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and Brain
Sciences Unit



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Biophysics of fMRI and the BOLD signal

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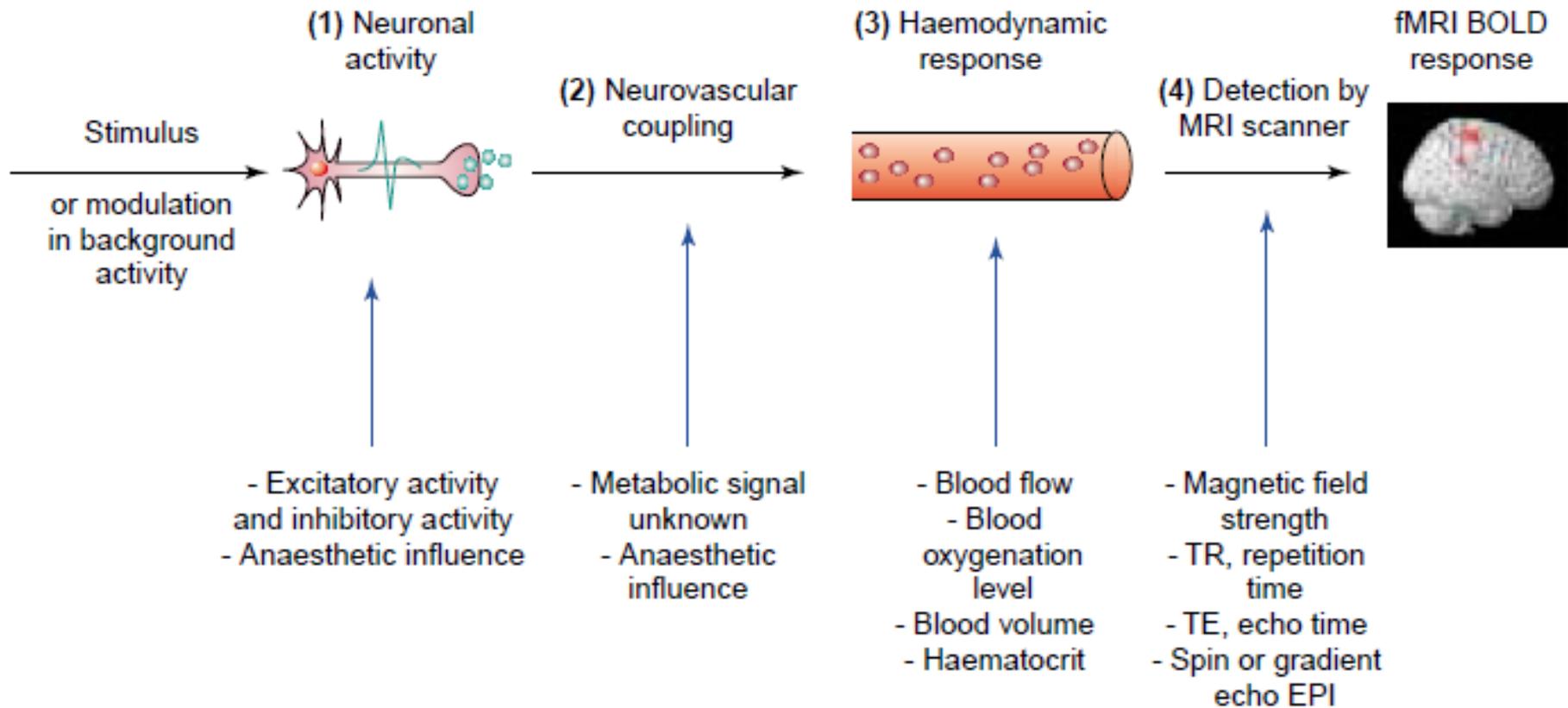
Overview

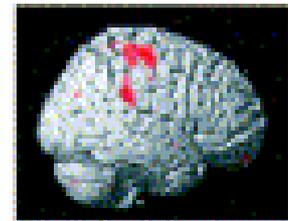
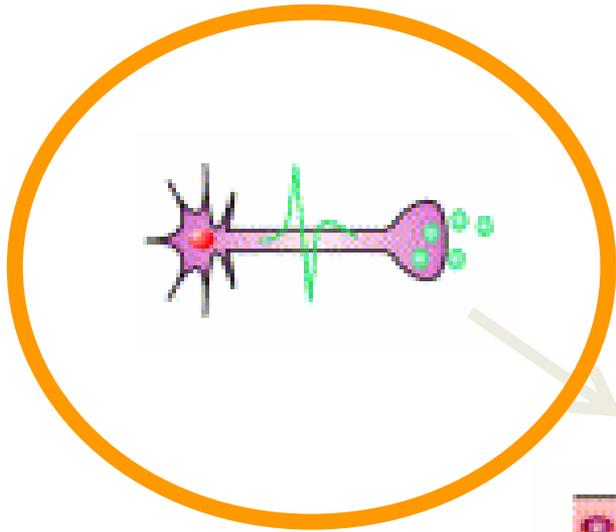
- **Biophysics of functional MRI**
 - Haemodynamic response
 - Haemodynamic – MRI coupling
 - Measuring the BOLD signal

- **Common Image artefacts**
 - EPI distortion
 - Movement artefacts
 - Signal dropout

Part I: Biophysics of functional MRI

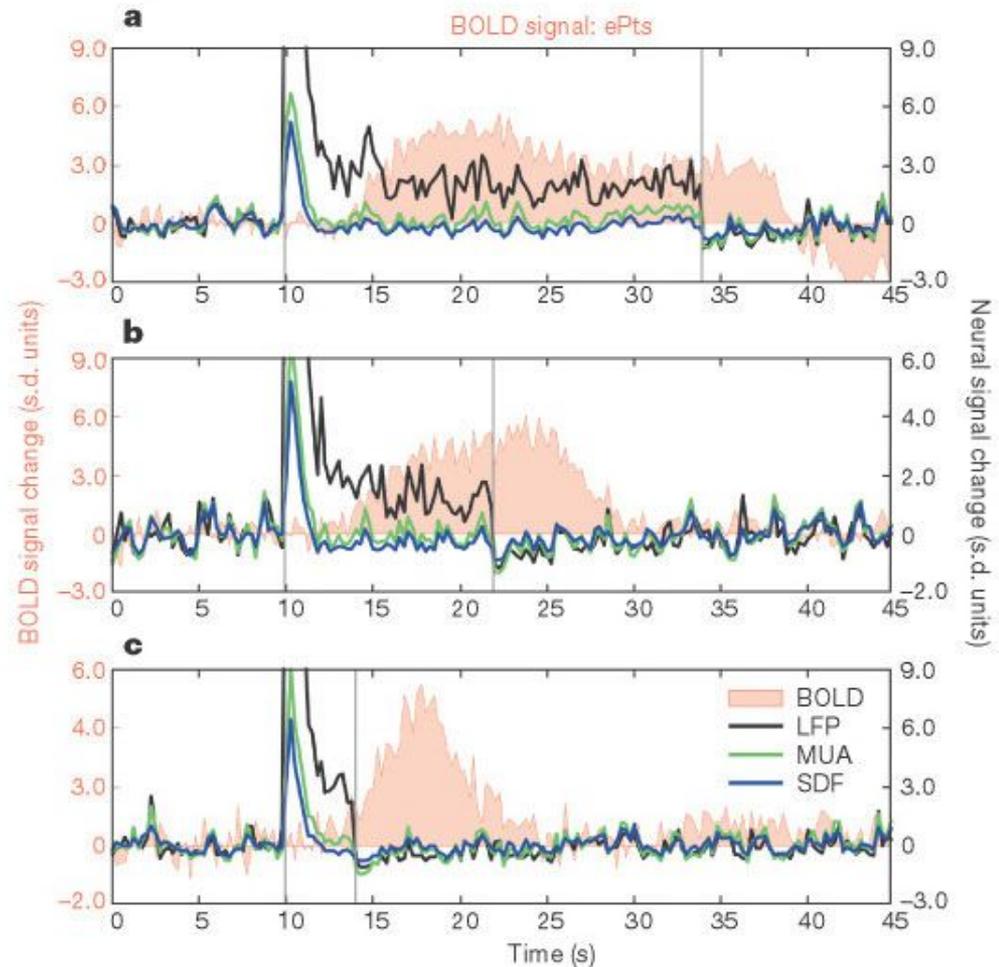
Key determinants of fMRI BOLD response





What aspects of neuronal activity determine the BOLD response?

- **Local Field Potentials** (Logothetis et al, 2001)
 - Simultaneous BOLD fMRI & electrophysiological recording
 - Measured **Local Field Potentials** (pre-synaptic, input) and Multi Unit Activity (spiking, output)
 - MUA adapts a couple of seconds after stimulus onset, with **LFP** remaining the only signal correlated with the BOLD response.



What aspects of neuronal activity determine the BOLD response?

- The BOLD response primarily reflects **synaptic input and local cortical processing**, rather than neuronal output.
- This suggests that fMRI is most sensitive to **population-level integrative processes** (e.g. dendritic activity, synaptic currents).

See also:

Logothetis (2008), Nature – review of fMRI principles

Goense & Logothetis (2008), Current Biology – BOLD also correlates with LFPs in visual cortex

Buzsaki et al. (2012), Nature Rev Neurosci. – physiological origin of LFPs

What aspects of neuronal activity determine the BOLD response?

- **Is the BOLD signal driven by energy consumption or signalling mechanisms?**
 - Early models assumed that increased blood flow directly reflected local metabolic demand, particularly in presynaptic terminals or glia.
 - If energy usage did control blood flow, then BOLD signals would reflect the activity of the cellular processes consuming most energy.
 - Assessment of energy use by different processes (Attwell & Iadecola, 2002)
 - Concluded that **most brain energy is used to power postsynaptic currents and action potentials** rather than presynaptic or glial activity.
 - Evidence suggests that cerebral **blood flow is regulated primarily by neurotransmitter-mediated signal, not energy depletion.**
 - The haemodynamic response is better understood as an **active, regulated process** rather than a passive response to energy use.

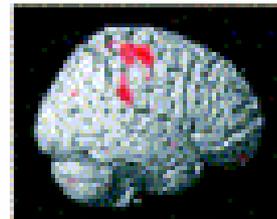
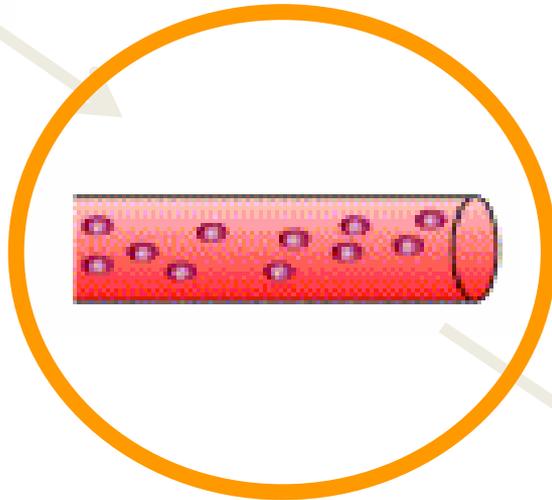
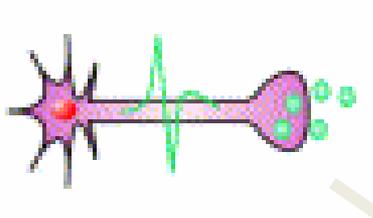
What aspects of neuronal activity determine the BOLD response?

- **Is the BOLD signal driven by energy consumption or signalling mechanisms?**

See also:

Attwell et al. (2010), Nature – review of neuronal control of blood flow

Iadecola (2017), Neuron – review of neurovascular coupling mechanisms

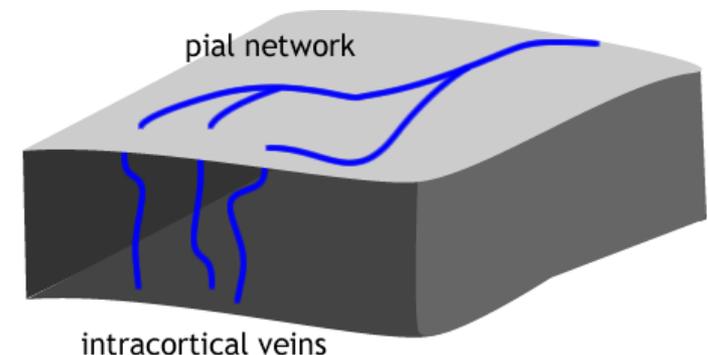
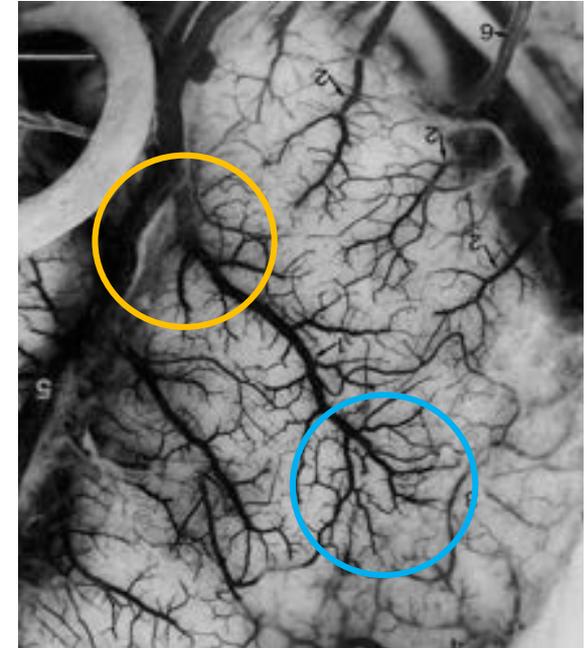


Hemodynamic response (HDR)

- **Increase in blood volume**
 - Increase in volume throughout system, from arterioles to capillaries, venules & veins
 - Fastest and greatest response in arterioles (Vanzetta, Hildenshen & Grinwald, 2005)
- **Large increase in blood flow**
- **Oxygenation**
 - Initial de-oxygenation in capillaries (Vanzetta et al, 2005)
 - Then, flow increase leads to a increase in oxygenation relative to the baseline state (Ogawa et al, 1990; Bandettini et al, 1997)

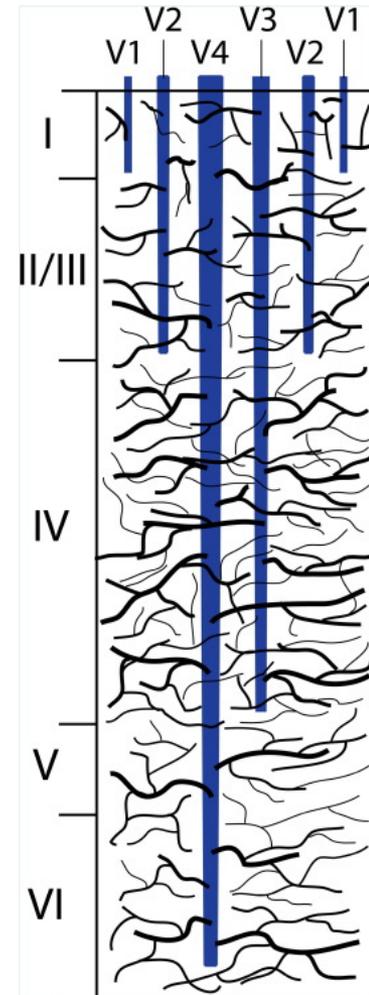
Haemodynamic response: spatial characteristics

- **What determines the spatial specificity of the BOLD response?**
 - The spatial distribution of the BOLD signal is strongly influenced by **vascular architecture**.
 - Because veins drain blood away from active neurons, **BOLD signal changes can appear downstream from the true site of neural activity**.
 - Spatial specificity improves when signal contributions from **smaller vessels and capillaries** dominate.



Haemodynamic response: spatial characteristics

- **What determines the spatial specificity of the BOLD response?**
 - The spatial distribution of the BOLD signal is strongly influenced by **vascular architecture**.
 - This is a **significant confound for laminar fMRI** studies.
 - Intracortical veins run perpendicular to the cortical surface and drain blood from all layers they pass through.
 - Stronger, but less specific, signal observed near the superficial layers – **superficial bias**.



Haemodynamic response: spatial characteristics

- **What determines the spatial specificity of the BOLD response?**

See also:

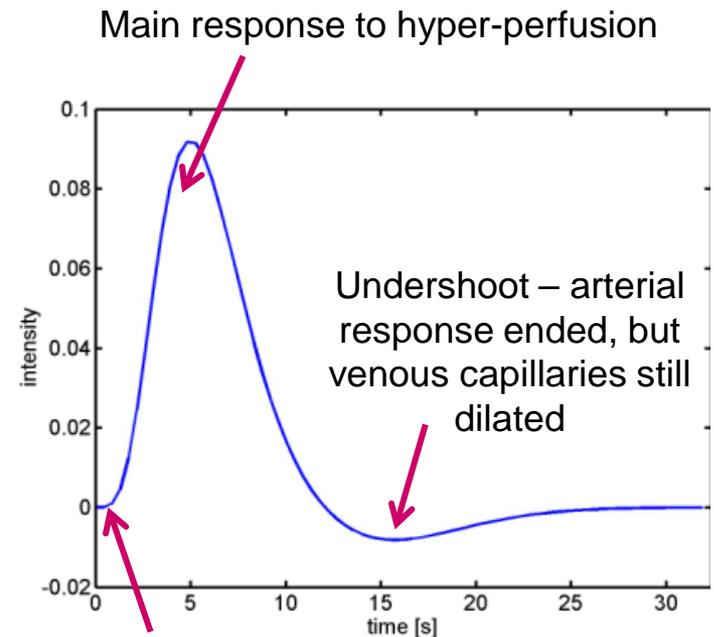
Polimeni et al. (2010), Neuroimage – laminar fMRI and vascular bias

Markuerkiaga et al. (2016), Neuroimage – quantitative vascular model

Havlicek & Uludag (2020), Neuroimage – a dynamical model of BOLD response

Haemodynamic response: temporal characteristics

- Temporal characteristics influenced by:
 - Neurovascular coupling in arterioles/capillaries
 - Flow times
 - Function of vessel size.
 - Blood velocity proportional to radius – delay in small vessels.
 - Mixing due to laminar flow within vessels (de Zwart, 2005).
 - Regional vascular architecture (Aquino et al., 2014).

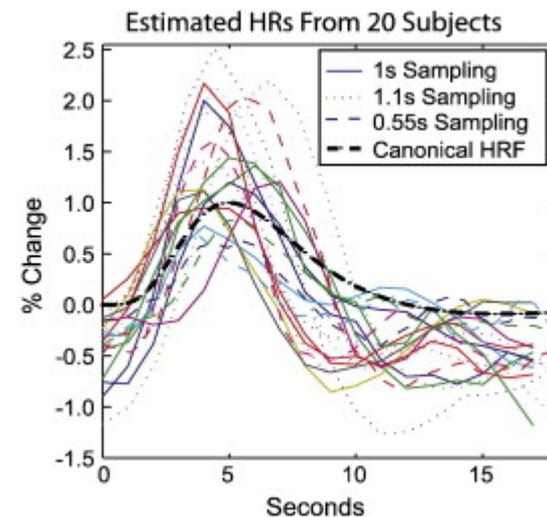
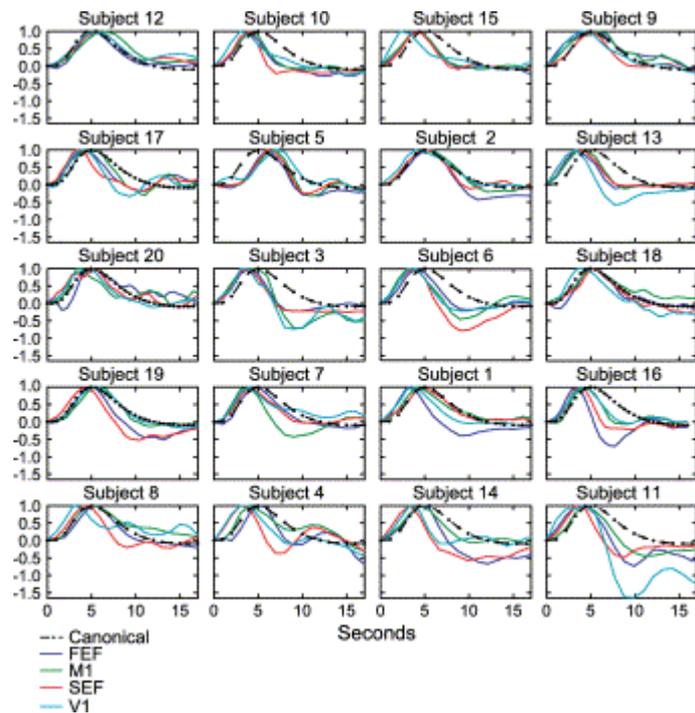


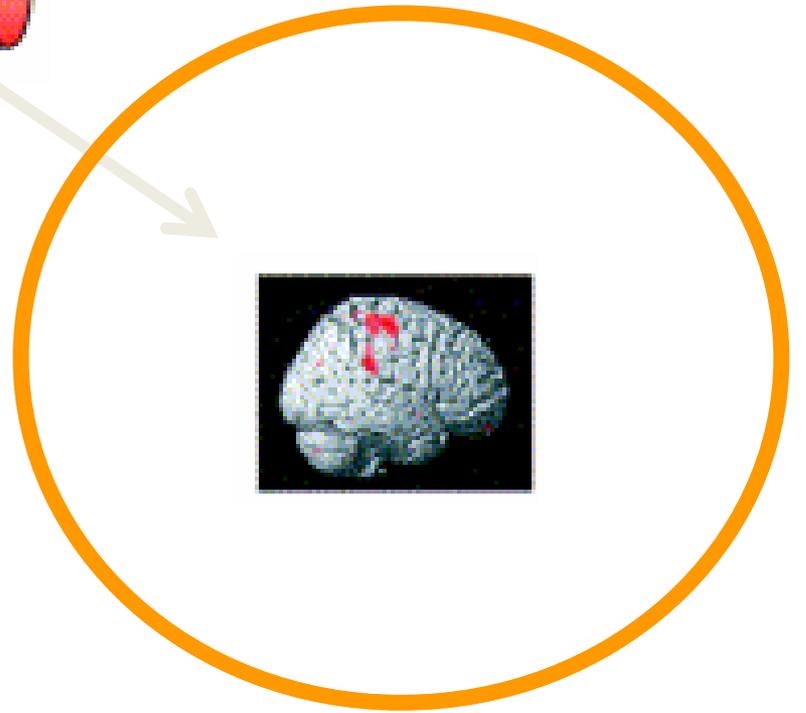
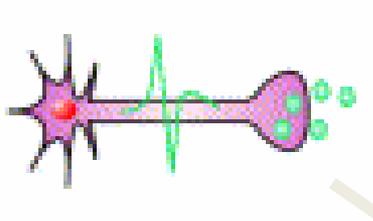
Initial dip?

Prior to vascular response, so spatially precise, but weak and controversial

Haemodynamic response: temporal characteristics

- Variability in HRF timing across brain regions and individuals is **systematic and meaningful**, not just noise (Handwerkwer et al., 2004; Handwerkwer et al., 2012).





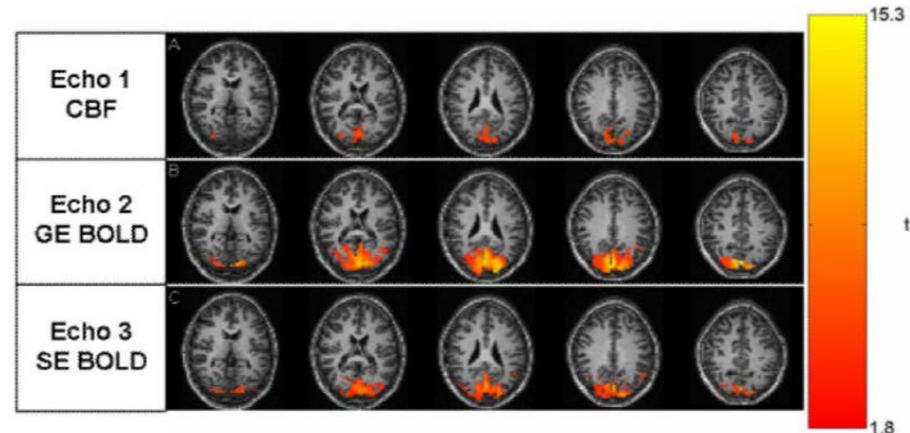
Hemodynamic-MRI coupling

- HDR affects MRI signal through several mechanisms:
 - Reduced field gradients around blood vessels - change in T2*
 - Reduced phase mismatch between signal from inside and outside venules & veins
 - Change in blood volume
- Affected by parameters of MR acquisition
 - Field strength (higher field – more sensitivity, particularly to smaller vessels/capillaries) (Haacke, 1994; Yacoub et al, 2003)
 - Gradient echo vs. spin echo

Hemodynamic-MRI coupling

- Sequence dependence of the BOLD signal: GE vs SE (e.g., Glielmi et al., 2010)

- Gradient-echo (GE) BOLD
 - High sensitivity
 - Greater contribution from larger veins
- Spin-echo (SE) BOLD
 - Reduced sensitivity
 - Improved spatial sensitivity



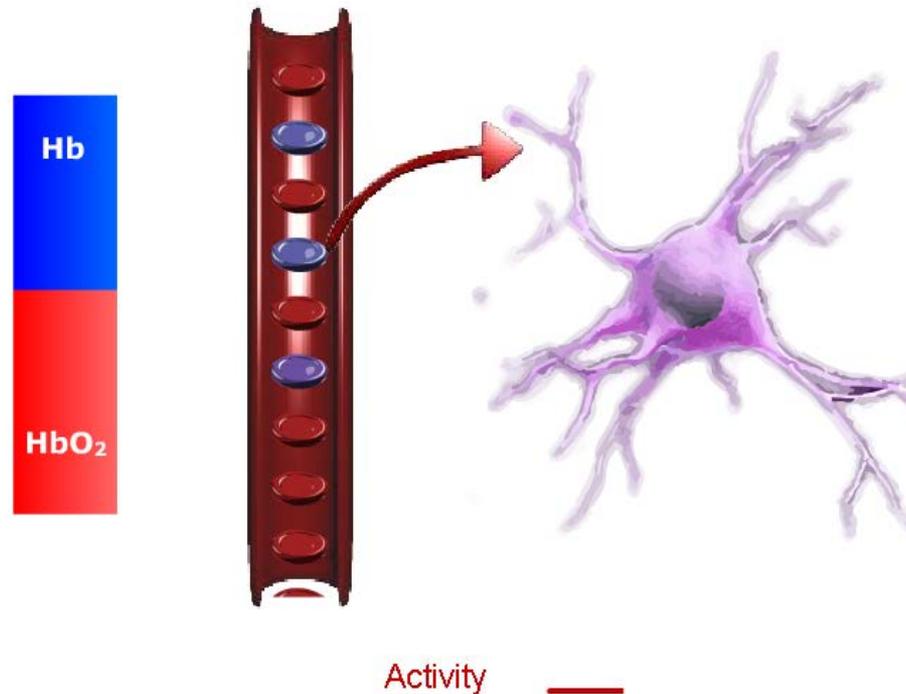
- Modern approaches exploit this trade-off for laminar and mesoscale fMRI (Huber et al., 2017).

Detecting HDR with MRI – BOLD signal

- BOLD – Blood **Oxygenation** Level Dependent
- BOLD fMRI employs haemoglobin as a convenient contrast agent
- It relies on the magnetization difference between oxy- and deoxyhaemoglobin to create the MRI signal.

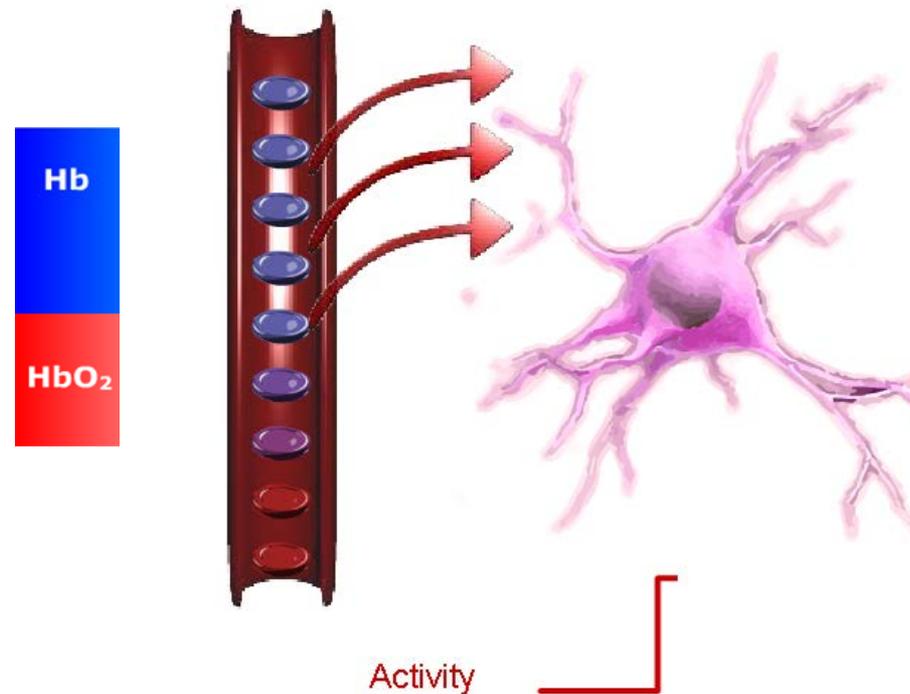
BOLD contrast step-by-step (1)

- The neuronal metabolism is dependent on blood oxygen supply, as the production of energy from glucose is mainly of the aerobic type.



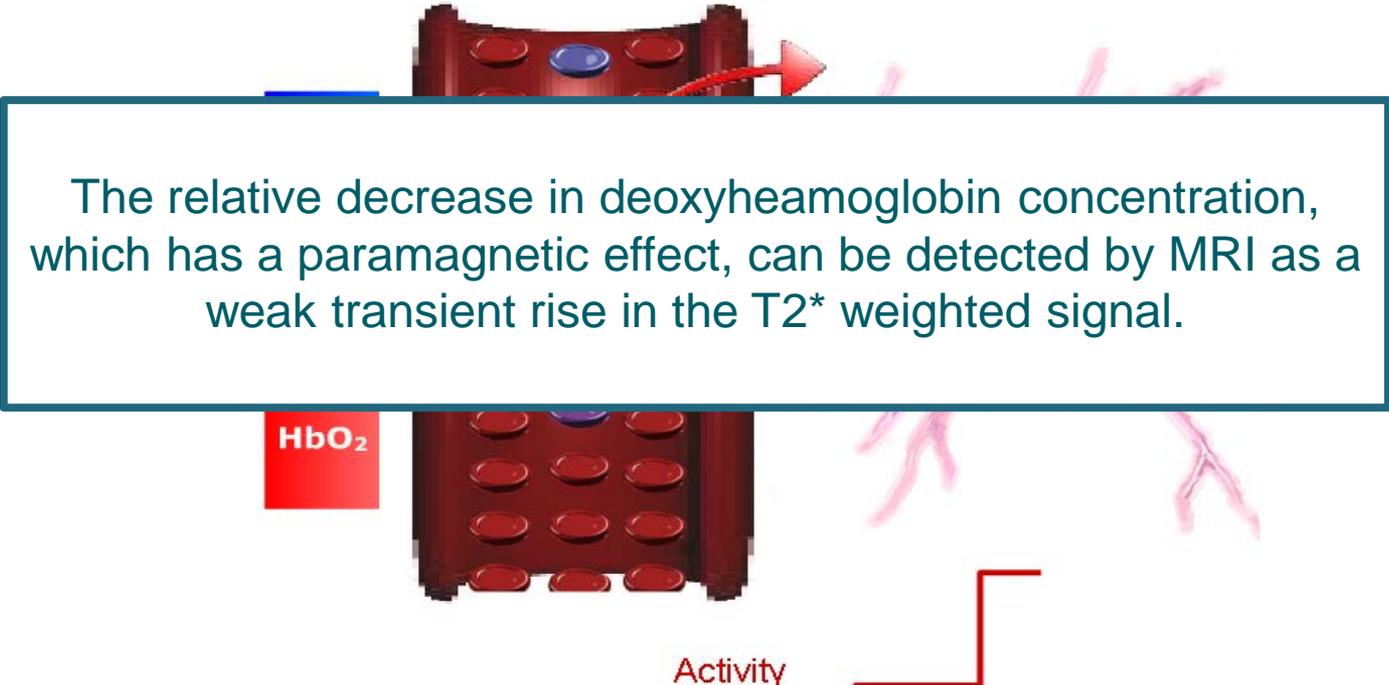
BOLD contrast step-by-step (2)

- Neuronal activity provokes an increase in oxygen consumption and an even higher increase in local blood flow (neurovascular coupling).



BOLD contrast step-by-step (3)

- As the increase in flow exceeds the increase in oxygen consumption, neuronal activity is expressed as a relative increase in oxyhemoglobin compared to deoxyhemoglobin in the activated zones.



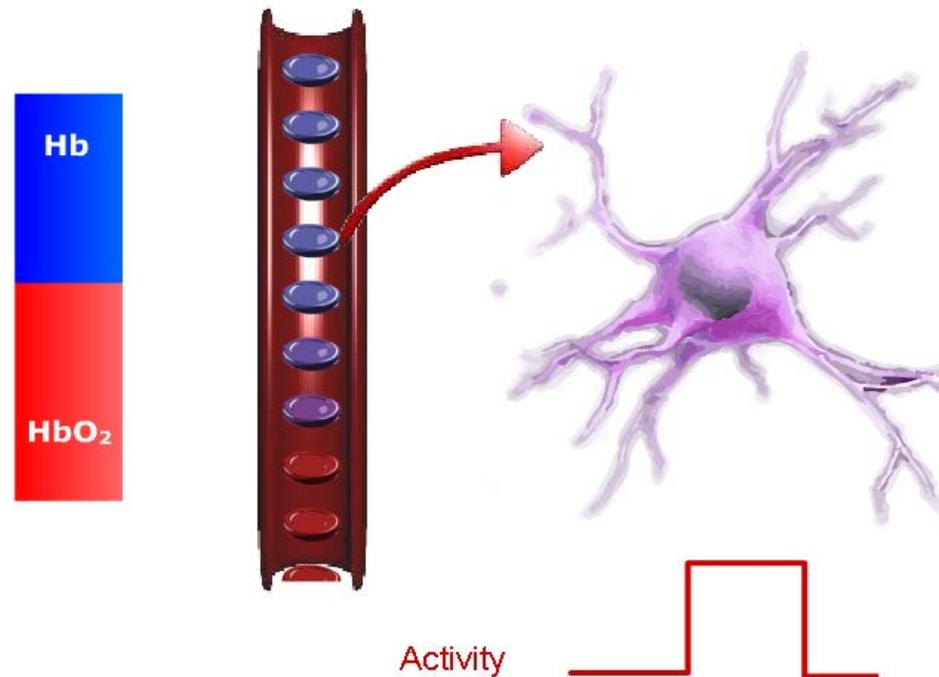
The relative decrease in deoxyhemoglobin concentration, which has a paramagnetic effect, can be detected by MRI as a weak transient rise in the T_2^* weighted signal.

HbO₂

Activity

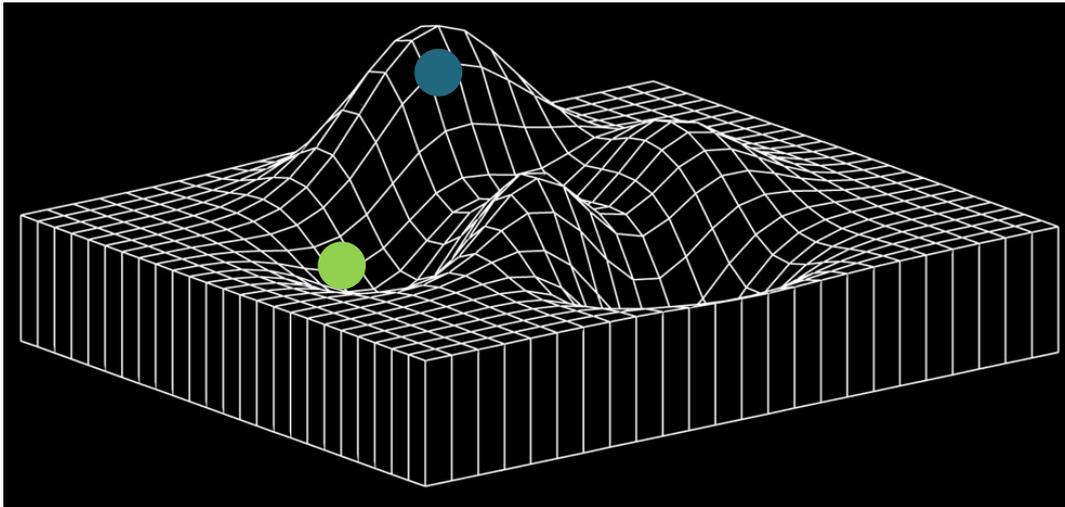
BOLD contrast step-by-step (4)

- As the neural activity goes back to baseline so does the oxy:deoxyhaemoglobin ratio and consequently the MRI signal



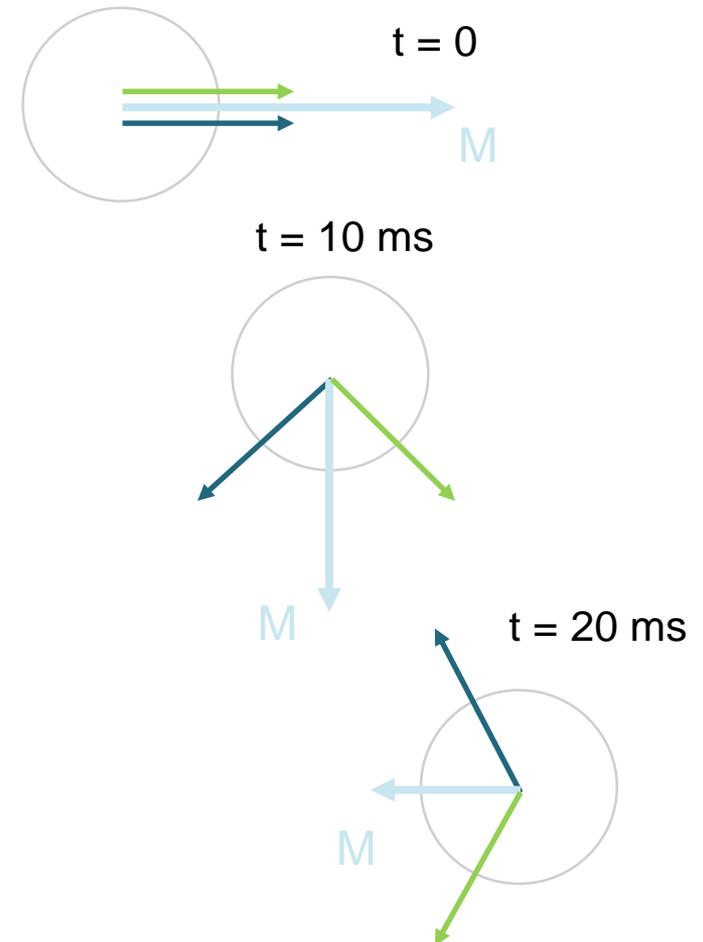
How does haemoglobin change
T2*?

From this morning: Signal loss due to B_0 inhomogeneity



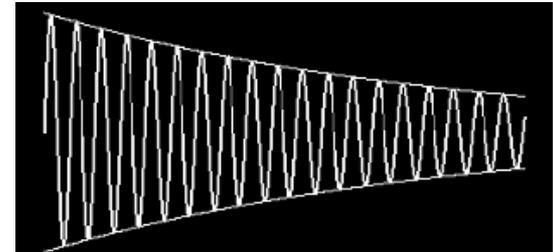
$$\omega_0 = \gamma B_0$$

● has higher frequency than ●

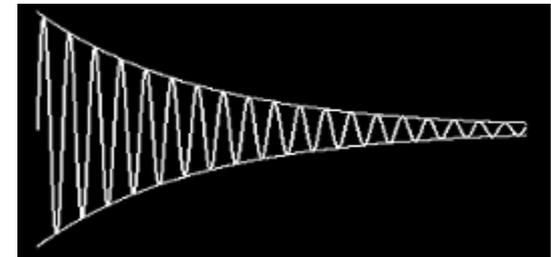


From this morning: Effective transverse relaxation (T_2^*)

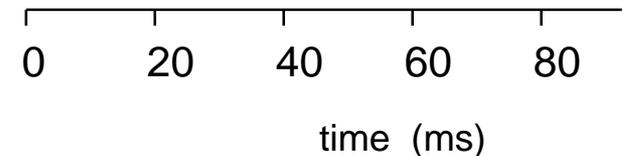
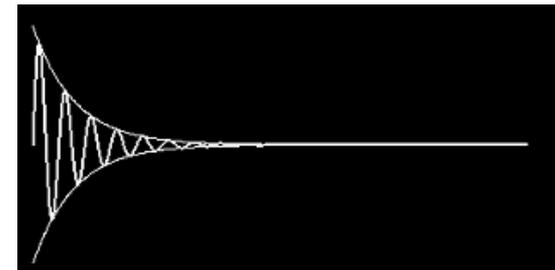
No inhomogeneities
($T_2^* = T_2 = 100$ ms)



Moderate inhomogeneities
($T_2^* = 40$ ms)



Strong inhomogeneities
($T_2^* = 10$ ms)

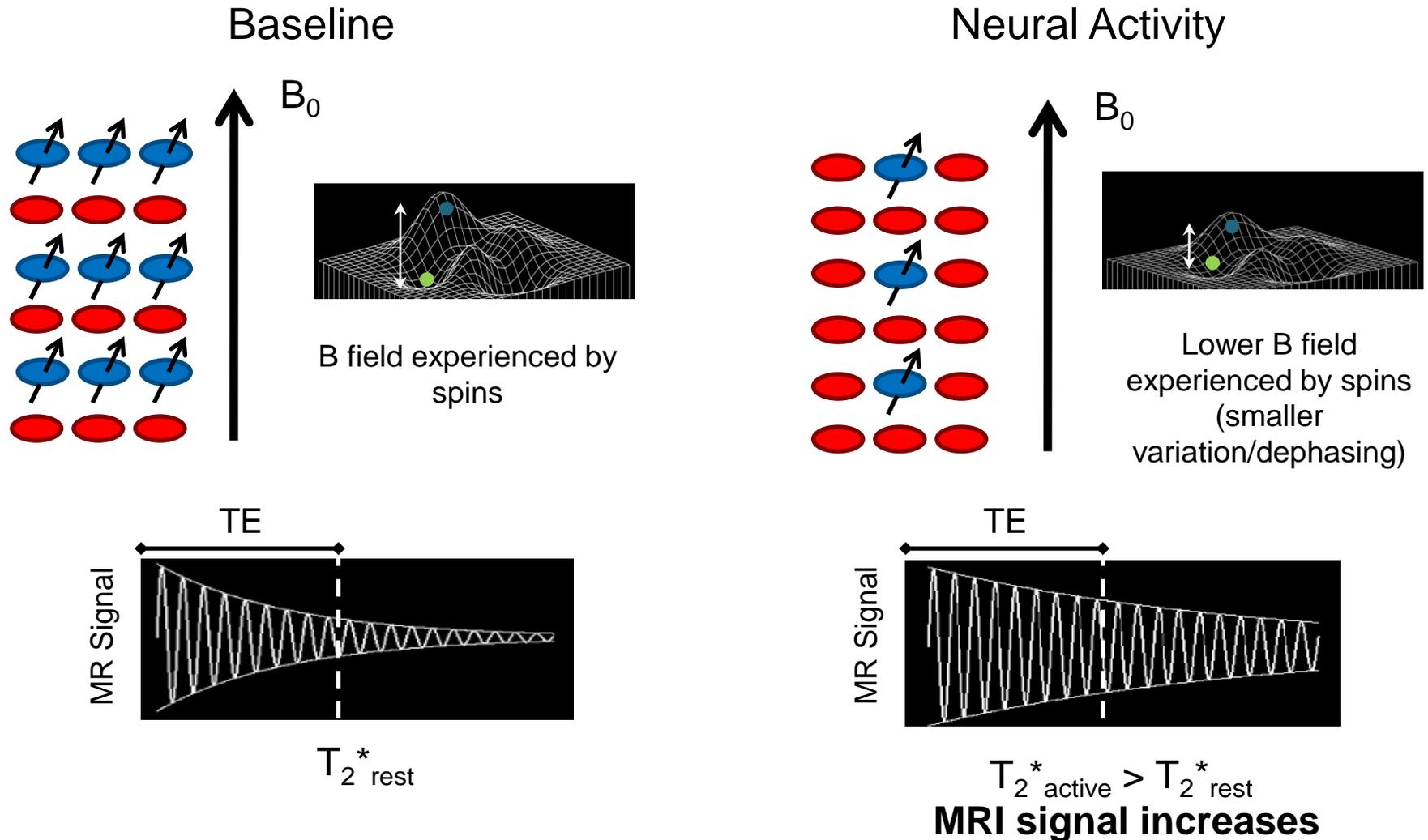


How does haemoglobin change T2*?

- Since oxygen is not very soluble in blood, it is transported bound to the large iron-containing molecule, **haemoglobin**.
- The presence of iron atoms in the molecule mean that haemoglobin has **magnetic properties**.
- The location of the oxygen binding sites determines that deoxyhaemoglobin is **paramagnetic** (having a significant effect on its environment) while oxyhaemoglobin is **diamagnetic** (having a neglectable effect).

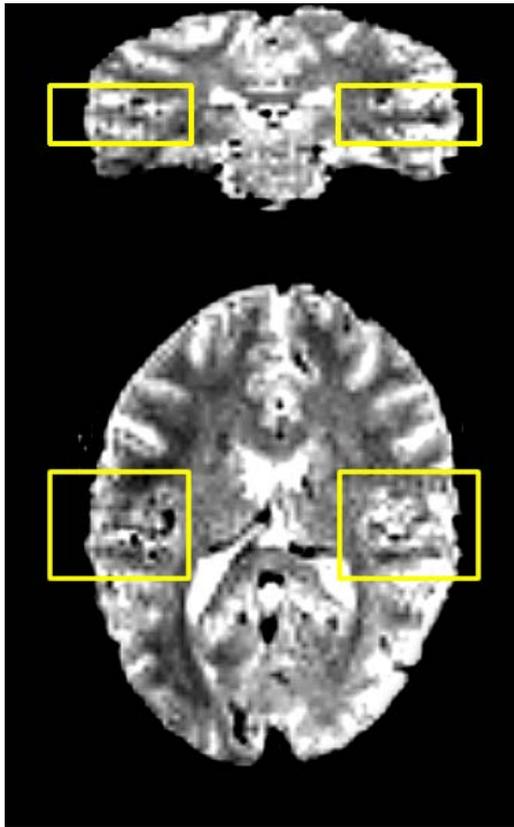


How does haemoglobin change T2*?

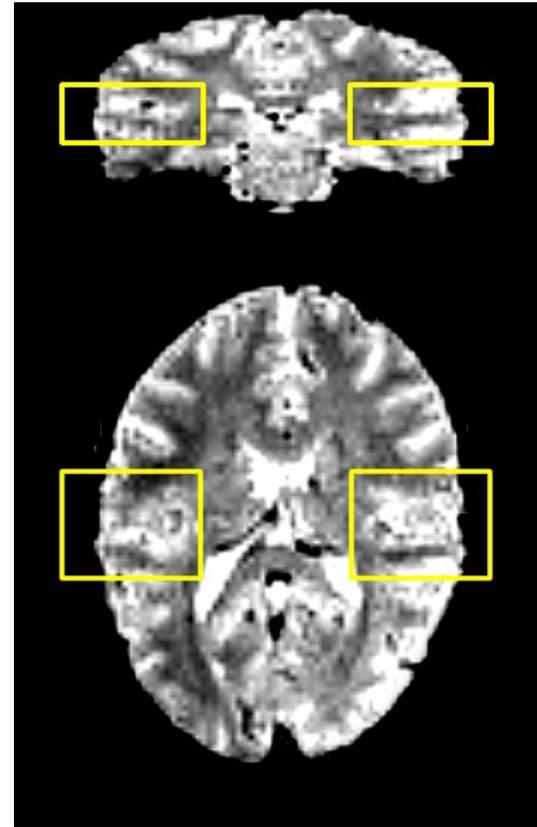


Example: auditory cortex activation

Baseline



Neural Activity



How should we interpret the BOLD signal?

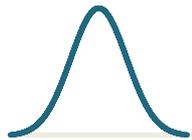
- **Some key limitations**
 - BOLD is an **indirect measure** of neural activity
 - Reflects **synaptic processing** more than spiking
 - Strongly shaped by **vascular anatomy**
 - Varies across:
 - Brain regions
 - Individuals
 - Acquisition parameters
- **Take home messages**
 - BOLD \neq neural activity
 - BOLD reflects **neural processing filtered through vascular physiology.**

Part II:

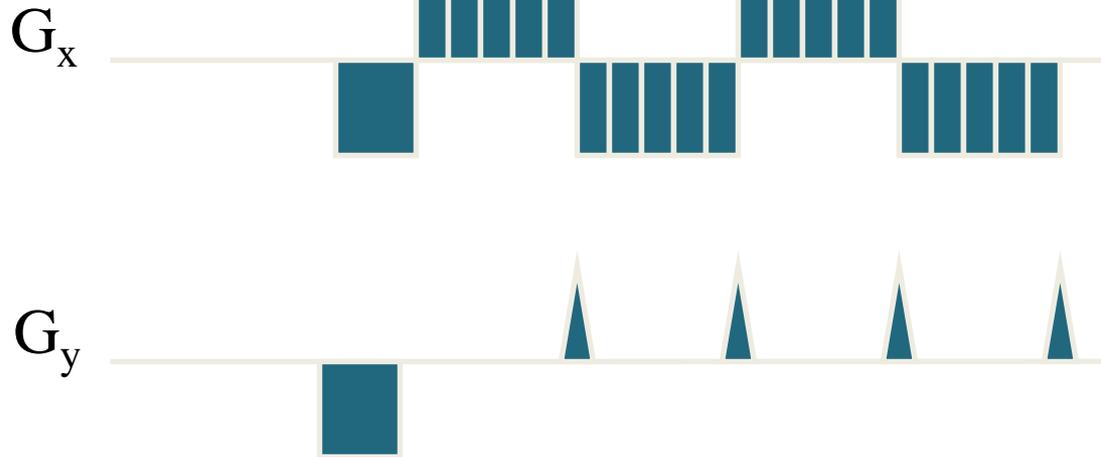
Common image artefacts

From this morning: Echo Planar Imaging (EPI)

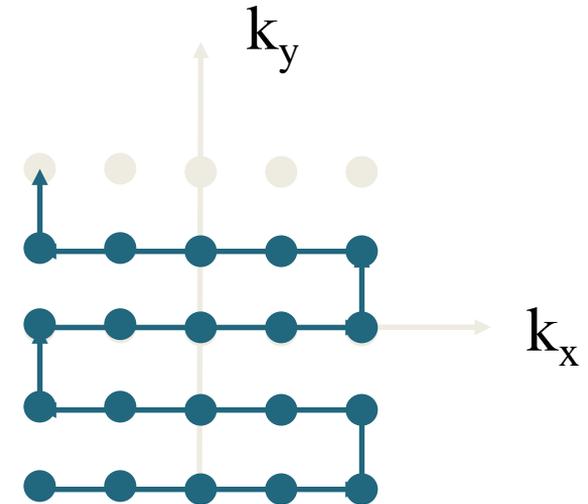
Selective excitation



Signal acquisition
(digital sampling)

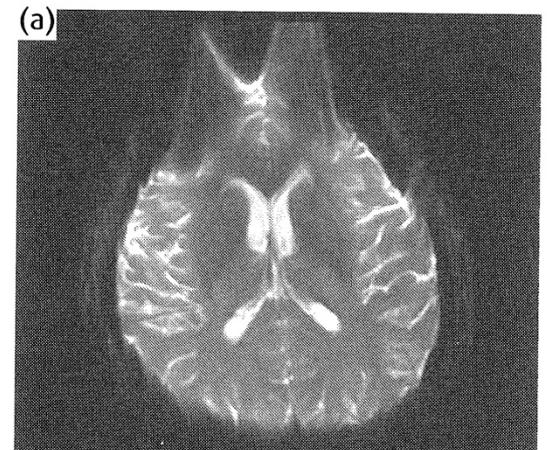


K space



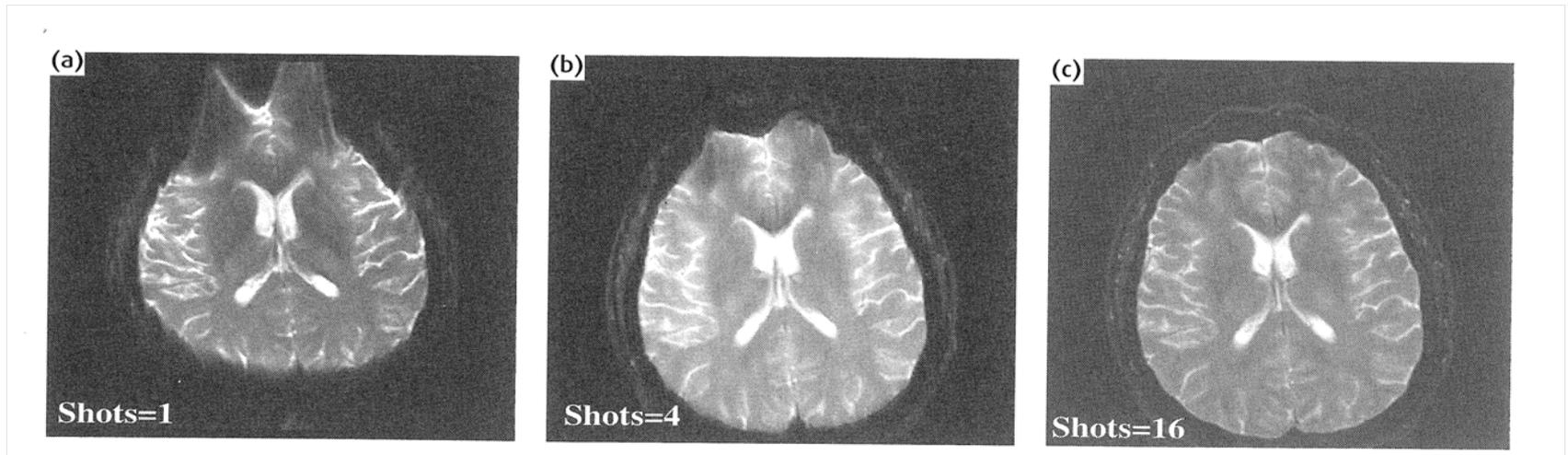
EPI distortion: the price we pay for fast imaging

- **Bandwidth** is a measure of frequency range (the range between the highest and lowest frequency allowed in the signal).
- The echo planar technique suffers from a very low bandwidth in the phase encode direction.
- Typically, the bandwidth per pixel is <20 Hz.
- A local shim inhomogeneity of 100 Hz (as is quite typical close to the frontal sinuses at 3.0 T) can lead to a mis-localisation of the signal in that region by ~ 5 pixels.



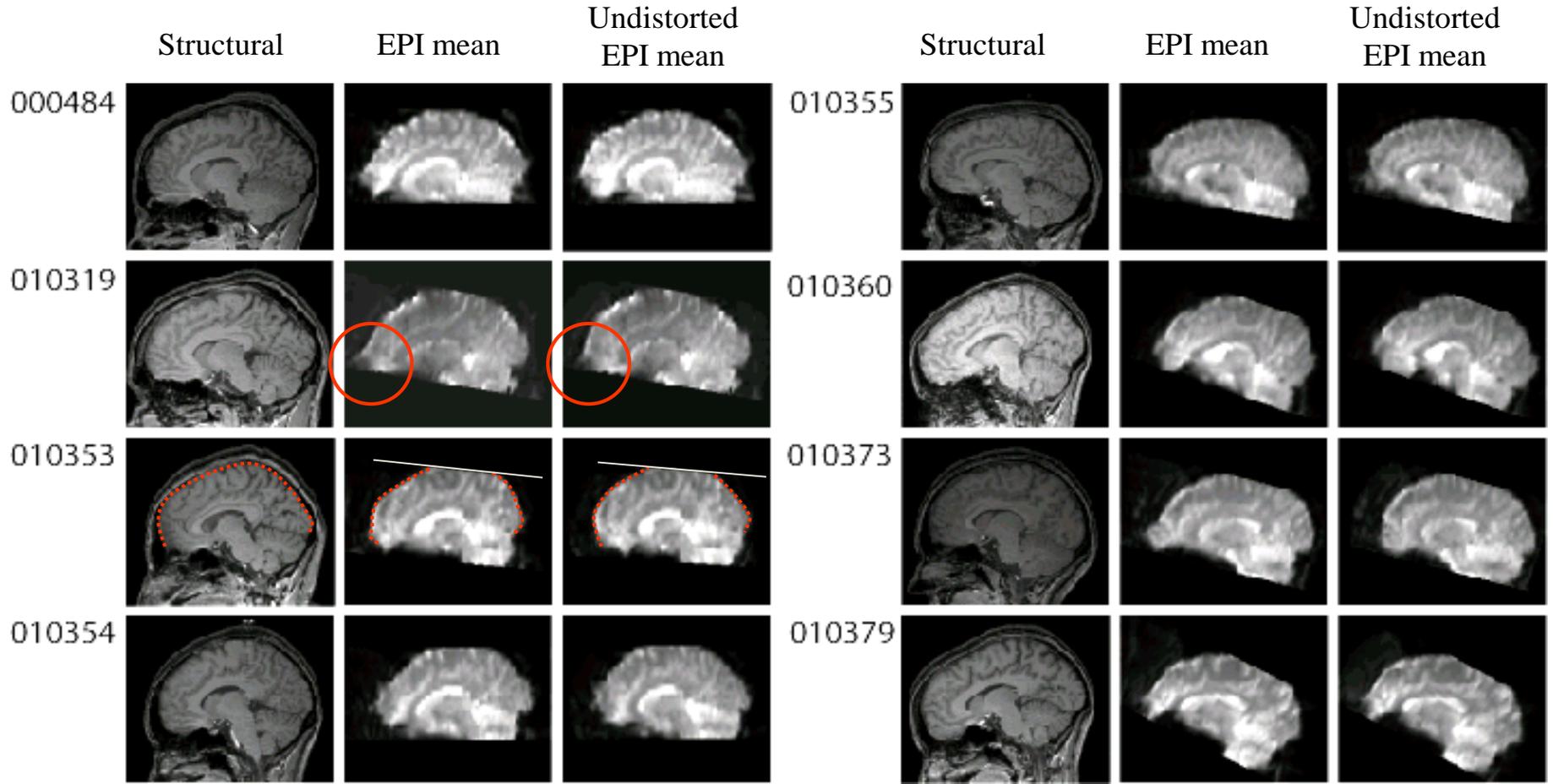
Tackling artefacts I

- **Distortion**
 - Optimise acquisition
 - Parallel acquisition (GRAPPA, SENSE)
 - Multi-shot EPI



- Acquire fieldmaps & undistort

Fieldmap undistortion: evaluation by eye



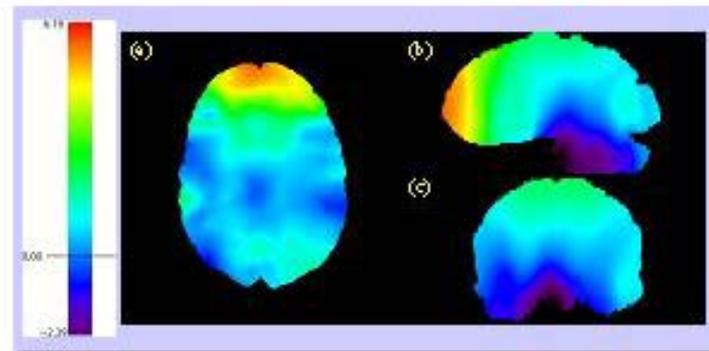
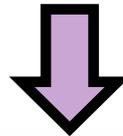
Cusack, Brett & Osswald (2004)

EPI distortion correction - TOPUP

+

Phase encode
direction P>>A

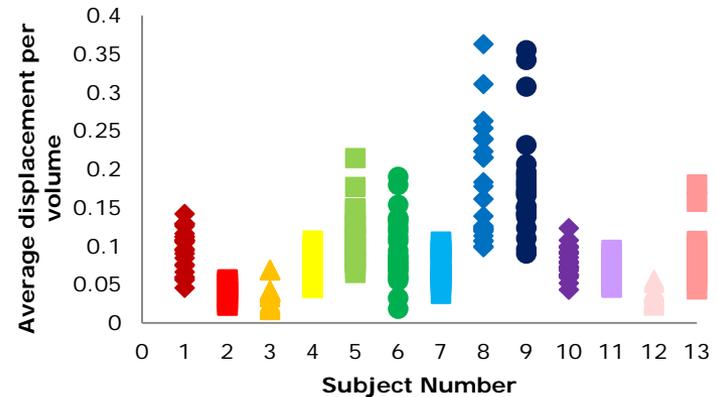
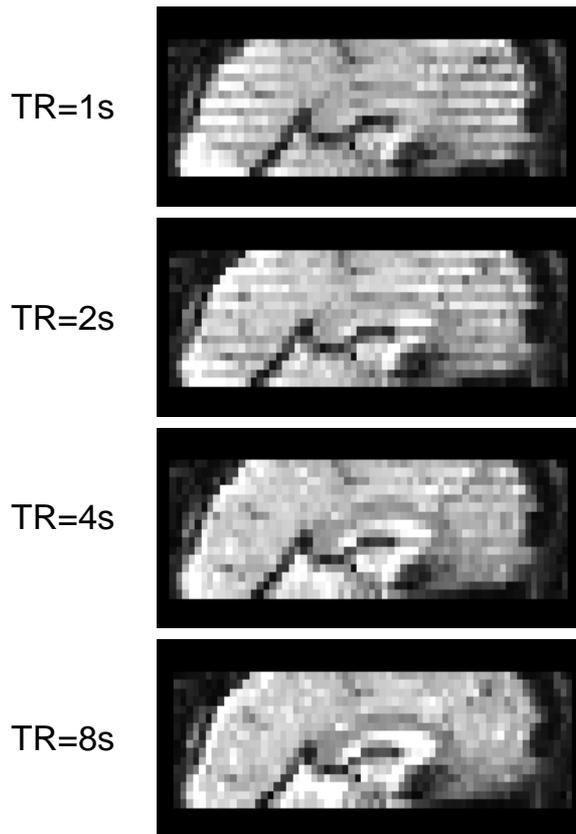
Phase encode
direction A>>P



EPI distortion map. The colour coding shows the amount of displacement in pixel units.

Tackling artefacts II

- **Distortion by movement**

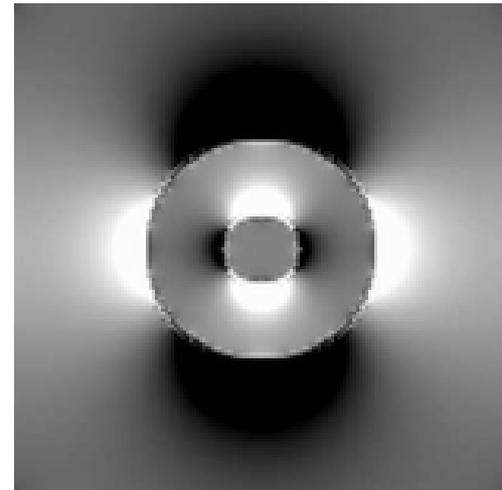


- Maximise subject comfort in the scanner
- Apply post-acquisition motion correction
- Include movement parameters in the model
- Prospective motion correction (watch this space!)

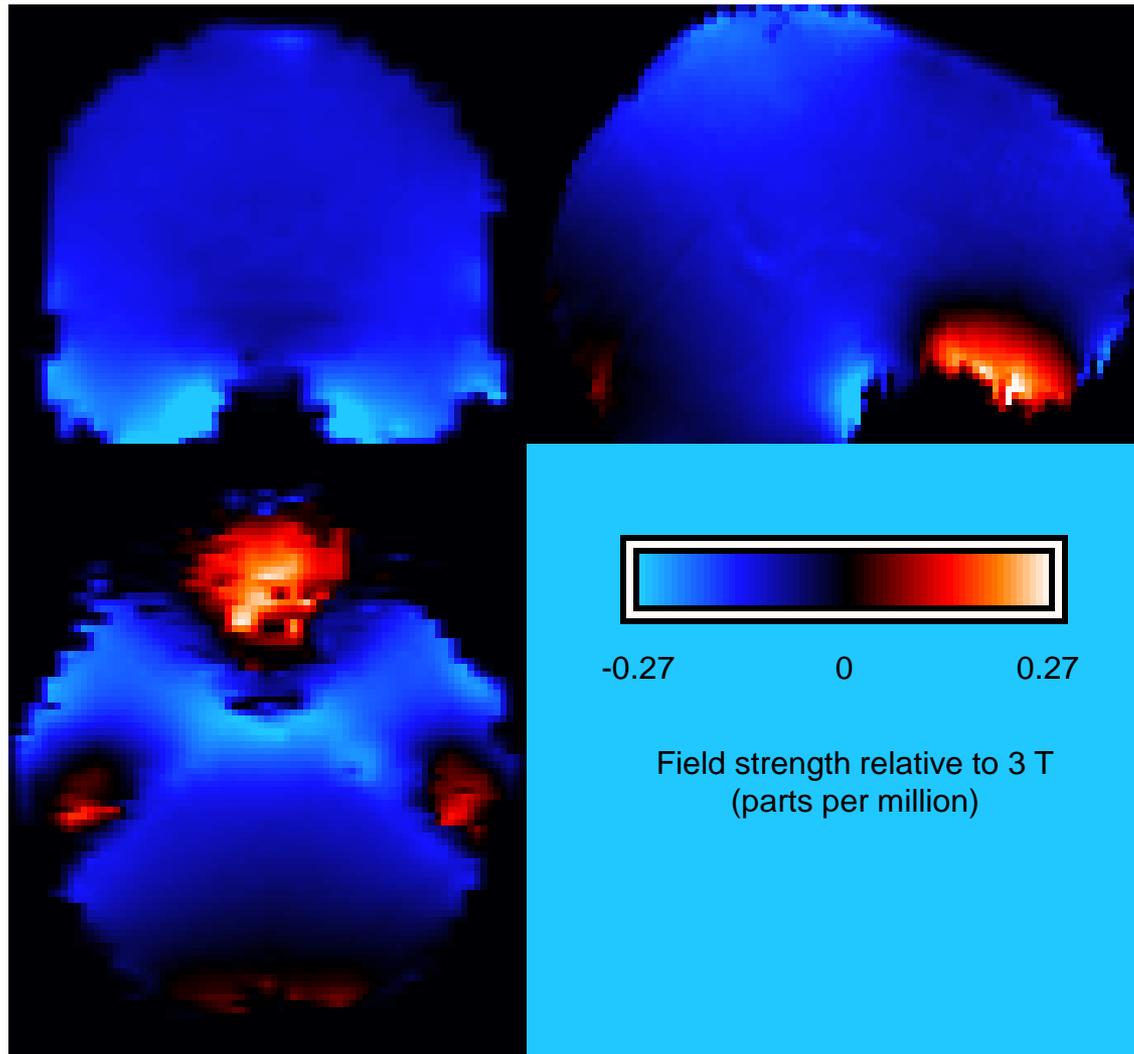
The B_0 field should be homogeneous, but...

- MRI scanners apply a strong magnetic field (3T at CBU)
- Ideally, field should be homogeneous
 - Easy to do when the scanner is empty, but ruined as soon as a head is put in
- Different materials interact differently with external magnetic fields and act to strengthen or weaken them

Free space	1.00000000
Air	1.00000040
Water	0.99999096
Fat	0.99999221
Bone	0.99999156
Blood	0.99999153
Grey matter	0.99999103
White matter	0.99999120
Iron	150-5000



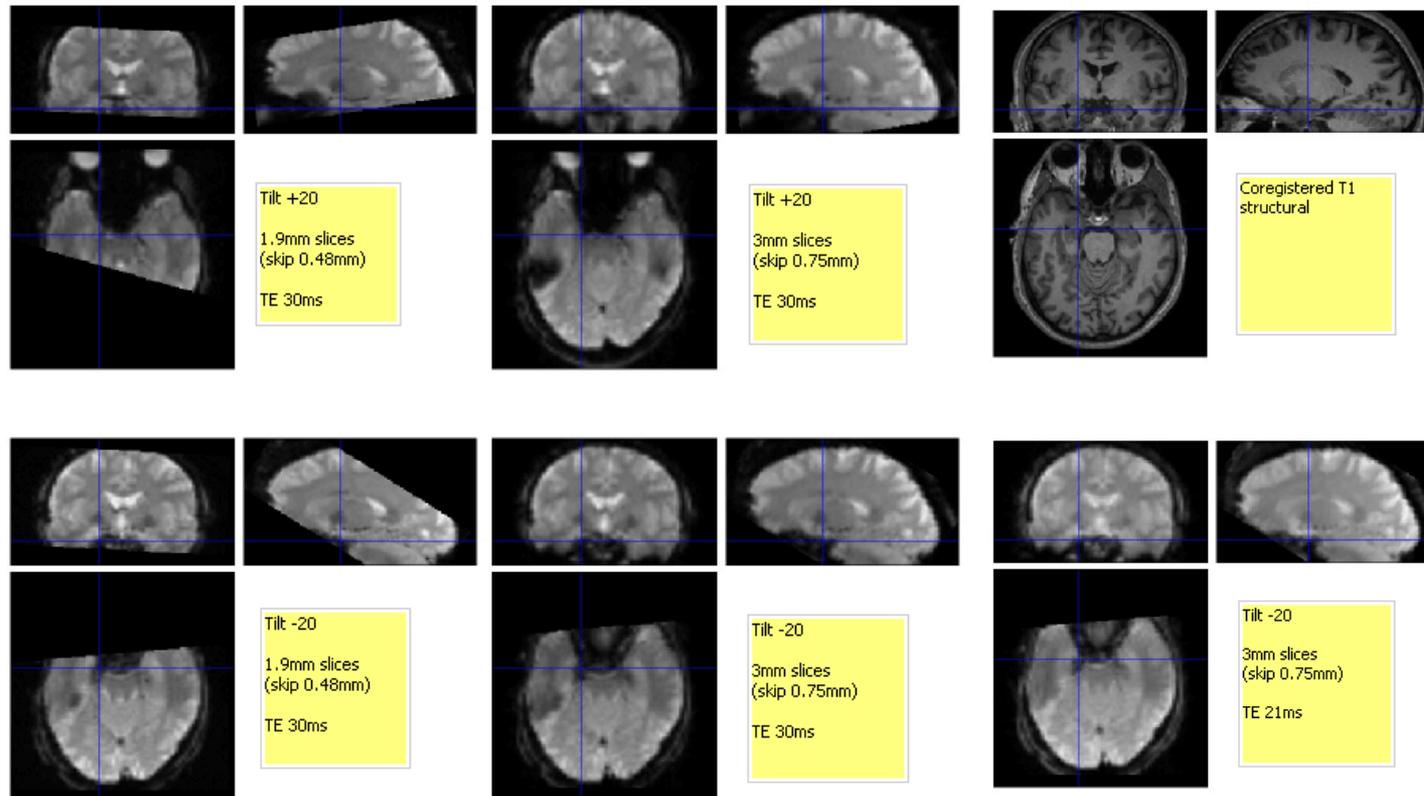
The B_0 field should be homogeneous, but...



Tackling artefacts III

- **Dropout**
 - Optimise acquisition parameters (e.g., TE, slice orientation, voxel size and slice thickness)
 - Z-shimming
 - Use spin-echo/ multi-echo
 - Passive shimming (Wilson, Jezzard and colleagues; Cusack et al, 2004)

Optimising parameters to reduce dropout



From Rik Henson

Summary

- BOLD fMRI involves a complicated set of couplings
 - Be careful when interpreting effects, or comparing fMRI with other imaging modalities
- It can fail in many ways
 - Optimise acquisition and analysis
 - Perform quality control

Questions?

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