Pharmacological fMRI: methodological concerns

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Outline

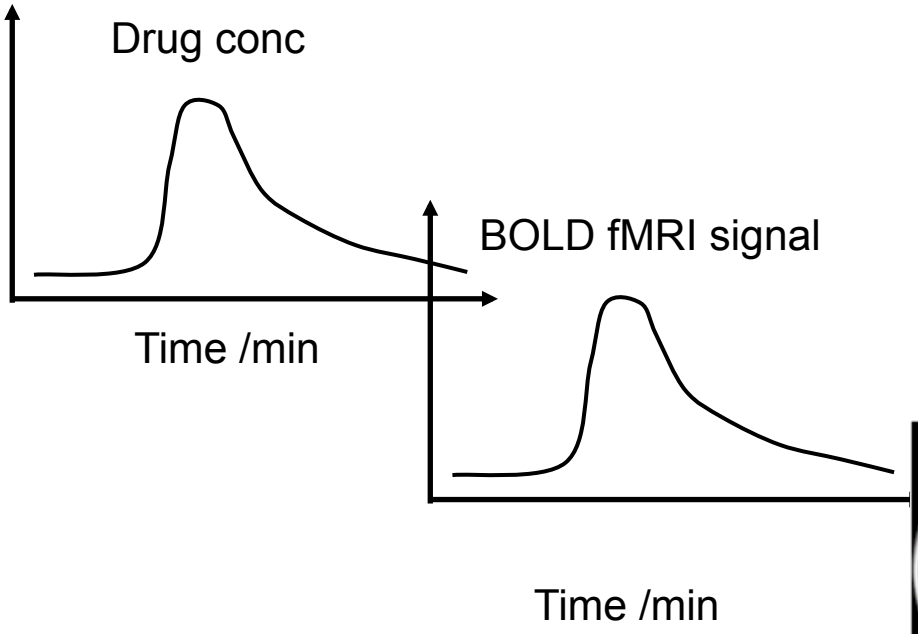
- What is Pharmacological FMRI and why do we do it?
- What are the challenges of interpretation?
- The need for quantitation: measurements of oxygen metabolism as a good candidate.

Pharmacological FMRI: why?

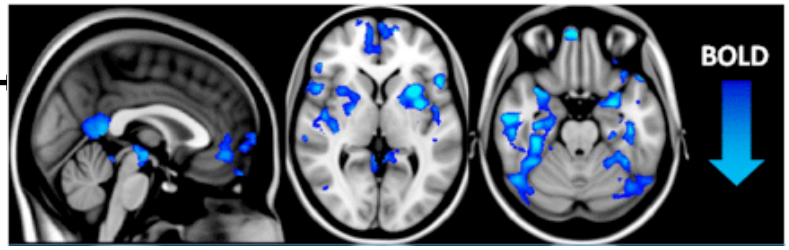
- Demonstrate a drug effect on central activity
  - Central penetration?
  - Choosing a dose
- Provide confidence for go/no-go decisions in drug development
- Investigate mechanisms of action at a brain systems level
  - Comparing compounds with different mechanisms
- A neuroscientific tool for modulating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

Pharmacological FMRI: what?

- FMRI experiment (generally BOLD) + drug administration
- Pharmacological modulation of
  - Brain 'activity' over pharmacokinetic timescales



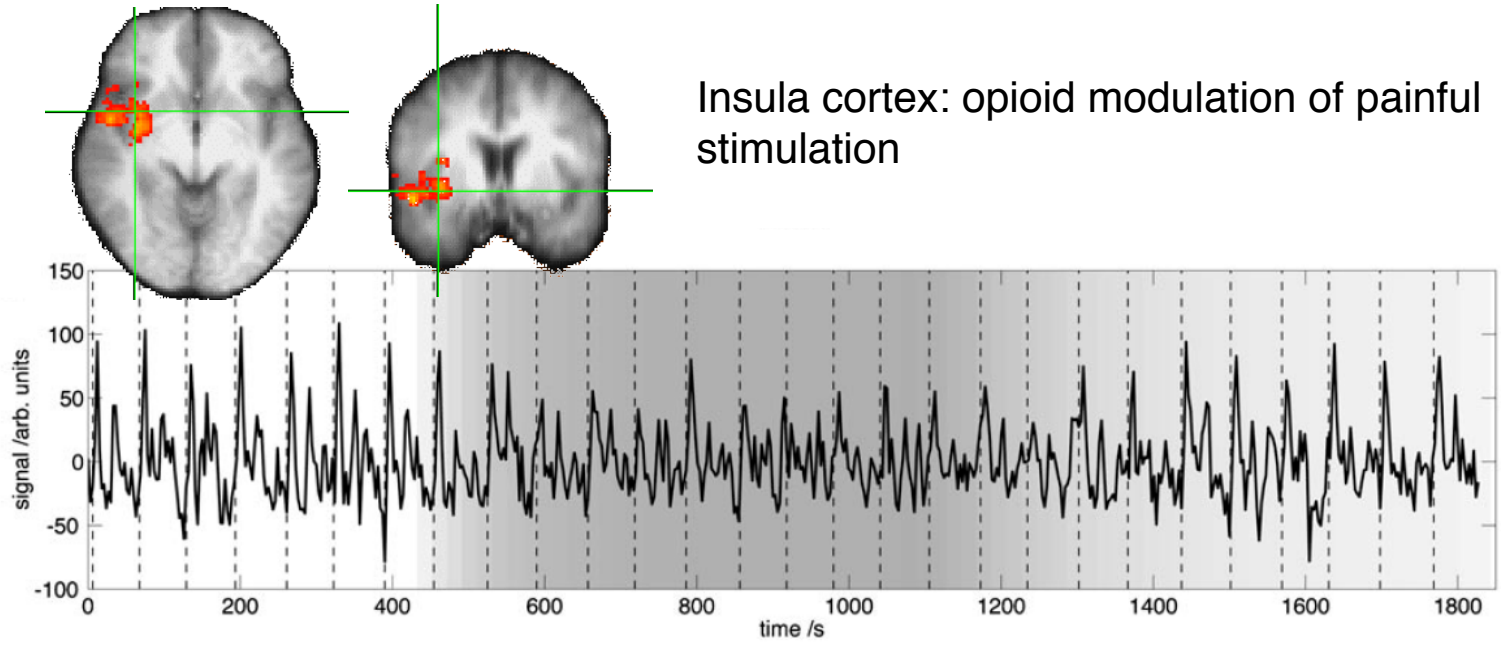
BOLD signal decreases with Psilocybin



Carhart-Harris et al PNAS 2012

Pharmacological FMRI: what?

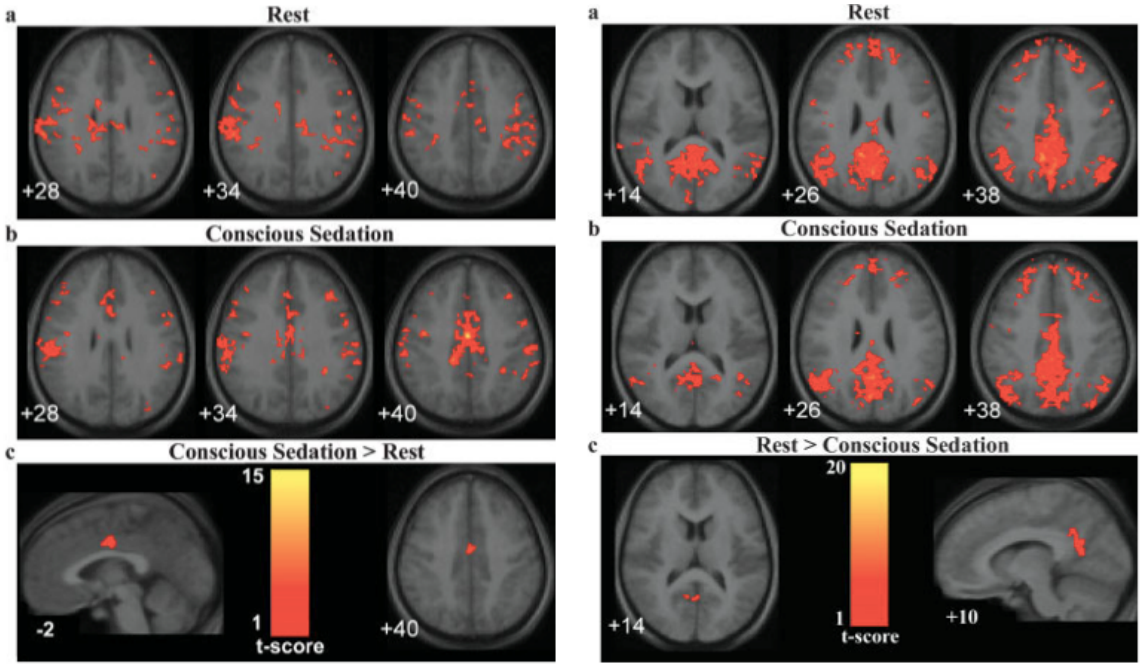
- FMRI experiment (generally BOLD) + drug administration
- Pharmacological modulation of
  - Task related brain activity



Wise et al Neuropsychopharmacology 2004

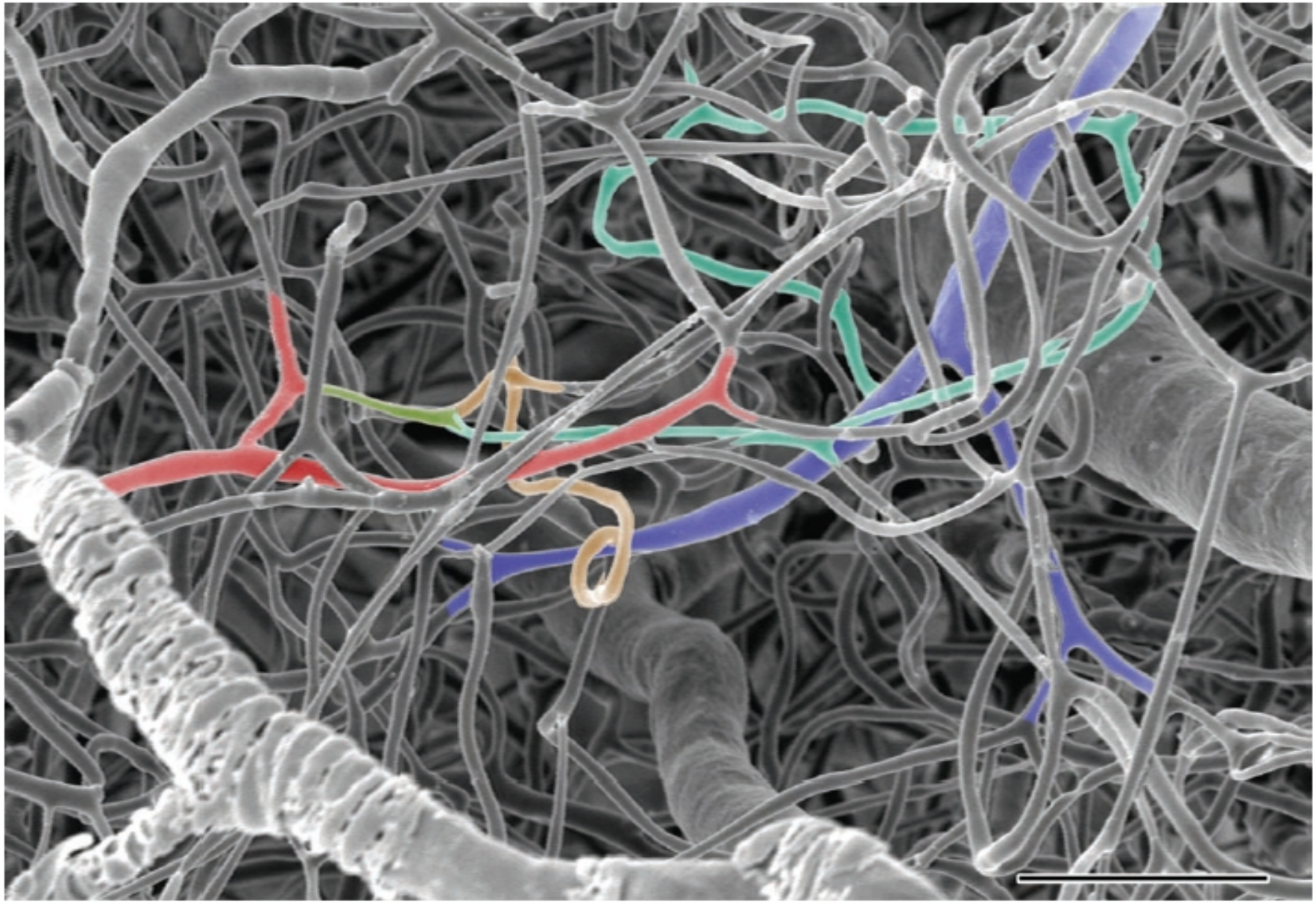
Pharmacological FMRI: what?

- FMRI experiment (generally BOLD) + drug administration
- Pharmacological modulation of
  - Resting state activity / networks / connectivity



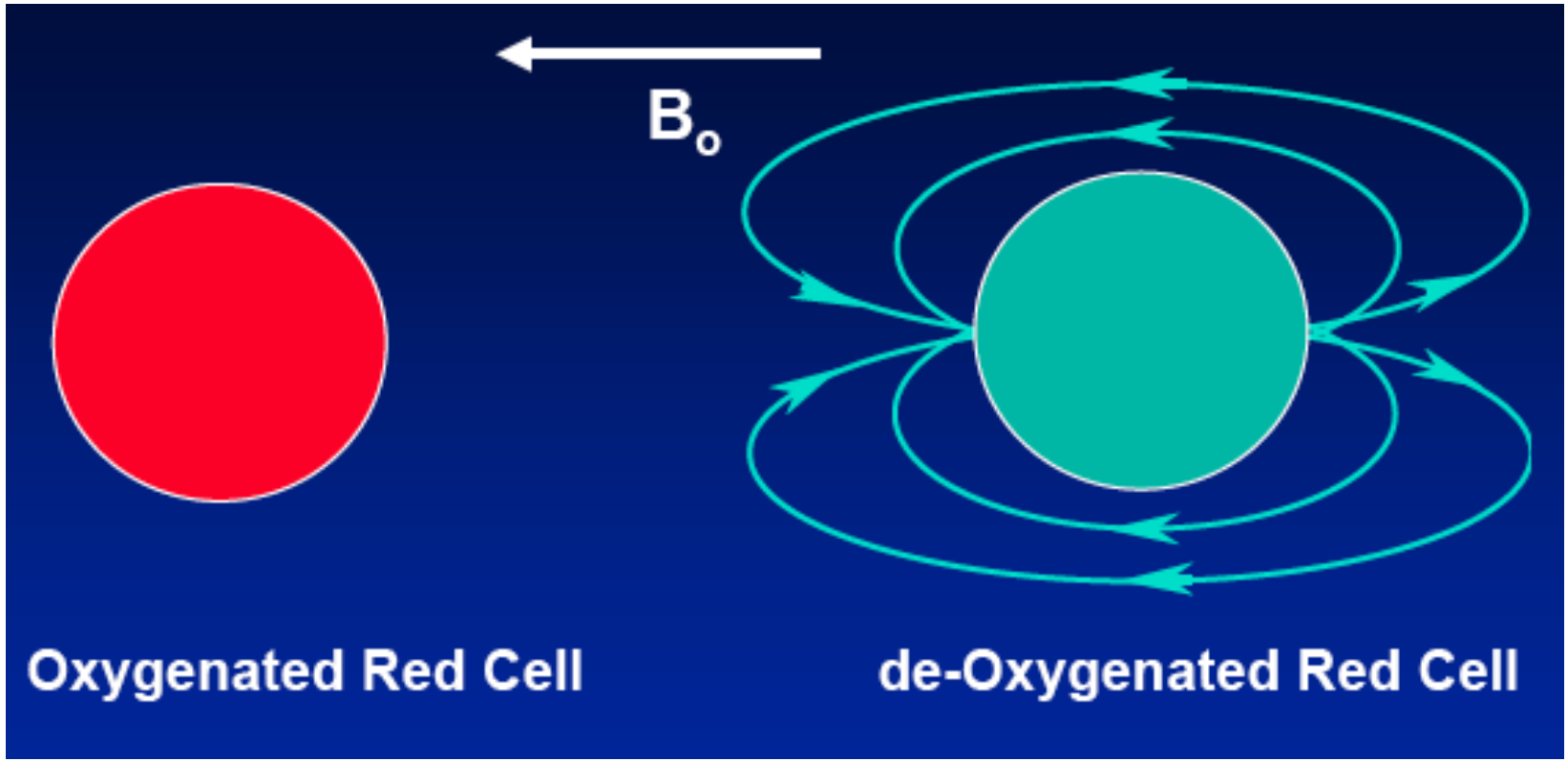
Conscious sedation with midazolam

Greicius et al Human Brain Mapping 2008

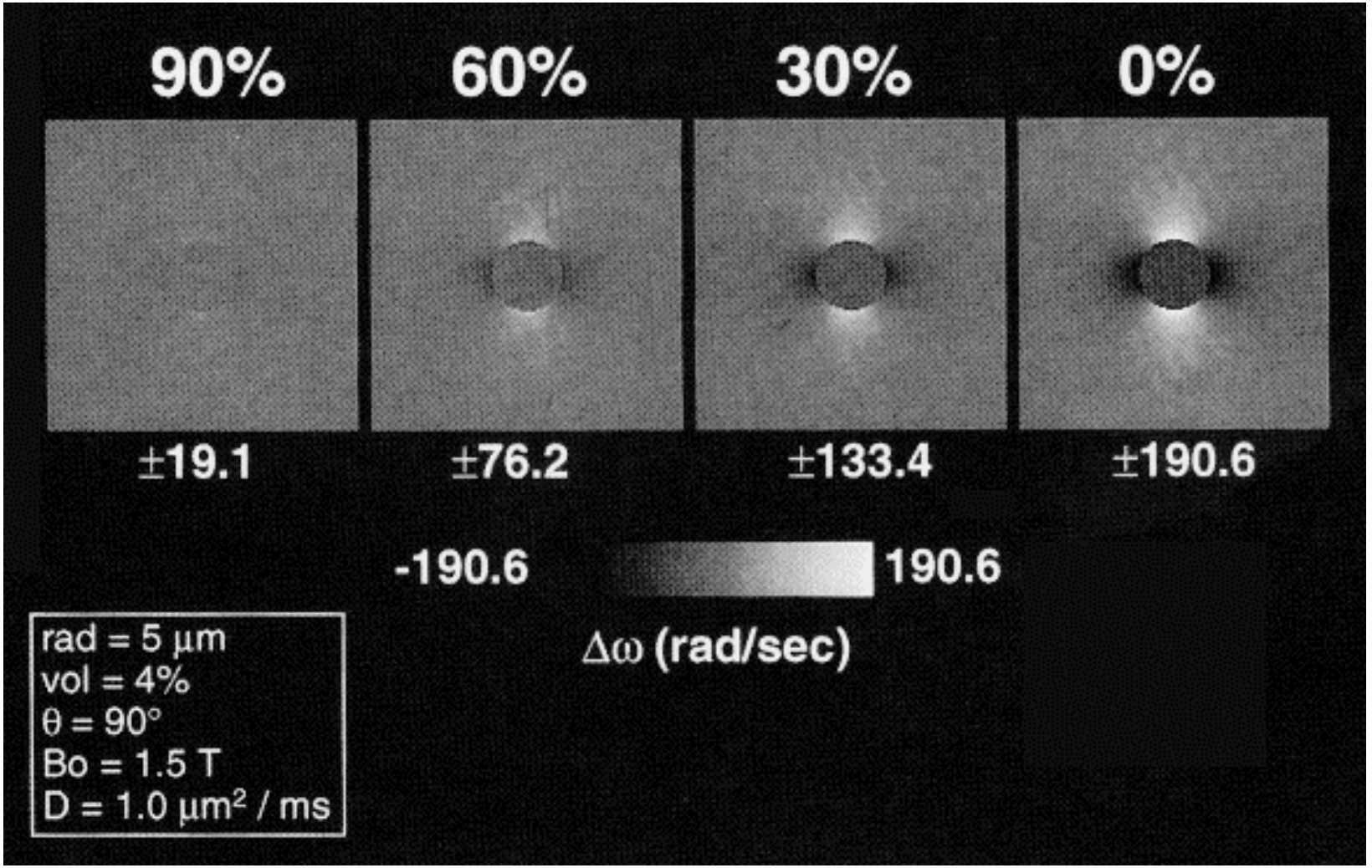


Harrison RV et al. Cerebral cortex. 2002

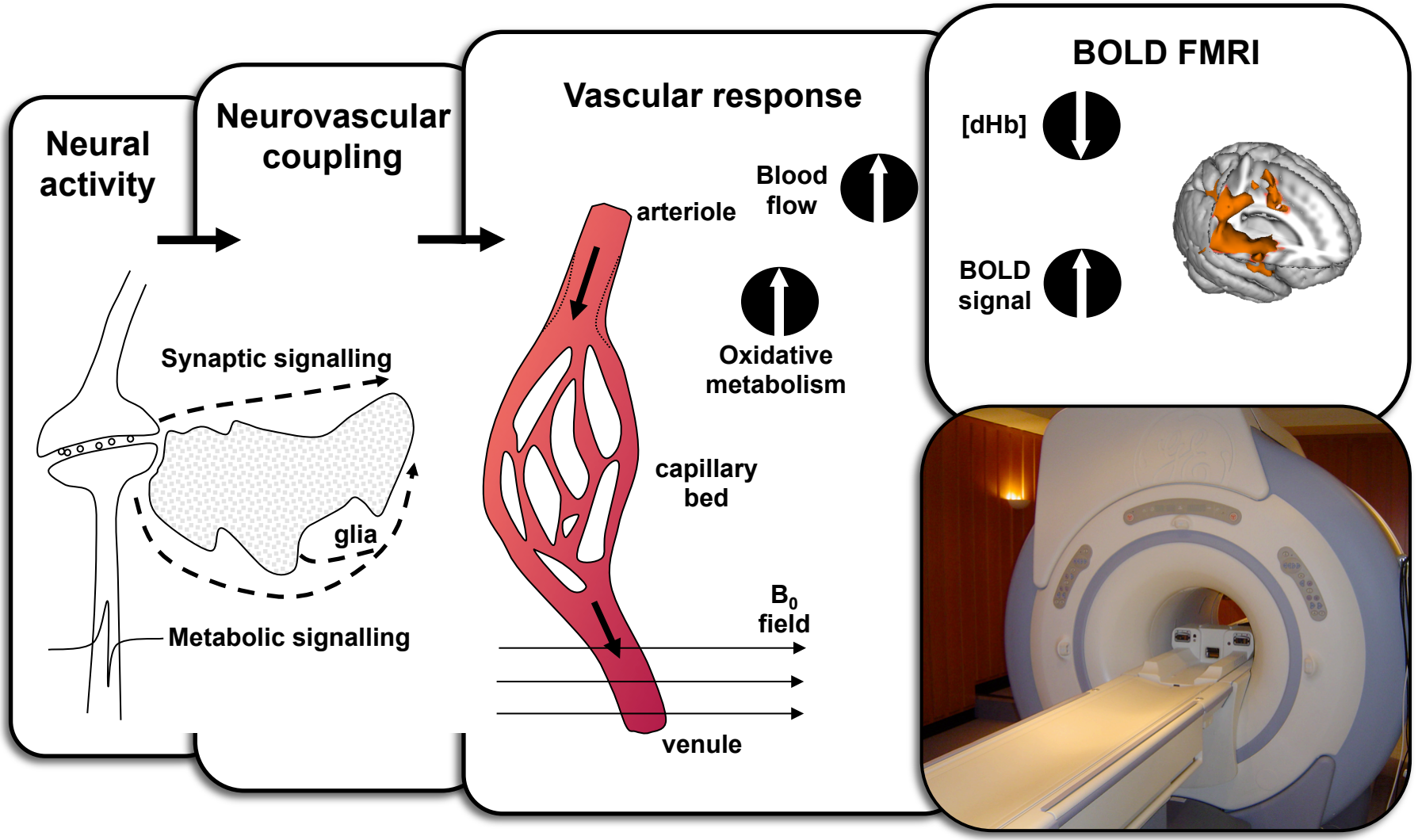
Field homogeneity & oxygenation state

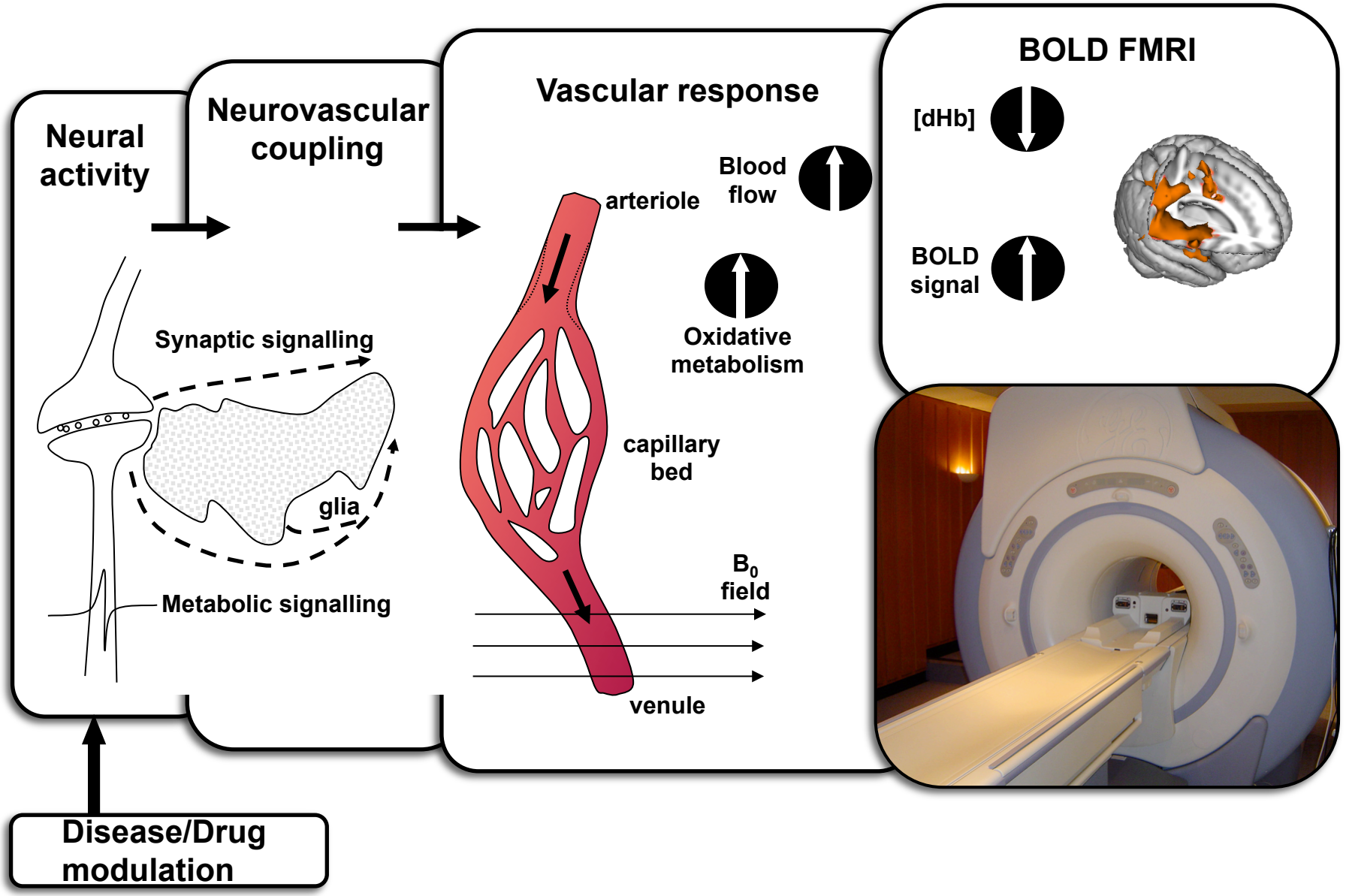


Blood oxygenation



Bandettini and Wong. Int. J. Imaging Systems and Technology. **6:**133 (1995)


Neural activity
Neurovascular coupling
Vascular response
BOLD FMRI
Synaptic signalling
glia
Metabolic signalling
arteriole
Blood flow
Oxidative metabolism
capillary bed
B_0 field
venule
[dHb]
BOLD signal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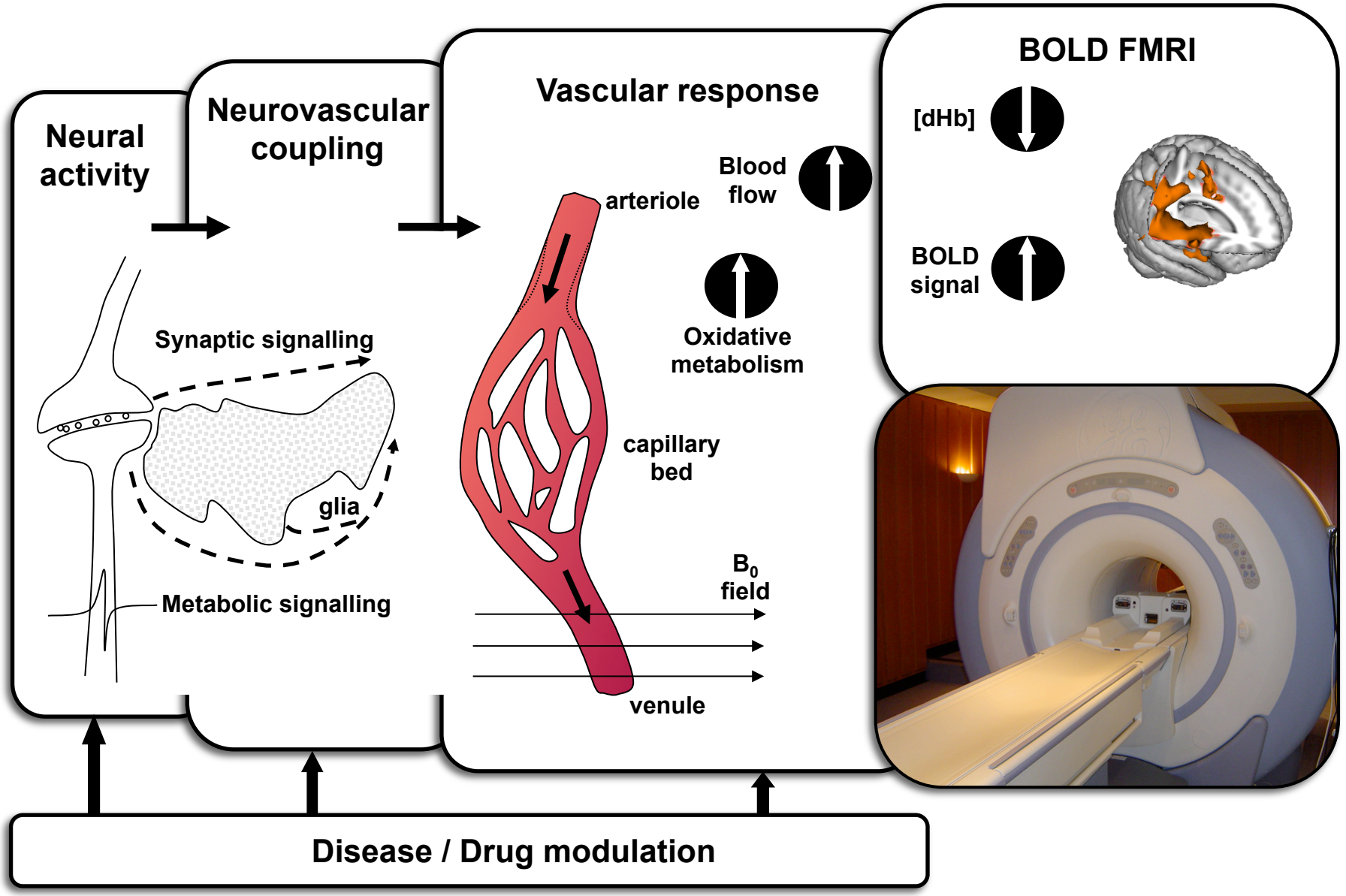
Disease/Drug modulation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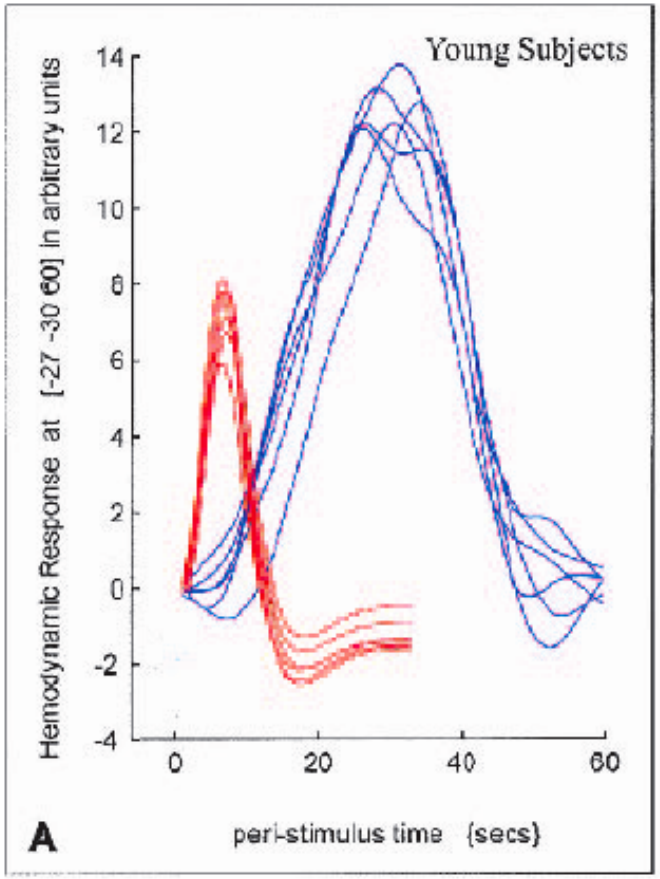
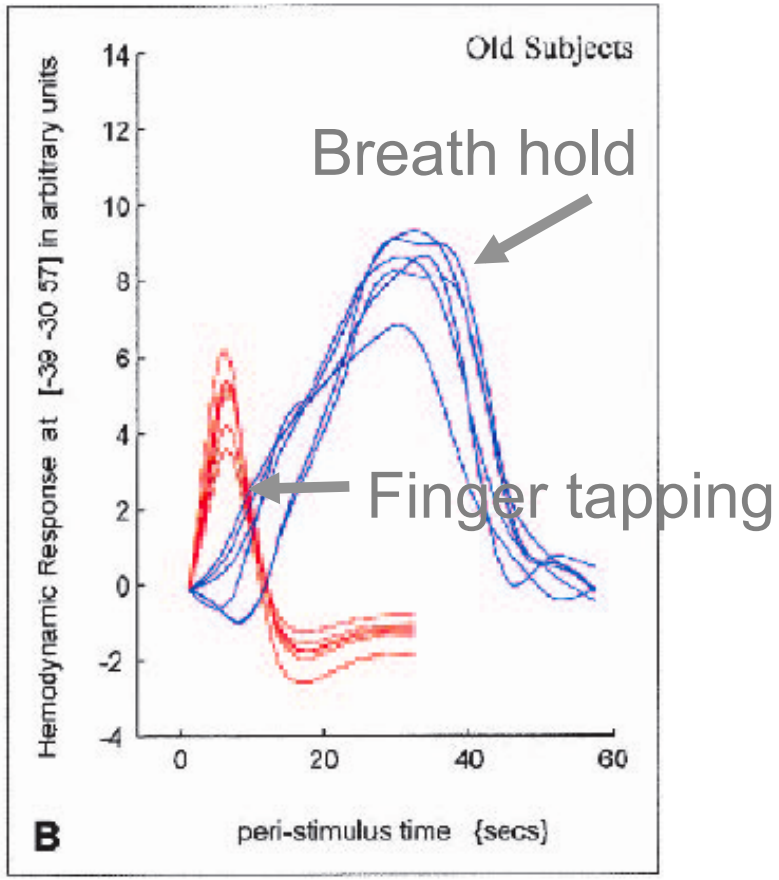
Disease / Drug modulation

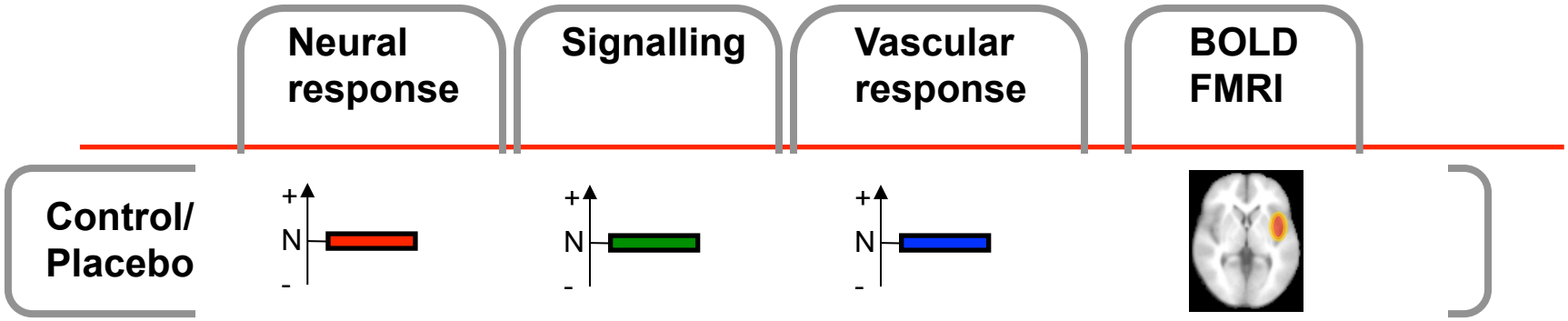
Reduced vascular reactivity: aging as an example

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





N = normal response



Iannetti & Wise 2007

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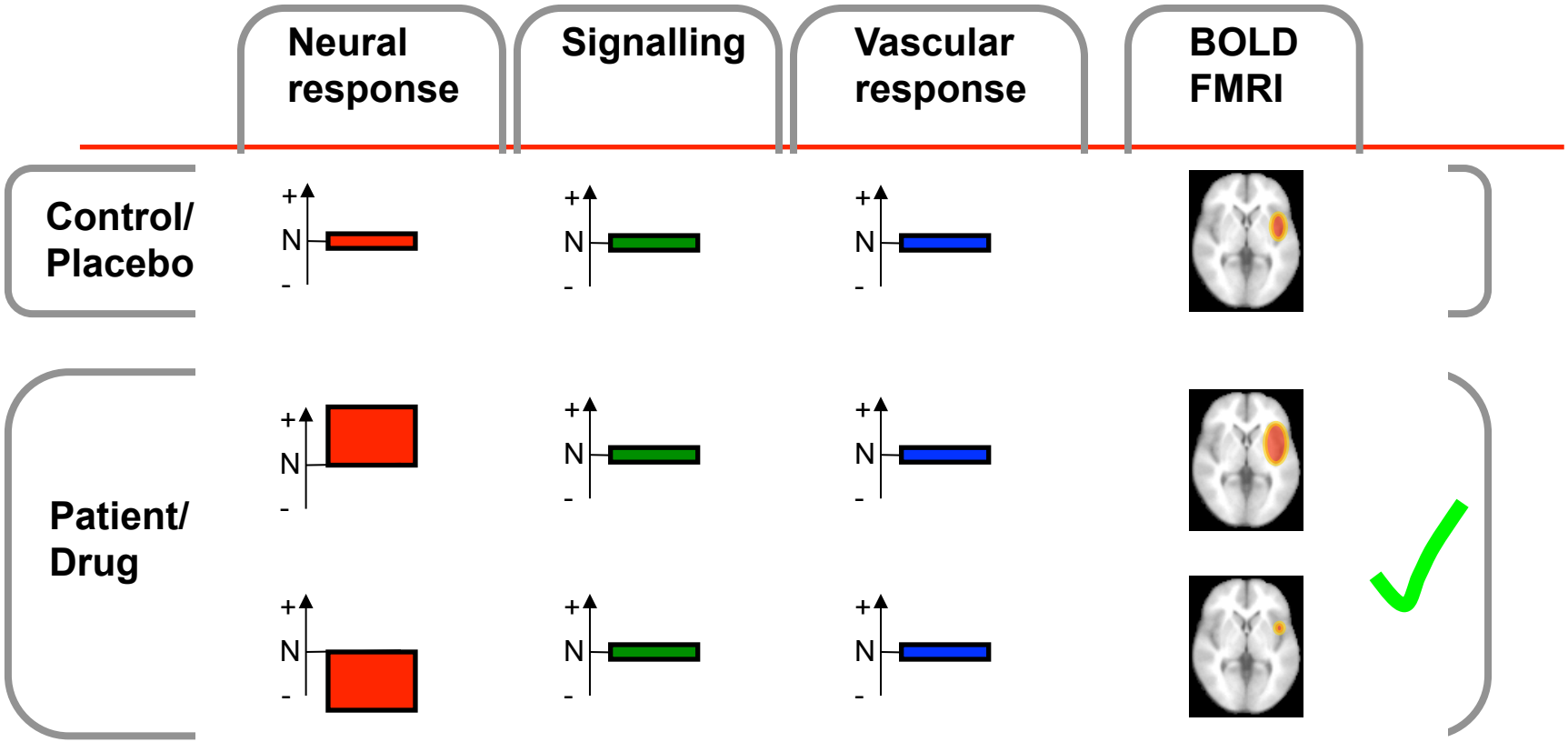

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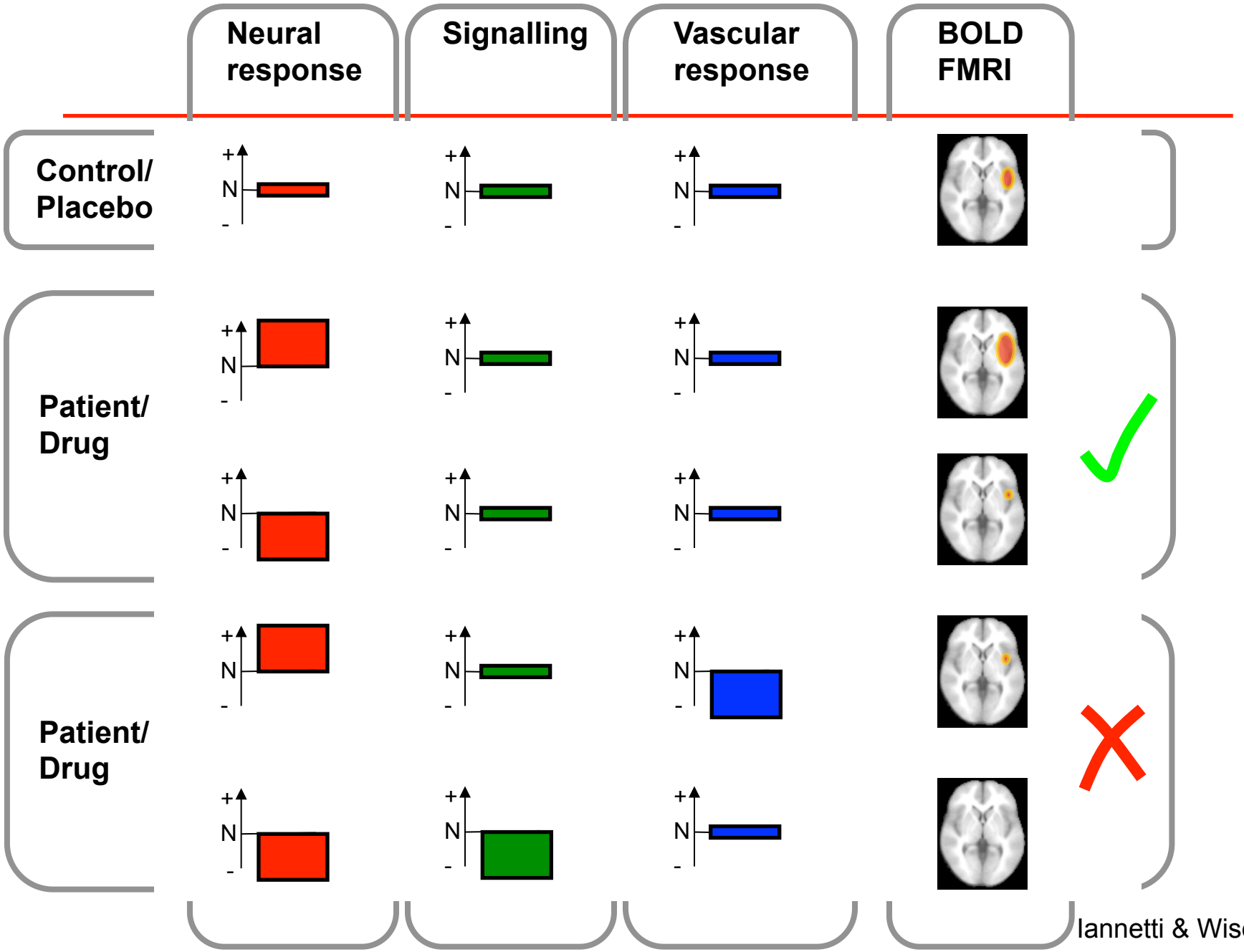
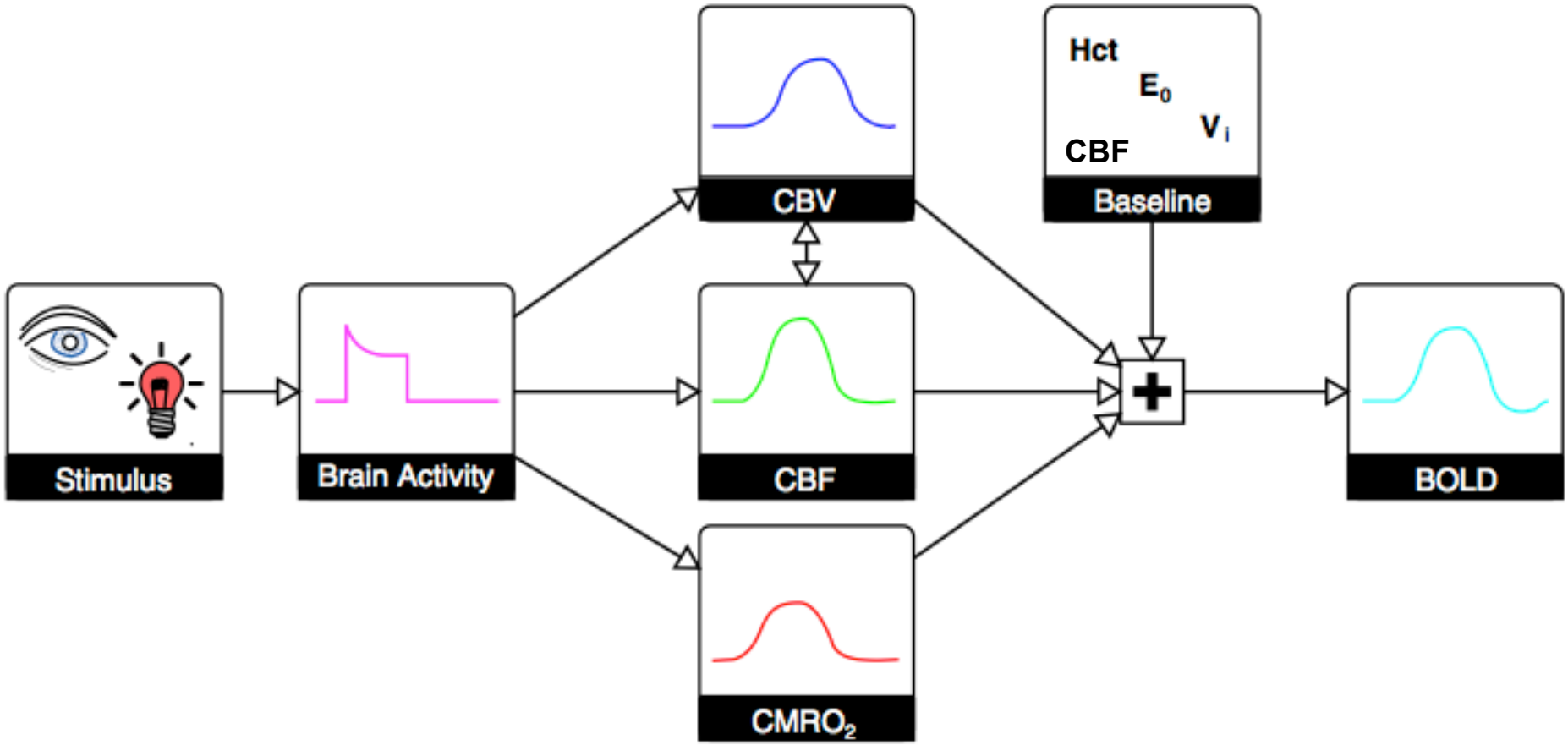


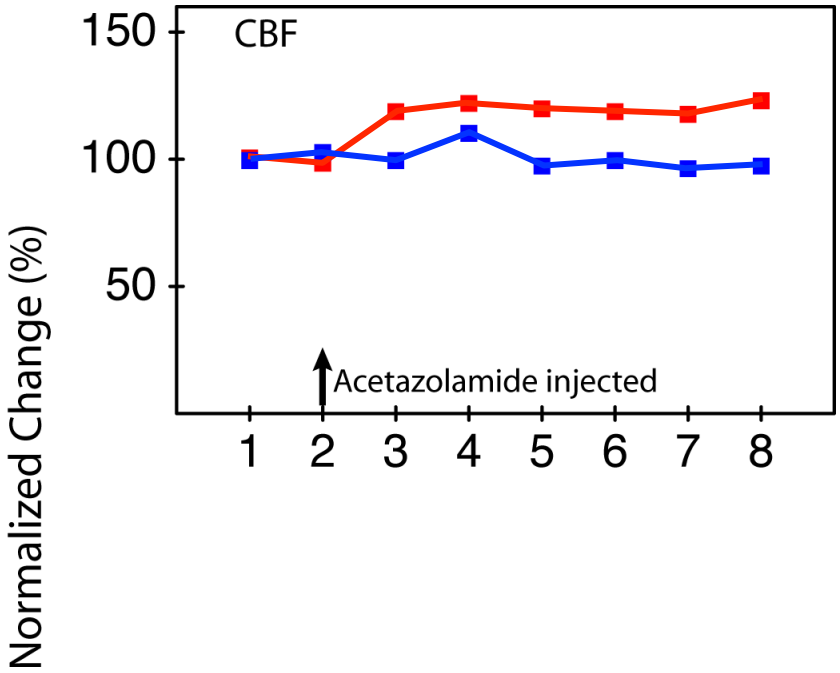
Iannetti & Wise 2007

Physiology of BOLD signal



Blockley et al NMR Biomed (2012)

Effect of Acetazolamide on fMRI Response



20% increase in baseline CBF

G. Brown et al, JCBFM 2003

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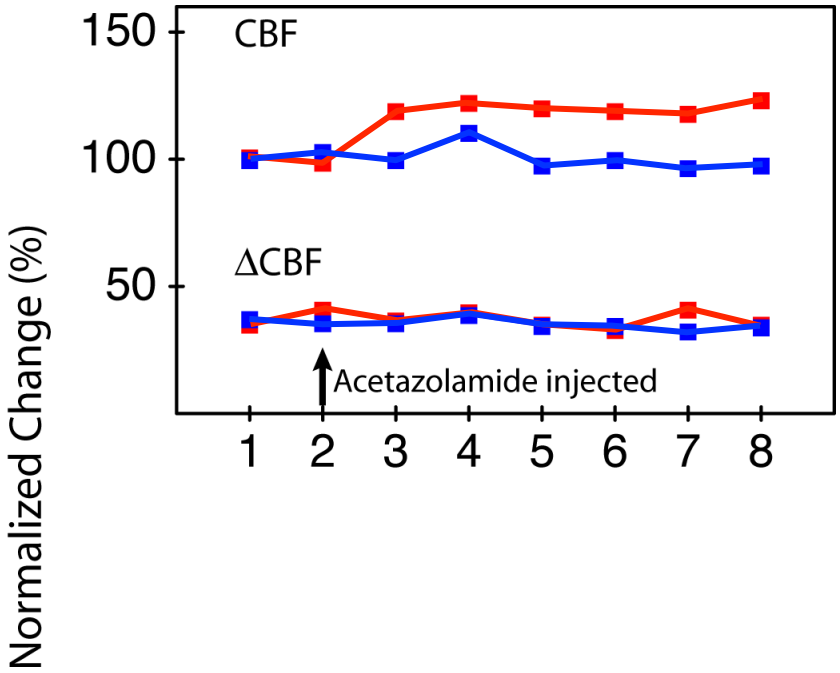

20% increase in baseline CBF
→ no effect on ΔCBF with finger tapping,

G. Brown et al, JCBFM 2003

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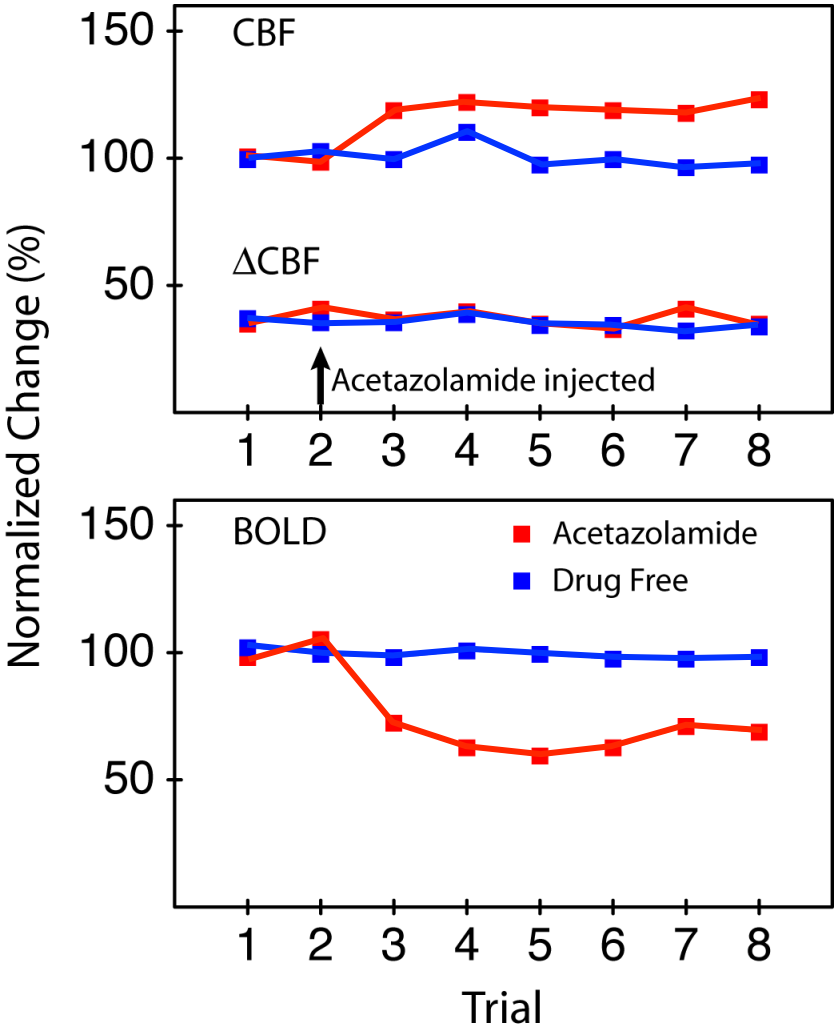
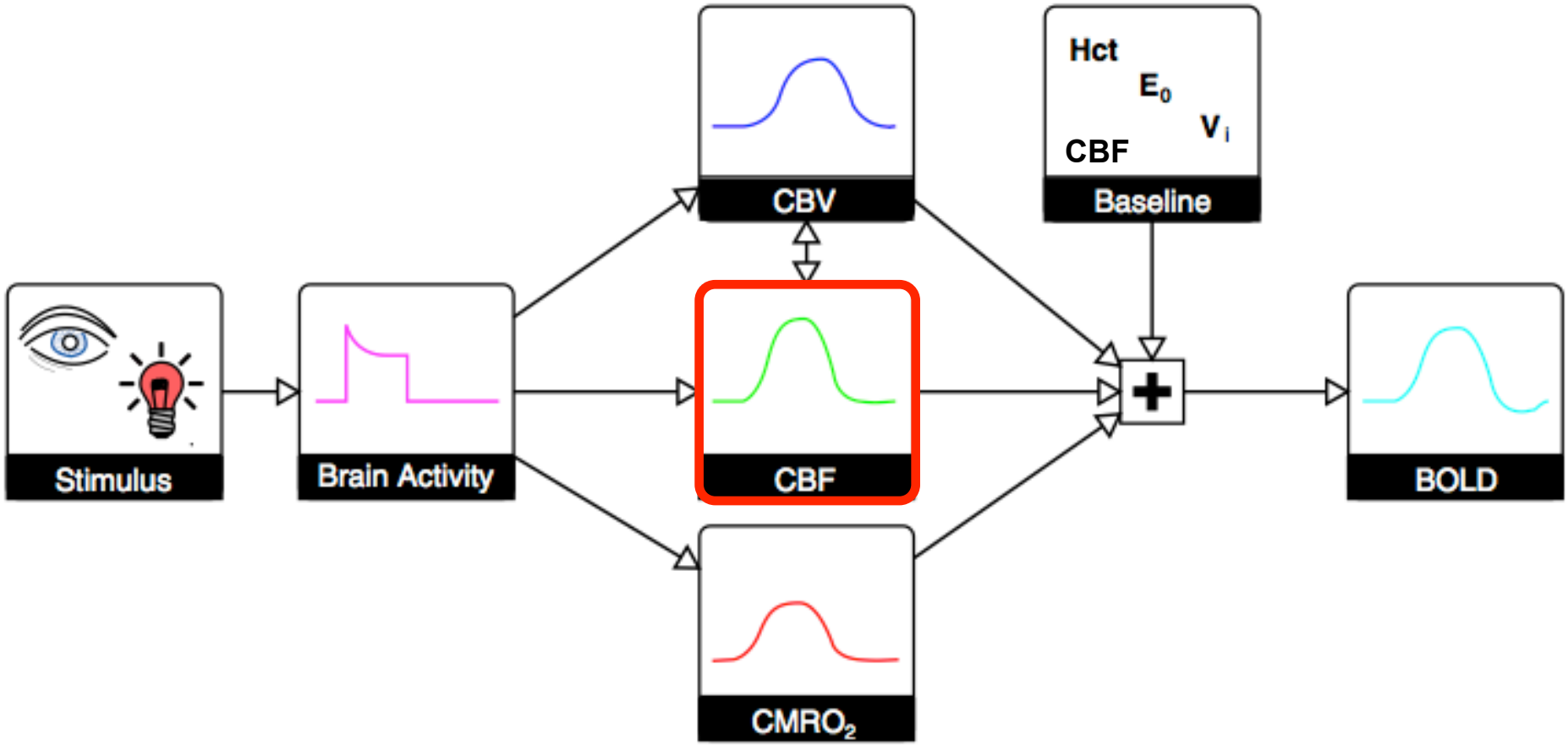


20% increase in baseline CBF
→ no effect on ΔCBF with finger tapping,

→ but BOLD response to finger tapping reduced by 35%

G. Brown et al, JCBFM 2003

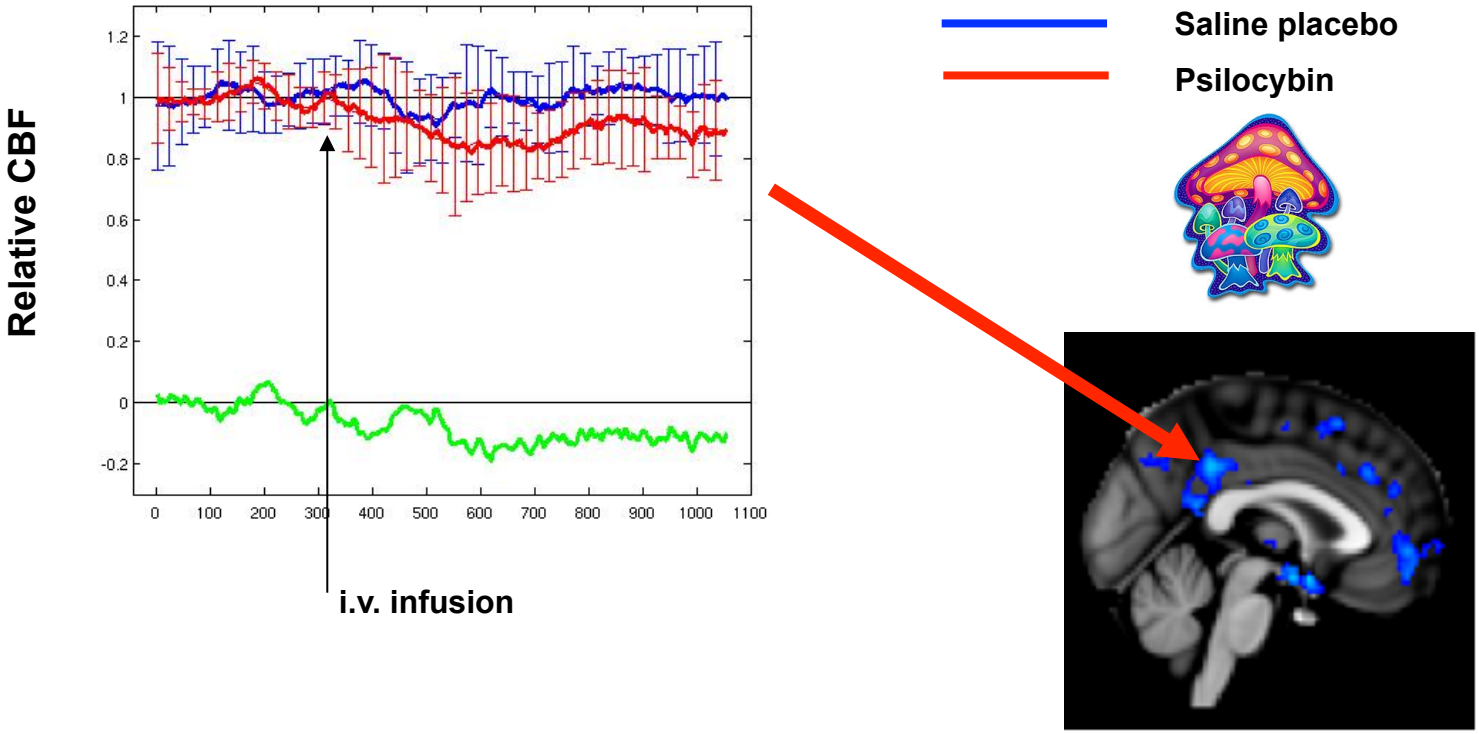
Physiology of BOLD signal



CBF changes contribute to BOLD signal

Blockley et al NMR Biomed (2012)

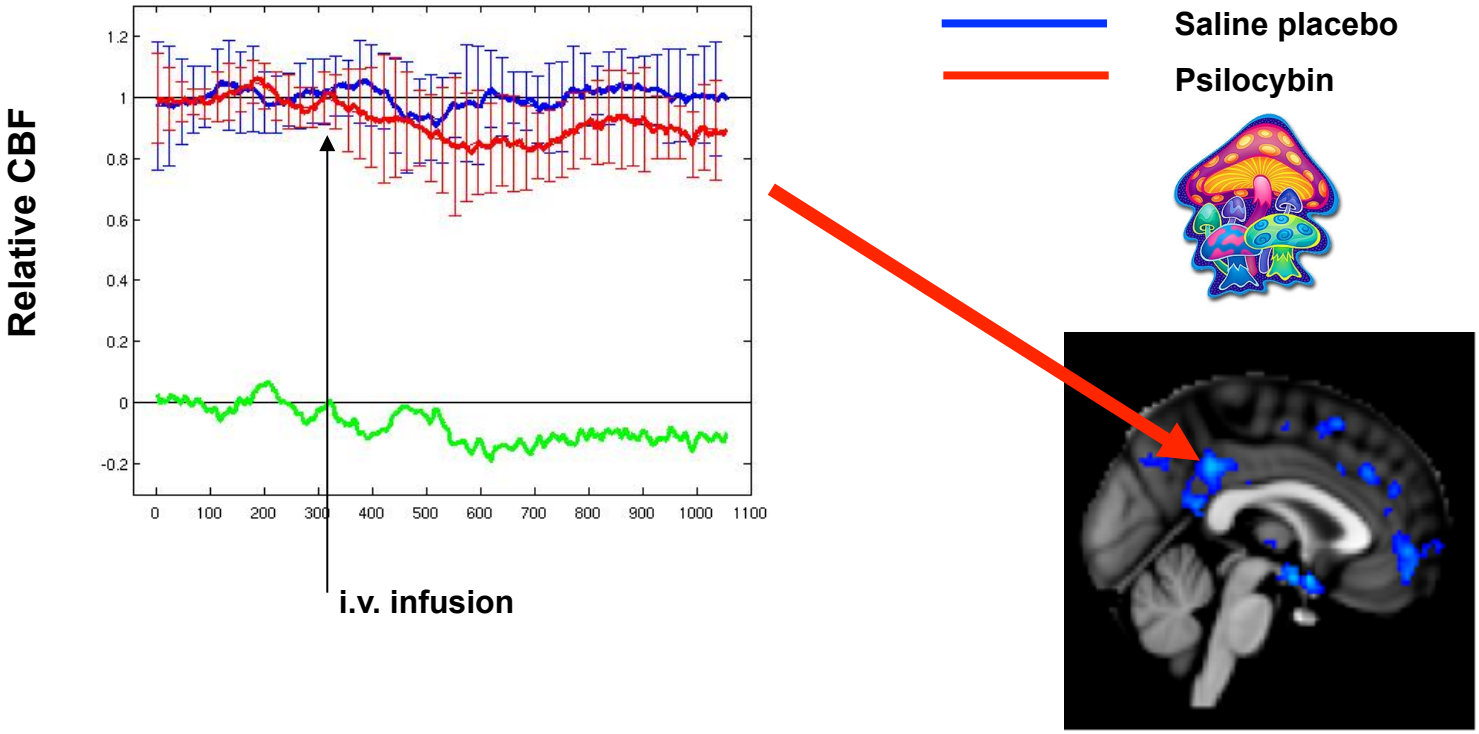
Psilocybin effects on cerebral blood flow



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

Carhart-Harris et al PNAS (2012)

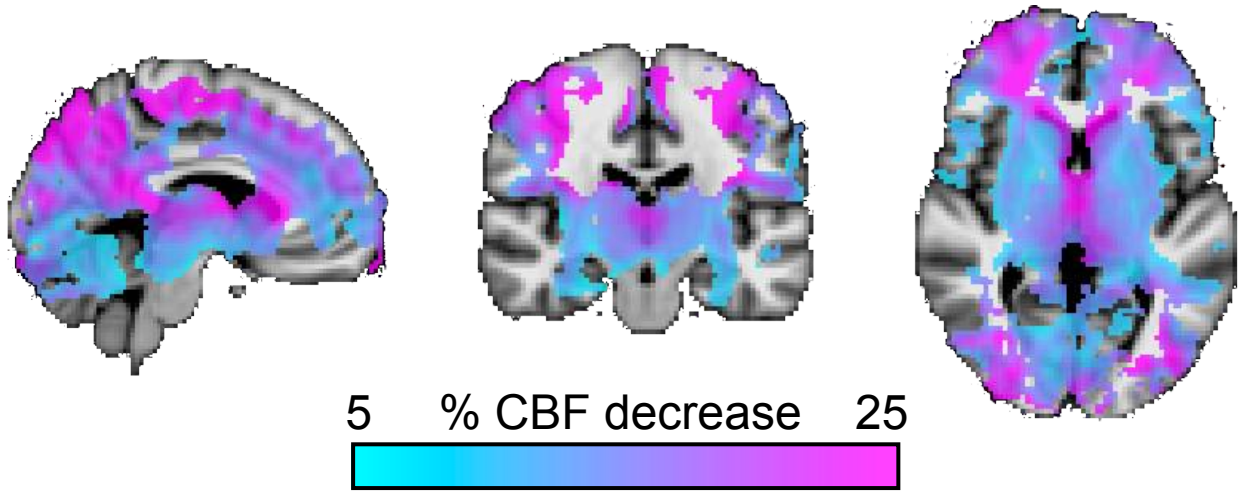
Psilocybin effects on cerebral blood flow



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

Carhart-Harris et al PNAS (2012)

CBF drug effects: caffeine



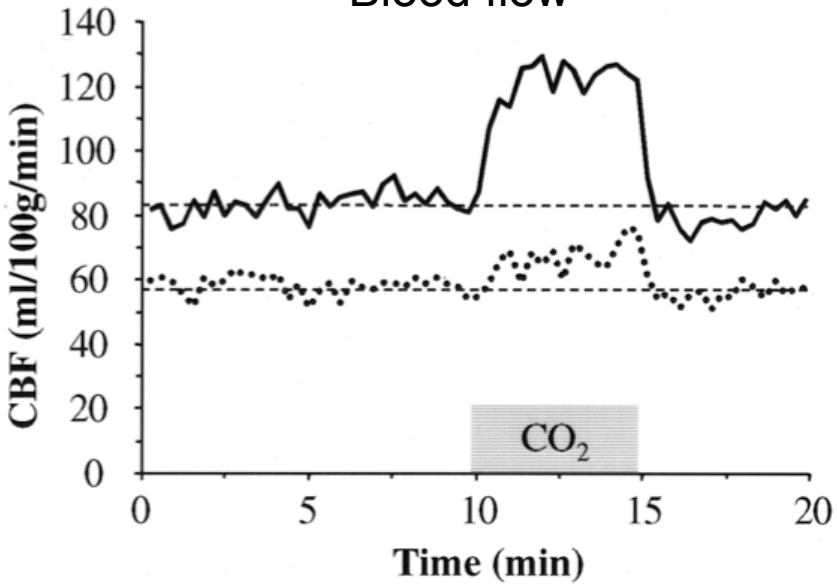
- Another example, of a ‘drug effect’
- This is almost completely a vascular effect. Substantial global decreases in neuronal activity are unlikely.
- … so can we go further in the search for quantification of ‘activity’ than CBF?

Diukova et al Neuroimage (2012)

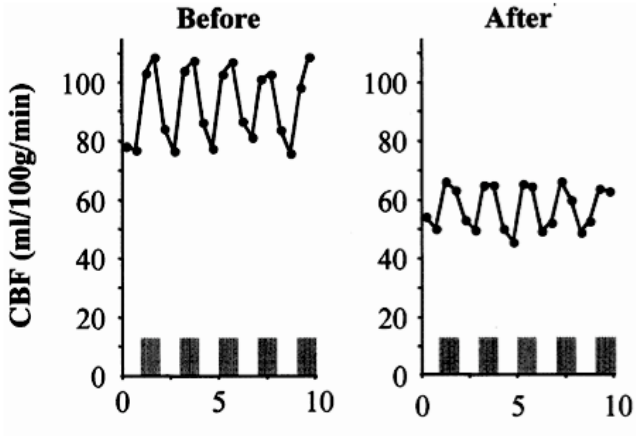
Drug induced change in vascular response

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

Blood flow



CBF response to finger tapping



St Lawrence et al MRM 2003

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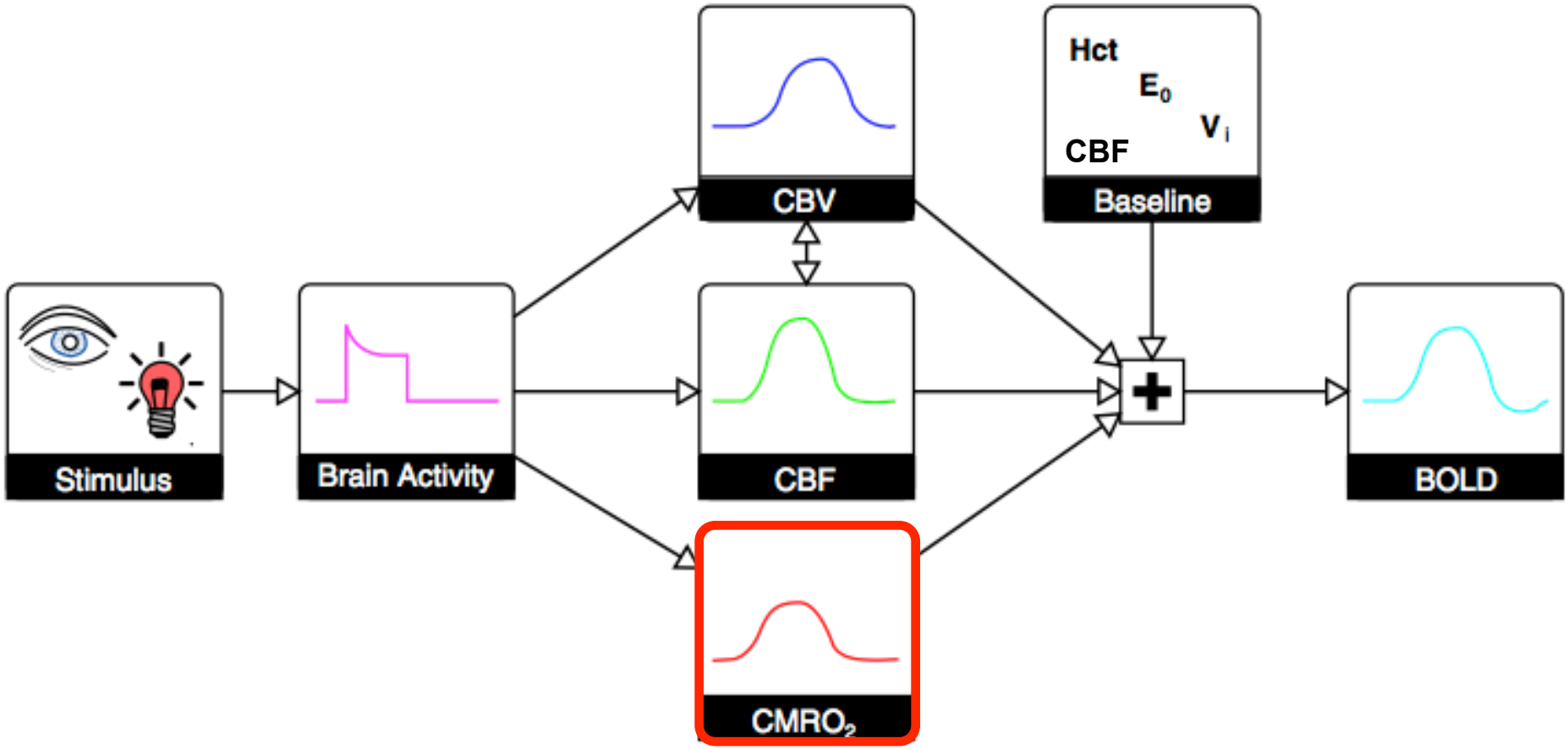
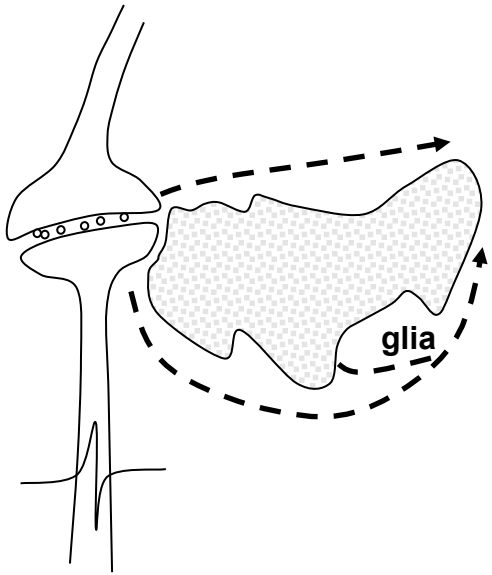


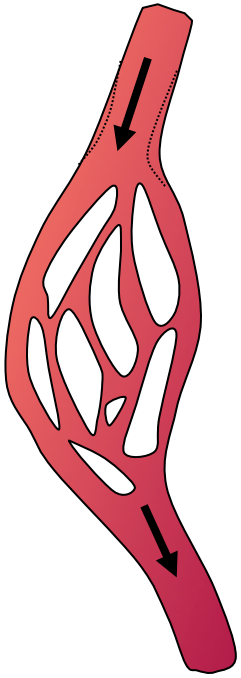
Oxygen consumption

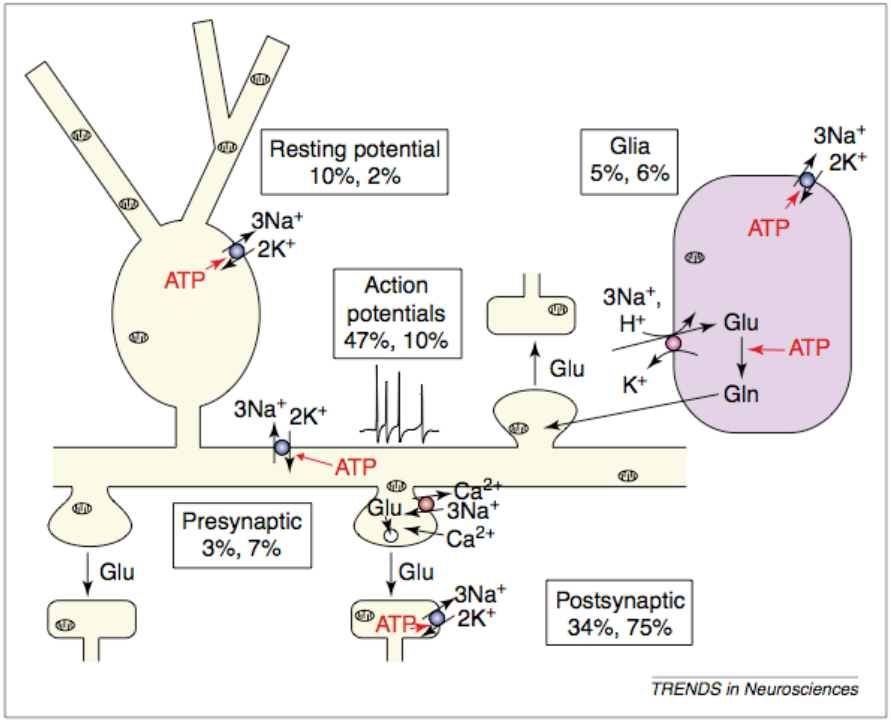
Blockley et al NMR Biomed (2012)

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)



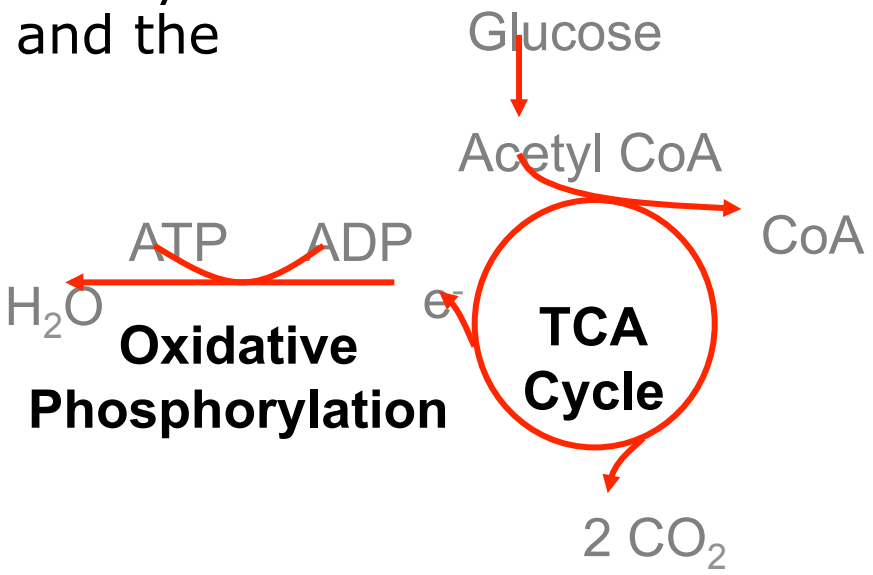




Attwell & Iadecola 2002

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.

Proc. Natl. Acad. Sci. USA
Vol. 95, pp. 316–321, January 1998
Neurobiology

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*

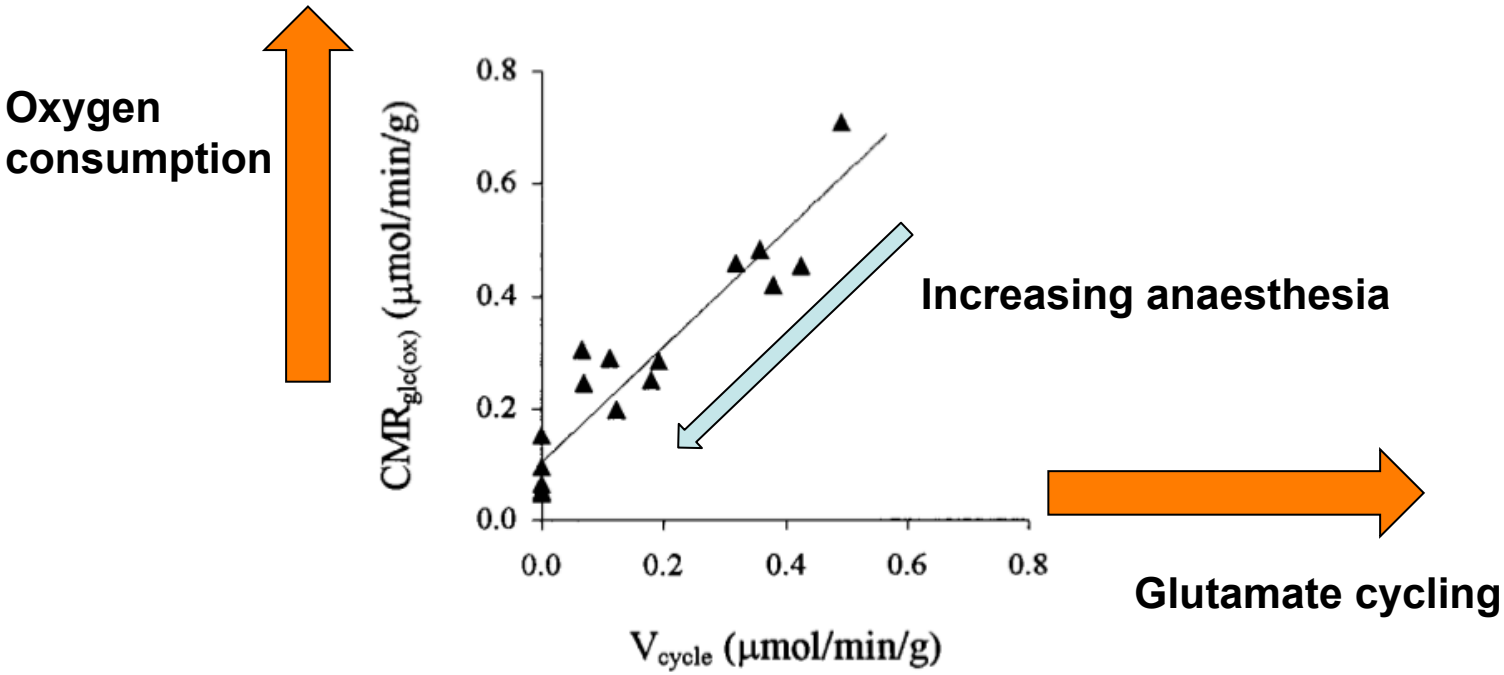
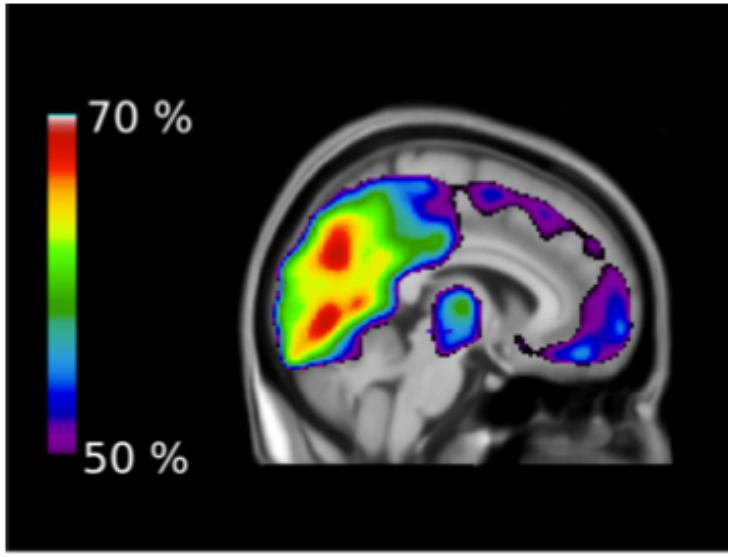


FIG. 3. Graph demonstrating the correlation between the rate of oxidative Glc consumption ($CMR_{Glc(ox)}$) and the rate of glutamate–neurotransmitter cycling (V_{cycle}).

Anaesthesia

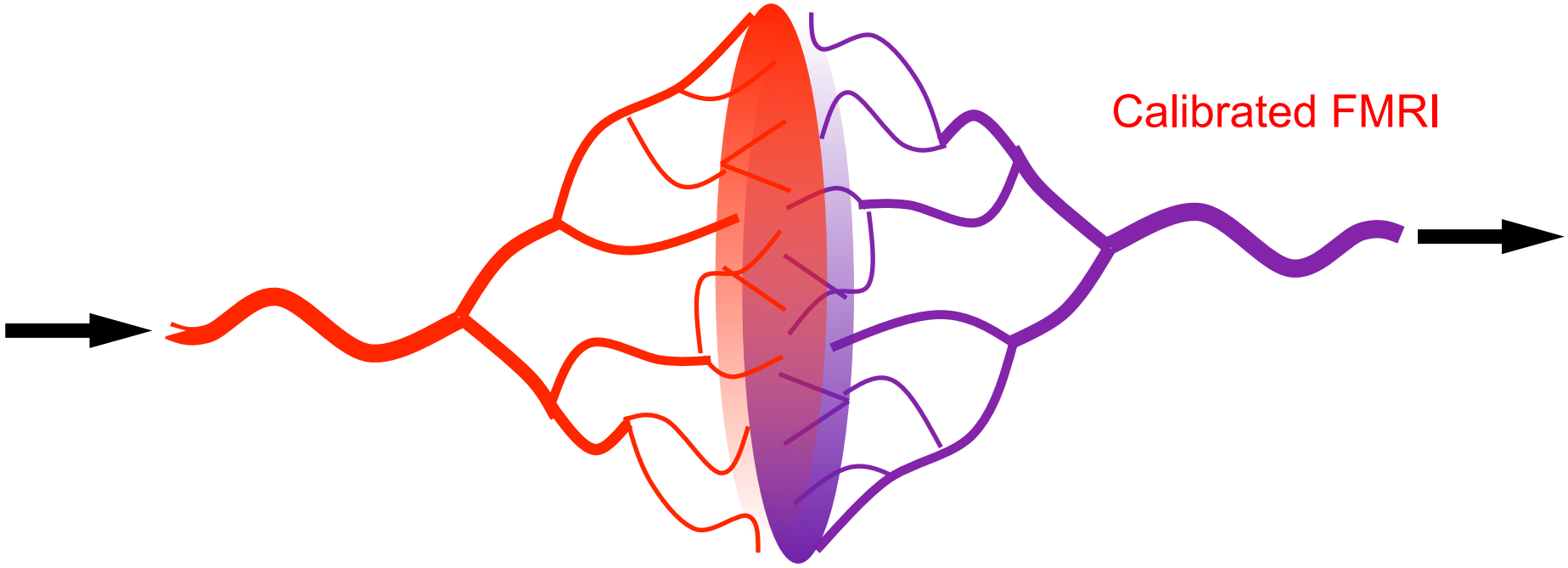
- Glucose metabolism (18 FDG) PET
- % Decreases during anaesthesia



Schlunzen et al Acta Anaesthesiol Scand 2012

Rate of cerebral metabolic oxygen consumption

$$CMRO_2 = C_aO_2 \times OEF \times CBF$$



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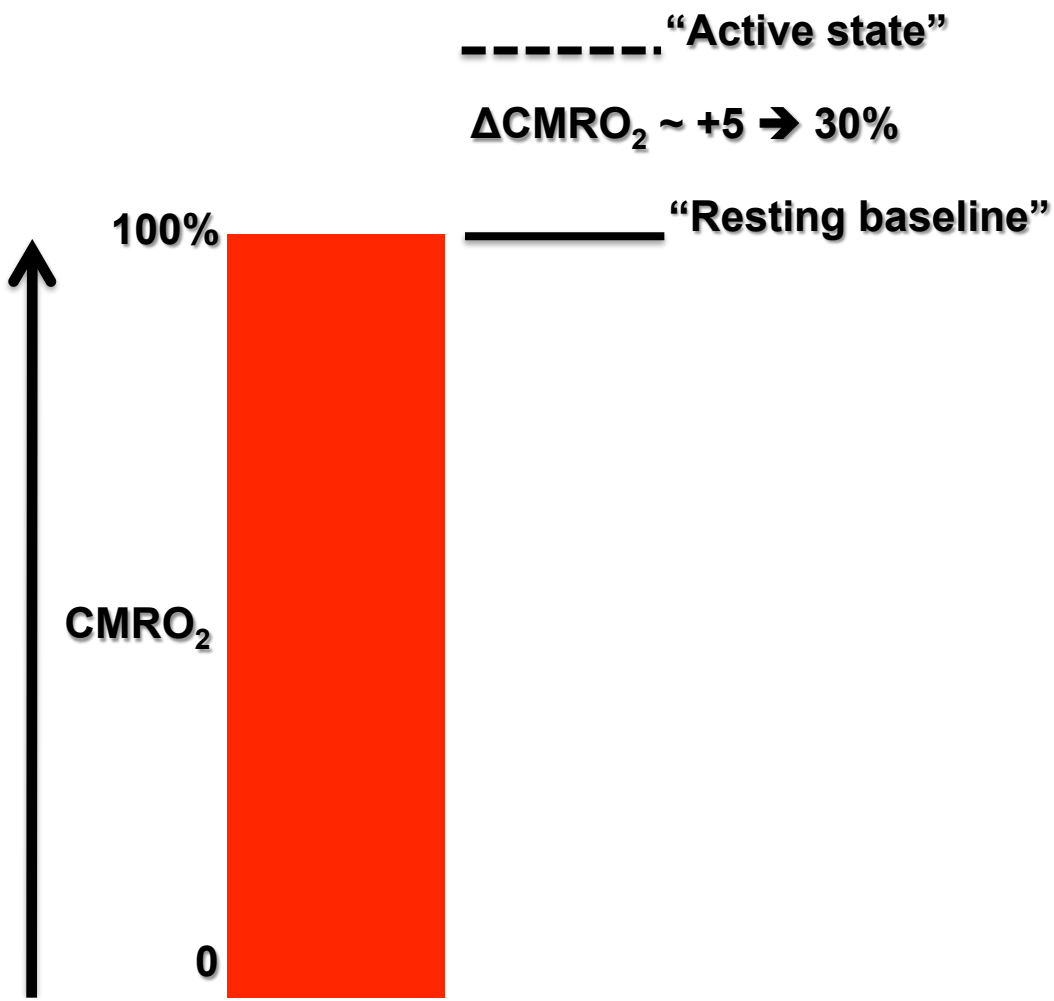

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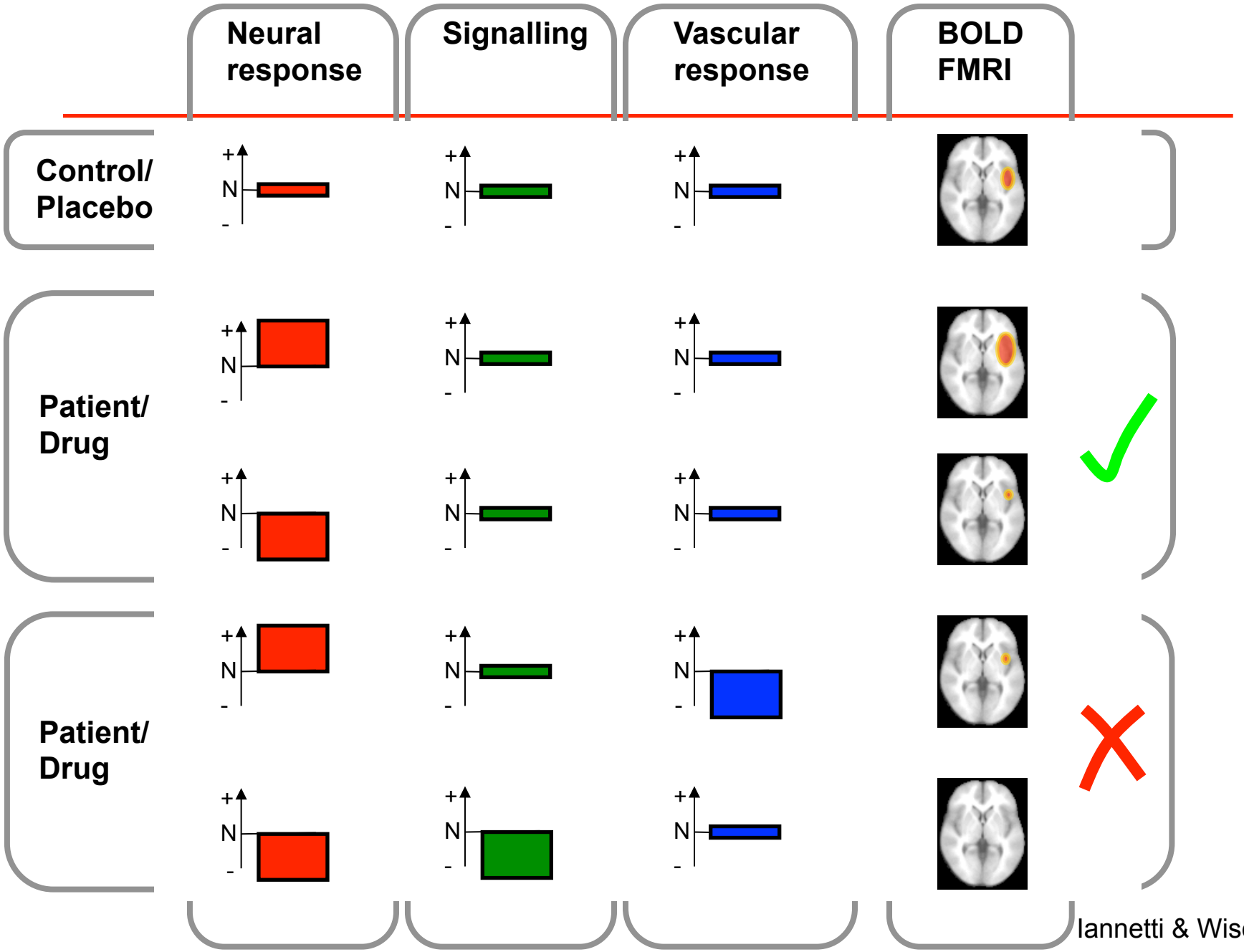

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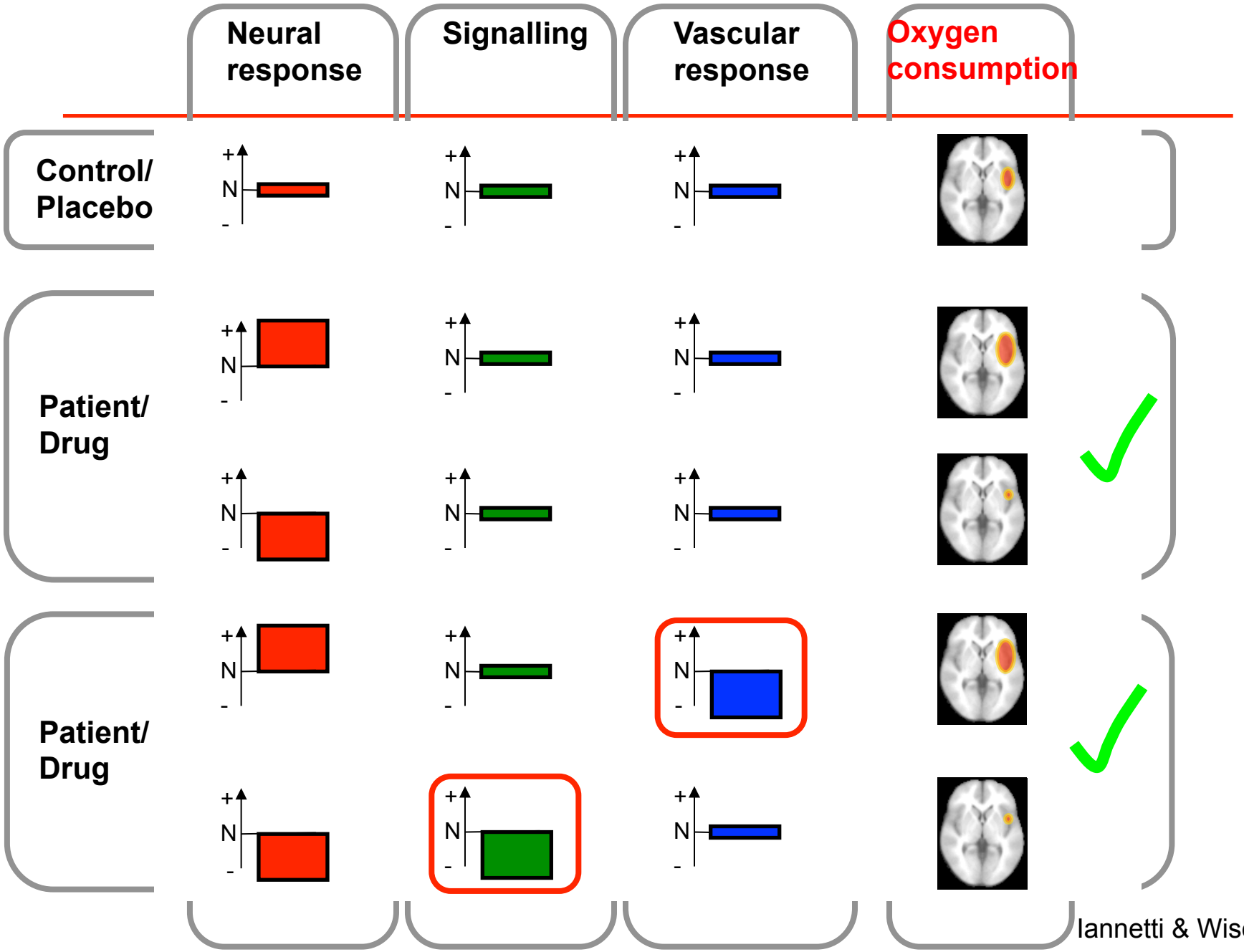

Iannetti & Wise 2007

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.

Acknowledgements

- CUBRIC
  - Kevin Murphy
  - Alan Stone
  - Esther Warnert
  - Ashley Harris
  - Judith Hall
  - Mike Germuska
- HEFCW
- EPSRC
- Wellcome Trust