Pharmacological fMRI: methodological concerns

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Outline

• What is Pharmacological FMRI and why do we do it?

• What are the challenges of interpretation?

• The need for quantitation: measurements of oxygen metabolism as a good candidate.
Pharmacological FMRI: why?

- Demonstrate a drug effect on central activity
  - Central penetration?
  - Choosing a dose
- Provide confidence for go/no-go decisions in drug development
- Investigate mechanisms of action at a brain systems level
  - Comparing compounds with different mechanisms
- A neuroscientific tool for modulating brain systems
Pharmacological FMRI: what?

- FMRI experiment (generally BOLD) + drug administration

- Pharmacological modulation of
  - Brain ‘activity’ over pharmacokinetic timescales

BOLD signal decreases with Psilocybin

Carhart-Harris et al PNAS 2012
Pharmacological FMRI: what?

- FMRI experiment (generally BOLD) + drug administration

- Pharmacological modulation of
  - Task related brain activity

Wise et al. Neuropsychopharmacology 2004
Pharmacological FMRI: what?

- FMRI experiment (generally BOLD) + drug administration

- Pharmacological modulation of
  - Resting state activity / networks / connectivity

Conscious sedation with midazolam

Greicius et al. Human Brain Mapping 2008
Field homogeneity & oxygenation state

Oxygenated Red Cell  de-Oxygenated Red Cell
Blood oxygenation

Neural activity

Neurovascular coupling

Vascular response

BOLD FMRI

Metabolic signalling

Synaptic signalling

arteriole

Blood flow

Oxidative metabolism

capillary bed

B_0 field

venule

[dHb]

BOLD signal
Neural activity → Neurovascular coupling

- Synaptic signalling
- Metabolic signalling

Vascular response

- Arteriole
- Blood flow
- Oxidative metabolism
- Capillary bed
- Venule
- $B_0$ field

BOLD FMRI

- [dHb] down
- BOLD signal up

Disease/Drug modulation
Neural activity
  
  Neurovascular coupling
  
  Vascular response
  
  oxidative metabolism
  
  capillary bed
  
  BOLD signal
  
  Blood flow
  
  arteriole
  
  venule
  
  BOLD FMRI
  
  [dHb]
  
  disease / drug modulation
  
  synaptic signalling
  
  metabolic signalling
  
  glia
Reduced vascular reactivity: aging as an example

- Reduced vascular reactivity to a motor stimulus
- Reicker et al 2003 JCBFM
- Altered neurovascular coupling with age
N = normal response

Neural response  Signalling  Vascular response  BOLD FMRI

Control/Placebo

Iannetti & Wise 2007
Neural response

Signalling

Vascular response

BOLD FMRI

Control/Placebo

Patient/Drug

N = normal response

Iannetti & Wise 2007
<table>
<thead>
<tr>
<th>Control/Placebo</th>
<th>Patient/Drug 1</th>
<th>Patient/Drug 2</th>
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<td><strong>Neural response</strong></td>
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<td><strong>BOLD FMRI</strong></td>
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**N = normal response**

Iannetti & Wise 2007
Physiology of BOLD signal

Blockley et al NMR Biomed (2012)
Effect of Acetazolamide on fMRI Response

- 20% increase in baseline CBF
- No effect on ΔCBF with "finger tapping"
- But BOLD response to finger tapping reduced by 35%

G. Brown et al, JCBFM 2003
Effect of Acetazolamide on fMRI Response

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G. Brown et al, JCBFM 2003
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G. Brown et al, JCBFM 2003
Physiology of BOLD signal

CBF changes contribute to BOLD signal

Blockley et al NMR Biomed (2012)
Psilocybin effects on cerebral blood flow

- Psilocybin - partial agonist of 5-HT2A receptor
- Focal perfusion decreases (15 subjects)

Carhart-Harris et al PNAS (2012)
Psilocybin effects on cerebral blood flow

• But has energy usage changed or just the function of the blood vessels?

Carhart-Harris et al PNAS (2012)
Another example, of a ‘drug effect’
This is almost completely a vascular effect. Substantial global decreases in neuronal activity are unlikely.
… so can we go further in the search for quantification of ‘activity’ than CBF?
Drug induced change in vascular response

- Indomethacin
  - Non-steroidal anti-inflammatory drug
  - Inhibits Cox1 & 2 that participate in prostaglandin synthesis
- Vasocostrictive effects

St Lawrence et al MRM 2003
Physiology of BOLD signal

Oxygen consumption

Blockley et al NMR Biomed (2012)
Energy metabolism: synaptic activity

- Action potentials at pre-synaptic cell, release glutamate
- Open ion channels on post-synaptic cell
- Reuptake of glutamate by astrocytes (glucose metabolism)
- Pump ions out of cell to restore ionic gradients
- Approx 75% of energy usage (consequences of glutamate release)

Attwell & Iadecola 2002
Metabolic Activity

• This energy is provided in the form of ATP.

• ATP is produced from glucose by oxidative phosphorylation and the **Kreb’s cycle**.

• Rate of **oxygen consumption** by oxidative phosphorylation is a good measure of neural activity.
Stoichiometric coupling of brain glucose metabolism and glutamatergic neuronal activity

Nicola R. Sibson*†, Ajay Dhankhar*, Graeme F. Mason†, Douglas L. Rothman‡, Kevin L. Behar§, and Robert G. Shulman*

![Diagram](image)

**Fig. 3.** Graph demonstrating the correlation between the rate of oxidative Glc consumption (CMR_Glc(ox)) and the rate of glutamate–neurotransmitter cycling (V_cycle).
Anaesthesia

- Glucose metabolism (18 FDG) PET
- % Decreases during anaesthesia

Rate of cerebral metabolic oxygen consumption

\[ \text{CMRO}_2 = C_a\text{O}_2 \times \text{OEF} \times \text{CBF} \]

Arterial \( \text{O}_2 \) content
\( \text{O}_2 \) Saturation \( \sim 100\% \)

\( \downarrow \text{O}_2 \)  

Venous \( \text{O}_2 \) content
\( \text{O}_2 \) Saturation \( \sim 60\% \)
Rate of cerebral metabolic oxygen consumption

ΔCMRO₂ ~ +5 → 30%

“Active state”

“Resting baseline”
N = normal response

Control/Placebo

Patient/Drug

Patient/Drug

Iannetti & Wise 2007
Iannetti & Wise 2007

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<tr>
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<th>Neural response</th>
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Summary

• Pharmacological FMRI has proved useful, but challenging in mapping drug effects in the human brain.

• Interpretation of BOLD needs to consider potential confounding drug effects.

• Improved quantitation by measuring the rate of cerebral oxygen consumption should improve interpretability of observed drug effects in the brain.
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