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

Drug development process ...

Long and costly





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

Role of imaging in clinical trials



Drug penetration into the brain



Adjunct to subjective response



Study design



Resting state changes

Midazolam sedation
 Sensory motor



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

Acute drug response





• 1 min injection of nicotine

DOSE

15

Pharmacokinetic response



Wise et al. Neuropsychopharmacology. 2004

Drugs tested





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?

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





Study design

Parallel Trial



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

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Imaging slow stimuli doesn't work well

BOLD

30s

1min

2min

4min

8min

1h



ASL has greater sensitivity for long duration stimuli

strength

Response to ketamine infusion



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...



What does fMRI measure?



Multi-echo (ME) fMRI.







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

20

Volume

30



10

-1

Ω





 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

• 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:
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 - Use EEG-fMRI?

What does fMRI measure?



Neural or vascular changes?

N = normal response



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





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



Simultaneous EEG-FMRI



http://nld.tamu.edu/eeg





Possible, but not common...



Simultaneous EEG-fMRI setup



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: $\pm 200 \mu V$

MR environment artifacts

- Blink: $\pm 150 \mu V$
- Movement: < 1mV
- ECG: ± 20µV
- EMG: ± 50μV
- Helium pump: 40-60Hz and AC line





COMPARISON OF 4 BODY SIGNALS WITH HEART/BRAIN SPIKERSHIELD, SAME GAIN

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

Gradient artifact correction example

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BCG origins



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





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Motion interactions





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

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

800 [ms]

200

400

600

'Simulated' Example















EEG potentials sensitive to contrast and frequency









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



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PURDUE

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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

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

Planned repeat dose study.



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



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





