Pharmacological FMRI: principles and confounds

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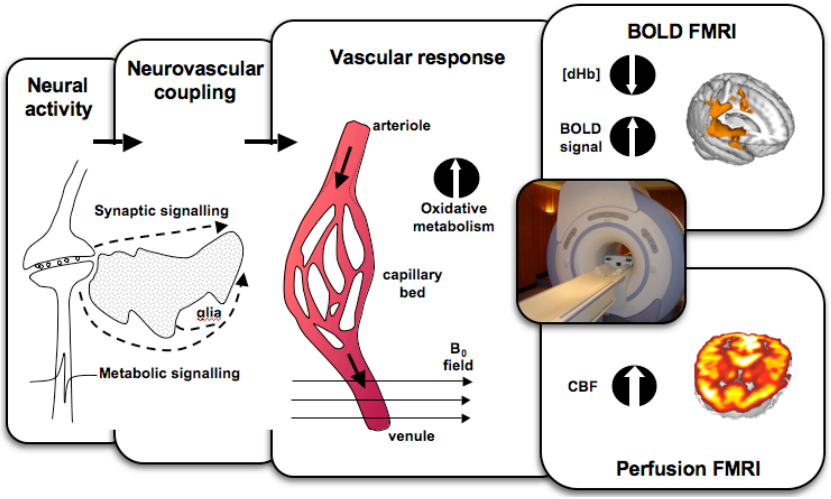
Overview



- What is pharmacological FMRI
  - Types of phFMRI experiment
- Potential limitations on interpretation
  - Vascular influences e.g. vascular reactivity
  - Changing baseline
- Multi-modal and alternative measurements
  - Cerebral blood flow (CBF)
  - EEG-FMRI
  - metabolism

PhFMRI: what do we want?

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

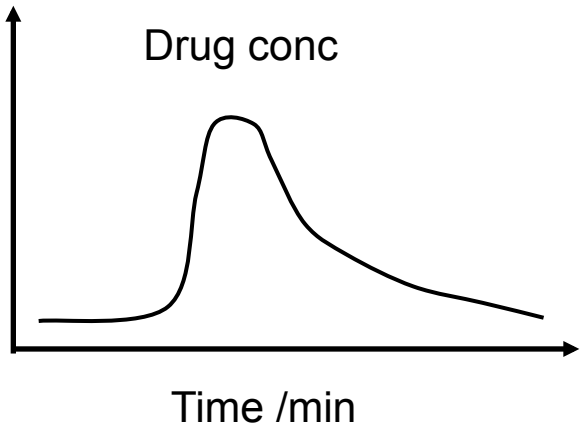
BOLD pharmacological FMRI

- A BOLD FMRI experiment + drug administration

- Blood Oxygenation Level Dependent Imaging
  - Signal changes are a function of changes in
    - Metabolic oxygen consumption
    - Cerebral blood flow
    - Cerebral blood volume

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

Modulation of baseline activity according to pharmacokinetics



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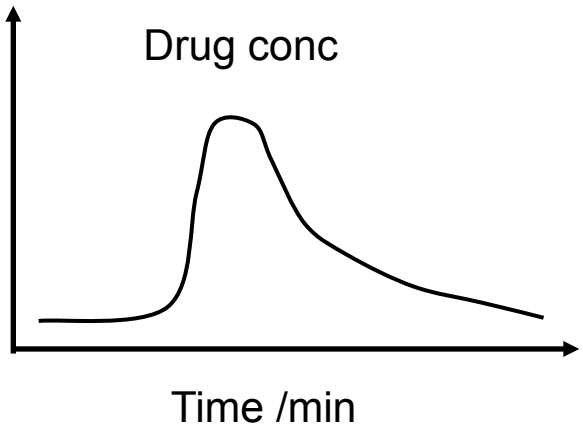

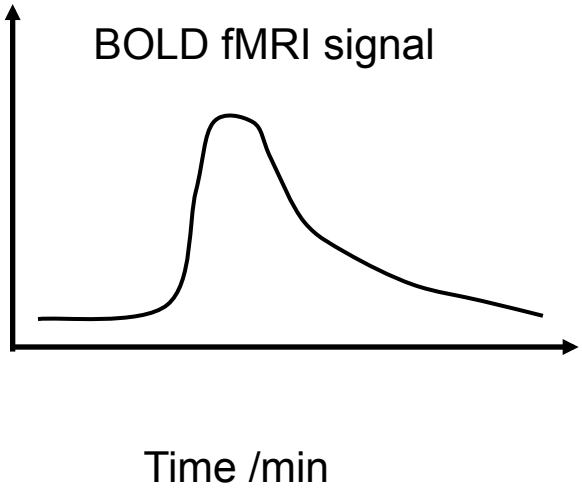

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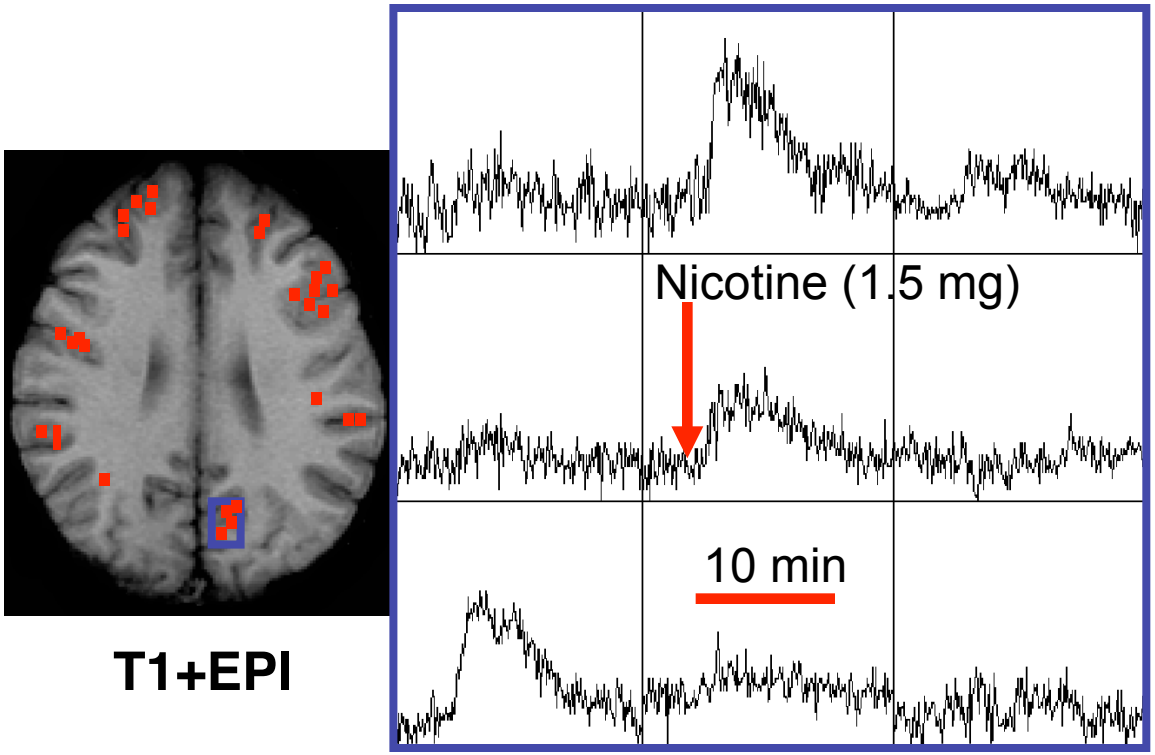
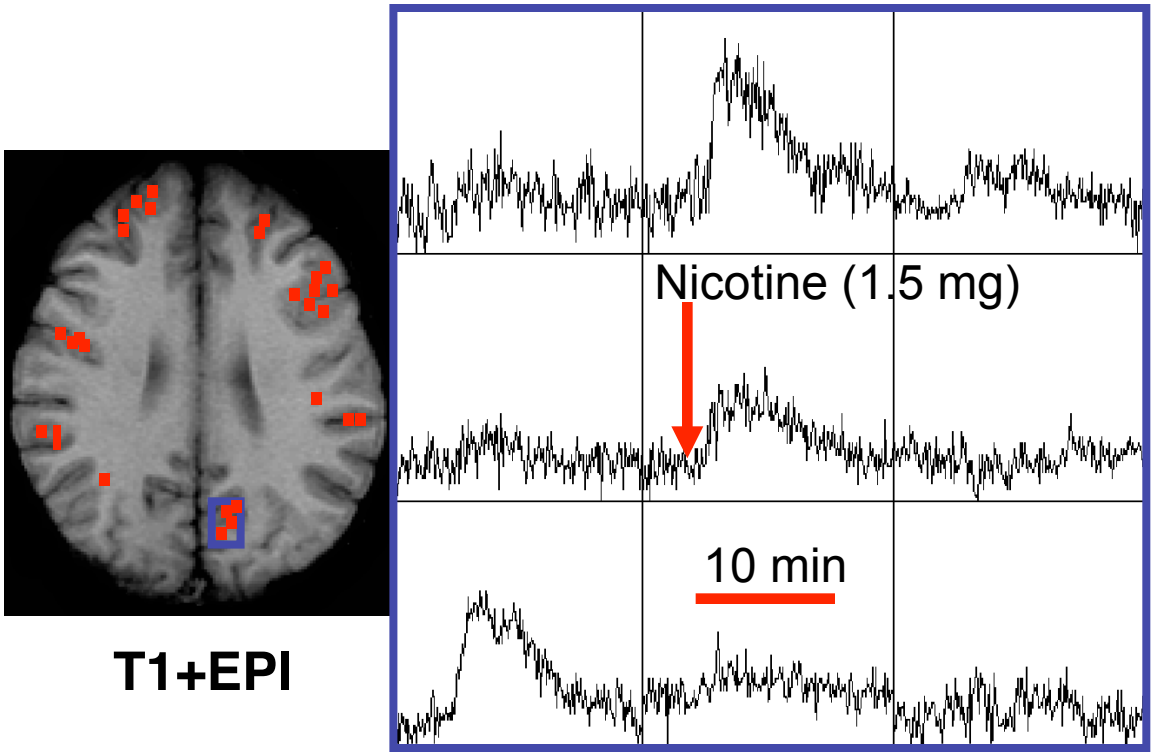


- Waveform analysis protocol (WAP) for BOLD signal

Bloom et al. HBM 1999, Am J Psych 1998

Modulation of baseline activity according to pharmacokinetics

- Slow changes in BOLD signal
  - Signal drifts problematic in man
  - More easily applied in animals (phMRI)



- Waveform analysis protocol (WAP) for BOLD signal

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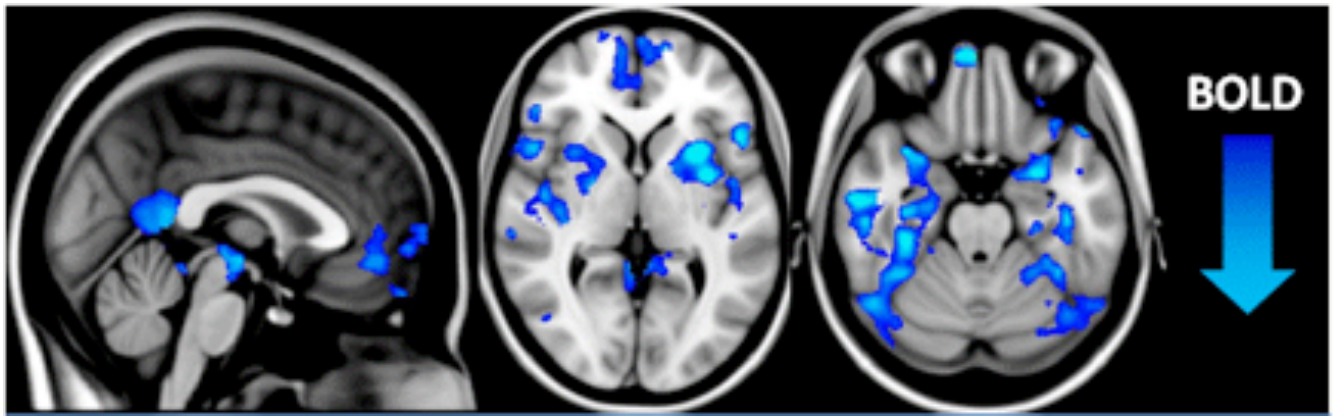
Modulation of baseline activity following psilocybin infusion

- Slow changes in BOLD signal modelled from the time-course of subjective effects (approx 10 mins)



- Linear modelling of BOLD signal

Carhart-harris et al PNAS (in press)

Modulation of baseline activity following psilocybin infusion

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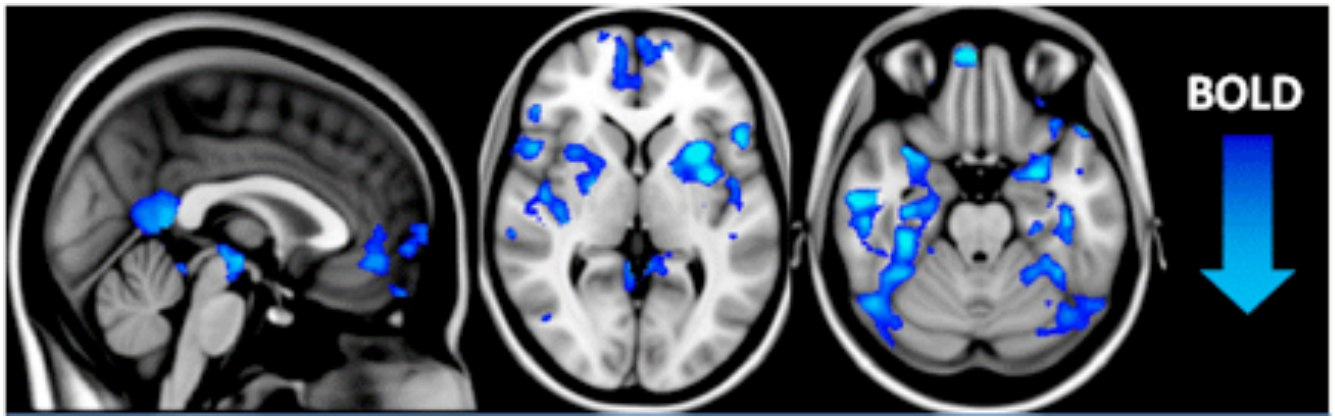

- Can also be assessed with arterial spin labelling (ASL) cerebral blood flow (CBF) measurement (more later)

- Linear modelling of BOLD signal

Carhart-harris et al PNAS (in press)

Modulation of baseline activity following psilocybin infusion

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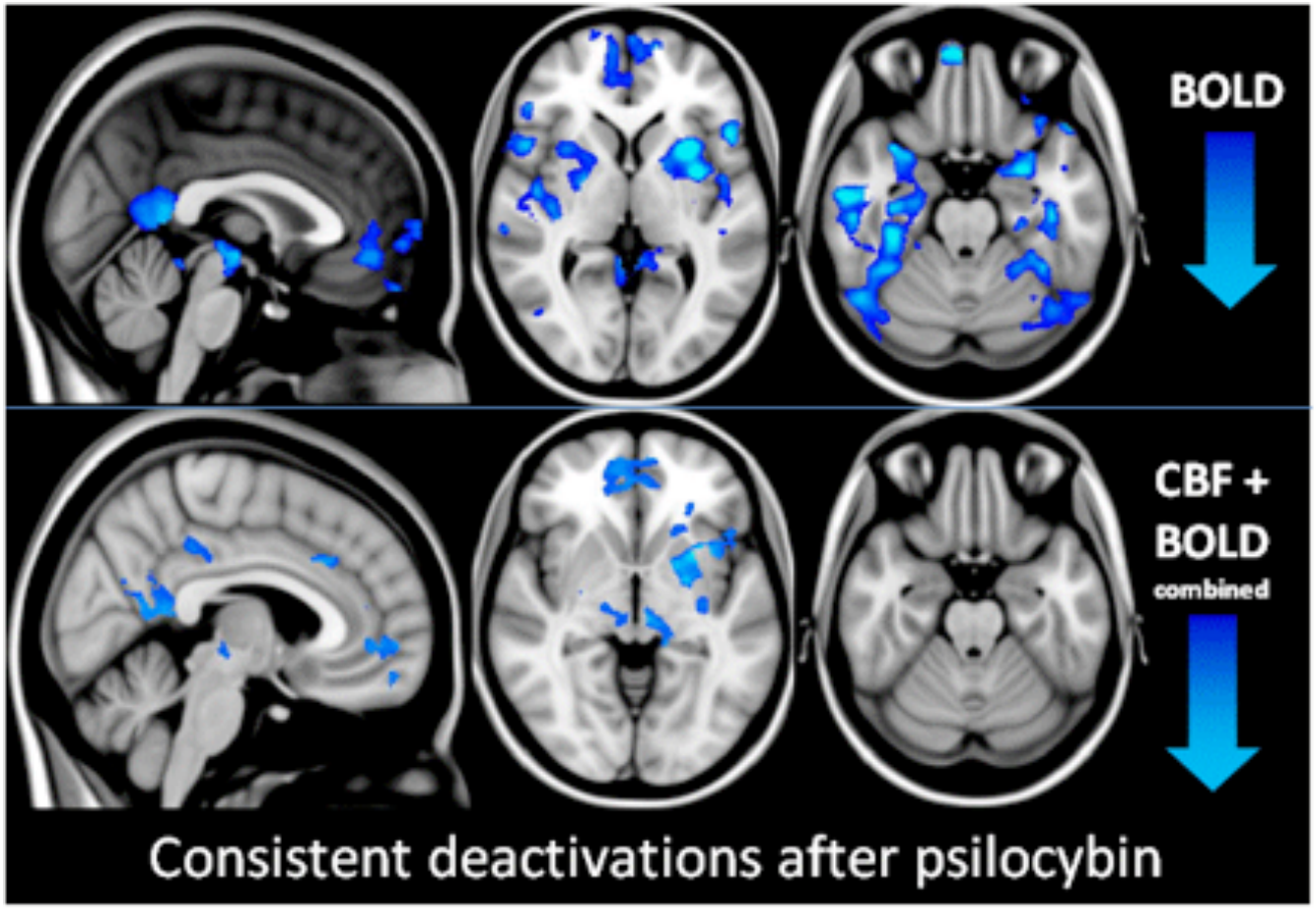
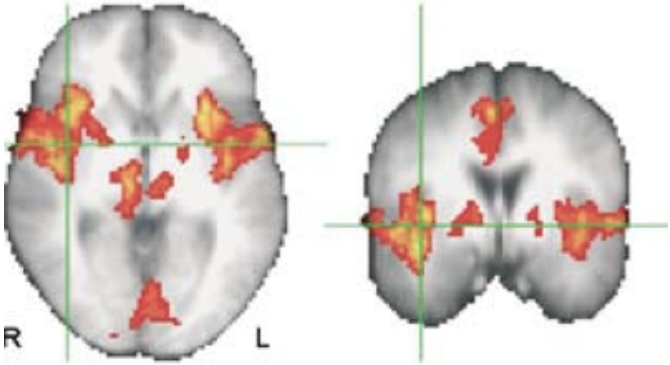


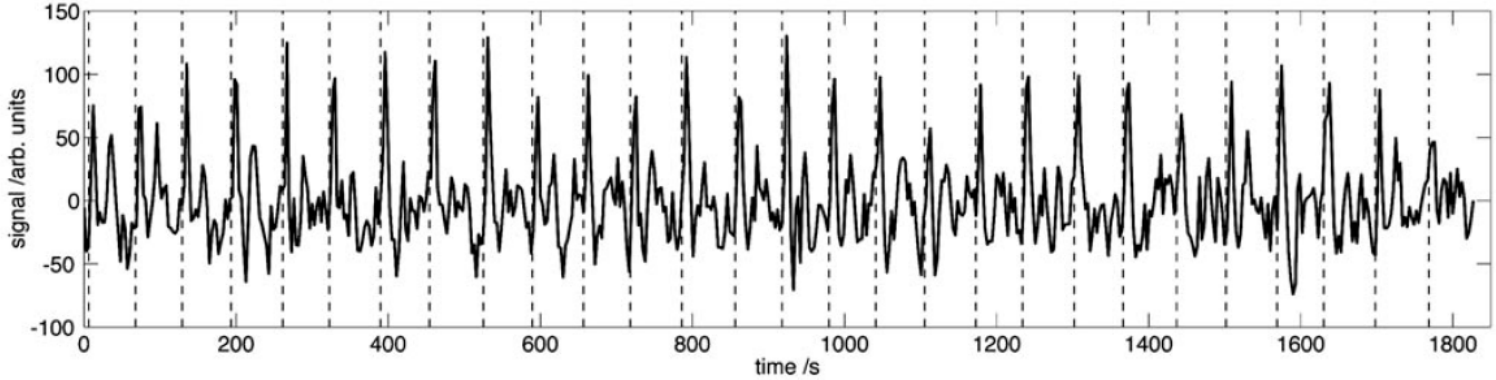
Carhart-harris et al PNAS (in press)

Modulation of task-related activity

- Stimulus-induced BOLD response

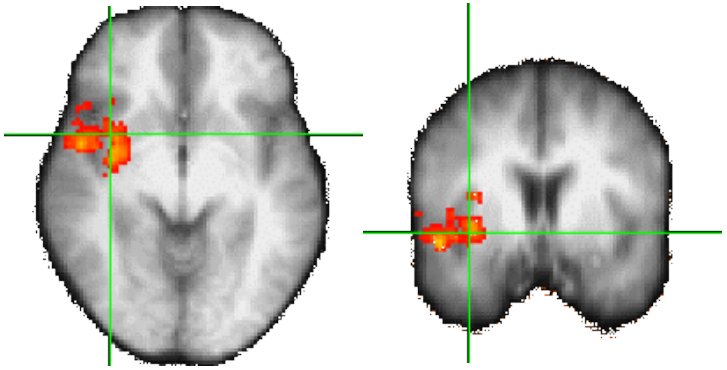


Wise et al Neuropsychopharmacology 2004, **Thermal pain, brain activity**



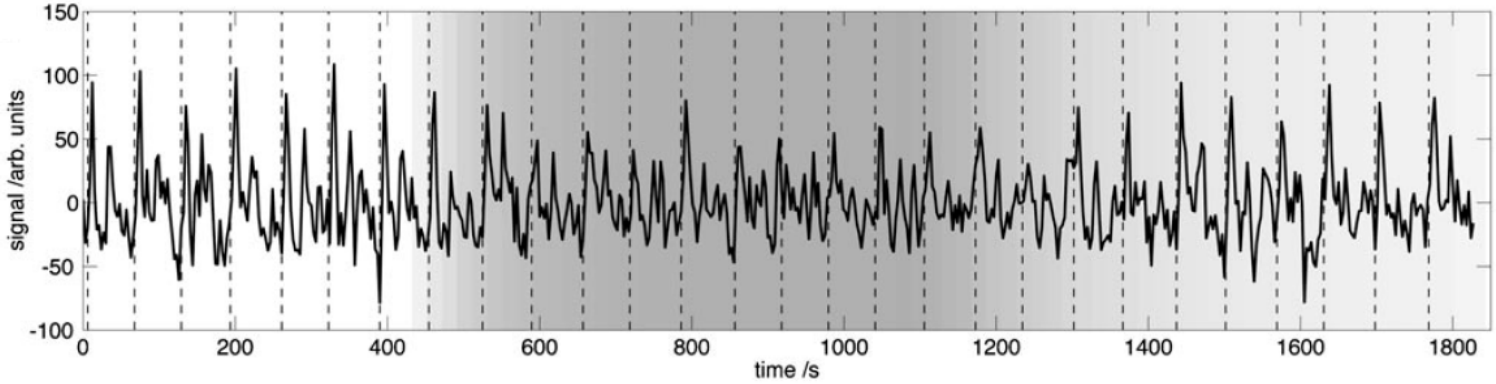
Modulation of task-related activity

- Stimulus-induced BOLD response - reduced by mu-opioid

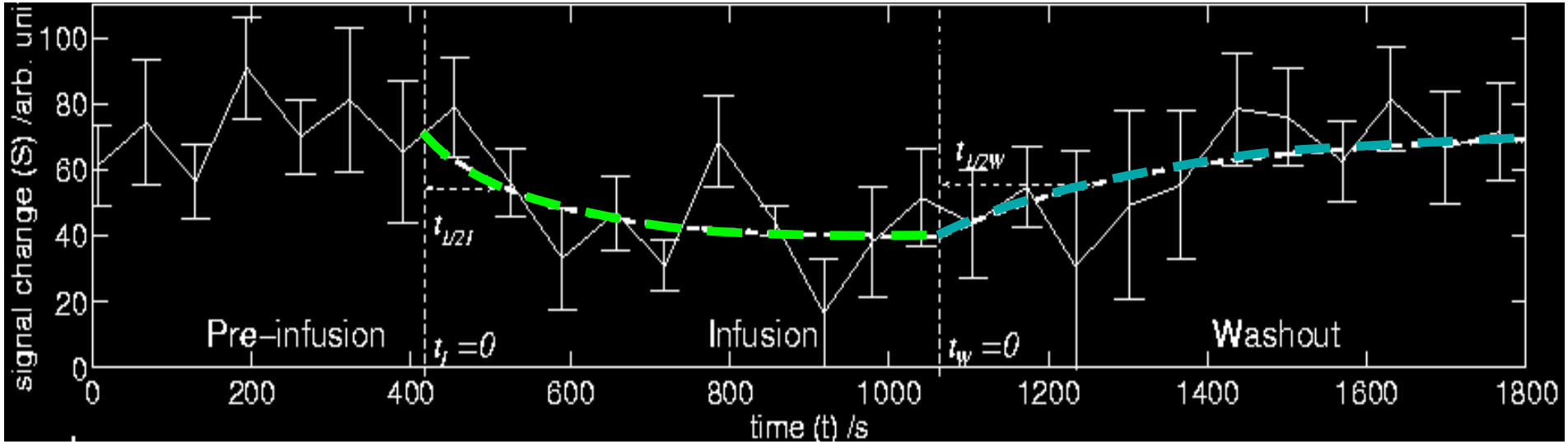


Insula, FMRI derived

Wise et al Neuropsychopharmacology 2004, **Thermal pain, brain activity**



Time of action: PK/PD measurement



Pre-infusion:
mean amplitude
S_0

During-infusion:
final amplitude
S_1

Washout:
modelled amplitude

$$S(t_w)=S_0-(S_0-S_1).\exp(-t_w.\ln 2/t_{1/2})$$

Wise et al. Neuropsychopharmacology. 2004

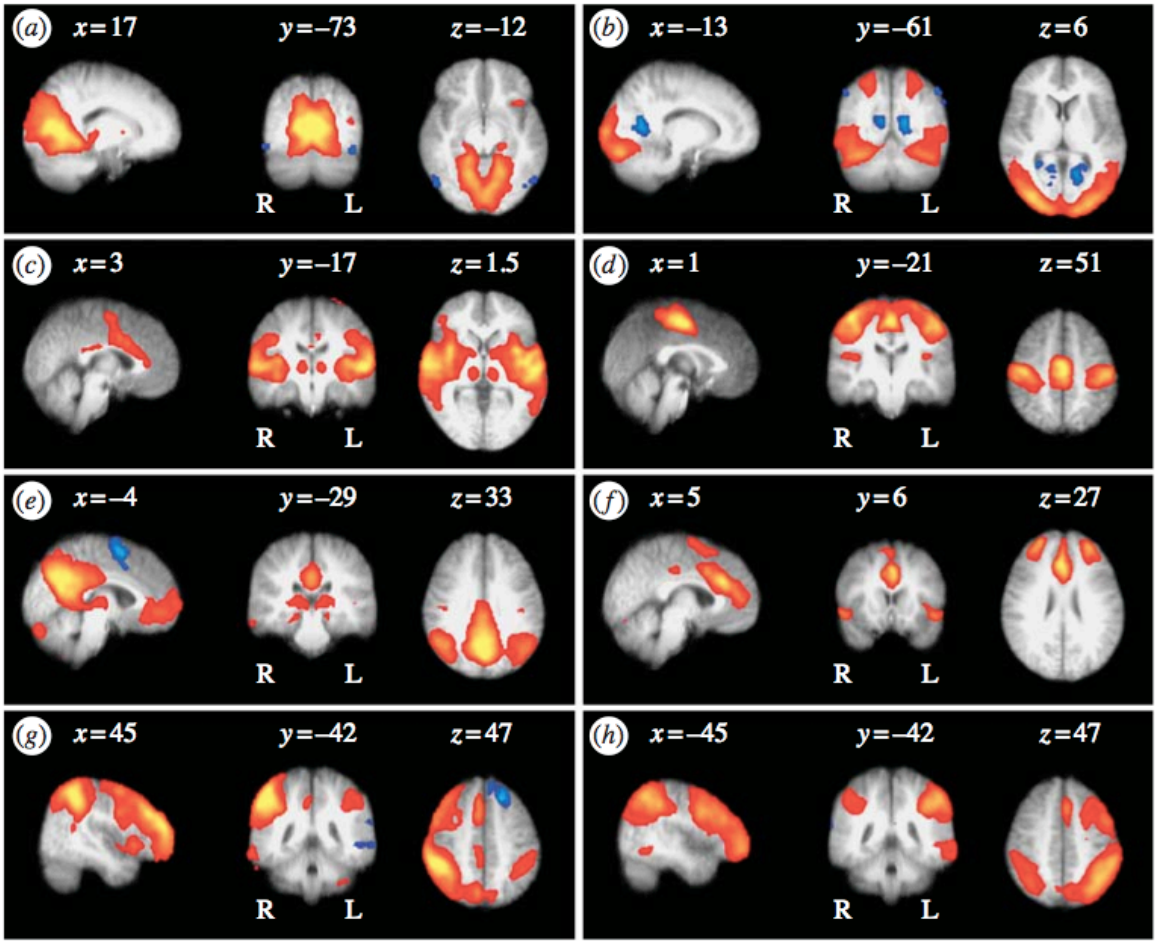
Time of action: PK/PD measurement

	FMRI signal (insular cortex)	Reported pain intensity
Onset equilibration time $t_{½}$ k_{e0} (95%CI) min	1.62 (-2.52 5.76)	2.80 (-0.12,5.73)
Offset half-life $t_{½}$ (95%CI) min	3.20 (0.58,5.82)	2.80 (1.12,4.48)

- Minto et al. Anesthesiology. 1997
- $t_{1/2}k_{e0}$ from: EEG 1.6±0.9 min, analgesia 1.3±1.5 min
- $t_{1/2}$ from: EEG 3-5 min, plasma conc 3.2±0.9 min

Modulation of resting-state activity

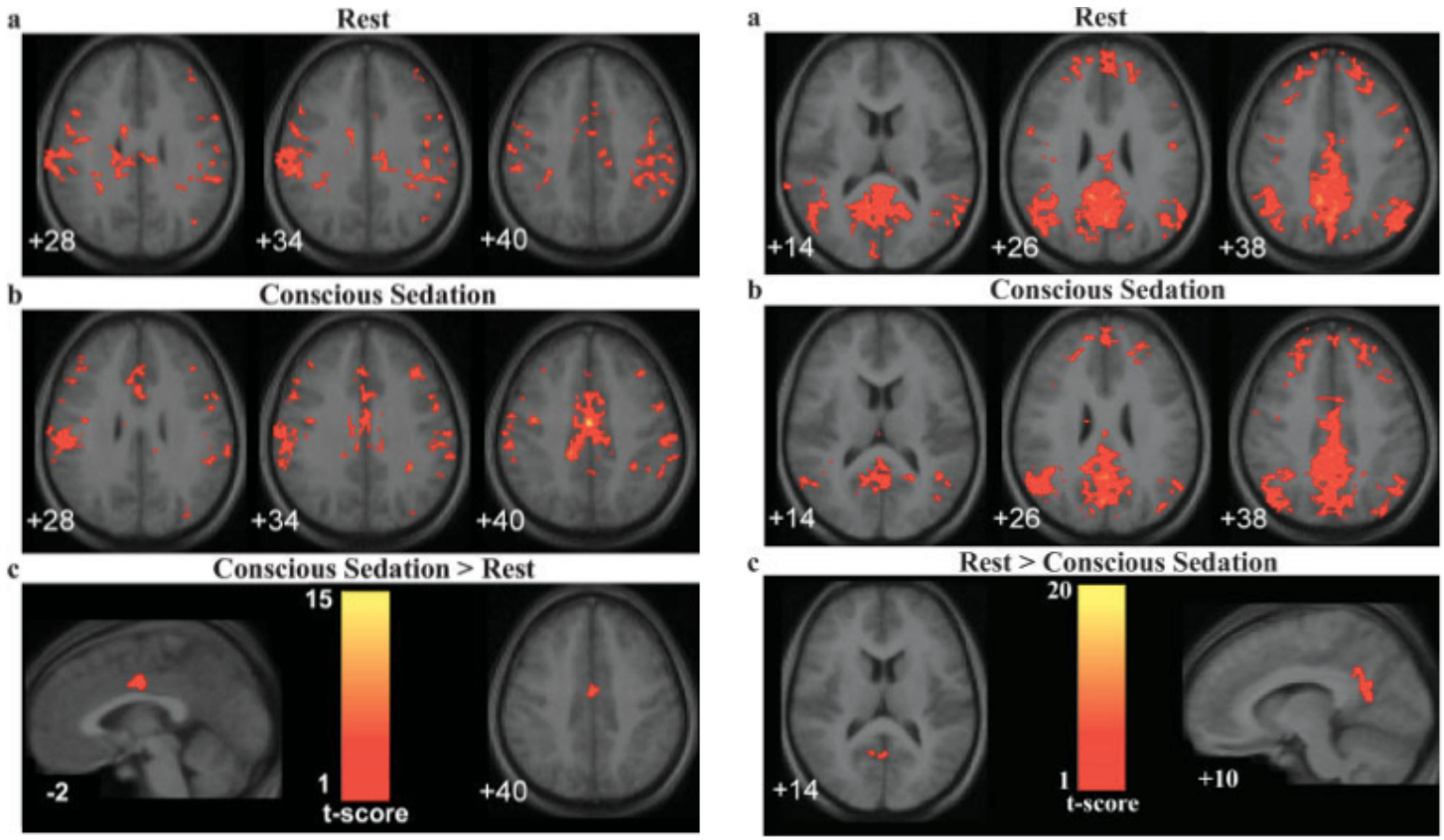
- BOLD signal oscillations implying synchronised network activity (assumed neural)



Beckmann et al
Phil. Trans. R. Soc.
B 2005

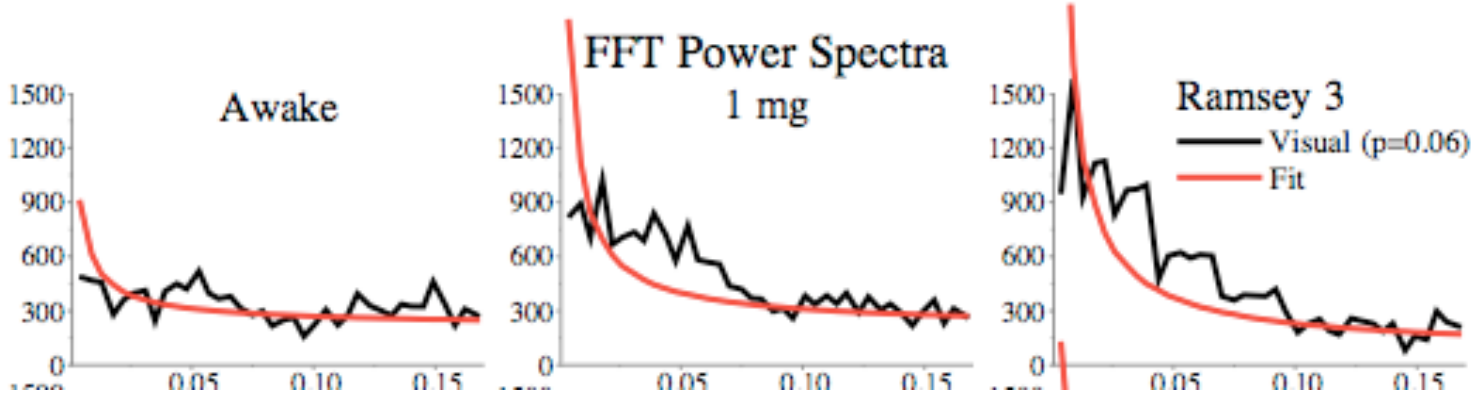
Modulation of resting-state activity

- BOLD signal oscillations implying synchronised network activity (assumed neural)
  - Midazolam sedation (Greicius, Hum Brain Mapp, 2008)
    - Altered 'functional connectivity'

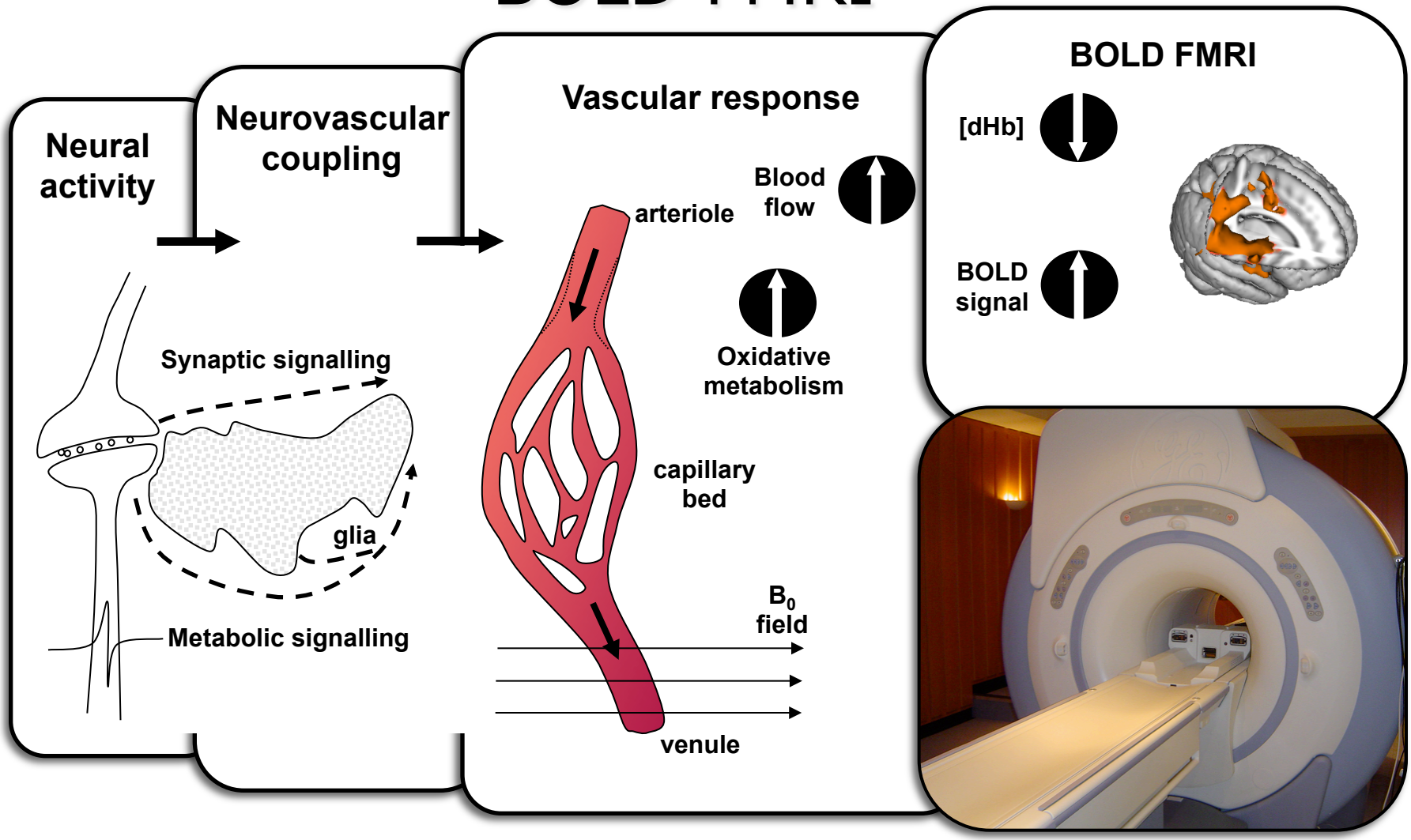


Modulation of resting-state activity

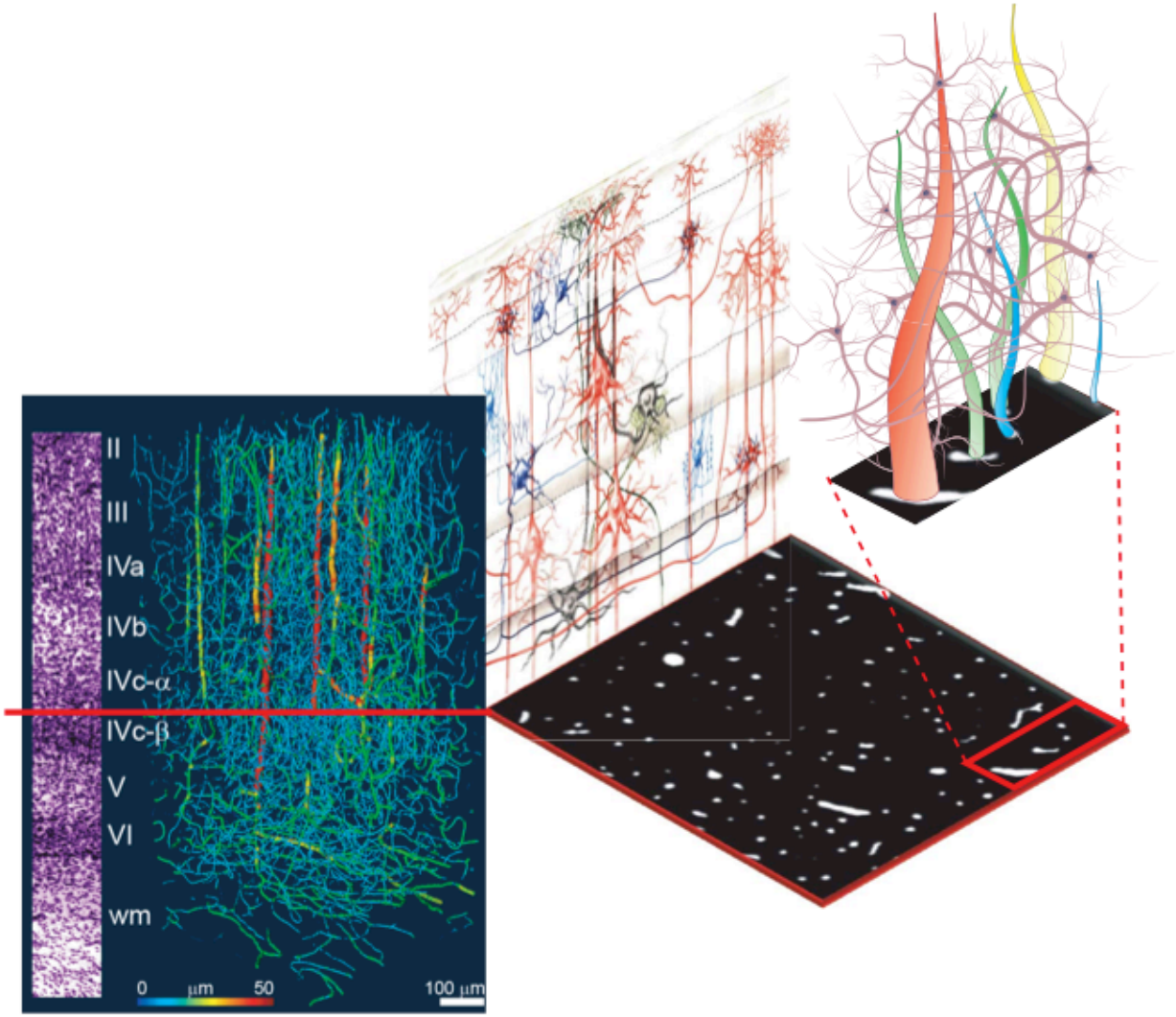
- BOLD signal oscillations implying synchronised network activity (assumed neural)
  - Midazolam sedation (Kiviniemi, Magn Reson Imag, 2005)
    - Altered general low frequency BOLD oscillations … neural or vascular?
    - Vasomotion and CO2 effects



BOLD FMRI


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

What's in an image voxel?



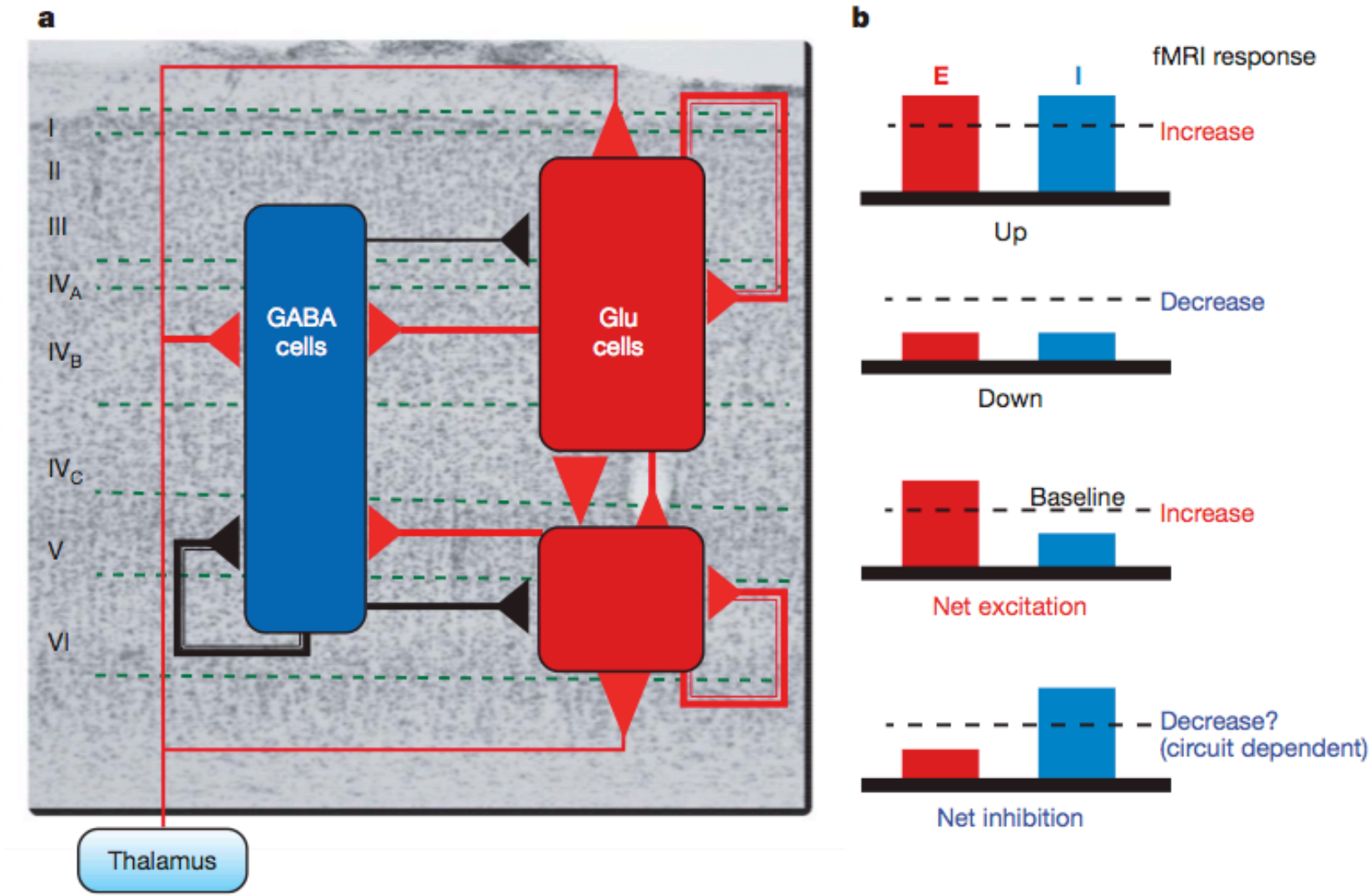
55 µl of stuff

- 3% **vessels**
- 5.5×10^6 **neurons**
- 5.5×10^{10} **synapses**
- 22 km of **dendrites**
- 220 km **axons**

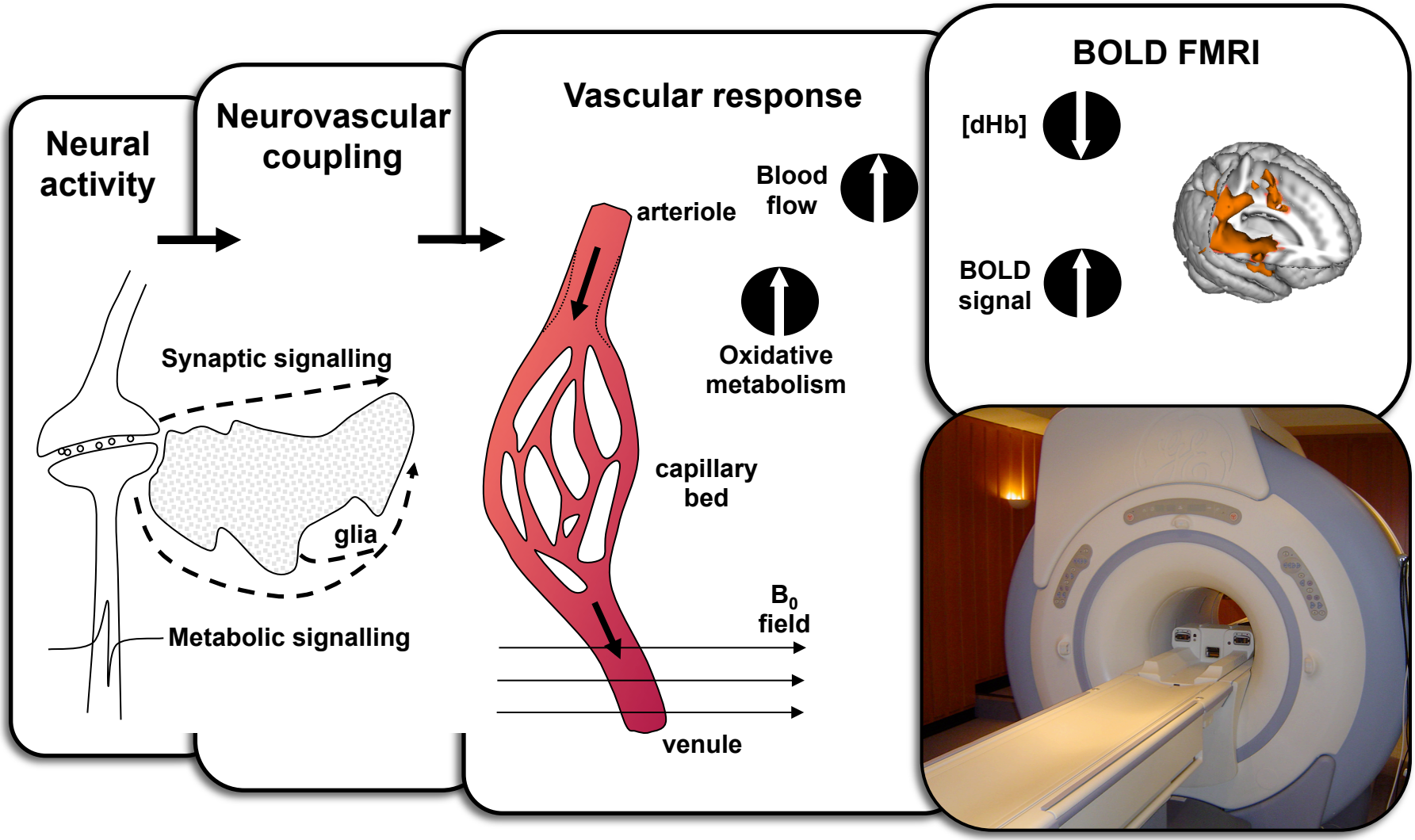
Logothetis, Nature 2008

BOLD: a balance between excitation and inhibition

cortex



Logothetis, Nature 2008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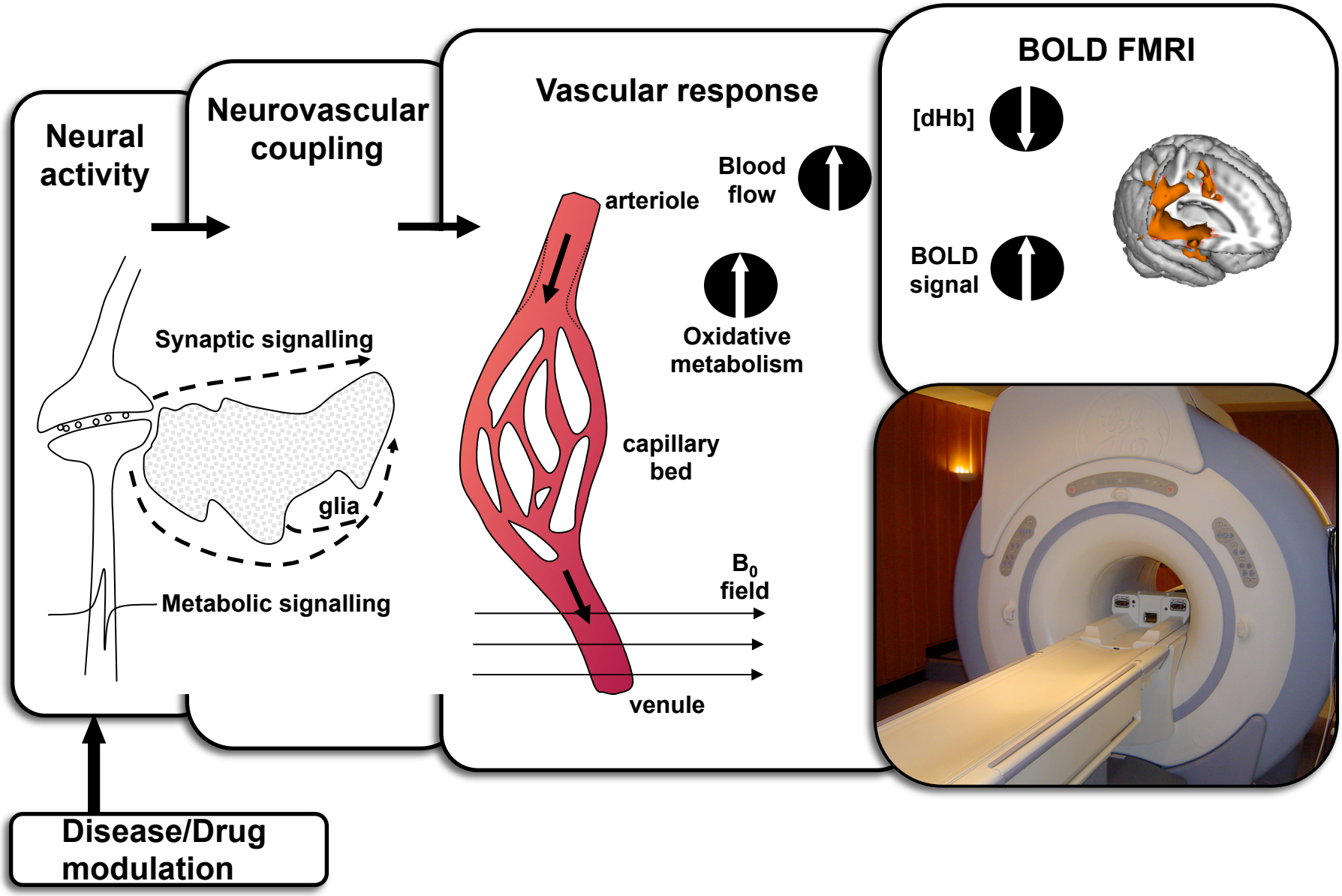
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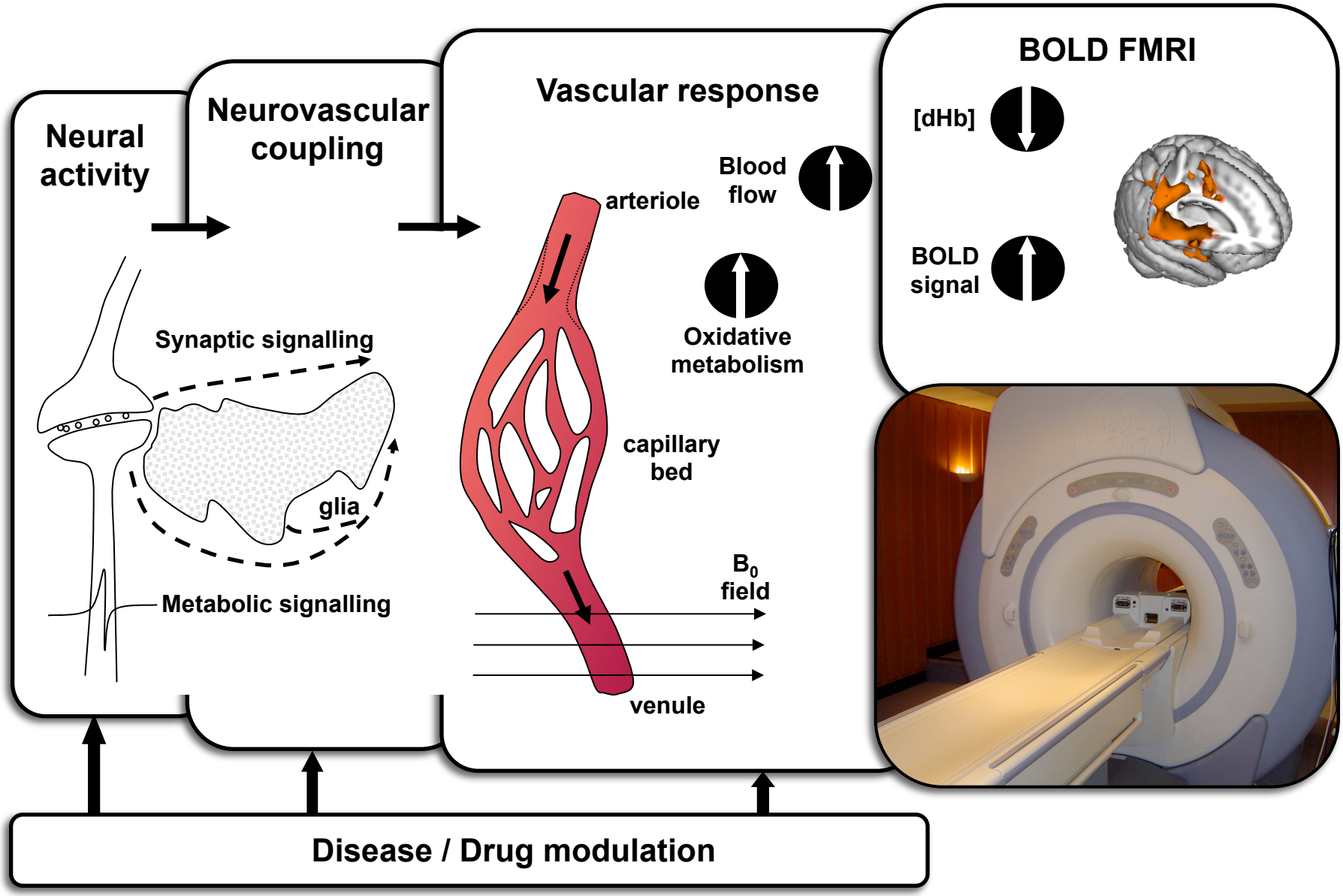
BOLD FMRI
[dHb]
BOLD signal
Disease/Drug modulation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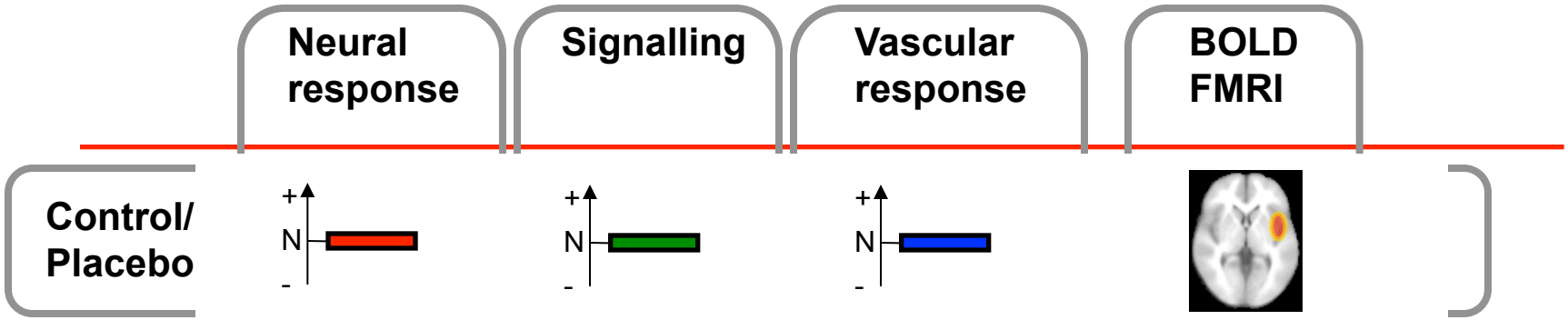
BOLD signal
Disease / Drug modulation

N = normal response



Iannetti & Wise
2007

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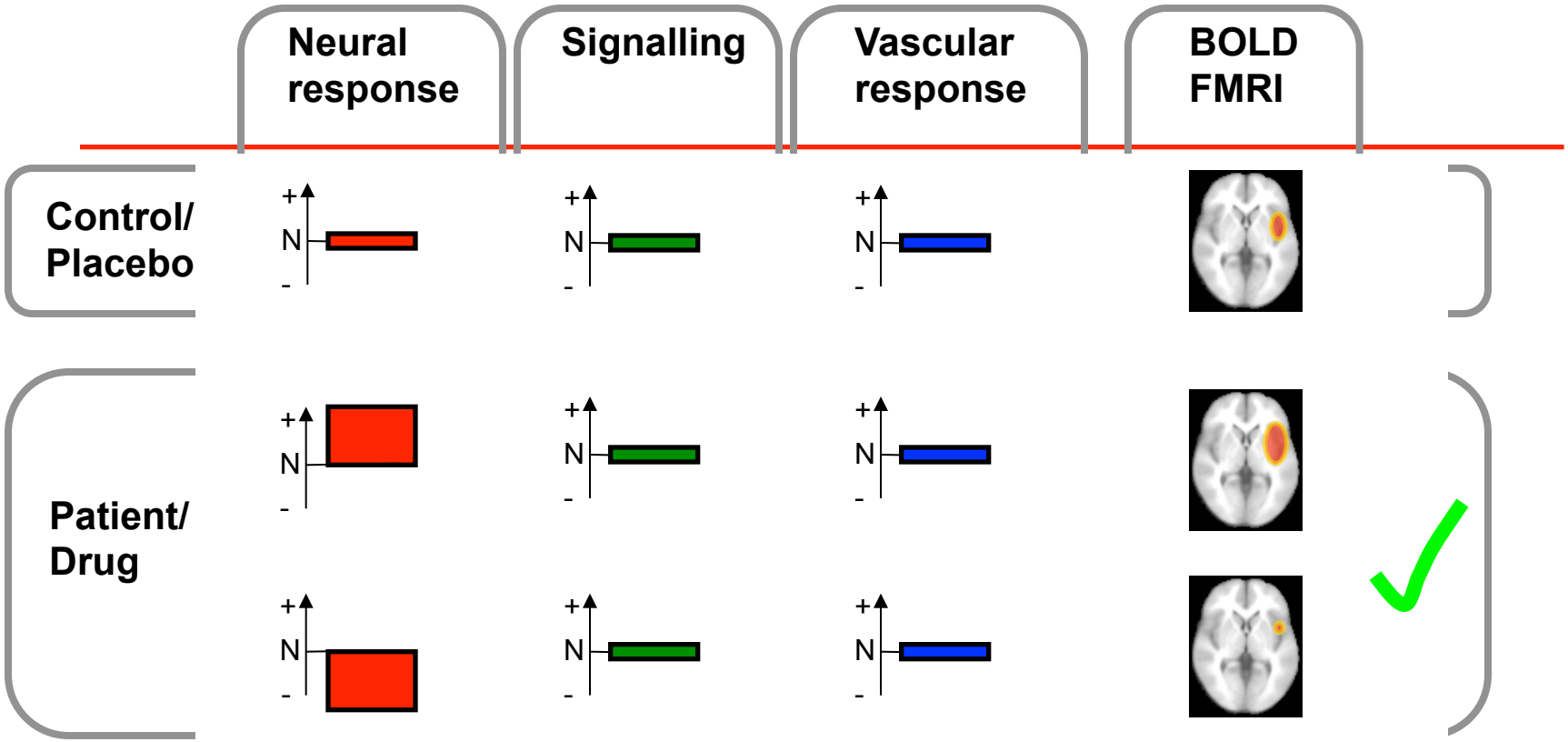

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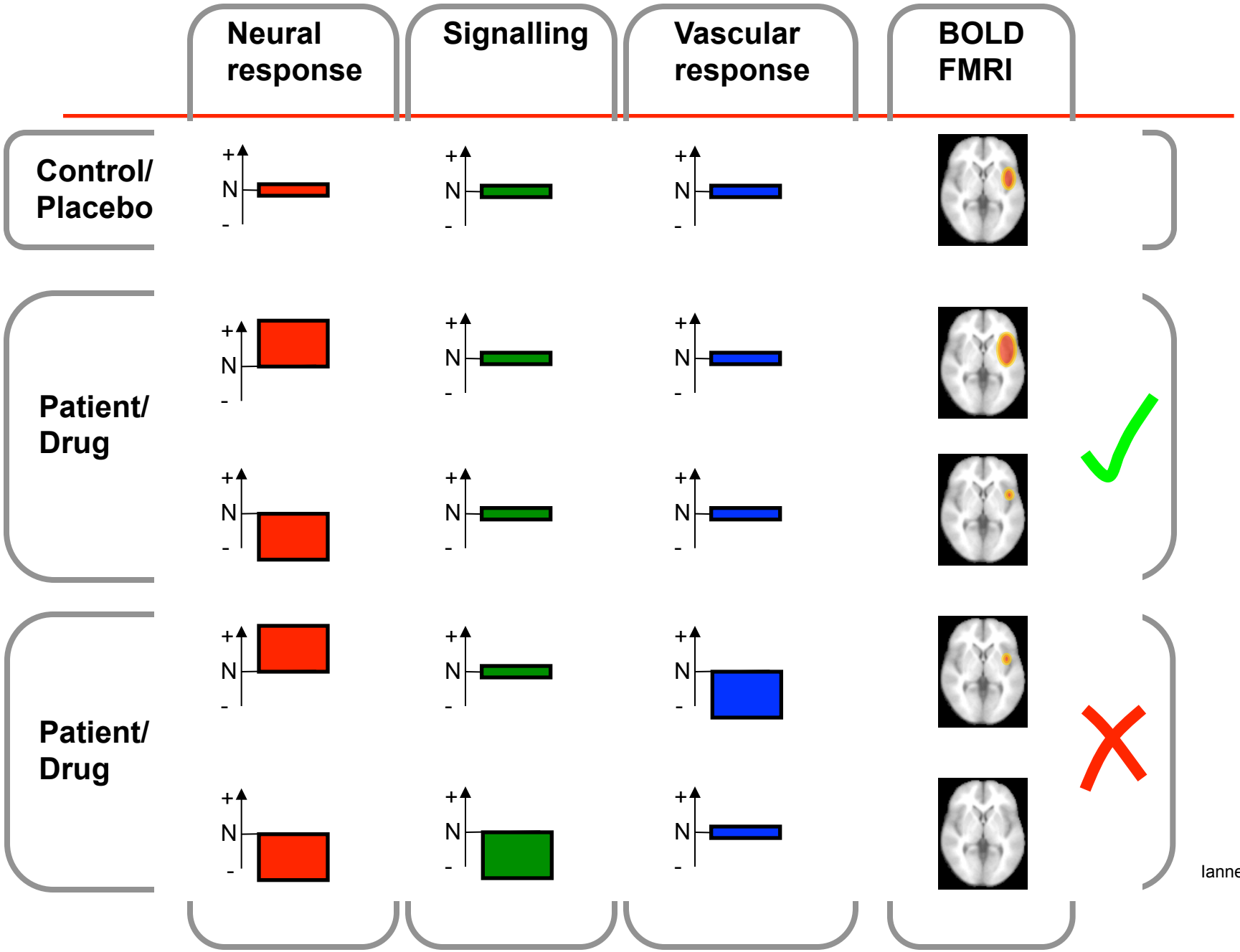
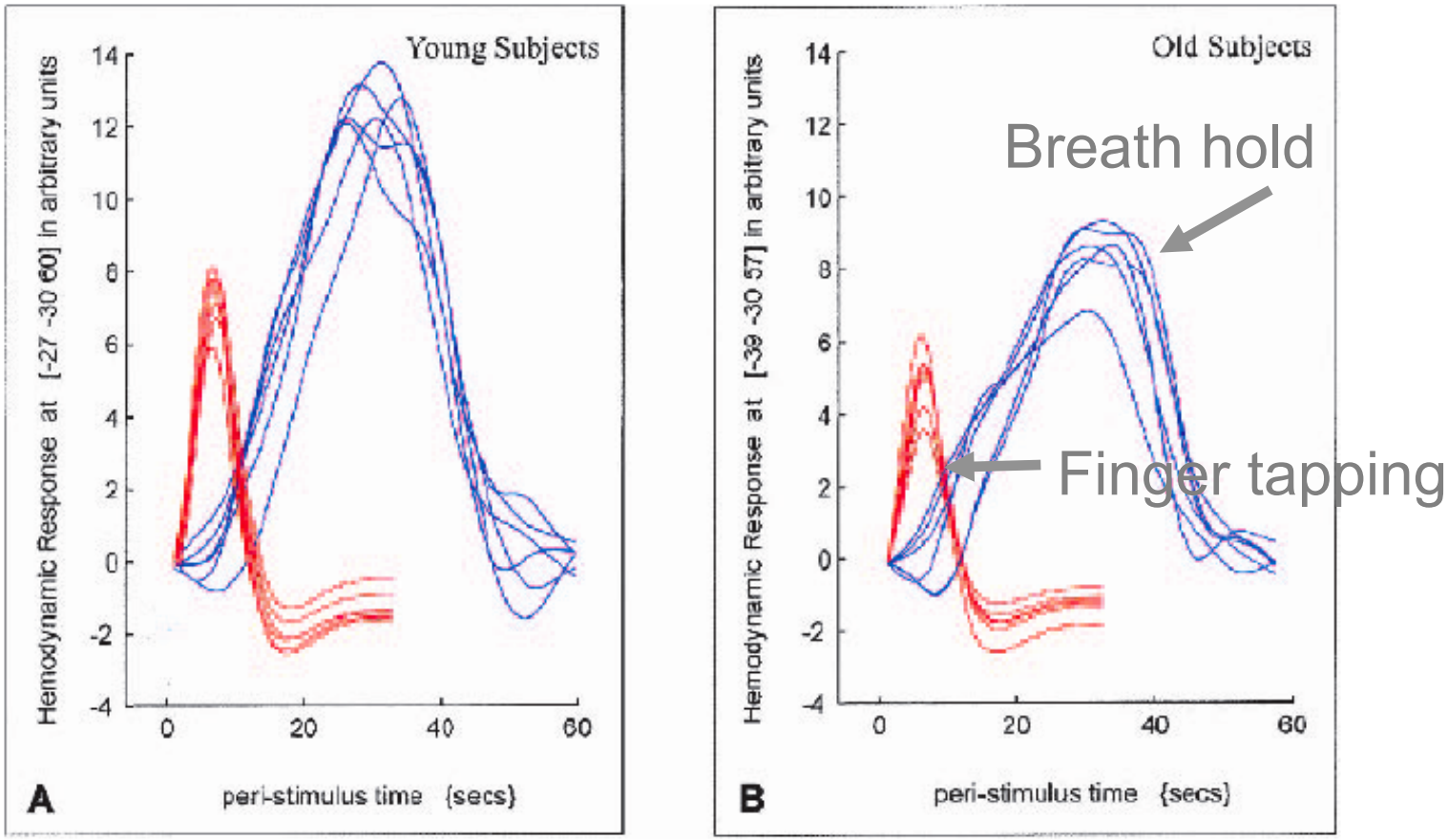


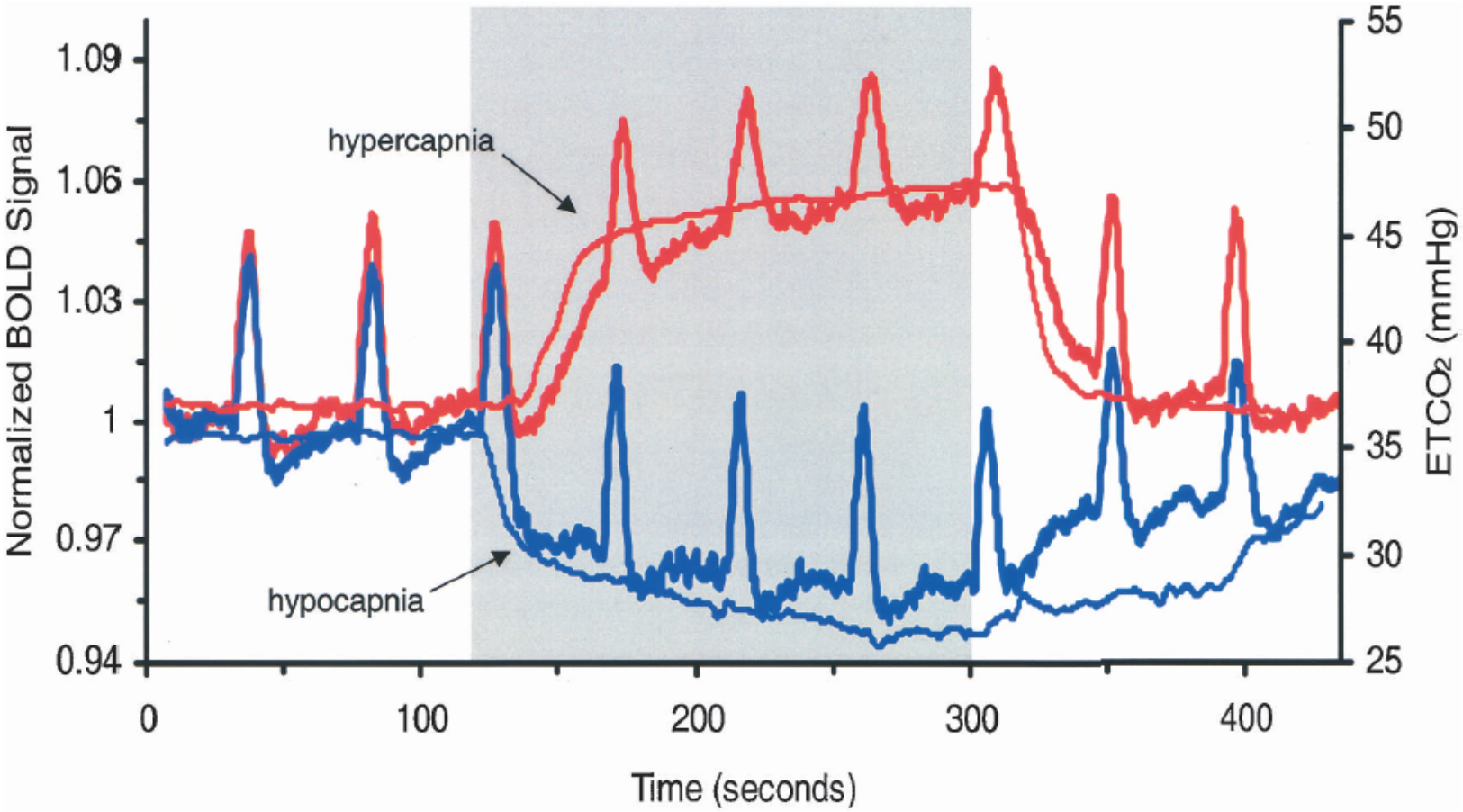
Iannetti & Wise 2007

Reduced vascular reactivity: aging as an example

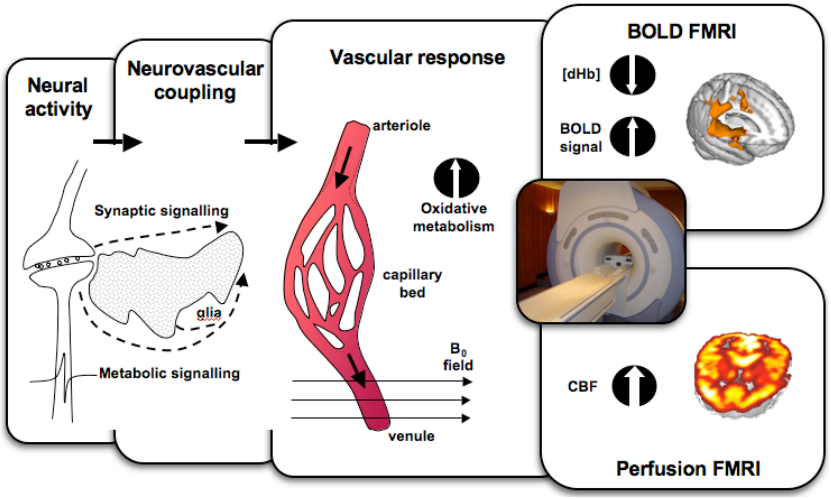
- Reduced vascular reactivity to a motor stimulus
- Reicker et al 2003 JCBFM
- Altered neurovascular coupling with age



Baseline perfusion affects BOLD contrast



Cohen et al JCBFM 2002

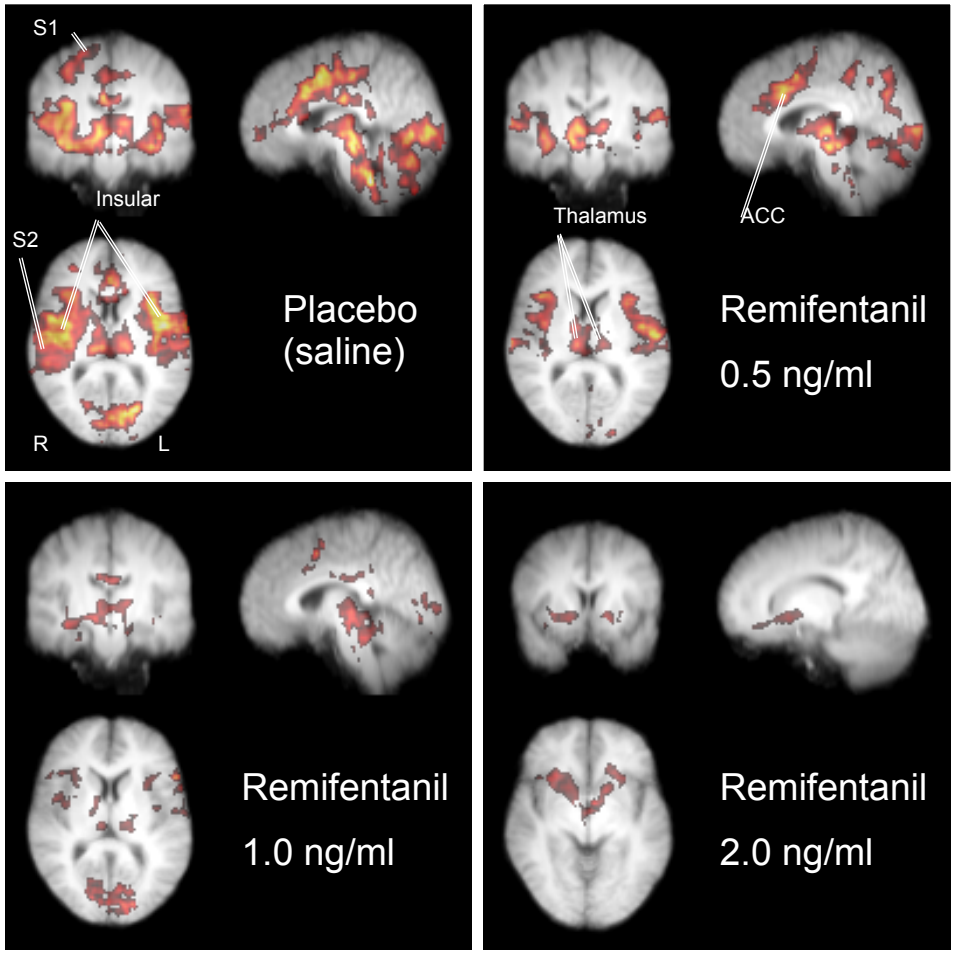


Investigating and controlling such issues …

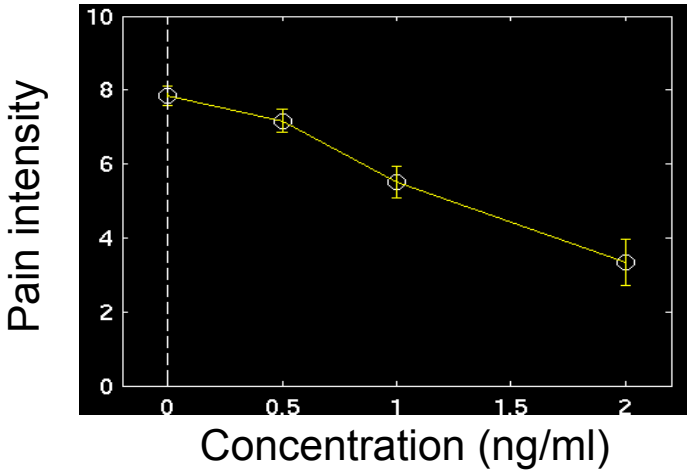
A case study: mu-opioid and pain

- Does it produce the expected behavioural effect?
  - Reported pain
- Does this drug globally modulate the BOLD response?
  - A specificity task
- Is there an electrophysiological correlate?
  - EEG, laser evoked potentials
- Does this drug affect vascular reactivity?
  - CO_2 a probe of vascular reactivity

FMRI of opioid analgesia: reduced pain activity

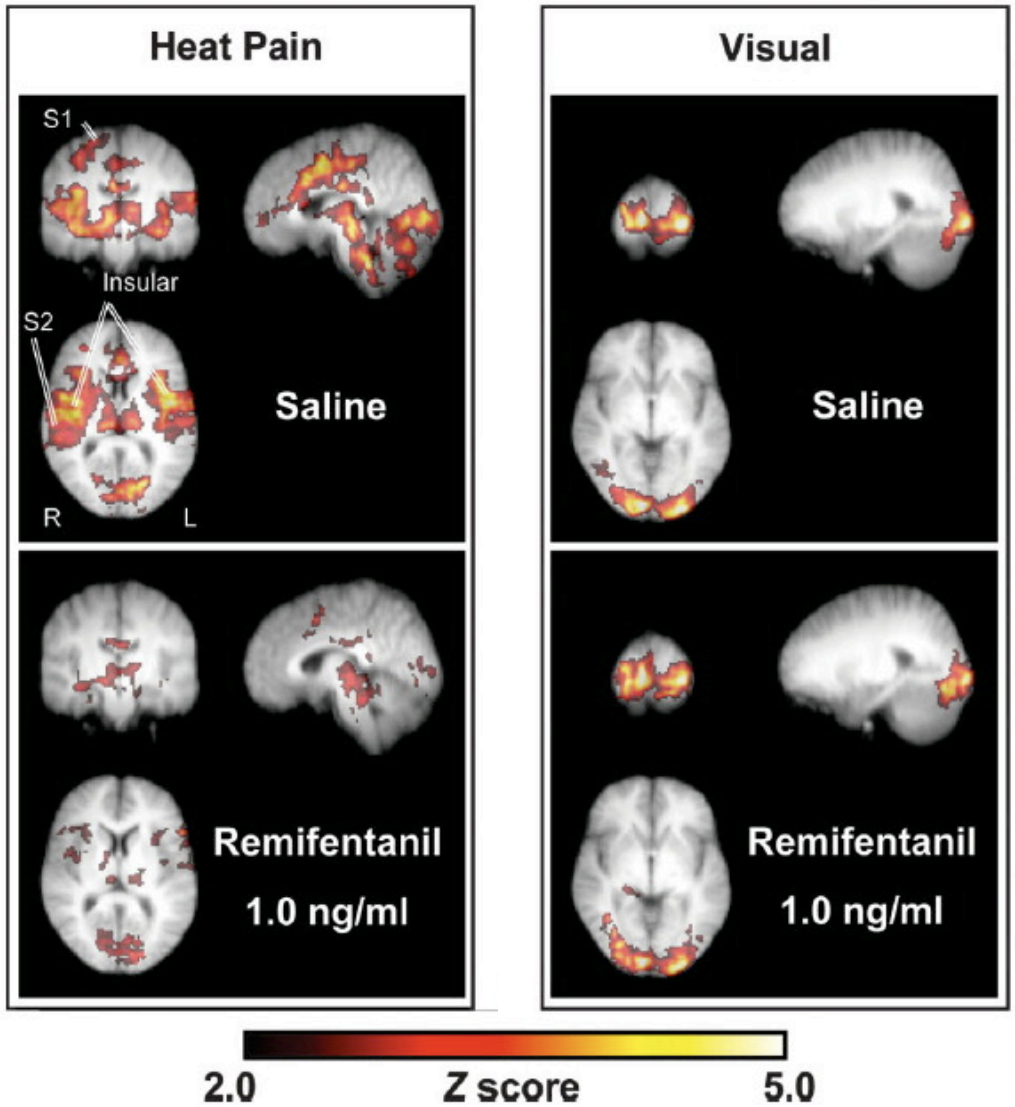


Perceived pain intensity



Wise et al 2002, 2004

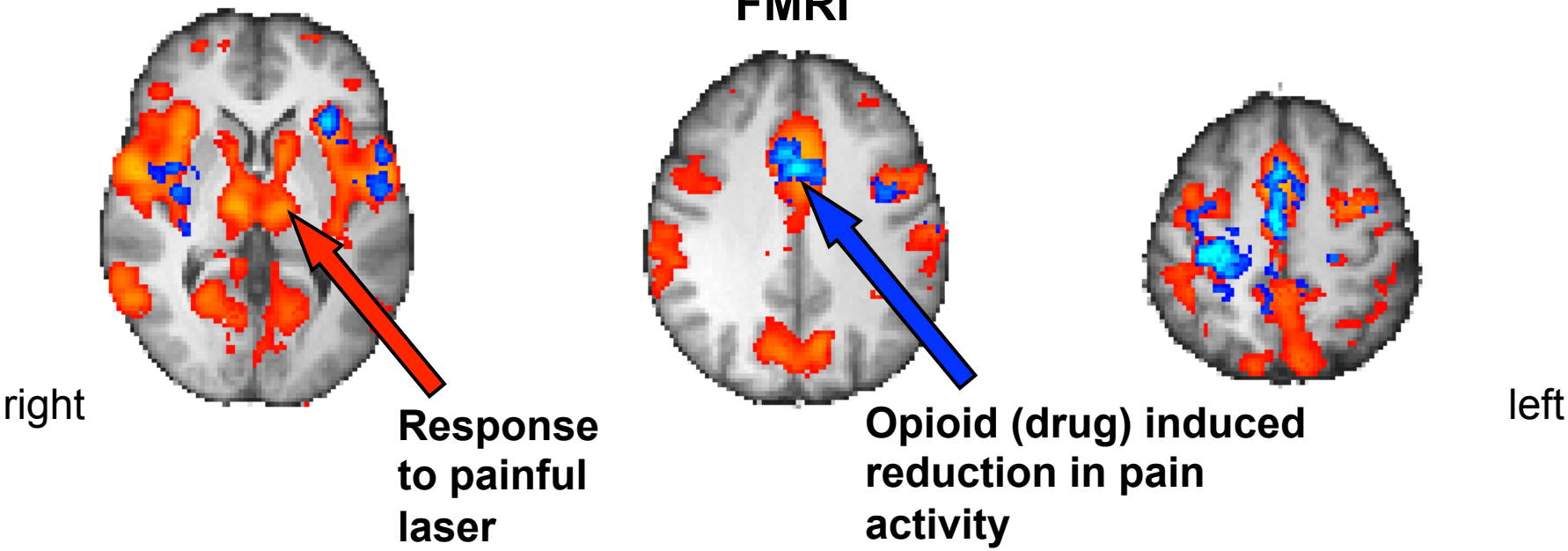
Control task: visual activity, unaffected



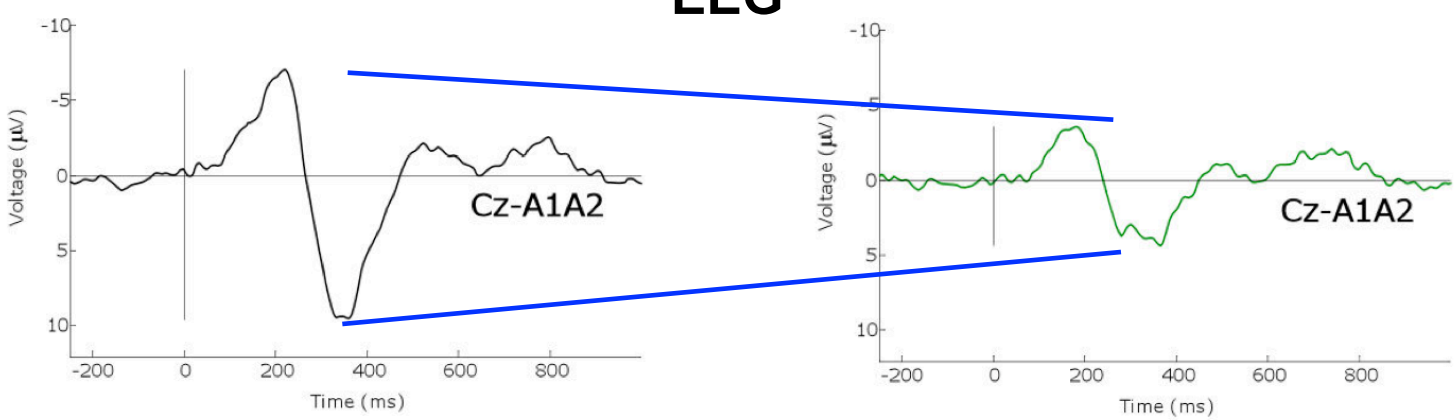
Tracey and Wise, J Pharm Prac 2001

EEG (evoked potentials) consistent with FMRI

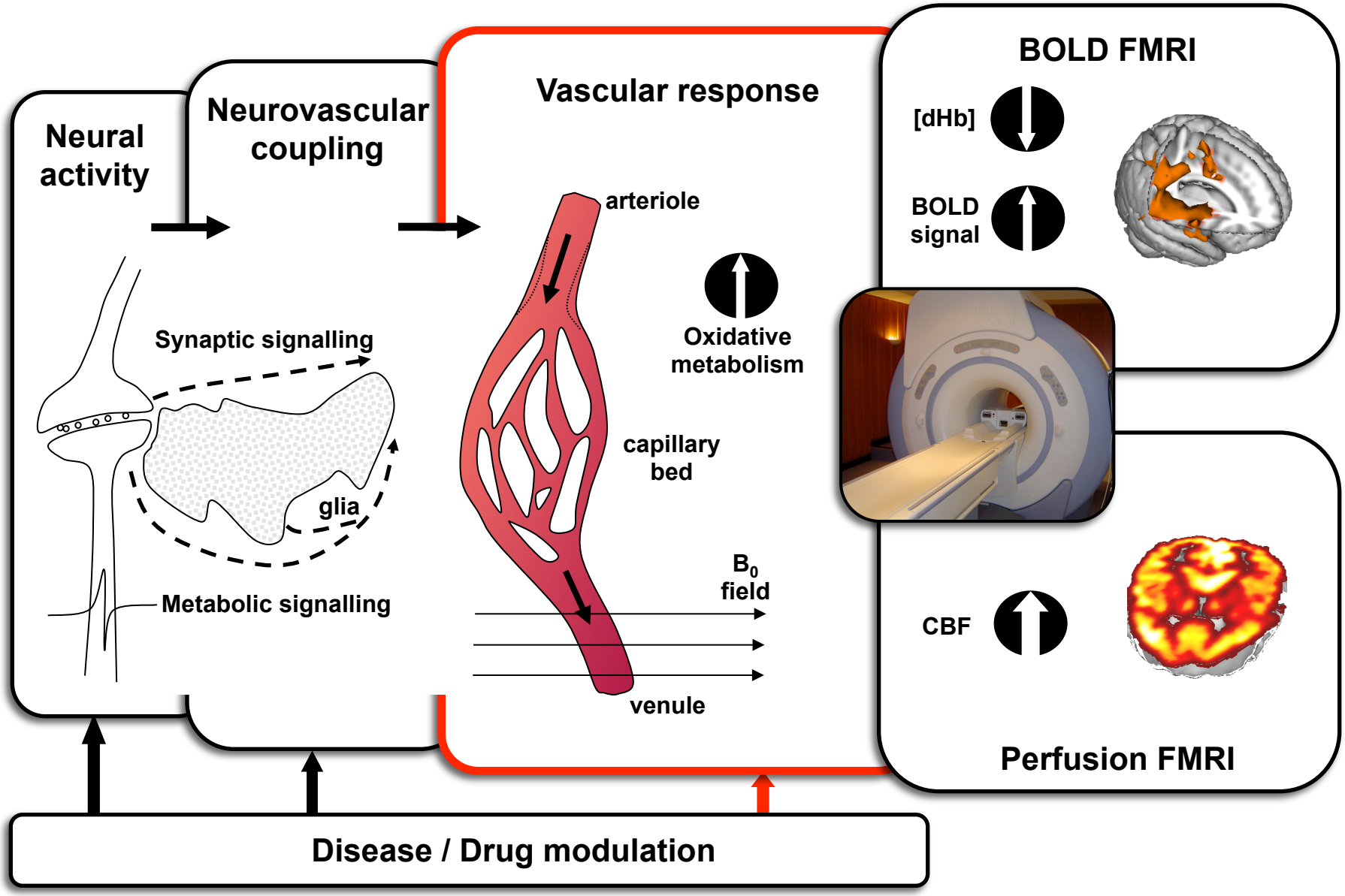
FMRI



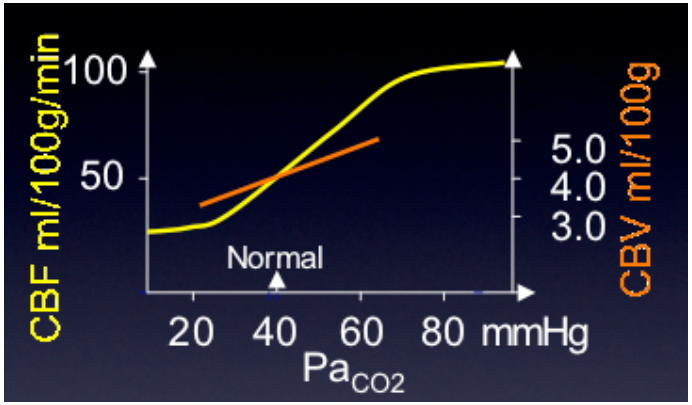
EEG



Vascular reactivity



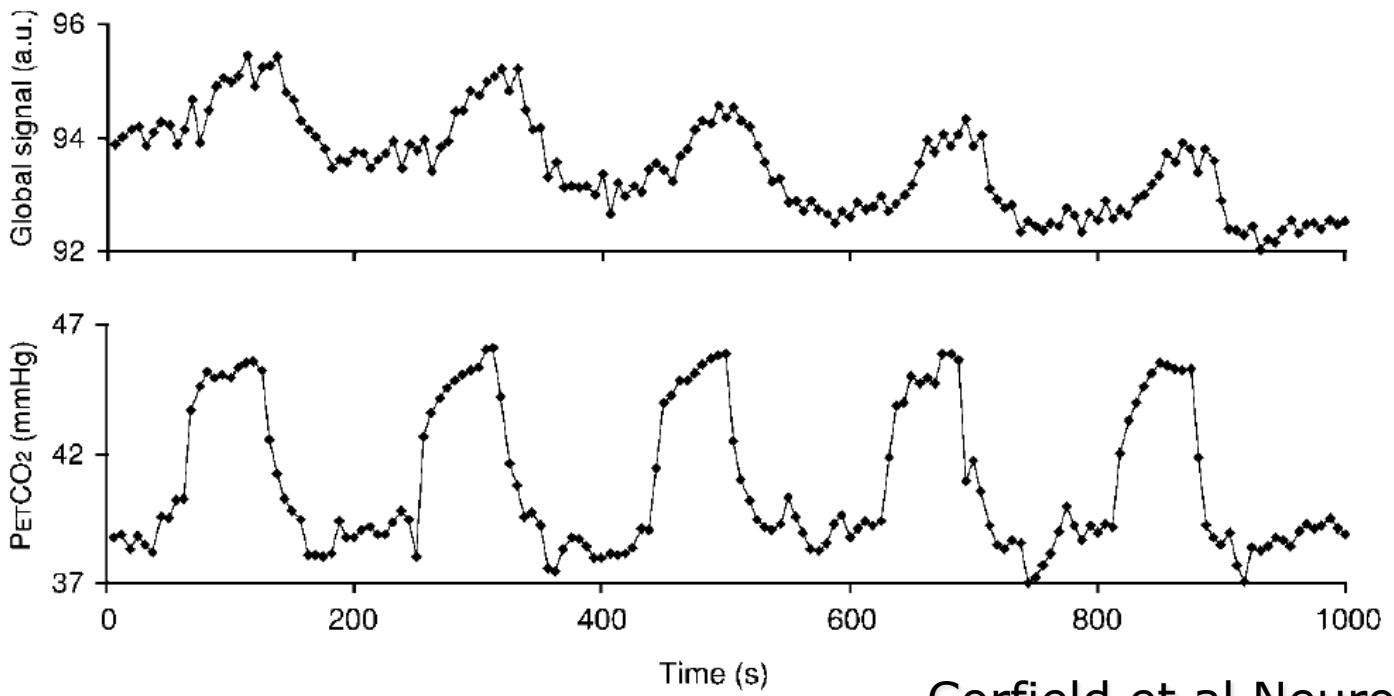
BOLD response to CO_2



$$\Delta R2^* \propto (1-Y)^{\beta}\ CBV$$

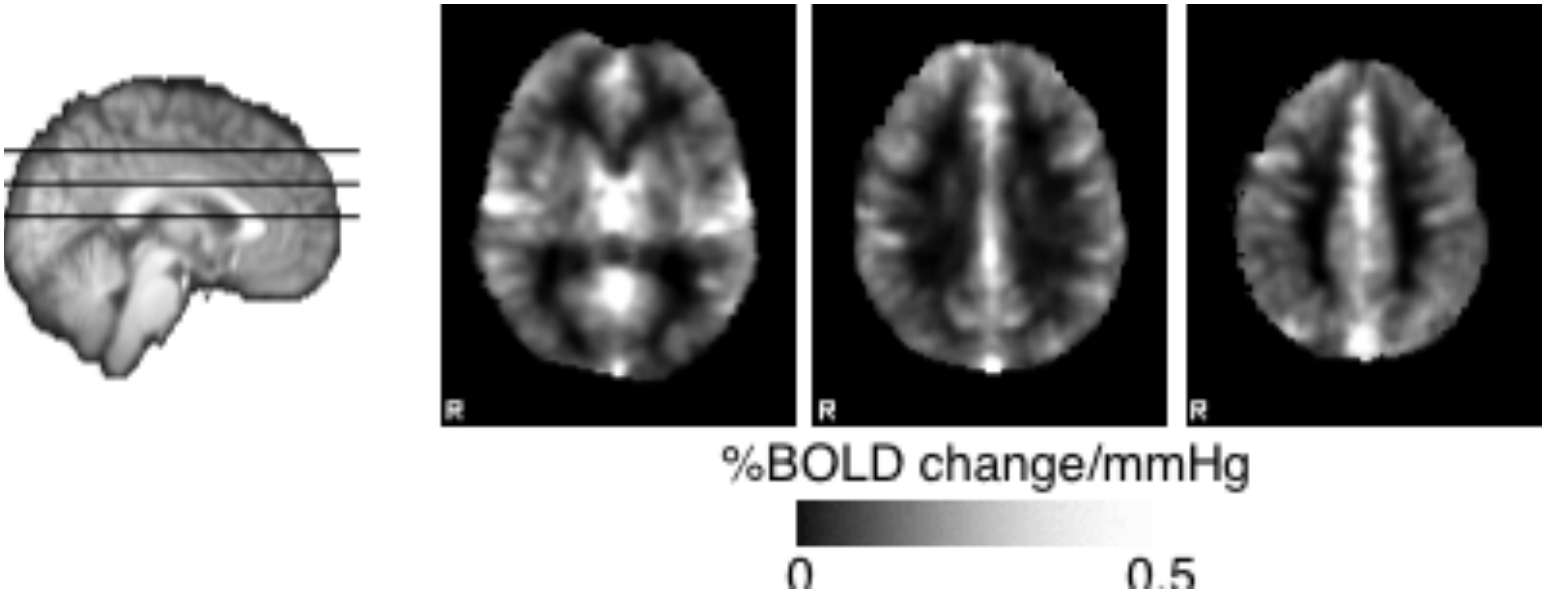
$Y = O_2$ saturation

$b \sim 1.5$



Corfield et al Neuroimage 2001

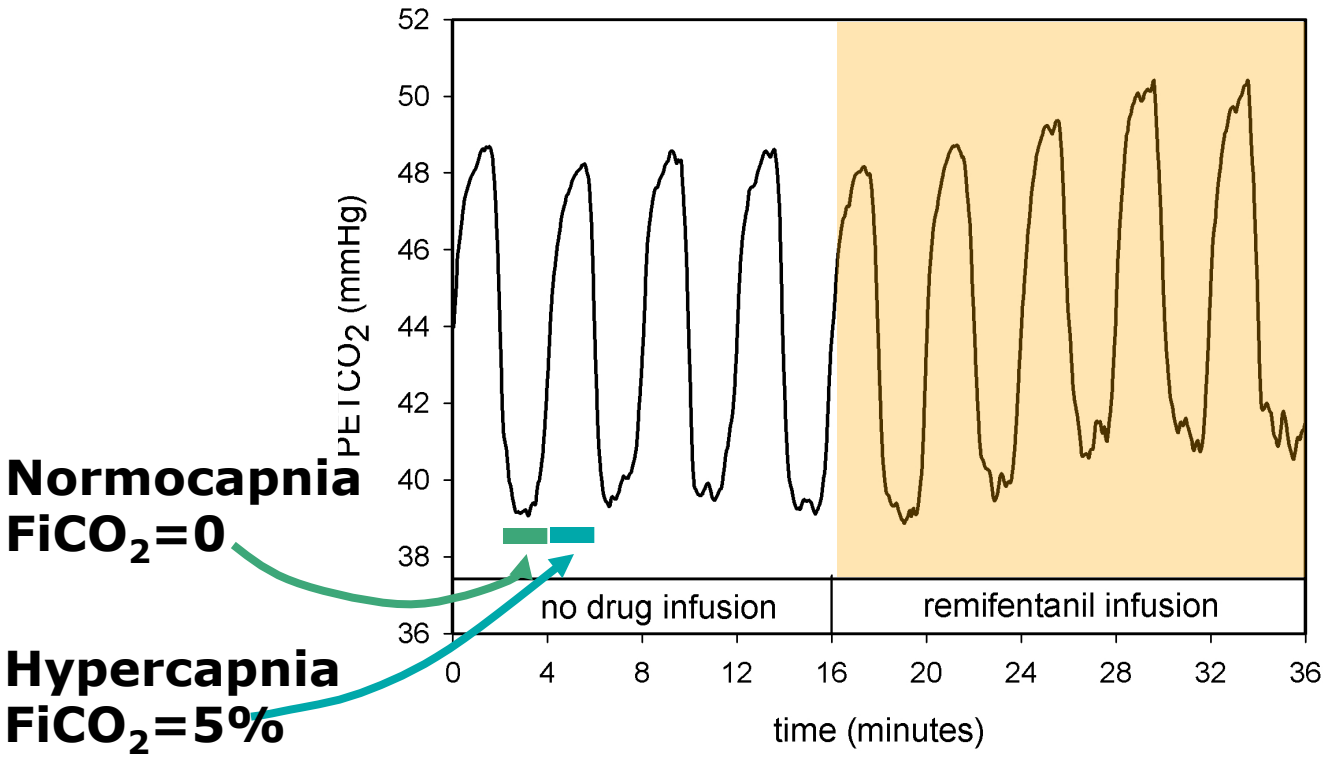
BOLD response to CO_2



Wise et al JCBFM 2007

Opioids: vascular response to CO_2

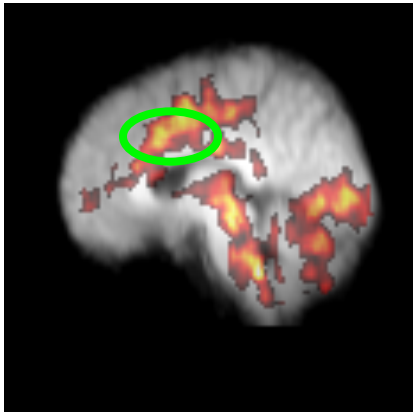
- Test with a global vascular challenge (hypercapnia)

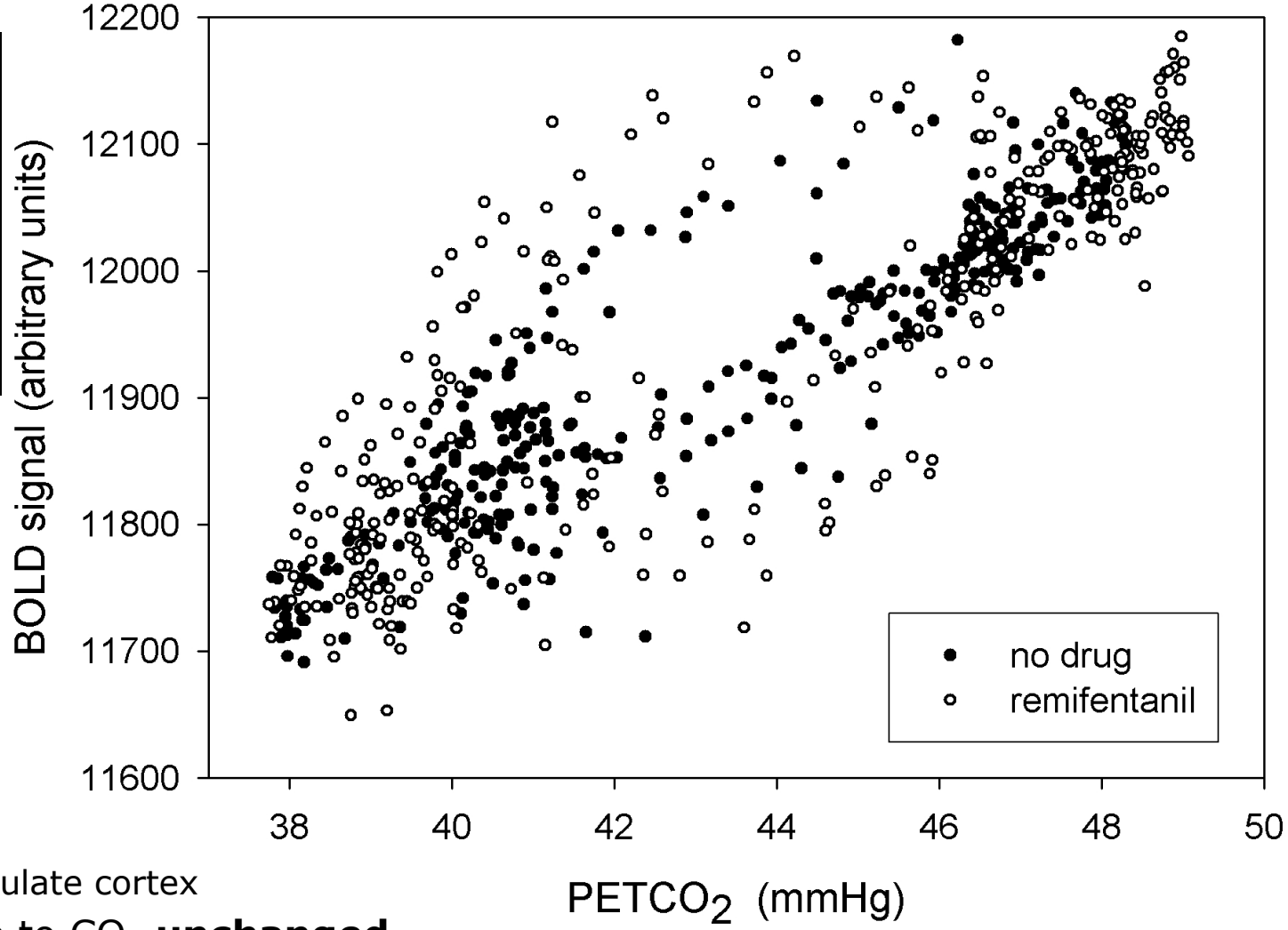


Map BOLD response to CO_2

Pattinson et al JCBFM 2007

Test vascular responsiveness with CO_2





- Pain area
  - anterior cingulate cortex
- BOLD response to CO_2 **unchanged**

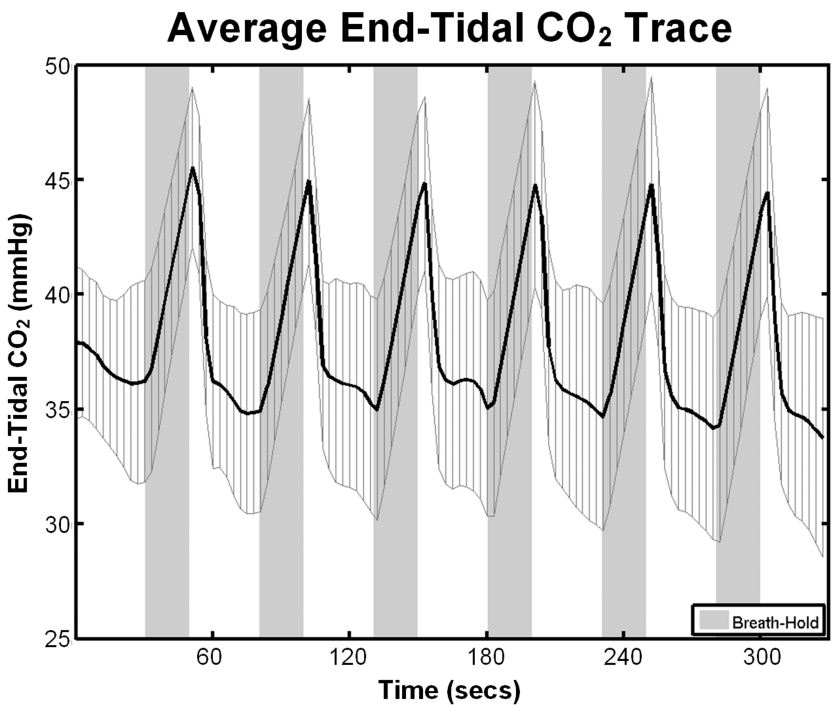
Pattinson et al JCBFM 2007

Robustly accounting for vascular reactivity differences using breath-hold

- CO2 - a global vascular probe
- Breath-hold is easier than feeding in CO_2
- Aspects of breath-hold (BH) derived BOLD measures are often neglected
  - BH needs to be done in a controlled manner
  - increases in arterial CO_2 due to breath-hold differ between subjects … factor this in
    - BOLD signal reactivity per mmHg rise in end-tidal CO_2

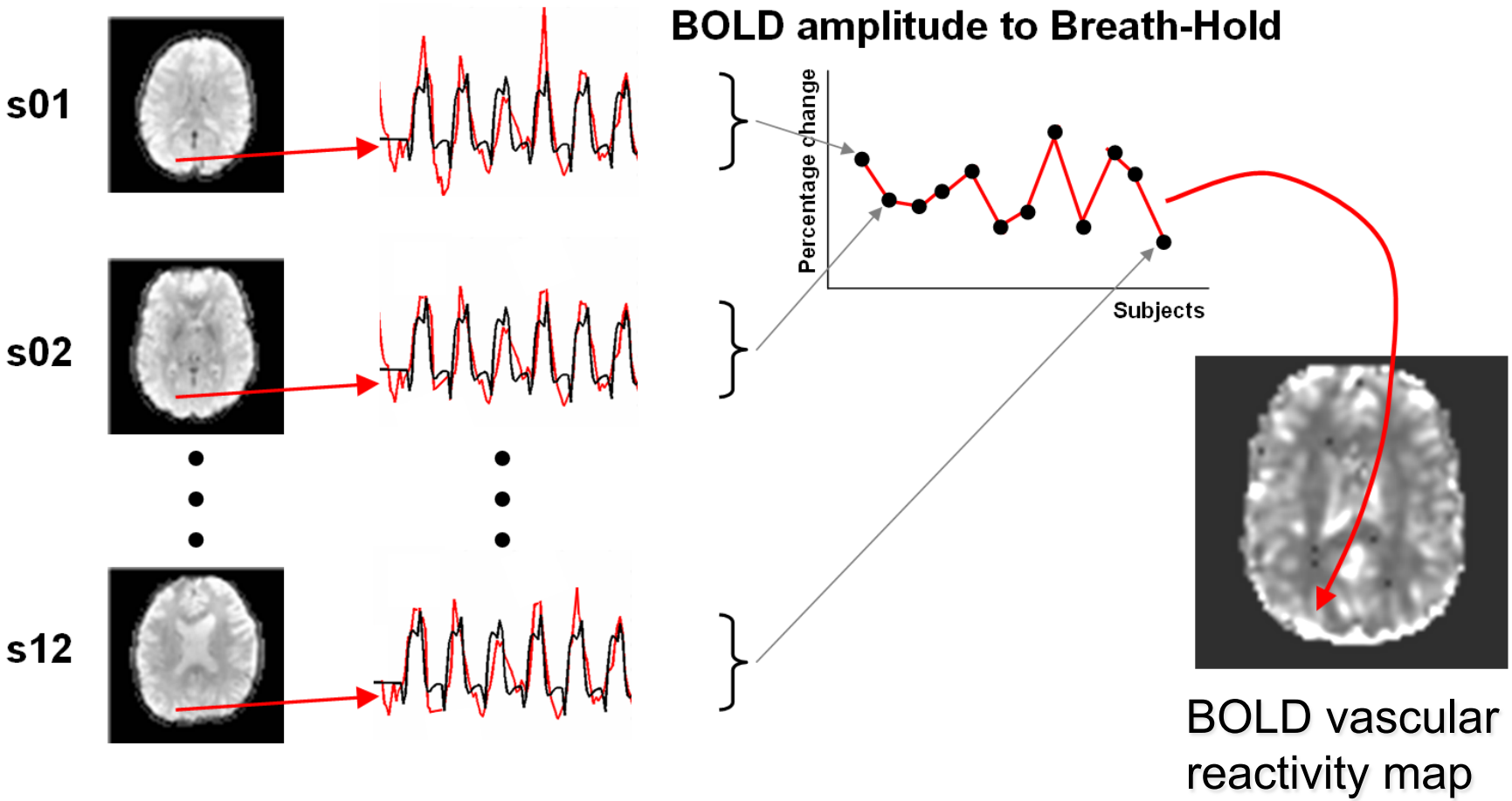
Murphy et al, Neuroimage 2011

End-tidal CO_2 response to breath-hold



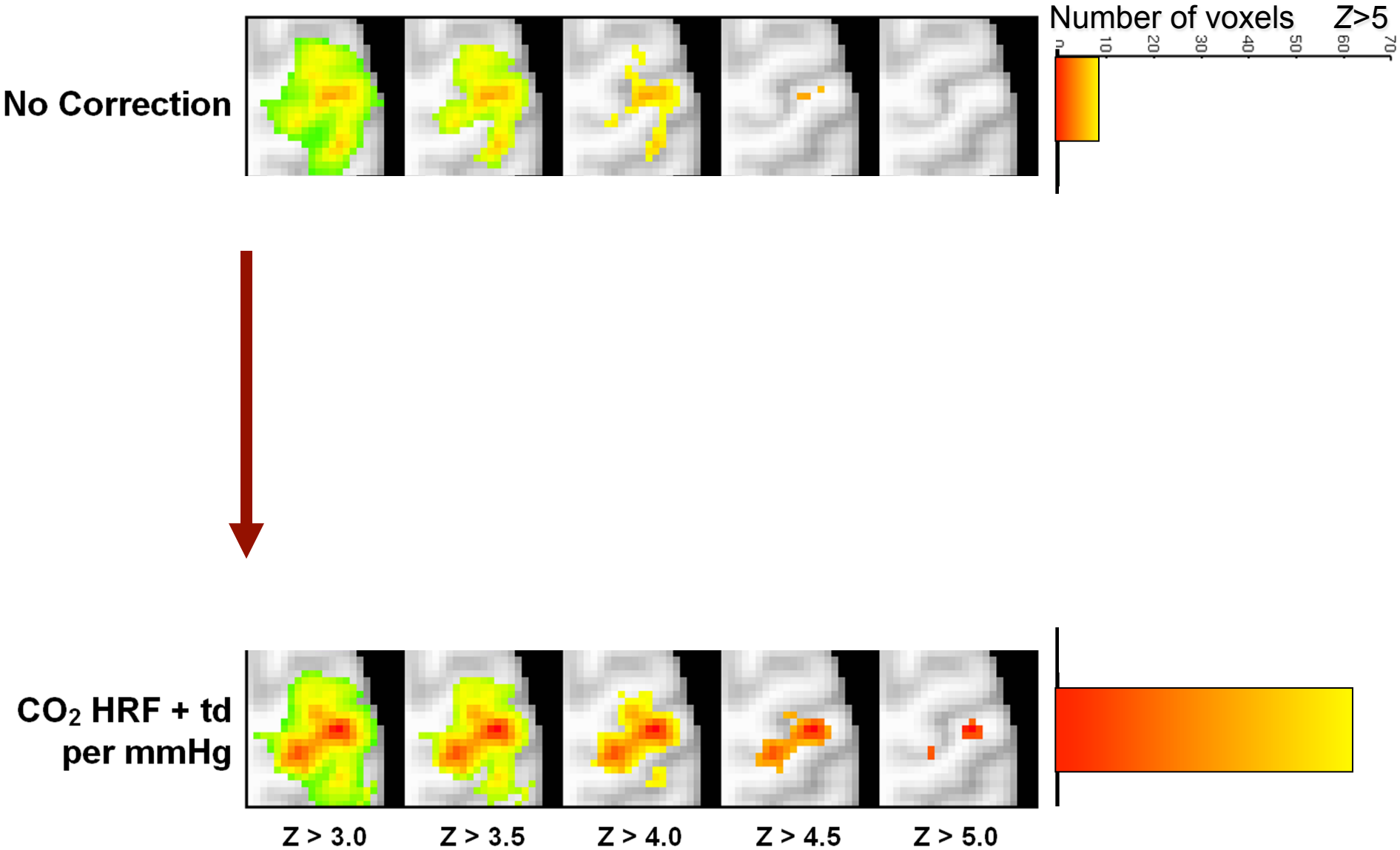
- Mean end-tidal CO_2 levels = 39.7 mmHg, range 35.8 – 44.4 mmHg
- End-tidal increases: 13.4 ± 2.2 mmHg (range: 9.5 – 17.3 mmHg)

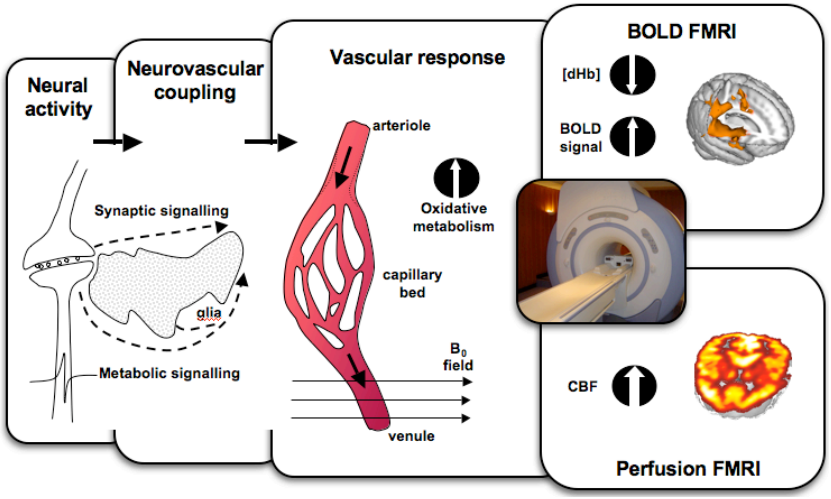
Group level model of breath-hold signal change



- Include as a *voxel-dependent* covariate in your group analysis to account for *between-subject/scan* variability

Group level vascular covariate: motor activity

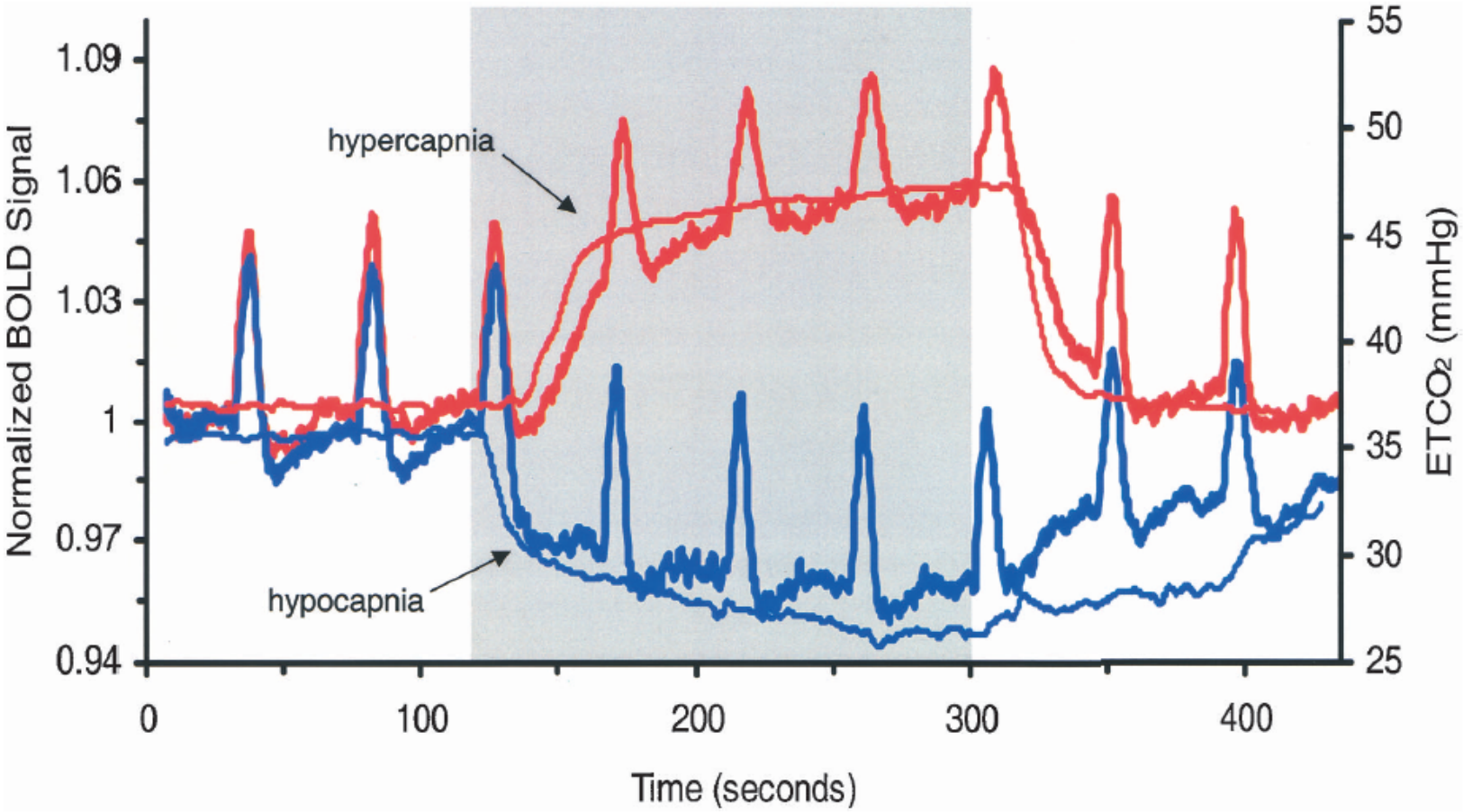




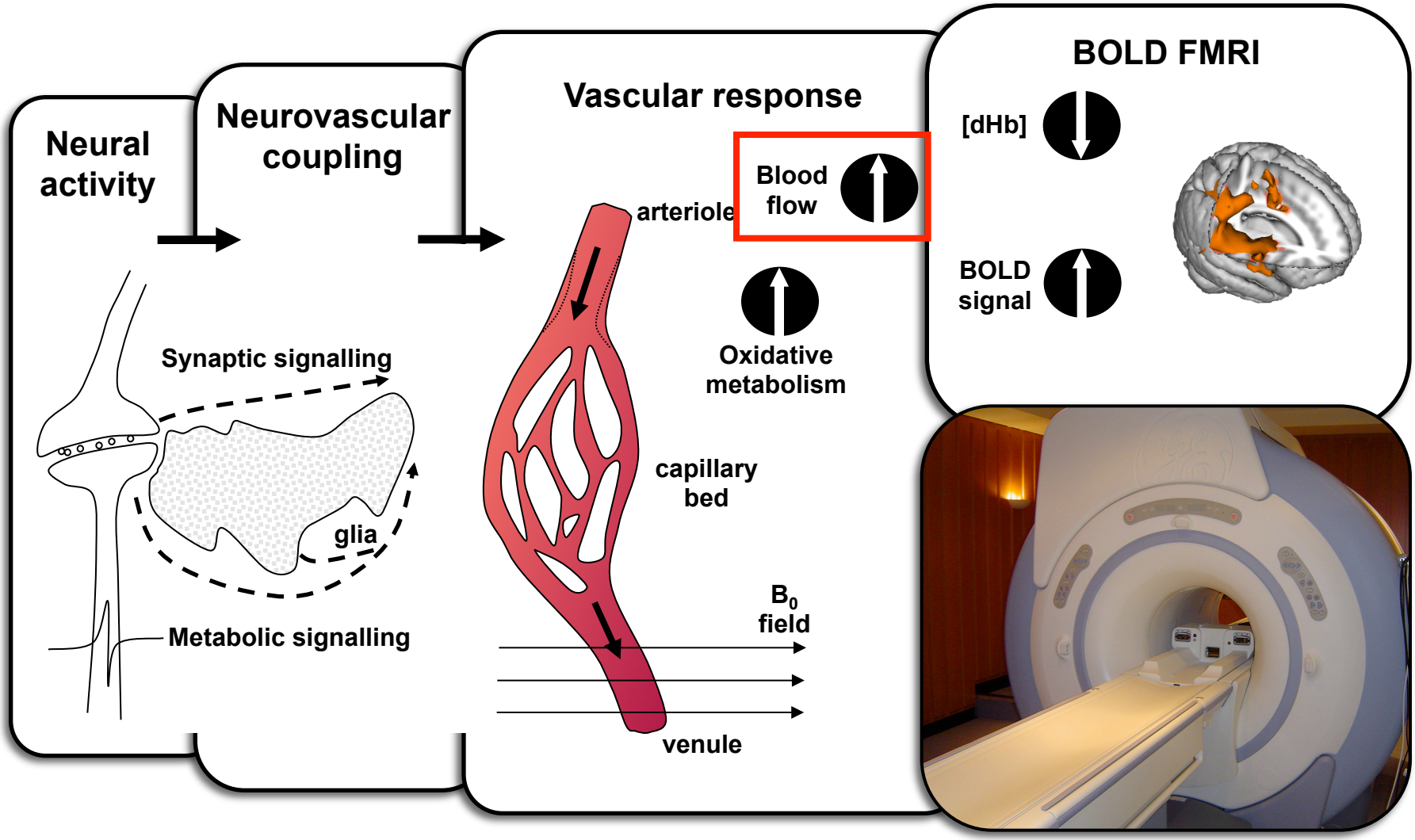
- BOLD signal provides a measure of short term activity within session relative to the *baseline*
  - % signal change

- What can we do with
  - Changing baseline
  - Longer term changes in ‘activity’ levels

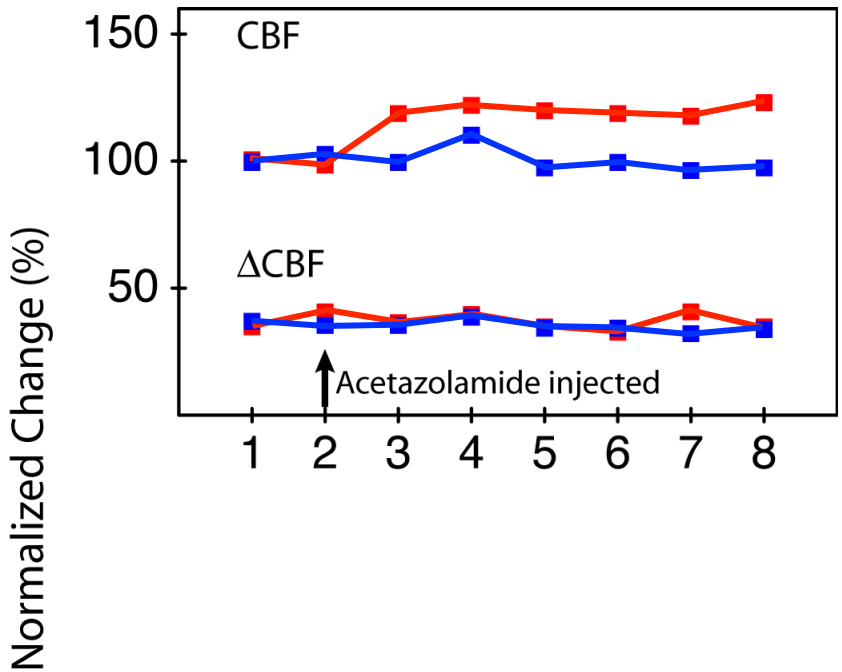
Baseline perfusion affects BOLD contrast



Cohen et al JCBFM 2002


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

Effect of Acetazolamide on fMRI Response

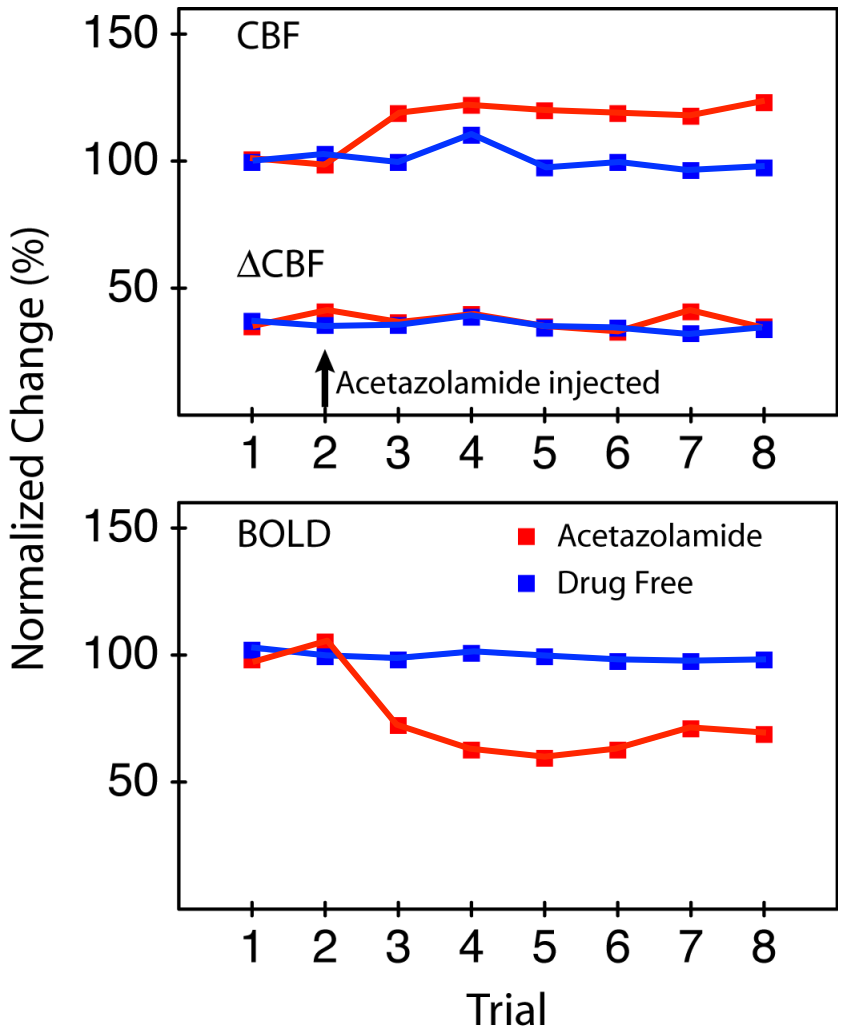


20% increase in baseline CBF
→ no effect on ΔCBF with finger tapping,

Trial

G. Brown et al, JCBFM 2003

Effect of Acetazolamide on fMRI Response

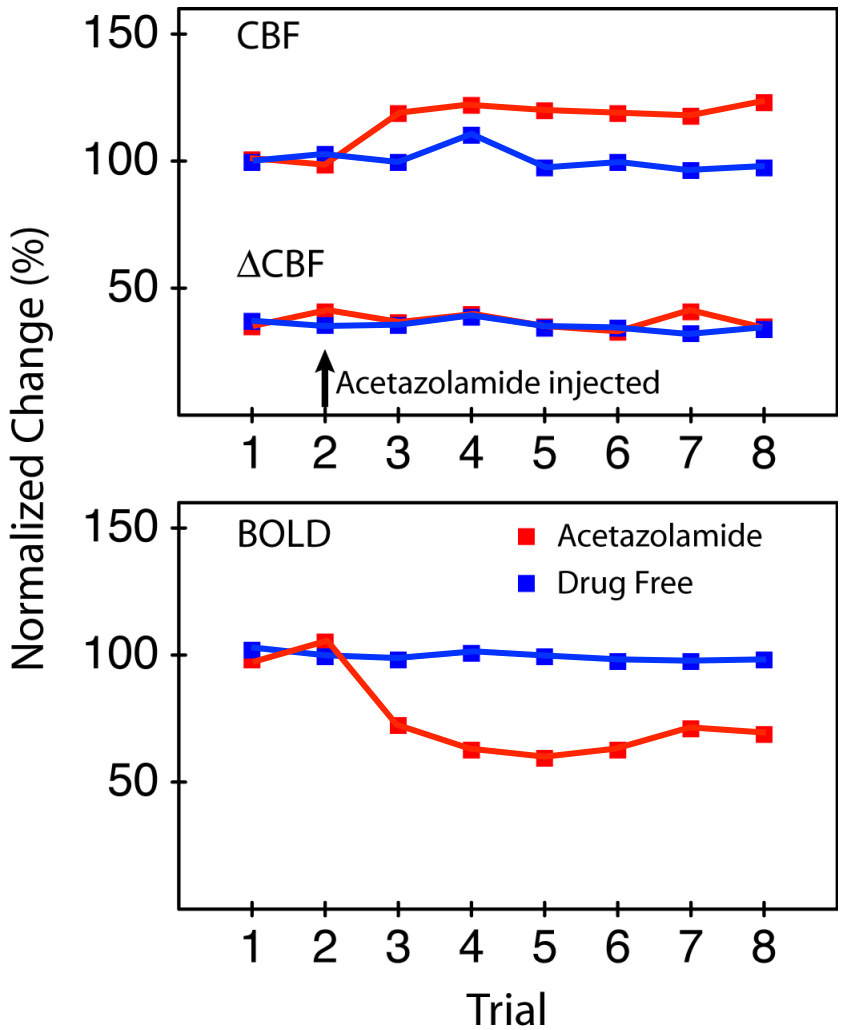


20% increase in baseline CBF
→ no effect on ΔCBF with finger tapping,

→ but BOLD response to finger tapping reduced by 35%

G. Brown et al, JCBFM 2003

CBF (potentially) a better marker of neural activity

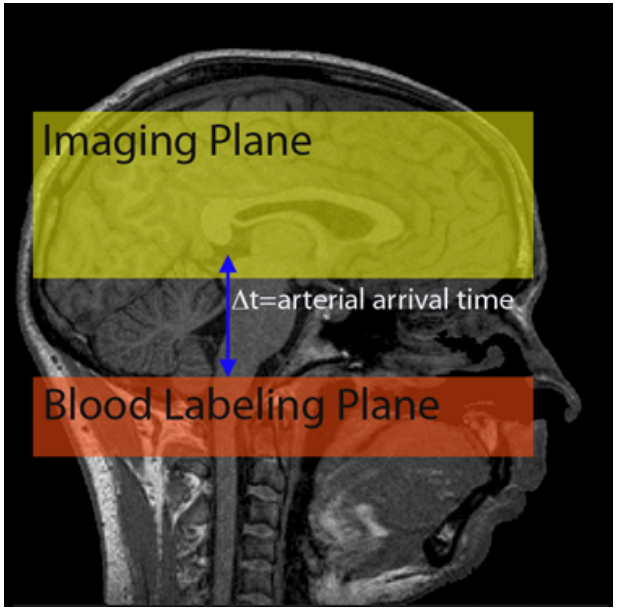


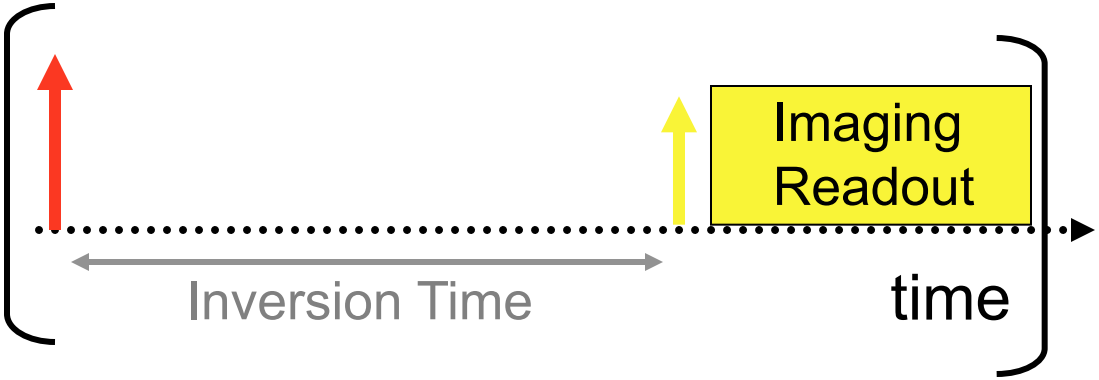
Feed-forward mechanism with neural activity driving an increase in CBF

G. Brown et al, JCBFM 2003

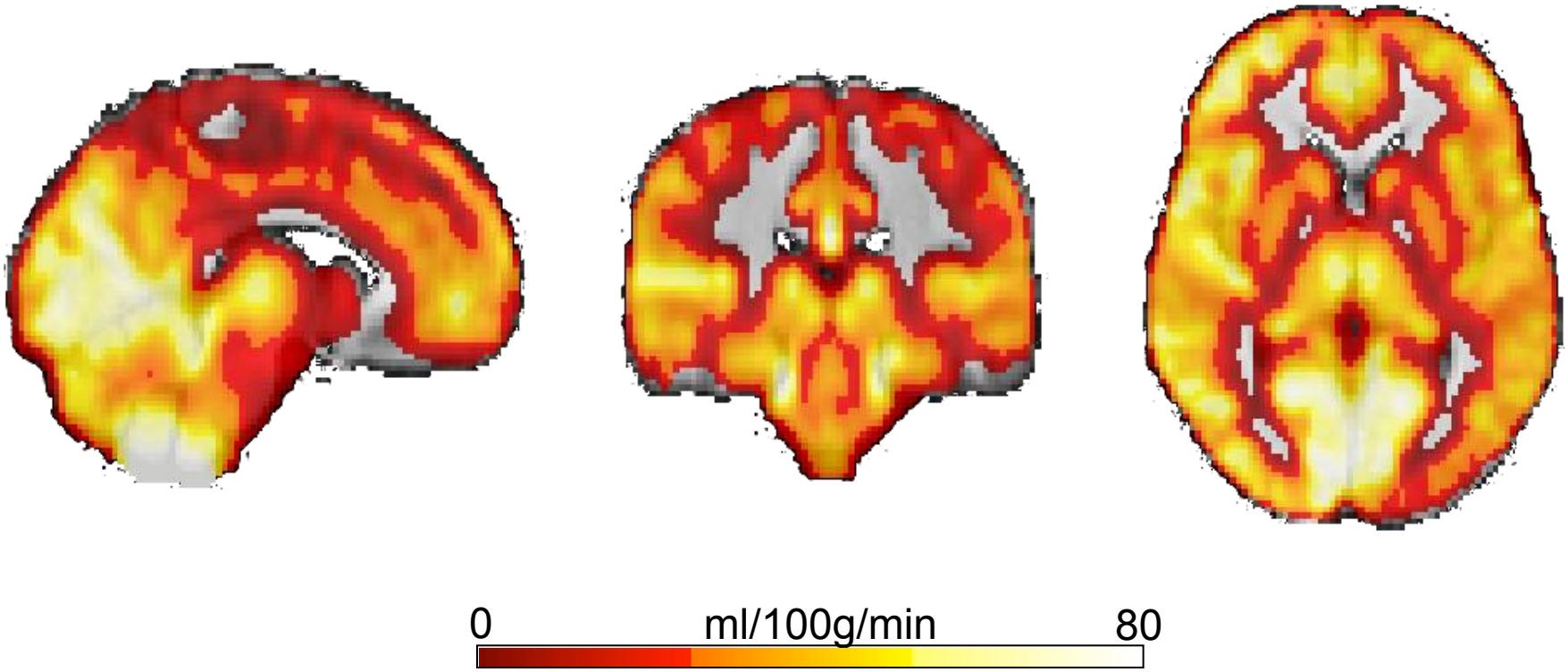
CBF Measurement: Principles of ASL

- Magnetically **label** water in the blood upstream of imaging plane
- **Wait** some period of time for blood to arrive
- **Acquire** images
- Repeat procedure in the **absence** of labeled blood

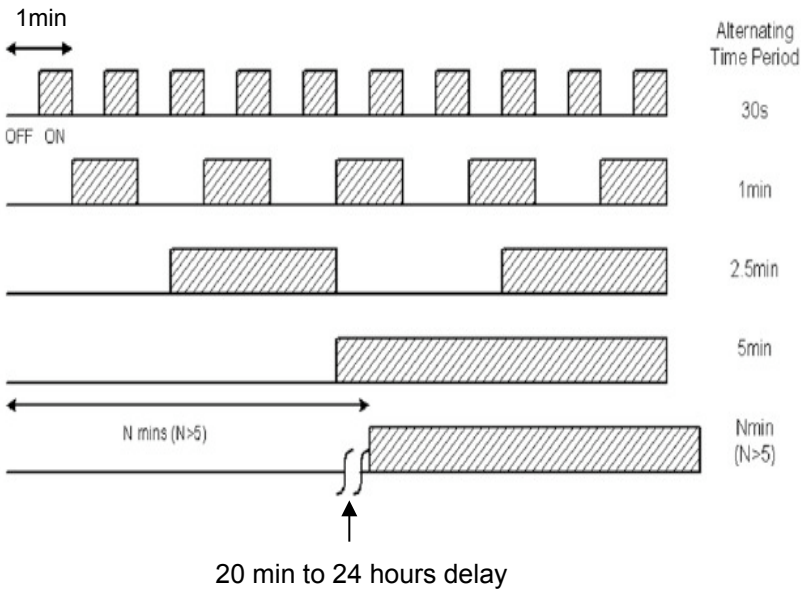


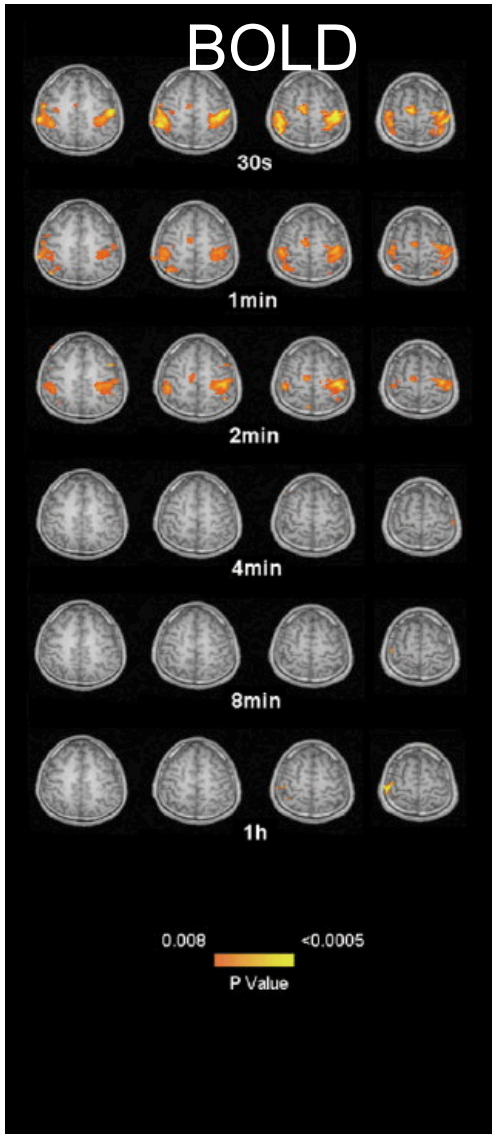


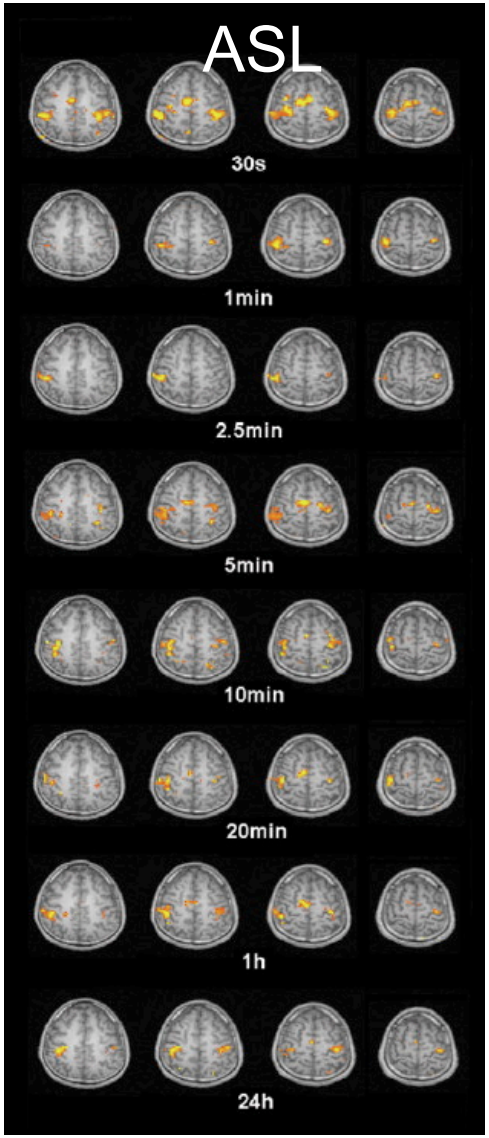
Typical resting CBF map



Stimulus frequency response of BOLD vs ASL







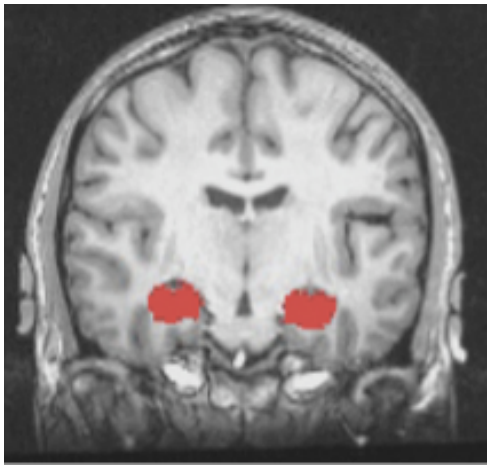
Wang et al. Magn Reson Med (2003)

- CBF measurement can help to interpret task related signal changes

ELSEVIER
Neurobiology of Aging 30 (2009) 1737–1748
www.elsevier.com/locate/neuaging

Cerebral perfusion and oxygenation differences in Alzheimer's disease risk

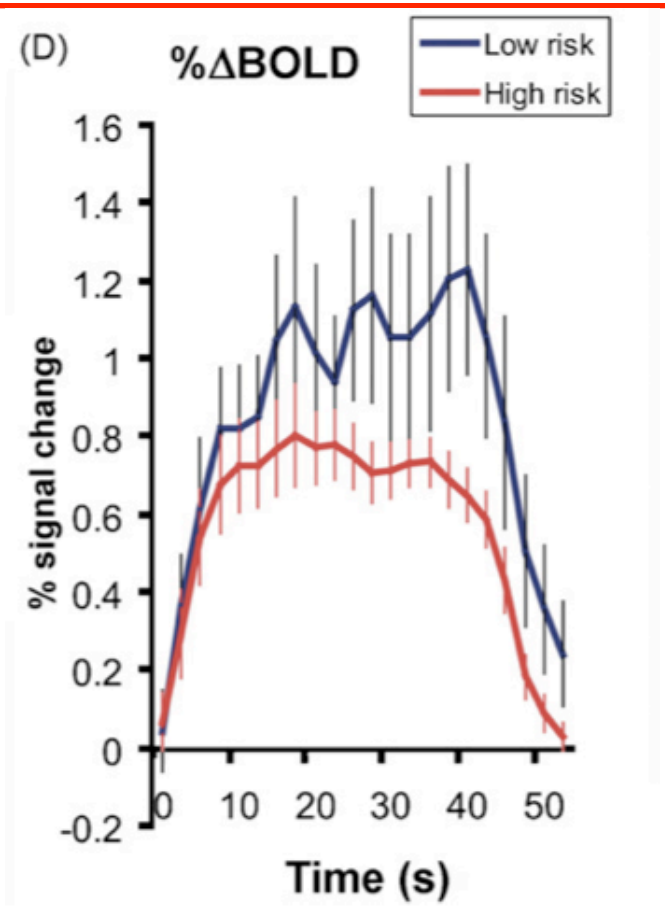
Adam S. Fleisher[a,*], Katherine M. Podraza[a], Katherine J. Bangen[a], Curtis Taylor[a], Ayesha Sherzai[a], Kunal Sidhar[c], Thomas T. Liu[b], Anders M. Dale[a,b], Richard B. Buxton[b]



- High and low risk of AD
- BOLD and CBF responses to an **associative learning task**
- Resting (baseline) CBF

Fleischer et al, Neurobiology of Ageing. 2009

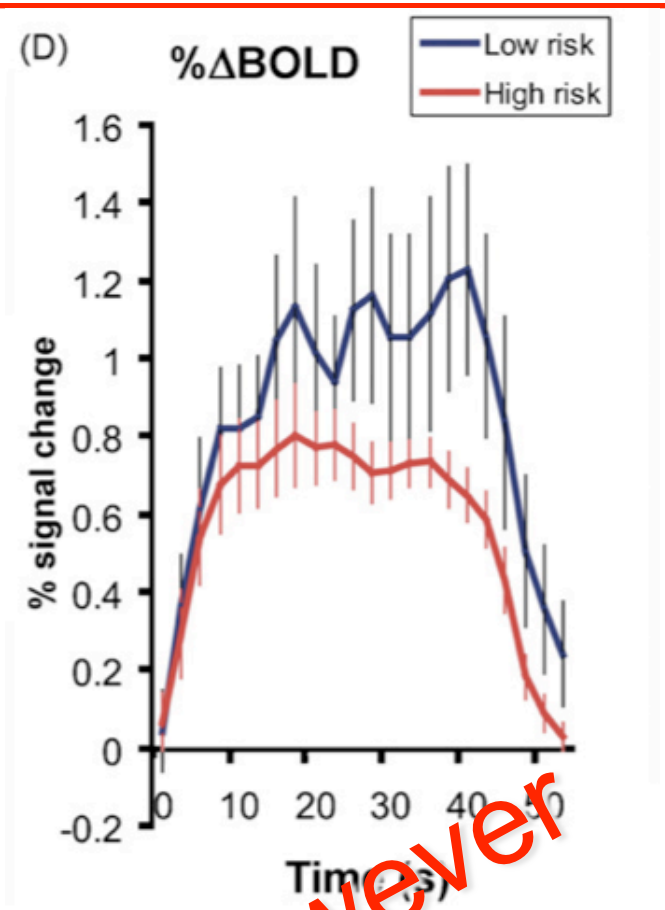
BOLD response to task



- Less *activity* during task where AD risk higher

Fleischer et al, Neurobiology of Ageing. 2009

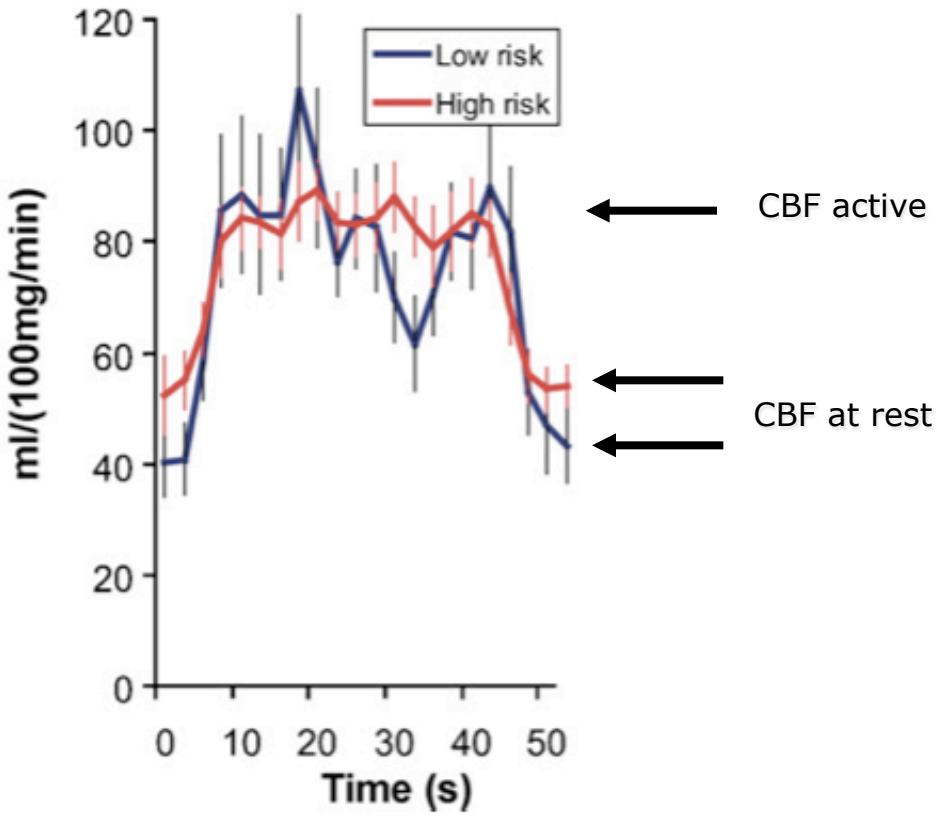
BOLD response to task



- Less *activity* during task where AD risk higher

Fleischer et al, Neurobiology of Ageing. 2009

…same perfusion in the active state



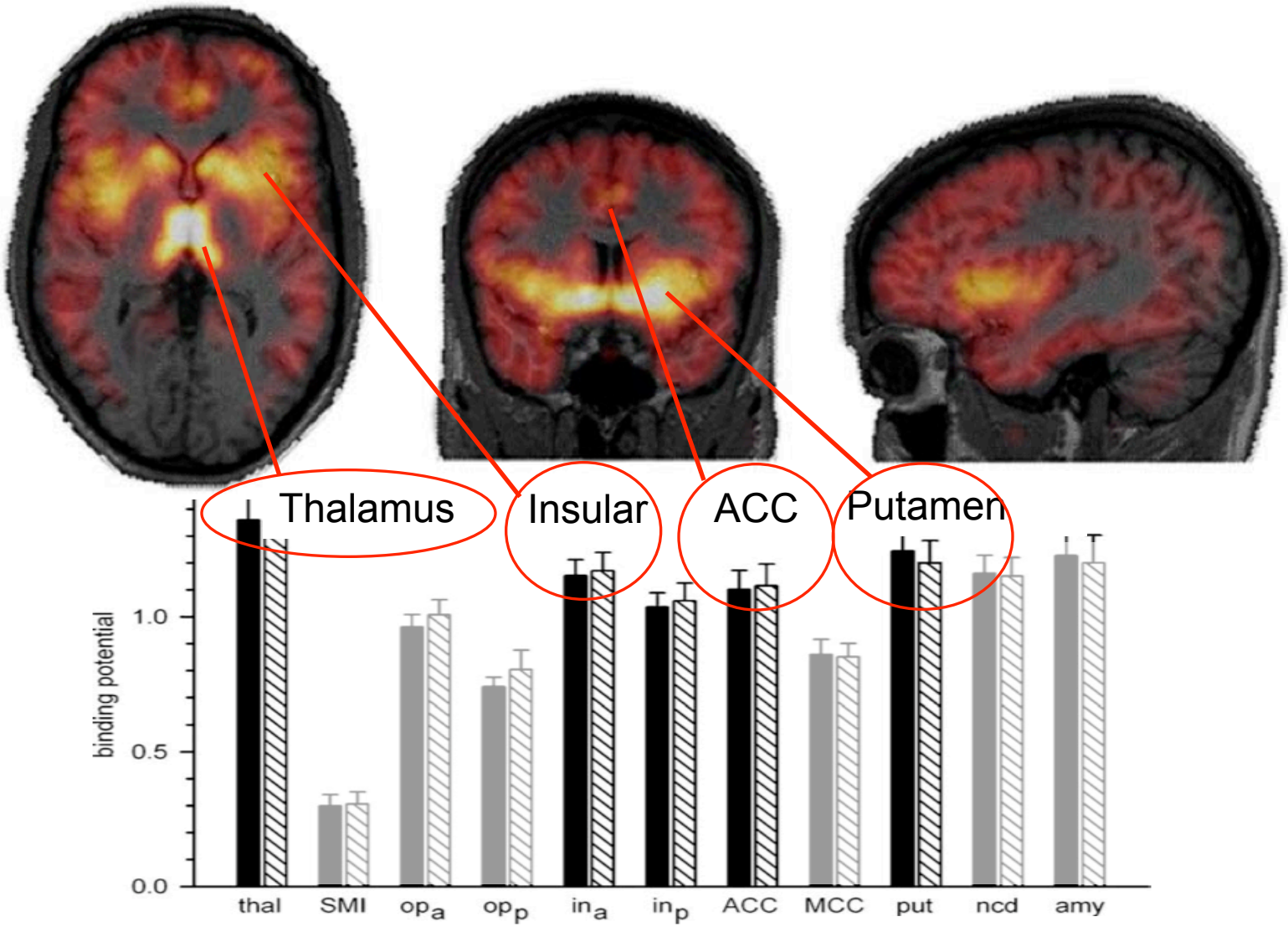
- Fractional changes in BOLD depend on the state of the brain at rest
- BOLD should not be taken as representing neuronal activity where underlying (neuro)physiology may be altered

Fleischer et al, Neurobiology of Ageing. 2009

CBF as a marker of drug activity

- Where is a drug *likely* to be having an effect?
  - Central penetration
  - Sites of metabolic/neuronal action, downstream of binding
  - Sites of vascular activity
- Back to our opioid analgesics

Opiate receptor binding potential



Baumgartner et al Neuroimage 2006

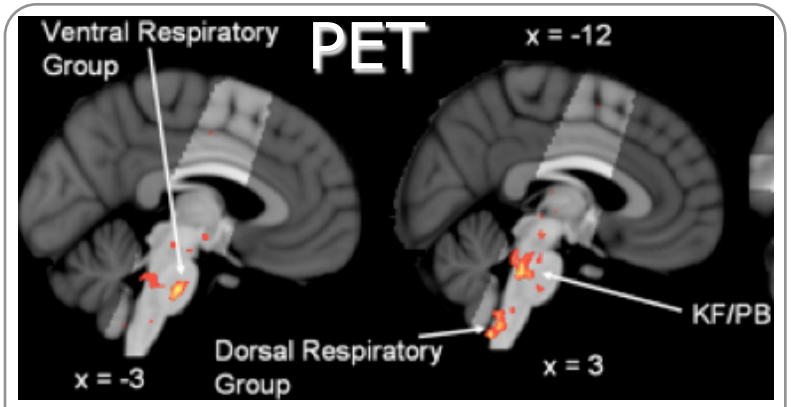
Hypothesis

"Where is a drug *likely* to be having an effect?"

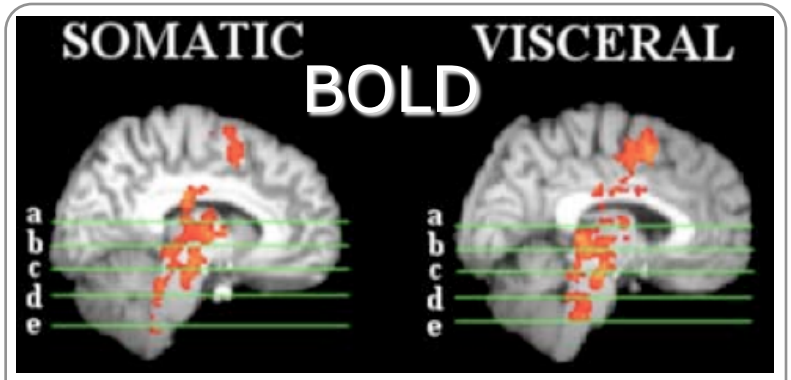
A CBF increase in response to remifentanil administration in those areas of high opioid receptor binding potential and networks responding to pain

- ACC, insular, brainstem, thalamus, striatum (deep grey)

Opioid-induced CBF increases and decreases



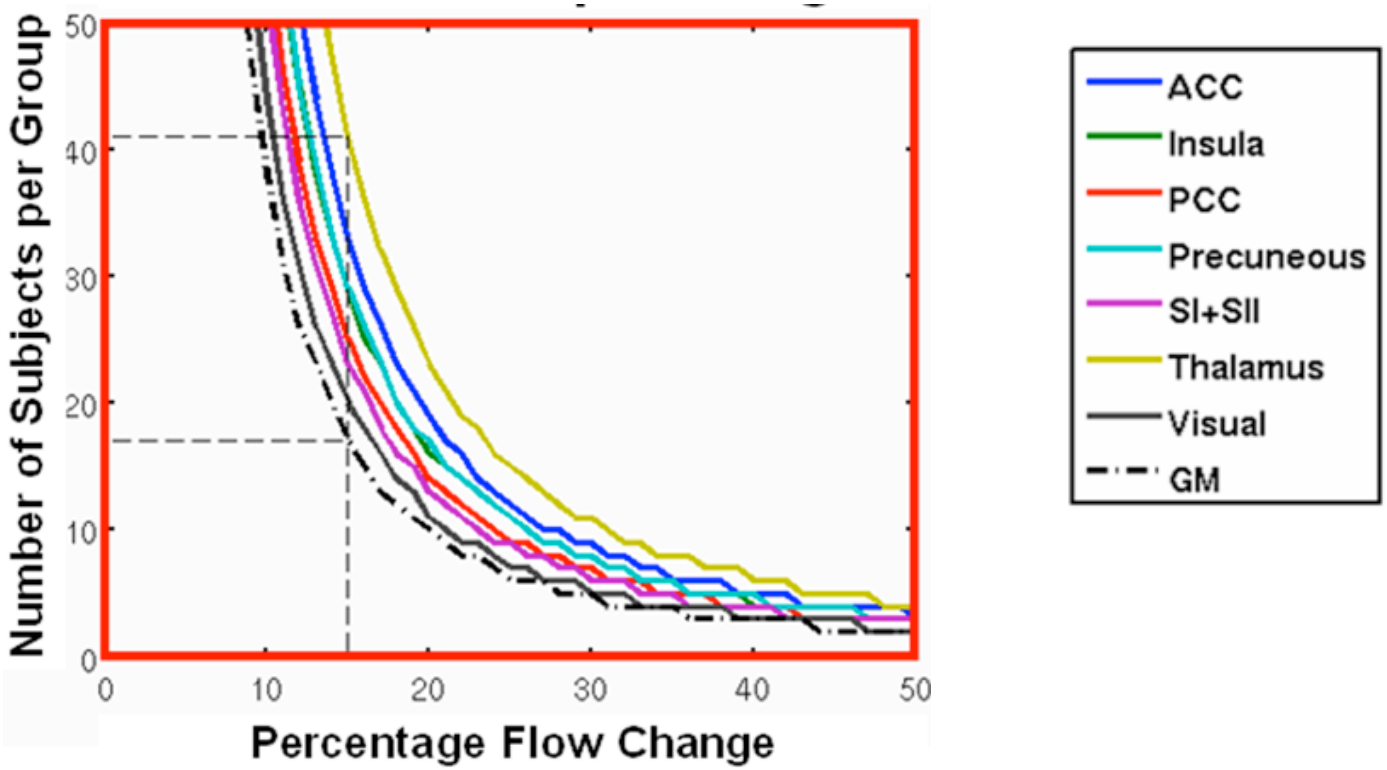
CO_2 & opioid sensitive brainstem <u>breathing activity,</u> Pattinson et al Neuroimage & J. Neurosci. 2009



<u>Pain</u> brainstem activity, Dunckley et al J. Neurosci. 2005,

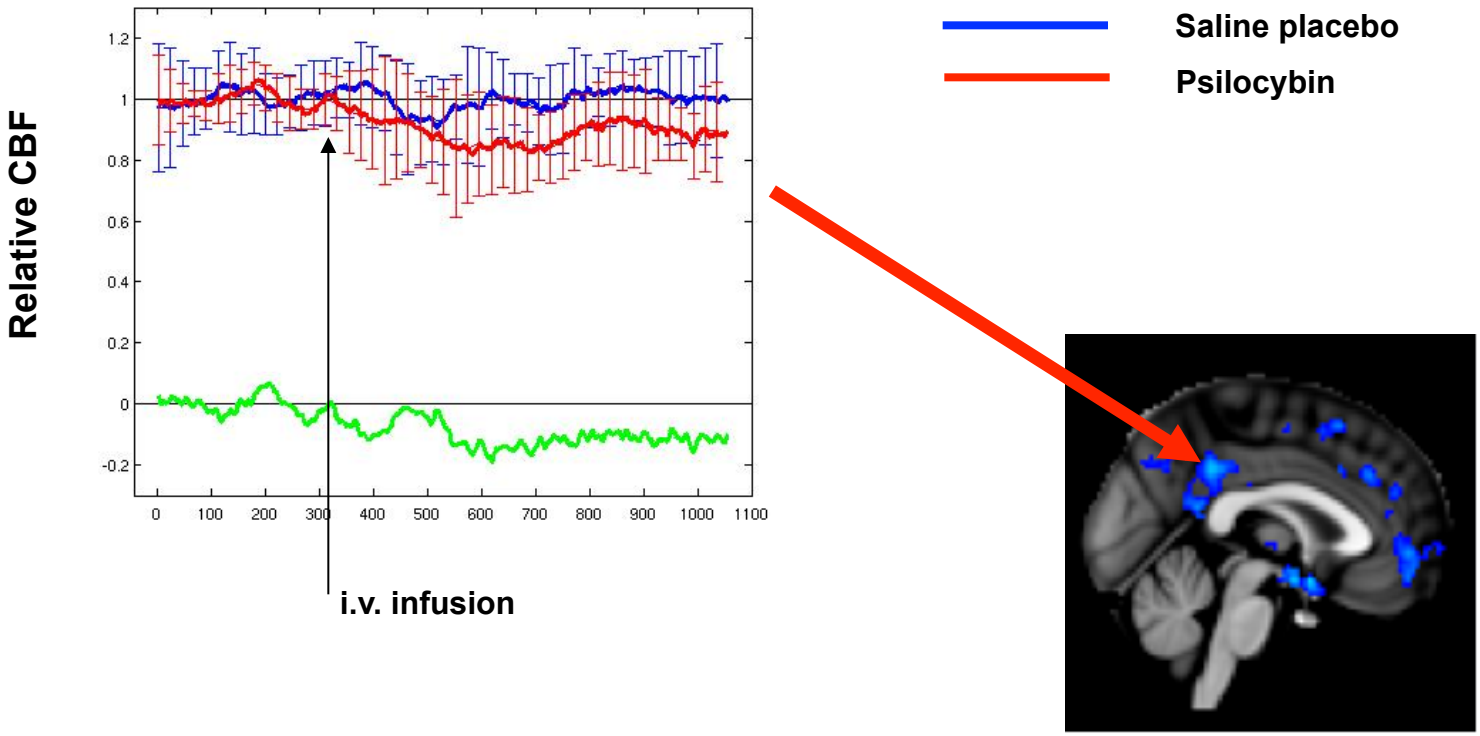
insula

Number of subjects for an ASL perfusion study

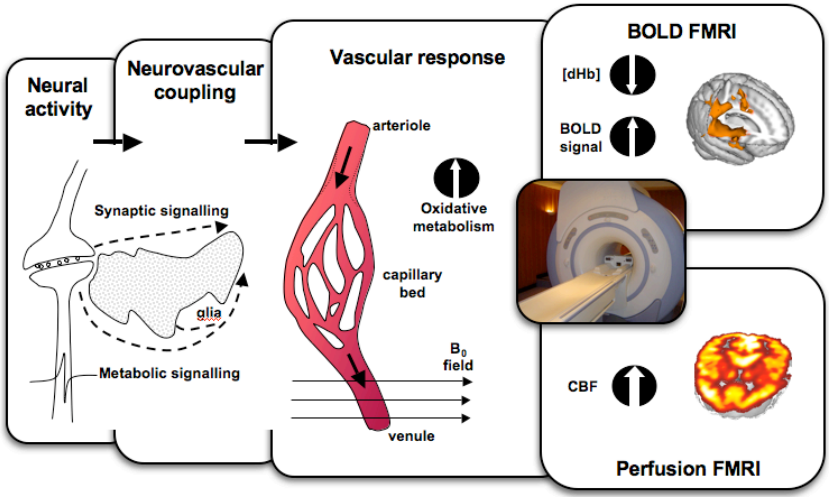


- 4 minute perfusion scan
- 15-40 subjects per group needed to detect a 15% change in CBF within a region of interest

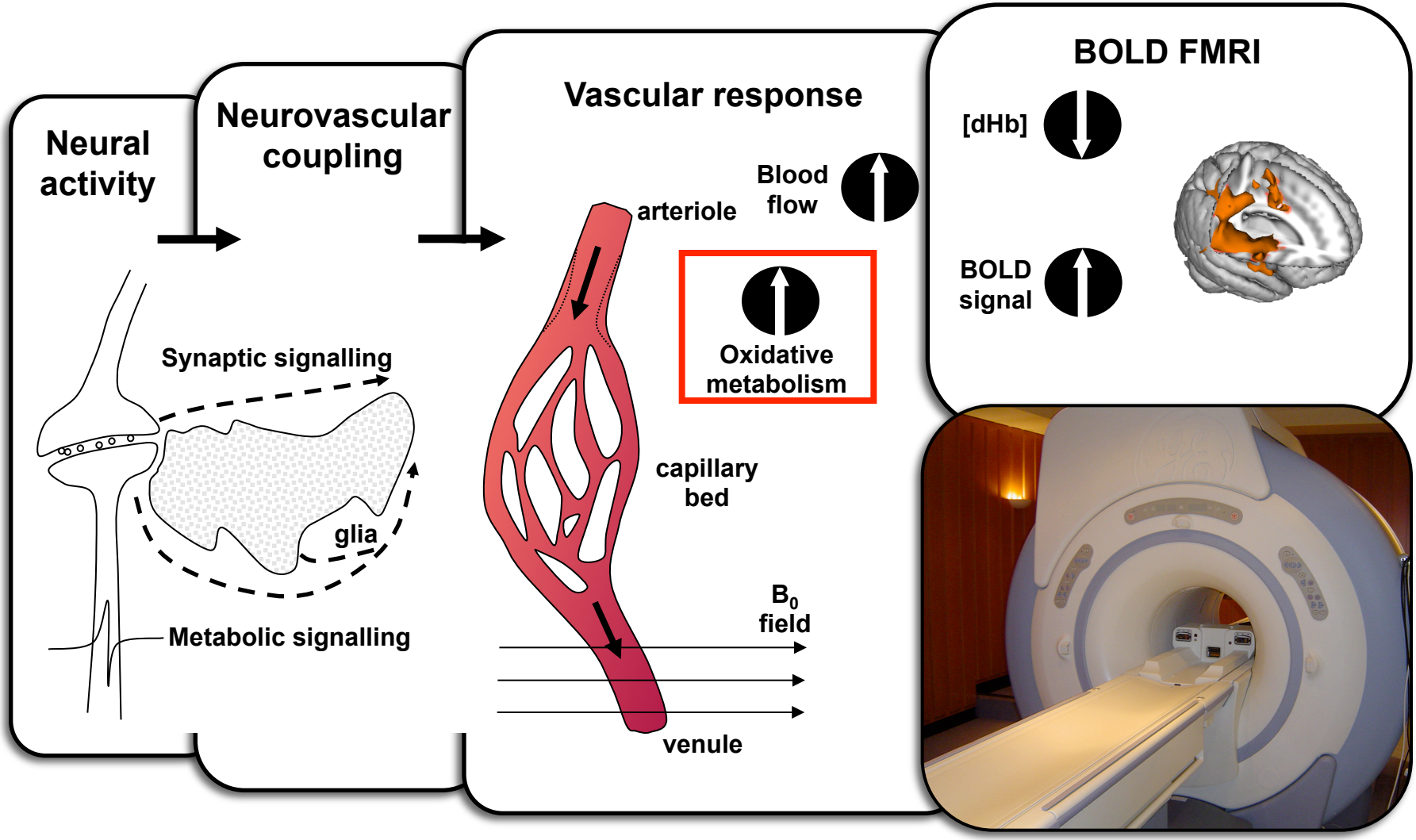
Psilocybin effects on perfusion



- Psilocybin - partial agonist of 5-HT2A receptor
- Focal perfusion decreases (15 subjects)
- Subjective effects correlate with perfusion decrease in rostral anterior cingulate / medial prefrontal cortex

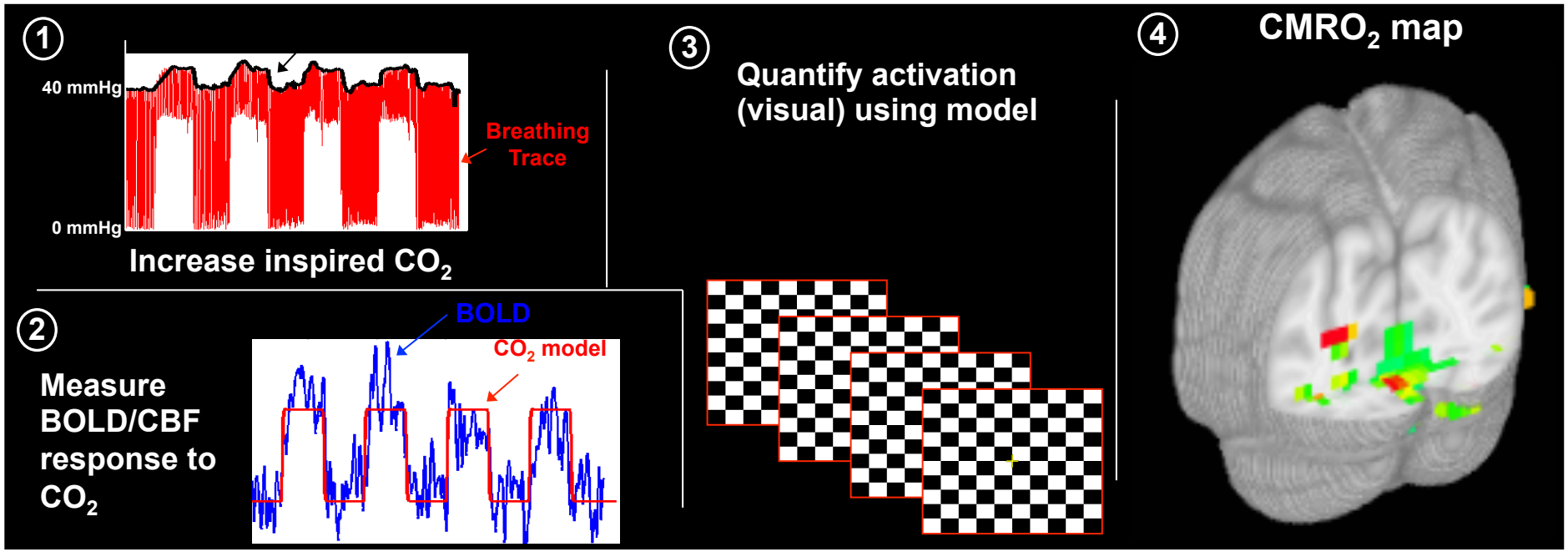


- Can we get closer to neural activity?
- What if neurovascular coupling / signalling is altered?


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

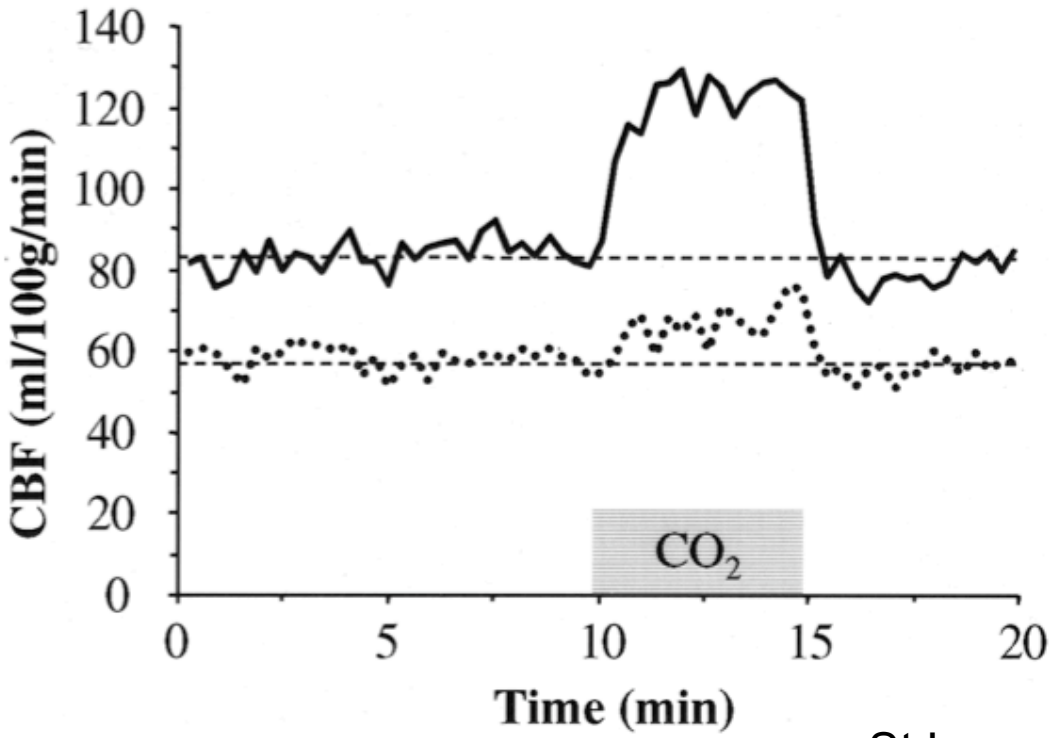
Calibrated FMRI: $CMRO_2$

- Measure changes in oxygen consumption ($CMRO_2$)
  - Calibrate the BOLD response to a pure change in flow / blood oxygen, *without* change in metabolism
    - Using CO_2 challenge
  - Difference between *calibration* and *task* scan gives relative oxygen metabolism



Drug induced change in vascular response

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



St Lawrence et al MRM 2003

Drug induced change in vascular response

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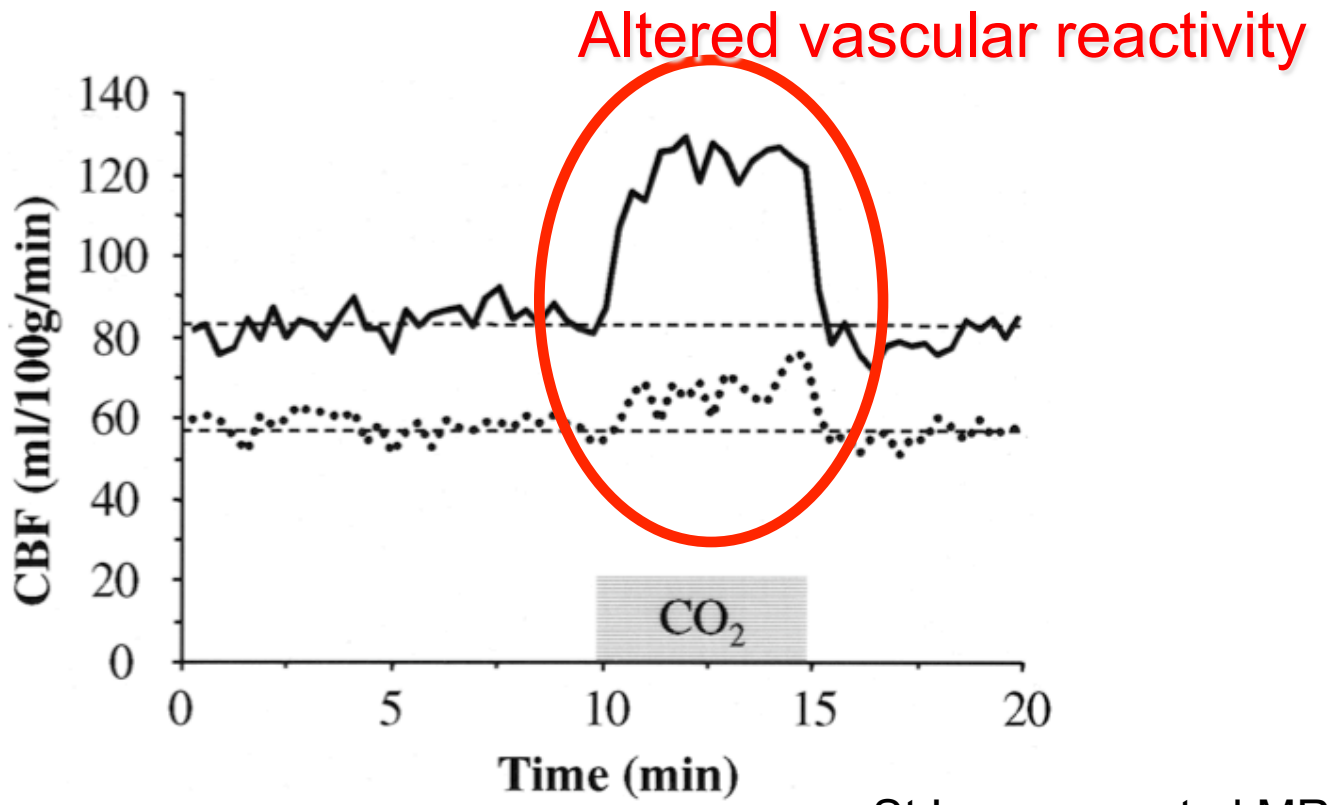
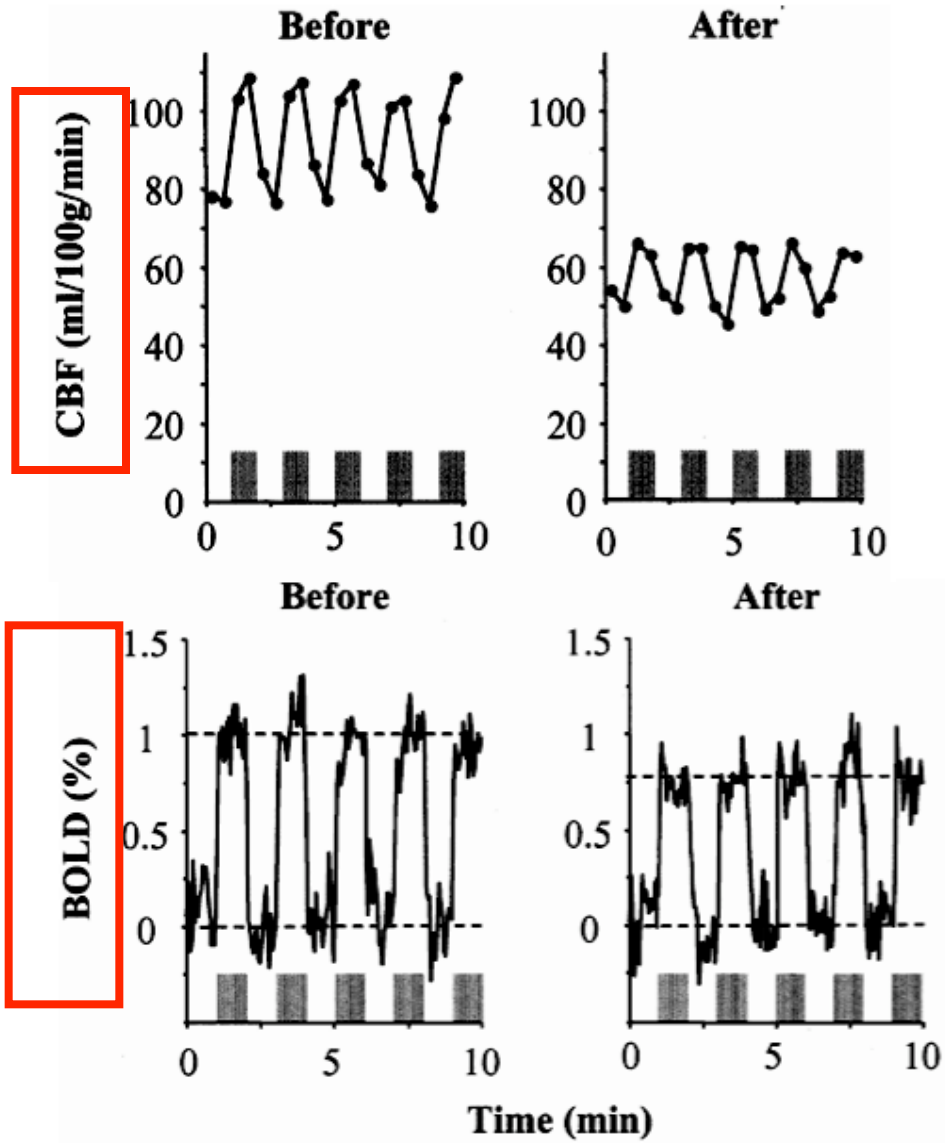


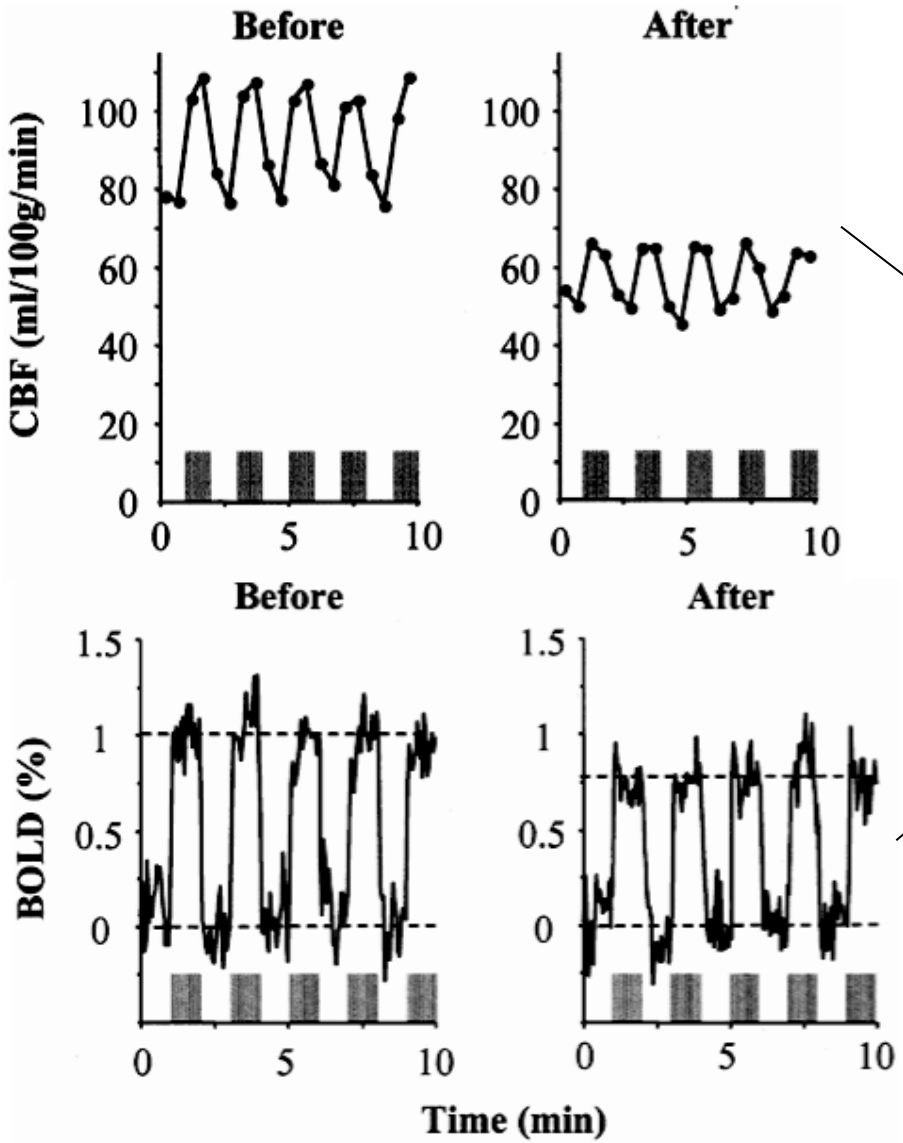
St Lawrence et al MRM 2003

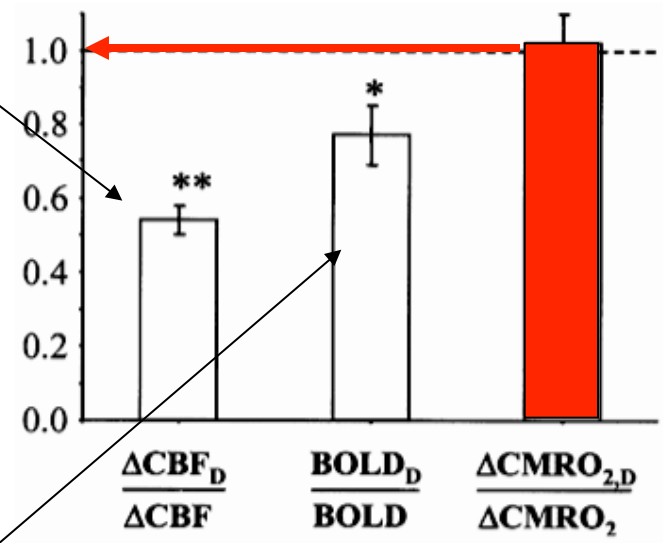
Reduced vascular response to finger tapping



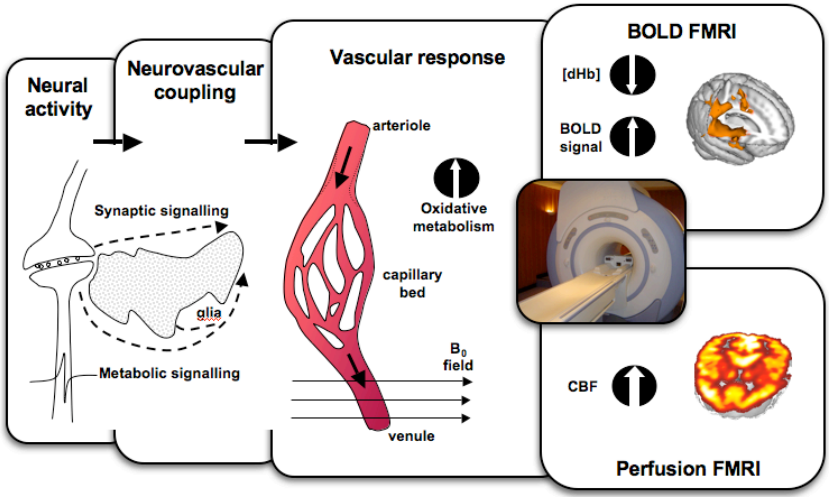
St Lawrence et al MRM 2003

$\Delta CMRO_2$ preserved: a better marker of neural activity

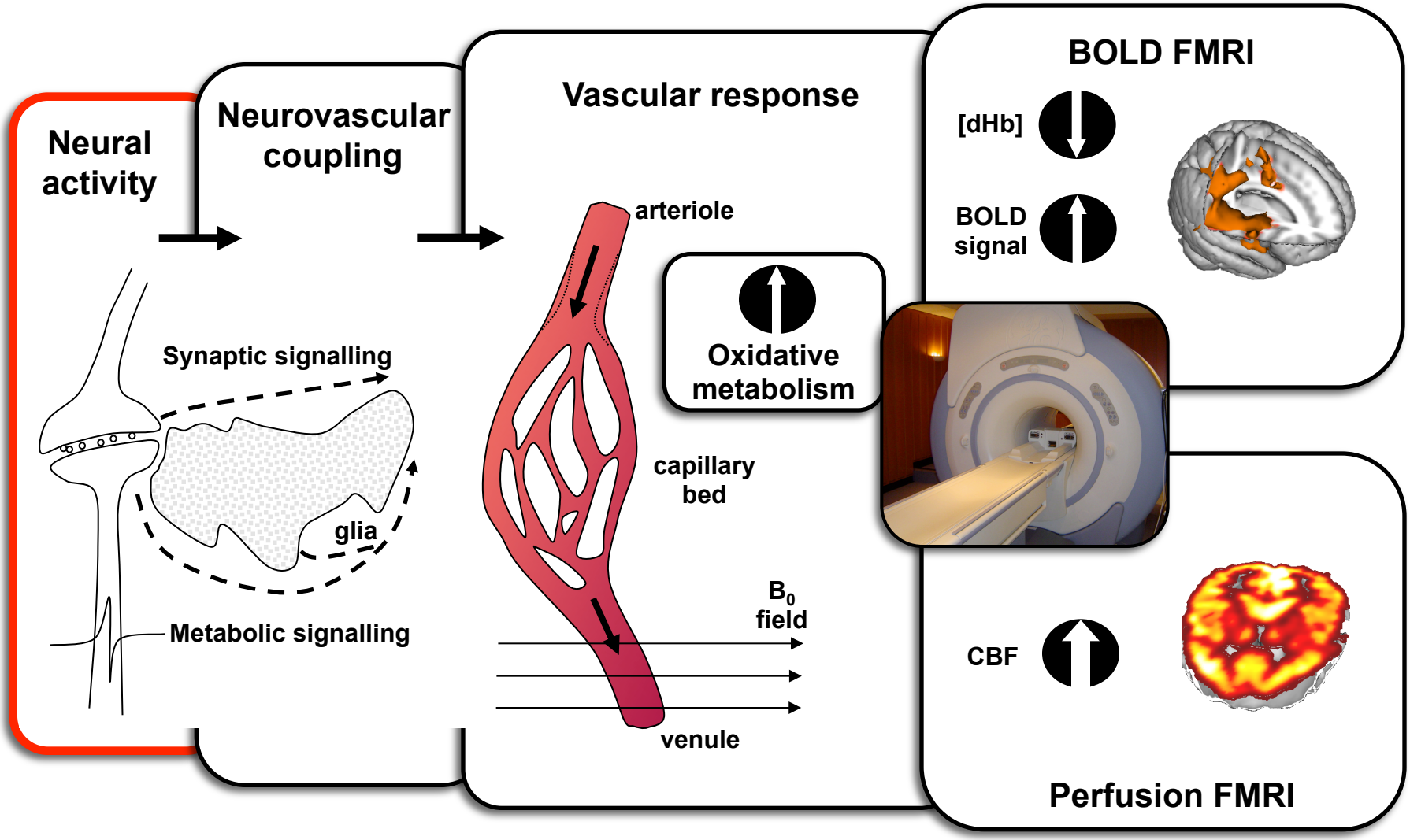




St Lawrence et al MRM 2003



- Direct measures of neuronal activity … electroencephalography


Neural activity
Neurovascular coupling
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Synaptic signalling
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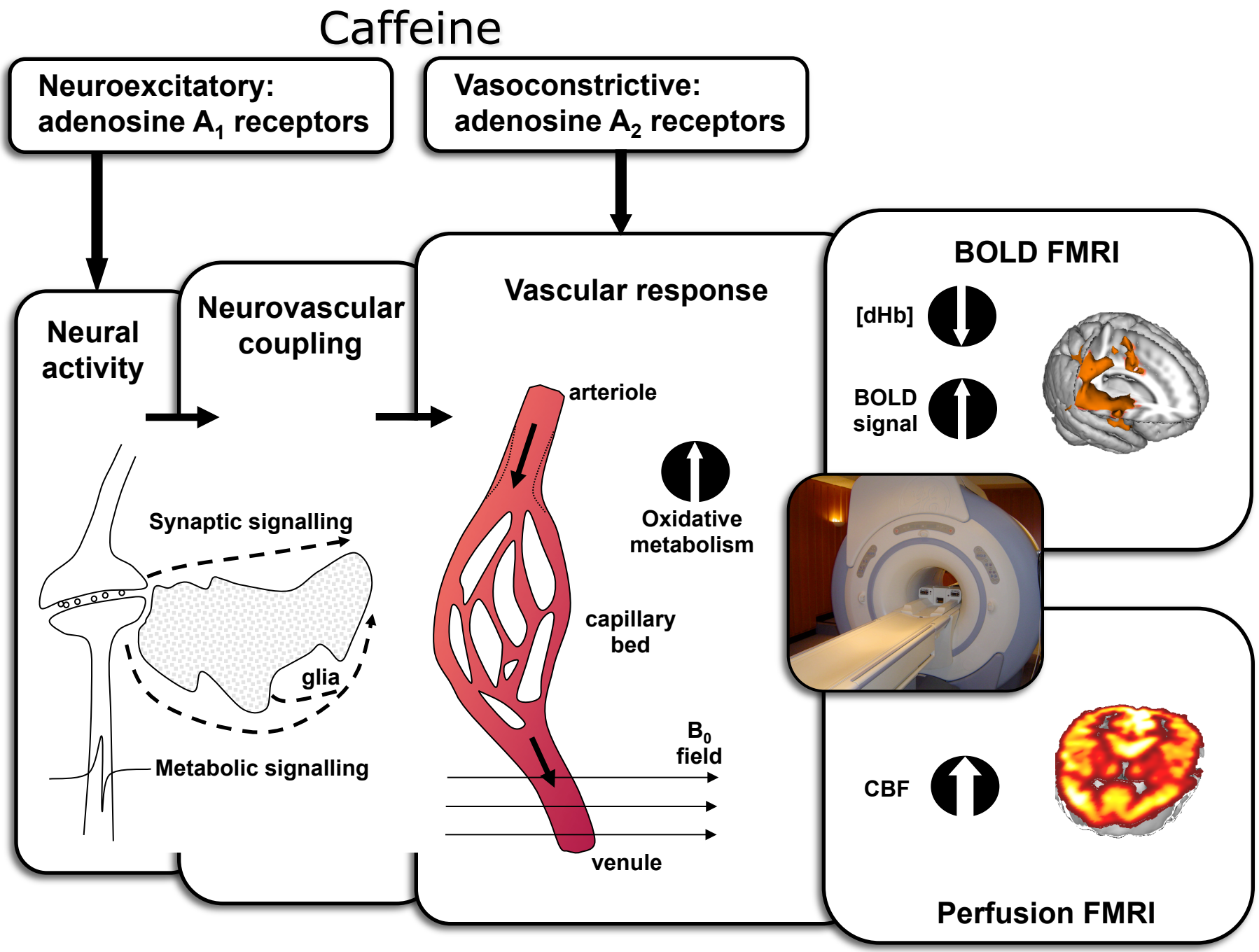
arteriole
capillary bed
venule
B_0 field
Oxidative metabolism
CBF
Perfusion FMRI


Caffeine
Neuroexcitatory: adenosine A_1 receptors
Vasoconstrictive: adenosine A_2 receptors
Neural activity
Neurovascular coupling
Vascular response
BOLD FMRI
[dHb]
BOLD signal
Synaptic signalling
glia
Metabolic signalling
arteriole
Oxidative metabolism
capillary bed
B_0 field
venule
CBF
Perfusion FMRI

Effects of caffeine on neurovascular coupling

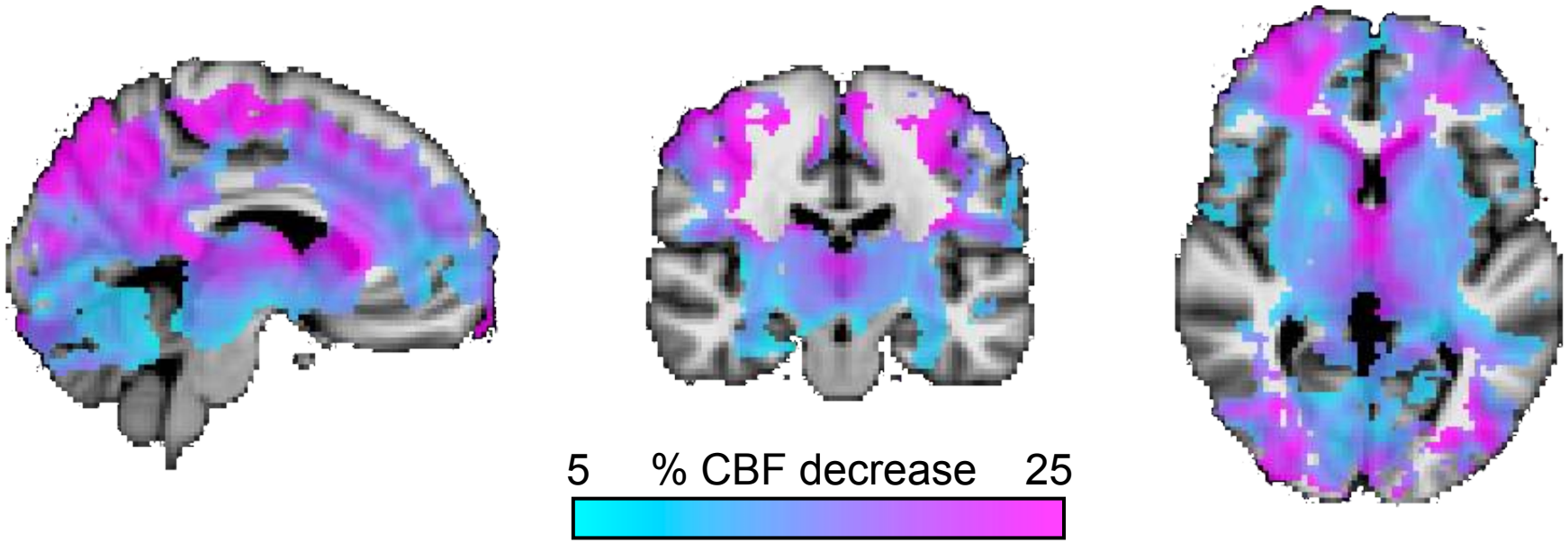
- Caffeine decreases cerebral perfusion and acts as a BOLD *contrast booster*
  - Mulderink et al Neuroimage 2002 (oral dose, variable consumers, abstain prior to experiment)

- BOLD response is boosted by caffeine in high users but decreased in low users
  - Laurienti et al Neuroimage 2002
  - receptor expression and affinity are a component of the formation of drug tolerance, which depends on individual caffeine intake
  - Differential weighting of A_1 (neurostimulant) and A_2 (vasoconstrictive) effects according to usage. Field et al Radiology 2003.

Separating haemodynamic and neuronal effects

- In low caffeine consumers we hypothesize that caffeine decreases CBF
  - Pulsed ASL CBF measurements
- We hypothesize a 'neuronal' effect of caffeine on a cognitive auditory-oddball task
  - Simultaneous EEG-FMRI, enhanced P300 novelty odd-ball response
- Use cognitively undemanding *control* tasks to identify general vascular influence of caffeine on BOLD contrast
  - Motor and visual

Caffeine: decreases in grey matter flow



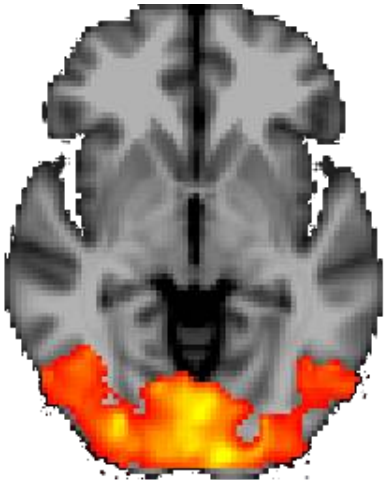
BOLD: Visual stimulus

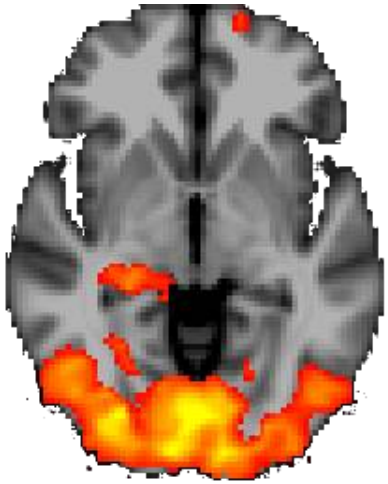
Placebo

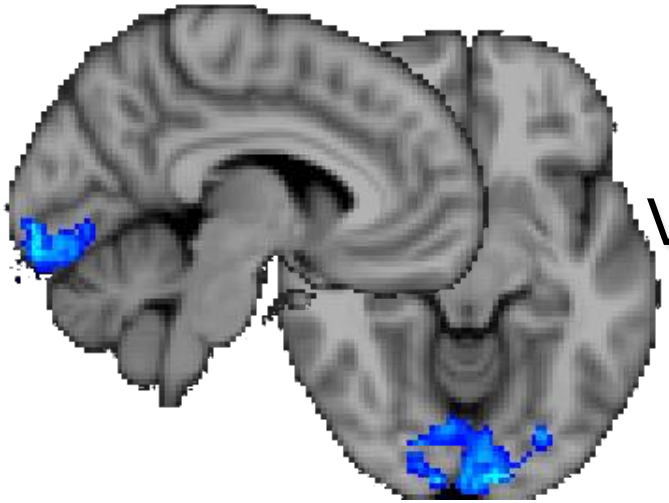
Caffeine

Placebo-Caffeine

VIS







VIS

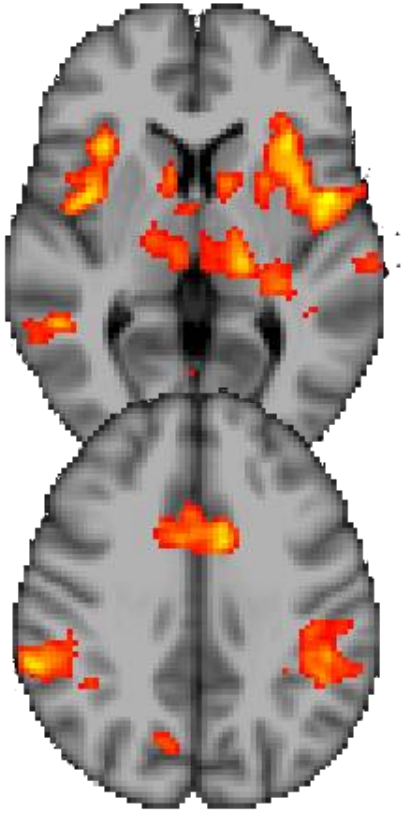
2.3 *Z* score 5

2.3 *Z* score 3.5

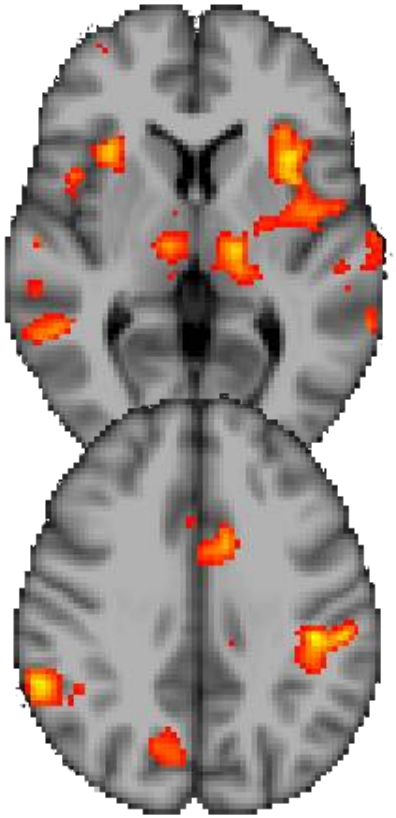
P<0.05 corrected

Auditory Oddball (target-nontarget)

Placebo

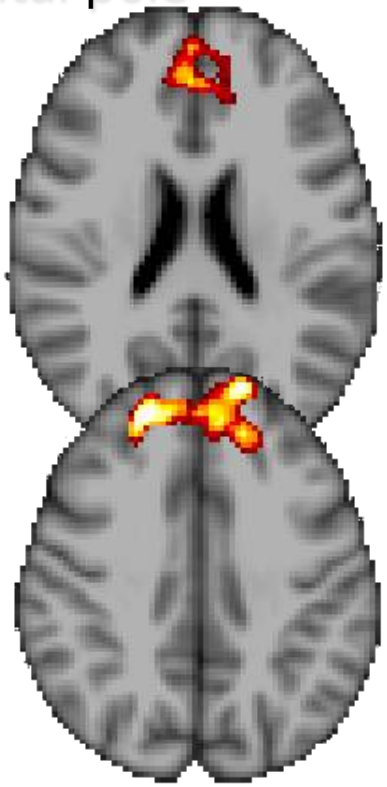


Caffeine



Caffeine-Placebo

Increased activity at frontal pole



3 *Z* score 4.5

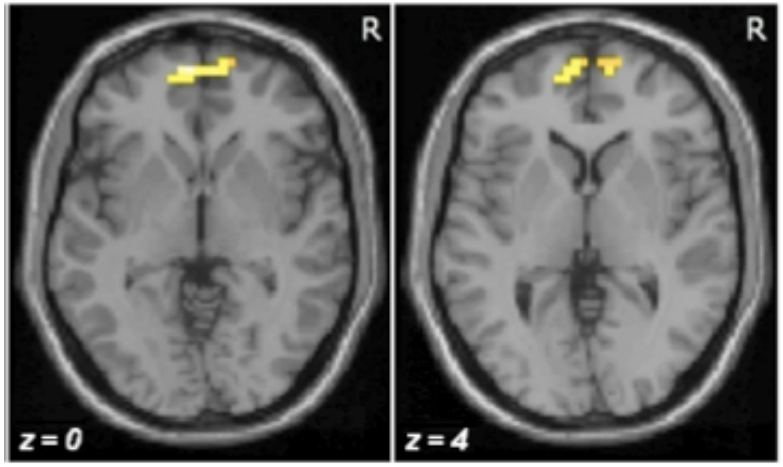
2.3 *Z* score 4

P<0.05 corrected

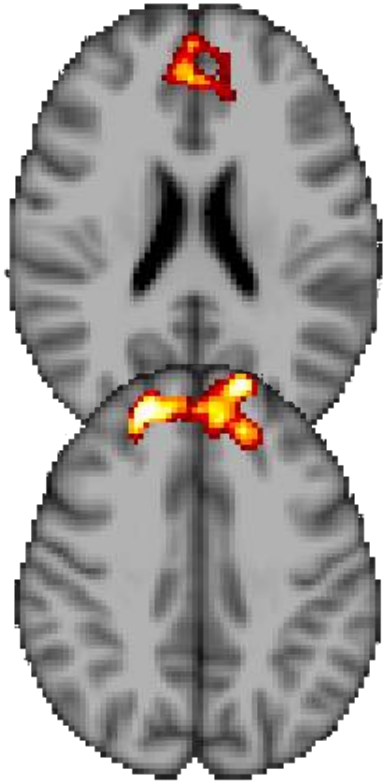
Working Memory and Auditory Oddball

Caffeine effect on working memory task (n-back)

Koppelstaetter et al. Journal of Alzheimer's disease. In Press



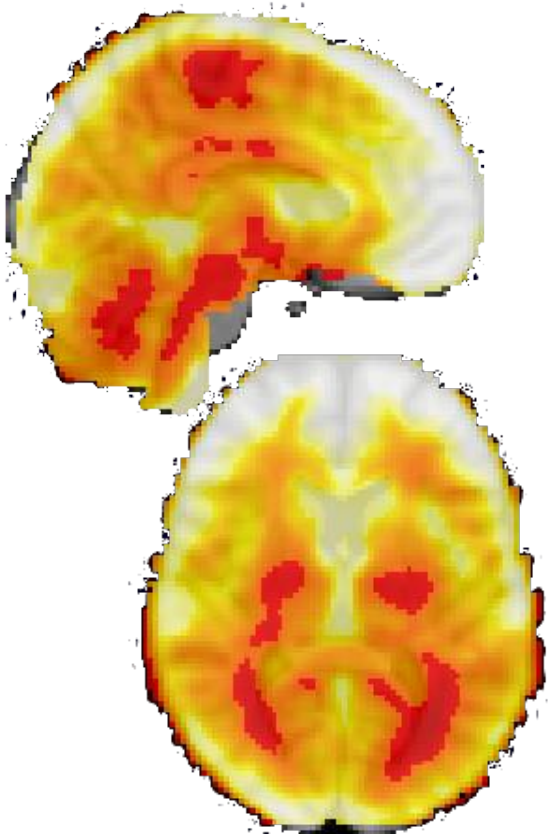
Caffeine-Placebo Auditory oddball



P<0.05 corrected

Caffeine: vascular ‘oscillations’

Placebo

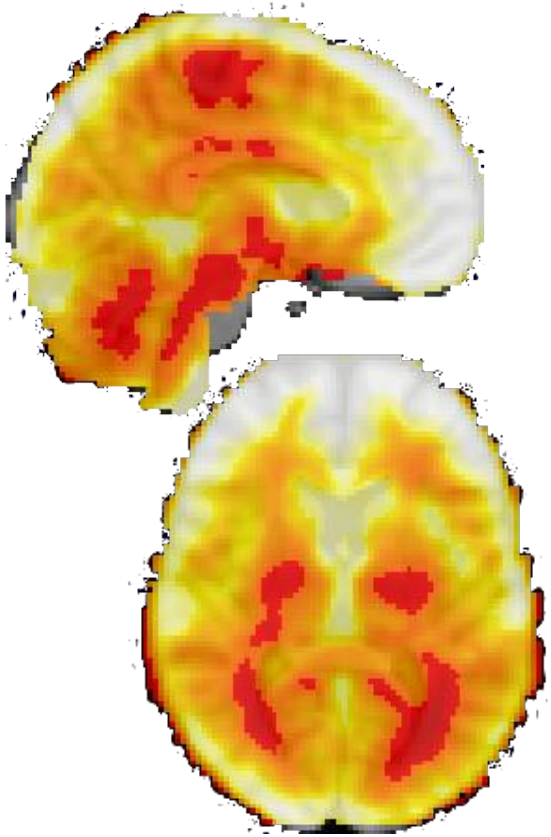


% temporal standard deviation

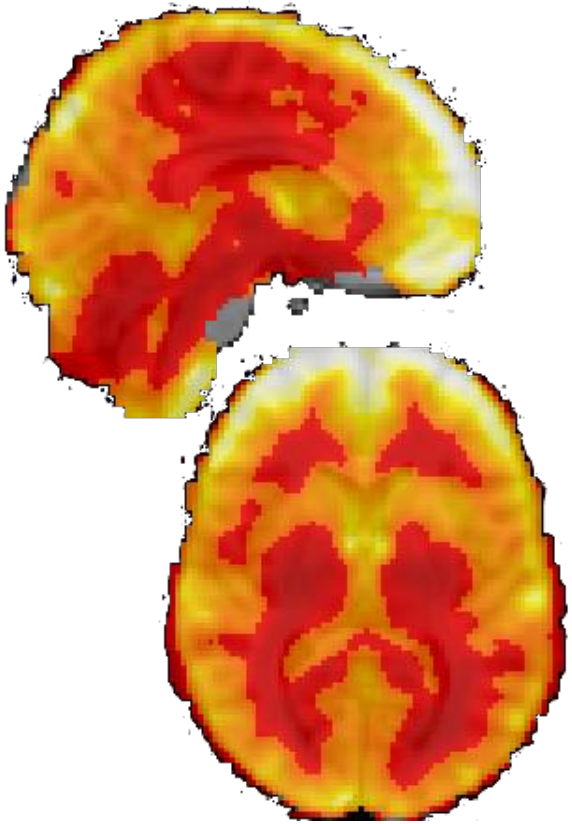
0  0.6

Caffeine: decreases vascular ‘oscillations’

Placebo



Caffeine

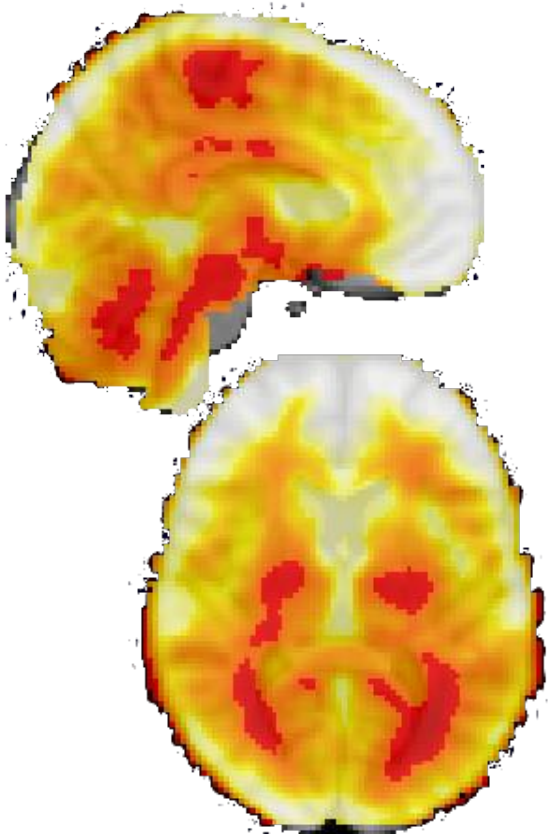


% temporal standard deviation

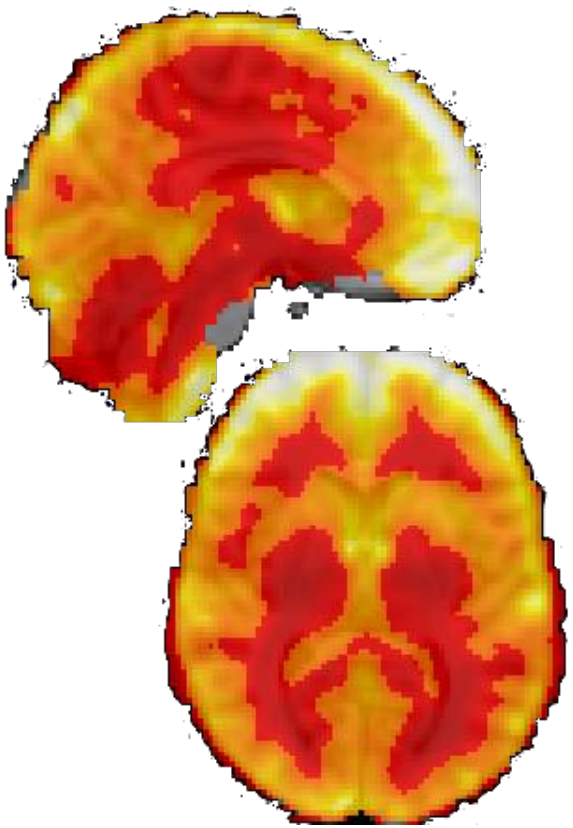
0  0.6

Caffeine: decreases vascular ‘oscillations’

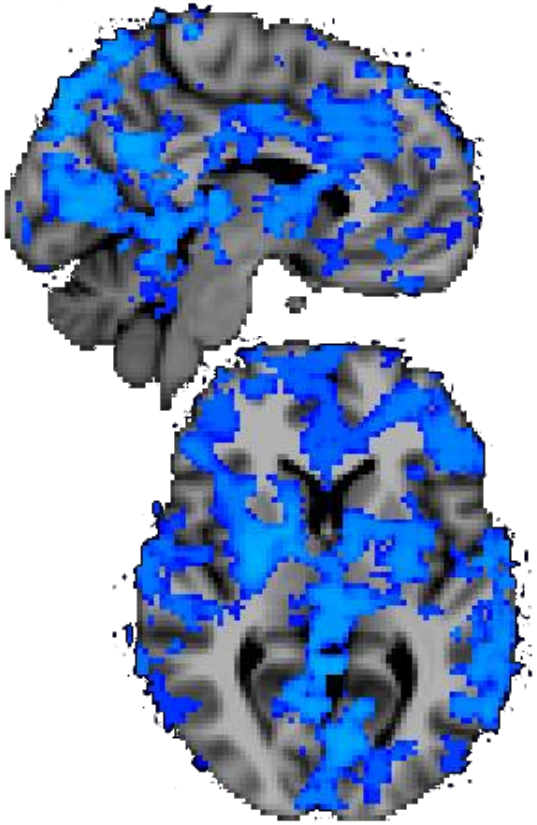
Placebo



Caffeine



Significant Tstd ↓



% temporal standard deviation

0  0.6

P<0.05 corrected

Caffeine: decreases vascular ‘oscillations’

Caffeine reduces resting-state BOLD functional connectivity in the motor cortex

Anna Leigh Rack-Gomer, Joy Liau, Thomas T. Liu *

Center for Functional Magnetic Resonance Imaging, University of California San Diego, La Jolla, CA 92093-0677, USA
Department of Radiology, University of California San Diego, La Jolla, CA 92093-0677, USA
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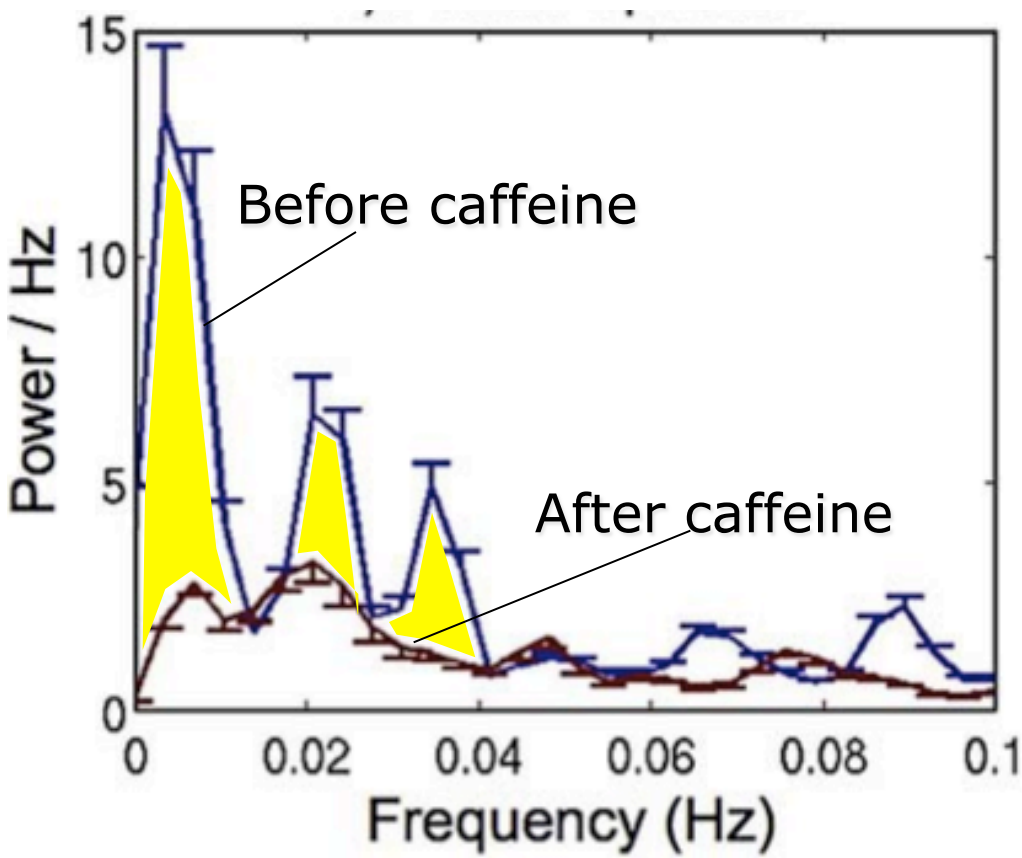
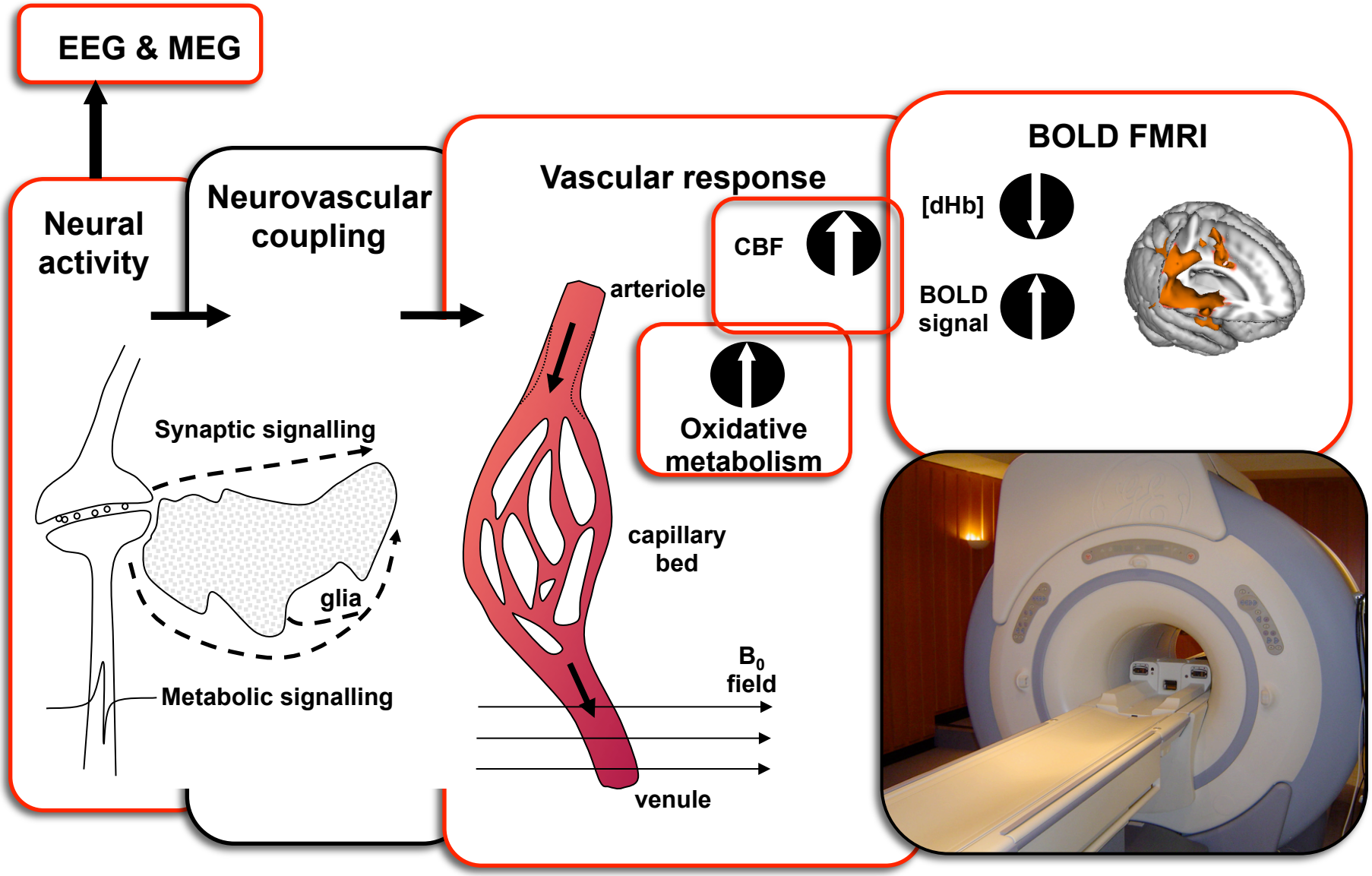
NeuroImage 46 (2009) 56–63




EEG & MEG
Neural activity
Neurovascular coupling
Vascular response
BOLD FMRI
[dHb]
BOLD signal
CBF
arteriole
Oxidative metabolism
Synaptic signalling
glia
Metabolic signalling
capillary bed
B_0 field
venule

Summary: in pharmacological FMRI…

- BOLD is rarely enough on its own as there can be problems with interpretation
  - Task related / PK / resting-state functional connectivity

- Measure vascular state
  - Vascular reactivity to aid FMRI interpretation
  - CBF measurement as a marker of
    - Disease, recovery, reorganisation, drug action
    - Aids interpretation of BOLD
  - Metabolism as a marker of neural activity

- EEG (or MEG) for clues over neural effects

- … these methods are becoming more and more practical for drug and disease studies

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