Intro to pharmacological (ph)MRI

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06Jul18

FMRIF Summer Course

Outline

- Pharmacological MRI
  - Role of fMRI in drug discovery
  - Types (study design)
    - examples
  - Confounding factors & how to mitigate them
- 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

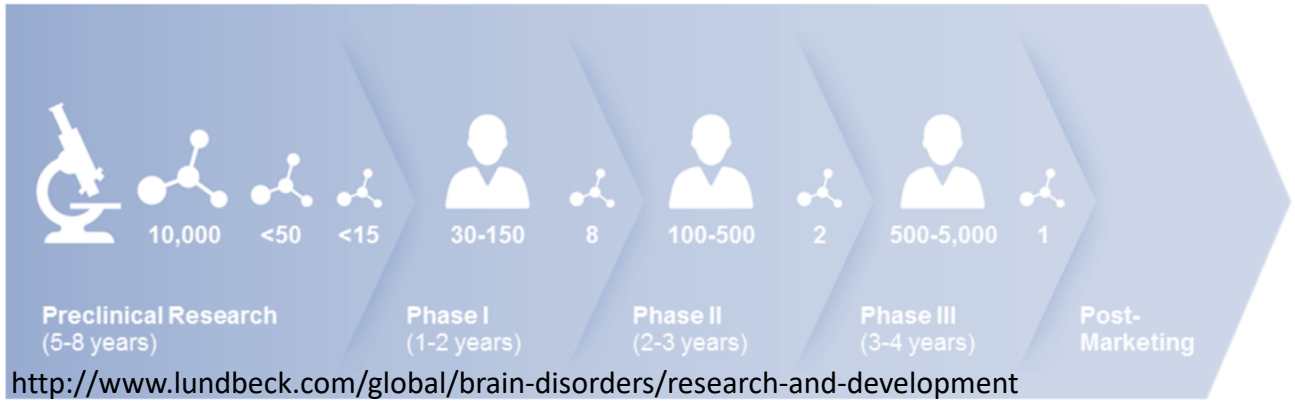
Pharmacological imaging

- 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

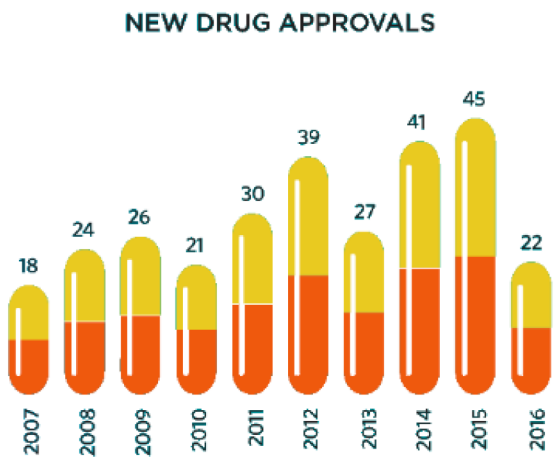
Wise R.G.

Drug development process …

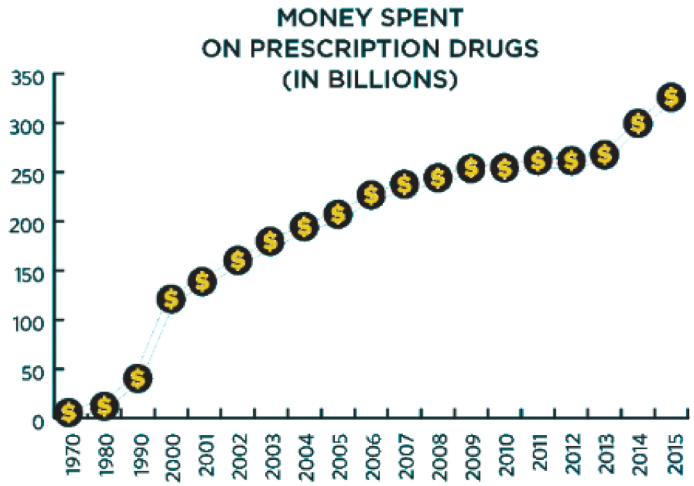
- Long and costly



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



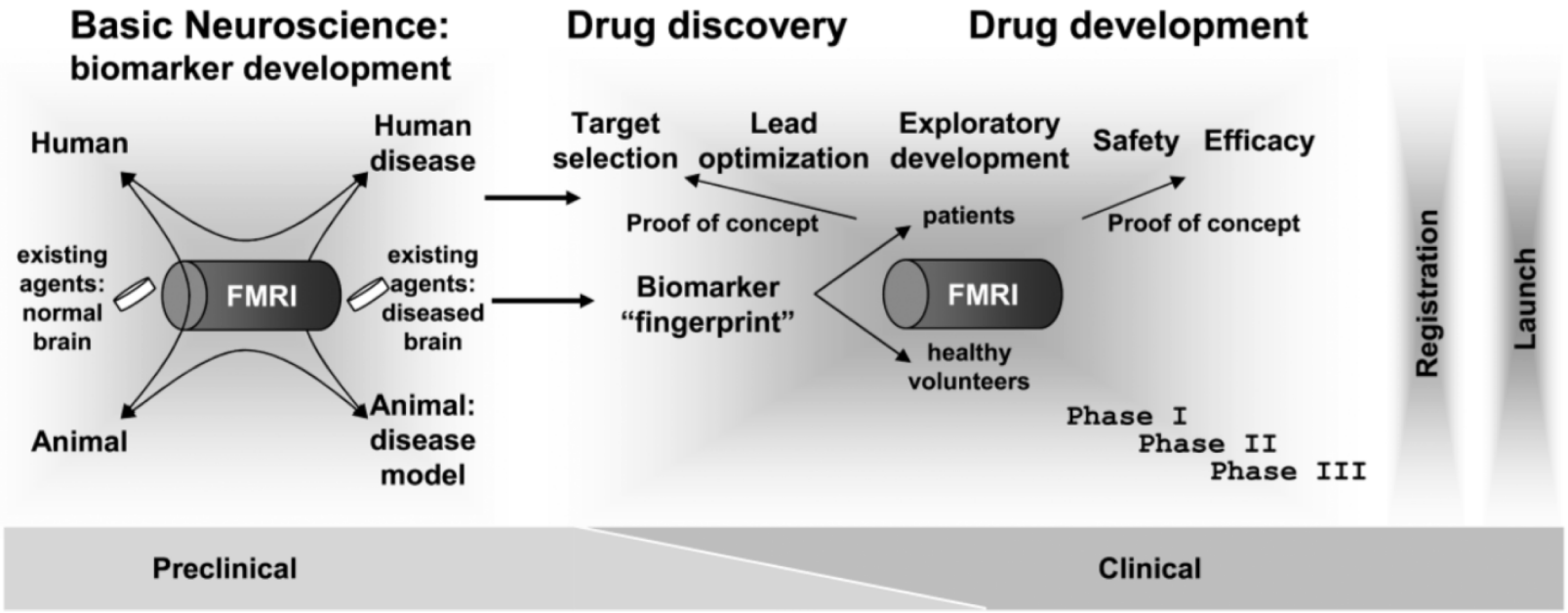
Only 22 novel drugs were approved last year—
a 57 percent drop from approvals in 2015.



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

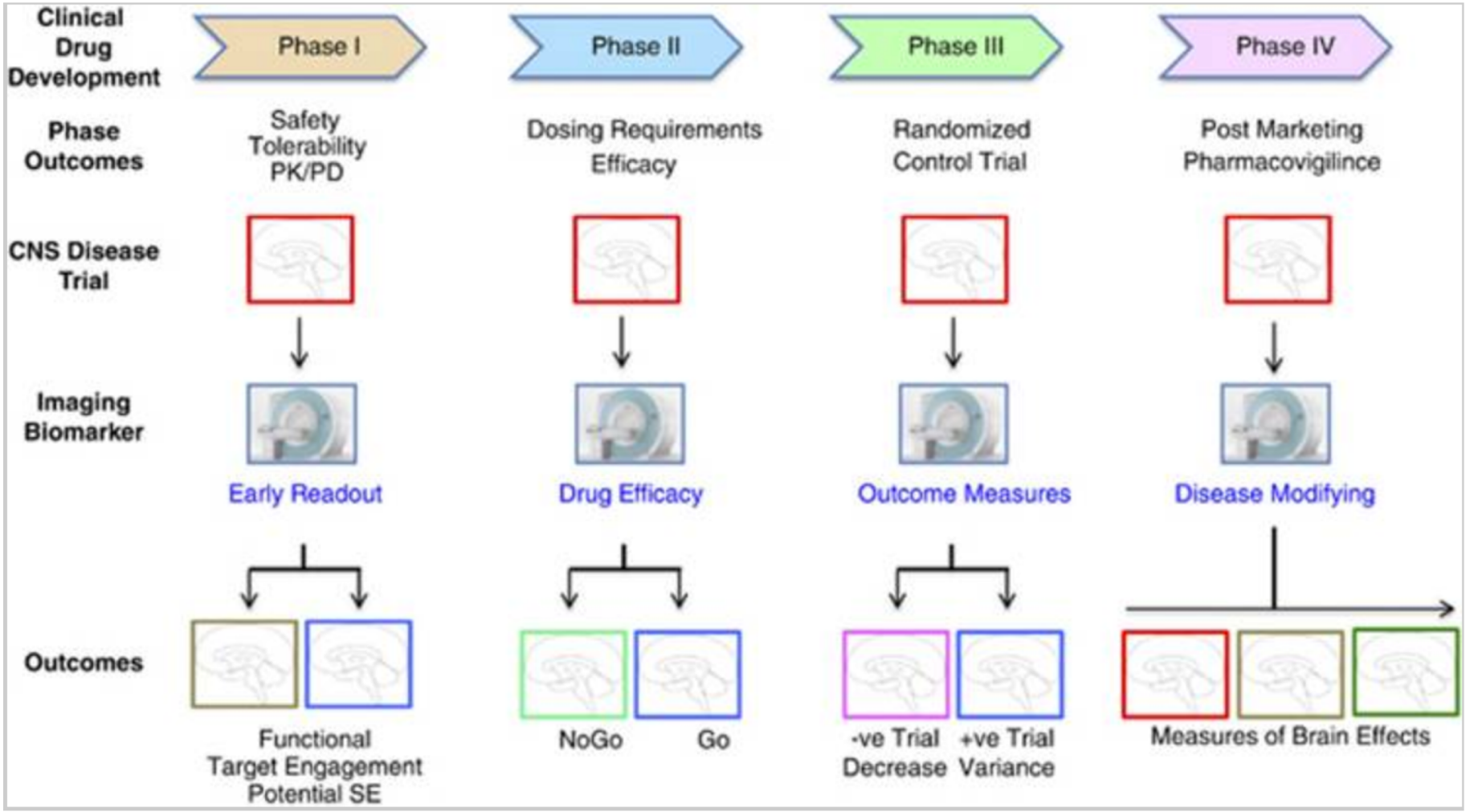
(CNS) Drug development



- 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

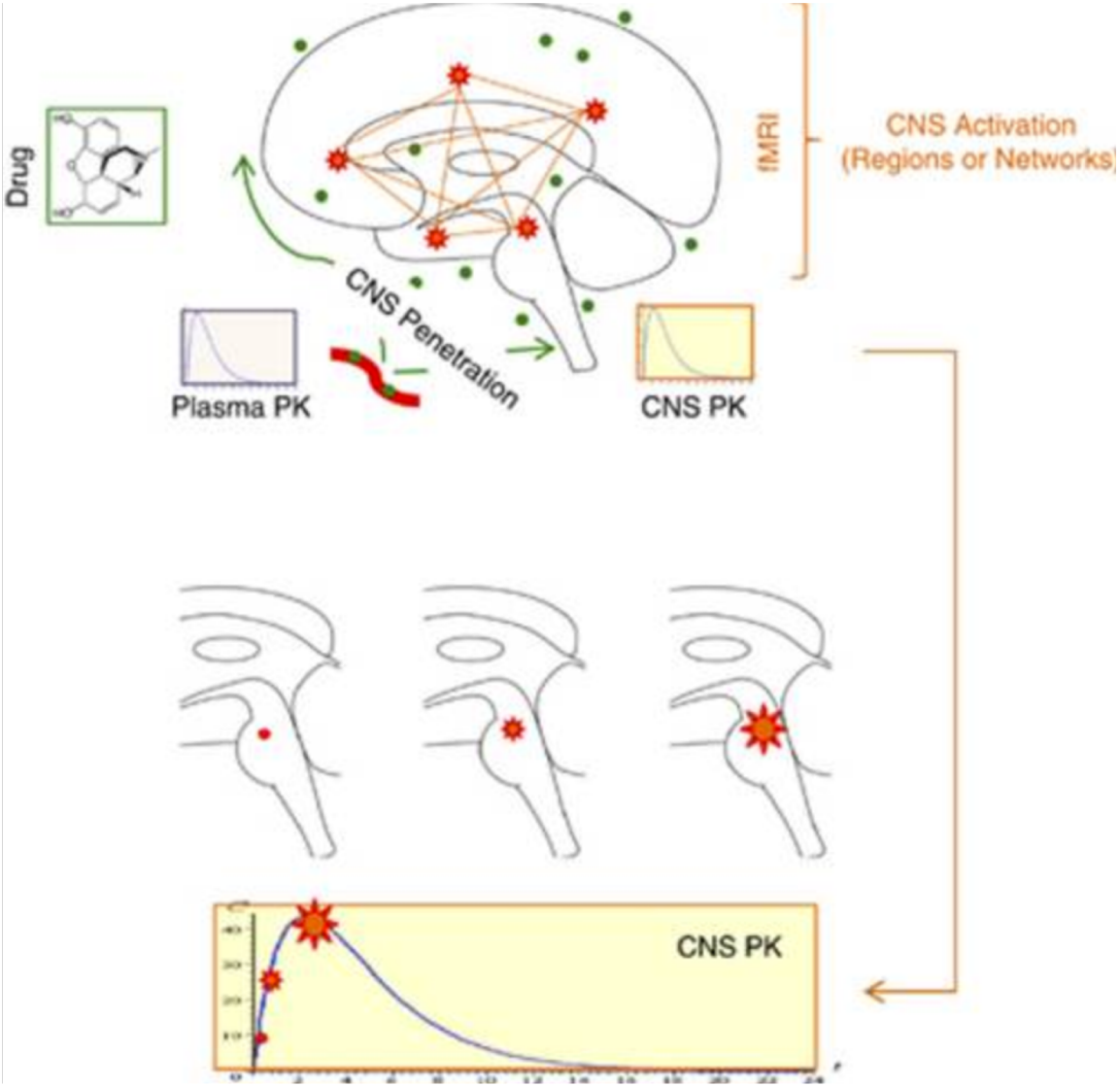
Wise, RG, et al, JMRI, 23:862–876 (2006)

Role of imaging in clinical trials



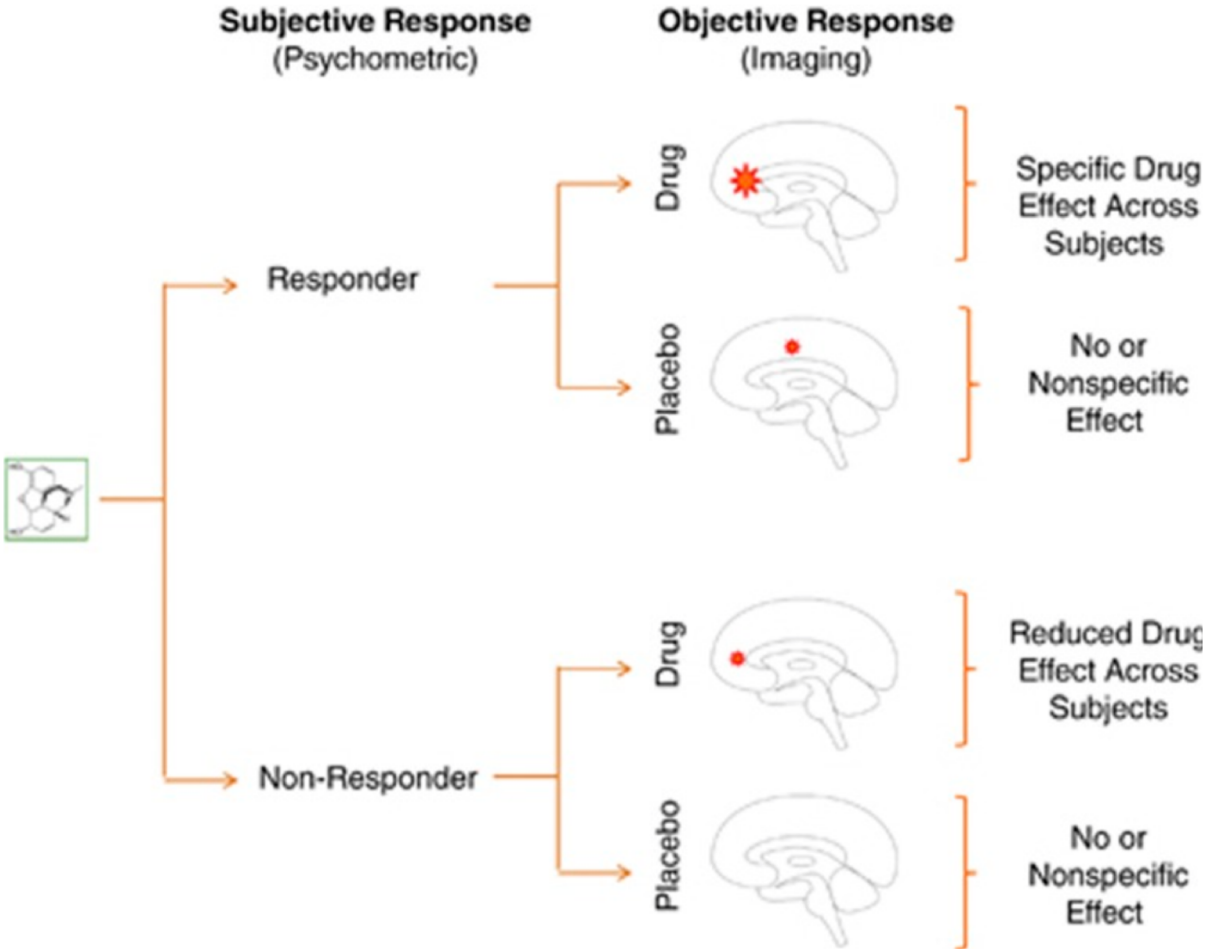
Borsook, D. et al, Transl Psychiatry. 2013 Jul 16;3:e282

Drug penetration into the brain



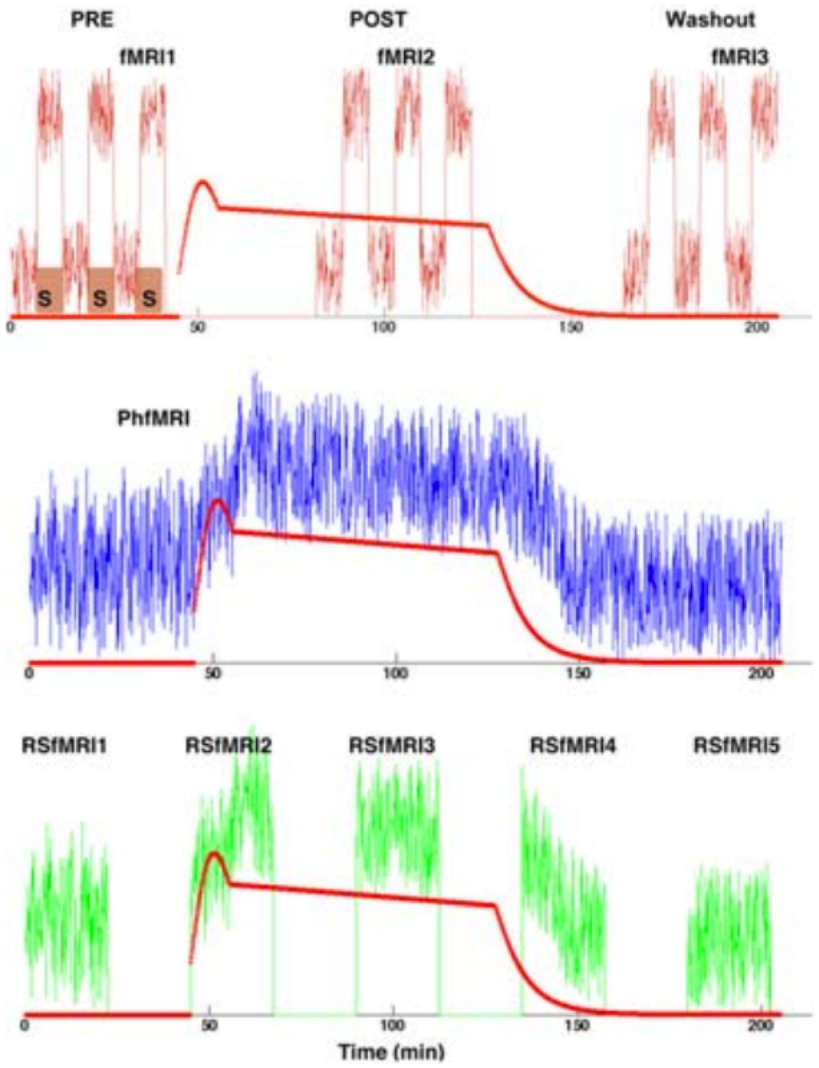
Borsook, D. et al, Transl Psychiatry. 2013 Jul 16;3:e282

Adjunct to subjective response



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

Study design

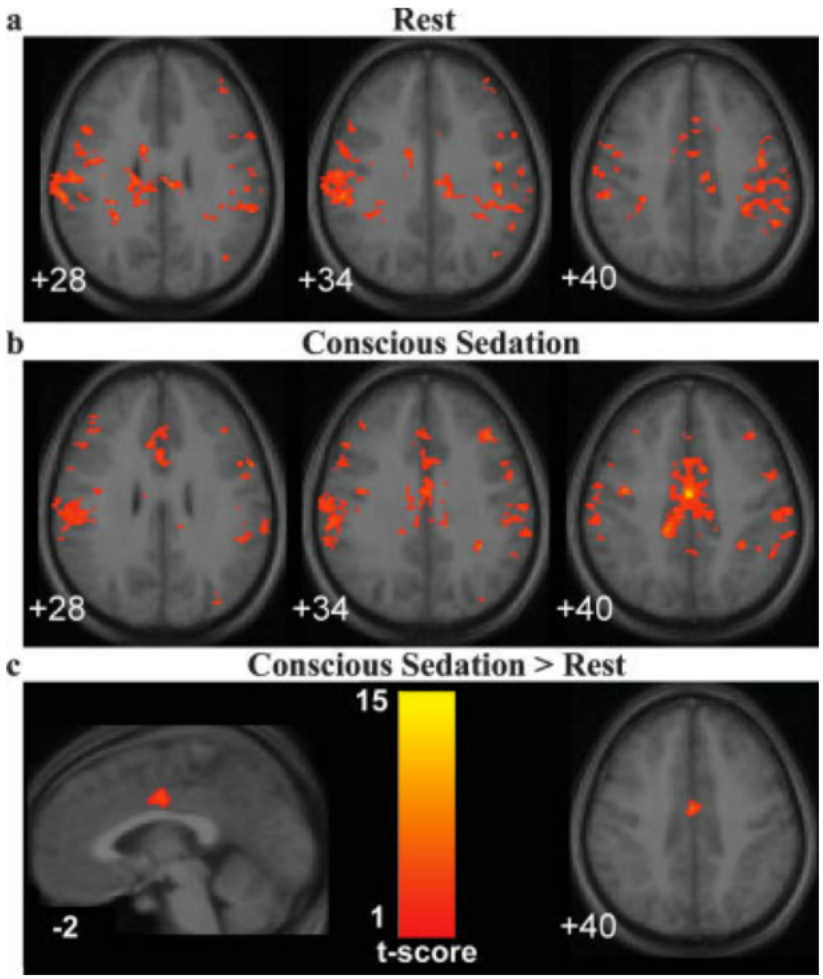


Khalili-Mahani N et al Human Brain Mapping. 2017.

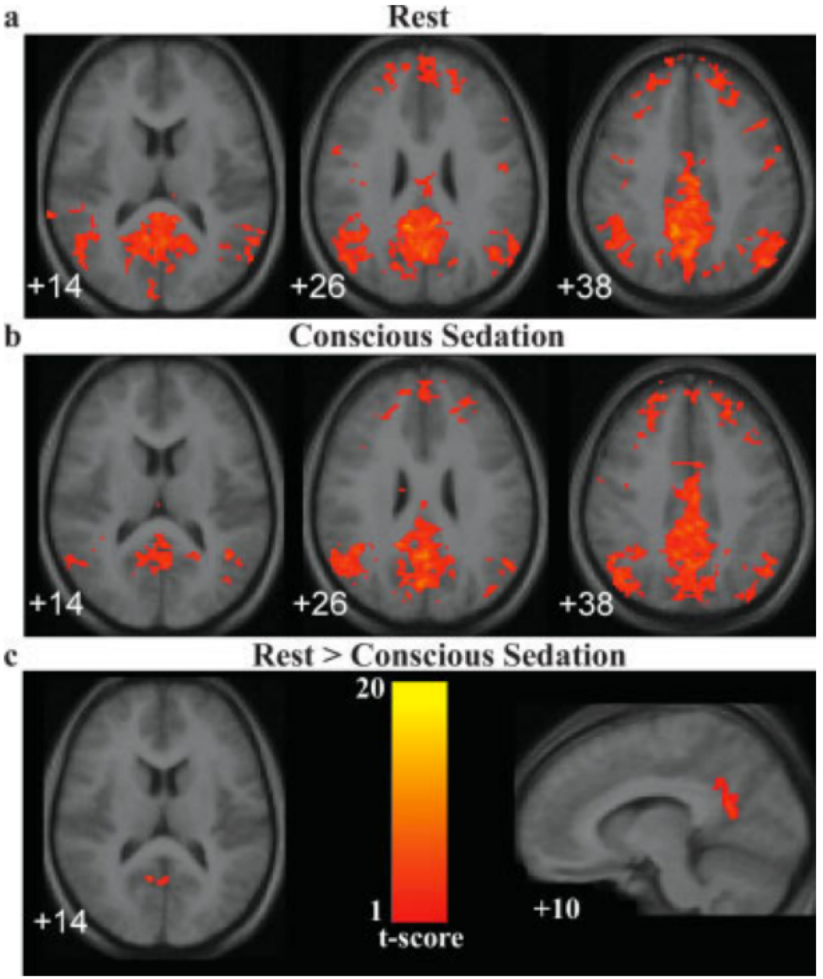
Resting state changes

- Midazolam sedation

Sensory motor

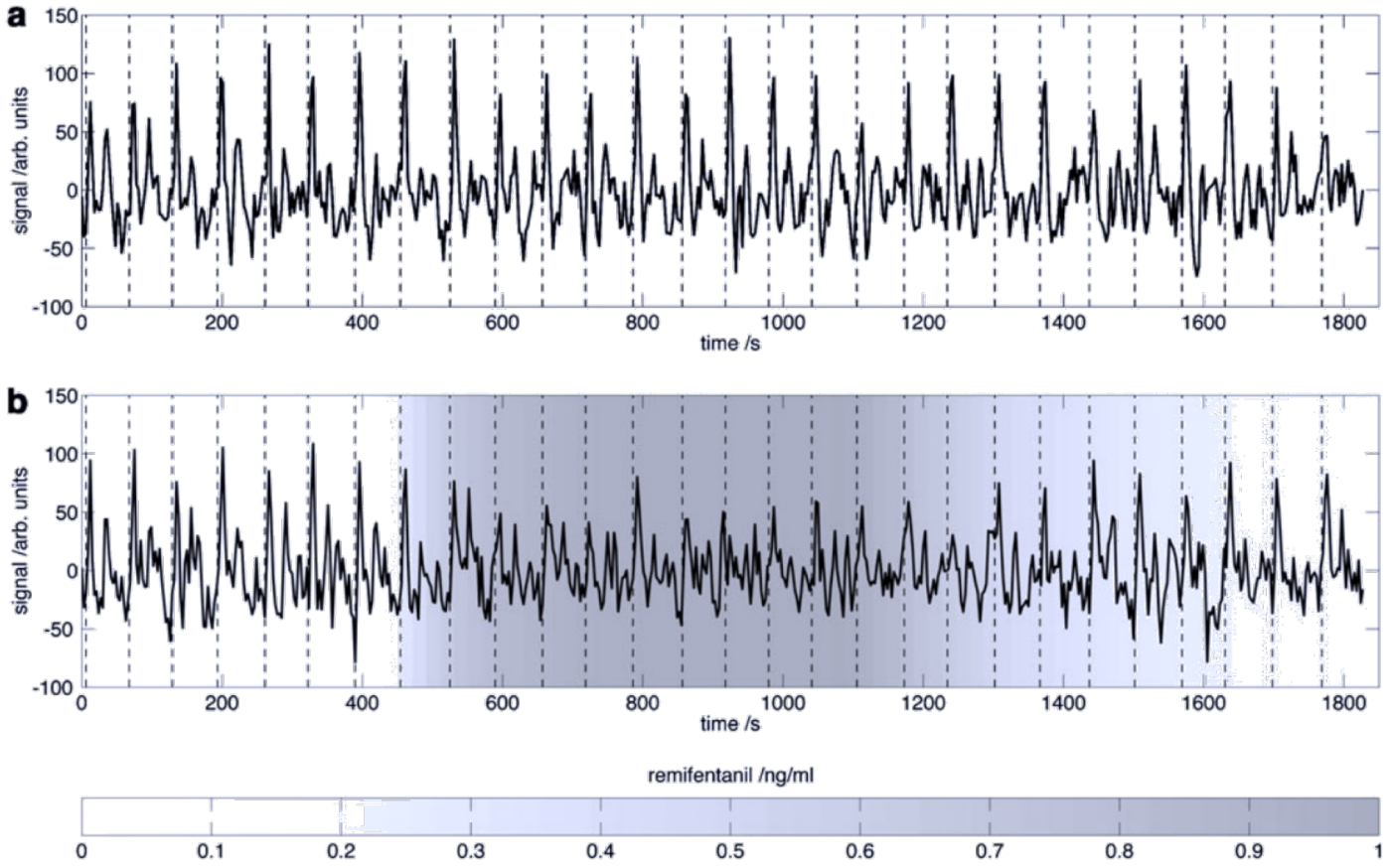


Default mode



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

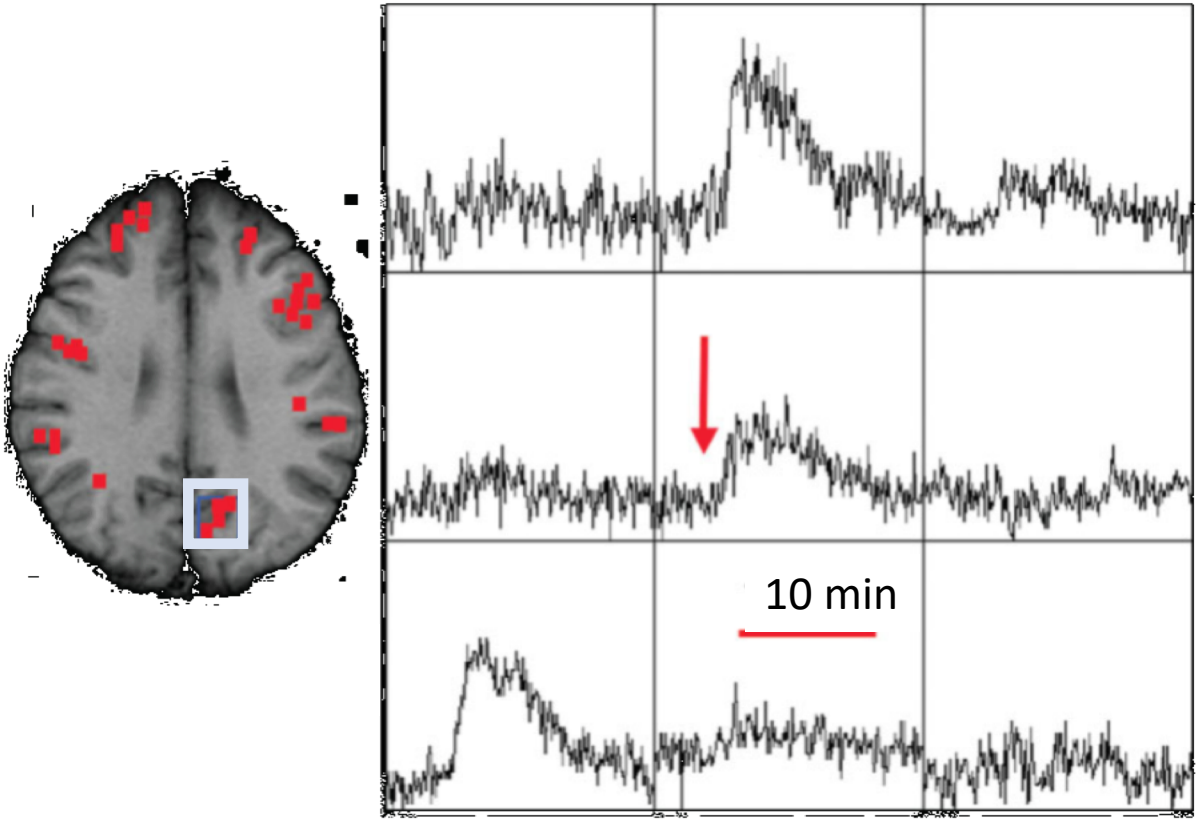
Response changes

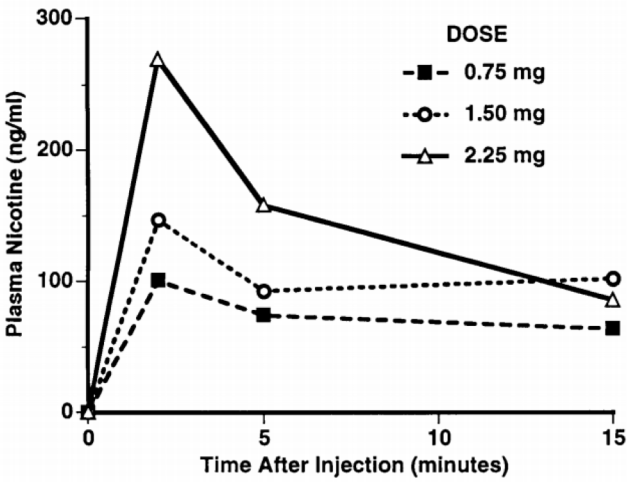


- Decrease in the response to painful stimulus (dashed lines) during drug administration

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

Acute drug response

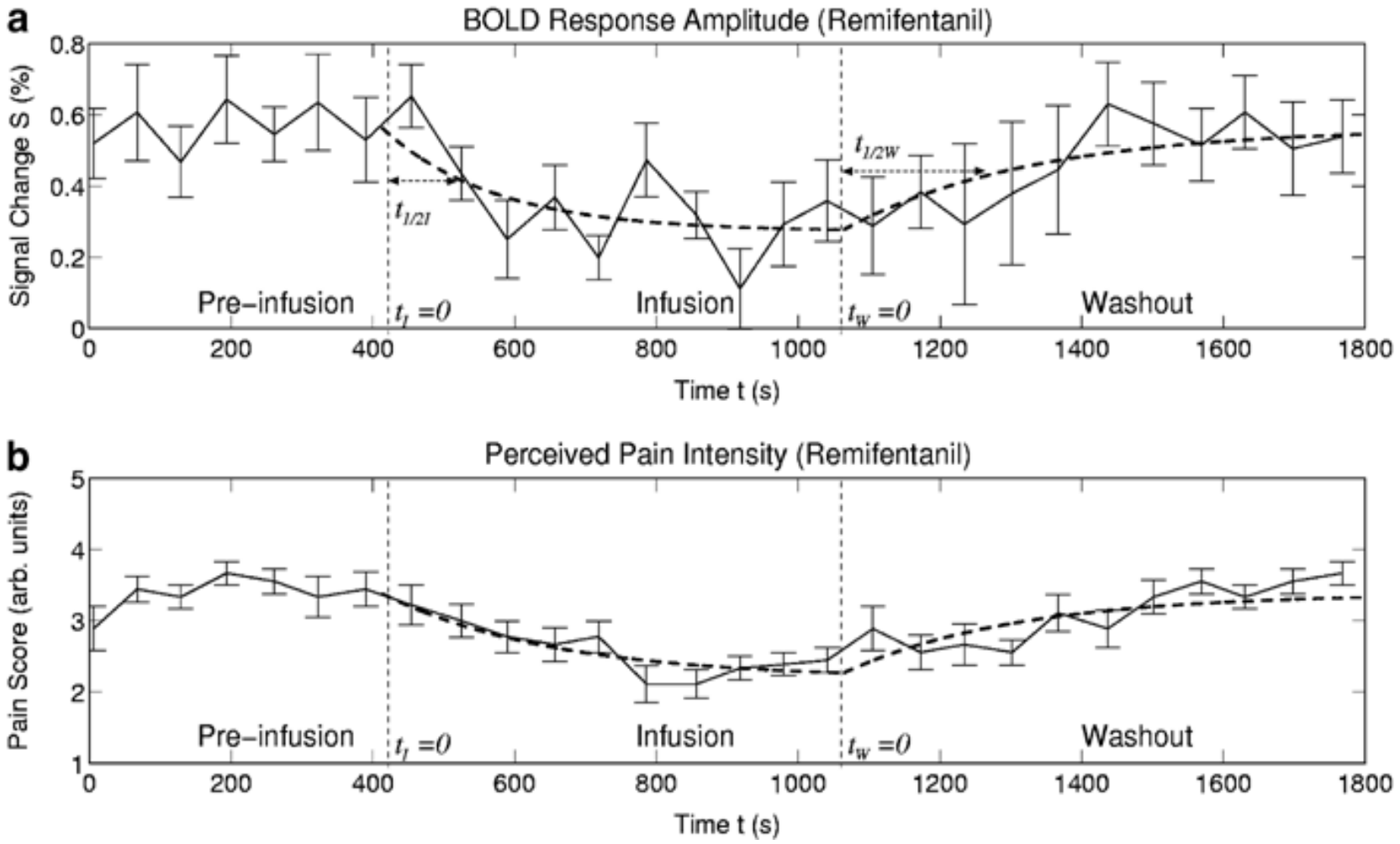




- 1 min injection of nicotine

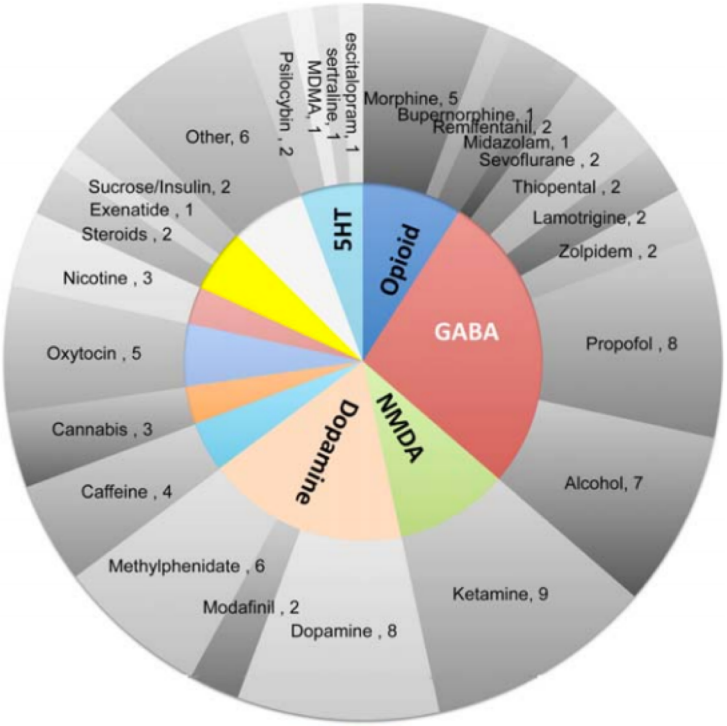
Stein E et al. Am J Psychiatry. 1998 Aug;155(8):1009-15.

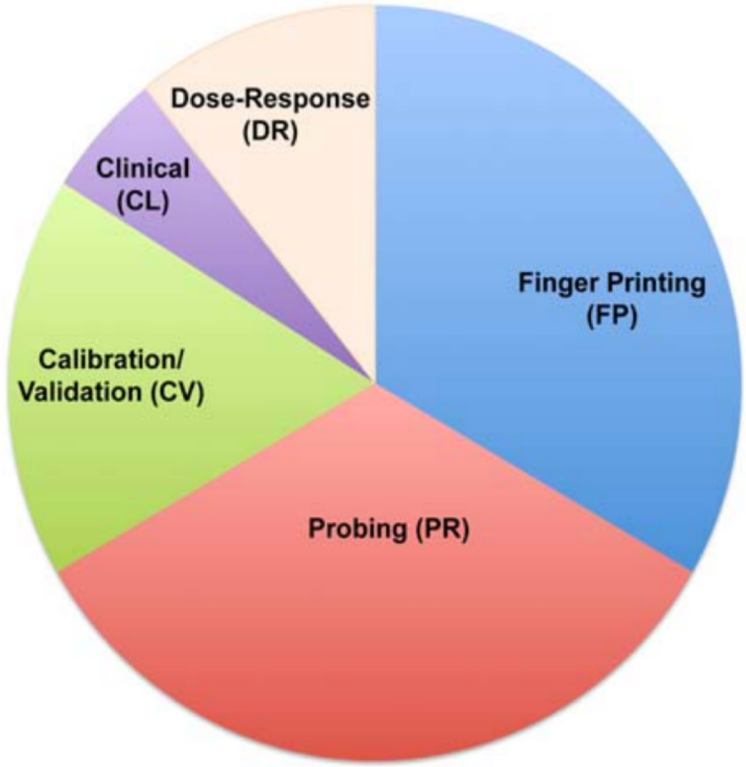
Pharmacokinetic response



Wise et al. Neuropsychopharmacology. 2004

Drugs tested





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

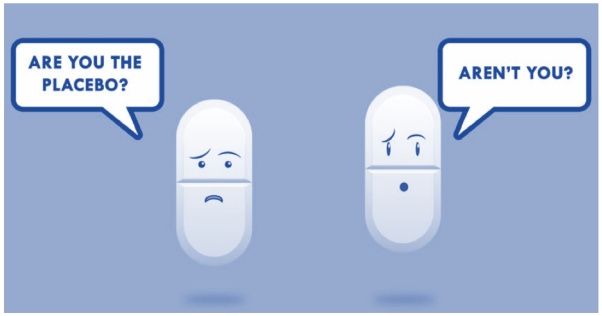
Possible confounding factors…. and solutions

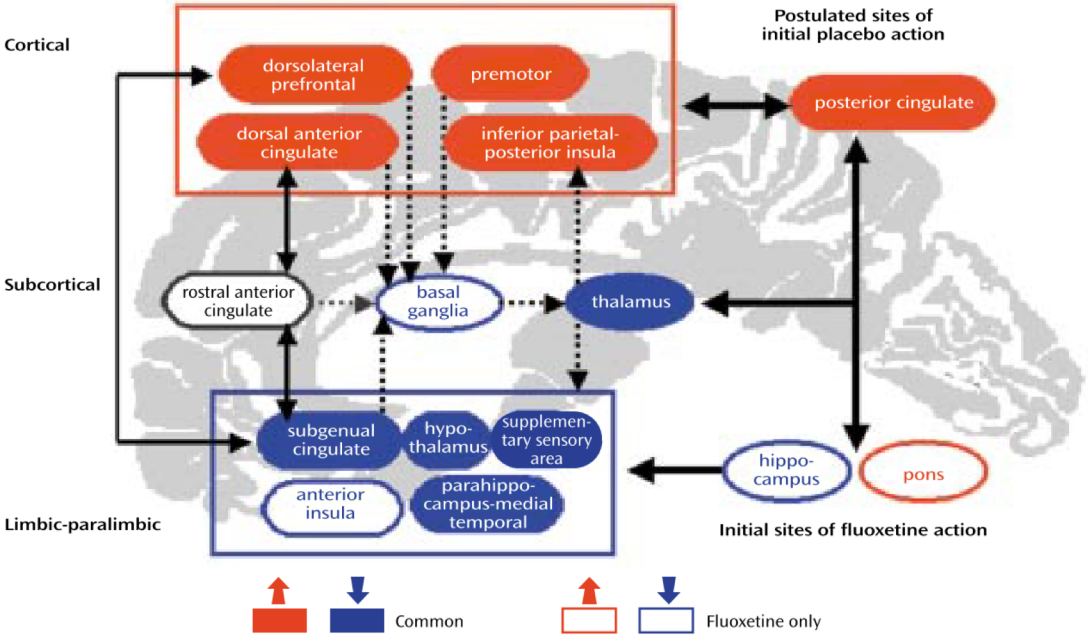
- Cognitive:
  - Placebo effect
    - Study design
- Acquisition:
  - These changes are slow (minutes) and on the same scale as drift artifacts
    - Use multi-echo fMRI?
- Signal:
  - BOLD signal is affected by changes in blood flow/volume
    - Use EEG-fMRI?
    - Use ASL?

Wise, RG. JMRI(2006)

Placebo effect

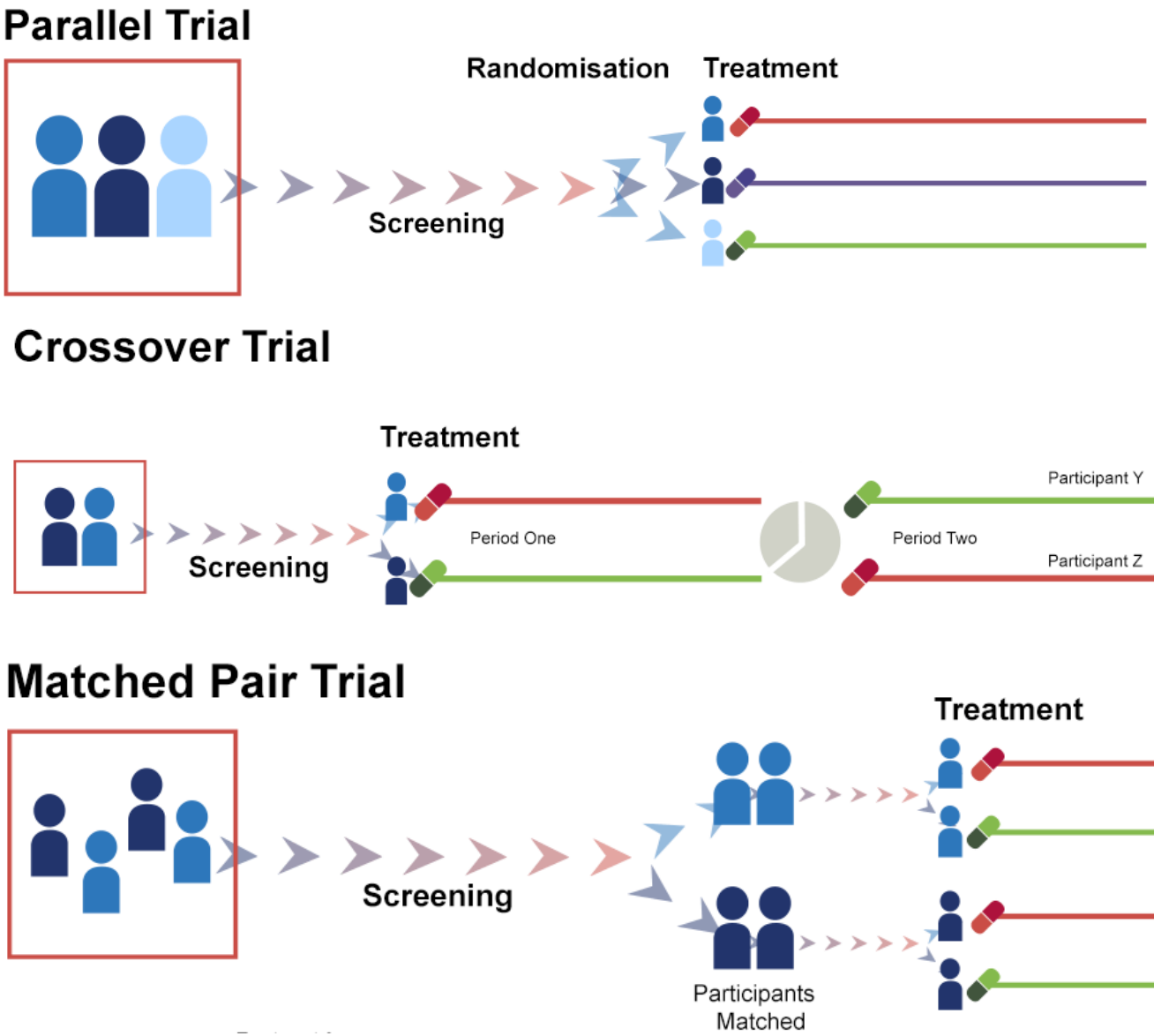
- Driven by the expectation that the treatment will bring relief
- Has been shown to have significant overlap with brain regions that are associated with drug response





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

Study design



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

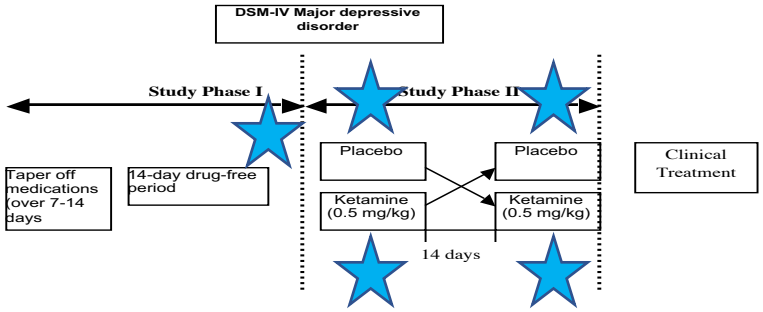
Study design considerations

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

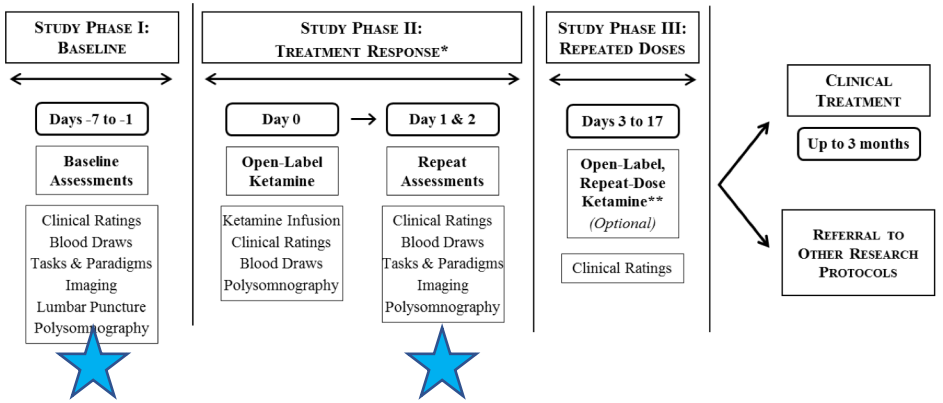
- Considerations
  - Number of subjects
  - Baseline?
  - Speed of drug action / duration / crossover effects
  - Reliability/repeatability of measurement

ETPB examples

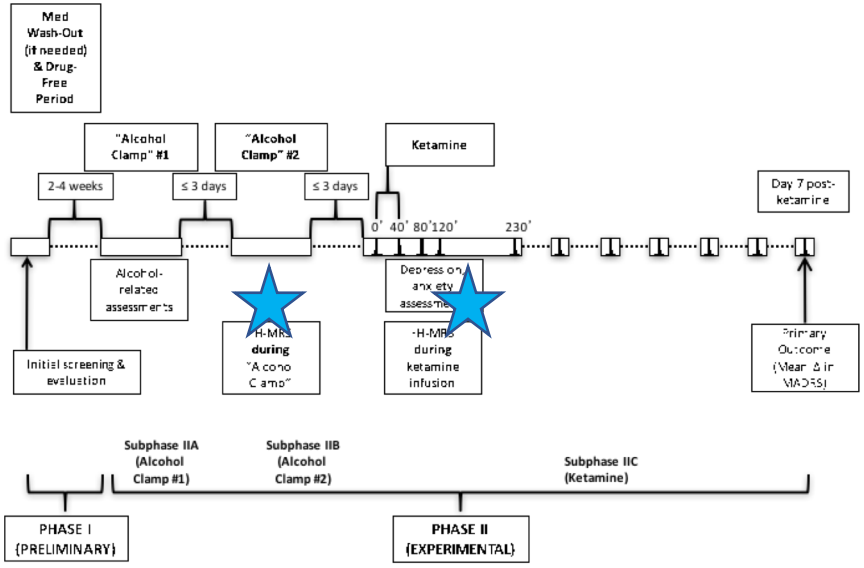
04-M-0222 – Ket-MOA



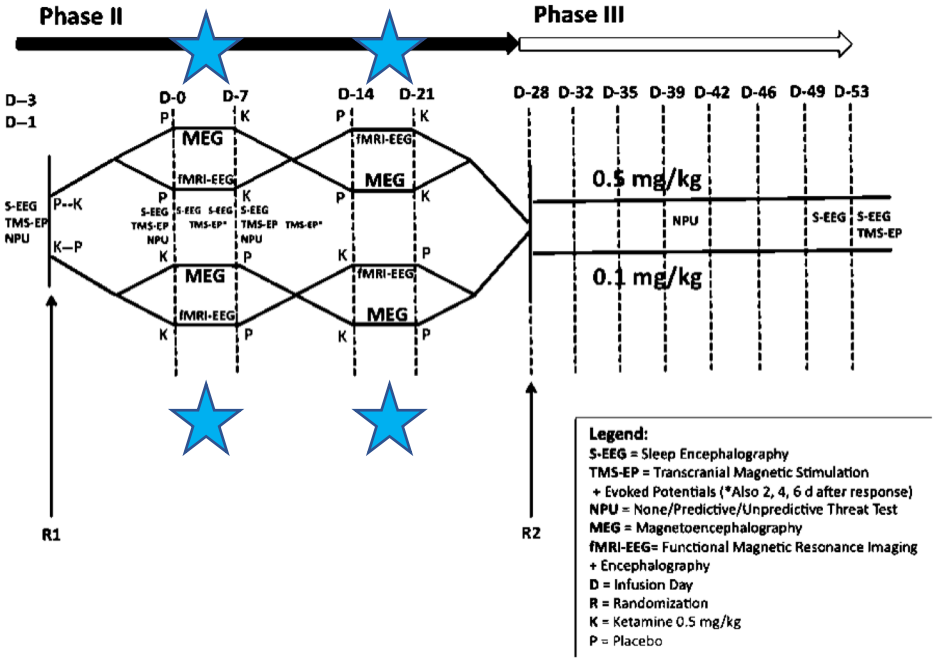
15-M-0188 - RISC



14-M-0085 – Ket-Alc



17-M-0060 – Repeat Dose



Schematics courtesy of Alex Noury

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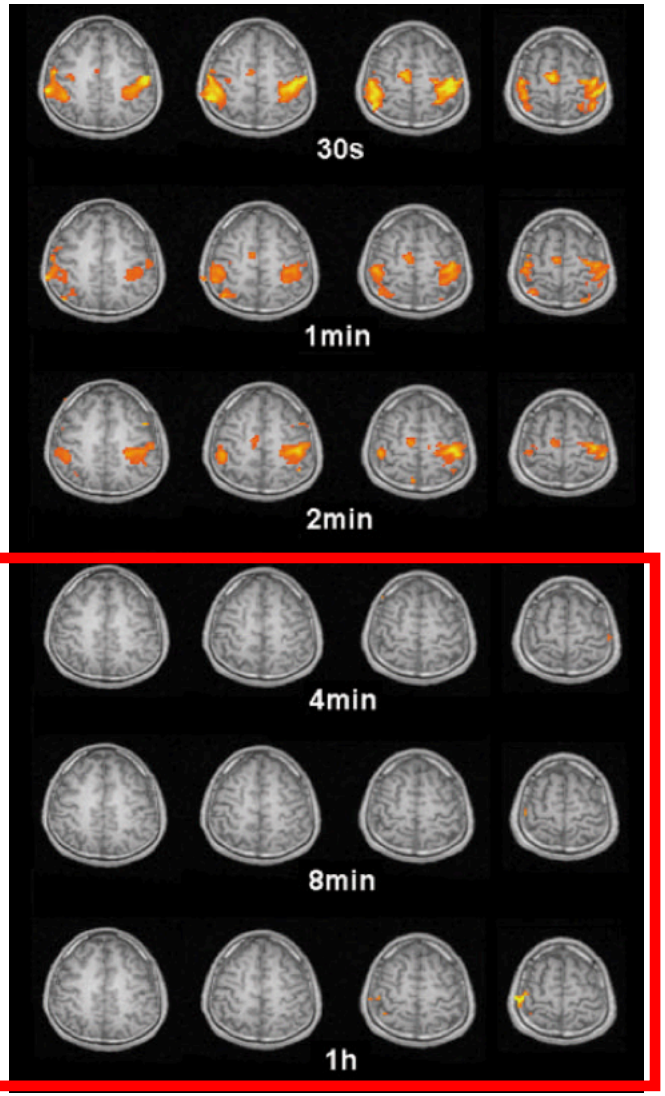
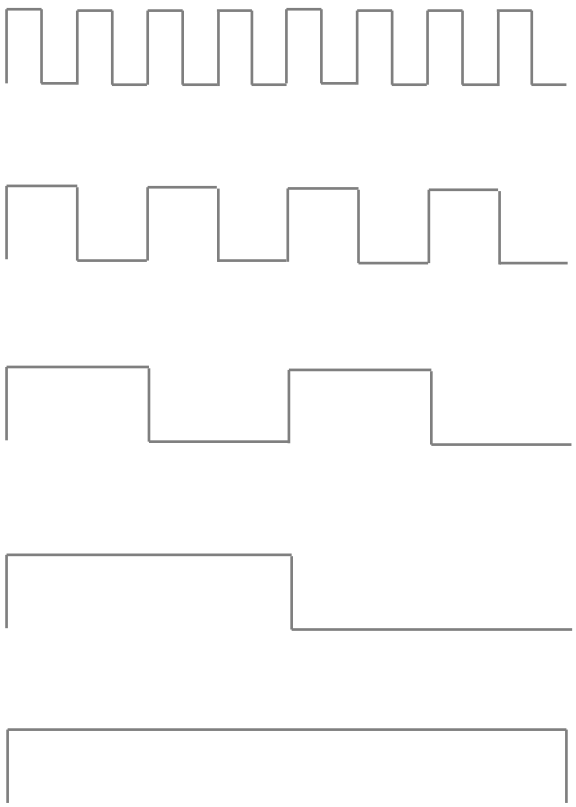
Wise, RG. JMRI(2006)

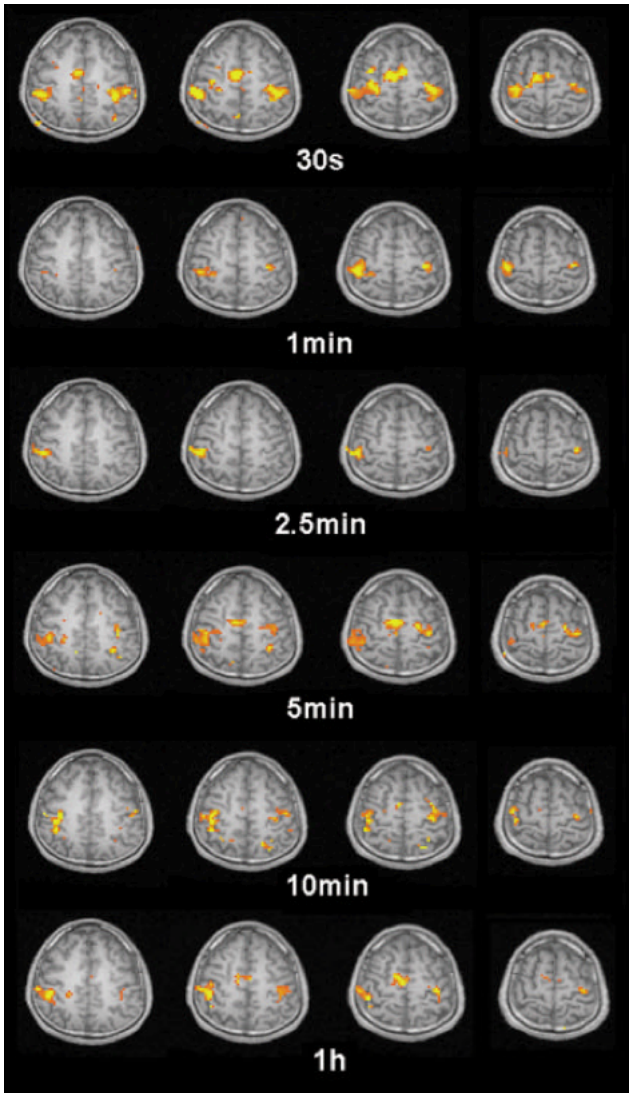
Imaging slow stimuli doesn't work well

BOLD





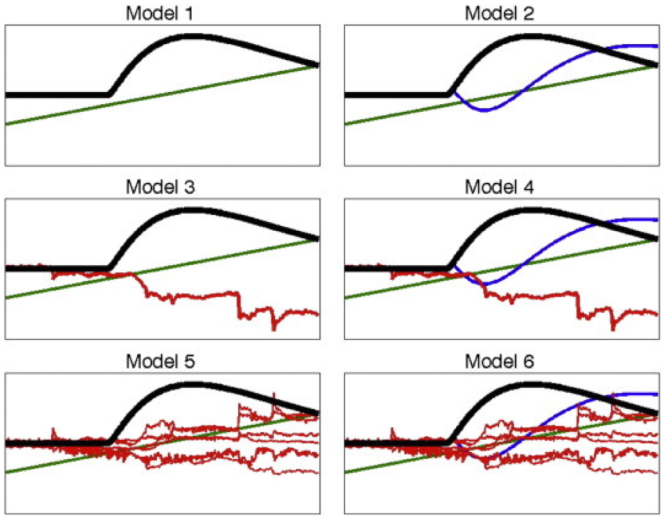
ASL

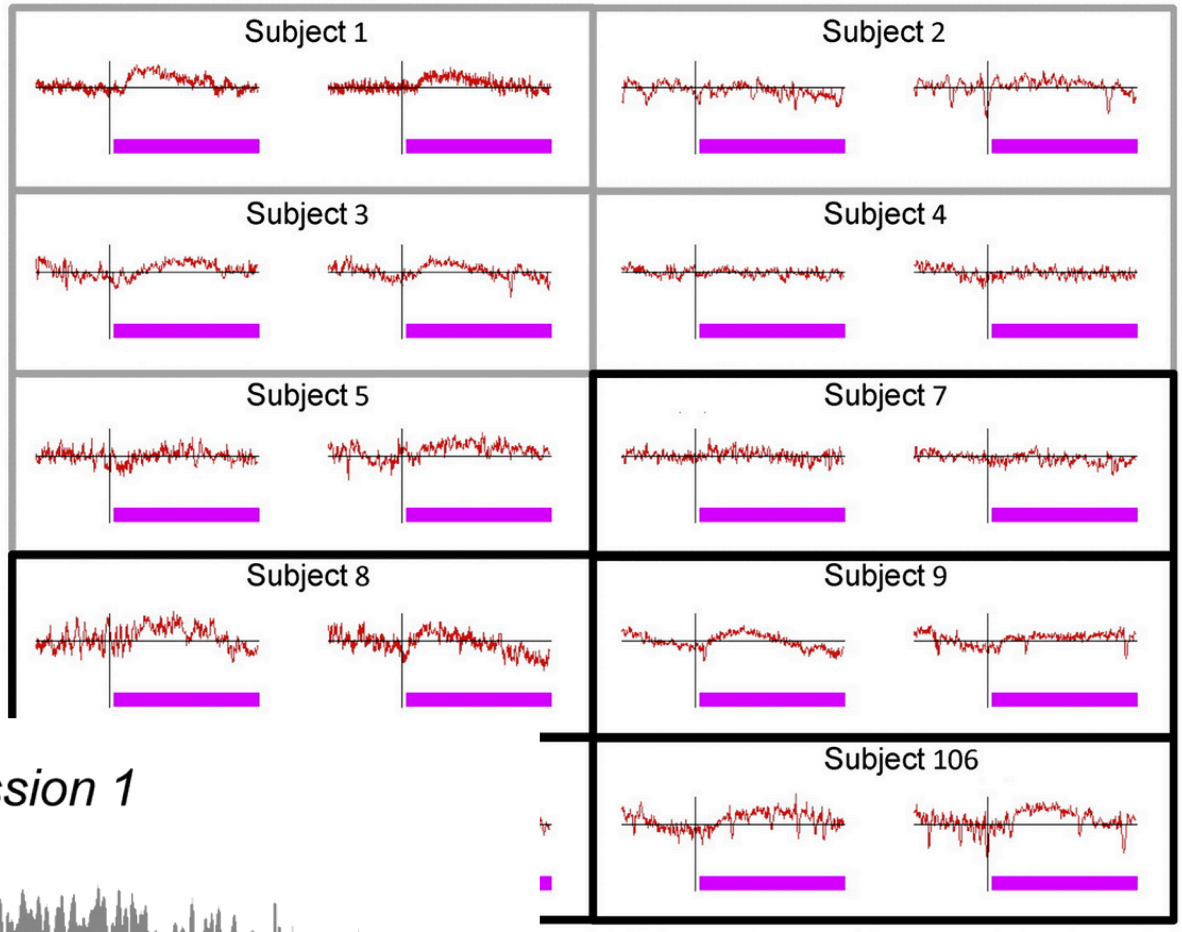


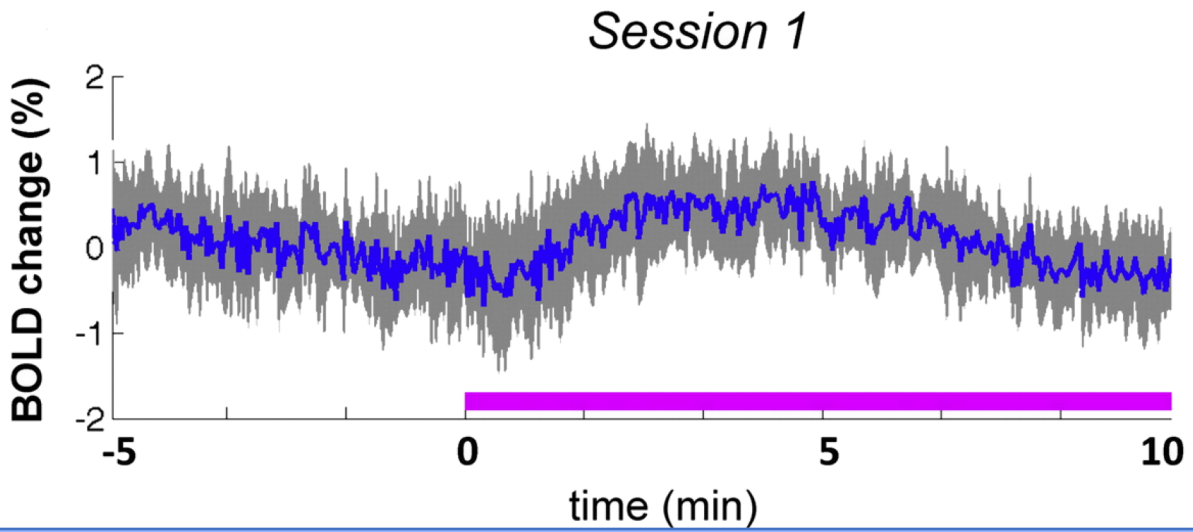
- BOLD has greater signal strength
- ASL has greater sensitivity for long duration stimuli

Wang et al, MRM (2003)

Response to ketamine infusion



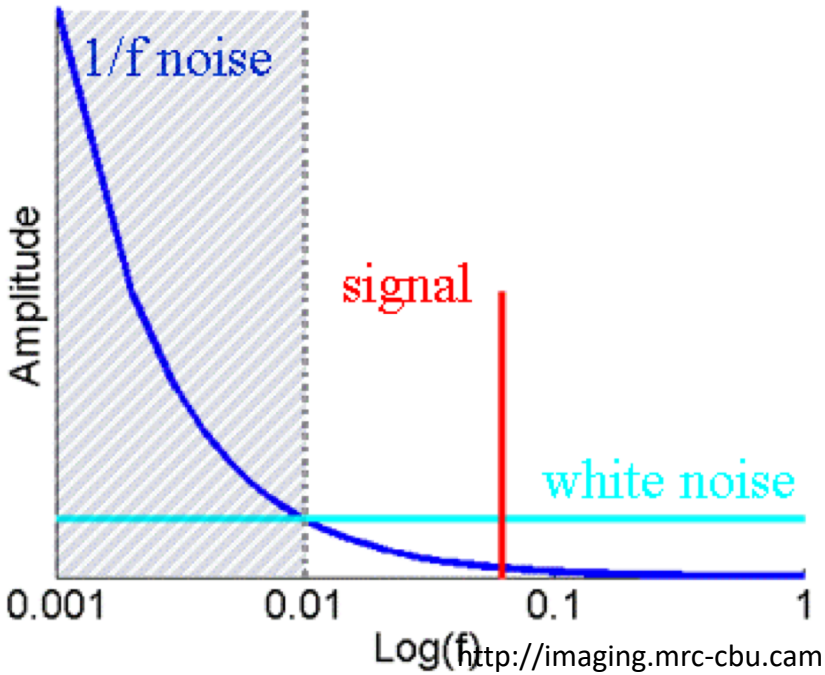




De Simoni et al, Neuroimage (2013)

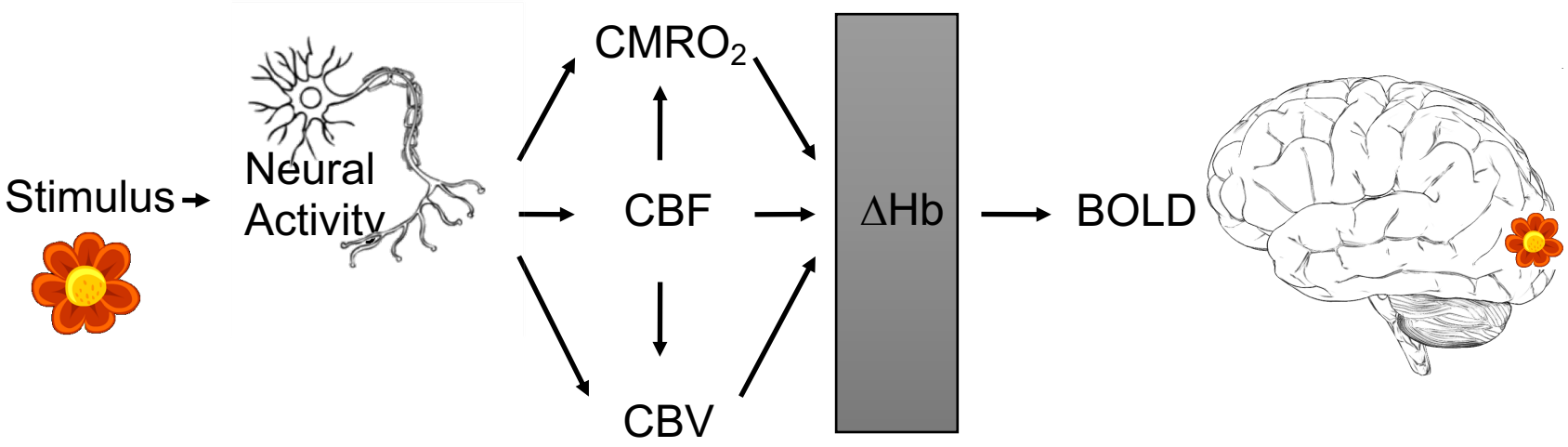
The problem

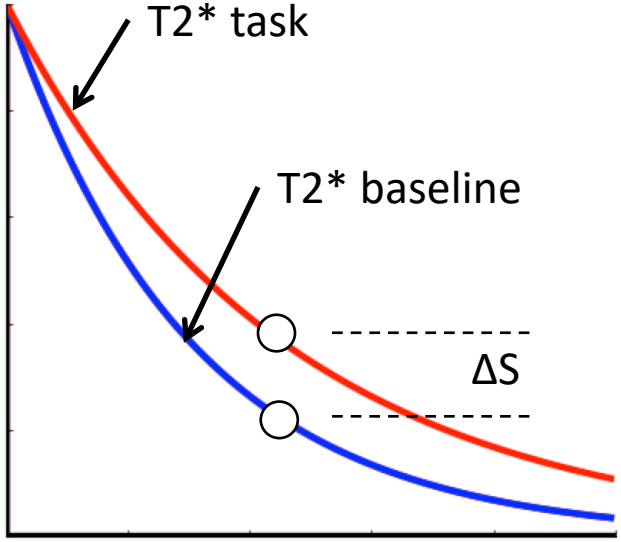
- With single echo data artifactual drifts are indistinguishable from BOLD signal
  - High pass filter, model
  - set the task frequency higher
  - remove ICA components…



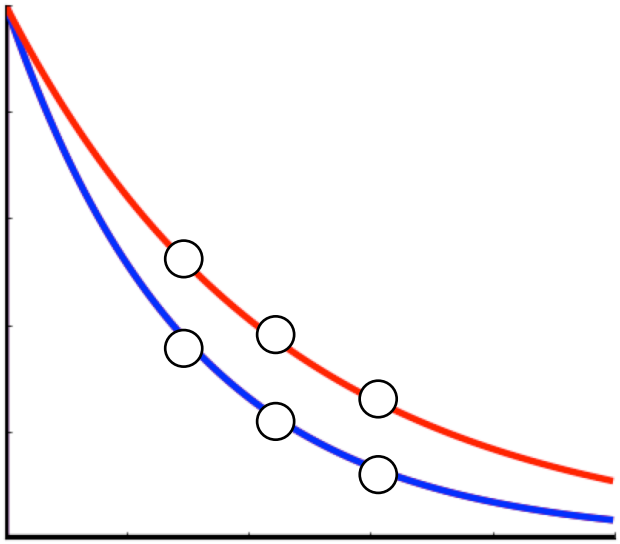
http://imaging.mrc-cbu.cam.ac.uk/imaging/DesignEfficiency#A_fig8

What does fMRI measure?





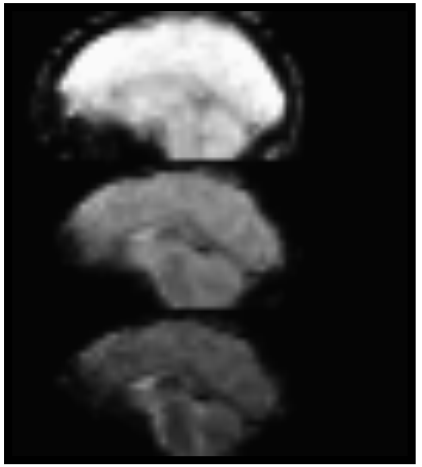
Multi-echo (ME) fMRI.

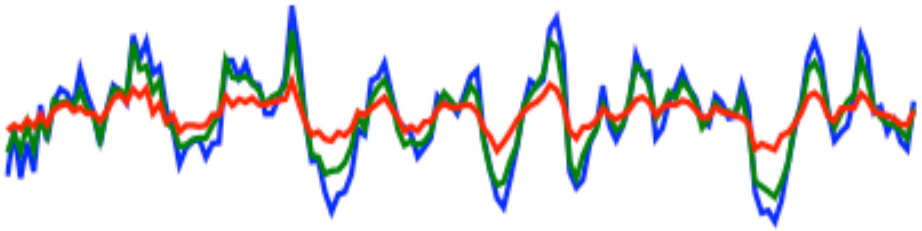


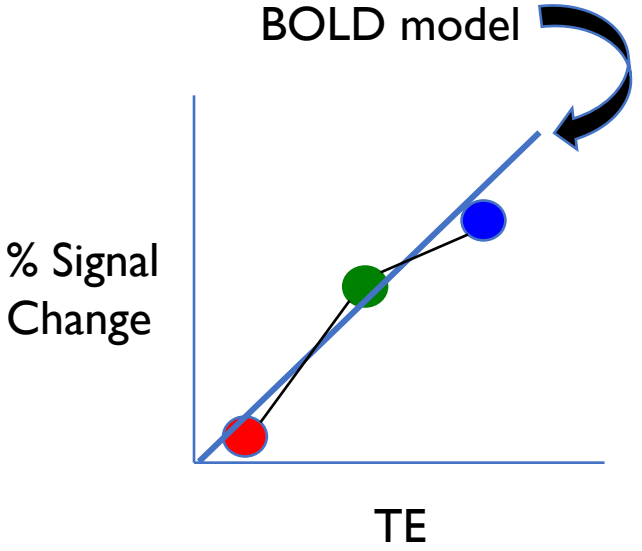
TE 1

TE 2

TE 3



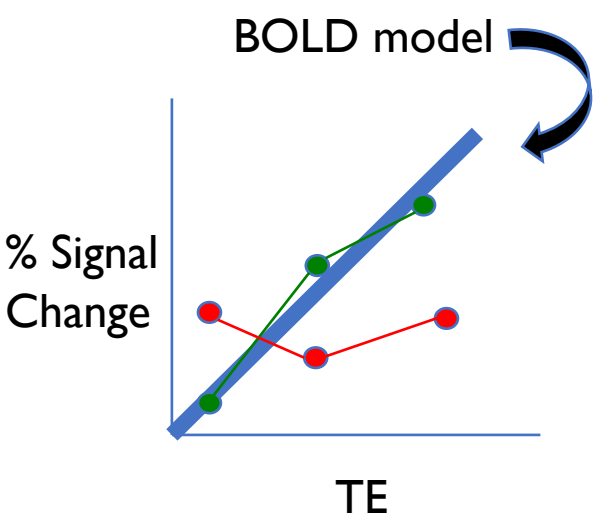


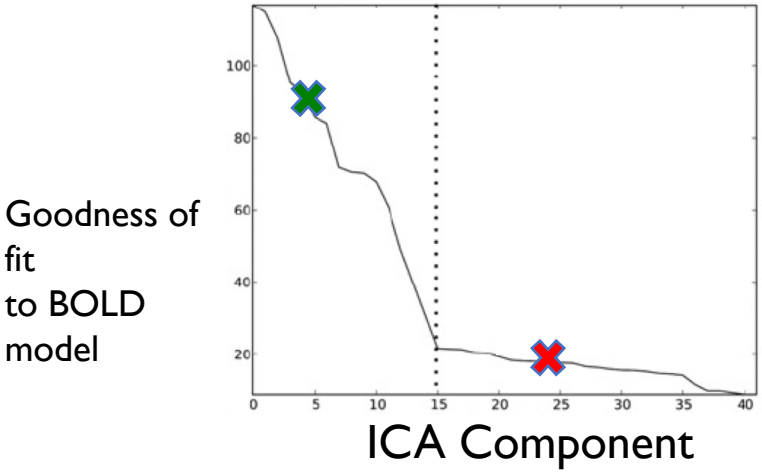


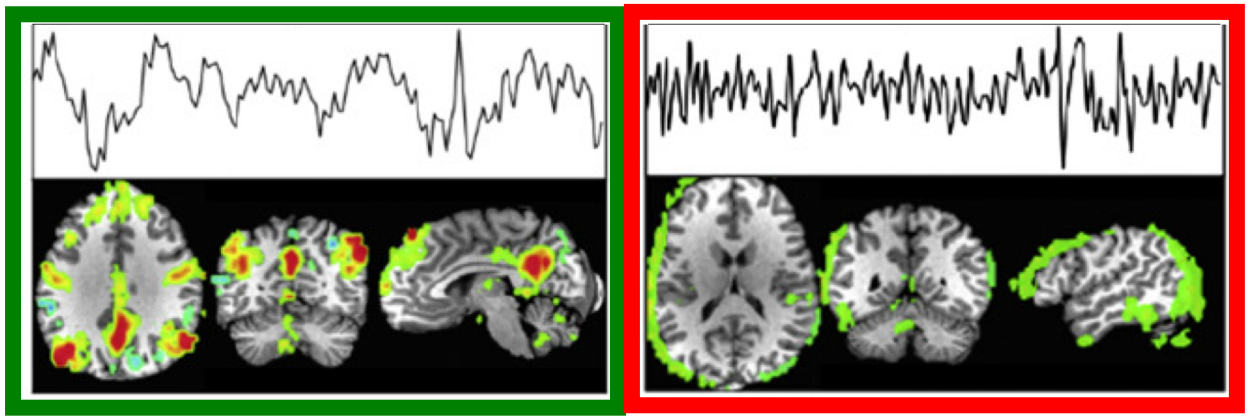
Kundu, P, Inati, S, Evans, JW et al (2012) NeuroImage Vol 60, Iss 3 2012 1759 - 1770

Multi-echo denoising

- Enables the identification of signals that scale with measured TEs

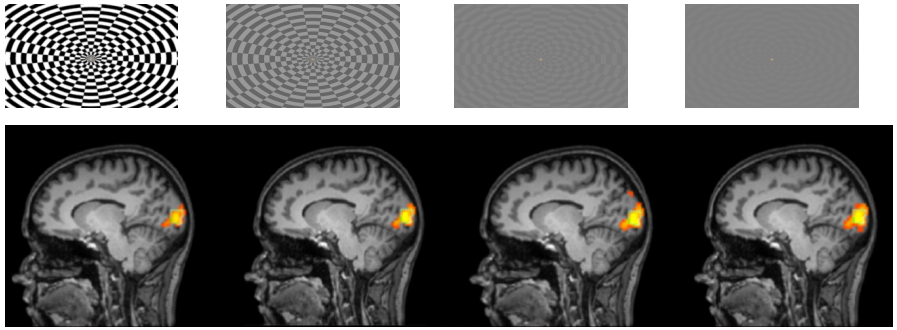


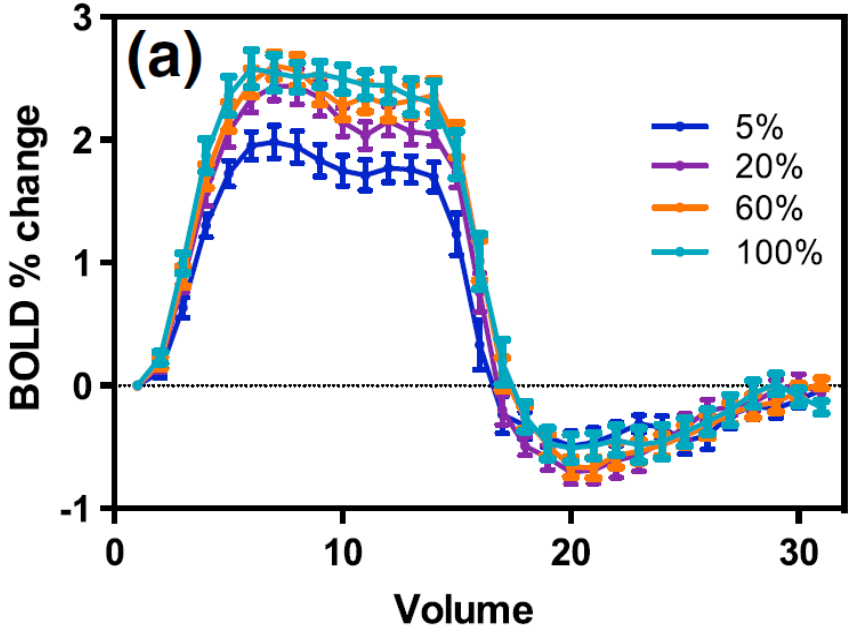


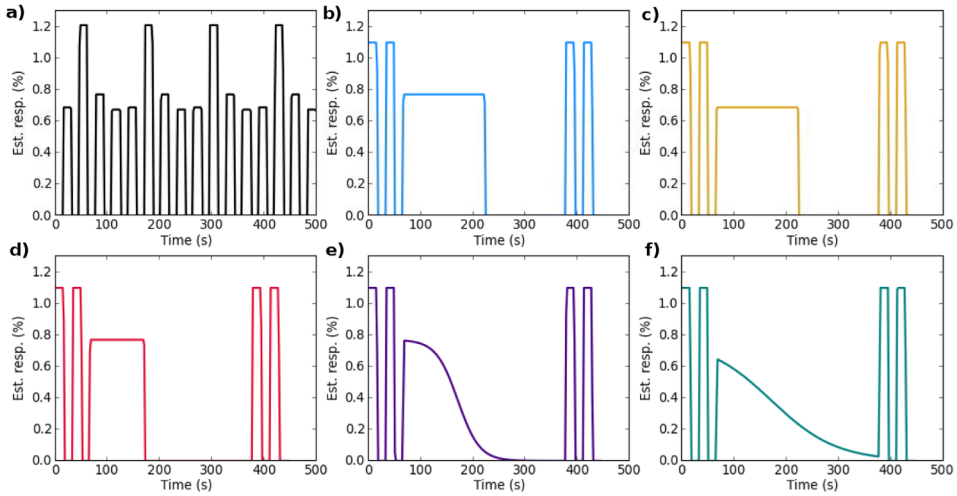


BOLD, EEG signals and visual contrast change.

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

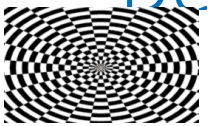


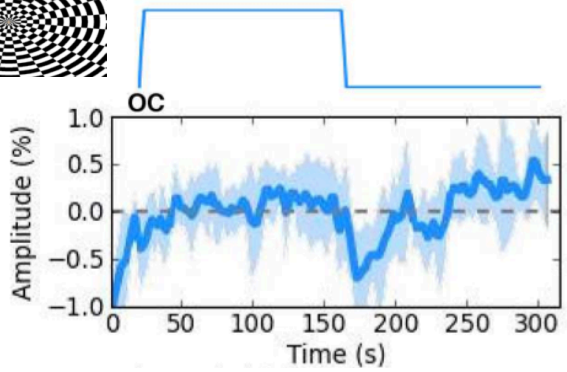


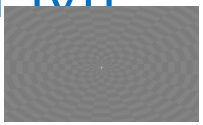


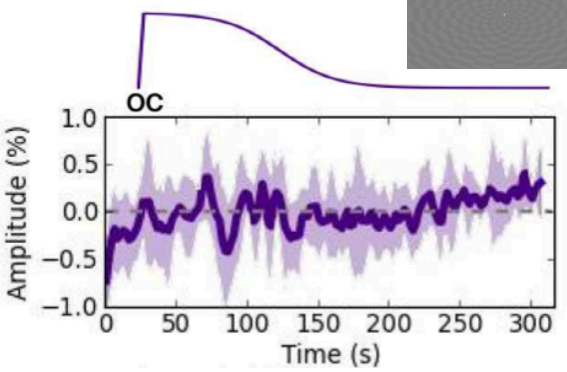
Chiachiaretta et al, Neuroimage (2013)

Detection of slow BOLD with ME







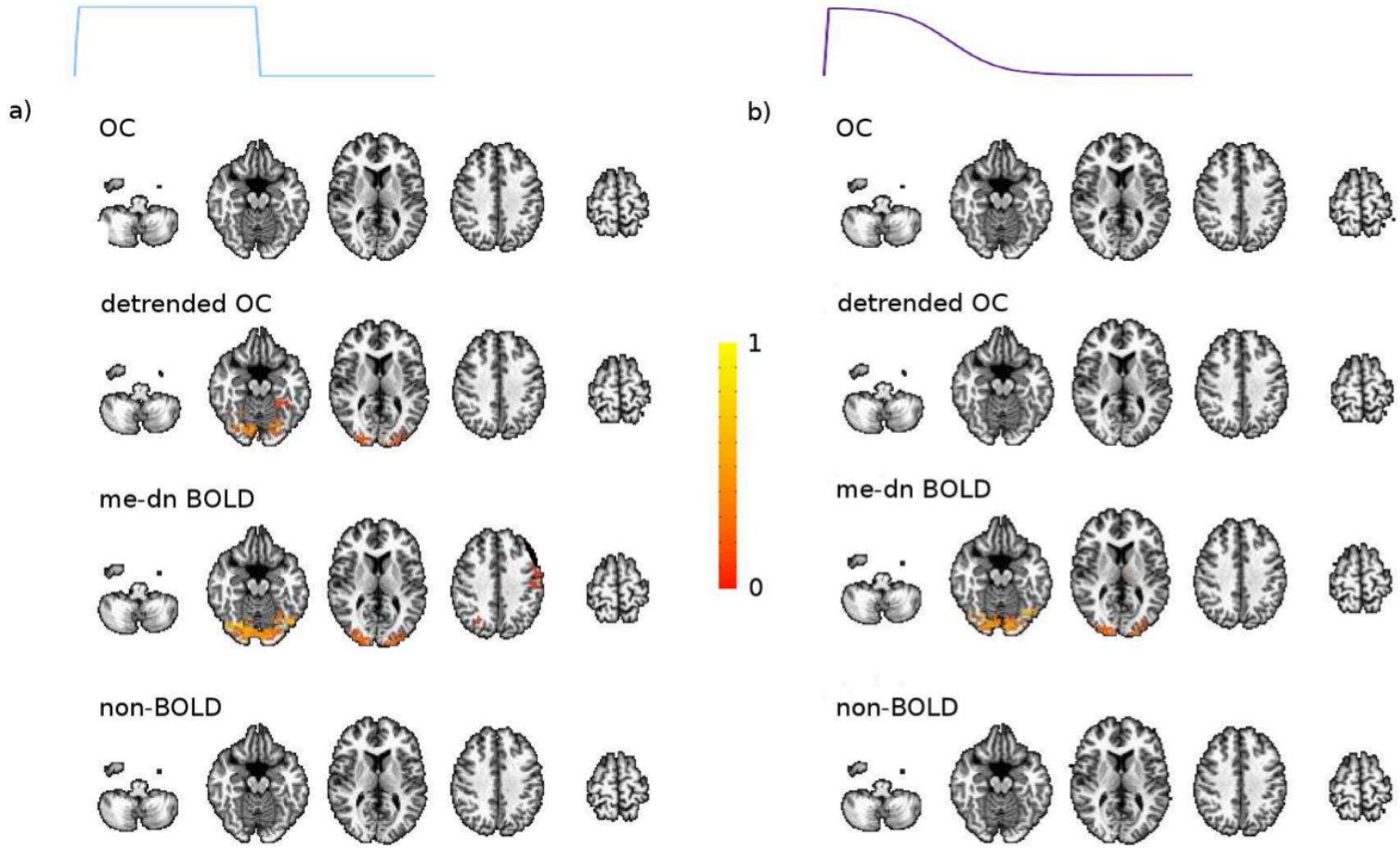


- Group average timeseries taken over voxels in V1 for a visual block and ramp contrast task
- The thick line is the mean and the shading is the standard error.
- Slope task is not visible in OC or detrended data
- Both tasks are clear in the me-dn BOLD data
- The scanner specific drift is visible in 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

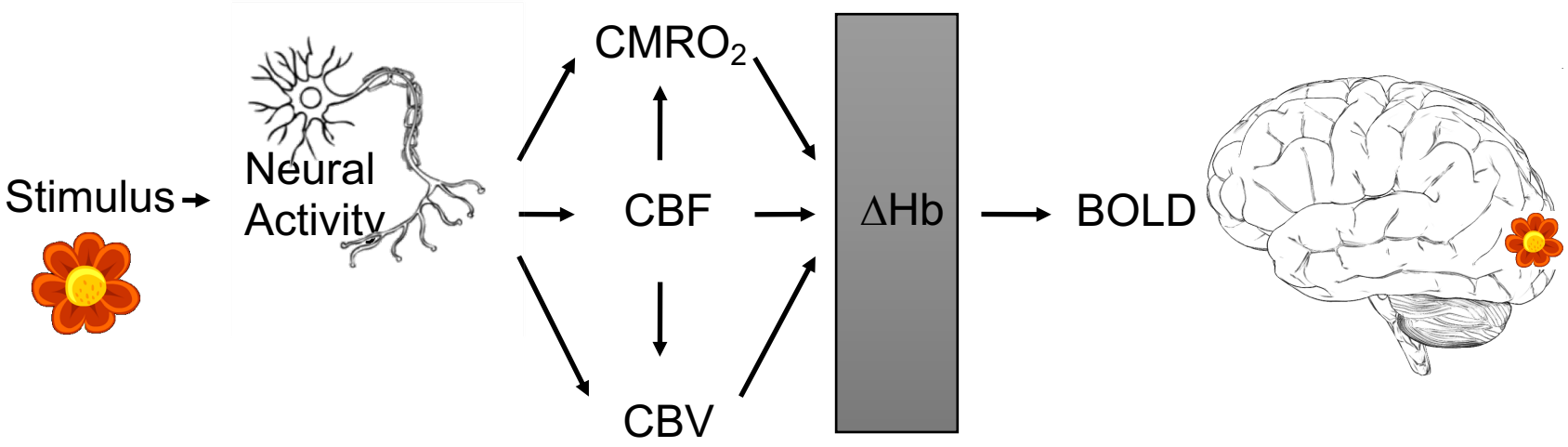
Evans, J.W., et al. NeuroImage 105, 189–197.

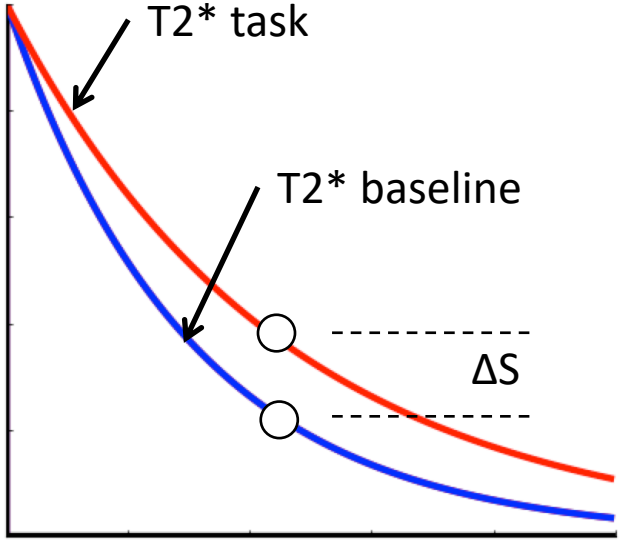
Possible confounding factors…. and solutions

- 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
  - Physiological changes
    - Use EEG-fMRI?
    - Use ASL?

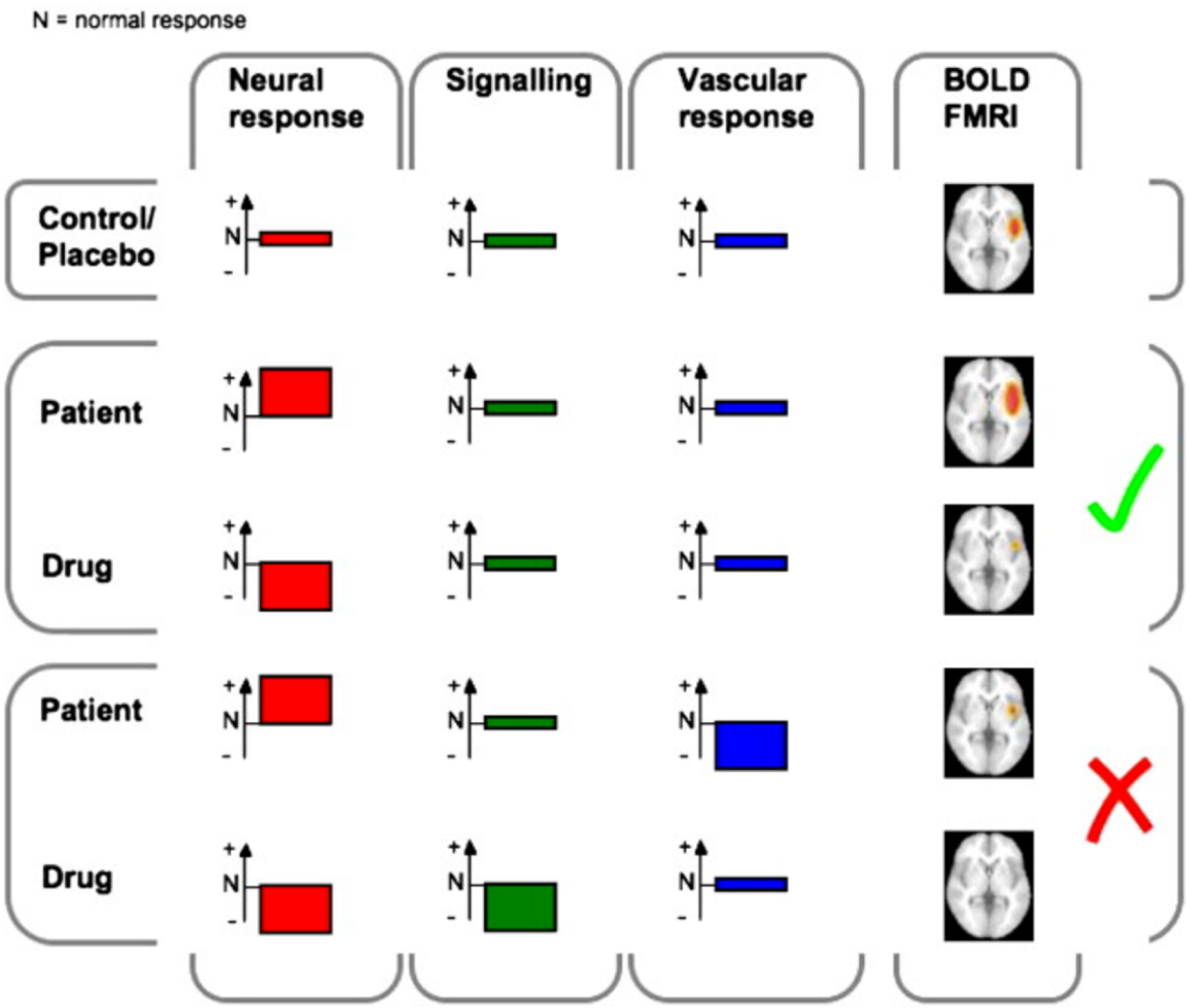
Wise, RG. JMRI(2006)

What does fMRI measure?





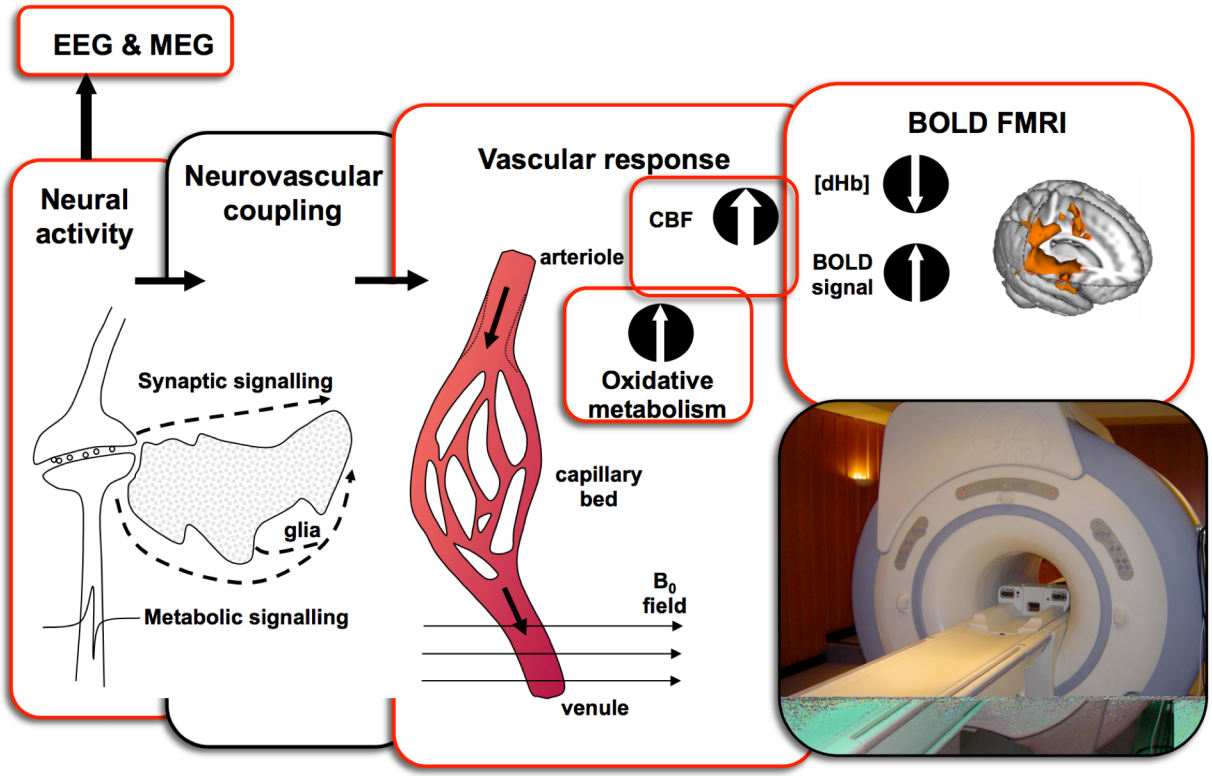
Neural or vascular changes?



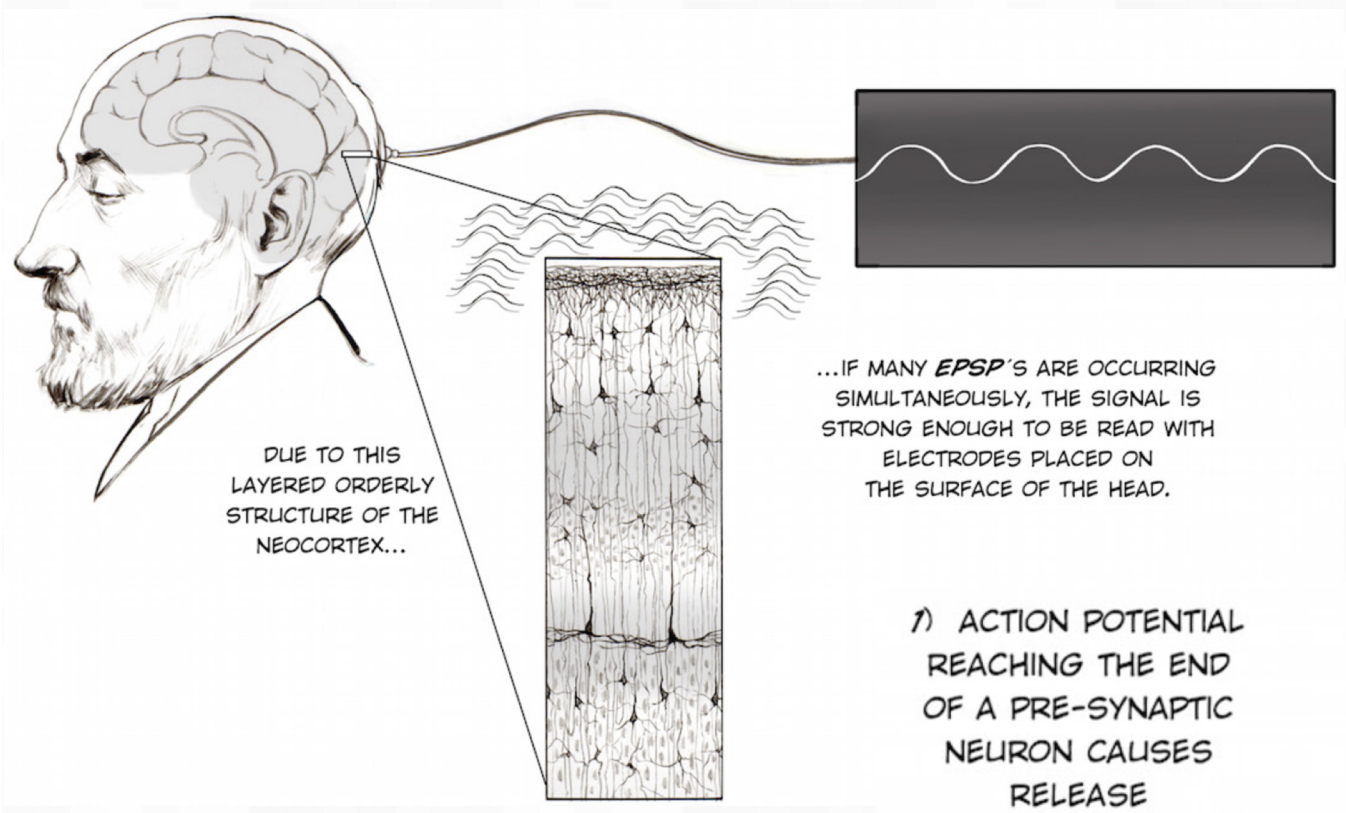
Mag Res. Imaging 2007 Jul;25(6):978-88.

BOLD imaging confounds

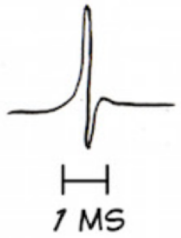
- BOLD is rarely enough on its own as there can be problems with interpretation
- Use MEG/EEG?



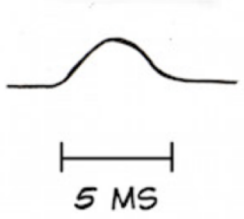
EEG signal origins



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.

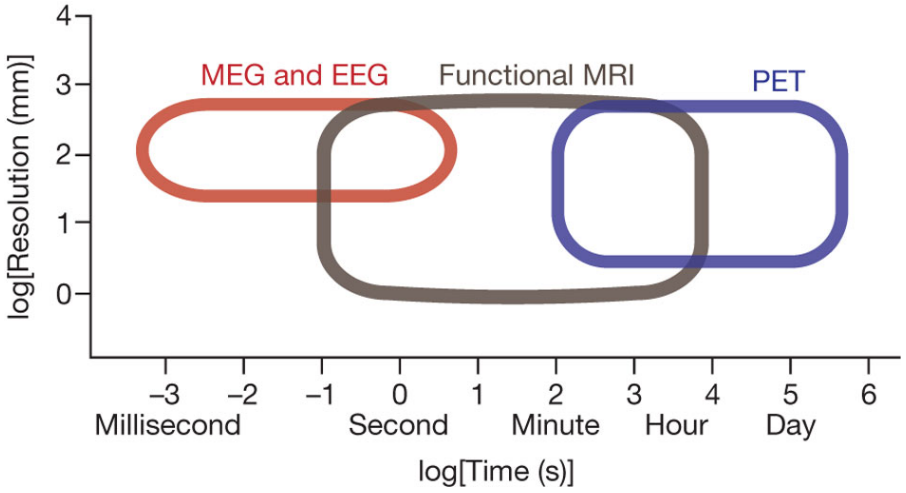


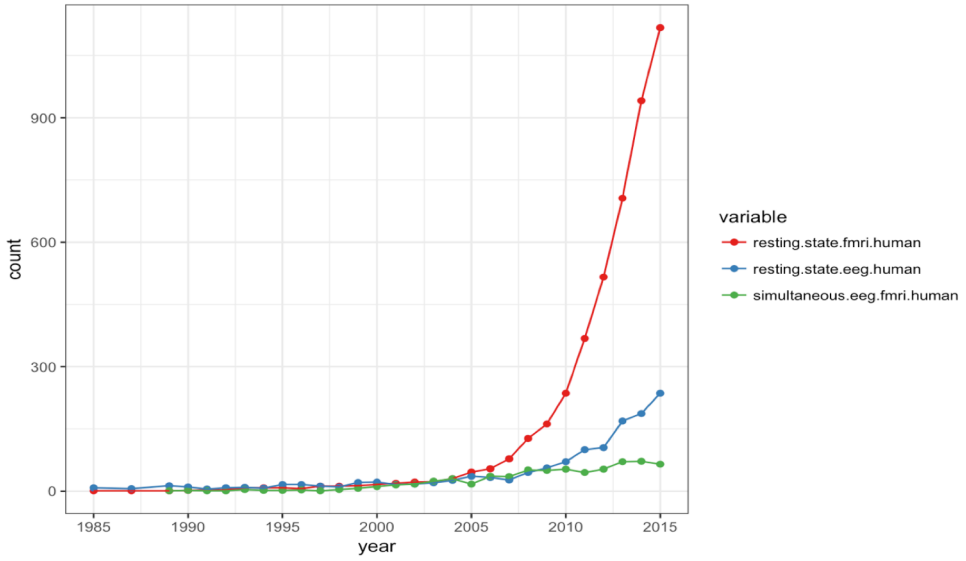
https://backyardbrains.com/experiments/EEG

Simultaneous EEG-FMRI

+

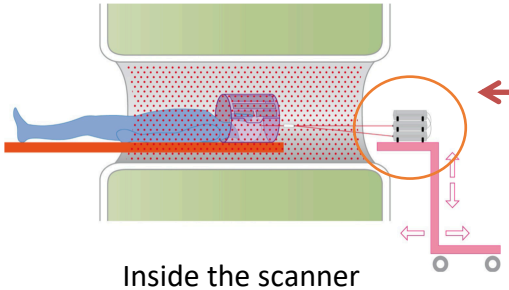
http://nld.tamu.edu/eeg



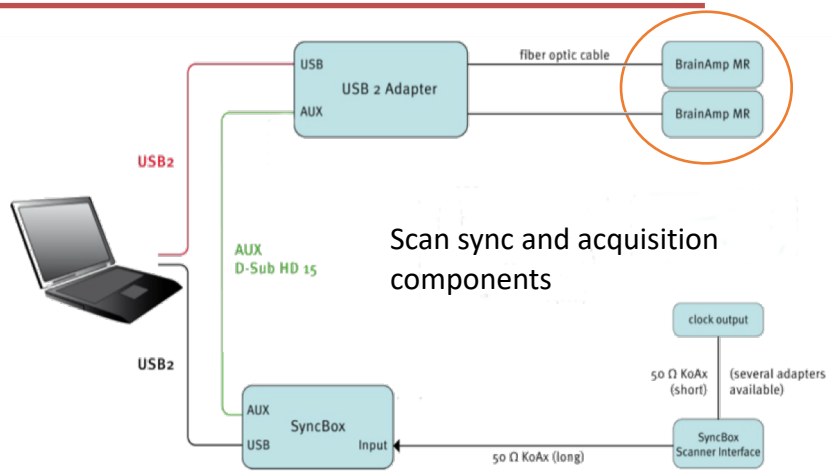


A Meyer-Lindenberg *Nature* **468**, 194-202 (2010)

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

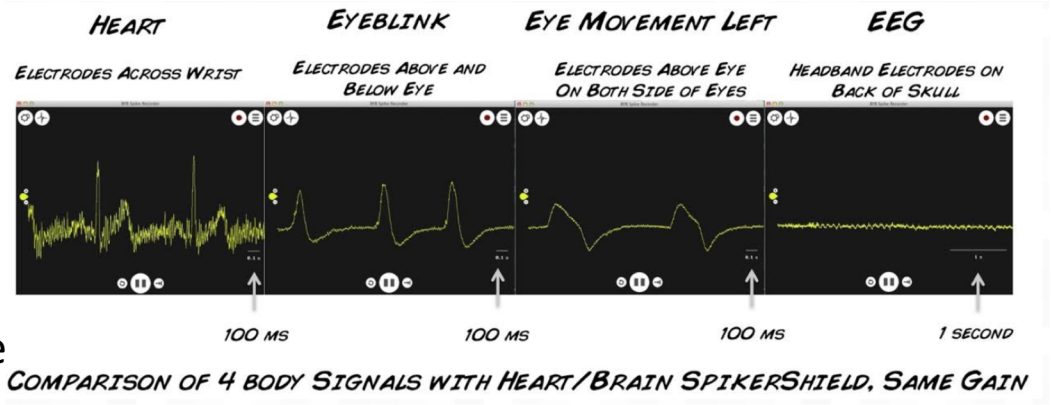
Signal of interest

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

MR environment artifacts

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

Physiological contributions



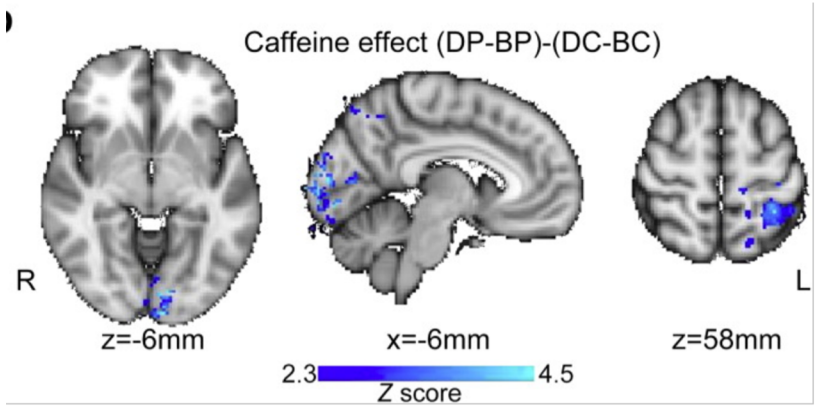
- Helium pump: 40-60Hz and AC line

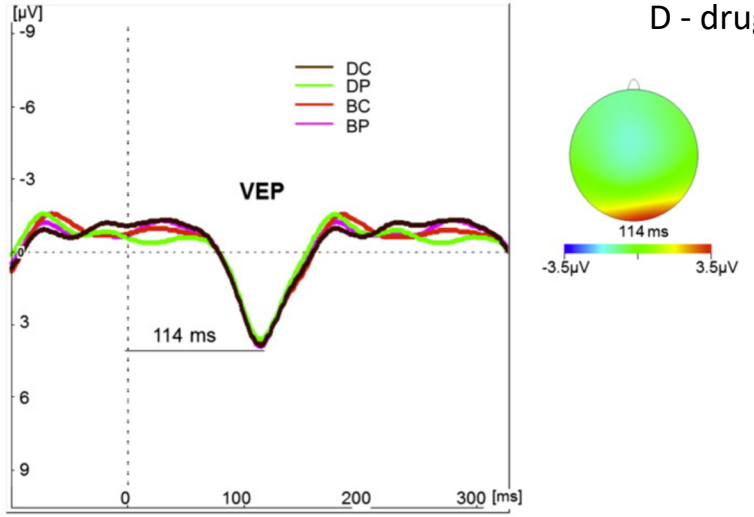
https://backyardbrains.com/experiments/EEG

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

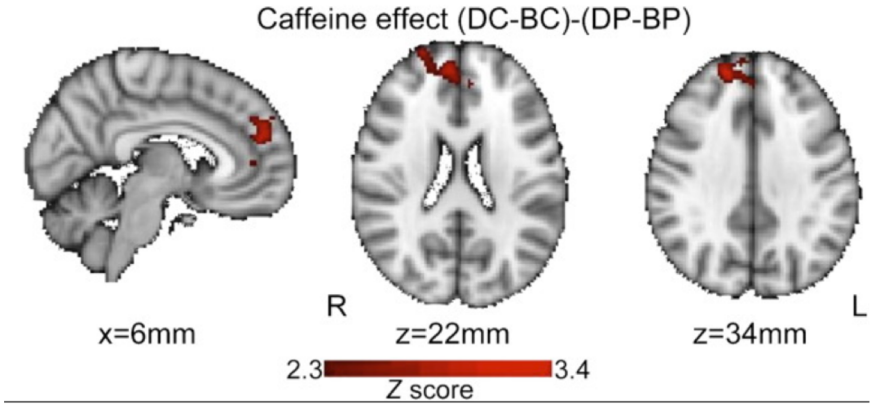
Example: effect of caffeine

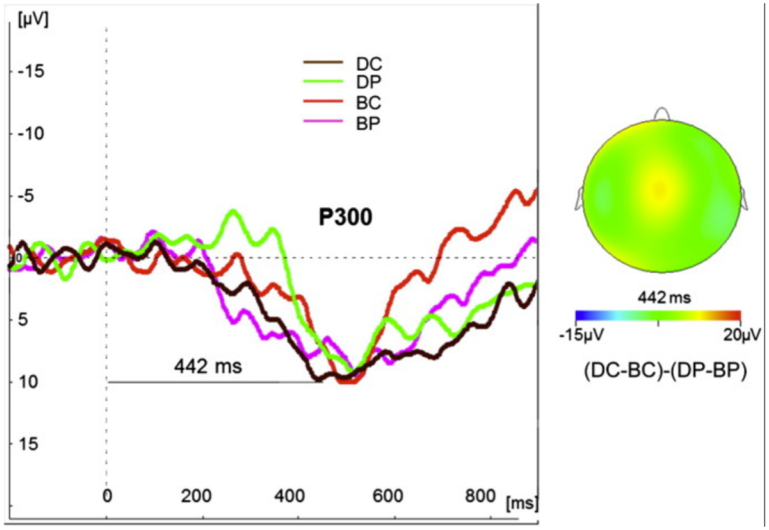
Simple visual task





Auditory oddball

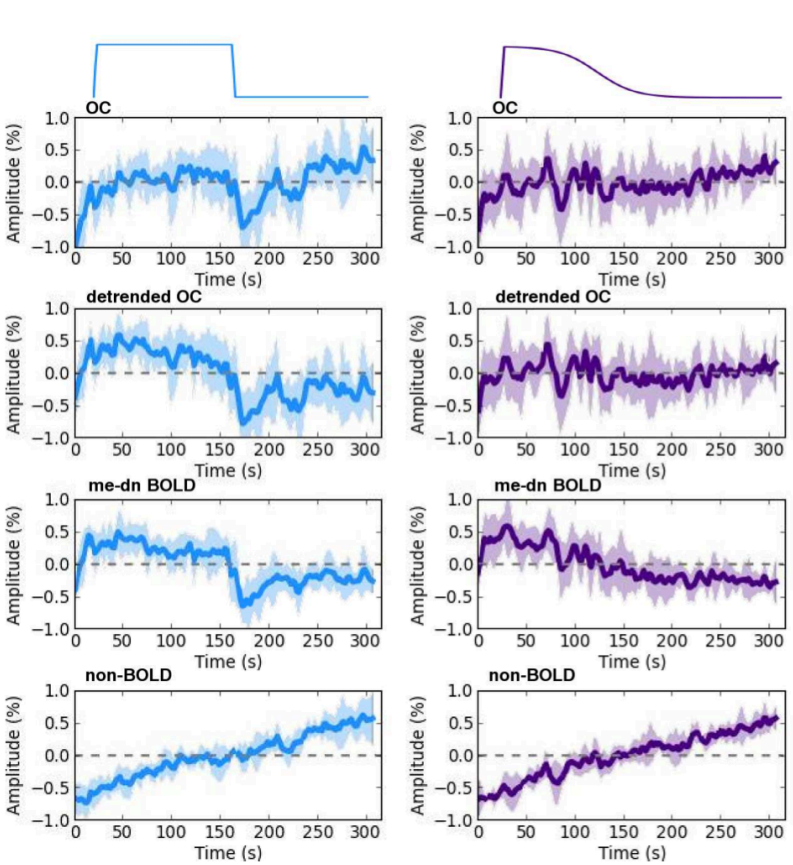


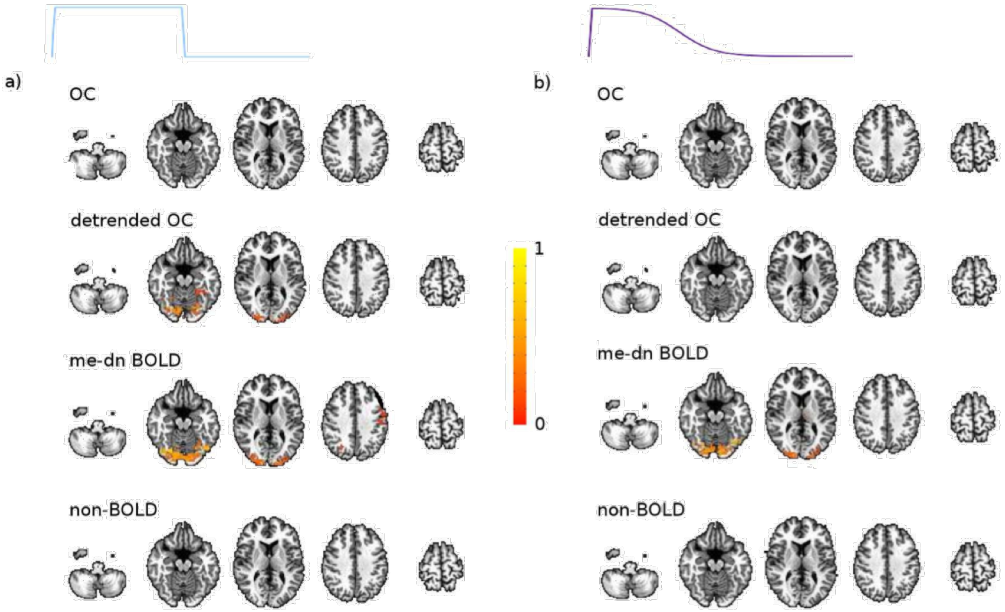


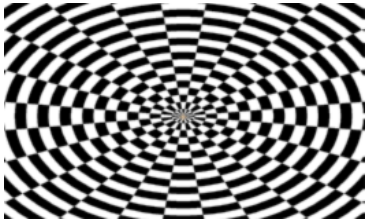
- Shortened P300 response in the complex task, little change in the simple visual task

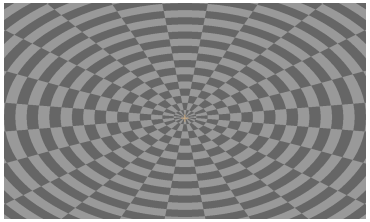
Diukova A, et al. *Neuroimage*. 2012;62(1):239 249.

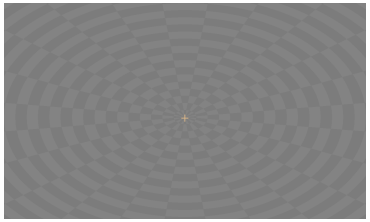
‘Simulated’ Example

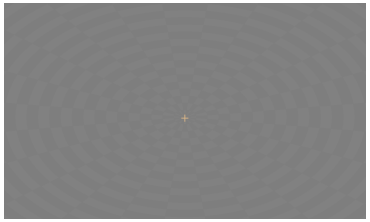




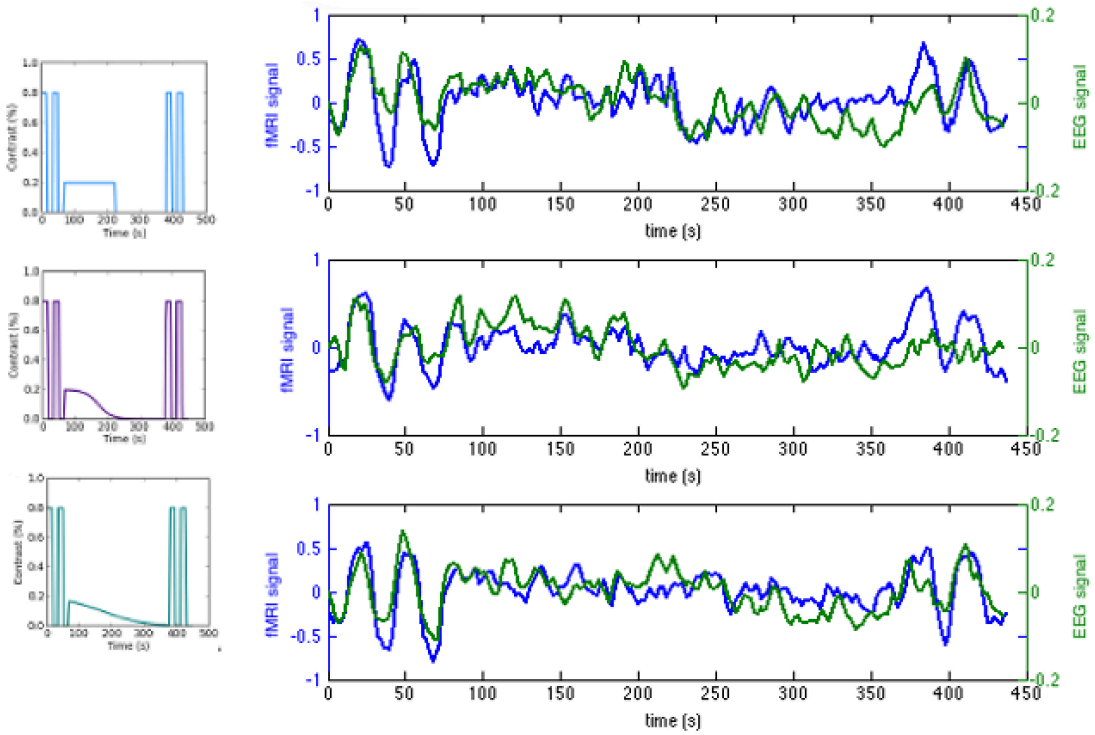


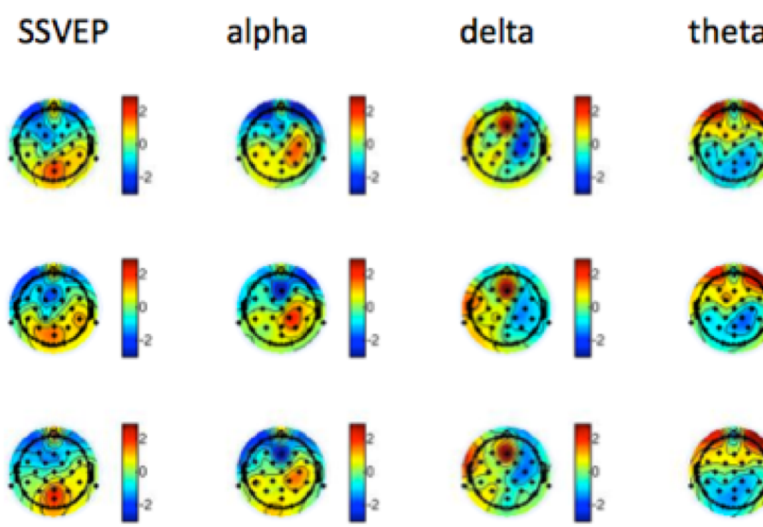






EEG Validation





- 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

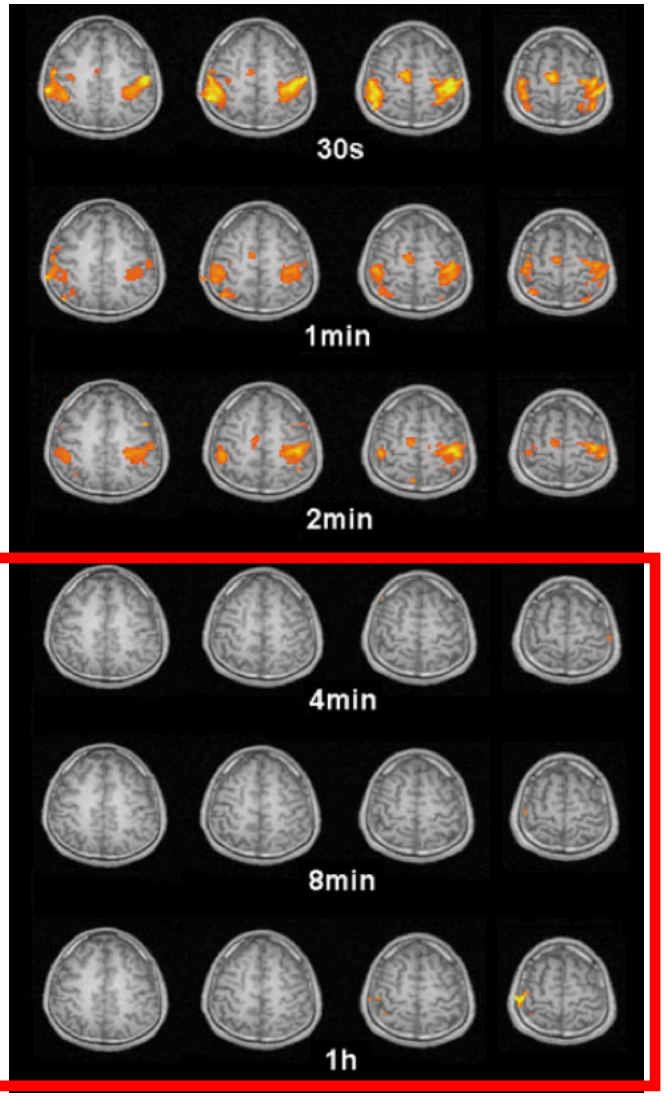
Possible confounding factors…. and solutions

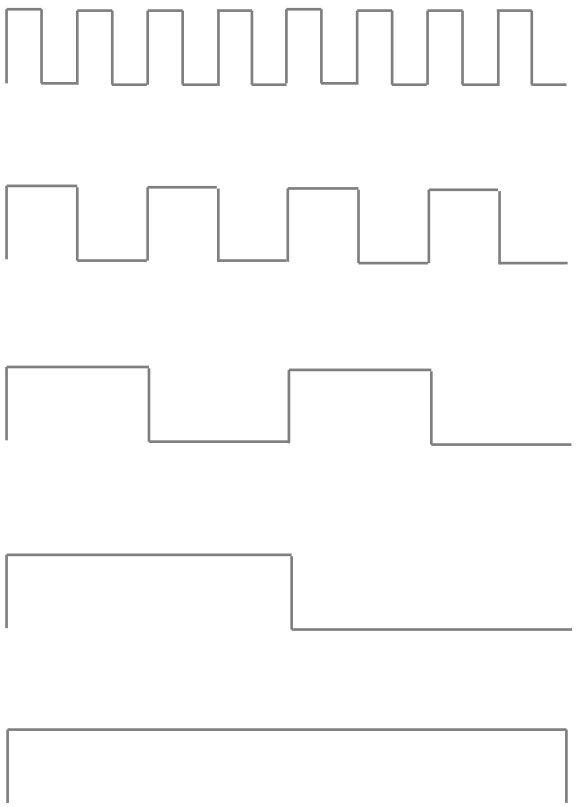
- Cognitive:
  - Placebo effect
    - Study design
- Acquisition:
  - These changes are slow (minutes) and on the same scale as drift artifacts
    - Use multi-echo fMRI?
- Signal:
  - BOLD signal is affected by changes in blood flow/volume
    - Use EEG-fMRI?
    - Use ASL?

Wise, RG. JMRI(2006)

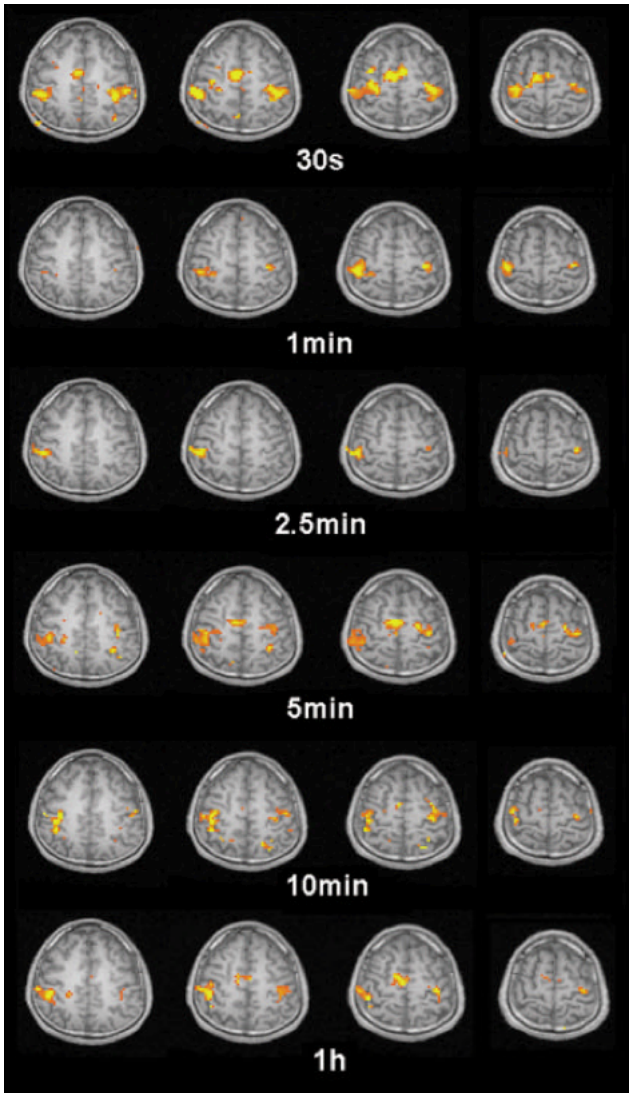
Imaging slow stimuli doesn't work well

BOLD





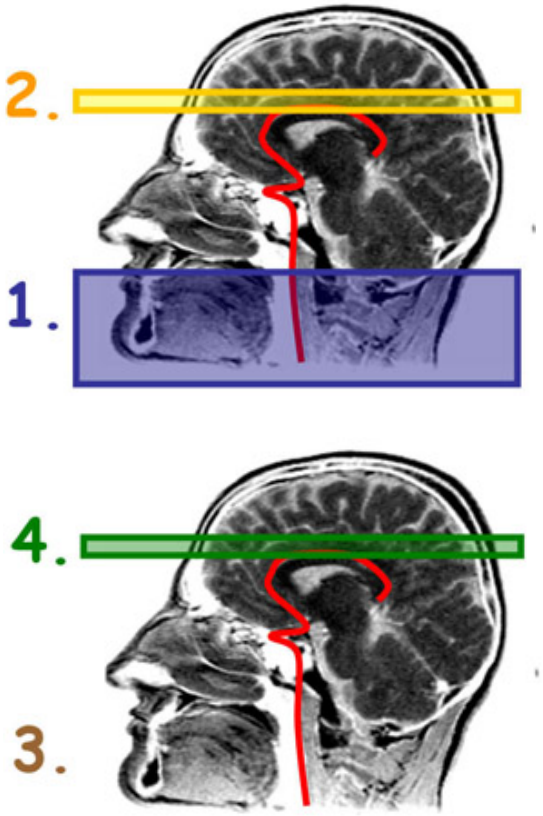
ASL

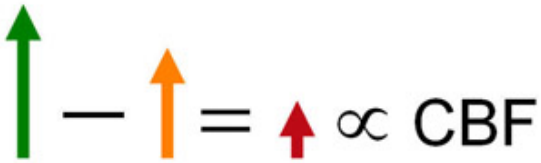


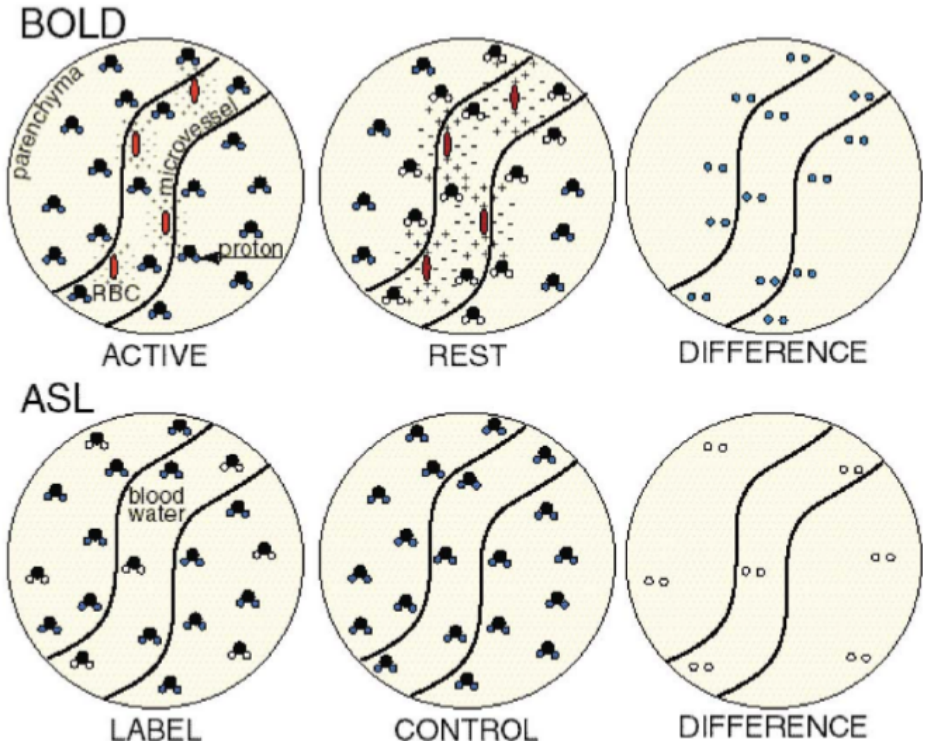
- BOLD has greater signal strength
- ASL has greater sensitivity for long duration stimuli

Wang et al, MRM (2003)

ASL vs. BOLD



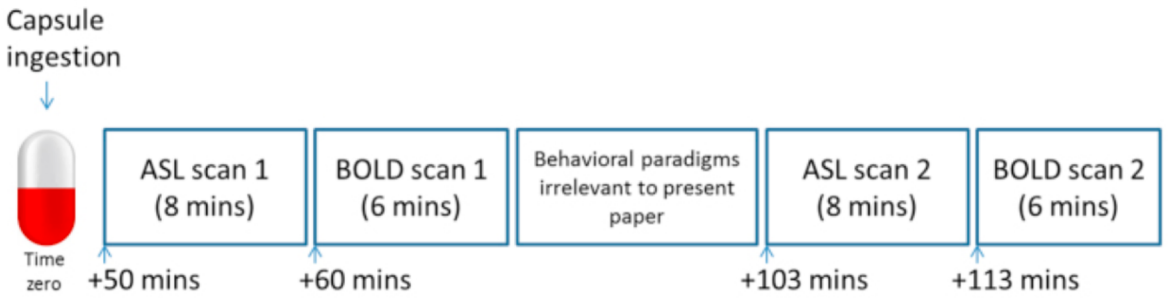




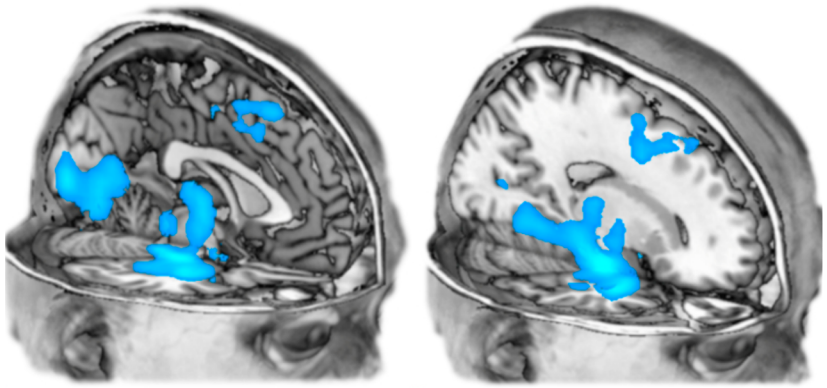
http://fmri.research.umich.edu/research/main_topics/asl.php

Detre JA et al., Clinical Neurophysiology (2002)

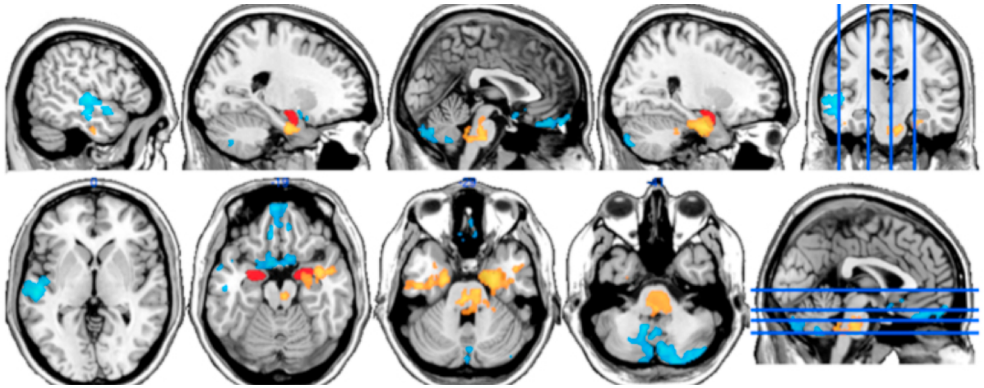
ASL-BOLD example



ASL – CBF decreases MDMA - placebo

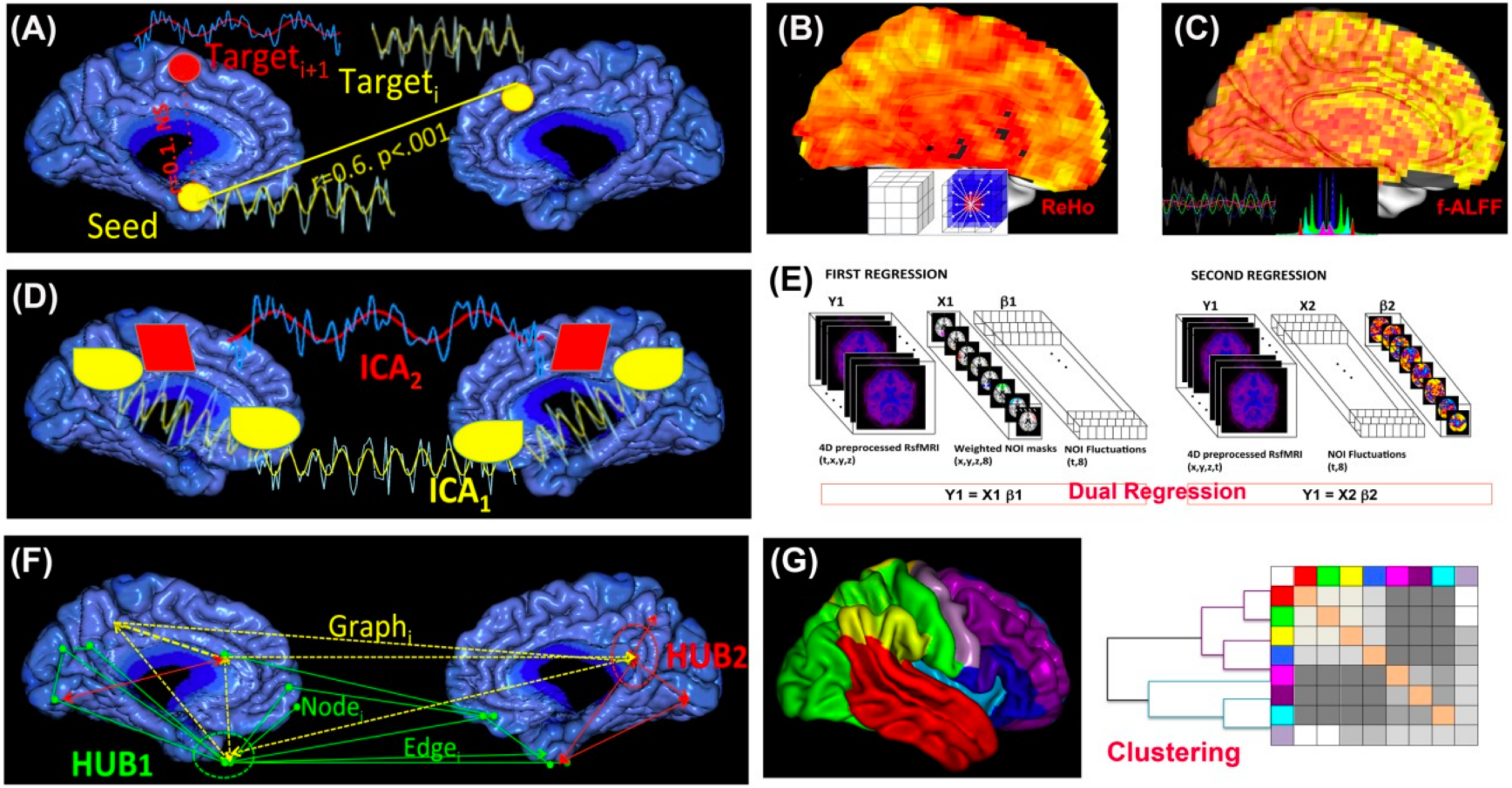


Amygdala connectivity changes



Carthart-Harris, R et al. Biol Psychiatry. 2015 Oct 15; 78(8): 554–562.

Other analysis?



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)

Acknowledgements

National Institute of Mental Health

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Pete Molfese

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