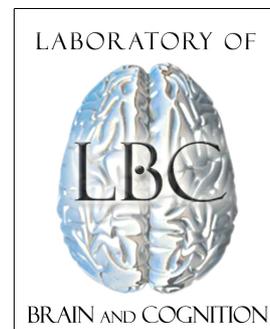
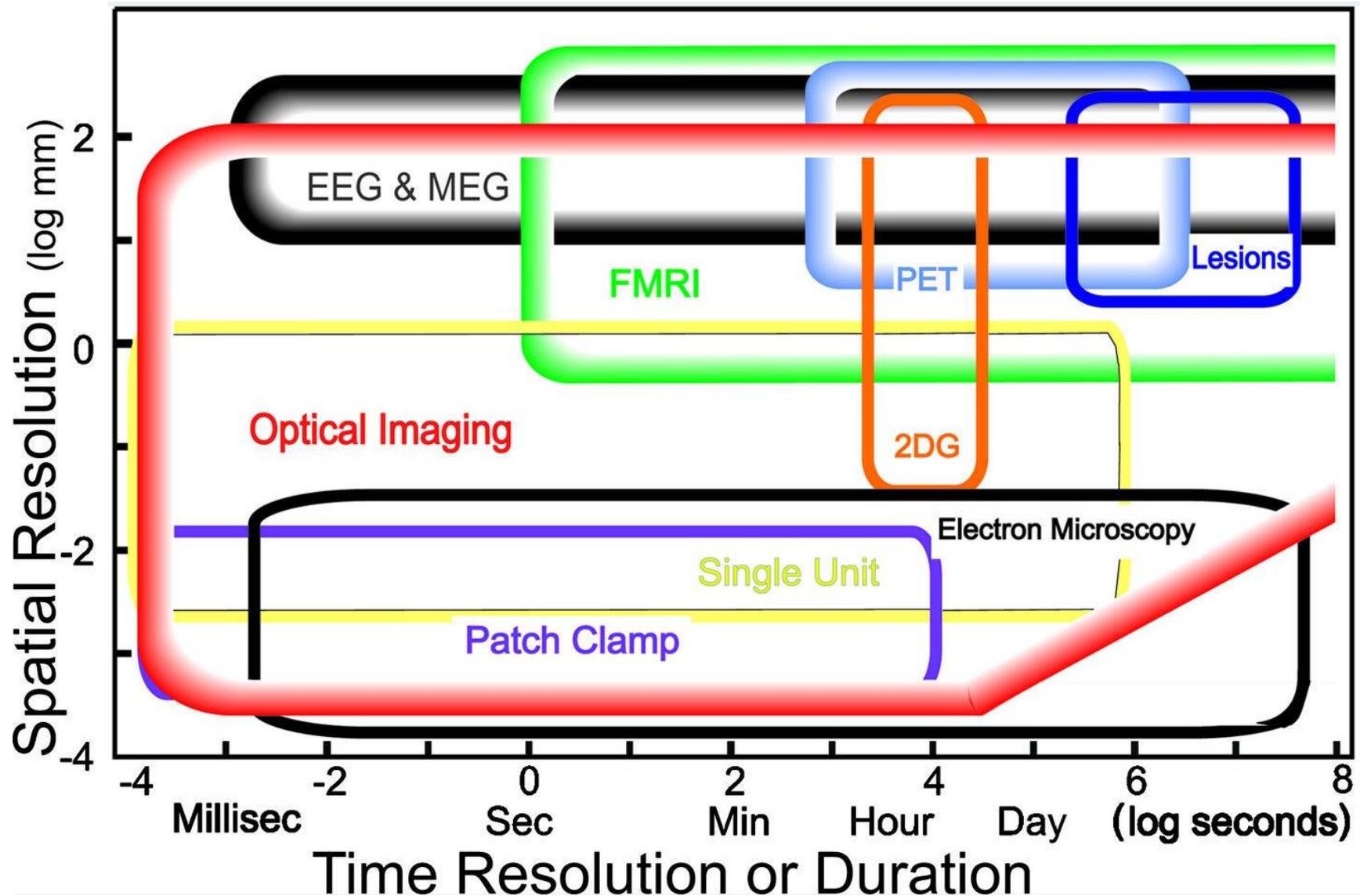


Basic tradeoffs and constraints in fMRI methodology and applications

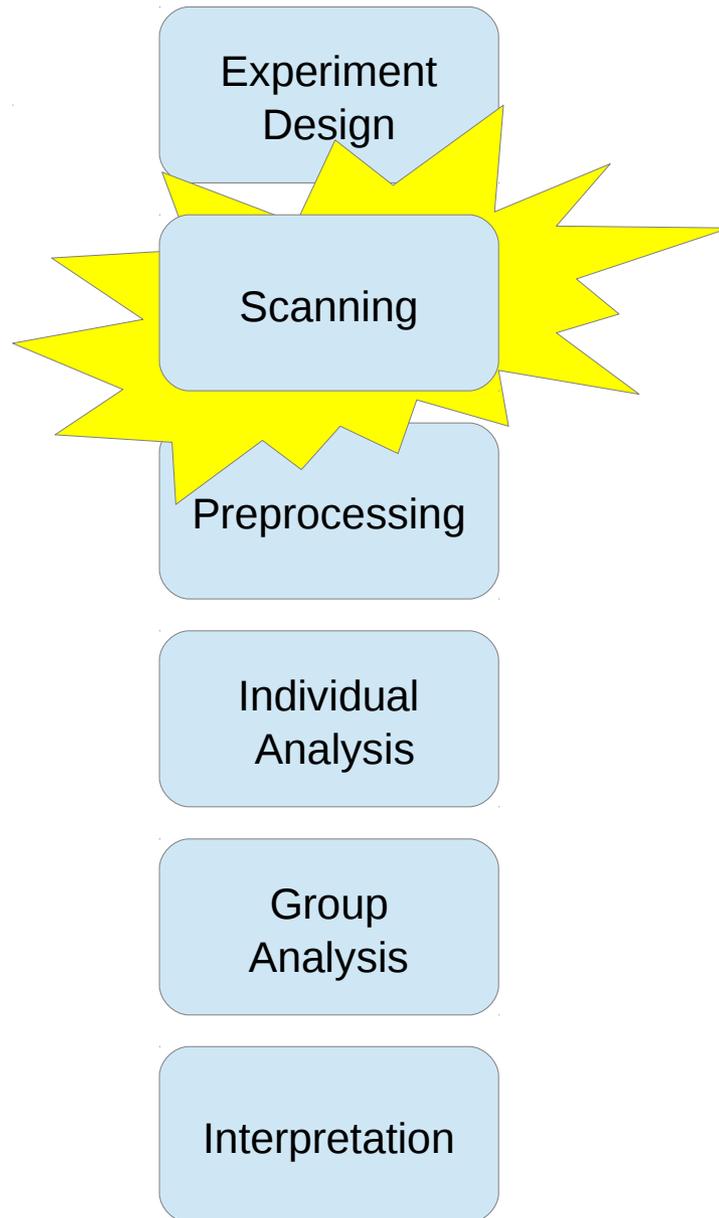
Jennifer Evans



fMRI in temporal – spatial perspective



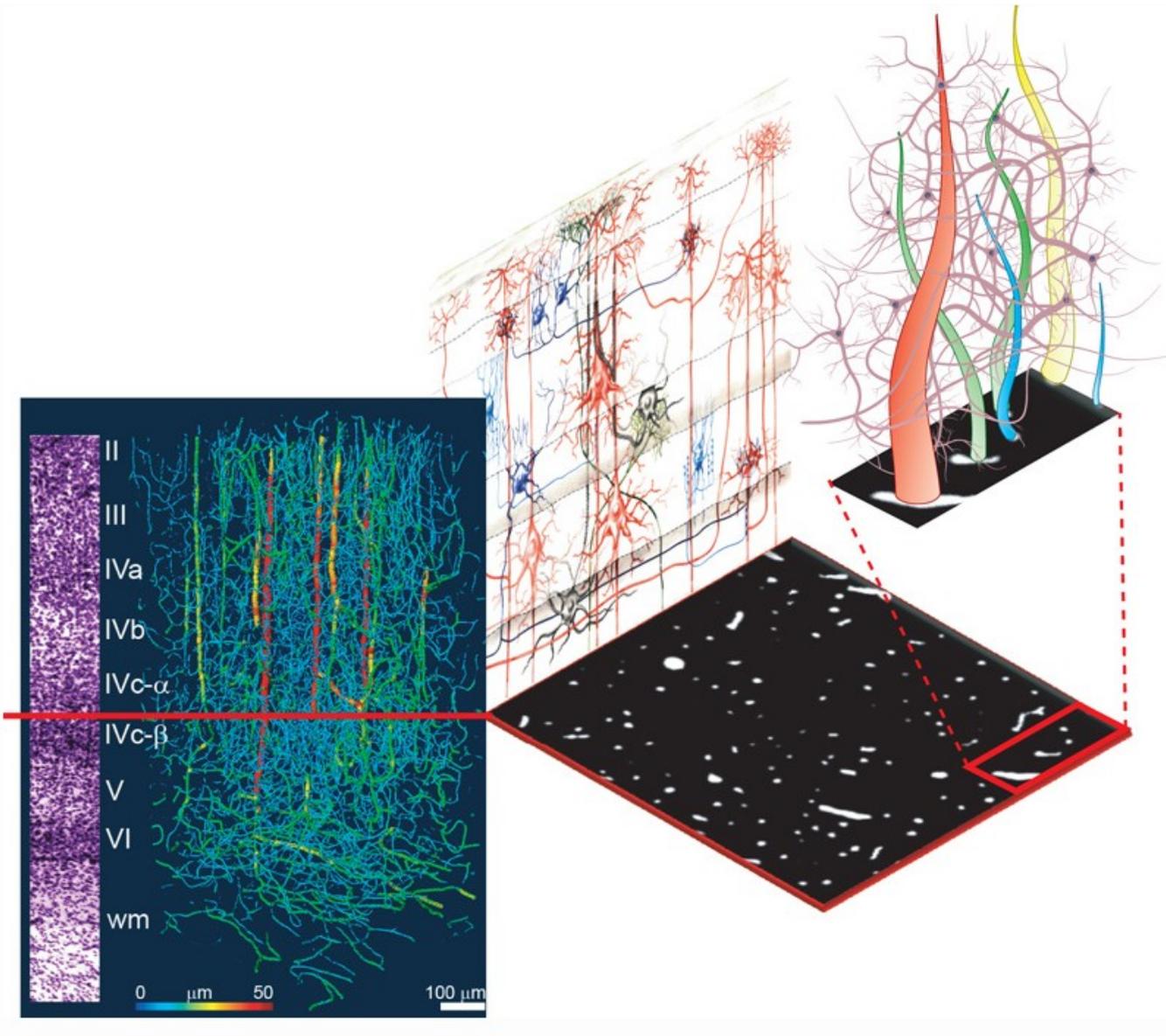
FMRI data pipeline



Outline

- Limitations based on the biophysical constraints
 - voxel contents
 - neurovascular coupling
 - hemodynamic response
- Limitations based on imaging constraints
 - Space – time tradeoffs (optimal voxel size)
 - Pulse sequence contrasts
- Summary

What's in a voxel?



- Neurons
- Synapses
- Axons
- Dendrites

- Vasculature
- Capillaries
- Arterioles/venules
- Arteries/Veins

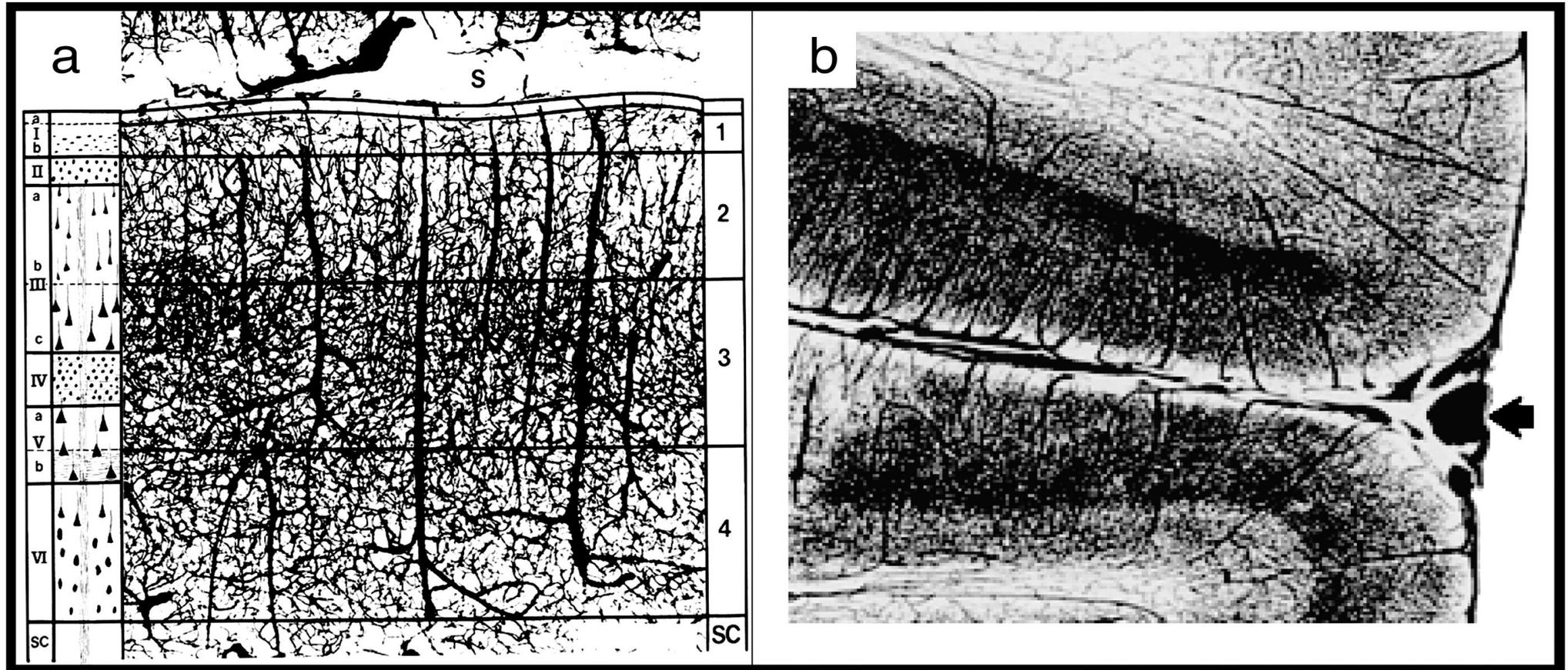
Average size of fMRI voxels

- In plane resolution of 9-16 mm² (3x3, 4x4)
- Slice thickness 5-7 mm
- Average voxel size: 55 mm³

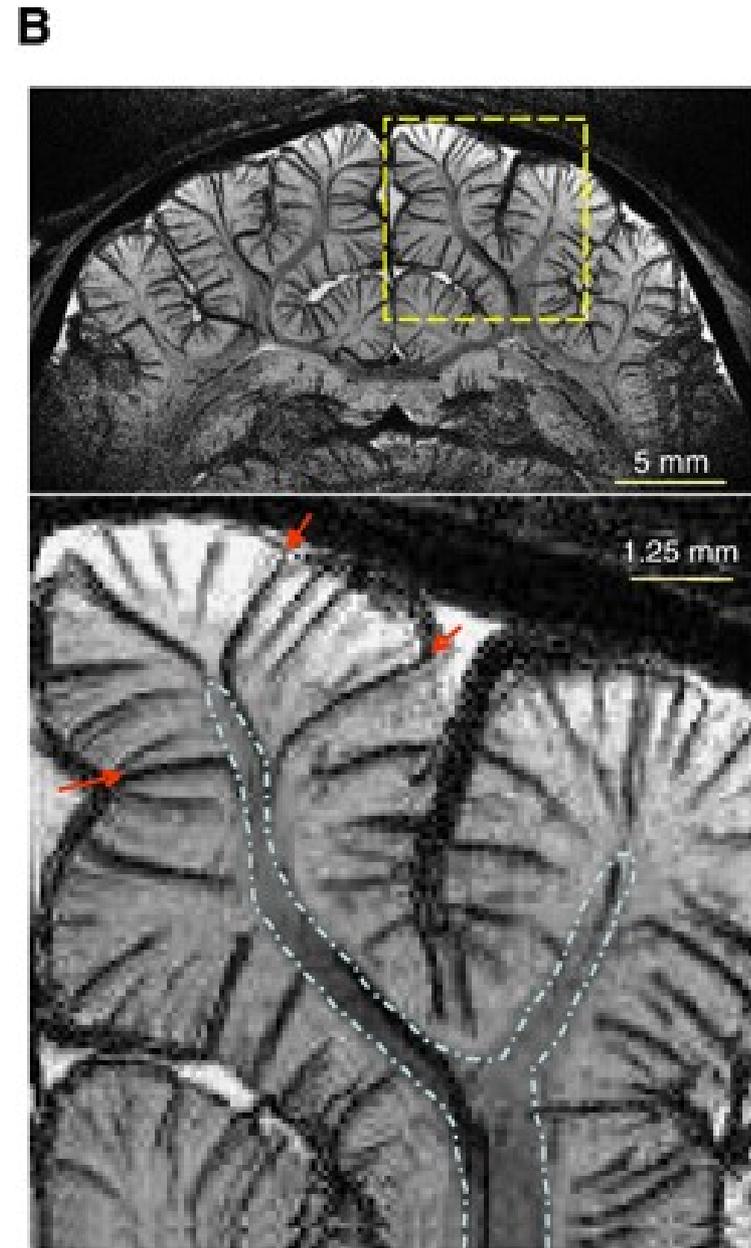
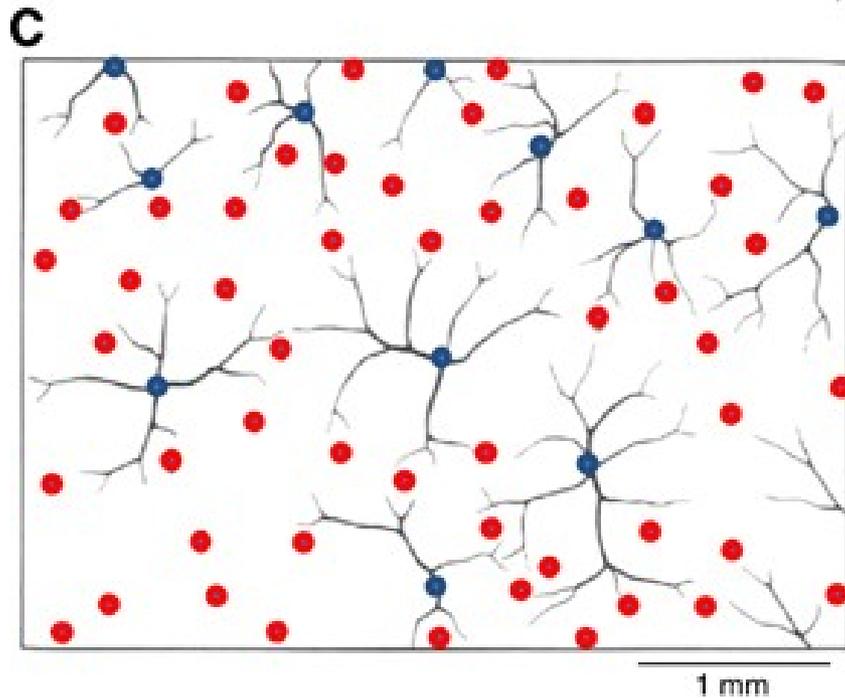
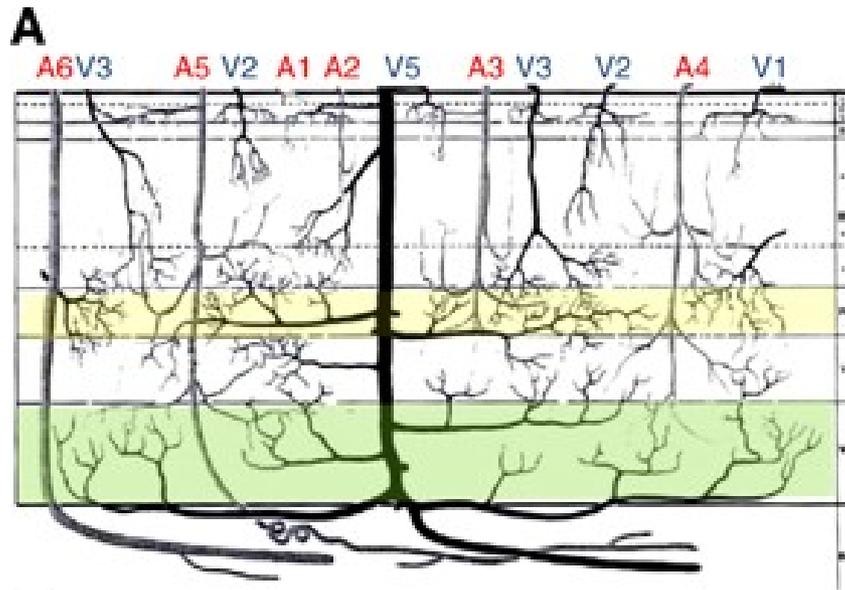
5.5 million neurons
2.2-5.5 10¹⁰ synapses
22 km of dendrites
220 km of axons



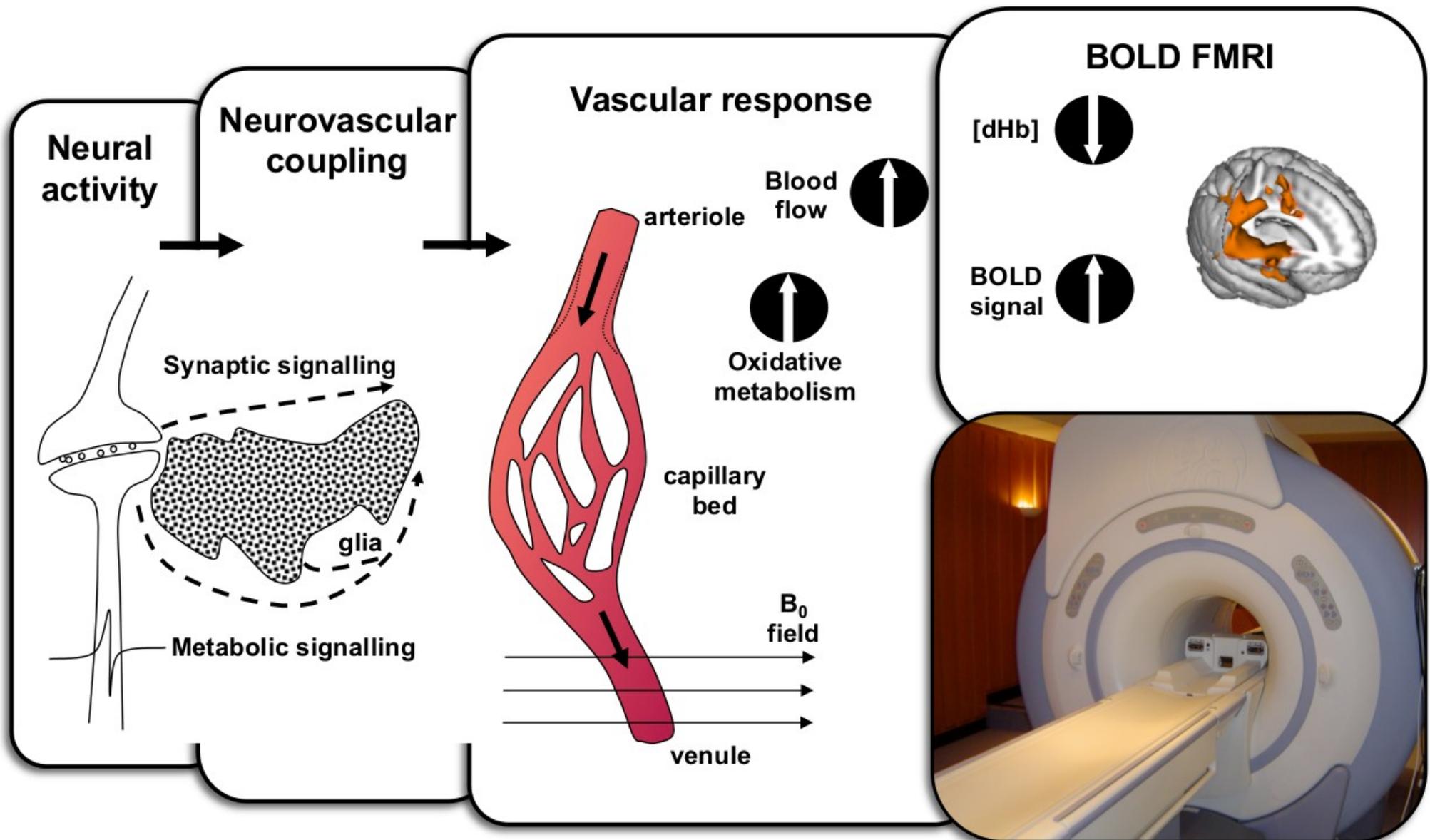
And vasculature ...



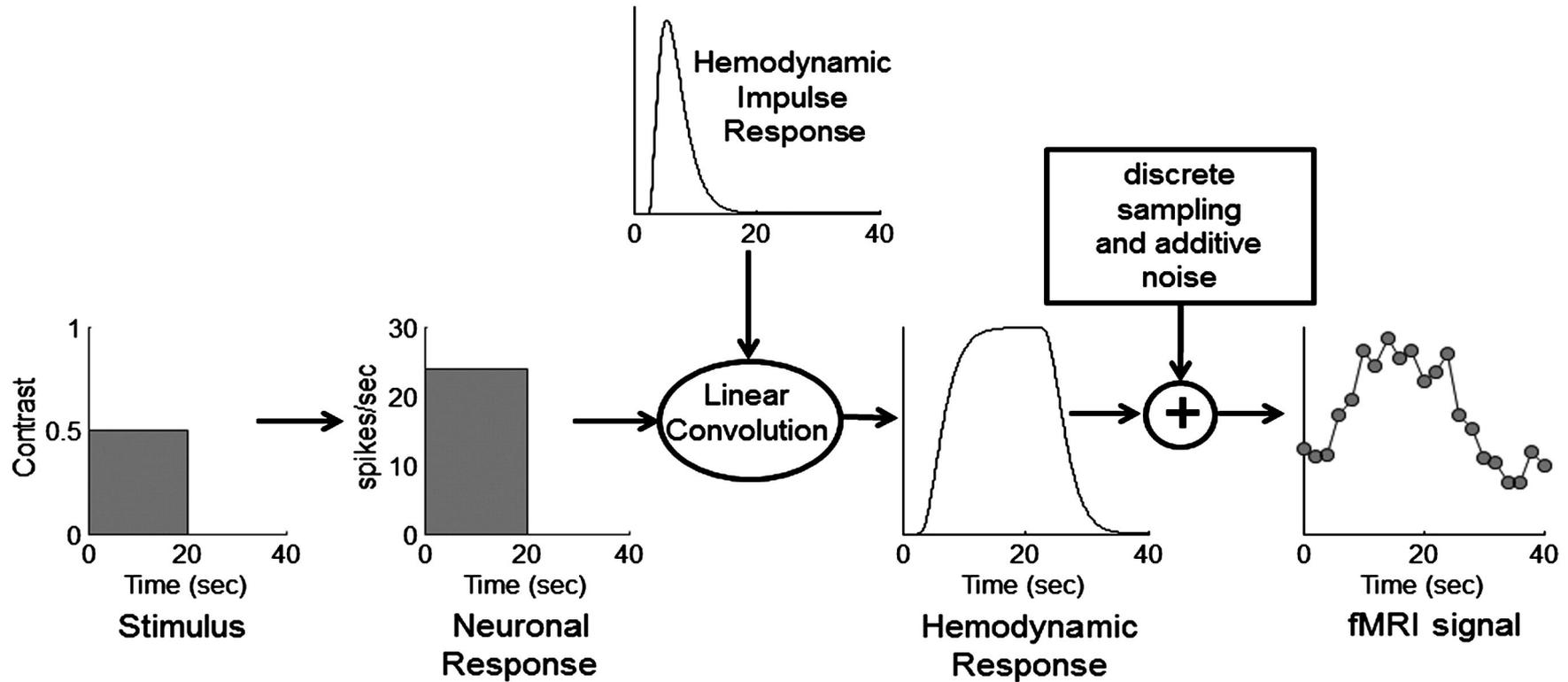
Spatial inhomogeneity of vasculature



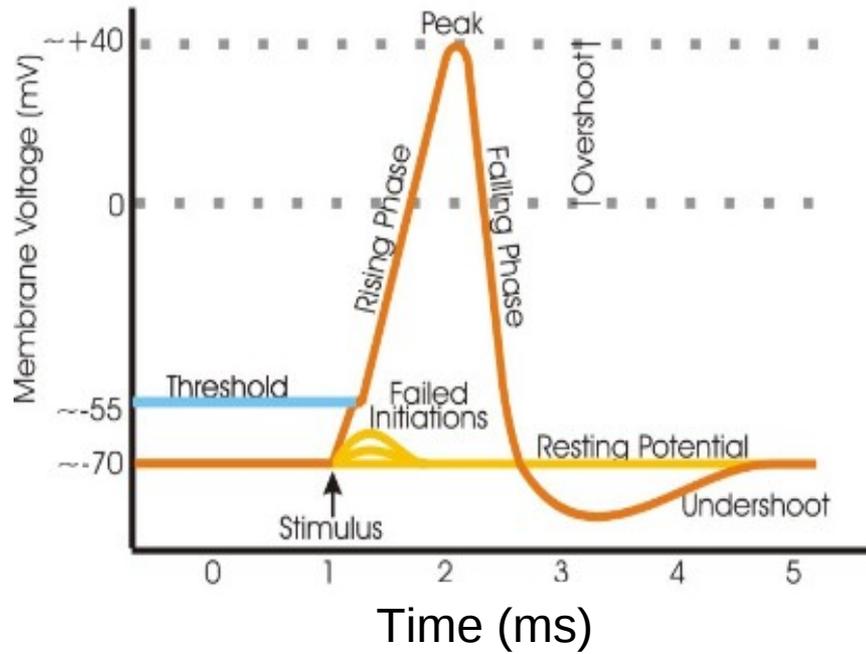
Back to BOLD ...



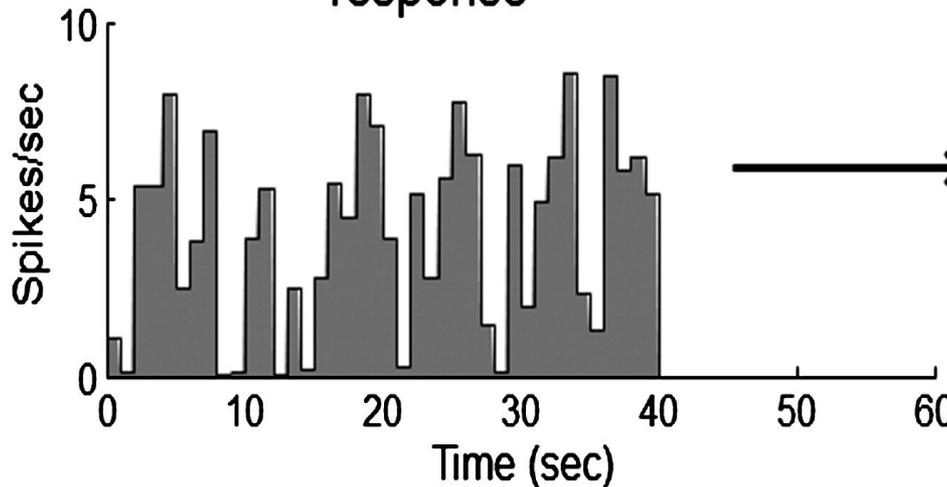
From neurons to fMRI / metabolic pathway



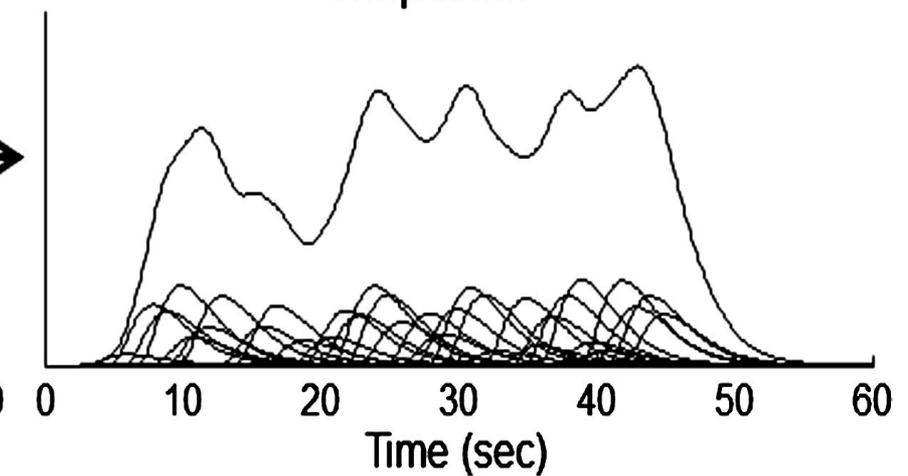
Temporal: neural speed, hemodynamic response



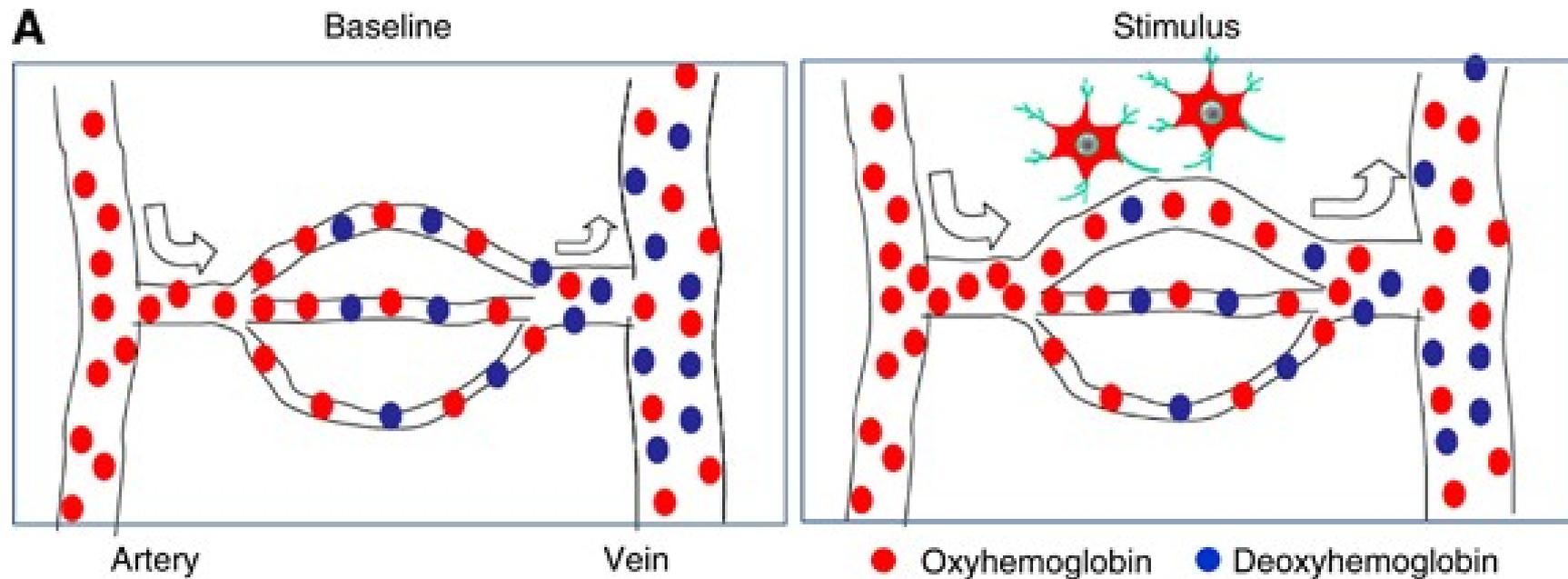
Neuronal response



Hemodynamic response



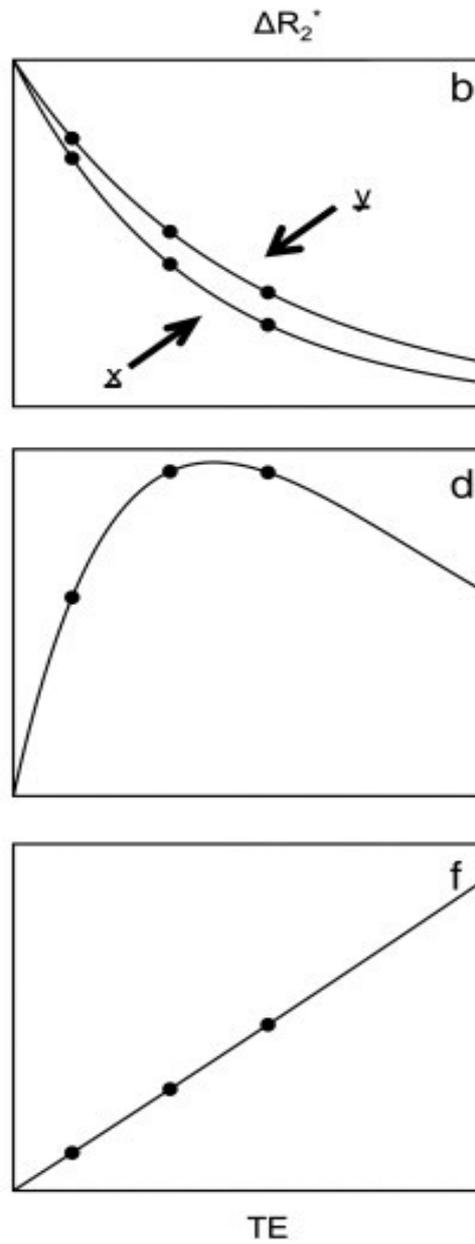
Extra- and intra-vascular responses to stimulus



B Expected stimulus-induced changes in MR-related parameters

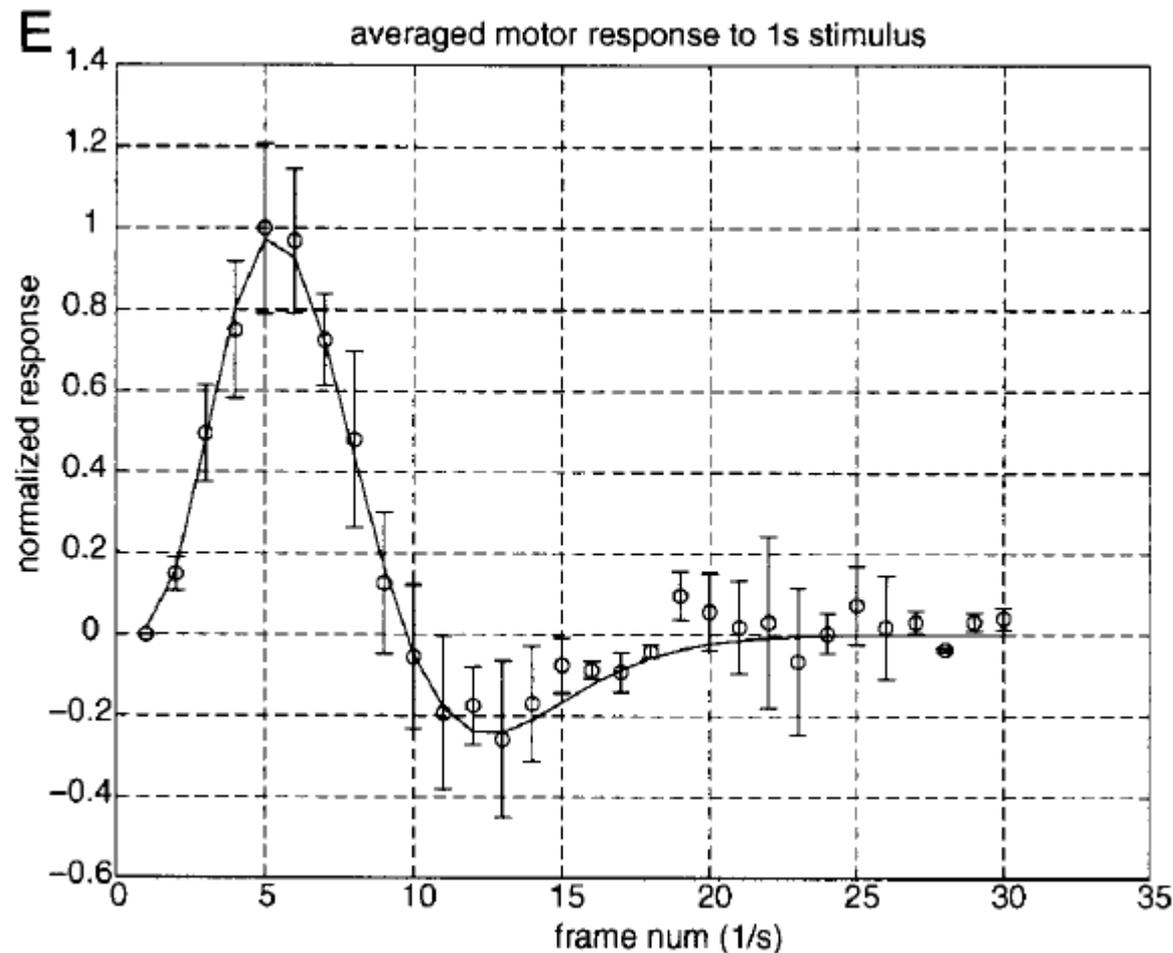
	Arterial Blood	Extravascular Tissue	Venous Blood	Cerebrospinal Fluid
Volume Fraction (V)	↑	↓	↑	↓
Inflow/perfusion Effect (R_1^*)	↑	↑	↑	↔
BOLD Effect (R_2 and R_2^*)	↔	↓	↓	↓

BOLD effect

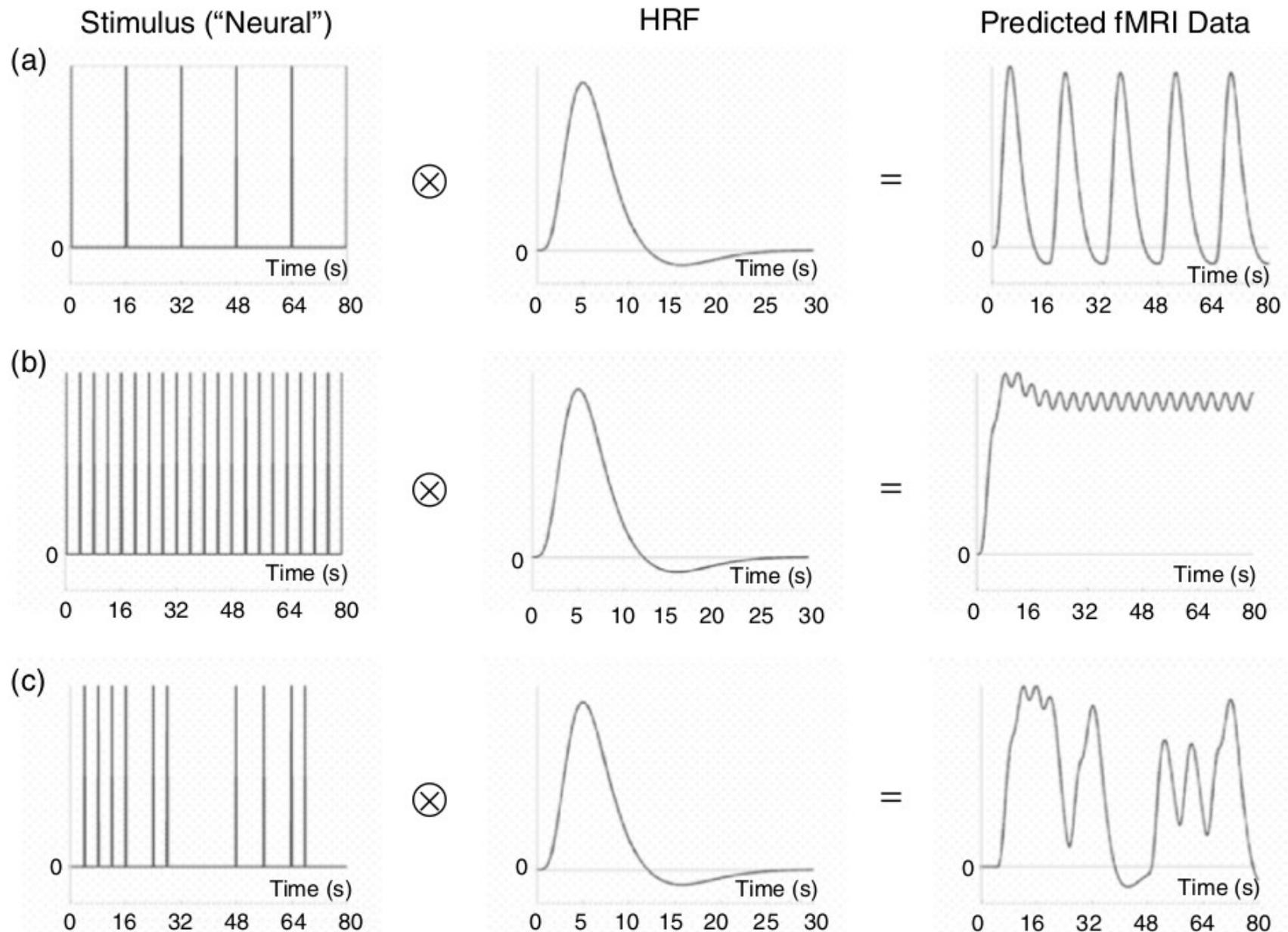


Hemodynamic Response speed

- Slow response, delayed 4-6 s, lasts ~ 4-6 s, returns to baseline much later
- Post and pre stimulus undershoot, vascular variation

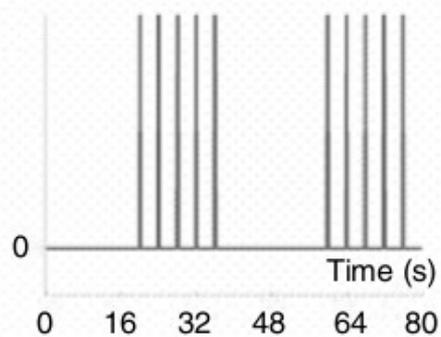


Minimum time between stimuli

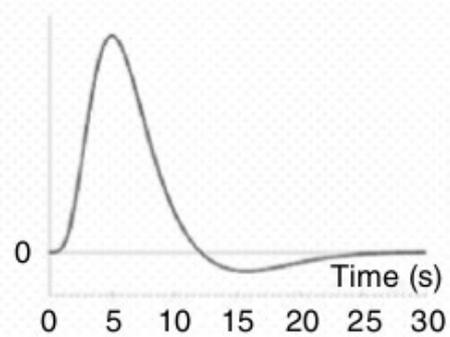


Hemodynamic response as a filter

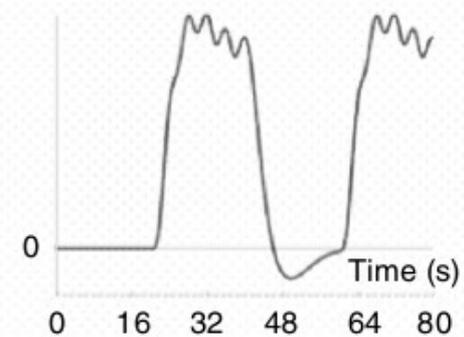
(a) Stimulus ("Neural")



HRF



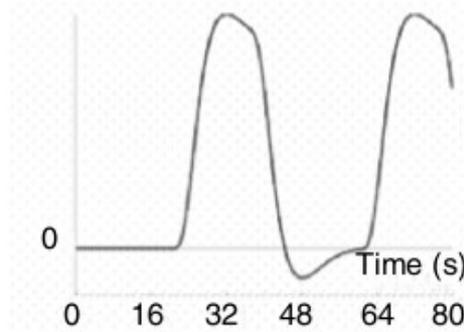
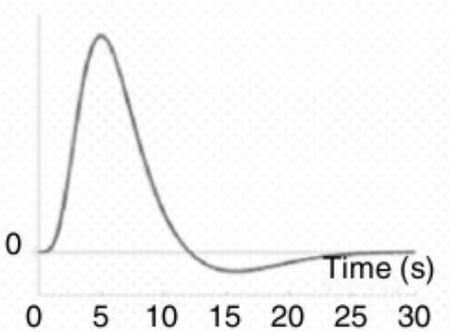
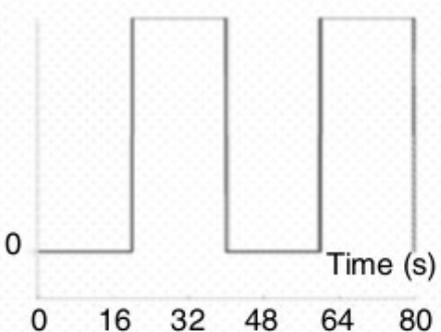
Predicted fMRI Data



\otimes

$=$

(b)

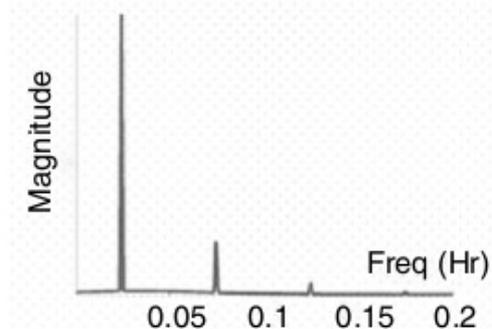
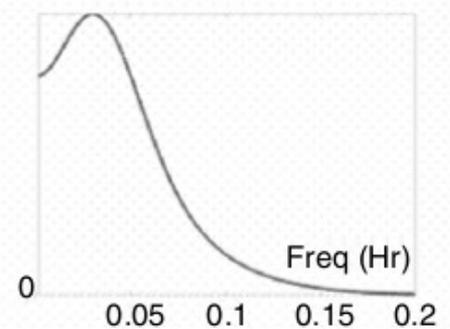
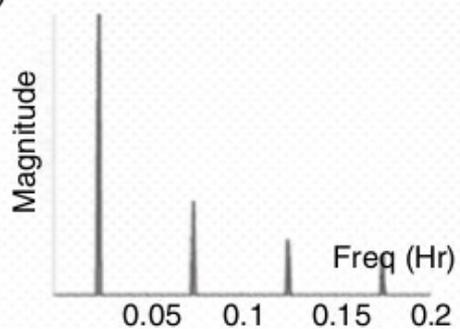


\otimes

$=$

Fourier Transform

(c)



\times

$=$

fMRI acquisition

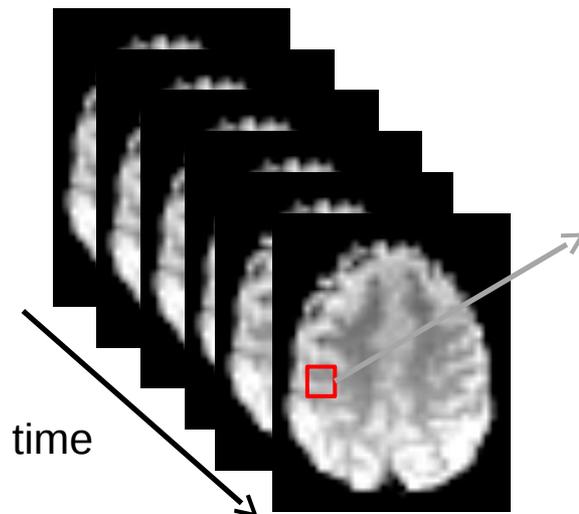


Anatomic



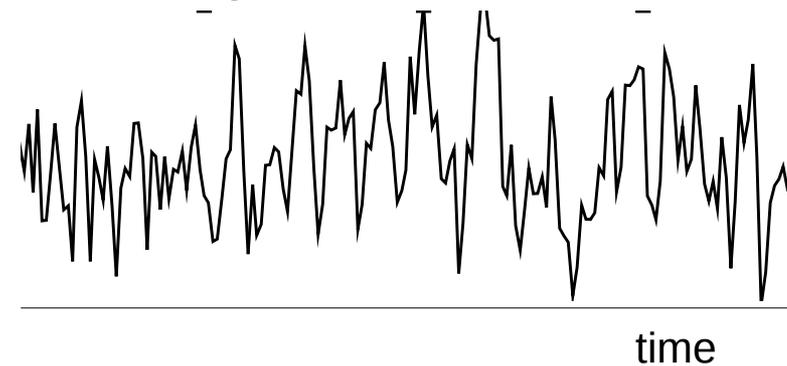
One image / 3-5 min

Functional

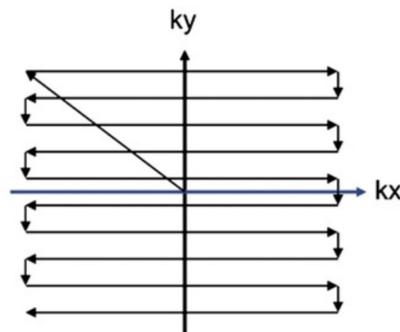
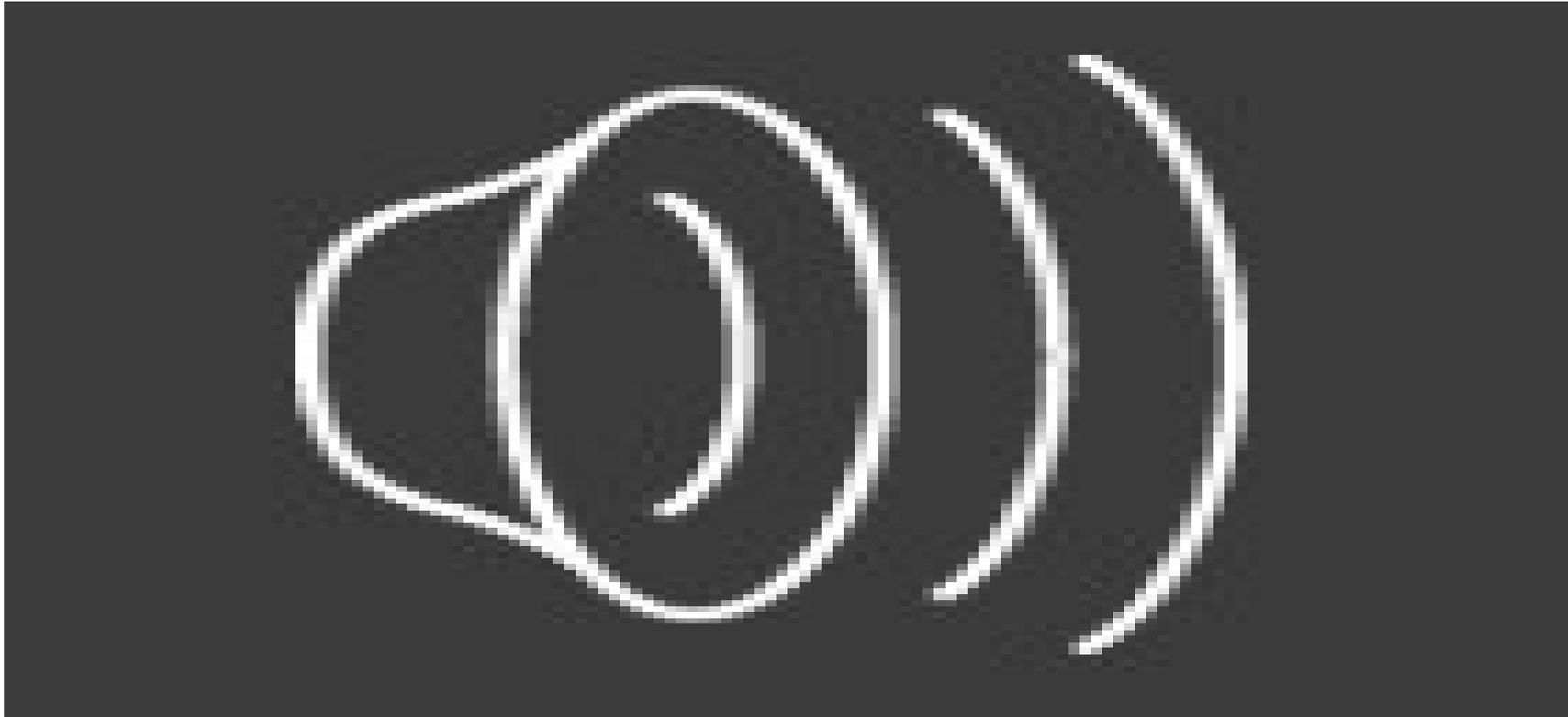


One image / 2 s for 5 min

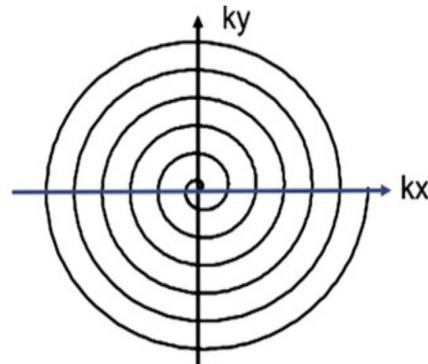
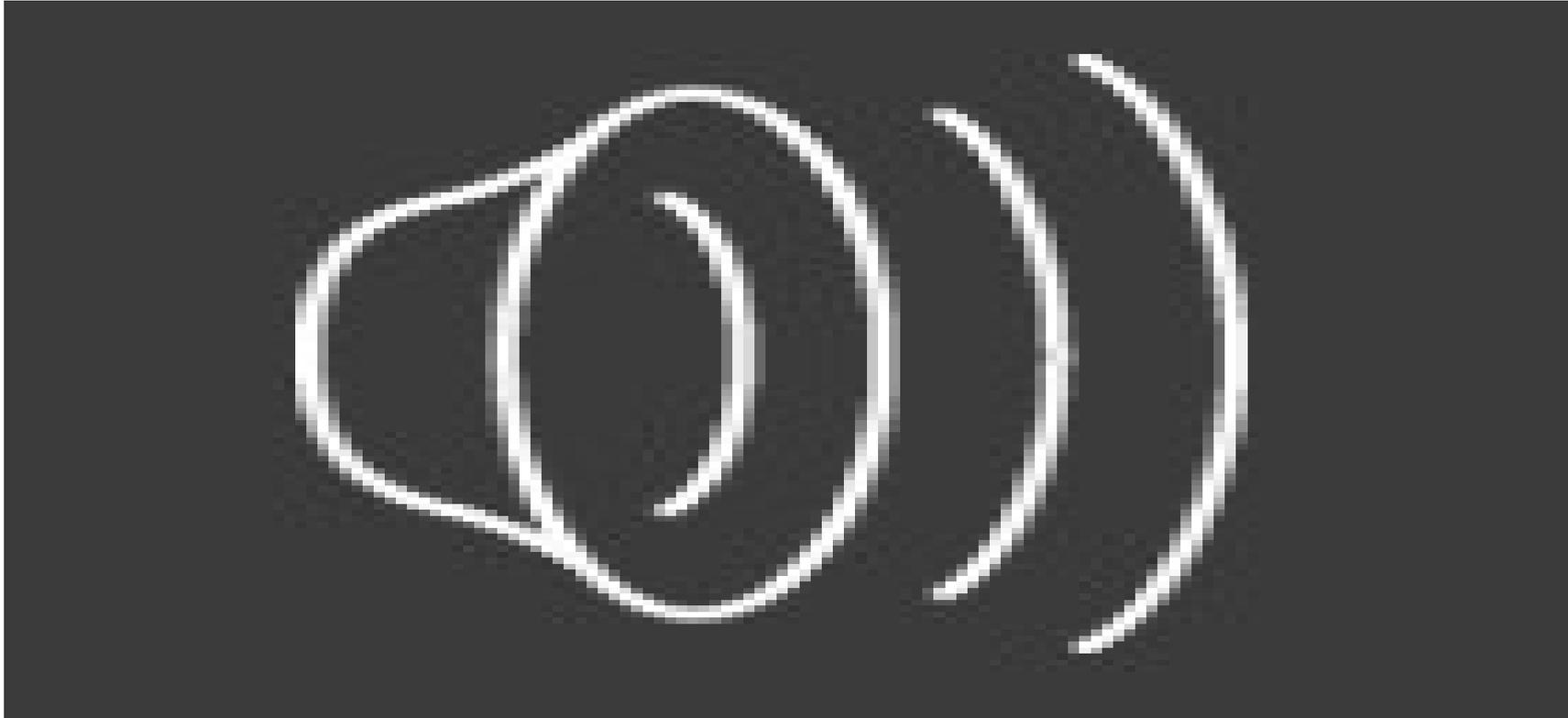
BOLD signal time series



Filling k-space, one line at a time

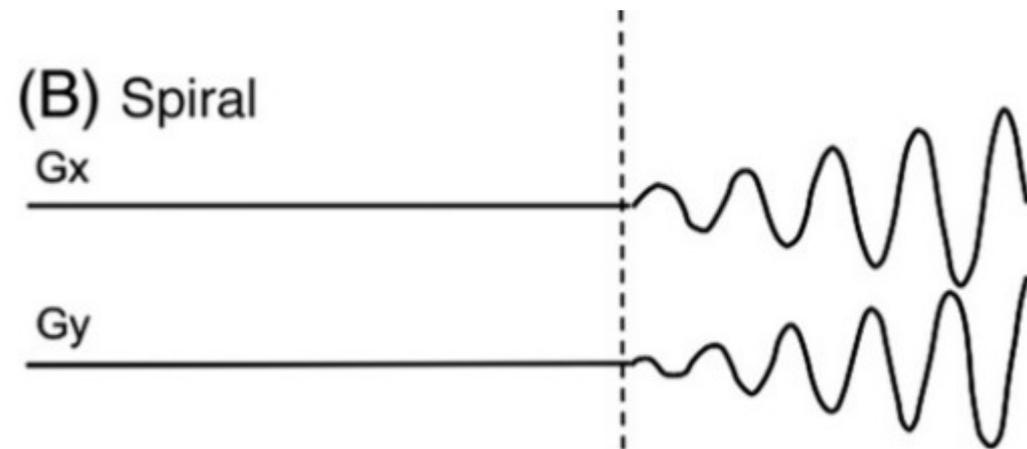
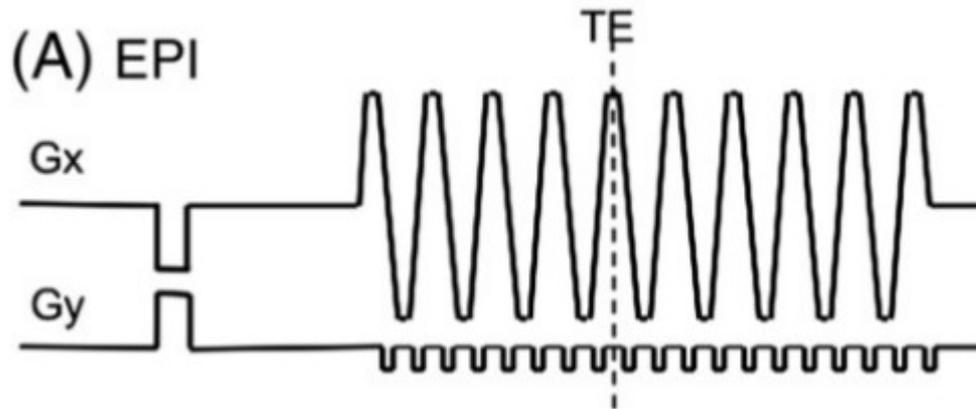
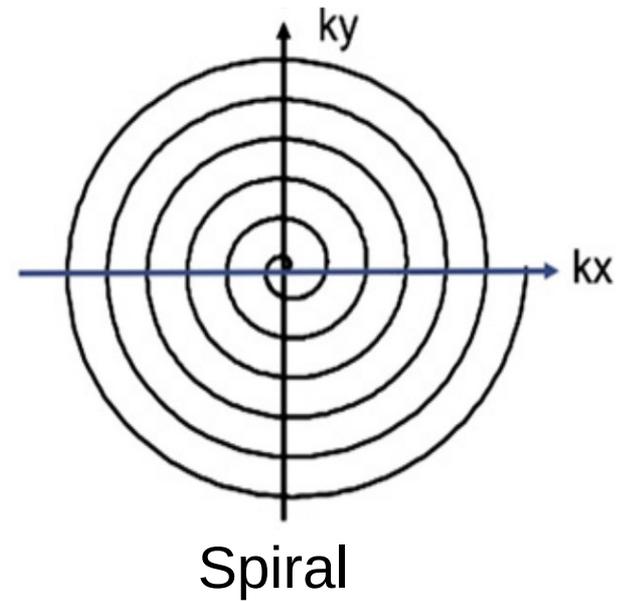
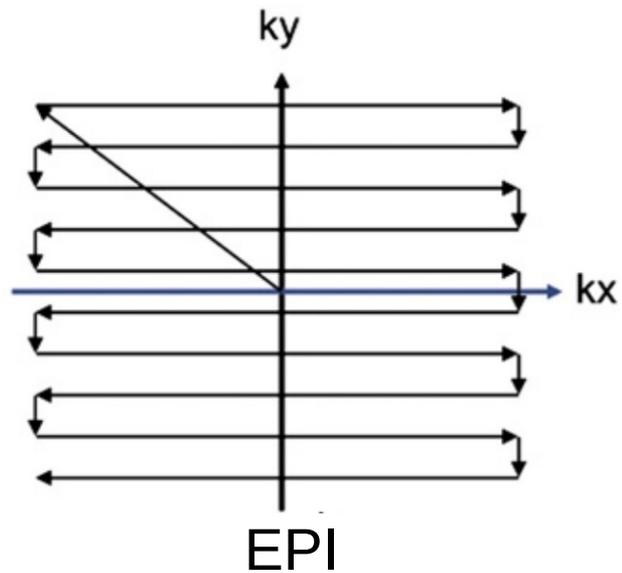


Filling k-space, center out

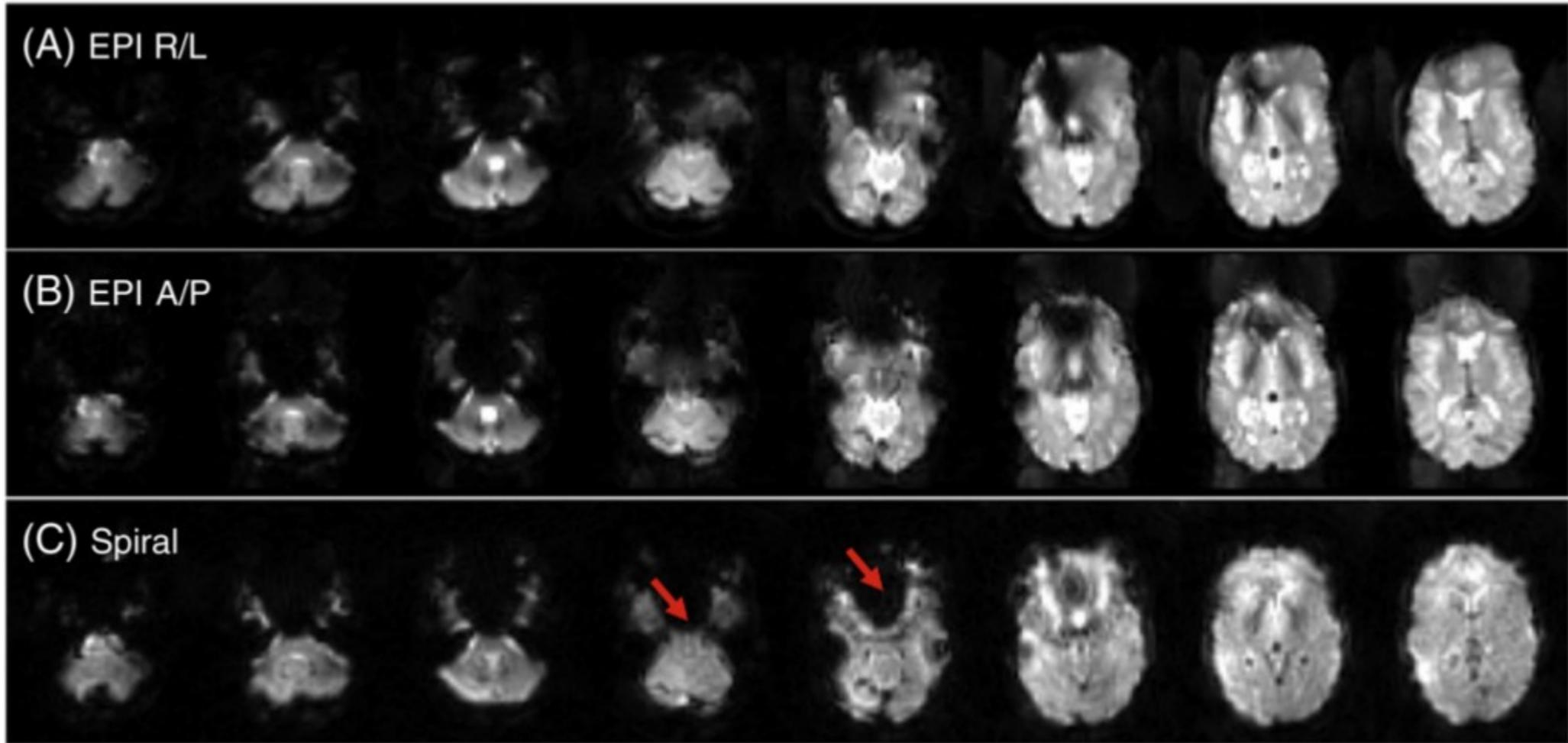


Courtesy of Nick Bock, McMaster

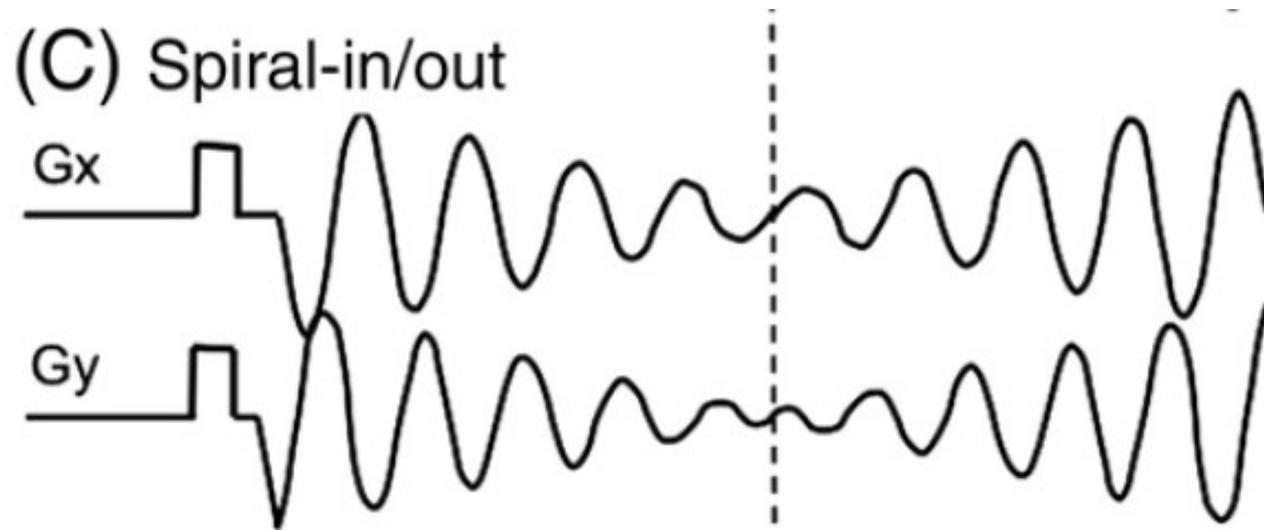
Standard pulse sequences



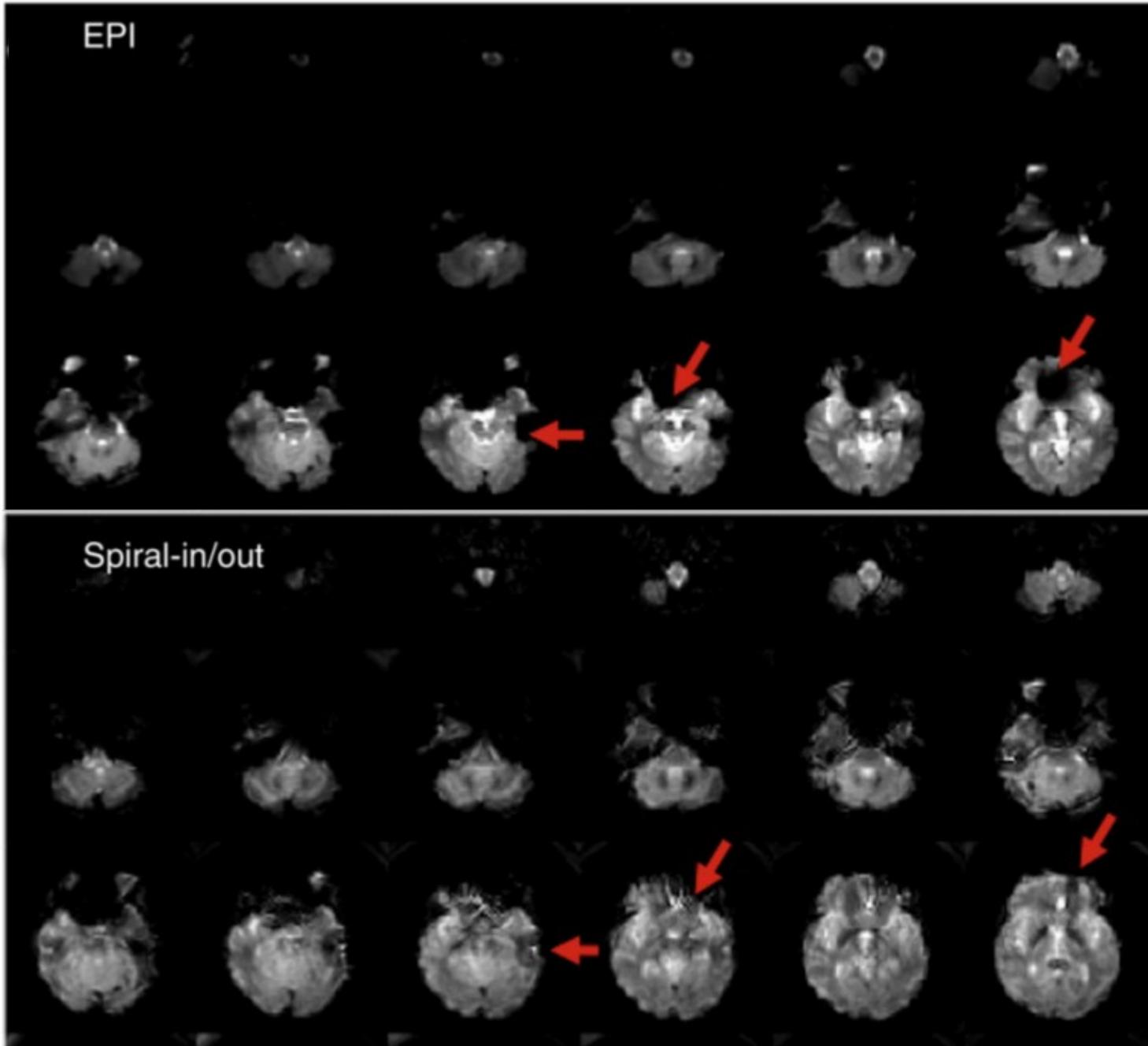
Example EPI/Spiral images ... susceptibility



Spiral in/out



Susceptibility reduction



Voxel size

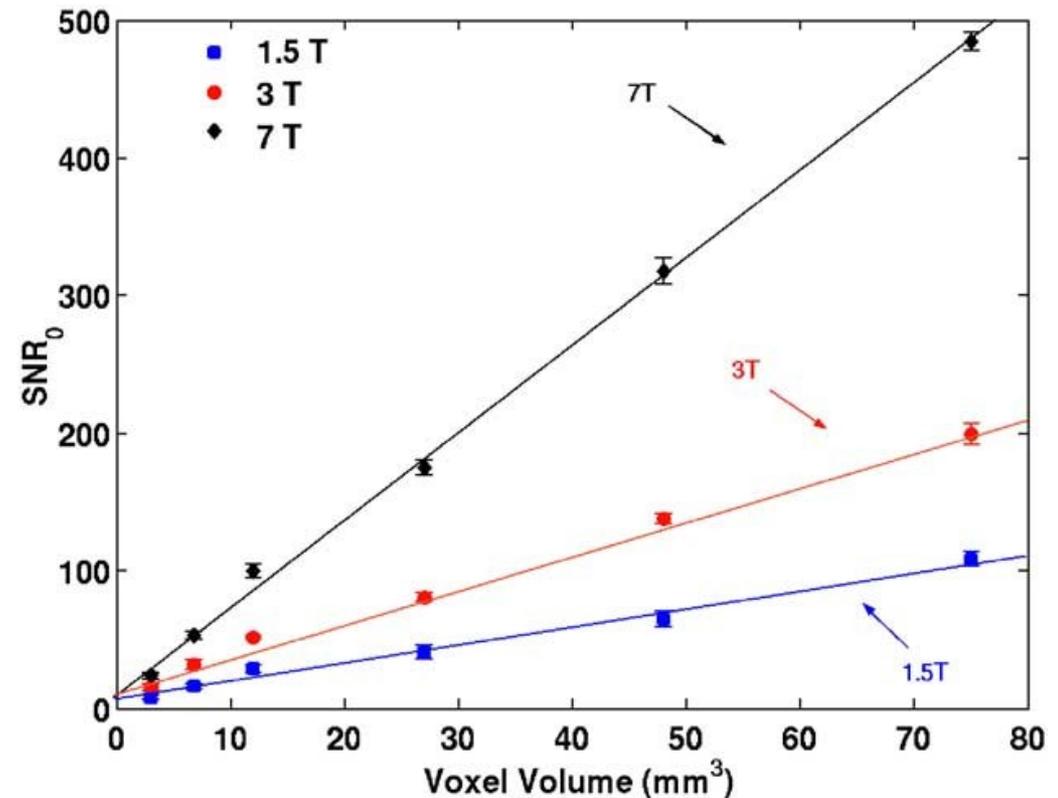
- In going smaller voxel size is primarily limited by SNR
- smaller is usually desirable to reduce partial volume effects, physiological noise

-Voxel SNR is given by

$$SNR \propto p^2 w \sqrt{T_{acq} N}$$

Where p is the voxel size, w is the slice thickness, T is the acquisition time, and N is the number of time frames

T_{acq} is about 20-30ms for single shot EPI.



fMRI acquisition

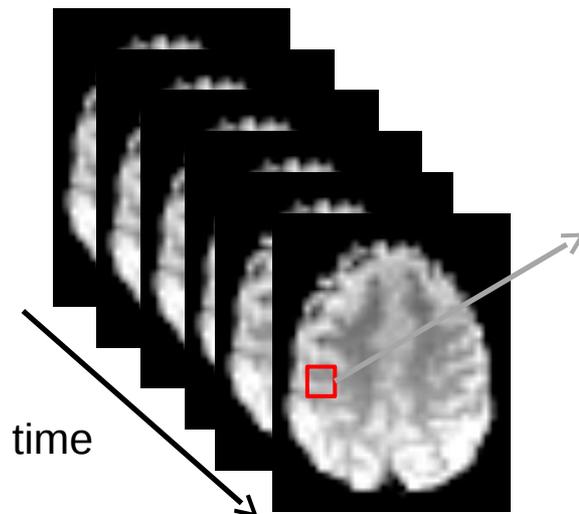


Anatomic



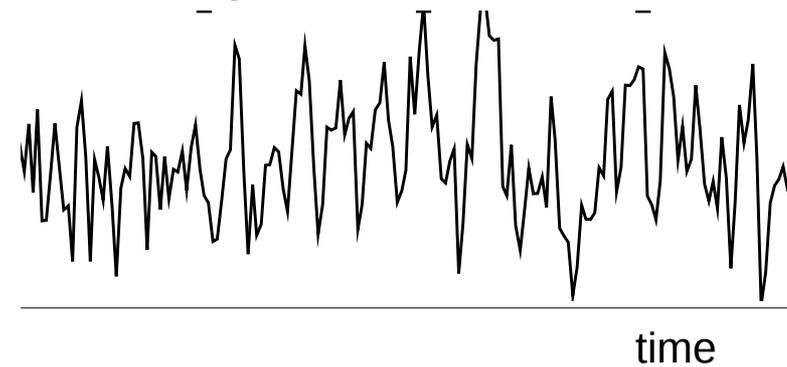
One image / 3-5 min

Functional

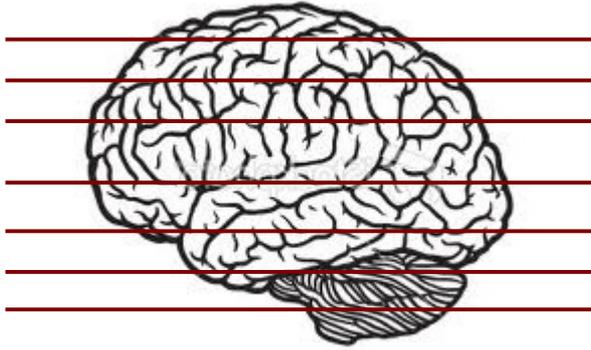


One image / 2 s for 5 min

BOLD signal time series



Whole brain vs. Partial coverage



Increasing **number** of slices:

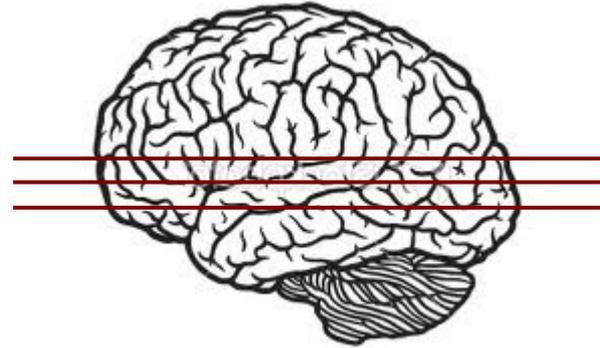
- Decreased temporal **or**
- Decreased in-plane resolution

Increasing slice **thickness**:

- Increased partial voluming
- Increased susceptibility artifacts

Useful for:

- cognitive studies
- resting state

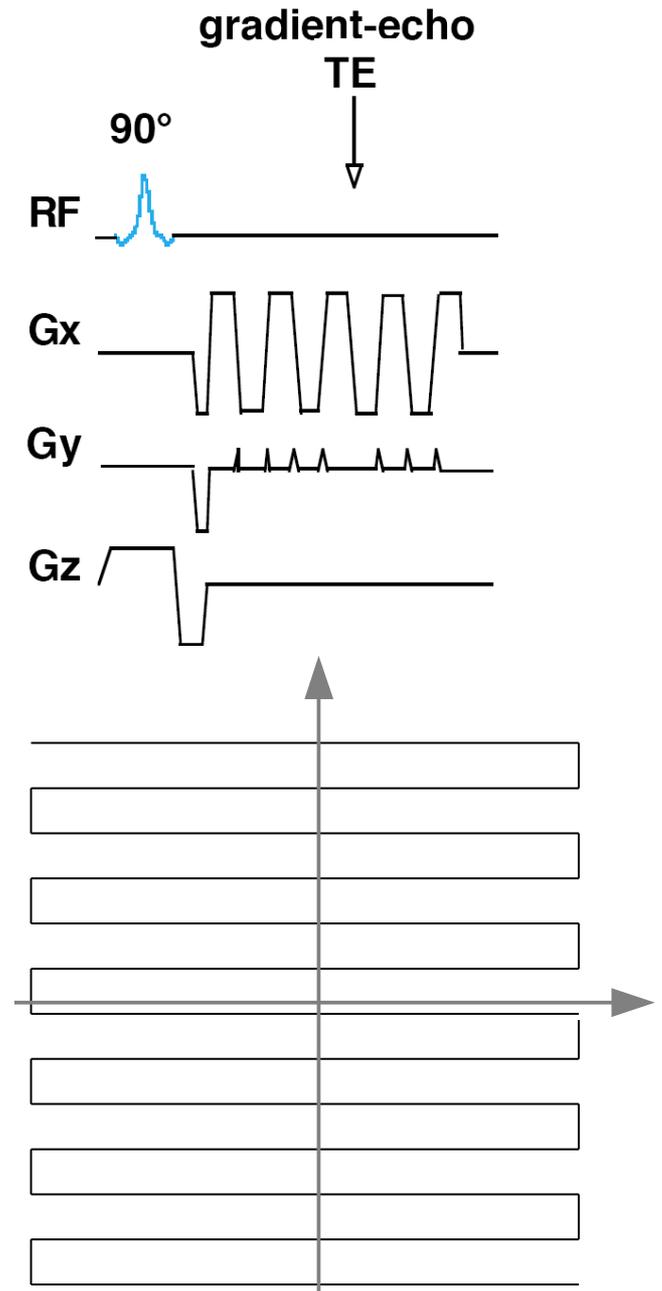
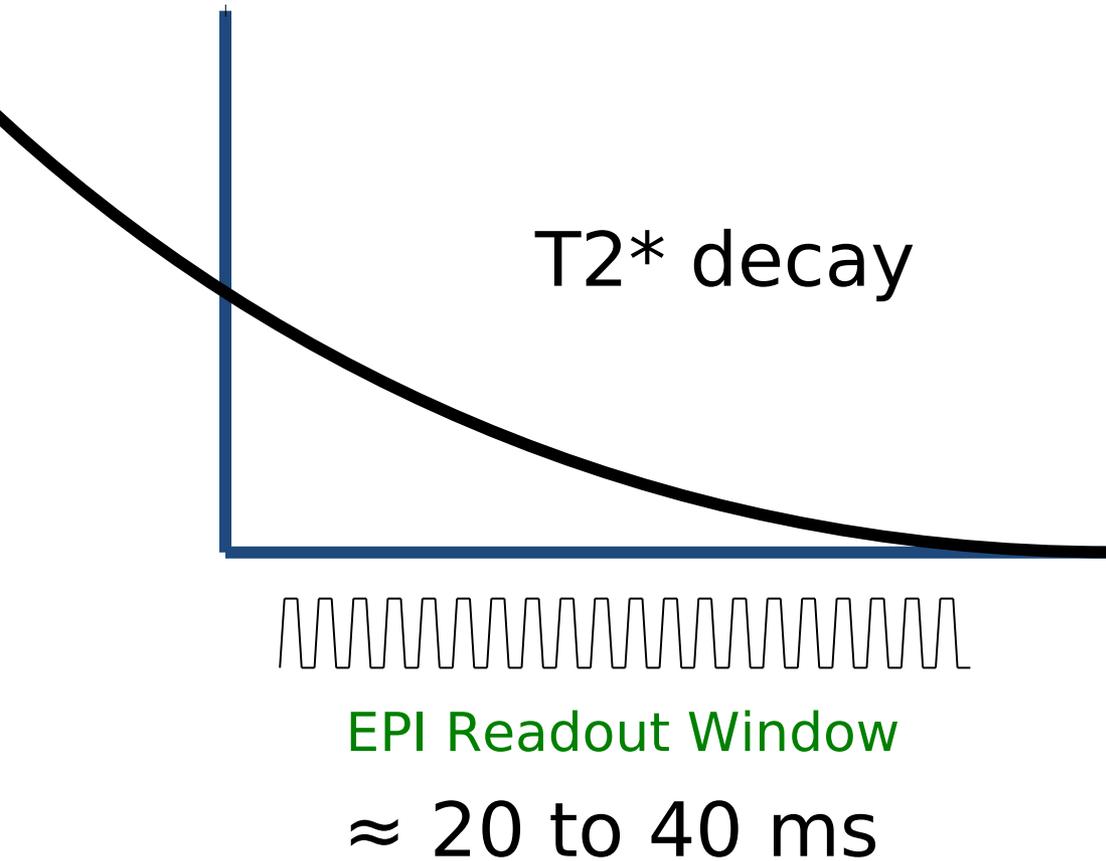


- Thinner slices for short TRs
- Increased in-plane resolution
- shorter TR

Useful for:

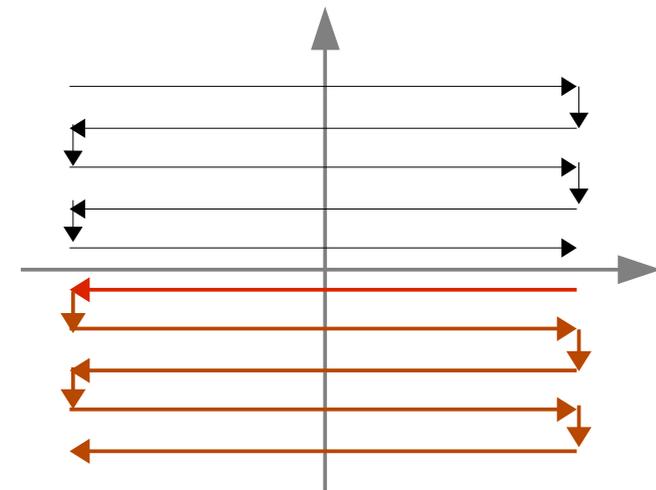
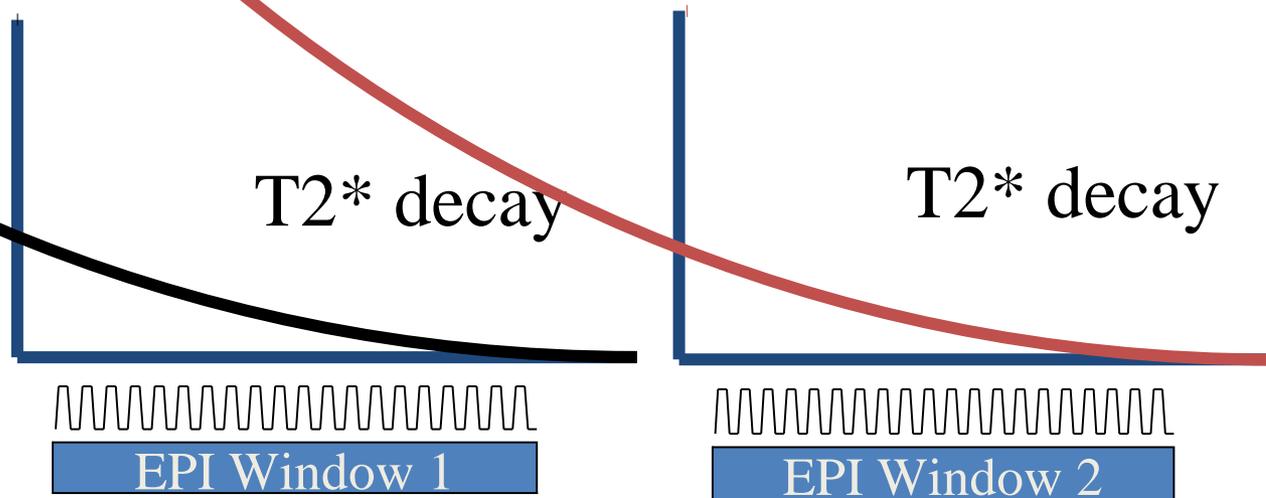
- Specific ROIs

Single shot EPI

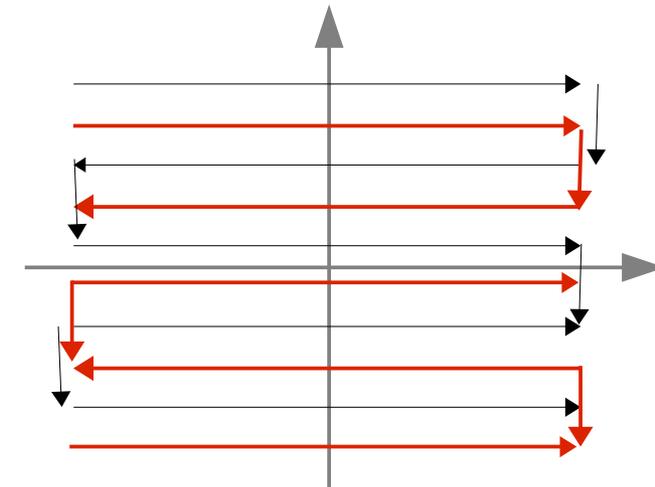


Courtesy of Peter Bandettini

Multi-shot EPI

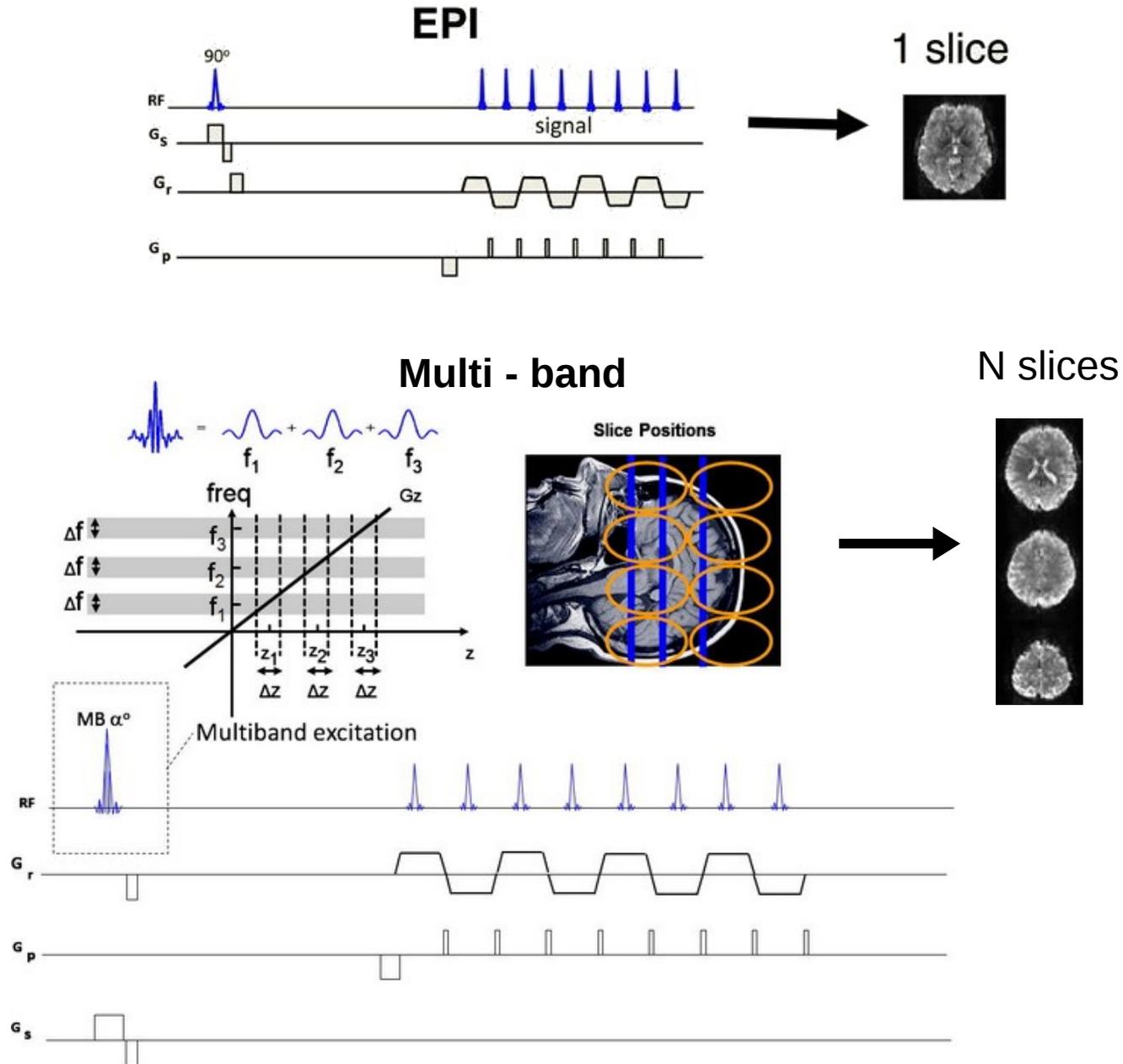


Shot 1
Shot 2

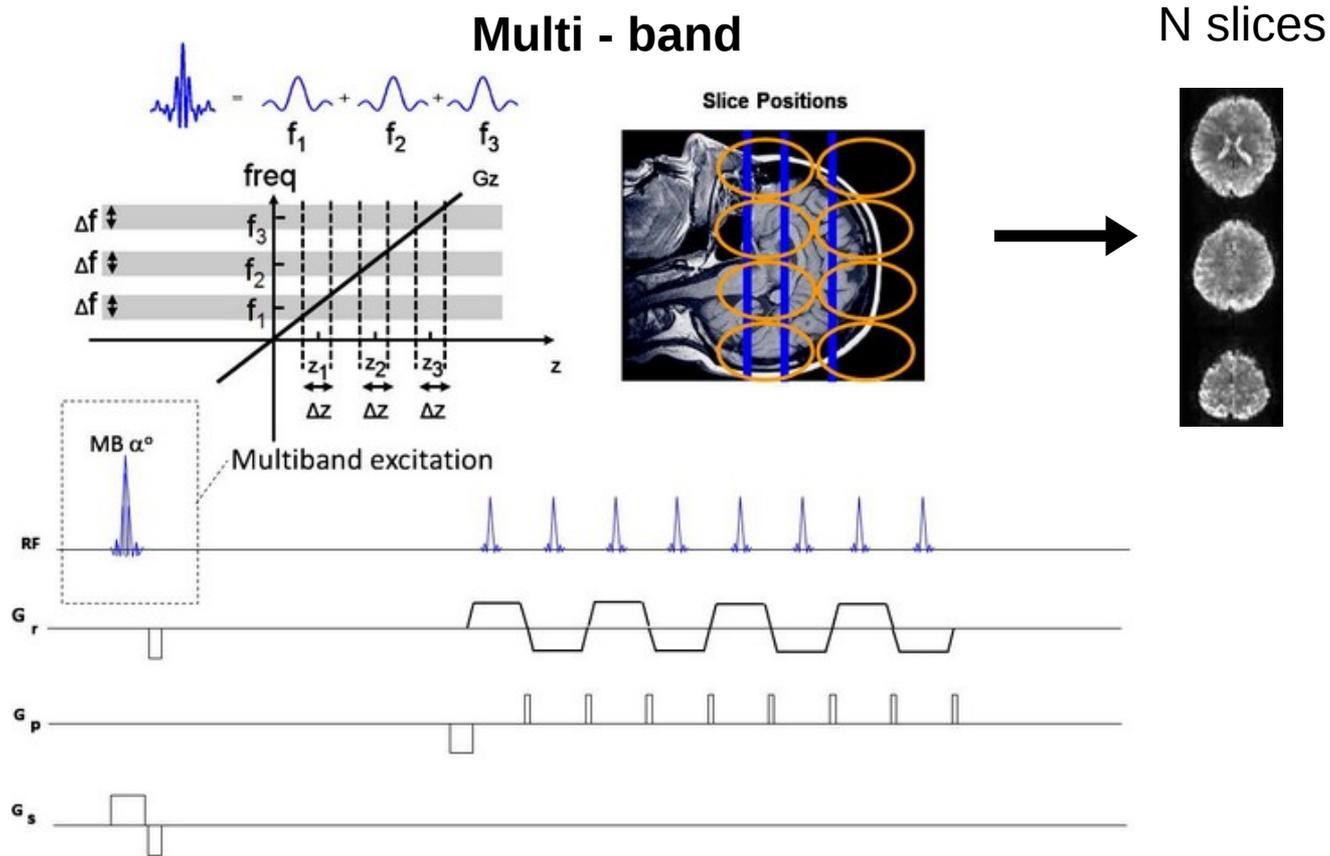


- All lines acquired in a single “shot” with one RF pulse
 - Pros: Fast
 - Cons: Long readout => distortions
- Split the acquisition into parts
 - Pros: acquire higher resolution
 - Cons: phase errors, ghosting, requires more time

Multi-slice or mutli-band excitation



Multi-slice or mutli-band excitation



- excites multiple slices at once,
- uses coil sensitivity profiles to unmix the images
- sub TR whole brain images are achievable
- loss in SNR
- long reconstruction times

What is the optimal voxel size?

- Also need to take into account noise fluctuations over time
- Thermal sources, physiological noise

$$\sigma = \sigma_{thermal} + \sigma_{physio}$$

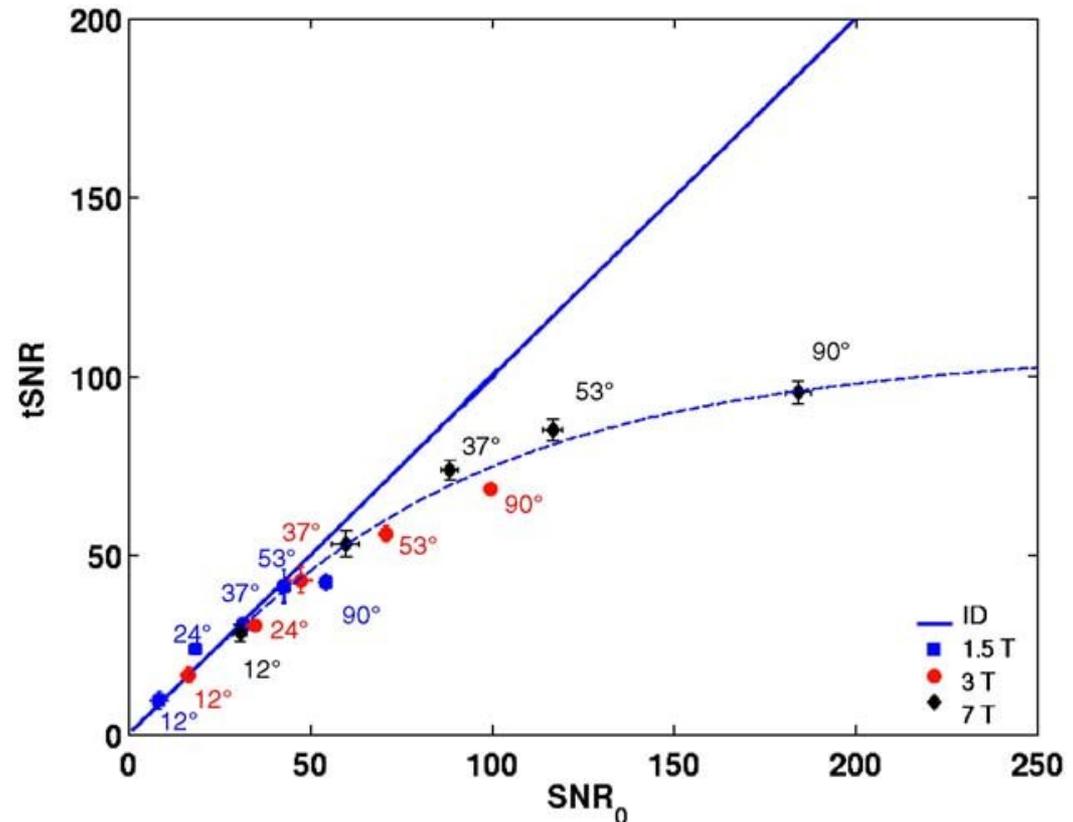
$$\sigma_{thermal} \propto B_0$$

$$\sigma_{physio} \propto S$$

- TSNR is the ratio over the average voxel time course signal over the time course standard deviation.

$$tSNR = \frac{\bar{S}}{\sqrt{\sigma_{thermal}^2 + \sigma_{physio}^2}}$$

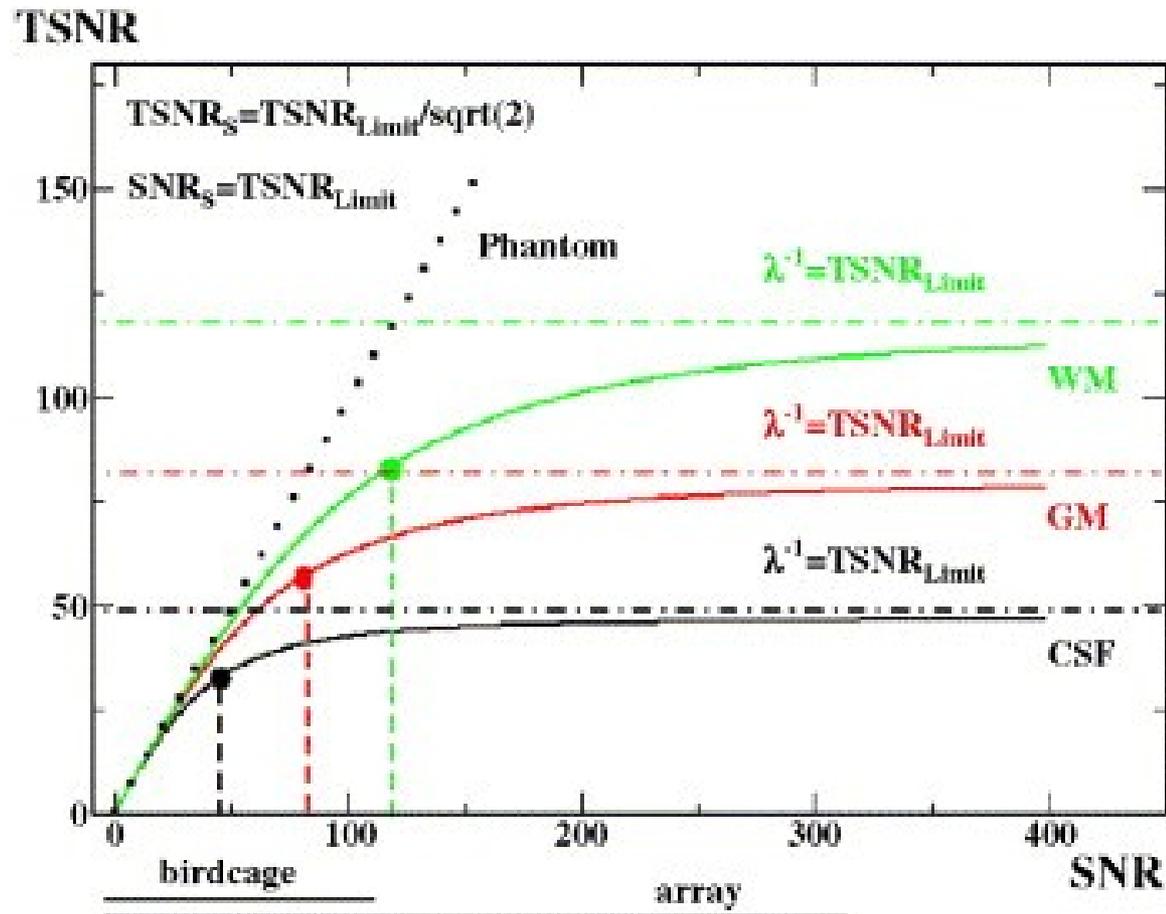
- TSNR has a nonlinear relation with image SNR



Optimal voxel size?

$$\sigma_{thermal} = \sigma_{physio}$$

Has been suggested as a guide to choosing voxel size given a particular image SNR
Based on tissue types and imaging parameters



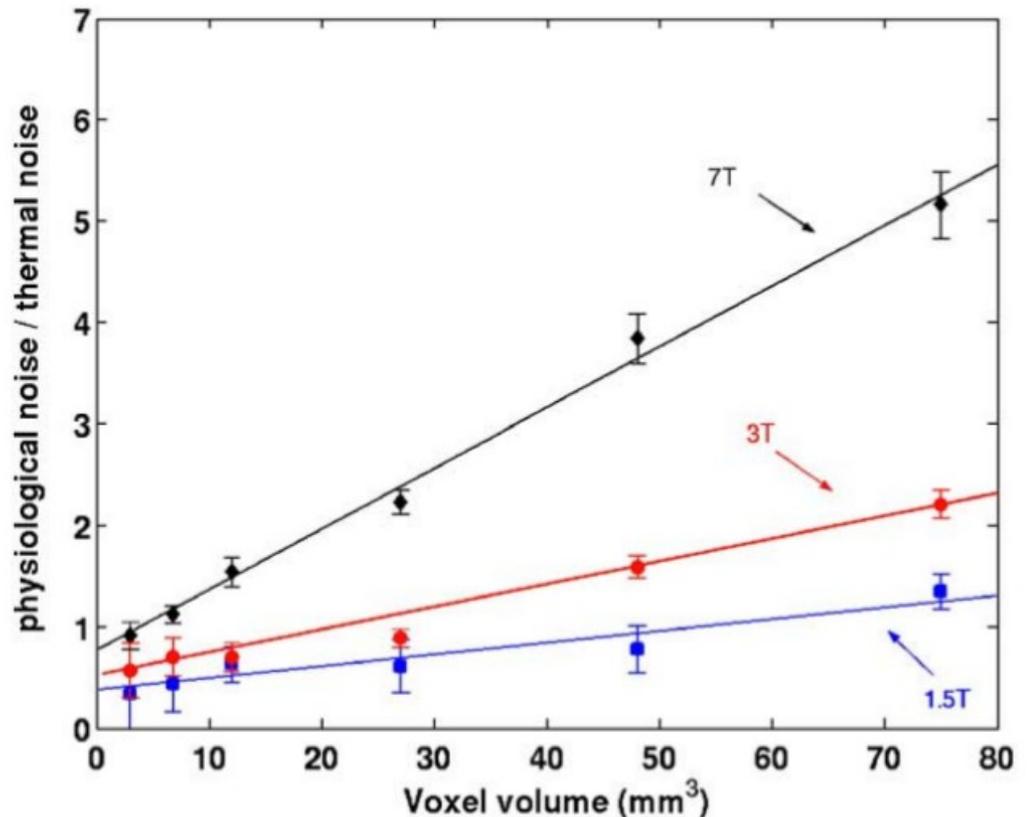
Field Strength

Pros

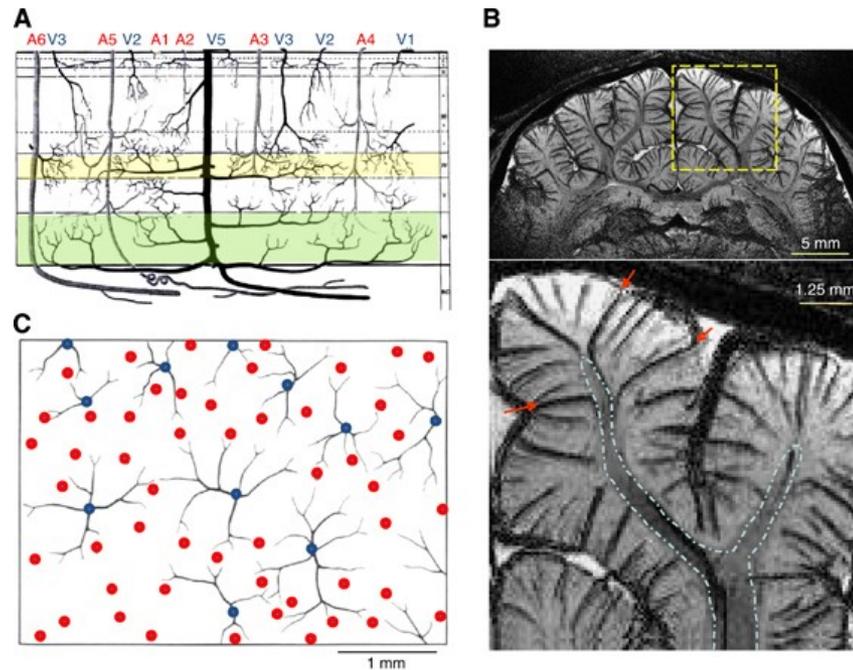
- Higher SNR (1.6 times at 7t v 4t)
- => potential increased resolution / specificity

Cons

- shorter T2*
- => faster readout/ acceleration needed
- long TR
- =>longer repetition time to get signal
- larger field perturbations/ inhomogeneities
- SAR limitations



What's the effective spatial resolution?

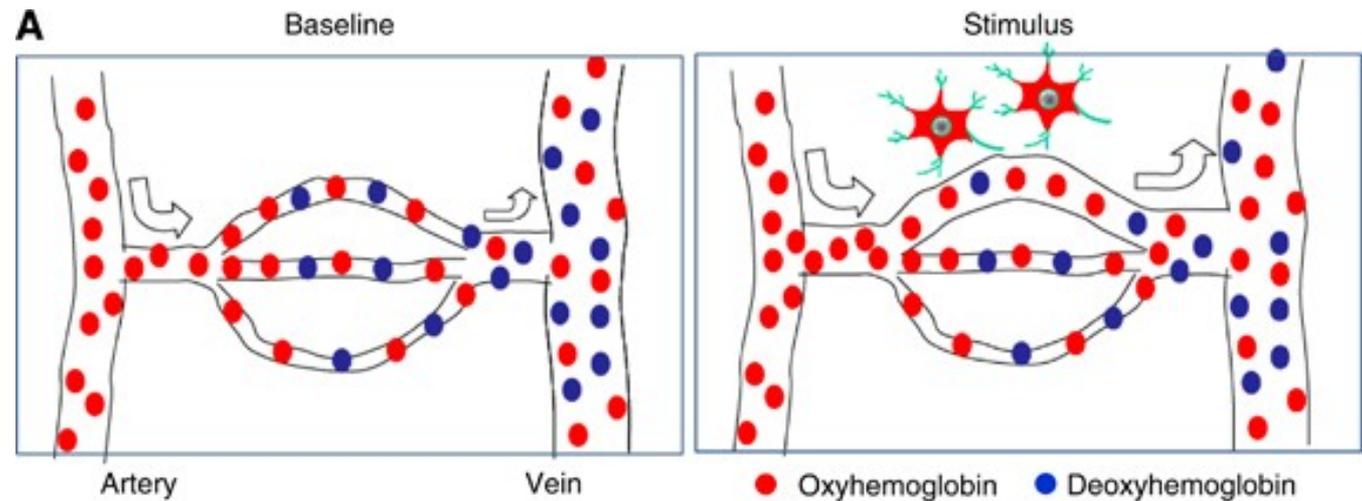


- imaging limit ~ 0.5 mm, easily 2mm, standard 3 ish mm
- hemodynamic PSF 3.5 mm (Engel, 1997)
- higher at 7T ~ 2.3 mm
- smoothing improves reproducibility, alignment between subjects ~ 10 mm (Strother 2005)

Contrast Options

Different pulse sequences:

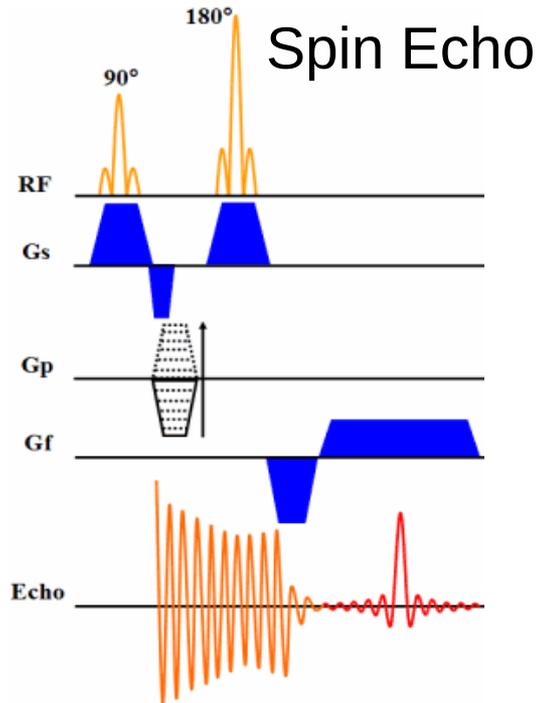
- Spin echo
- Diffusion weighted
- Arterial spin labeling
- Multi-echo



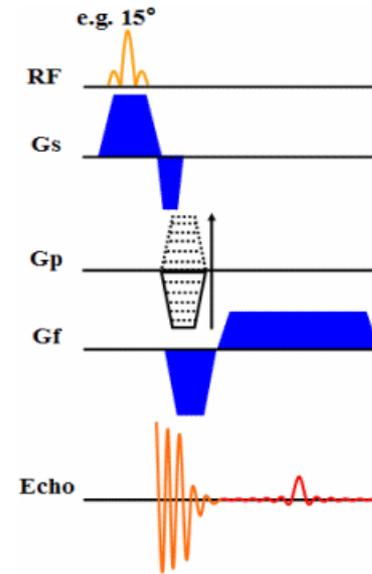
B Expected stimulus-induced changes in MR-related parameters

	Arterial Blood	Extravascular Tissue	Venous Blood	Cerebrospinal Fluid
Volume Fraction (V)	↑	↓	↑	↓
Inflow/perfusion Effect (R_1^*)	↑	↑	↑	↔
BOLD Effect (R_2 and R_2^*)	↔	↓	↓	↓

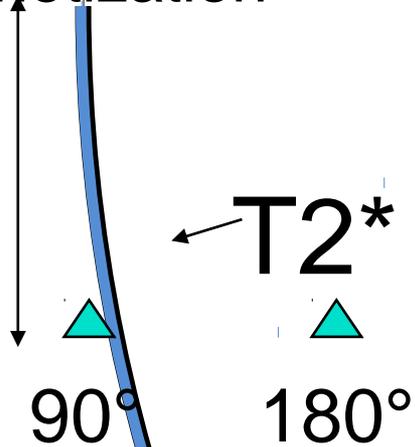
Pulse sequences



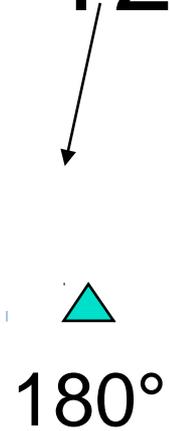
Gradient Echo



transverse magnetization

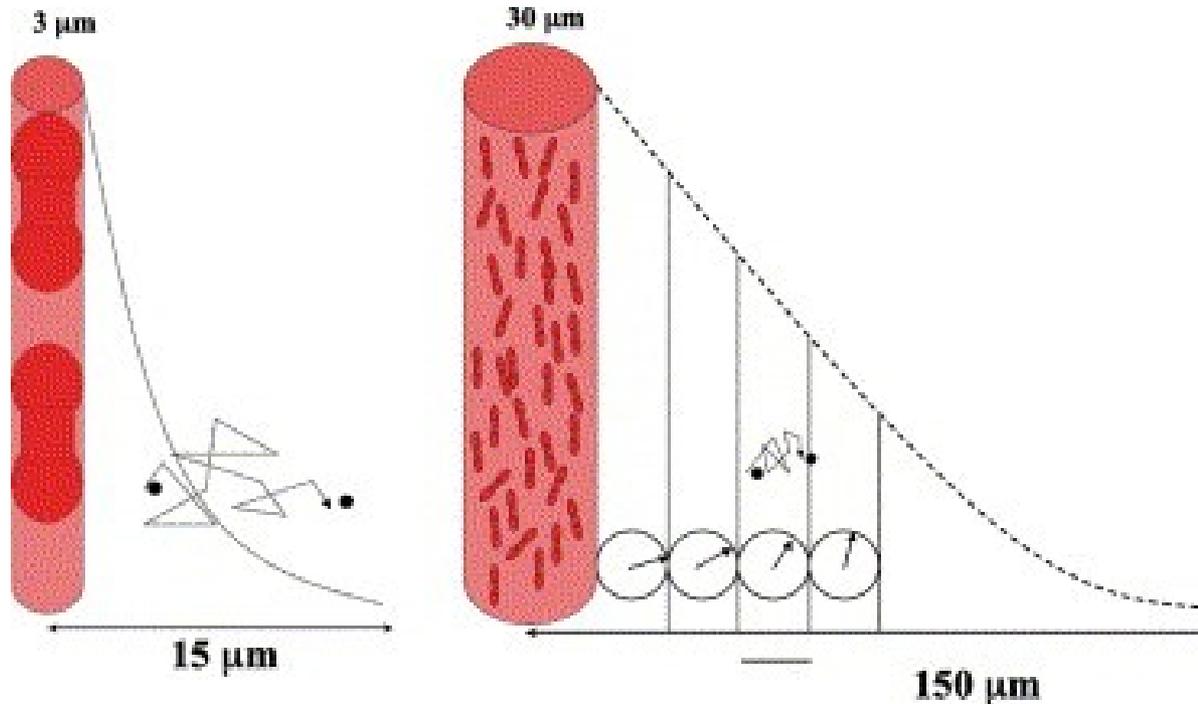
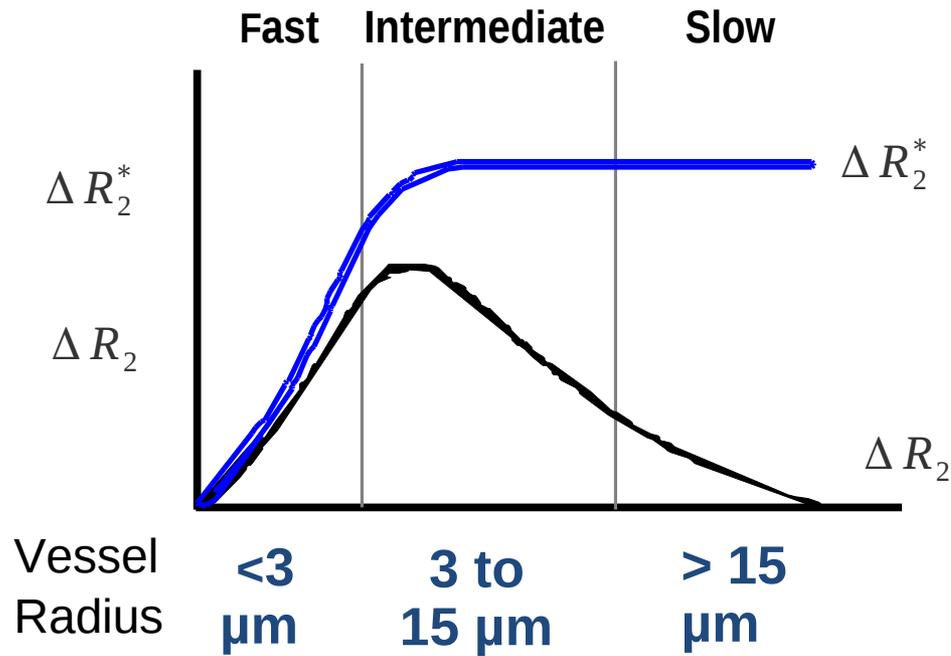


$T2$



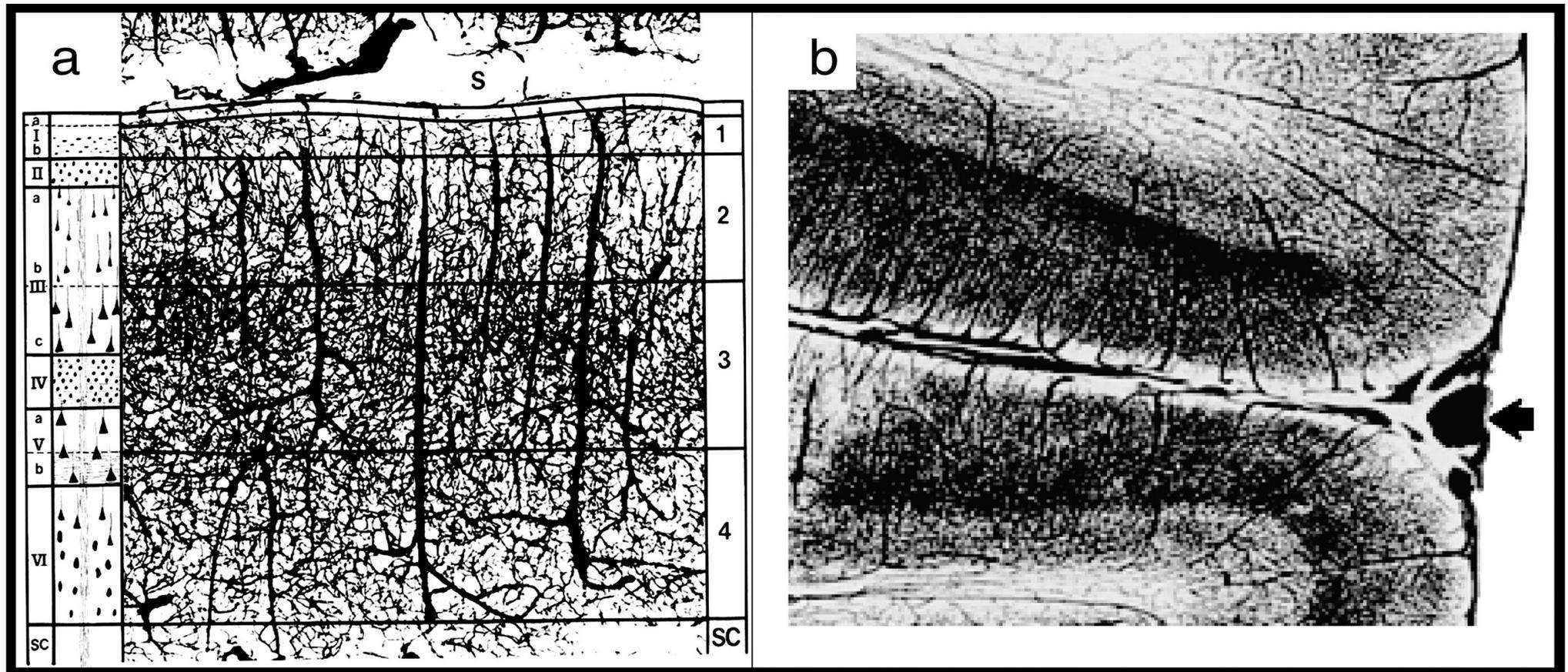
Increased specificity with SE

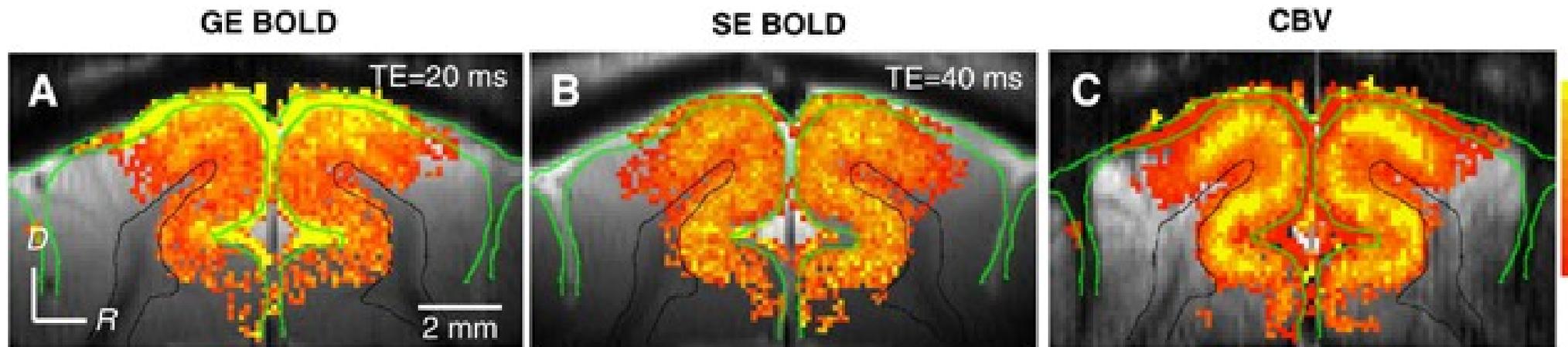
Courtesy of Peter Bandettini



Kim, Methods (2003)

And vasculature ...





GE BOLD fMRI (A) has the highest percent signal change at the cortical surface, where large pial vessels are located (green contours)

Large vessel contributions are suppressed in SE BOLD

the highest CBV change is at the middle of the visual cortex in layer 4 that has the highest metabolic and CBF responses

Spin echo summary

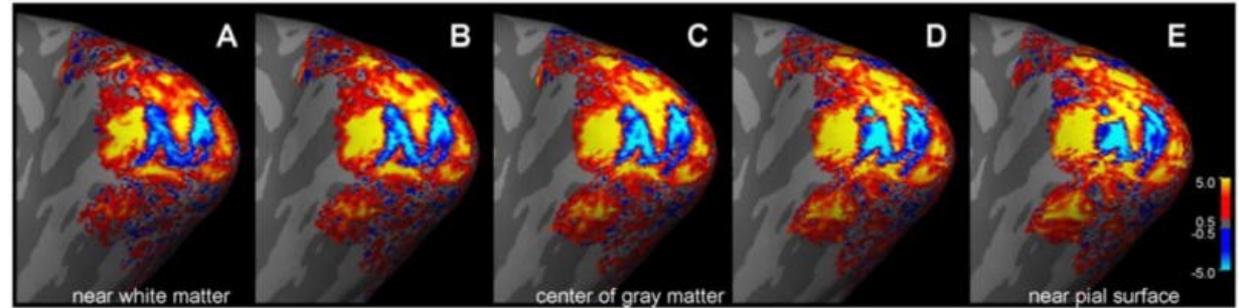
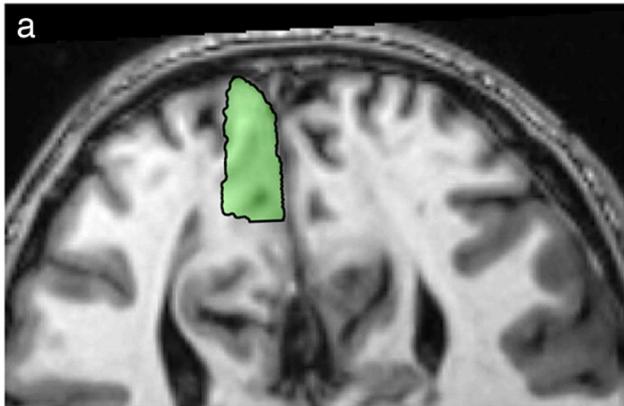
Pros

- Increased specificity (esp at high fields where IV signal is low)
- Less sensitive to rapidly flowing blood
- Less signal dropout.

Cons

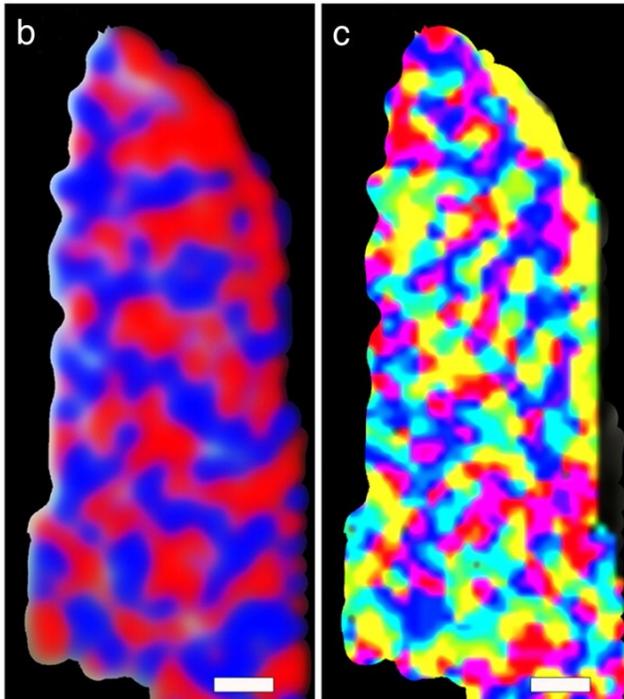
- Fewer slices per TR
- Lower fCNR by x 2 to 4.
- Acquisition window still T2*
- Very large IV signal still present at most field strengths.

High field applications of GE, SE



Polimeni JR et al, Neuroimage (2010)

Cortical layers using GE

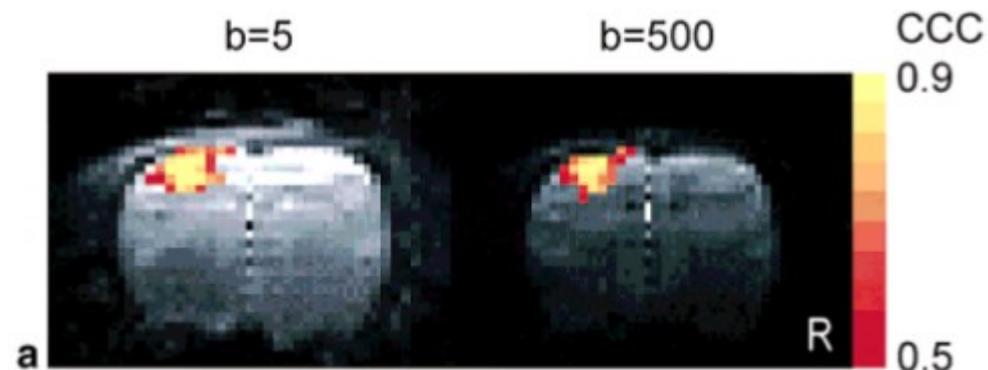
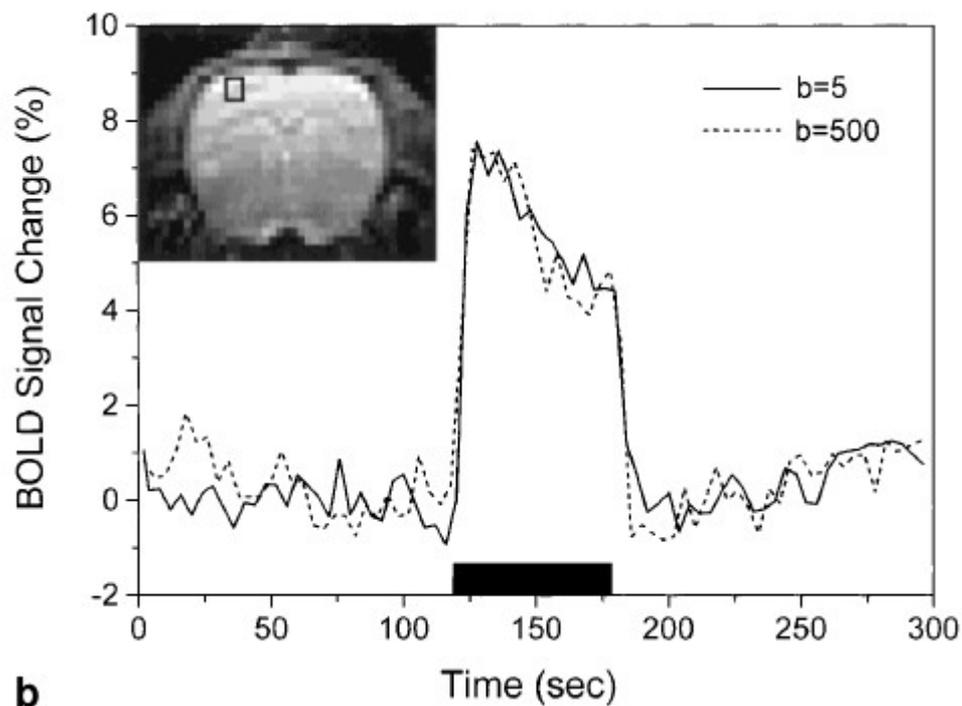
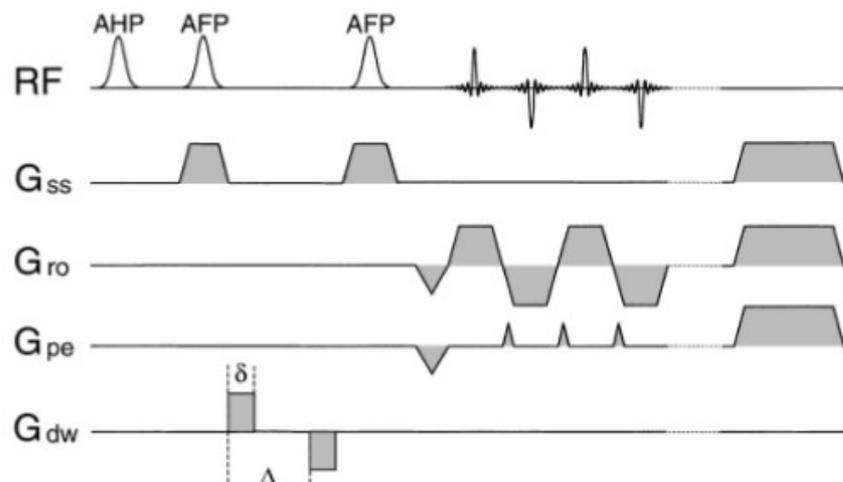


Optical orientation columns using SE

Yacoub E et al. PNAS 2008;105:10607-10612

Diffusion weighting

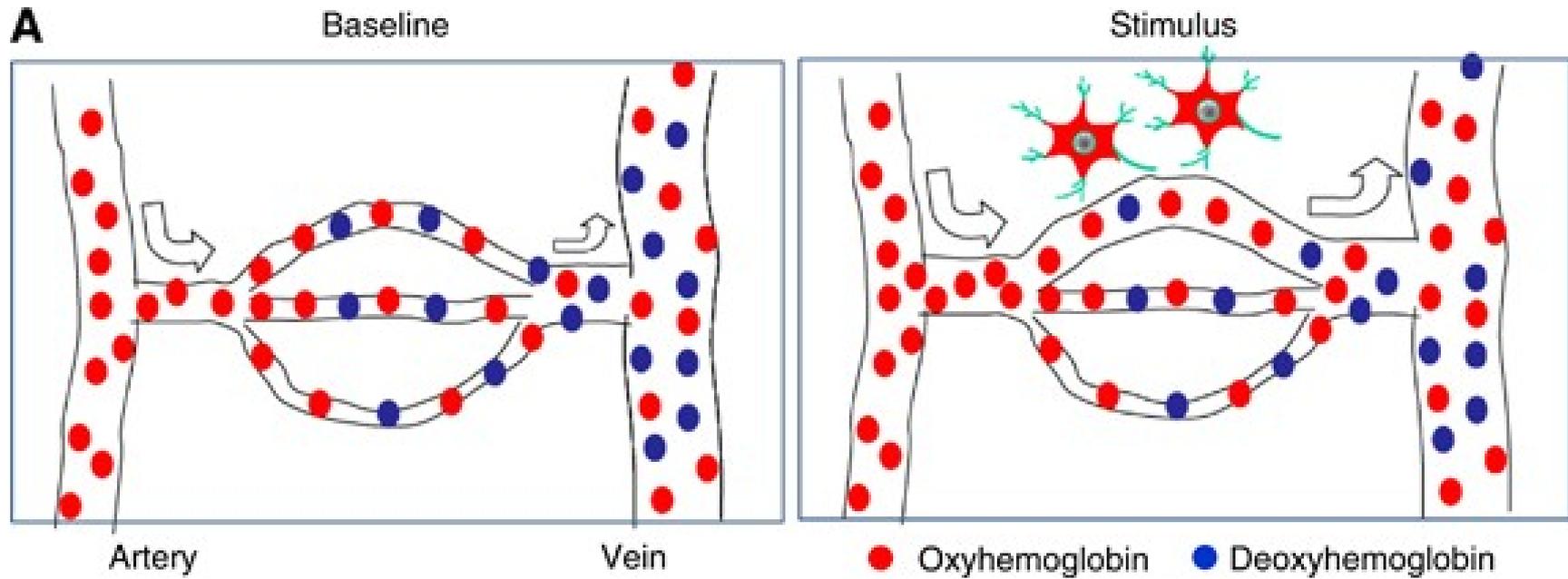
- add diffusion gradients to help separate out the intra and extra vascular components



Diffusion weighted things / intravascular contrast

- intravascular contribution decreases as magnetic field strength increases

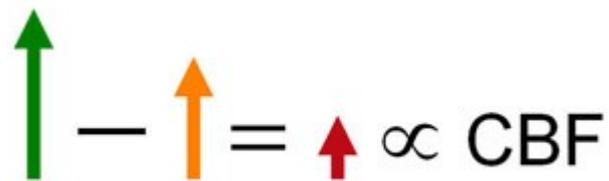
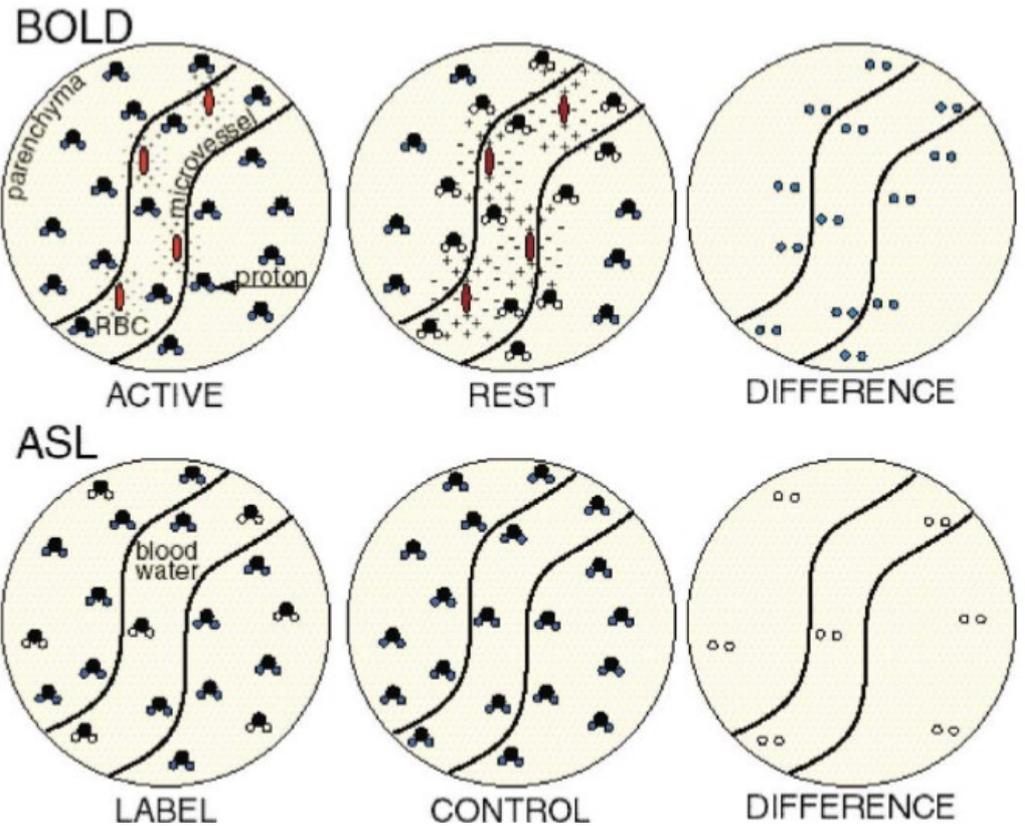
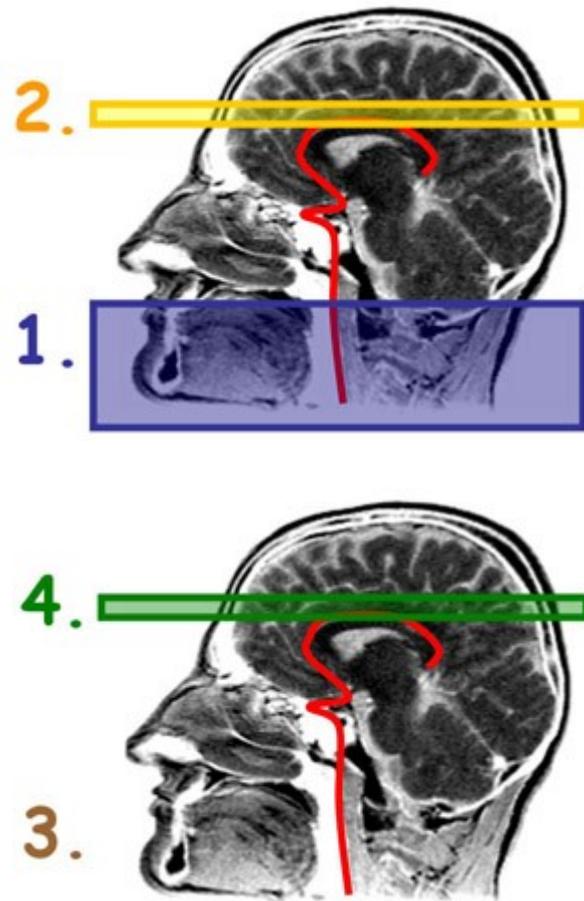
Magnetic field (T)	MR technique, echo time (ms)	b value (s/mm²)	Subject, brain region	Intravenous fraction	Reference
1.5	ASE, 165	10–690	Human, V1	0.5–0.7	Boxerman <i>et al</i> (1995)
	SE, 125	200–700	Human, V1	0.6–1.0	Zhong <i>et al</i> (1998) (Figure 4B)
	GE, 82	165–660	Human, M1	0.6–0.9	Song <i>et al</i> (1996)
	GE, 33–93	100	Human, V1	0.46–0.62 ^b	Donahue <i>et al</i> (2011) ^c
3.0	SE, 96.5	14–454	Human, V1	~0.5	Jochimsen <i>et al</i> (2004)
	GE, 32.7–70.7	100	Human, V1	0.22–0.4 ^b	Donahue <i>et al</i> (2011) ^c
4.0	SE, 32 and 65	40–400	Human, V1	0.2–0.75 ^b	Duong <i>et al</i> (2003)
	GE, 80	20–500	Human, V1	~0	Duong <i>et al</i> (2003)
7.0	SE, 32 and 55	40–400	Human, V1	0.1–0.2 ^b	Duong <i>et al</i> (2003)
	GE, 55	20–500	Human, V1	~0	Duong <i>et al</i> (2003)
	GE, 28.6–46.6	100	Human, V1	0.08–0.16 ^b	Donahue <i>et al</i> (2011) ^c
9.4	SE, 40	30–500	Rat, S1	~0	Lee <i>et al</i> (1999)
	SE, 16–70	200	Cat, V1	0–0.6 ^b	Jin <i>et al</i> (2006) ^d

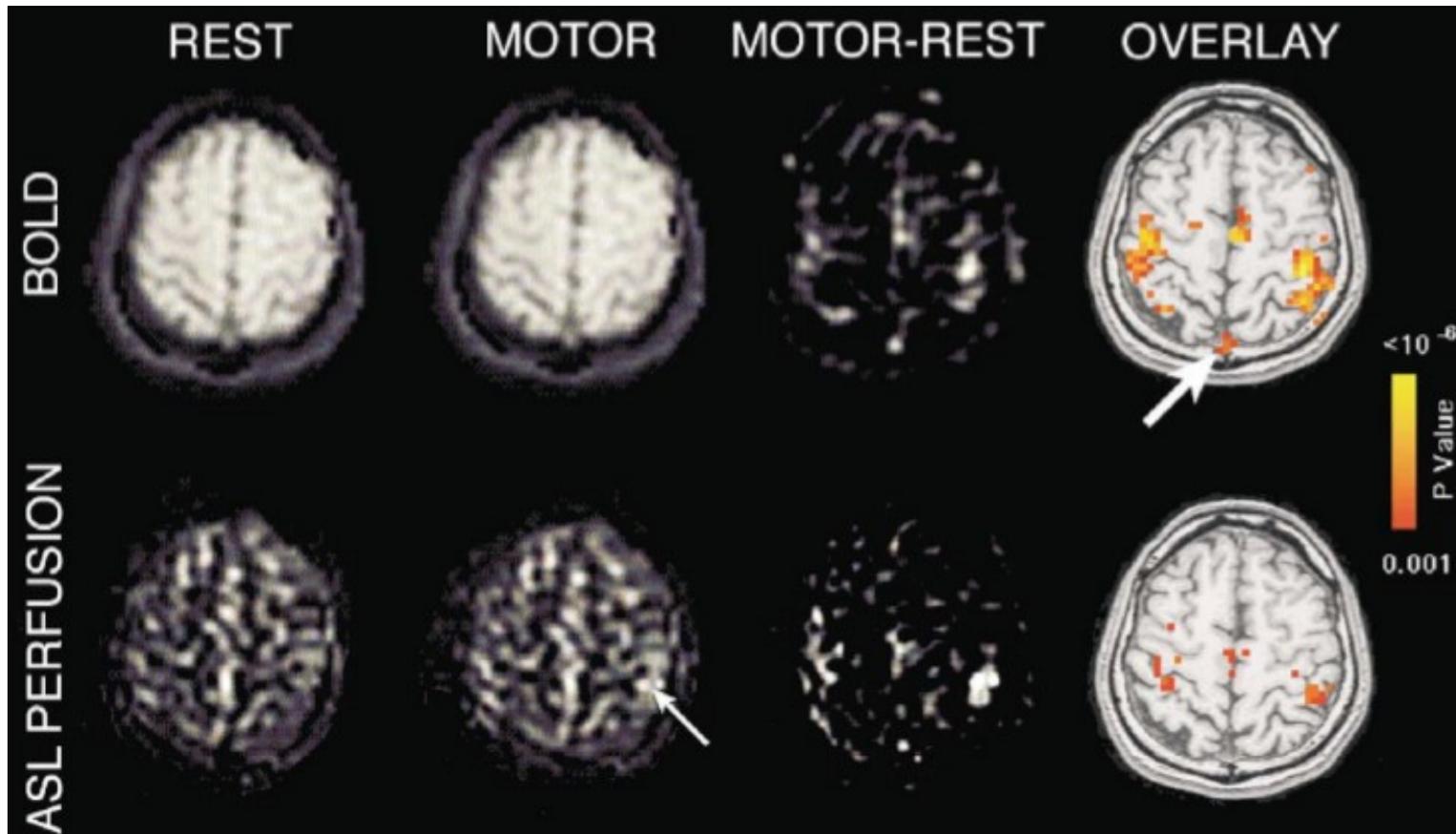


B Expected stimulus-induced changes in MR-related parameters

	Arterial Blood	Extravascular Tissue	Venous Blood	Cerebrospinal Fluid
Volume Fraction (V)	↑	↓	↑	↓
Inflow/perfusion Effect (R_1^*)	↑	↑	↑	↔
BOLD Effect (R_2 and R_2^*)	↔	↓	↓	↓

ASL vs. BOLD

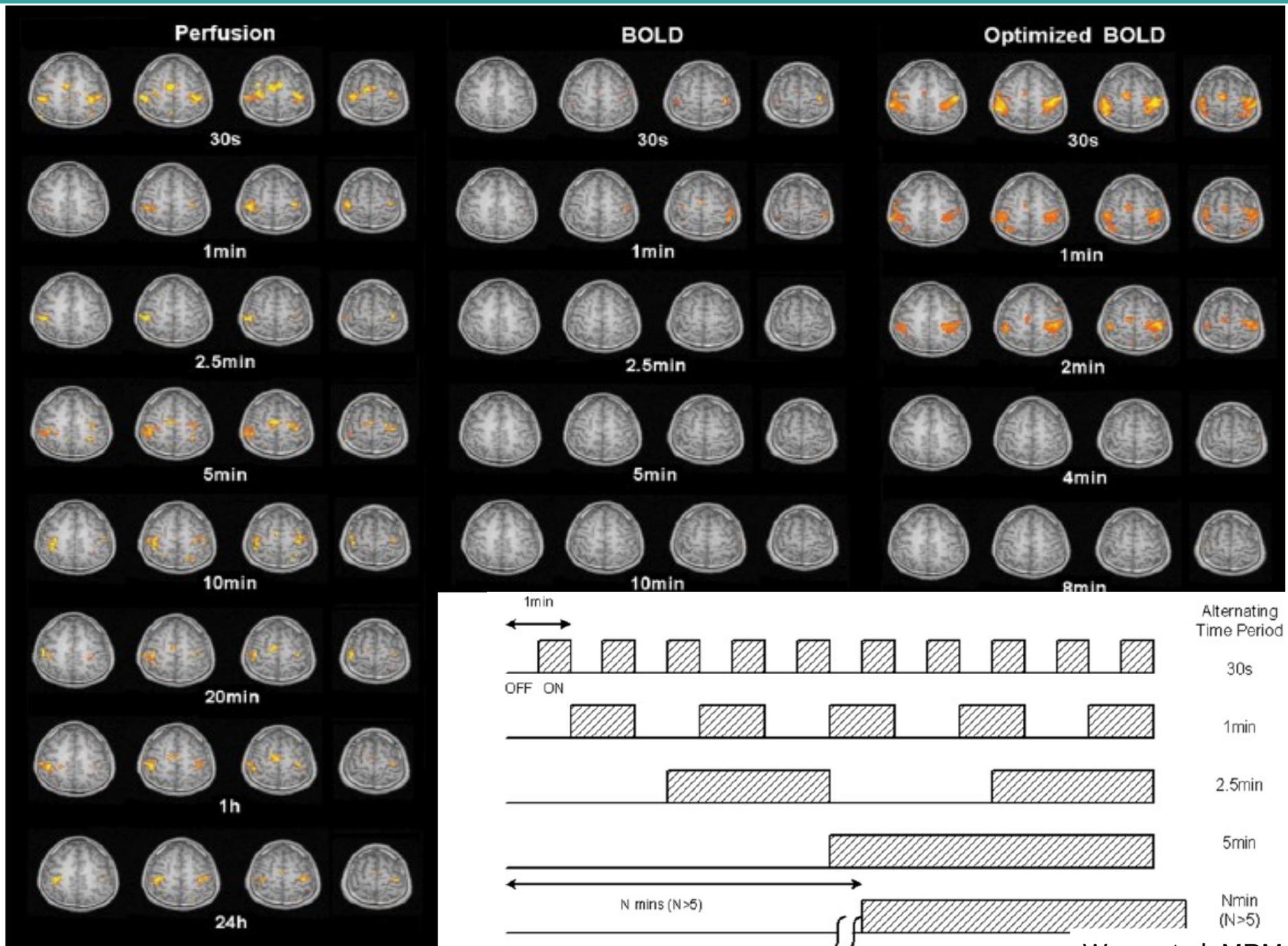




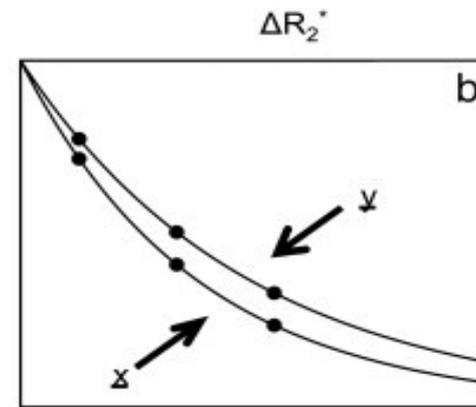
ASL vs. BOLD

	BOLD	ASL
Signal Mechanism	Blood flow, Blood volume, Oxygenation consumption	Blood flow
Contrast parameter	T2*	T1
Spatial specificity	Venules and draining veins	Capillaries, arterioles
Typical signal change	0.5-5 %	< 1 %
Imaging methods	Gradient-echo, spin-echo	Spin-echo
Sample rate (TR)	1-3 s per image	< 3-8s per perfusion image
Optimal task frequency (block design)	0.01 – 0.06 Hz (100 s - 16 s)	< 0.01 Hz
Intersubject variability	High	Low
Imaging coverage	Whole brain	Most of brain cortex
Major artifacts	Susceptibility, motion, baseline drift	Vascular artifact
Relative CNR	> 2 high task frequency < 0.5 low task frequency	1

Long duration stimulation: ASL vs. BOLD

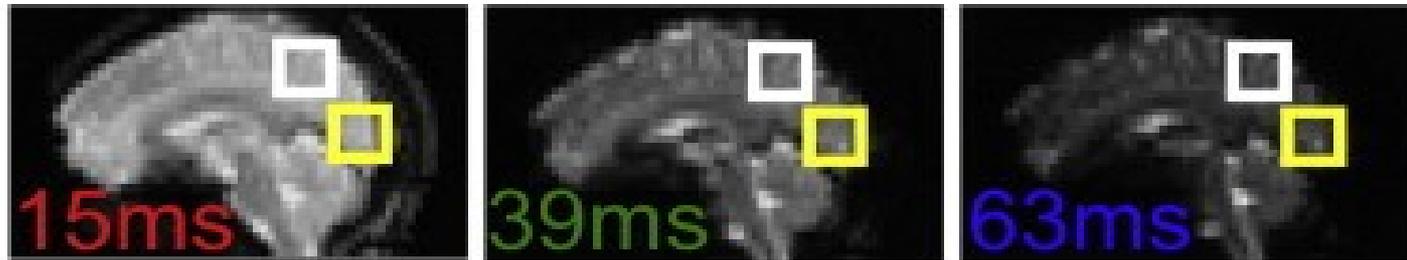


Separating BOLD from non-BOLD

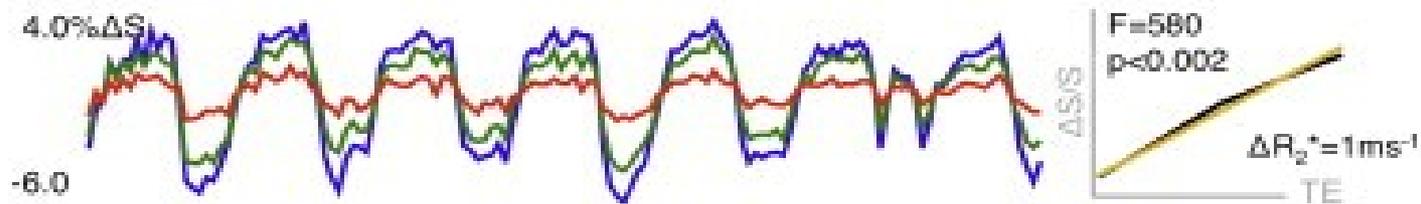


Signal scaling

a Multi-echo EPI images

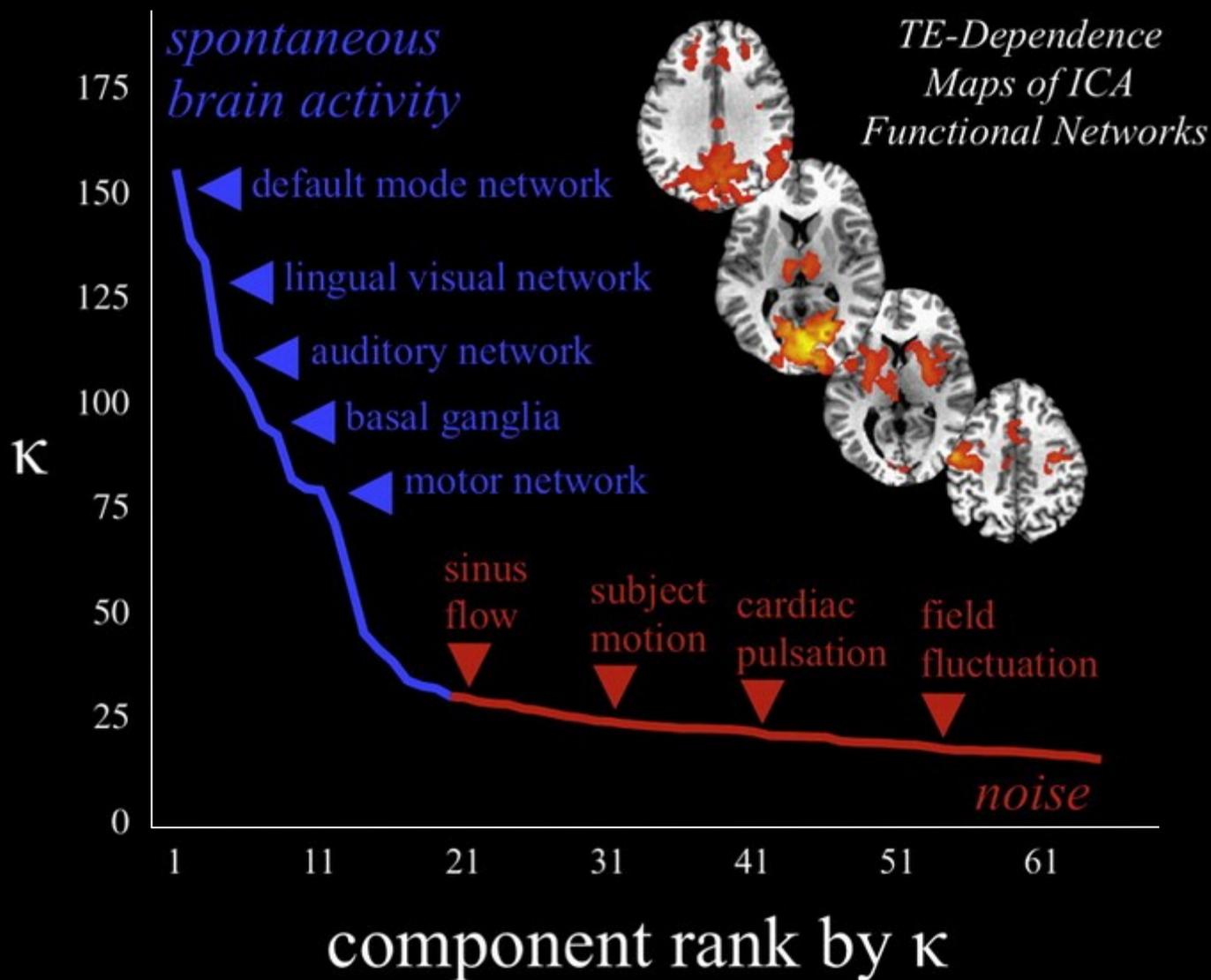


b Multi-echo EPI time courses for task (V1)



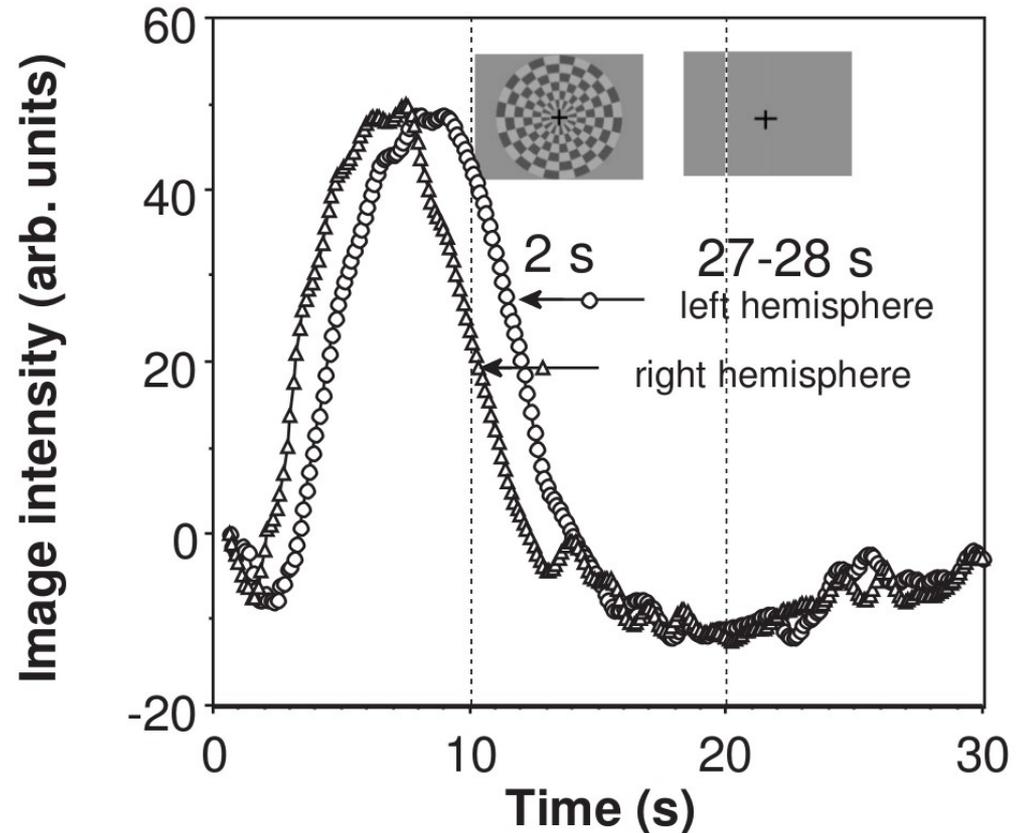
c Multi-echo EPI time courses for rest (precuneus)



κ spectrum

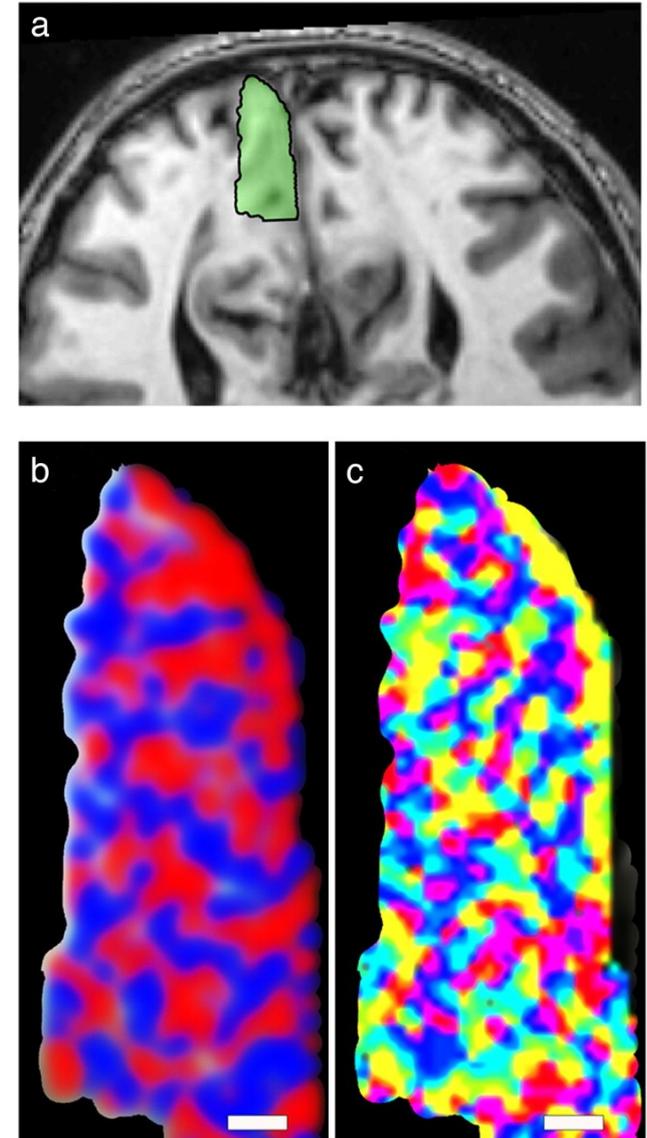
Temporal limits

- Create a functional image within 2 s for more robust activation or in less than 1s using acceleration
- Limited by filtering lag of hemodynamic response function 4-6 s
- Long (> 2 min) duration stimuli are hampered by baseline changes
- Can detect differences in the onset of hemodynamic responses down to 100 ms

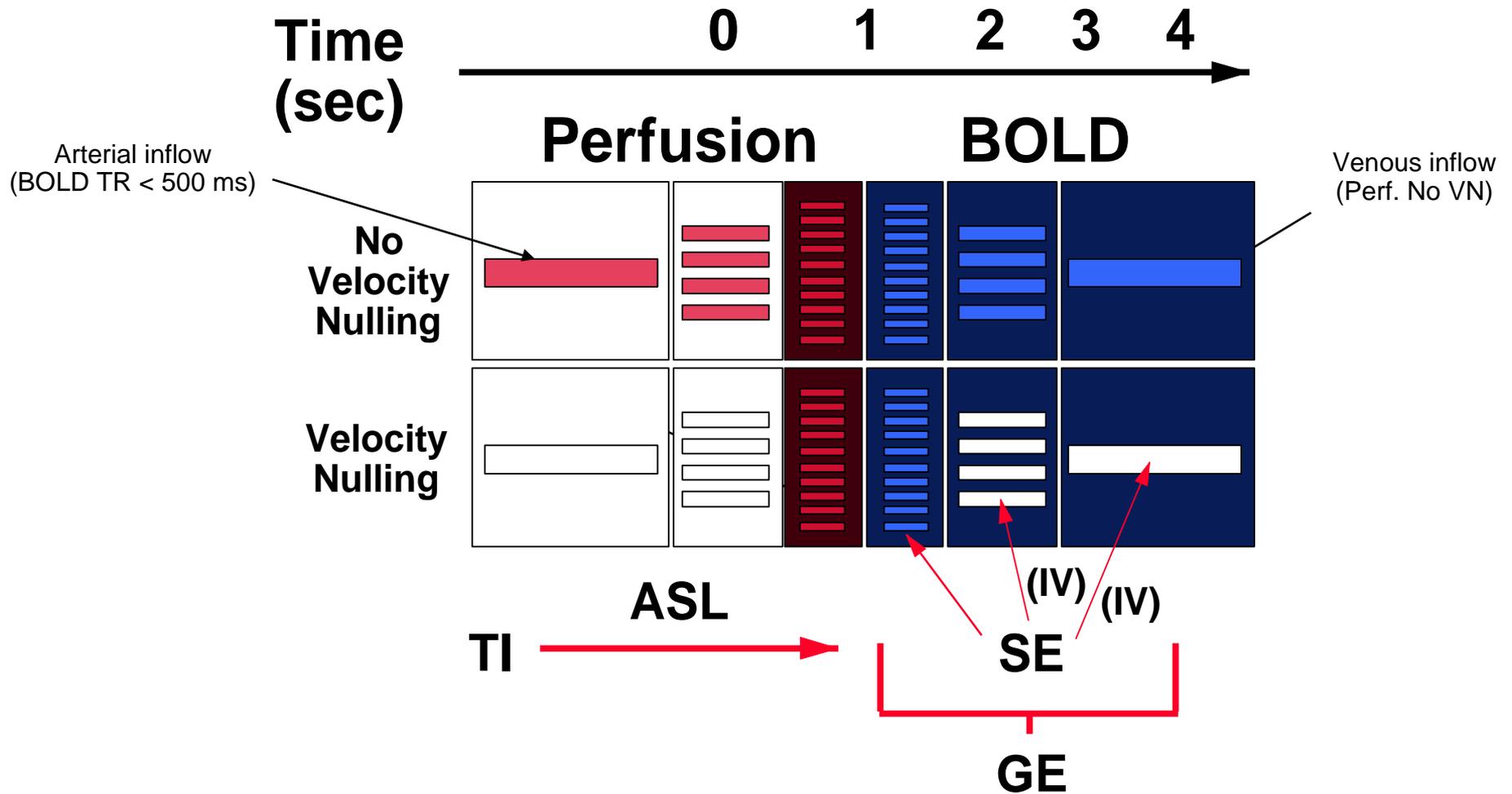


Spatial limitations

- At 3 T : $\sim 1.5 \text{ mm}^3$ resolution
 - The functional point spread function is about 3.5 mm.
- At 7 T, $\sim 0.5 \text{ mm}^3$ resolution
 - The functional point spread function can be as high as 1.5 mm.
- At 7 T, using spin-echo sequences, the smallest resolved functional unit was orientation columns (on the order of 0.5-mm width).
- Practically limited by smoothing kernels, template alignment in group studies.

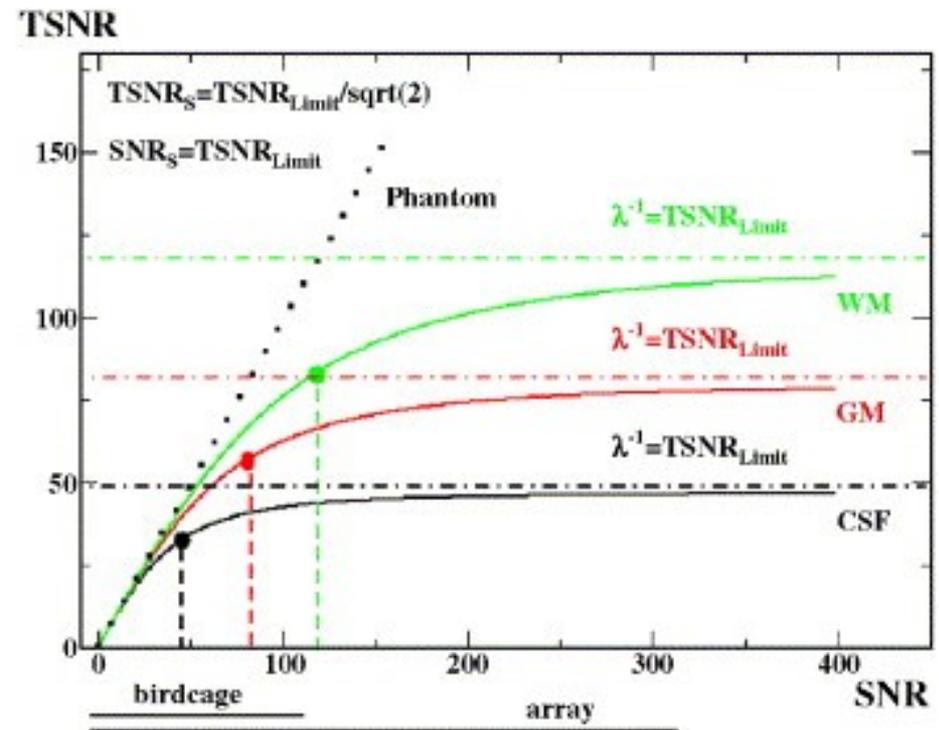


Hemodynamic Specificity



Sensitivity

- Limited to a temporal signal-to-noise ratio of about 100:1 across all field strengths by physiologic fluctuations that occur over time.
- Better modeling of the physiological fluctuations required



Interpretation

- BOLD signal change is not a quantitative measure.
 - Hemodynamic factors (baseline blood volume, neurovascular coupling) influence location, magnitude, and dynamics.
- Use of multi-echo, combination of contrasts
- Multimodal studies are needed to firmly establish the relationship between BOLD signal and neural activity.
- Developing techniques to measure neuronal currents (small signals...)

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