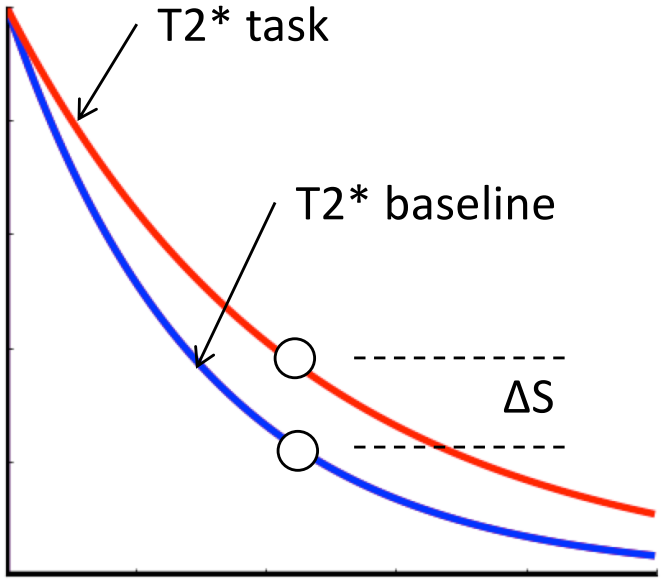
Possible confounding factors…. and solutions

- Cognitive:
  - Placebo effect
    - Study design
- Acquisition:
  - These changes are slow (minutes) and on the same scale as drift artifacts
    - Use multi-echo fMRI?
- Signal:
  - BOLD signal is affected by changes in blood flow/volume
    - Use EEG-fMRI?

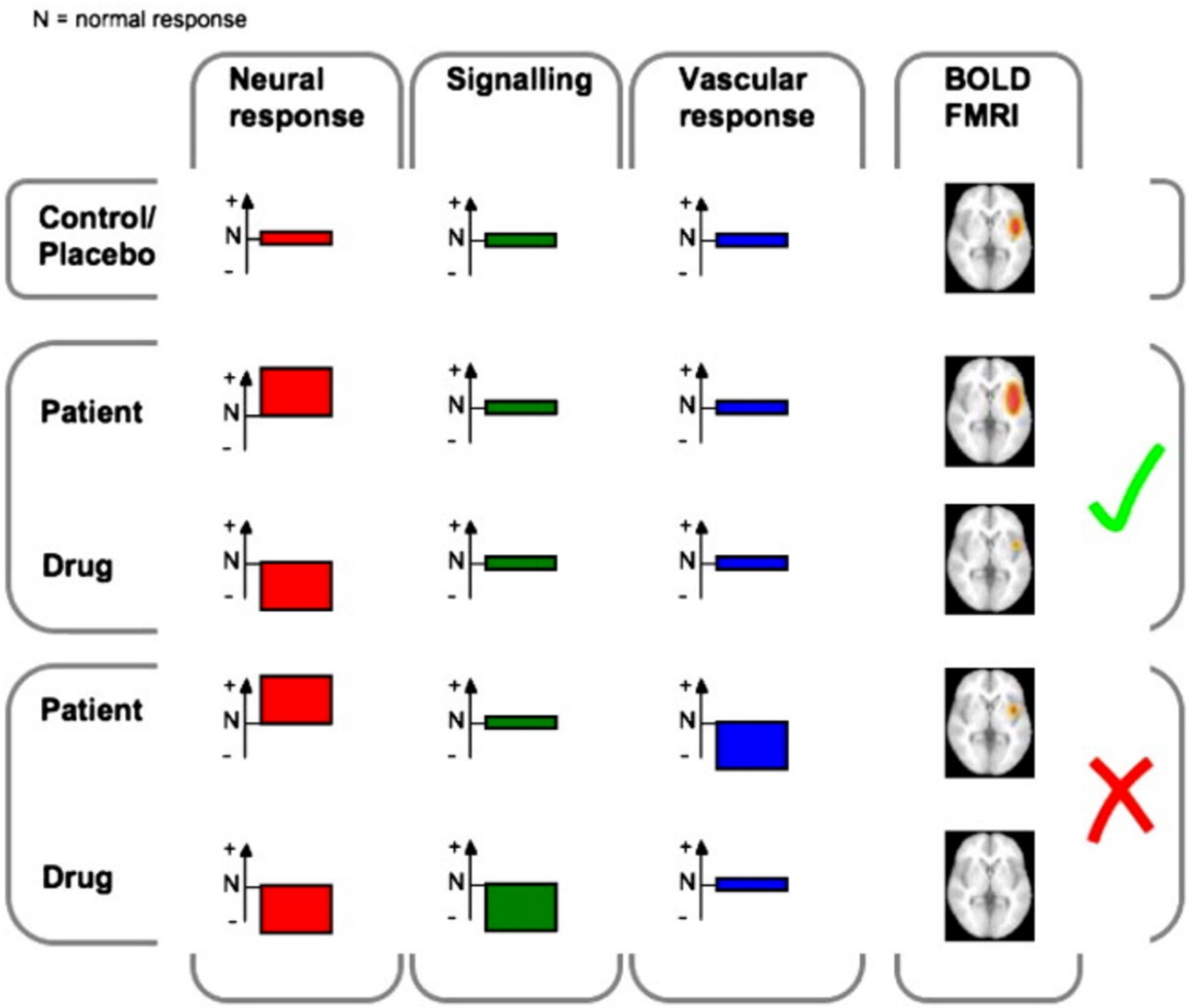
Wise, RG. JMRI(2006)

What does fMRI measure?





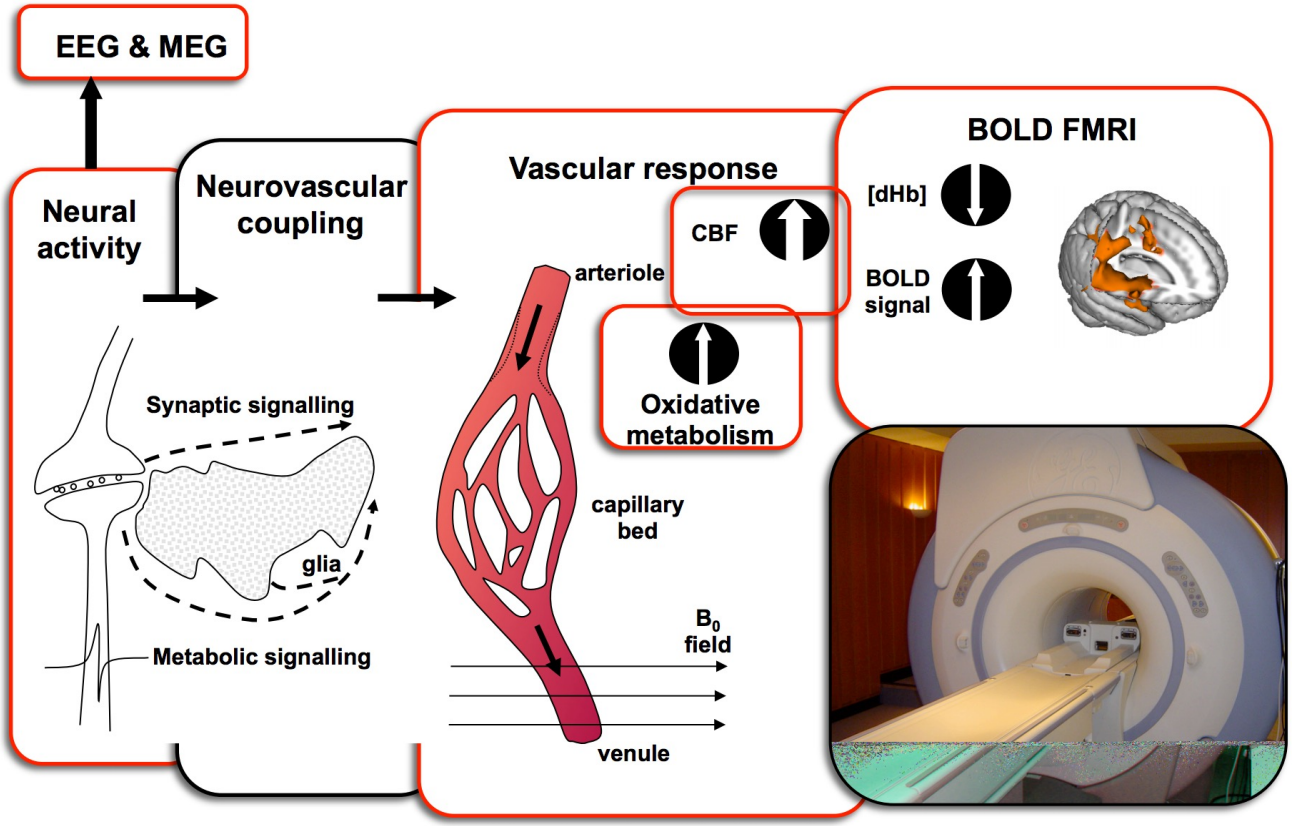
Neural or vascular changes?



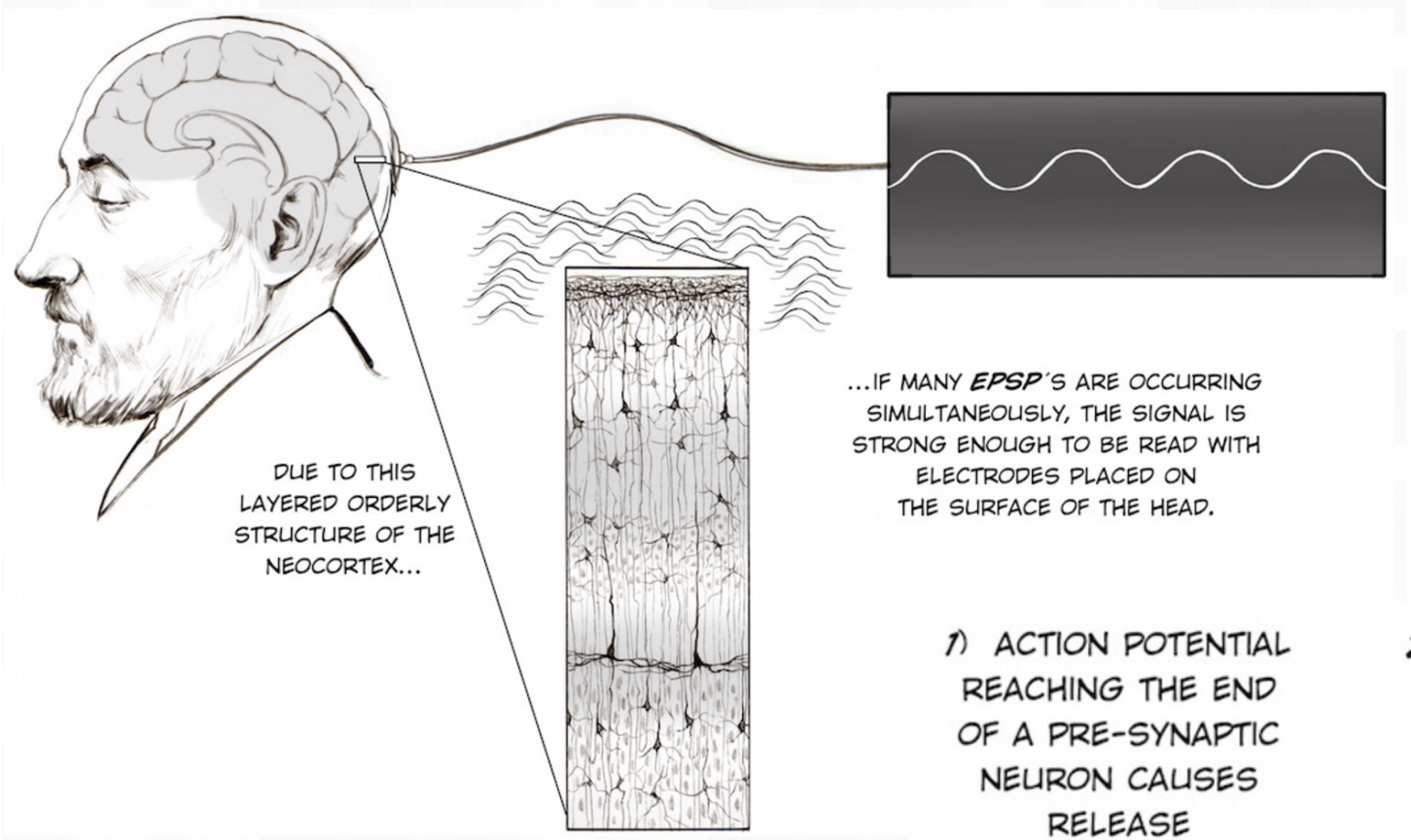
Mag Res. Imaging 2007 Jul;25(6):978-88.

BOLD imaging confounds

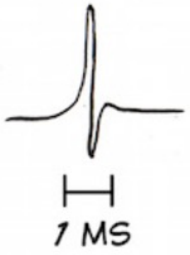
- BOLD is rarely enough on its own as there can be problems with interpretation
- Use MEG/EEG?



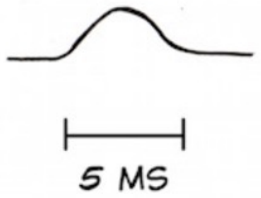
EEG signal origins



1) ACTION POTENTIAL REACHING THE END OF A PRE-SYNAPTIC NEURON CAUSES RELEASE OF GLUTAMATE.



2) GLUTAMATE BINDS TO POST-SYNAPTIC NEURON, CAUSING A SLOWER, LONGER CHANGE IN VOLTAGE CALLED AN EPSP.

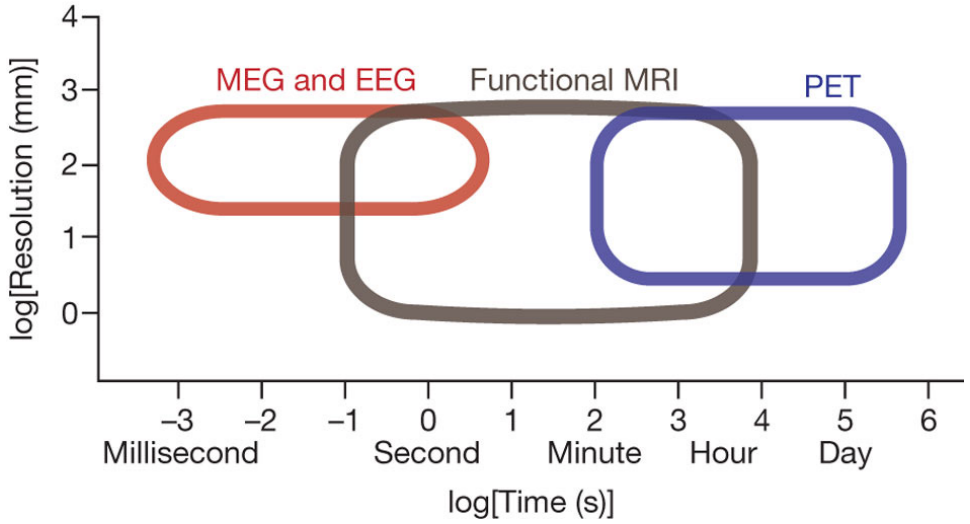


https://backyardbrains.com/experiments/EEG

Simultaneous EEG-FMRI

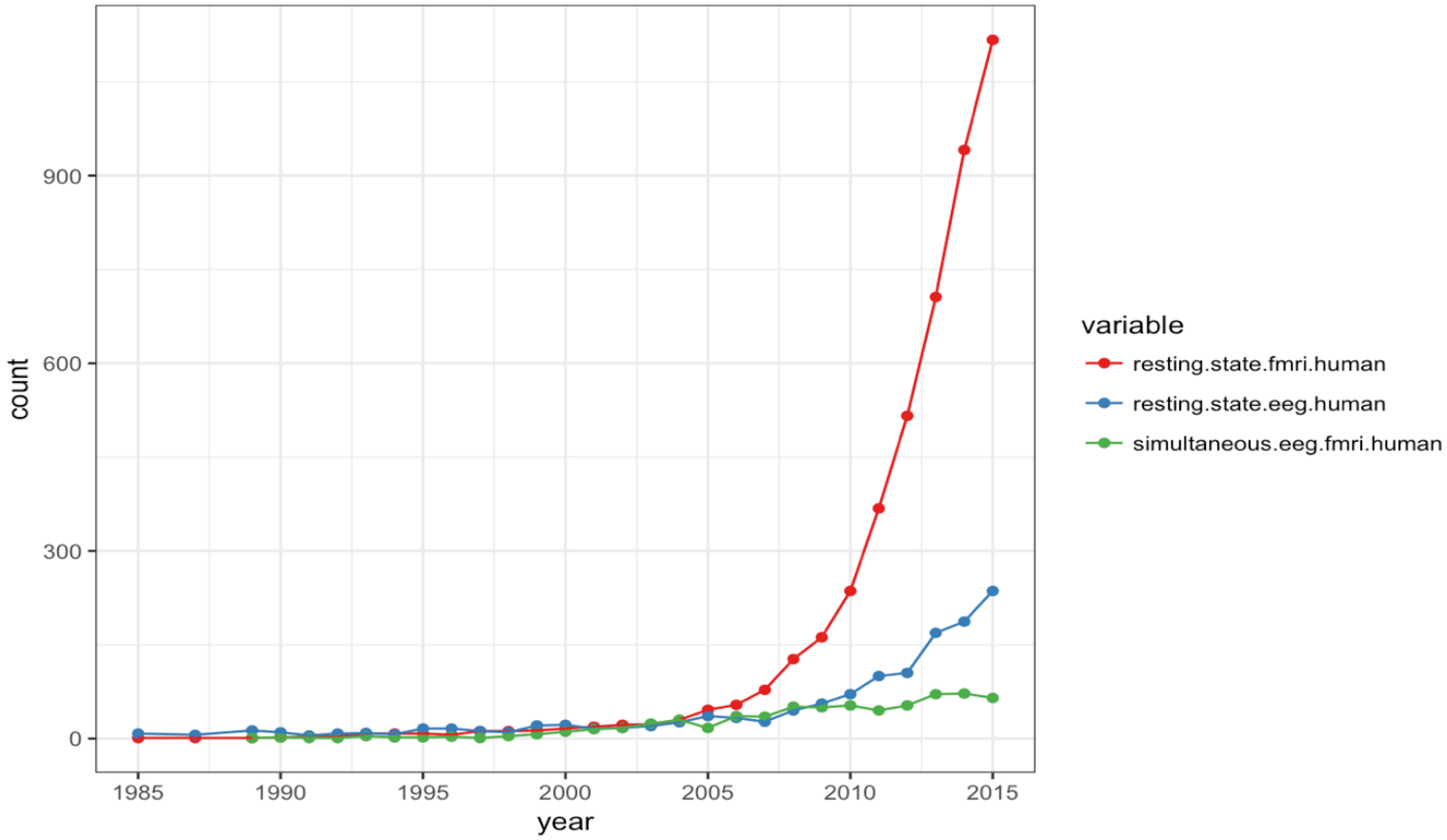
http://nld.tamu.edu/eeg

+

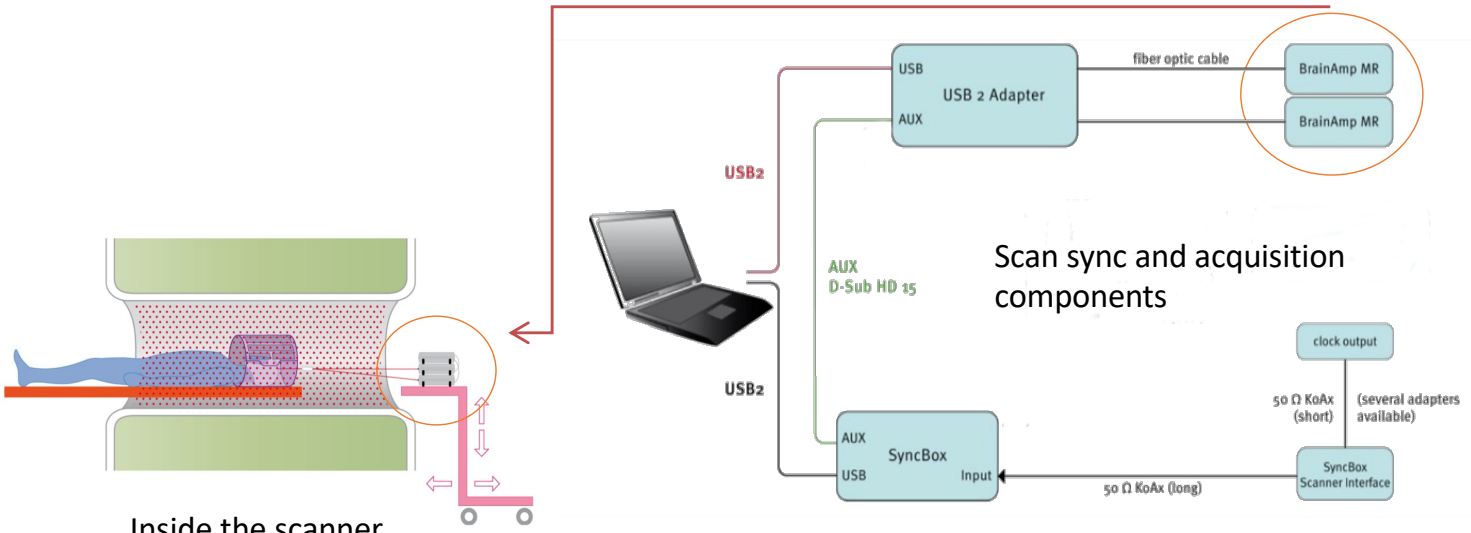


A Meyer-Lindenberg *Nature* **468**, 194-202 (2010)

Possible, but not common…



Simultaneous EEG-fMRI setup



Inside the scanner

Stim PC

Console room

Simultaneous EEG-fMRI - Technical issues

- The MR environment adds noise to the EEG recordings…

Approximate magnitudes of different signals

- EEG: ± 10-150µV

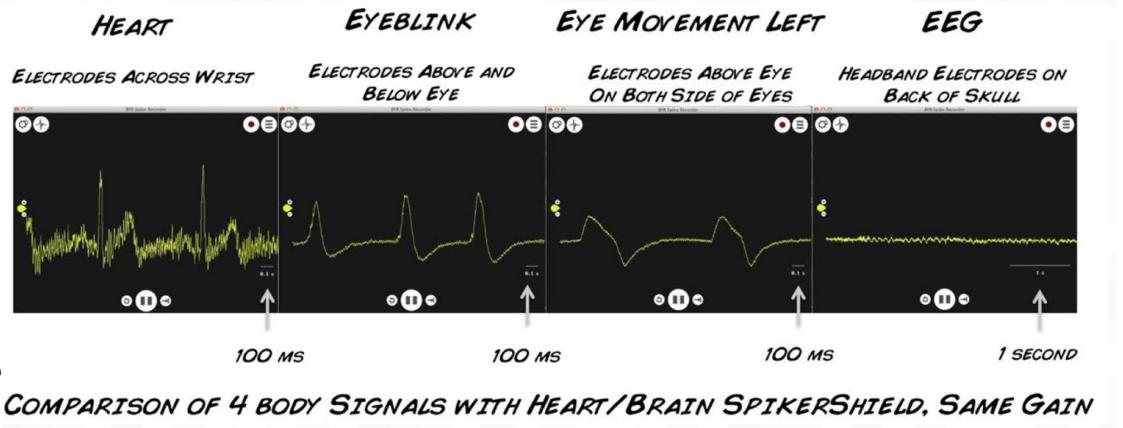
Signal of interest

- Gradient artifact : ± 10mV
- BCG artifact: ± 200µV

MR environment artifacts

- Blink: ± 150µV
- Movement: < 1mV
- ECG: ± 20µV
- EMG: ± 50µV

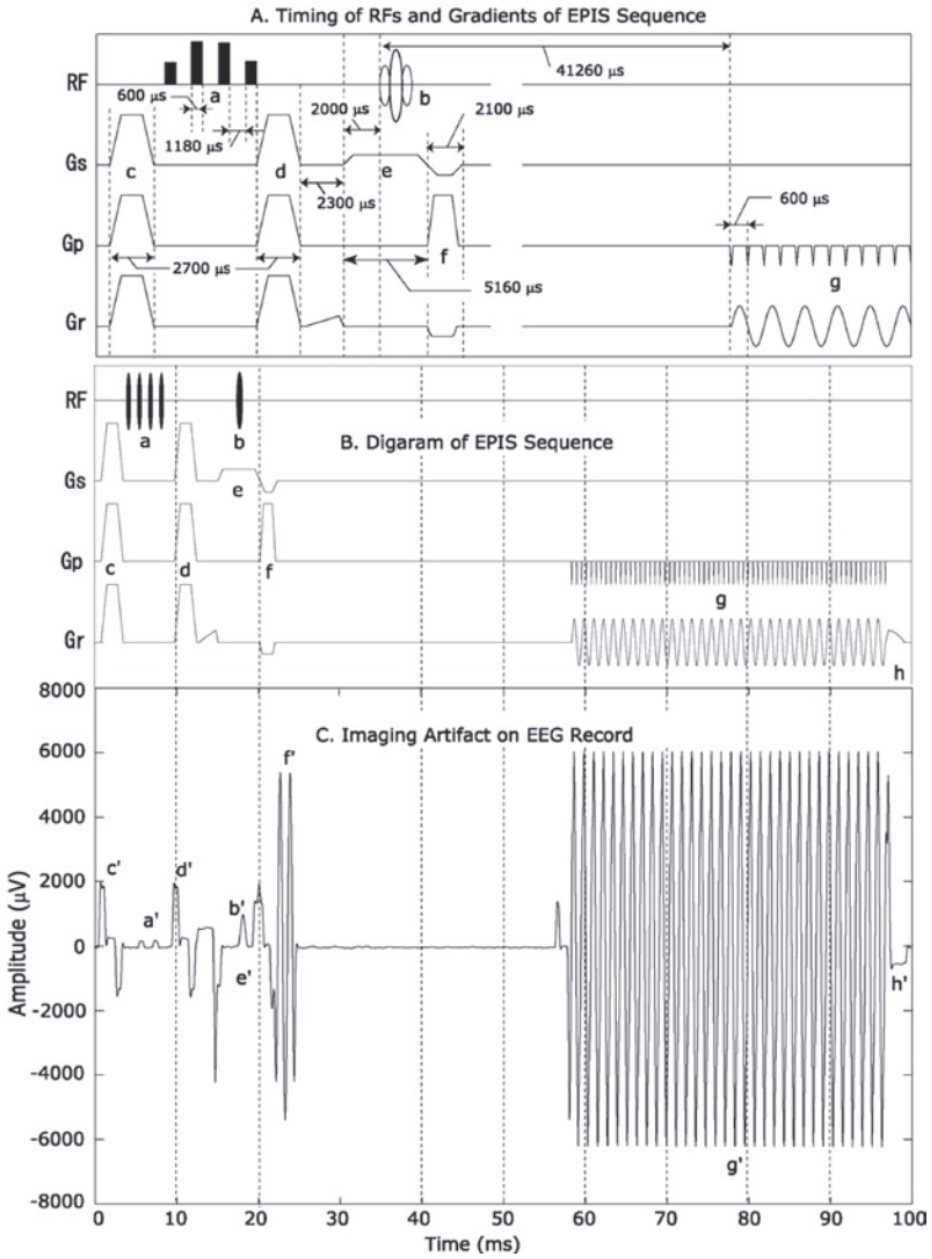
Physiological contributions

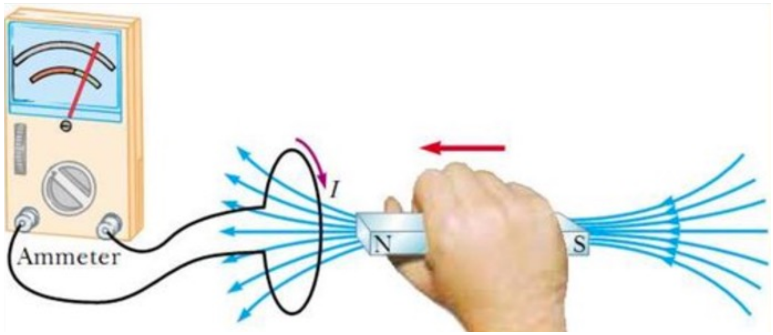


- Helium pump: 40-60Hz and AC line

https://backyardbrains.com/experiments/EEG

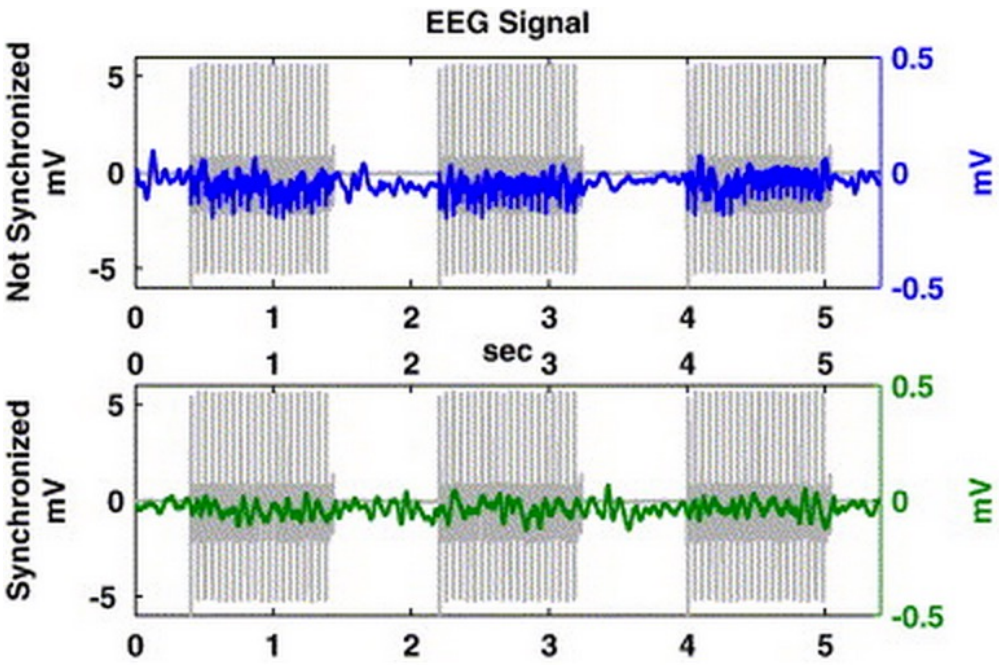
Gradient artifact origins

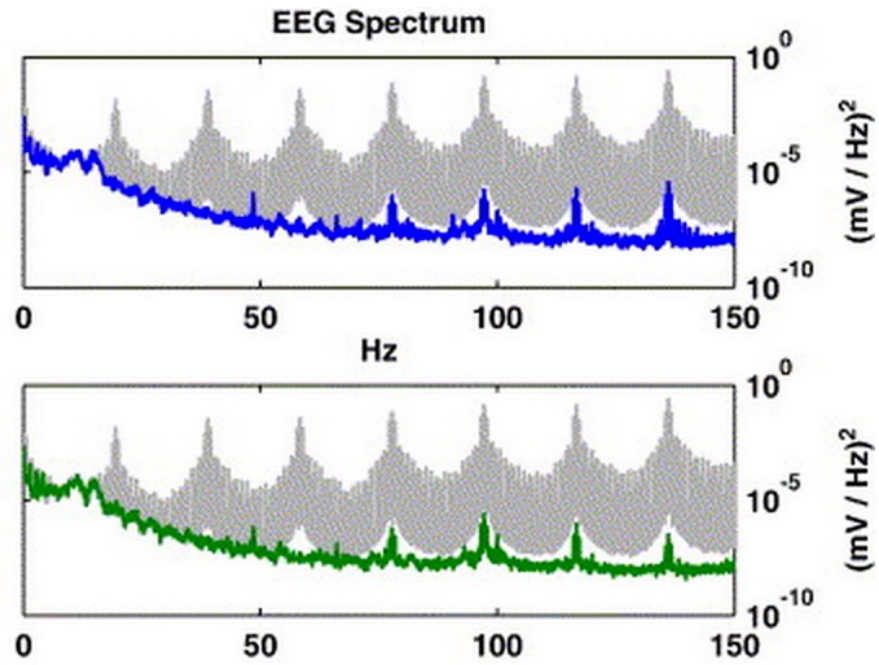




- Switching gradients used for creating MR images induce voltage in the EEG sensors
- Artifact is consistent for every slice

Importance of Synchronized Acquisition

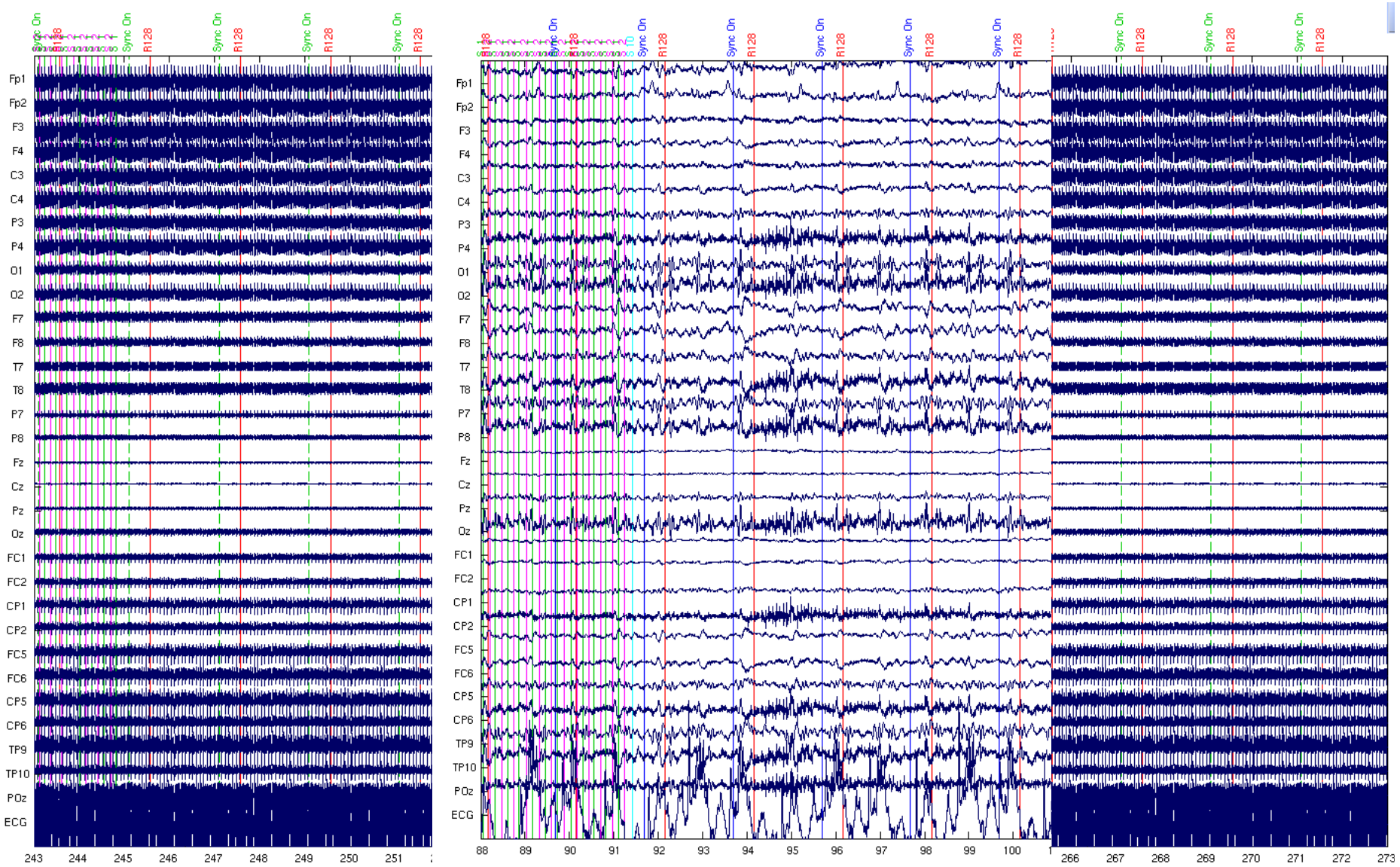




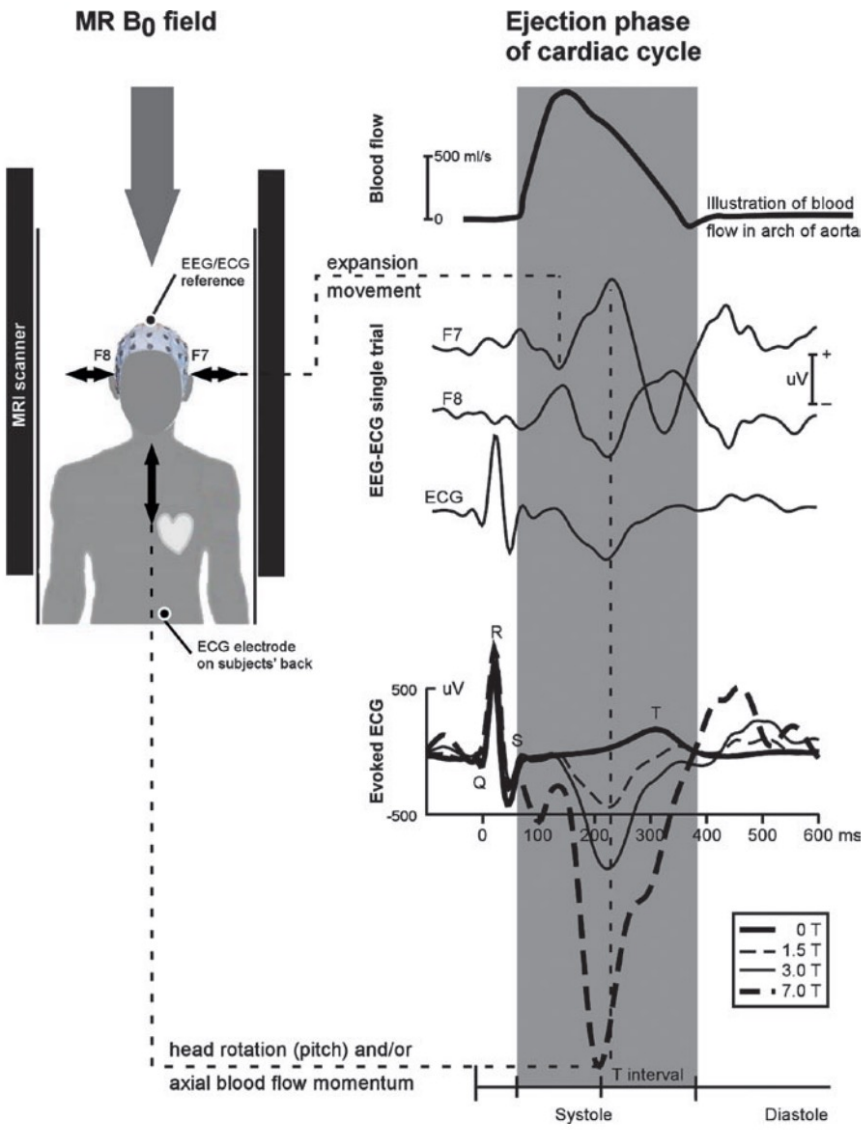
- Gradient artifacts (gray) for 3 acquisitions are not completely removed using template averaging (blue, green) if the EEG system and scanner are not synchronized.
- The residual power spectra show increased artifact contributions at high frequencies

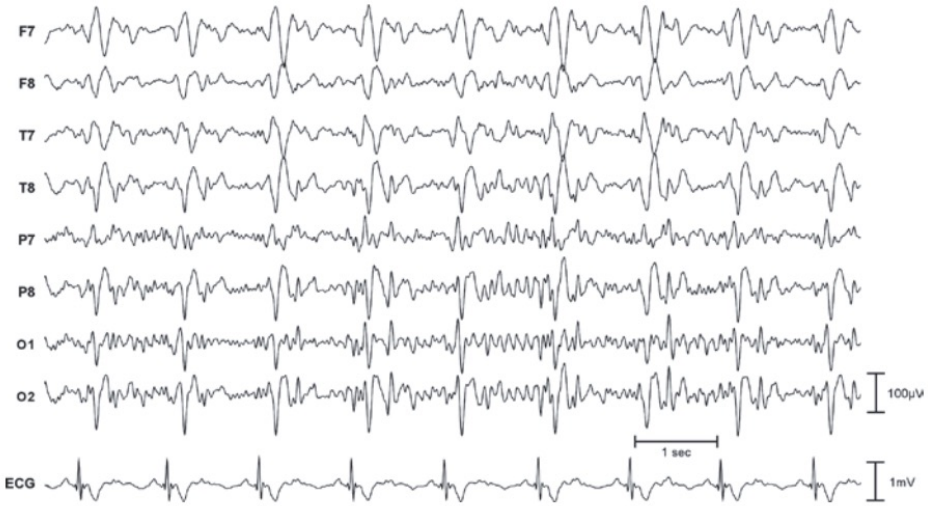
Mandelkow, H et al (2006) Neuroimage 32 (3) 1120-1126

Gradient artifact correction example



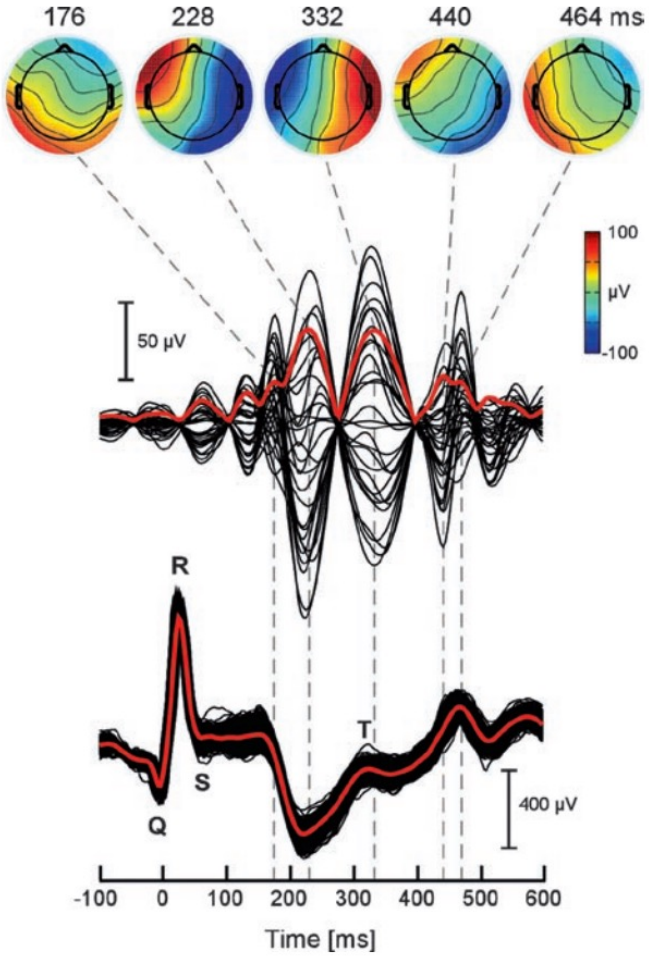
BCG origins

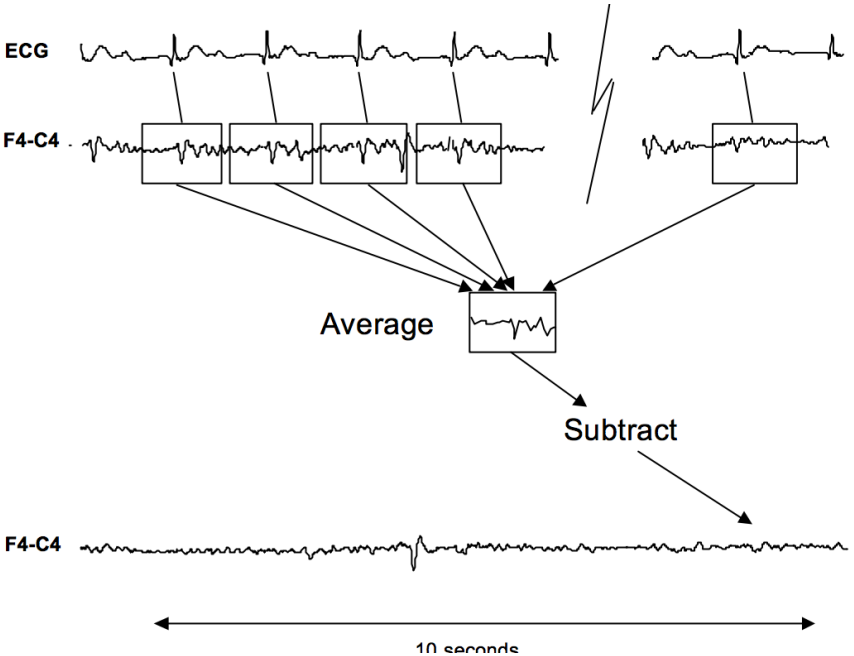


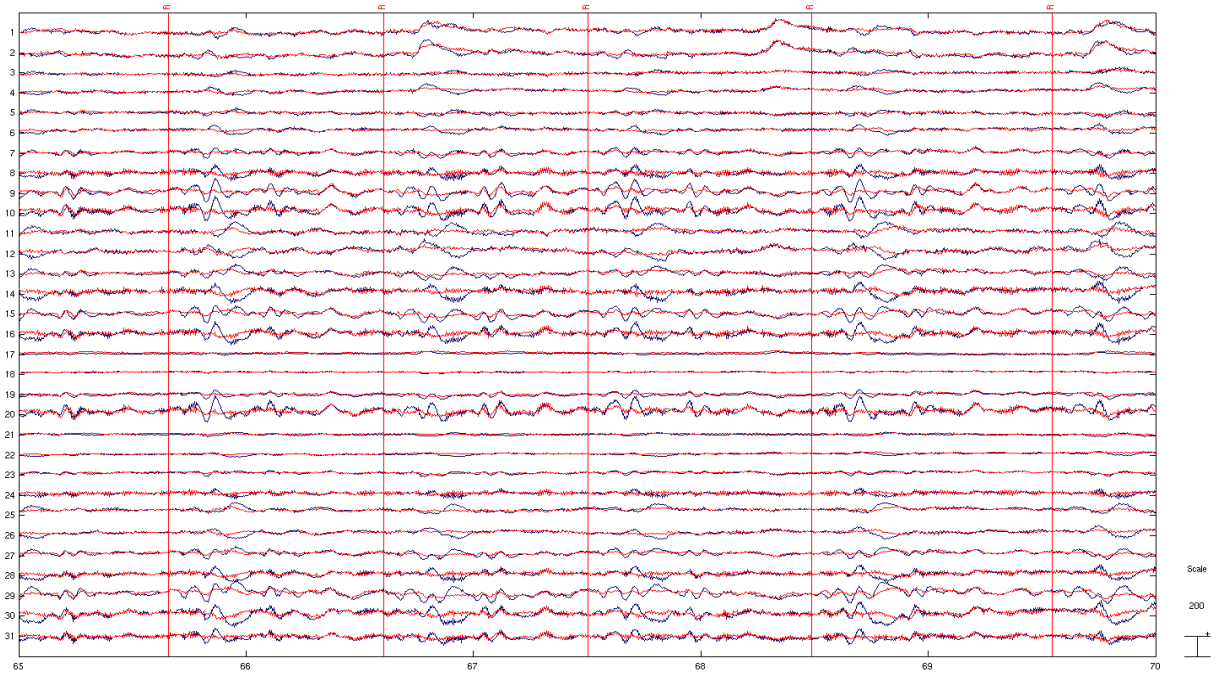


- Motion related to cardiac activity can give rise to induced voltage EEG recording leads
- Matched with heartbeats, consistent 200 ms delay

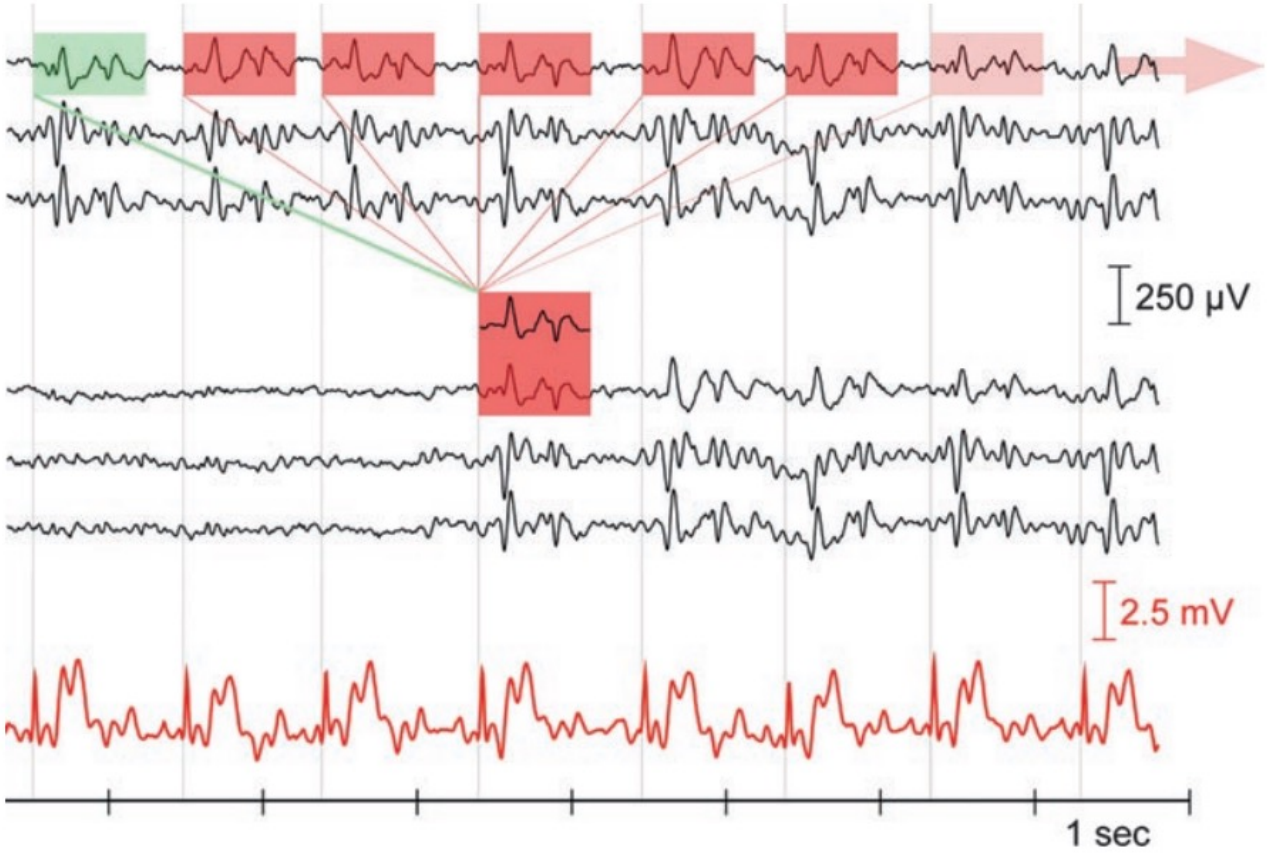
BCG artifact correction







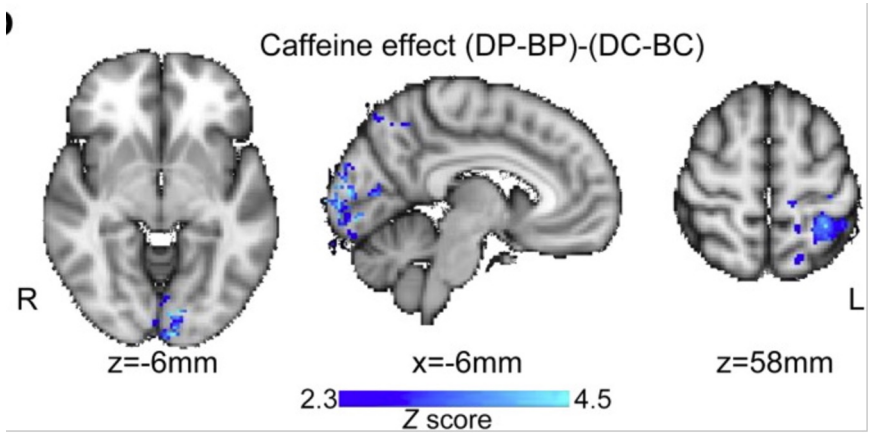
Motion interactions

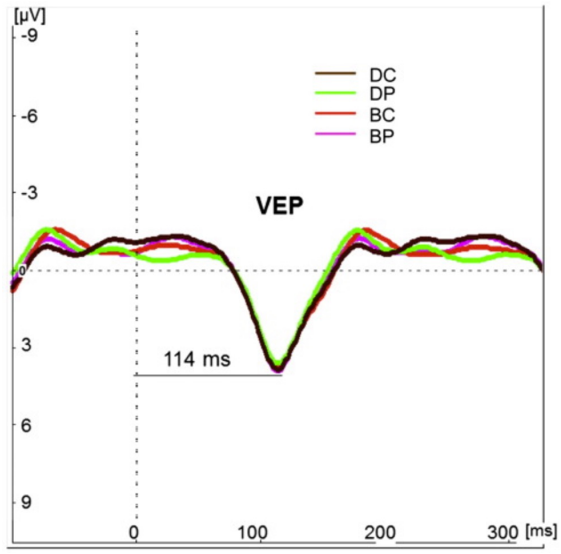


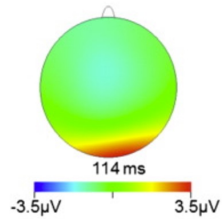
C – caffeine
P– placebo
B - baseline
D - drug

Example: effect of caffeine

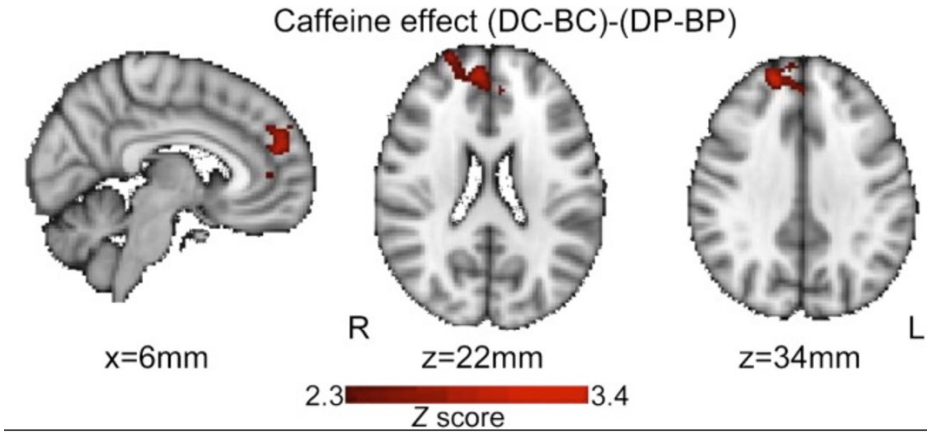
Simple visual task

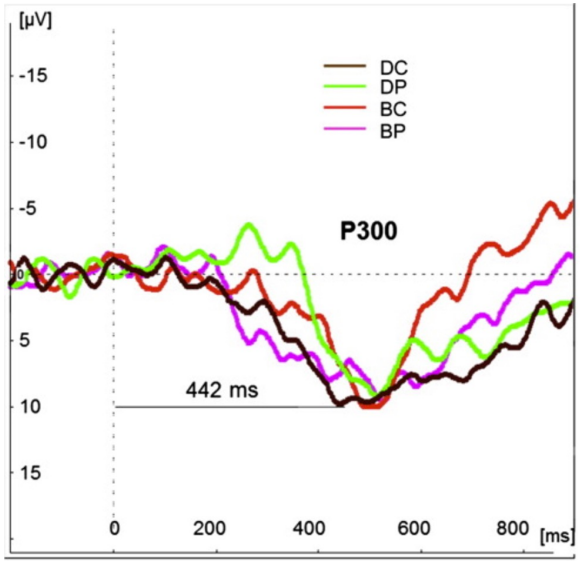


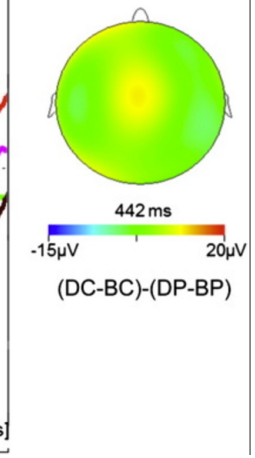




Auditory oddball



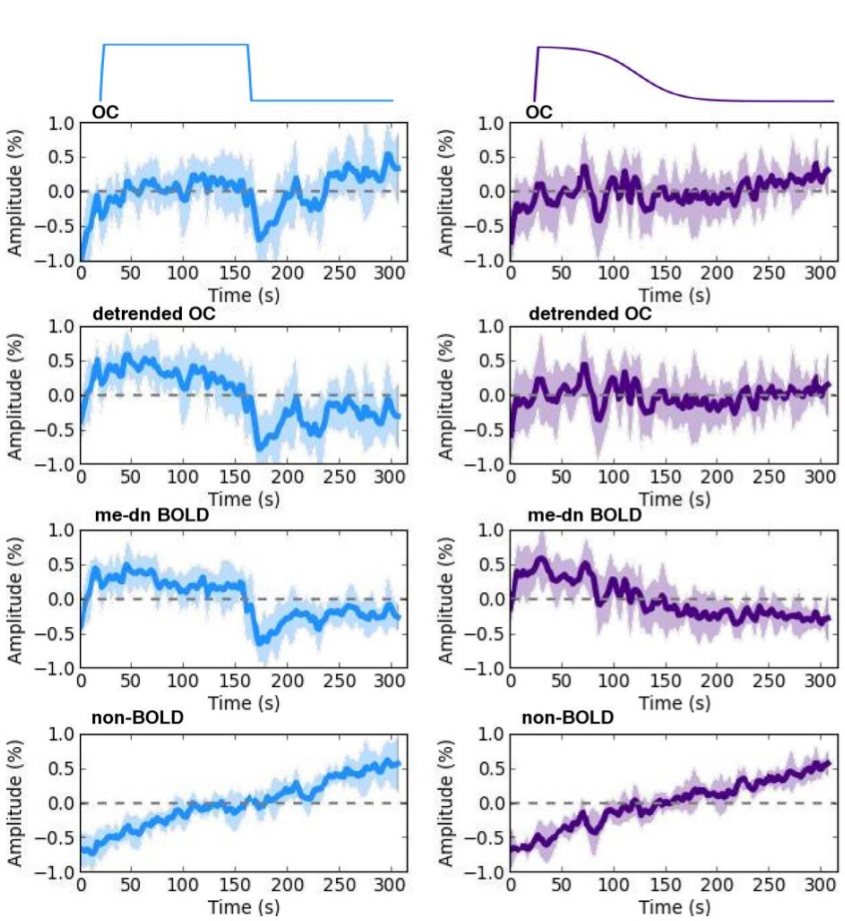


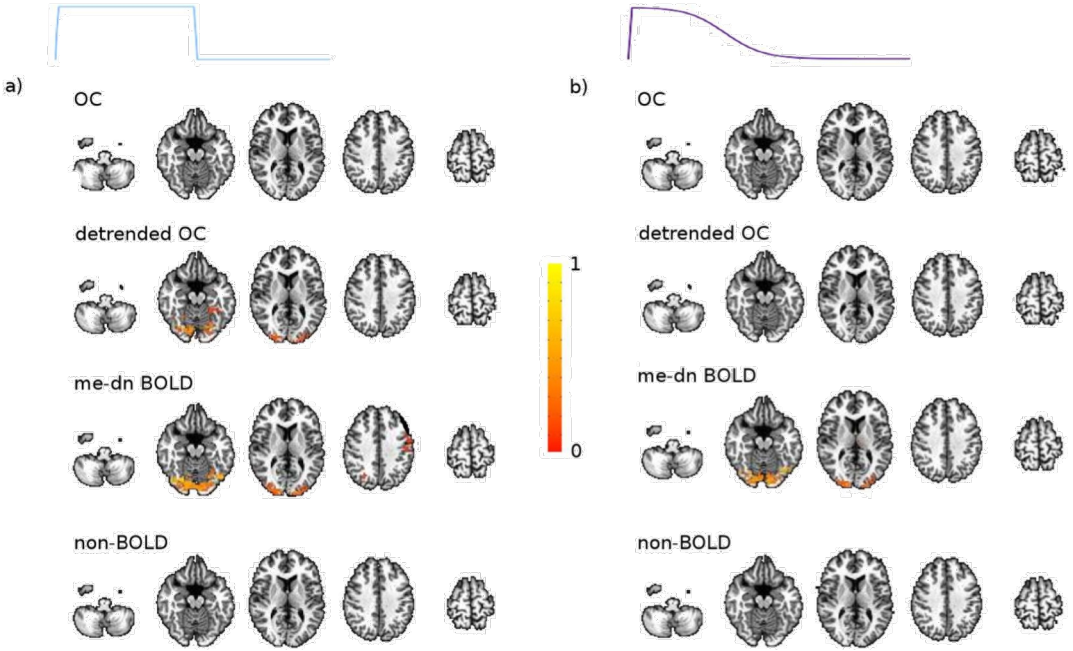


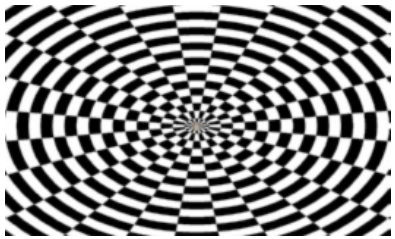
- Shortened P300 response in the complex task, little change in the simple visual task

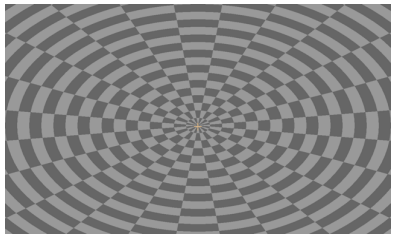
Diukova A, et al. *Neuroimage*. 2012;62(1):239 249.

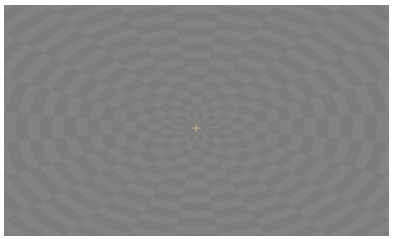
‘Simulated’ Example

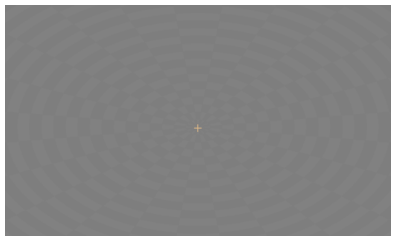




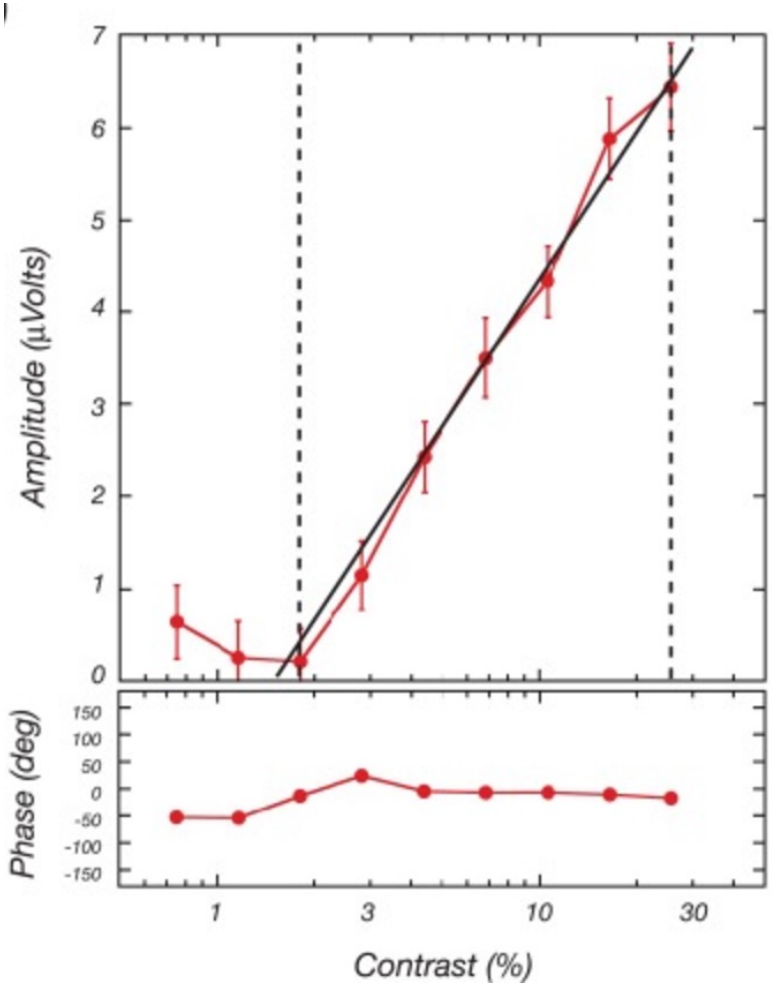




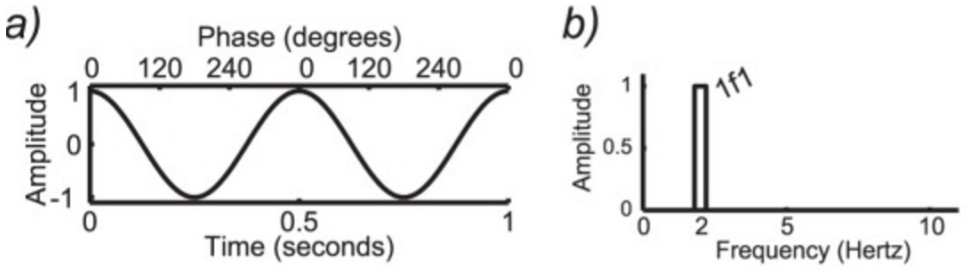


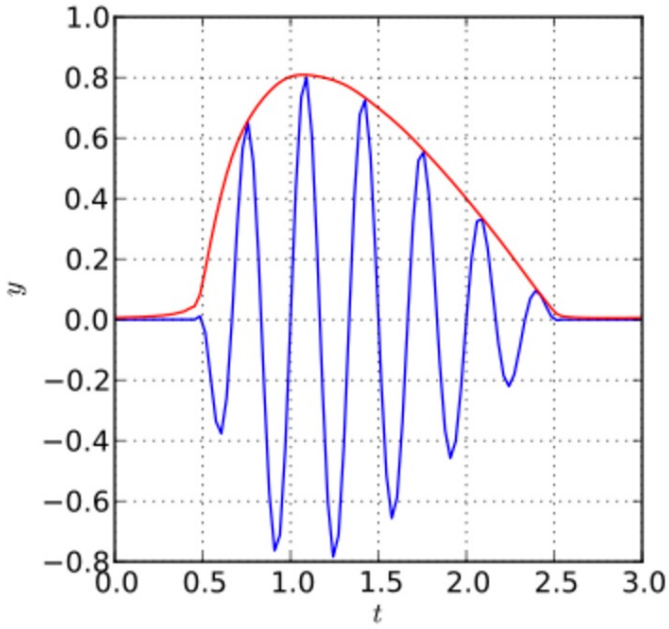


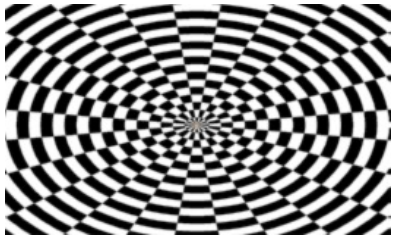
EEG potentials sensitive to contrast and frequency

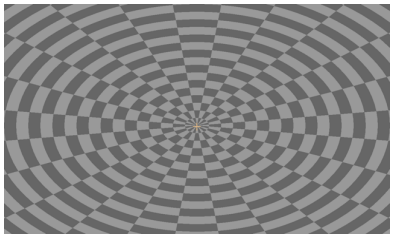


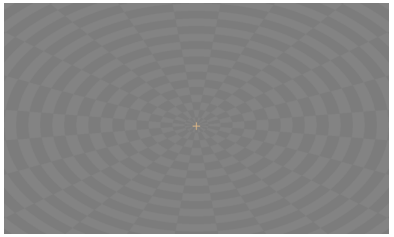
Norcia AM et al. *J Vis*. 2015;15(6):4.

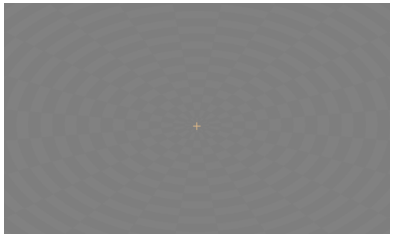




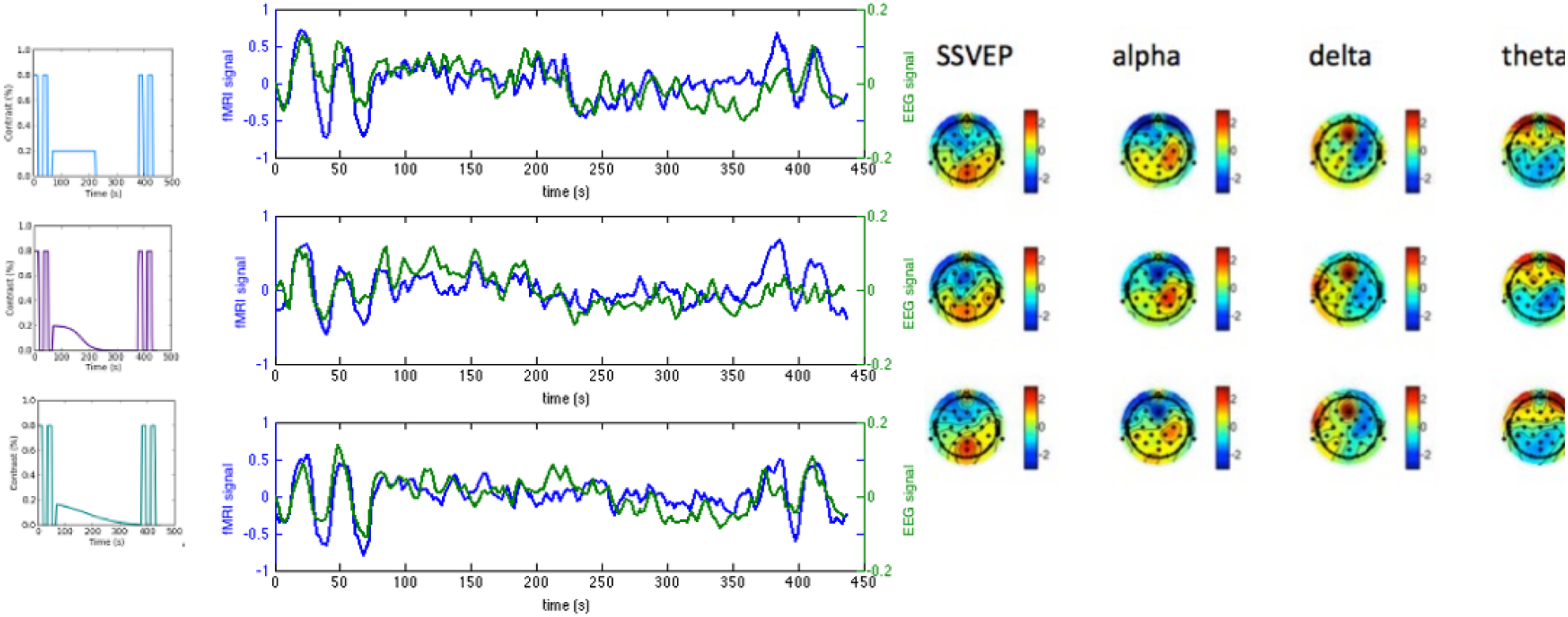








EEG Validation



- The envelope of the EEG signal at the task frequency agrees very well with the task BOLD response
- Confirms the ME-denoised data represents the true task

More examples in the next talks

- EEG/fMRI and the study of Language
  - Pete Molfese

- EEG/fMRI and Neurofeedback
  - Silvina Horovitz

Summary

- Pharmacological fMRI may have many benefits for mapping drug effects in the human brain but remains challenging
- Simultaneous EEG-fMRI is an example of an imaging adjunct to fMRI, there are others (ASL, PET)

Acknowlegements

National Institute of Mental Health

ETPB: Carlos Zarate

Allison Nugent	Wally Duncan	Charles Bender
Elizabeth Ballard	Laura Waldman	Peixiong Yuan
Lawrence Park	Nancy Brutsché	Bridget Shovestul
Mark Niciu	Madeline Gupta	Julia Yarrington
Bashkim Kadriu	Bruce Luber	Nadia Hejazi
Marc Lener	Sarah Lisanby	Yumi Yi
Erica Richards	Libby Jolkovsky	Thomas Radman
Jessica Reed	Alex Noury	Zhi Deng
Jessica Gilbert	Joanna Szczepanik	
Cristan Farmer	Nick Barker	

Mount Sinai Hospital

Prantik Kundu

National Institute of Neurological Disorders and Stroke

Catie Chang
Silvina Horovitz

Department of Health & Human Services USA

FIM
fim.nimh.nih.gov

Peter Bandettini
Pete Molfese

FMRIF
fmrif.nimh.nih.gov

Sean Marrett
Vinai Roopchansingh

Purdue University

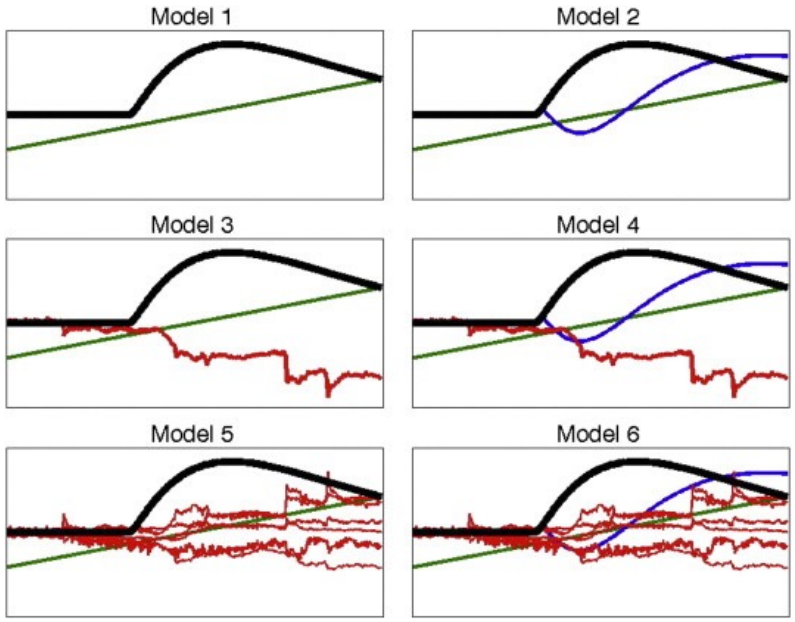
Zhongming Liu

Possible confounding factors….

- Regional changes from:
  - neuronal activity mediated by intact neurovascular coupling.
  - modified non-neuronally-induced metabolic activity, such as may result from local drug binding.
  - vascular tone and hence cerebral blood flow and volume
  - Global changes in cerebral blood flow or volume arising from altered heart rate, blood pressure, or breathing.
- Placebo effect
- These changes are slow (minutes) and on the same scale as drift artifacts

Wise, RG. JMRI(2006)

Baseline modeling …

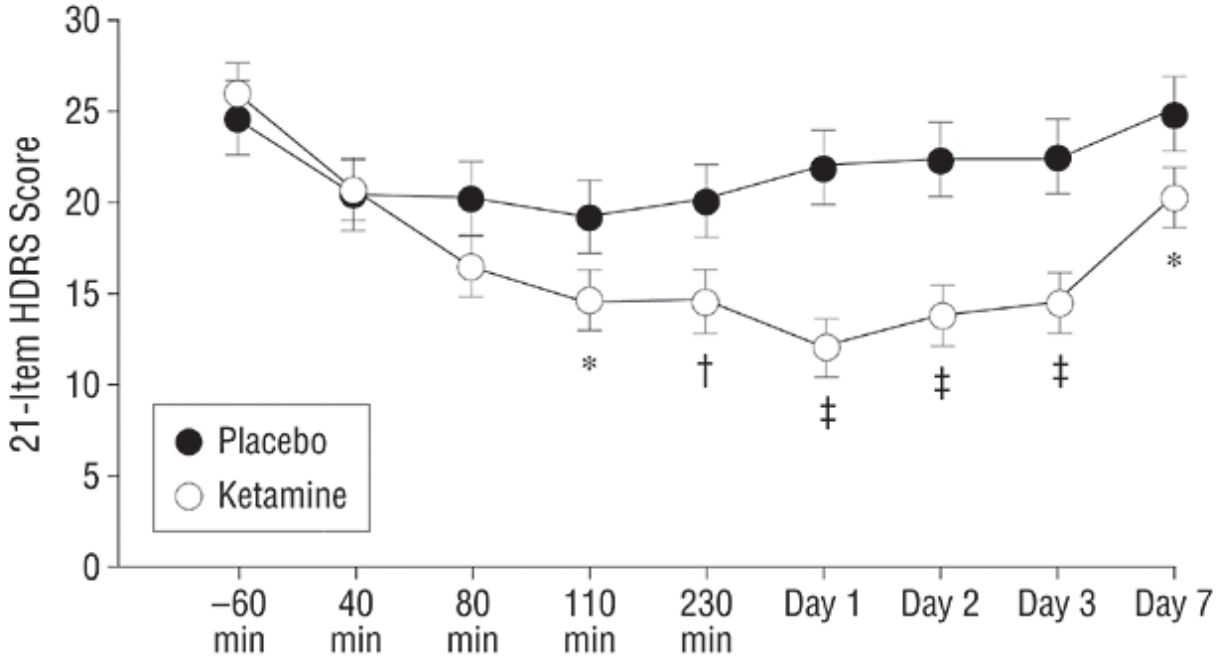


DeSimoni S. et al. (2013) NeuroImage 64:75–90

- GLM noise models may remove signal of interest
  - Decrease degrees of freedom
- ICA methods require training on prior data or manual component selection

Ketamine Tx of Major Depressive Disorder – NIMH Replication Study.

- 18 unmedicated treatment-resistant MDD pts.
- Randomized, cross-over trial trial of single subanesthetic ketamine vs. placebo infusion

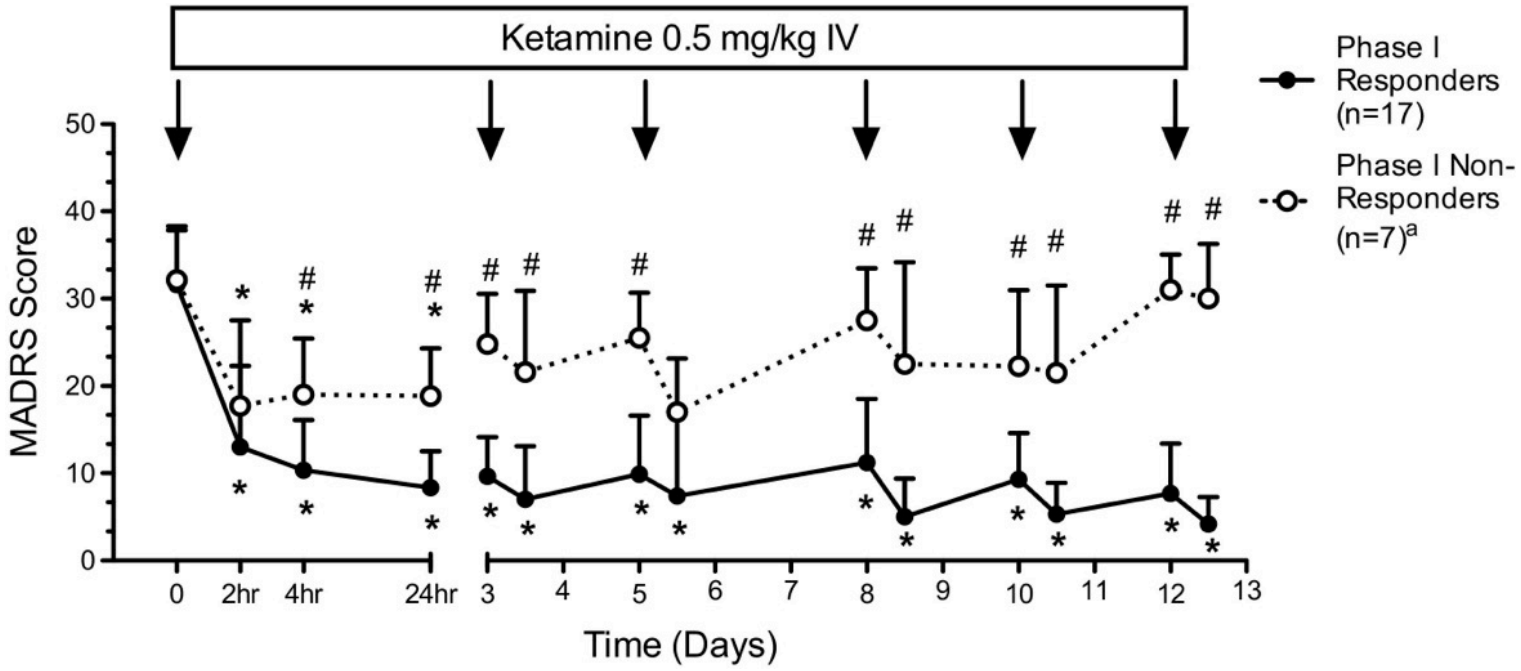


Adapted from Zarate et al. (2006) *Arch Gen Psychiatry* **63**(8): 856-64 – Figure 2

Courtesy of Mark Niciu, NIMH

Repeated-Dose Ketamine Infusions.

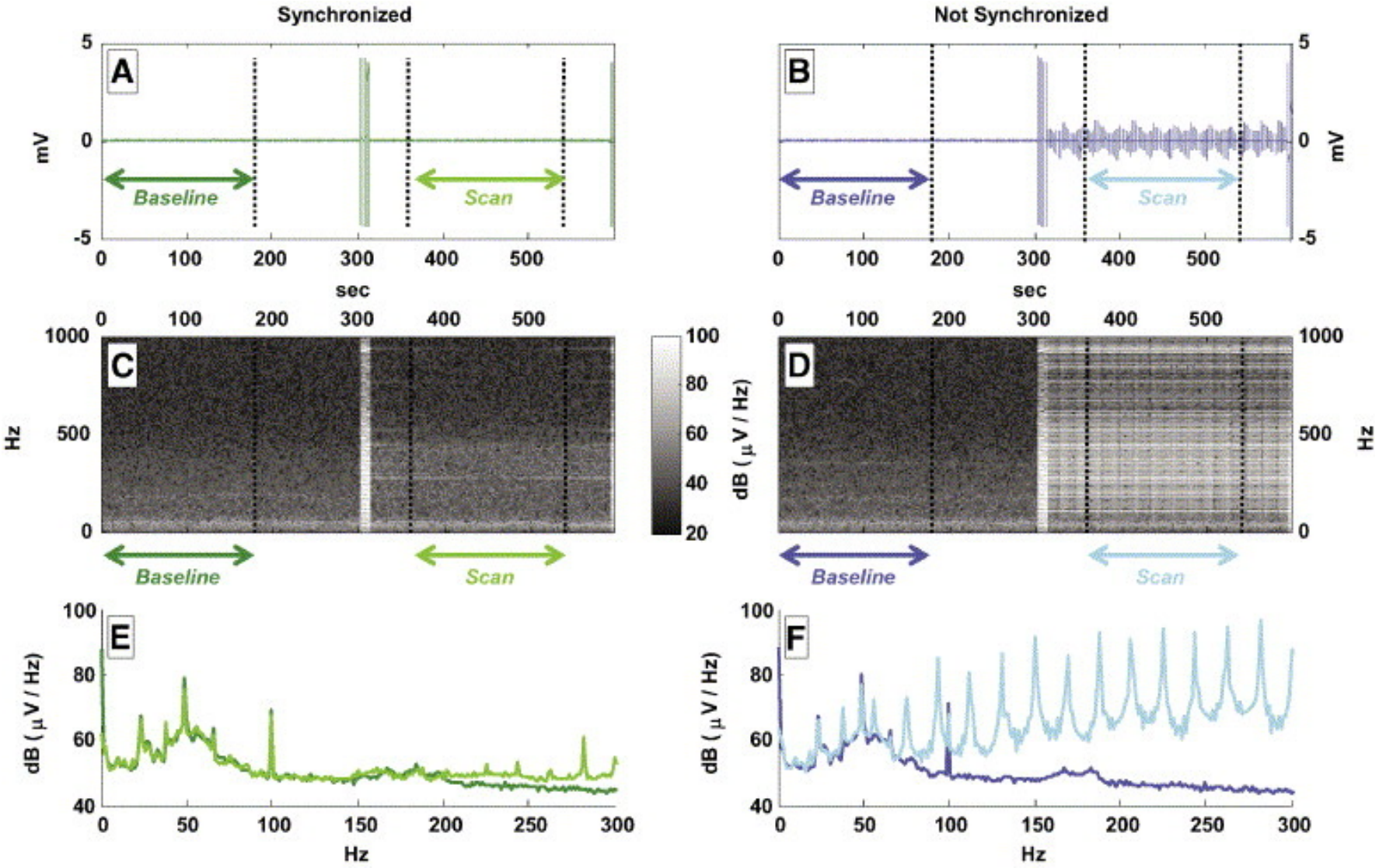
- 24 TRD pts.
- Open-label 0.5mg/kg ketamine infusion x 6 over 12 days
- Responders followed naturalistically for up to 83 days (to monitor for relapse)



Adapted from Murrough *et al.* (2013) *Biol Psychiatry* Epub Ahead of Print 26 Jul 2012 – Figure 1

Courtesy of Mark Niciu, NIMH

Gradient artifact correction

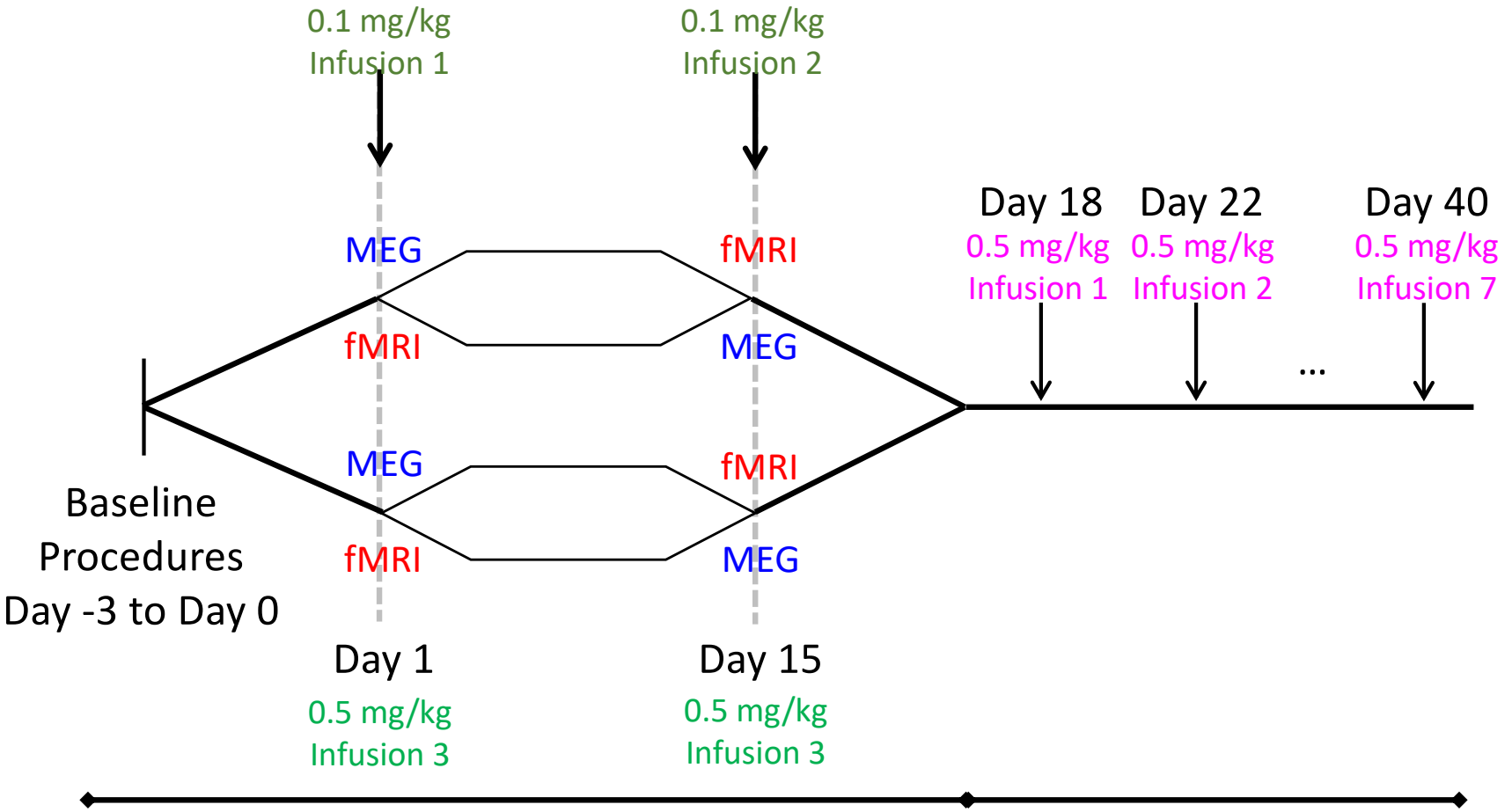


- The increased high frequency contamination is clear when compared to baseline (no gradients) data

Mandelkow, H et al (2006) Neuroimage 32 (3) 1120-1126

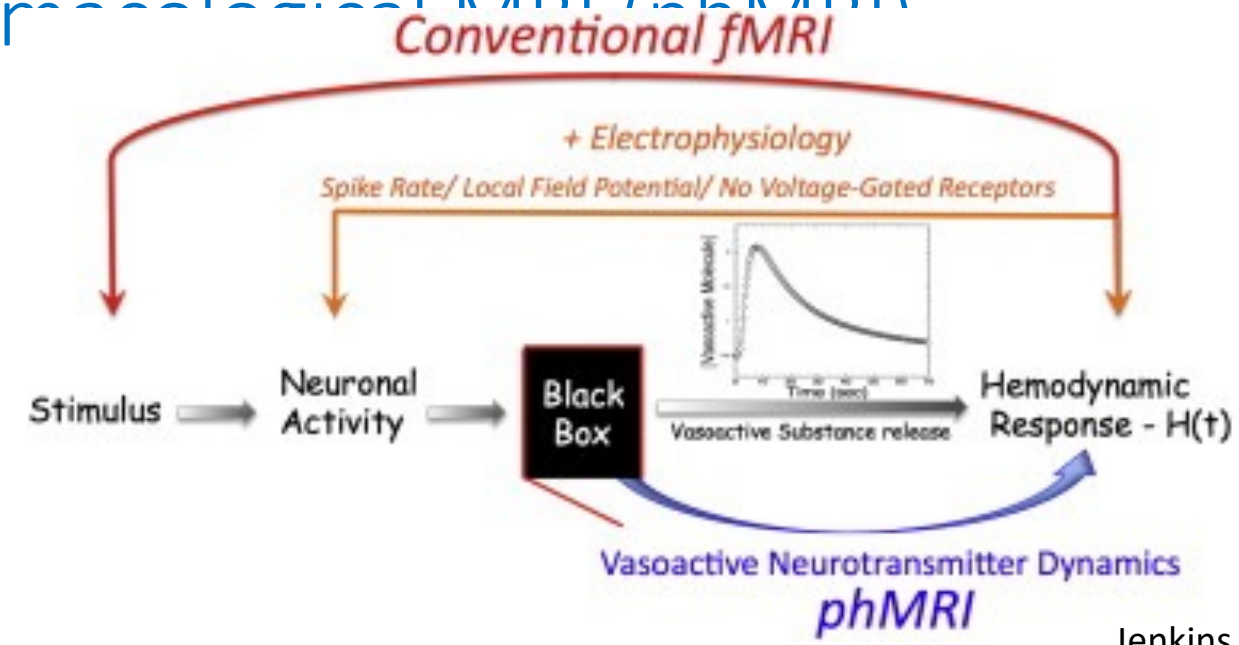
Courtesy of Allison Nugent, NIMH

Planned repeat dose study.

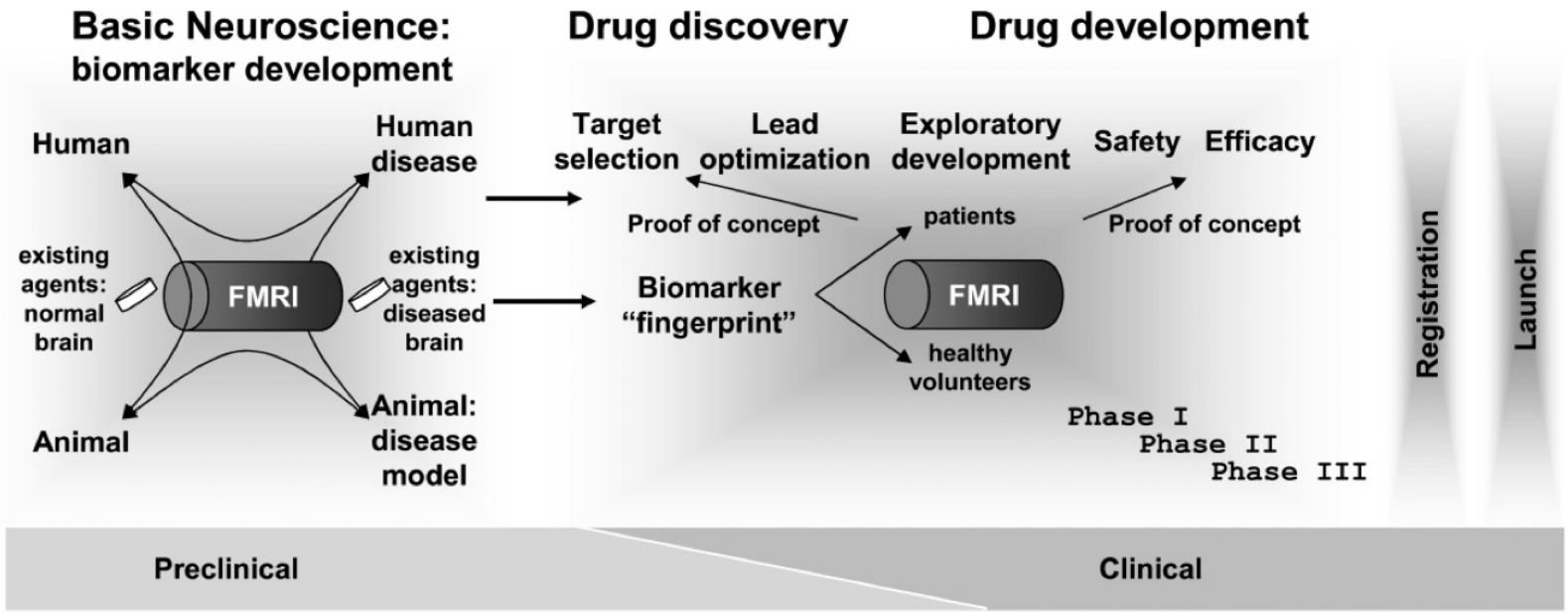


Phase I: DB KET + Pharmacodynamic Imaging **Phase II:** OL KET Repeat Dosing

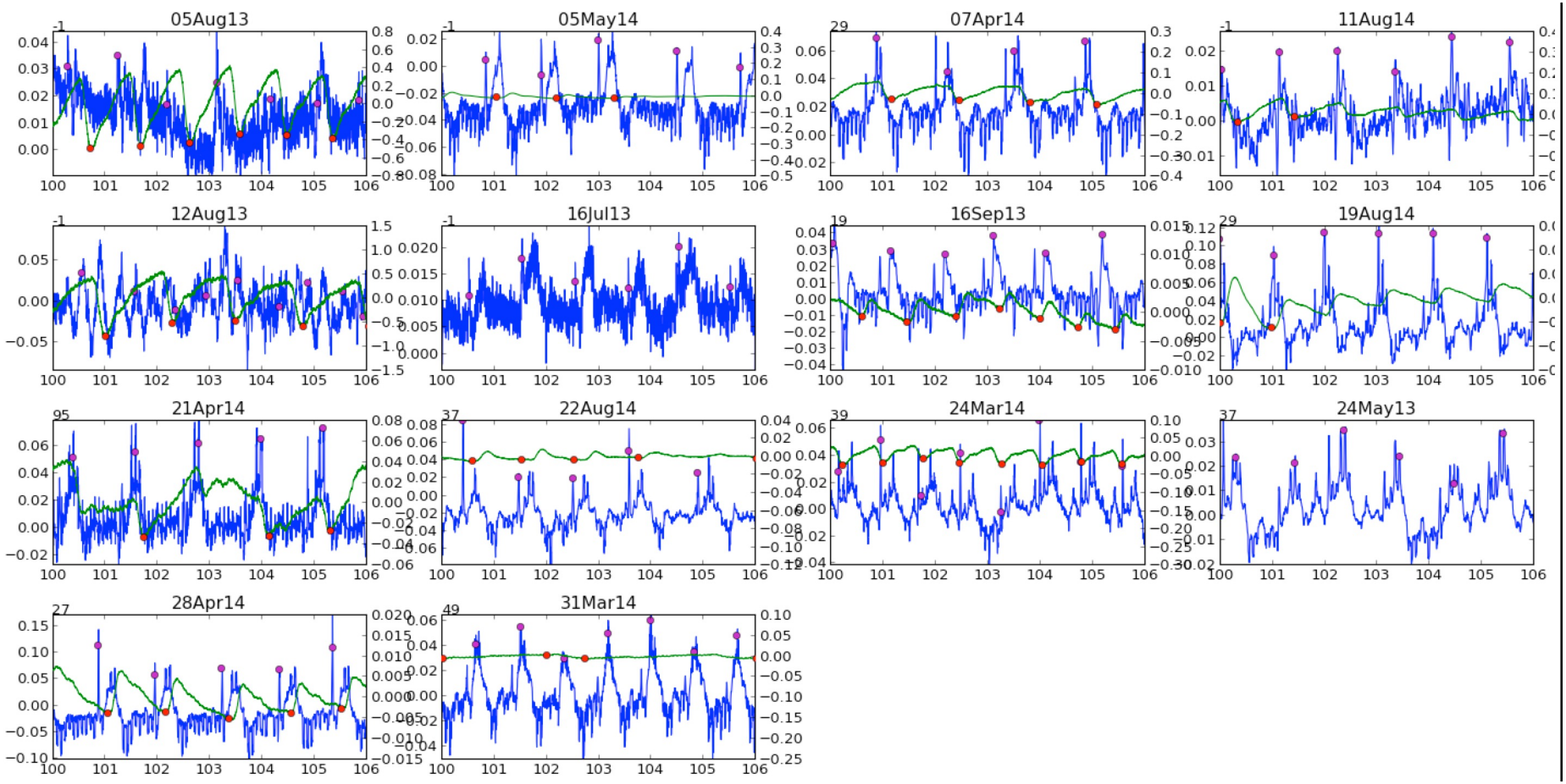
Pharmacological MRI (phMRI)



Jenkins, BG., Neuroimage (2012)

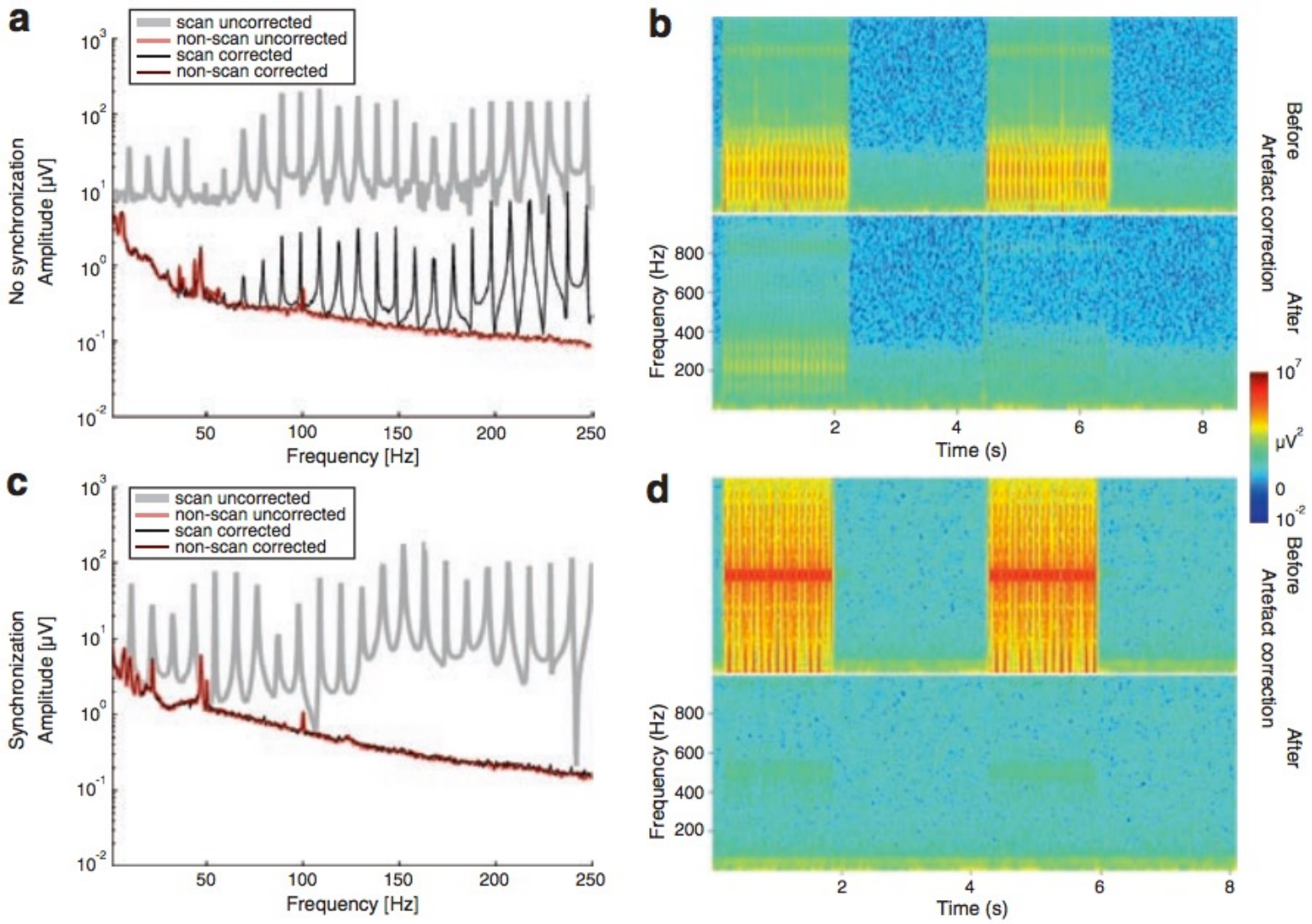


Wise, RG. JMRI(2006)

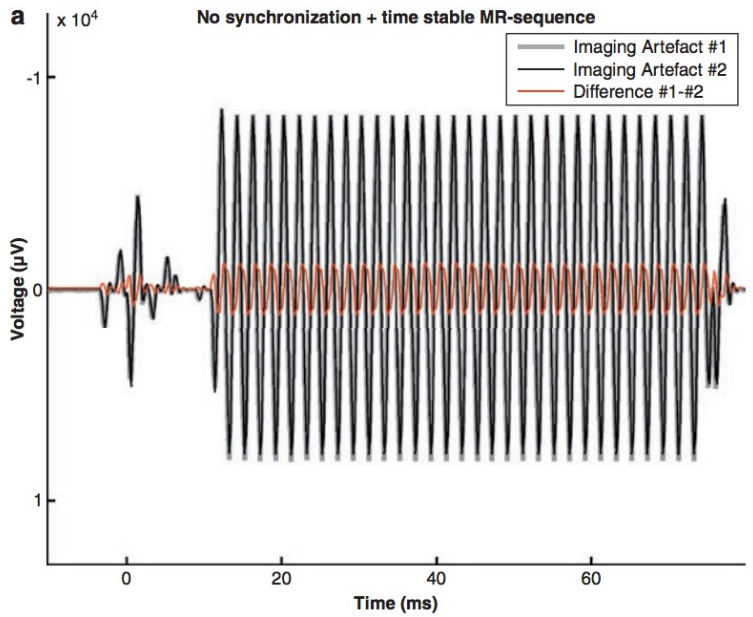


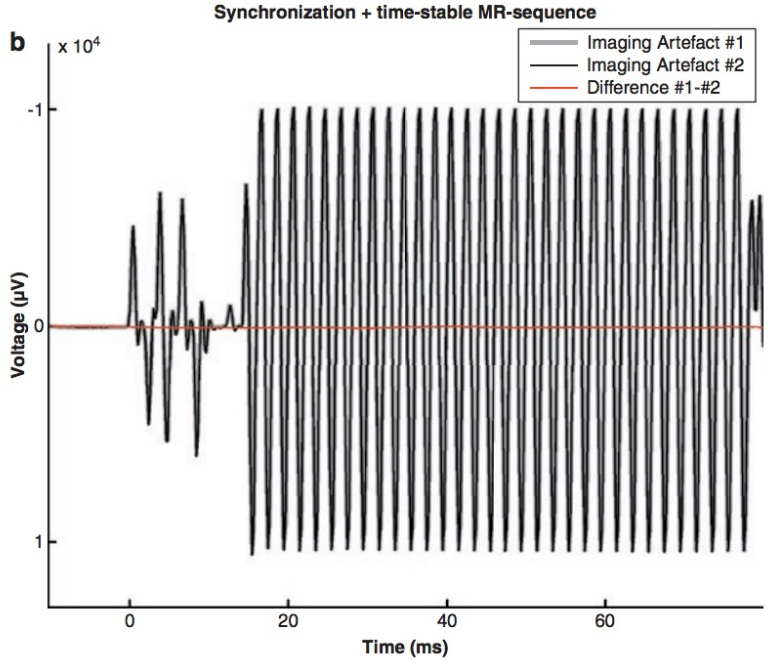
R peak detection native to both pulse ox and ECG data for the ramp task

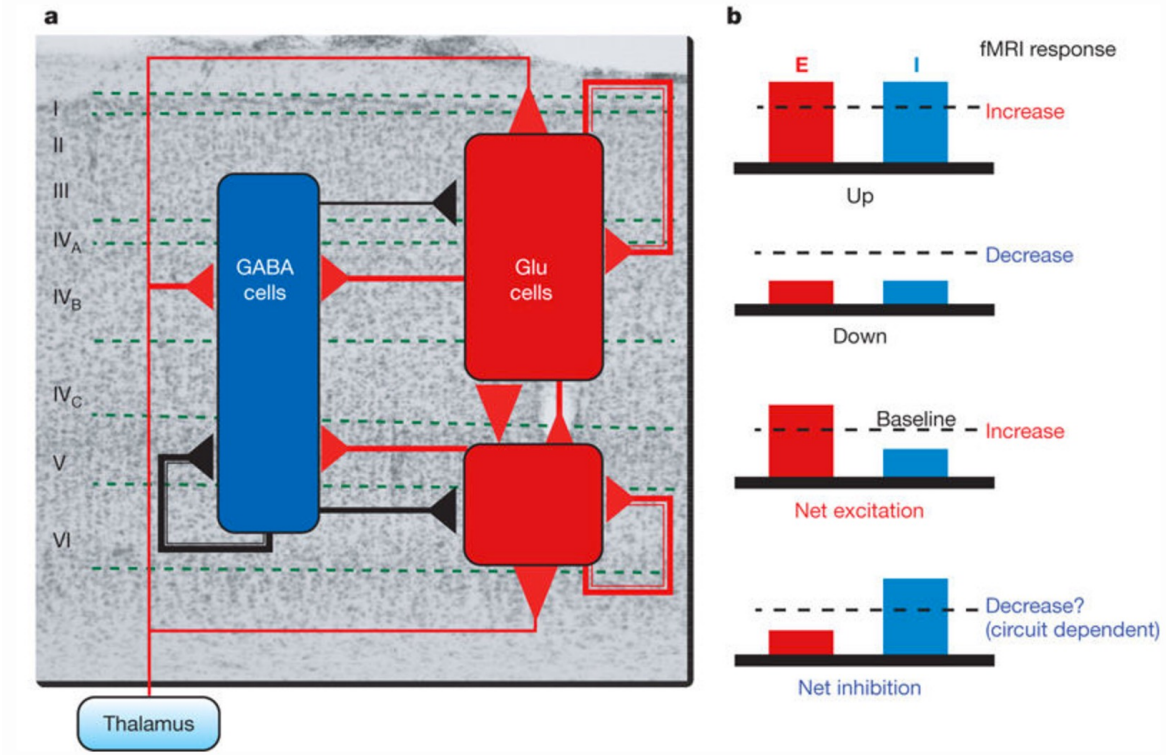
Gradient artifact correction



Artefact removal strategies






a
I
II
III
IV_A
IV_B
IV_C
V
VI
GABA cells
Glu cells
Thalamus
b
fMRI response
E
I
Increase
Up
Decrease
Down
Baseline
Increase
Net excitation
Decrease?
(circuit dependent)
Net inhibition