认知心理学进阶第七讲：磁共振生理（二）

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清华大学心理与认知科学系

Based on MIT MRI Open Course

1

Overview of Imaging Physiology Block

- Lecture 6:
  - Brain at baseline: neural activity, energy metabolism, and cerebral blood flow
  - “Activated” brain: changes in brain physiology in response to external stimuli, and Introduction to BOLD fMRI

2

Overview of Imaging Physiology Block

- Lecture 7:
  - BOLD fMRI in-depth
  - Beyond BOLD: state-of-the art fMRI techniques to directly image physiological parameters

3

Overview

- BOLD review
- BOLD response to *blocks* and *events*
- Linearity of BOLD response
- Modeling the BOLD signal
  - Main response
  - Post-stimulus undershoot
  - Initial Dip

4

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5

Review of BOLD fMRI

- dHb is paramagnetic agent; decreases signal in T_2/T_2^* -weighted MR imaging
- Neuronal activity leads to:
  - Small ↑ in $CMRO_2$ = Small ↑ in dHb
  - Large ↑ in CBF = Large ↓ dHb
  - **Net effect = ↓ in dHb:** *fresh oxygenated blood flushes out deoxygenated blood (dHB)*
  - ***MR signal increases***
- **This is BOLD in simplest terms**

6

Review of BOLD fMRI

1. External stimulus increases neural activity
2. $CMRO_2$ increases slightly, resulting in a transient *increase* in dHb, and a transient *decrease* in BOLD

Fast response: ↑ in $CMRO_2$ →
↑ dHb content → ↓ BOLD signal!

7

Review of BOLD fMRI

1. External stimulus increases neural activity
2. $CMRO_2$ increases slightly, resulting in a transient *increase* in dHb, and a transient *decrease* in BOLD
3. CBF begins to increase substantially, delivering more HbO2
4. HbO2 (now abundant) displaces dHb; BOLD signal increases

Slow response: ↑↑ CBF → ↓↓ dHb → ↑↑ BOLD signal!

8

Review of BOLD fMRI

- Thought question: *Ignoring timing, what if CBF and $CMRO_2$ both increased by the same percent? Would we see much of a BOLD effect?*
- Probably not; the increased dHb content (via oxygen removal from HbO_2 via metabolism) would be exactly compensated by fresh HbO_2 brought in by CBF
- dHb/HbO_2 ratio and thus dHb content would not appreciably change*

9

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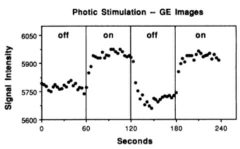
10

BOLD Response

- Recall first fMRI study



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11

BOLD Response

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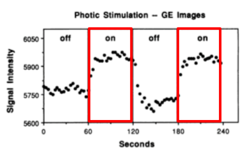

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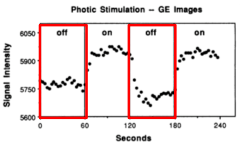
- Experiment involved using a long duration visual stimulus (60 s), i.e. the “on” period

12

BOLD Response

- Recall first fMRI study



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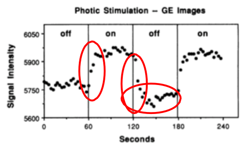
Kwong, K K, et al. "Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation." *PNAS* 89, no. 12 (1992): 5675-5679. Copyright © 1992, National Academy of Sciences, U.S.A.

- Experiment involved using a long duration visual stimulus (60 s), i.e. the "on" period
- Interleaved with long "off" periods (60 s)

13

BOLD review

- Even earliest study revealed some characterisc features of the BOLD response:



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Kwong, K K, et al. "Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation." *PNAS* 89, no. 12 (1992): 5675-5679. Copyright (c) 1992, National Academy of Sciences, U.S.A.

- *BOLD effect does not instantaneously follow stimulus*
- *There is a delay after stimulus onset and offset; undershoot after stimulus cessation*

14

BOLD: Epoch-related or blocked design

- This type of approach is known as a *blocked* or *epoch-related design*
- Sustained periods of stimulation produce sustained neural activity and a sustained BOLD response
- Employed by most early fMRI studies; provides a large response for maximal sensitivity

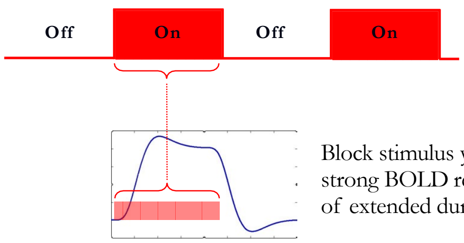
15

BOLD: Epoch-related or blocked design

Block stimulus yields strong BOLD response of extended duration

16

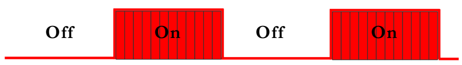
BOLD: Epoch-related or blocked design



Block stimulus yields strong BOLD response of extended duration

17

BOLD: Epoch-related → Event-related



"On" period can also be thought of as being composed of many individual repeating *events*, clustered together

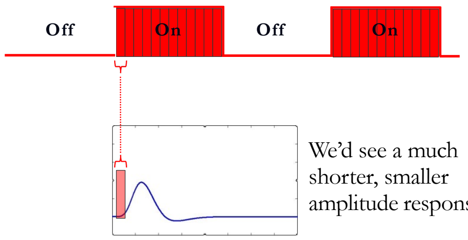
18

BOLD: Epoch-related → Event-related

Looking at the BOLD response from a *single* event …

19

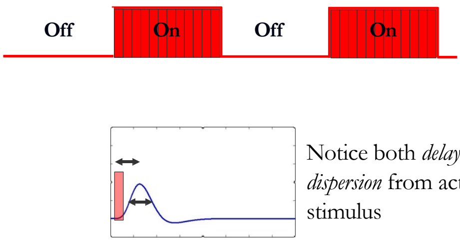
BOLD: Epoch-related → Event-related



We'd see a much shorter, smaller amplitude response

20

BOLD: Epoch-related → Event-related

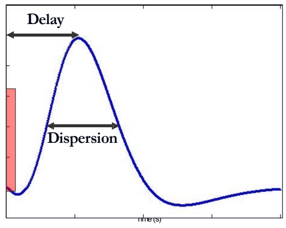


Notice both *delay* and *dispersion* from actual stimulus

21

BOLD: Event-related

- BOLD response to event is known as the *impulse response* or *hemodynamic response*

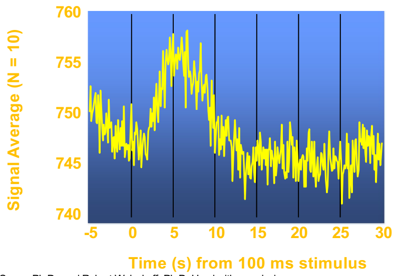


- Many implications for fMRI design and analysis

22

BOLD: Event-related

- Experimentally measuring the hemodynamic response requires averaging to reduce noise



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23

BOLD: Events and Epochs

- "*Event*" refers to a short-duration stimulus producing a *brief burst* of neural activity
- *"Epoch"* refers a block of consecutive events, clustered into "on" periods, interleaved with "off" periods, producing *sustained* neural activity

24

Overview

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25

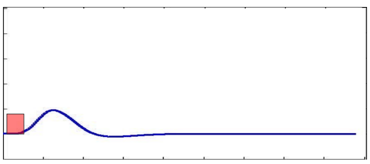
Linearity of BOLD hemodynamic response

- It has been shown that the BOLD hemodynamic response is roughly linear
- *Scaling* and *superposition* hold
- Scaling states that the output of a linear system is proportional to magnitude of its input
- Superposition states that the output of a linear system with more than one input is the sum of the responses to the individual inputs

26

Linearity of BOLD response

- *Scaling* property can be demonstrated by
  - Increasing stimulus intensity



27

Linearity of BOLD response

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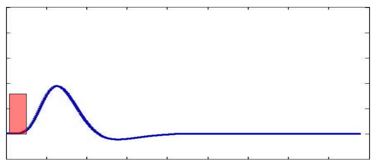

28

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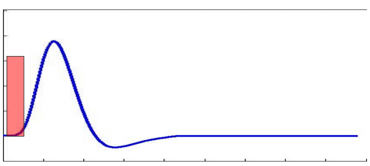
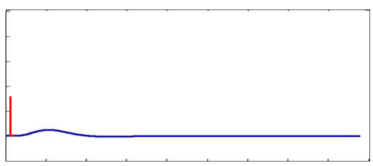


29

Linearity of BOLD response

- *Scaling* property can be demonstrated by
  - Doubling stimulus intensity
  - Doubling stimulus duration



30

Linearity of BOLD response

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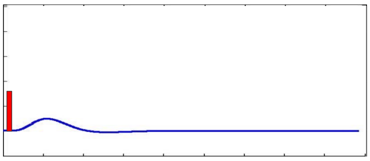

31

Linearity of BOLD response

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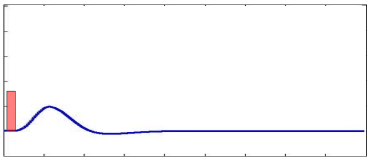
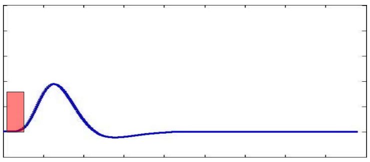


32

Linearity of BOLD response

- *Superposition* can be demonstrated by adding additional events at points in time
- Responses sum with appropriate lag



33

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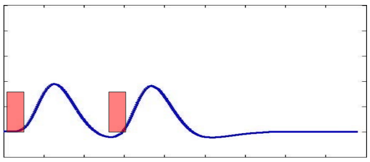

34

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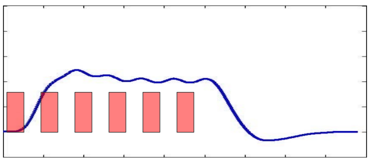

35

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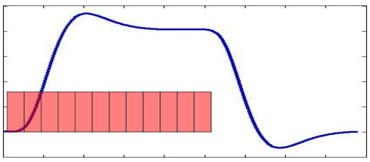
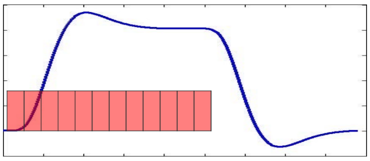


36

Linearity of BOLD response

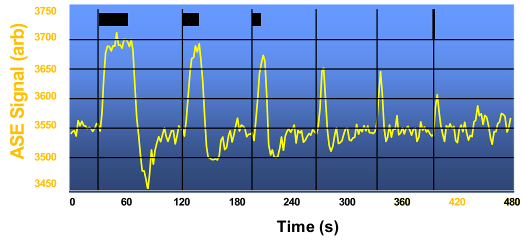
- Blocked design increase response amplitude significantly



37

Linearity of BOLD response

- In reality, signal response to short stimuli can be lost in noise



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38

Overview

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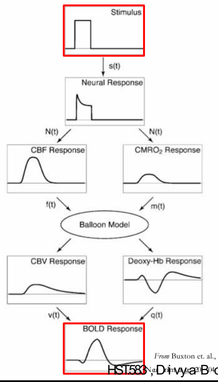
39

Modeling the BOLD response

- Response arises from a culmination of different physiological responses secondary to stimulus
- The nature of these response and how they are linked is an active area of research



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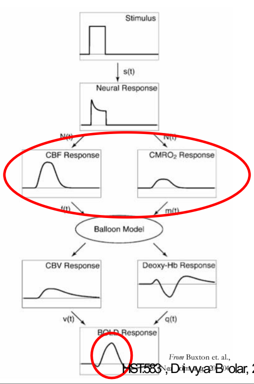
From Buxton et. al.,

HST.583: Divya Bolar, 2008

40

Modeling the BOLD response

- We have discussed the CBF/ $CMRO_2$ relationship
- Several competing hypotheses; difficult to test because imaging $CMRO_2$ difficult with MRI
- *Mismatch remains one of the most fundamental questions of functional neuroimaging*



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41

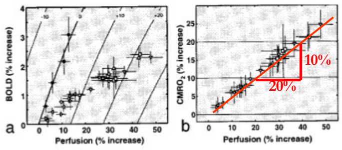
Why is increase in CBF so much larger than increase in $CMRO_2$?

1. Uncoupling between CBF and $CMRO_2$?
2. Coarse spatial control of CBF?
3. Oxygen limitation model?
4. Astrocyte-Neuron Lactate Shuttle Model?
5. Hemoneural hypothesis?
6. Other ideas?

42

1. Uncoupling between CBF and $CMRO_2$?

- **Hoge et. Al showed a strong linear relationship between CBF and $CMRO_2$**



Source: Hoge, R., et al. "Linear coupling between cerebral blood flow and oxygen consumption in activated human cortex." *PNAS* 96 no. 16 (August 3, 1999): 9403-9408.

- Graded hypercapnia was used to define isocontours of $CMRO_2$; graded visual stimulus experiments could be then used explore $CMRO_2$/ CBF relationship*
- Still doesn't explain why a much larger CBF change is *needed*; i.e. Rick's data shows a 2x increase in CBF versus $CMRO_2$!

43

2. Coarse spatial control of CBF?

- Malonek & Grinvald suggested that in fact a matching increase in oxygen delivery *is* required to support the small increase in $CMRO_2$ (oxygen consumption)
- However, vascular response is not precise enough to delivery CBF to *only* the region with increased $CMRO_2$
- Can only deliver CBF to a *larger containing area*, and thus a much larger than necessary response is required
- *"Watering the garden, for the sake of the thirsty flower"*

44

2. Coarse spatial control of CBF?

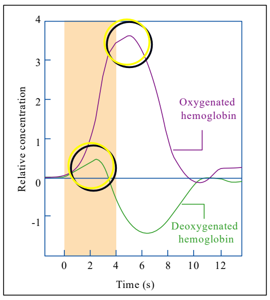


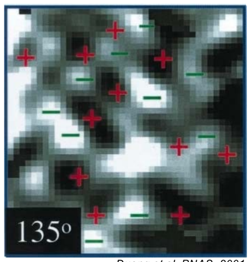
Figure by MIT OpenCourseWare.

After Malonek & Grinvald, Science, 1996

- In other words, Malonek and Grinvald asserted that CBF is controlled on a *coarse* spatial scale, while areas of increased $CMRO_2$ occur on a *fine* spatial scale
- Using optical techniques found that initial *transient rise* in dHb mapped to fine columnar structure of visual cortex
- Suggested that increased dHb correlates to increased $CMRO_2$ oxygen metabolism ***before*** CBF increase
- The spatial map of HbO_2 (i.e. the effect behind BOLD) did *not* reveal columnar structure, suggesting only coarse control

45

2. Coarse spatial control of CBF?



Duong et al, PNAS, 2001

 Source: Duong, T. Q. "Localized cerebral blood flow response at submillimeter columnar resolution." *PNAS* 98, no. 19 (September 11, 2001):10904-10909.

- Duong and colleagues used CBF-mapping MRI (ASL) to delineate orientation columns in cat visual cortex
- Suggested that hemodynamic-based fMRI could indeed be used to individual functional columns
- *Non-BOLD approach; eliminates venous large-vessel contribution*

46

2. Coarse spatial control of CBF?

- In addition to Duong, several studies of provide contradictory evidence to Malonek & Grinvald theory
- Woolsey & Rovainen, 1991, rat barrel cortex.
- *However*, these specialized cortices (i.e. visual and barrel) may be unique cases; brain in general may not have such fine spatial control of blood flow
- *If Malonek and Grinvald are correct, what does this imply about spatial resolution of BOLD imaging??*
- ***Suggests limit of BOLD fMRI spatial resolution is physiological, not technological!***

47

3. Oxygen limitation model?

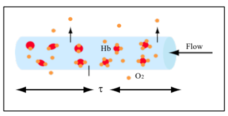


Figure by MIT OpenCourseWare.

Buxton & Frank, JCFMB, 1997
Buxton, Intro to fMRI, Cambridge 2002

- Assume O_2 extraction is limited at rest and CBF increases by increasing blood velocity (*not* by recruitment)

48

3. Oxygen limitation model?

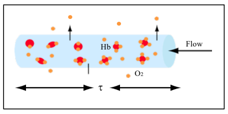


Figure by MIT OpenCourseWare.

ACTIVATION:
Increased capillary velocity
Reduced transit time
Decreased oxygen extraction

Buxton & Frank, JCFMB, 1997
Buxton, Intro to fMRI, Cambridge 2002

- Assume O_2 extraction is limited at rest and CBF increases by increasing blood velocity (*not* by recruitment)
- An increase in CBF will decreases capillary transit time
- A decrease in capillary transmit time will decrease O_2 extraction
- Results in nonlinear relationship between CBF and OEF
- Consistent with following equation: $CMRO_2 \propto OEF \cdot CBF$
- **Thus, a large increase in CBF is required to sustain a modest increase in $CMRO_2$!**

49

4. Astrocyte-Neuron Lactate Shuttle?

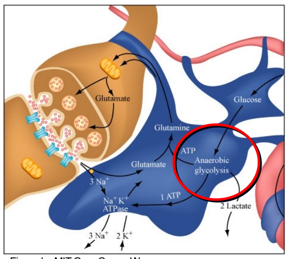


Figure by MIT OpenCourseWare.
After Huttel et al, *fRMI*, 2002.

After Magestretti et al, Science, 1999.

- Posits that initial increase in neuronal activity is followed by an immediate increase in *anaerobic respiration* (since it can respond faster)
- This suggests an ***initial uncoupling*** between CBF and $CMRO_2$; anaerobic respiration does not use O_2, so initial increase in $CMRO_2$ is small
- Using extended duration stimuli Mintun and colleagues have shown that $CMRO_2$ actually *increases* over time, perhaps ***recoupling*** with CBF
- ***Perhaps fast anaerobic response for immediate ATP demands, then slow aerobic response to sustain ATP demands***

50

5. Hemoneural hypothesis?

- While the increase in CBF is excessive from a metabolic standpoint, it may be appropriate if interpreted as having activity-dependent neuro-modulatory functions
- Authors posit that hemodynamics may impact neural activity through direct and indirect mechanisms

51

6. Other ideas (have any?!)

52

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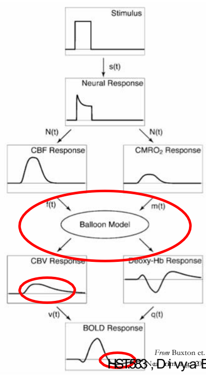
53

Modeling the BOLD signal

- Another key feature of the BOLD response is the *post-stimulus undershoot (PSU)*
- Until recently, two similar CBV models (i.e. the "balloon model" or "delayed venous compliance" model) were broadly accepted



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From Buxton et. al., NeuroImage, 2004

HST.583, Divya Bolar, 2008

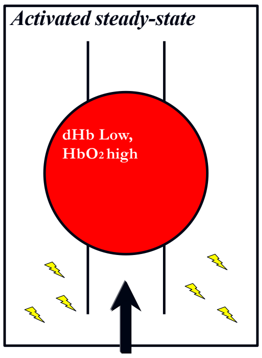
54

Balloon / Delayed Venous Compliance (DVC) Model

- Veins are compliant and distend in response to increased blood flow
- Distention leads to increased venous CBV, but CBV response lags CBF response
  - CBF returns to baseline quickly; thereby stops HbO_2 delivery and dHb flushing
  - dHb *concentration* starts returning to baseline
  - CBV_{venous} is still elevated, so *total* dHb *content* (content = $CBV_{venous}\cdot$[dHb]) is *increased* compared to baseline
- ***BOLD signal transiently decreases following stimulus cessation***

55

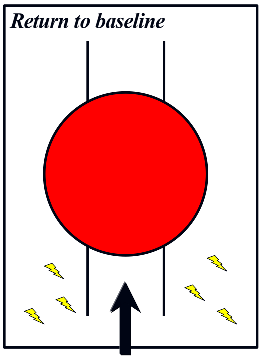
Balloon/DVC Model



1. During activation both CBF and CBV are elevated; dHb is **low**

56

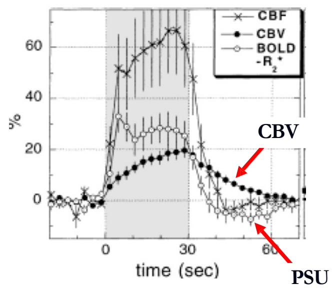
Balloon/DVC Model



1. During activation both CBF and CBV are elevated; dHb is **low**
2. After activation ceases, CBF returns to baseline quickly; [dHb] returns towards baseline
3. CBV takes much longer to return to baseline
4. Total dHb *content* increases; signal falls

57

Balloon/DVC Model



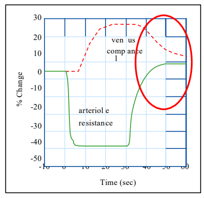


Figure by MIT OpenCourseWare. After Mandeville et al, JCBFM, 1999.

58

PSU: *Not* a volume effect!?

- New evidence suggests post-stimulus undershoot is NOT caused by elevated CBV (not biomechanical)

The post-stimulation undershoot in BOLD fMRI of human brain is not caused by elevated cerebral blood volume

Jens Frahm,[a,*] Jürgen Baudewig,[b] Kai Kallenberg,[b,c] Andreas Kastrup,[d] K. Dietmar Merboldt,[a] and Peter Dechent[b]

Another example of being on the edge of 50% right/ wrong!

59

PSU: Uncoupling of $CMRO_2$ and CBF?

- CBF returns to baseline quickly after stimulus ends, but $CMRO_2$ stays elevated.
- Oxygen consumption/ dHb production) > Oxygen delivery/ dHb removal)
- Net result: more dHb leading to transient decrease in BOLD signal
- Schroeter (NIRS), Frahm, Van Zijl (VASO), Devor

60

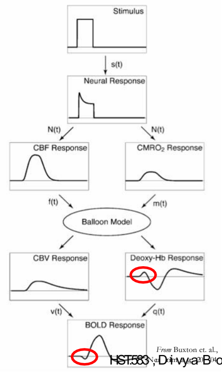
Overview

- BOLD review
- BOLD response to *blocks* and *events*
- Linearity of BOLD response
- Modeling the BOLD signal
  - Main response
  - Post-stimulus undershoot
  - Initial Dip

61

Modeling the BOLD signal

- An important, but controversial feature of the BOLD response is the *initial* or *early dip*.
- Initial *increase* in dHb content, leading to initial *decrease* in BOLD
- Many groups do not see initial dip, but this may be due to decreased sensitivity at lower fields
- *As imaging hardware improves, the initial dip may become an important indicator of activation*



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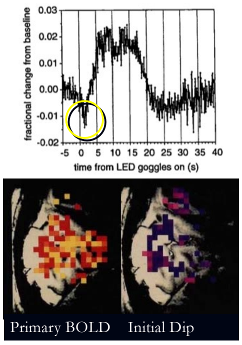
HST.583: Divya Bolar, 2008

62

The Initial or Early Dip

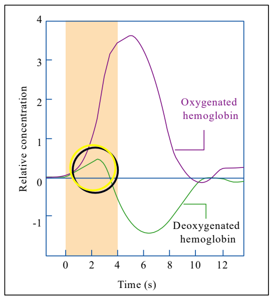


- Menon & colleagues reported first BOLD fMRI study at 4T
- Initial dip appeared more tightly correlated to cortical neurons than primary response
- Like Malonek & Grinvald, suggested that early surge in dHb was due to a fast increase in $CMRO_2$

Source: Menon, R.S. *MRM* 33, no. 3 (March 1995): 453-459.

63

The Initial or Early Dip



Malonek & Grinvald, Science, 1996

Figure by MIT OpenCourseWare.

- Menon & colleagues reported first BOLD fMRI study at 4T
- Initial dip appeared more tightly correlated to cortical neurons than primary response
- Like Malonek & Grinvald, suggested that early surge in dHb was due to a fast increase in $CMRO_2$

64

Summary: Some contributors to BOLD response

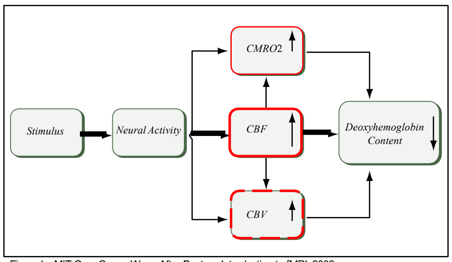


Figure by MIT OpenCourseWare. After Buxton, *Introduction to fMRI*, 2002.

65

Summary

- BOLD response to stimuli called hemodynamic response and is roughly linear
- Three main features of response: initial dip, primary positive response, and post-stimulus undershoot
- These features have different spatiotemporal properties, as they arise from different physiologic parameters

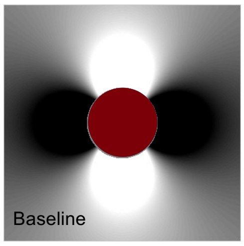
66

Part II

- BOLD Imaging II
  - Effects of diffusion on BOLD signal
  - Spatial source of BOLD signal contribution (extravascular versus intravascular)
  - BOLD sequence variants and parameters
- Beyond BOLD: State-of-the-art techniques to image activation physiology
  - CBF techniques (ASL)
  - CBV techniques (VASO)
  - Calibrated BOLD/ rel $CMRO_2$ techniques

67

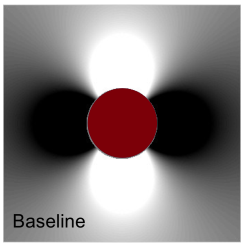
Physics of BOLD



The magnetic field within and surrounding the vessel is perturbed by paramagnetic dHb

68

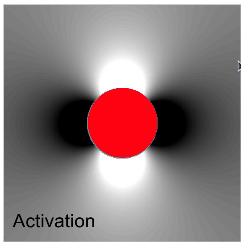
Physics of BOLD



At baseline, late capillary and post-capillary venular blood is substantially deoxygenated (SaO_2 = 60%) and contains dHb

69

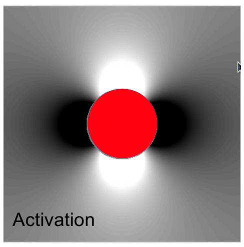
Physics of BOLD



During activation, CBF increases substantially and flushes out dHb. Late capillary and post-capillary venular blood become *more* oxygenated (SaO_2 = 80%)

70

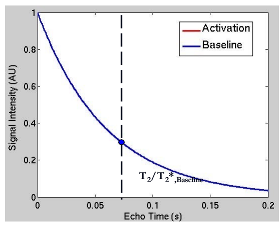
Physics of BOLD



The magnetic field perturbation is substantially attenuated, since there is less paramagnetic dHb

71

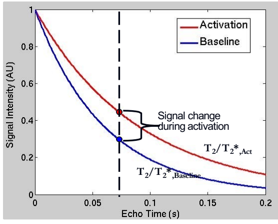
Physics of BOLD



BOLD fMRI involves acquiring data at a certain echo time (TE). At baseline the strong magnetic field perturbations lead to decreased T_2/T_2^*

72

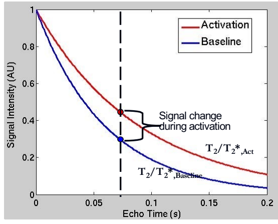
Physics of BOLD



During activation, T2/T2* *increases* due to less dHb. By choosing an optimal TE, this change can be exploited, leading to increased signal

73

Physics of BOLD



But from where do these changes originate??

74

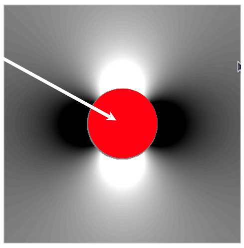
Spatial Origin of BOLD

- MRI signal predominantly comes from protons in water
- BOLD signal changes arises from magnetic field perturbations caused by dHb in red blood cells
- Magnetic field gradients are created around:
  - Individual RBCs containing dHb
  - Blood vessels carrying deoxygenated RBC's

75

Spatial Origin of BOLD

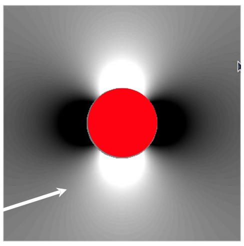
- Water protons *within* vessels are affected by strong fields around RBCs, leading to an *intravascular* BOLD effect



76

Spatial Origin of BOLD

- Water protons *within* vessels are affected by strong fields around RBCs, leading to an *intravascular* BOLD effect
- Water protons *around* vessels (i.e. in *tissue)* are affected by field around vessel, leading to an *extravascular* BOLD effect



77

Spatial Origin of BOLD

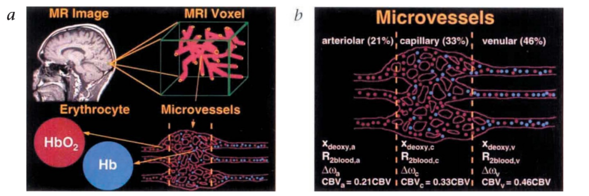


Fig. 1 The physiological origin of spin-echo fMRI signals. ***a***, In order to determine signal changes in an MRI voxel containing perfused tissue it is necessary to know its composition in terms of microvessels (arterioles, capillaries and venules) and tissue, as well as the oxygenation status of hemoglobin in each individual microvessel. The hemoglobin oxygenation status in the capillaries and veins is determined by the original arterial oxygenation level (Y_a) and the blood flow, oxygen metabolic rate and hematocrit in the particular perfused tissue [eqns. (4) and (5) in the text]. ***b***, The hemoglobin deoxygenation fraction $x_{deoxy,i}$ ($i \in a,c,v$) determines the local magnetic susceptibility shift differences ($\Delta\omega_i$) and spin-echo relaxation rates ($R_{2,blood,i}$) in the individual microvessels. These three blood relaxation rates are then combined with the tissue relaxation rate to determine the signal intensity in an MRI voxel. This is done by using the voxel composition (*b*) on the basis of microvessel and tissue morphometry data involving the individual microvessel blood volumes (CBV_i) and water densities for different tissues such as gray and white matter.

78

Extravascular BOLD effect

- Extravascular BOLD signal can be further subdivided into:
  - Effects around larg(er) vessels (late venules/ veins)
  - Effects around small microvessels (capillaries, early venules)
- ***Diffusion* heavily influences the degree of contribution**

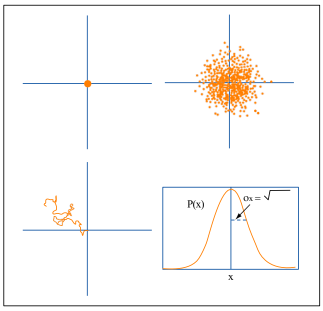
79

Diffusion and fMRI

- Due to thermal energy water molecules constantly experience random displacements
- This process is called diffusion
- Since most of the signal in MRI comes from protons in water, diffusion plays critical role in MR signal modulation

80

Basics of water diffusion



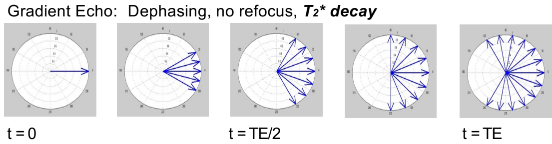
- Water molecules start from center
- Over time, these molecules spread out (*think ink*)
- Each molecule undergoes a *random walk*
- Mean of *all* molecule displacements is still zero
- Variance increases as a function of time

Figure by MIT OpenCourseWare. After Buxton, *Introduction to fMRI*, 2002.

81

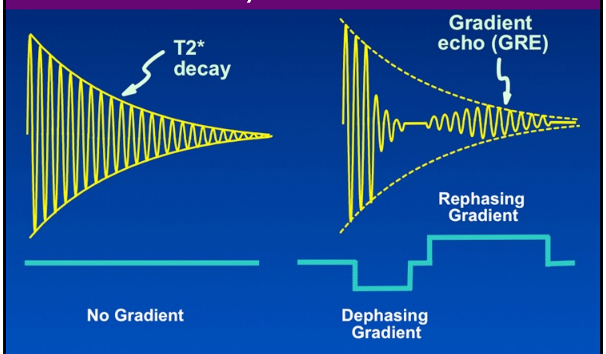
GRE/ SE Review

Gradient Echo: Dephasing, no refocus, ***T_2* decay***



82

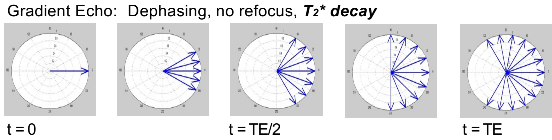
GRE/ SE Review



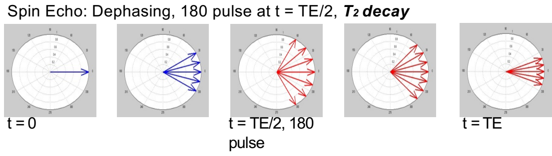
83

GRE/ SE Review

Gradient Echo: Dephasing, no refocus, ***T_2* decay***



Spin Echo: Dephasing, 180 pulse at t = TE/2, ***T_2 decay***

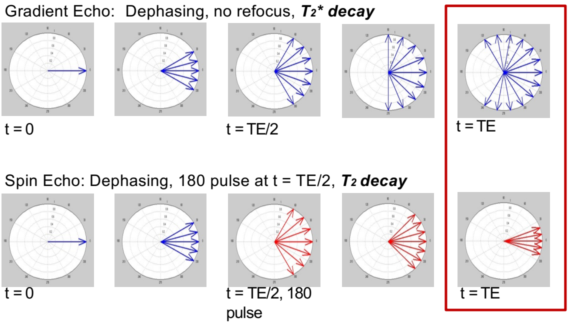


84

GRE/ SE Review

Gradient Echo: Dephasing, no refocus, T_2* *decay*

Spin Echo: Dephasing, 180 pulse at t = TE/2, T_2 *decay*



85

GRE/ SE Review

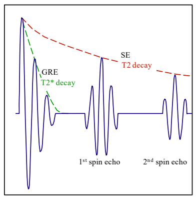


Figure by MIT OpenCourseWare.

- Because of dephasing, GRE decay (T_2*) is considerable

86

GRE/ SE Review

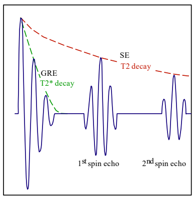
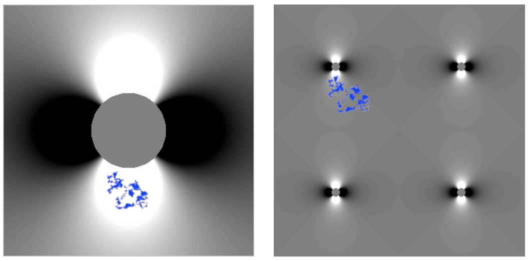


Figure by MIT OpenCourseWare.

- Because of dephasing, GRE decay (T_2*) is considerable
- Because of SE refocusing, some signal is recovered and decays with a T_2 time constant

87

Diffusion around vessels and the MR signal

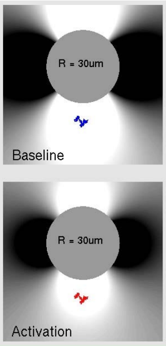


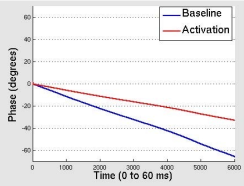
Large* Vessel (30 um) Small Vessels (3 um)

** Keep in mind "large" is a relative term here! 30 um is still quite small!!*

88

Diffusion around large vessels: GRE



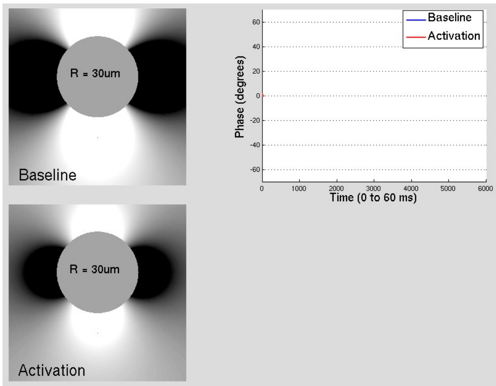


- Diffusion is small compared to venule or vein
- Water molecule therefore feels a relatively large, constant field
- Leads to *linear* phase accrual
- Magnitude of dephasing is large
- **Large change in GRE-BOLD via T_2*!**

Refer to supplemental animation of these diagrams and graph.

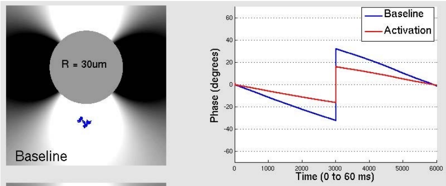
89

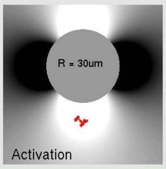
Diffusion around large vessels: GRE



90

Diffusion around large vessels: SE



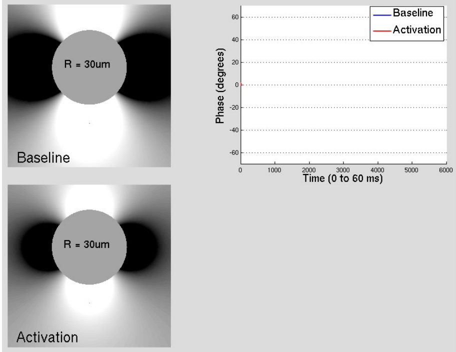


- In a spin echo sequence, a 180-pulse *inverts* spins to *refocus* linear phase accrual
- Dephasing is refocused; there is little change in T_2 during activation!!
- **There will be almost zero signal change around large vessels in SE-BOLD!**

Refer to supplemental animation of these diagrams and graph.

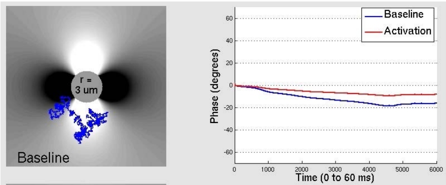
91

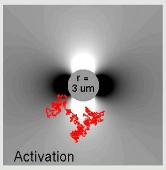
Diffusion around large vessels: SE



92

Diffusion around small vessels: GRE



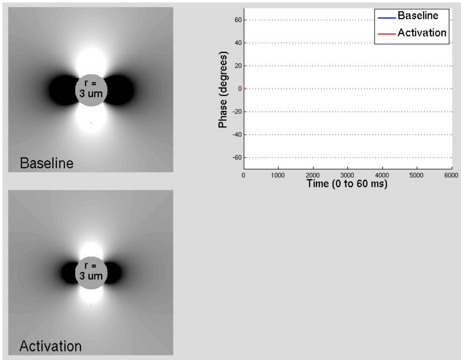


- Diffusion distance is larger or of comparable size to vessel
- Water molecules experience a range of field offsets
- The net phase experienced by a water molecule diffusing will reflect the average of these fields
- This reduces the phase dispersion of all diffusing spins
- The phase difference between activation and baseline is smaller than the large vessel situation
- **This results in a modest change in GRE-BOLD via T_2* effect**

Refer to supplemental animation of these diagrams and graph.

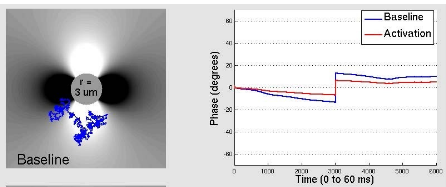
93

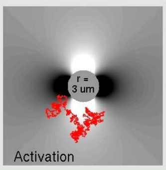
Diffusion around small vessels: GRE



94

Diffusion around small vessels: SE



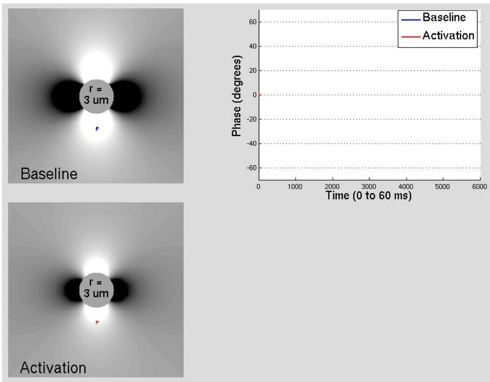


- Because of diffusion through a ***range*** of fields, a water molecule will see a ***different*** set of phase offsets in **first** and **second half** of echo time
- Phase offsets acquired during the first half will thus ***not*** be completely reversed by a spin echo
- There ends up being a net phase at TE, and a phase difference between the activated and inactivated state
- ***Activation changes T_2, resulting in a modest contribution to the total SE-BOLD signal***

Refer to supplemental animation of these diagrams and graph.

95

Diffusion around small vessels: SE



96

Extravascular Effect Summary

Around larger vessels
- Includes late venules and veins
- Diffusion size is much smaller than vessel diameter
- Water molecules feel large, constant field, leading to *static dephasing*
- Produces **large** T_2^* change and GRE-BOLD effect
- Static dephasing effects can be refocused via SE; T_2 change is **negligible**

Around smaller vessels
- Includes capillaries, early venules
- Diffusion size is on the order or slightly larger than vessel diameter
- Water molecules feel small, varying field, leading to *dynamic dephasing*
- Produces **modest** T_2^* change and GRE-BOLD effect
- Dynamic dephasing effects *cannot* be refocused via SE; therefore T_2 effects are also **modest**

97

GE versus SE BOLD

Gradient Echo BOLD
- Contrast based on changes in T_2^*
- Water molecules around large vessels contribute substantially
- Water molecules around small vessels contribute modestly
- ***Based on extravascular contribution alone, GRE-BOLD is weighted towards late venules and veins during activation***

Spin Echo BOLD
- Contrast based on changes in T_2
- Water molecules around large vessels have negligible contribution
- Water molecules around small vessels contribute modestly
- ***Based on extravascular contribution alone, SE-BOLD is weighted towards capillaries, early venules during activation***

98

Extrvascular Effects: GRE & SE BOLD

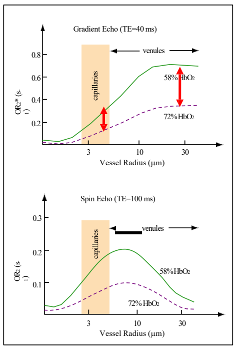


Figure by MIT OpenCourseWare, after Weisskoff, MRM (1994).

- GRE sensitizes us to T_2^* changes and thus weights us to larger vessels (although there is small vessel contribution)

99

Extrvascular Effects: GRE & SE BOLD

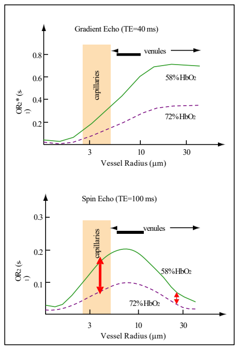


Figure by MIT OpenCourseWare, after Weisskoff, MRM (1994).

- GRE sensitizes us to T_2^* changes and thus weights us to larger vessels (although there is small vessel contribution)
- SE sensitizes us to T_2 changes and thus weights us to smaller microvessels (capillaries, early venules)

100

Extrvascular Effects: GRE & SE BOLD

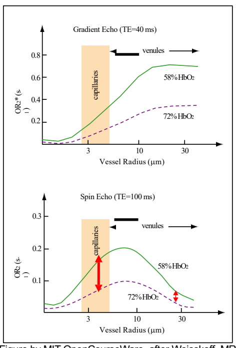
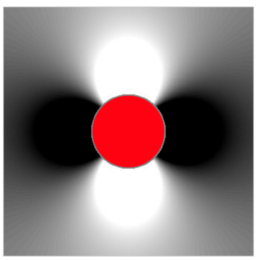


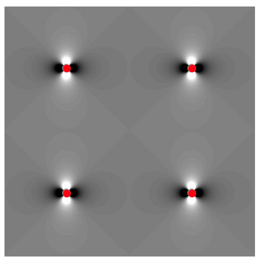
Figure by MIT OpenCourseWare, after Weisskoff, MRM (1994).

- GRE sensitizes us to T_2^* changes and thus weights us to larger vessels (although there is small vessel contribution)
- SE sensitizes us to T_2 changes and thus weights us to smaller microvessels (capillaries, early venules)
- ***Okay, but now what about intravascular contributions??***

101

Intravascular contribution


Large Vessel (30 um)


Small Vessels (3 um)

102

Intravascular Effects

- Despite small intravascular volume, intravascular signal contribution is *large*
- This is due to large gradient fields around RBCs containing dHb.
- T_2/T_2^* of *blood itself* changes during activation
- Intravascular signal contribution is comparable to extravascular contribution, despite the small volume fraction

103

GE versus SE BOLD

- Gradient Echo BOLD
- Contrast based on changes in T_2^*
- Water molecules around large vessels contribute substantially
- Water molecules around small vessels contribute modestly
- ***Intravascular water molecules contribute substantially!***

Spin Echo BOLD

- Contrast based on changes in T2
- Water molecules around large vessels have negligible contribution
- Water molecules around small vessels contribute modestly
- ***Intravascular water molecules contribute substantially!***
  - *Dynamic dephasing effects cannot be refocused!*

104

Spatial specificity to neuronal activity?

- Small microvessels (capillaries, early venules) are more likely to co-localize with neuronal activity
- Signal changes around larger vessels (late venules, veins) may be artifactual; i.e. may be well downstream of true neuronal activity
- So-called ***"Brain versus Vein"*** problem of BOLD imaging
- Possible ways to reduce large vessel contribution?

105

Spatial specificity of large and small vessels

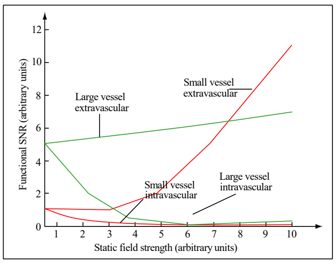


Figure by MIT OpenCourseWare. After Huttel et al, *fRMI*, 2004.

Functional Sensitivity versus Field Strength

106

Spatial specificity of large and small vessels

from Huettel, Song, &, McCarthy, Functional MRI, Sinauer, 2004

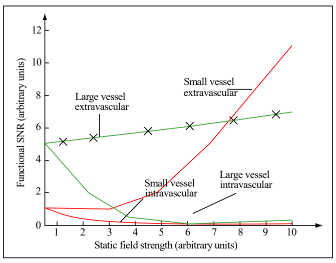


Figure by MIT OpenCourseWare. After Huttel et al, *fRMI*, 2004.

Functional Sensitivity versus Field Strength

- SE-BOLD can substantially reduce large vessel *extravascular* contribution

107

Spatial specificity of large and small vessels

from Huettel, Song, &, McCarthy, Functional MRI, Sinauer, 2004

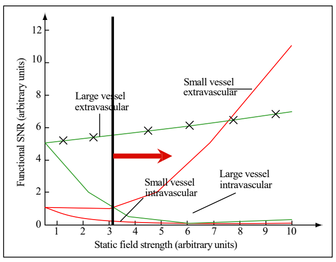


Figure by MIT OpenCourseWare. After Huttel et al, *fRMI*, 2004.

Functional Sensitivity versus Field Strength

- SE-BOLD can substantially reduce large vessel *extravascular* contribution
- T_2/T_2^* of blood both decrease significantly with increasing field; can reduce large vessel *intravascular* contribution

108

Spatial specificity of large and small vessels

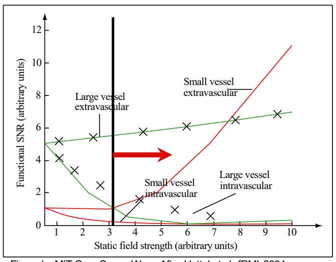


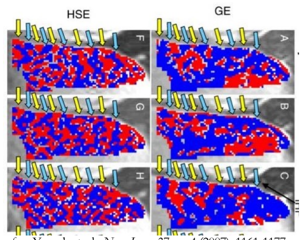
Figure by MIT OpenCourseWare. After Huttel et al, *fRMI*, 2004.

Functional Sensitivity versus Field Strength

- SE-BOLD can substantially reduce large vessel *extravascular* contribution
- T_2/T_2^* of blood both decrease significantly with increasing field; can reduce large vessel *intravascular* contribution
- Can also employ modest diffusion weighting* to eliminate large vessel *intravascular* signal

109

Spatial specificity of large and small vessels



from Yacoub et. al., *NeuroImage* 37 no. 4 (2007): 1161-1177.

Courtesy Elsevier, Inc., http://www.sciencedirect.com. Used with permission.

- SE-BOLD at 7T show robust detection of ocular dominance columns
- Superior to GE-BOLD, which was not able to resolve columns

110

Pulse sequences

- GRE-EPI (*EPI = echo planar imaging = fast*)
  - Most commonly used at 1.5T, 3.0T
  - Provides large signal changes; very sensitive to activation
  - Large vessel artifacts (*brain versus vein* problem)

111

Pulse sequences

- SE-EPI
  - Will attenuate large vessel extravascular signal, but at 1.5T/3.0T large vessel *intravascular* signal will become dominant
  - Lose SNR with SE due to refocusing and longer TE
  - ***May be ideal at 7T and above***
    - T_2/T_2^* blood shortens: intravascular effect will be substantially reduced
    - SNR increases linearly with field strength
  - Reduces distortions! If imaging frontal lobe, this may be worth considering

112

Pulse sequences

- Diffusion-weighted GRE-EPI
  - Will reduce large vessel intravascular effects, but will be prone to large vessel extravascular effects
- Diffusion-weighted SE-EPI
  - Will reduce large vessel intravascular and extravascular effects
  - Will lose considerable sensitivity; longer TE
  - May be possible at 1.5T/3.0T in targeting small vessel intravascular and extravascular effects

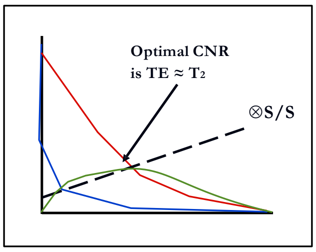
113

Pulse sequences

- Spiral Imaging
  - As fast (or faster) than EPI, but not prone to distortions
  - Non-trivial image reconstruction
- HASTE, FLASH, TSE, etc.
  - Used for very high resolution imaging, but speed is sacrificed
  - Typically not amenable to whole cortex/ brain coverage (~20-30 slices) with short TR
  - If specific region-of-interest eliminates necessity for whole brain acquisition, these approaches may be useful

114

BOLD Acquisition Parameters: TE choice



- Optimal CNR is a trade off between SNR and relative signal change (⊗ S/S)
- This ends up being close to TE=T_2, but not exactly
- There are many other factors that come into play, e.g. distortion, motion, etc.

115

BOLD Acquisition Parameters: TE choice

- Optimal GE-BOLD TE:
  - 50 – 60 ms at 1.5T
  - 45 ms at 3.0T
    - Fera et. Al (2004), JMRI 19, 19-26
- Optimal SE-BOLD TE:
  - 74 ms at 3T
  - 45 ms at 7T
    - Schafer, MAGMA
- Both empirically determined; not set in stone!

116

Example Acquisition Parameters for BOLD

- *Sensitivity* increases with larger voxels
- *Specificity* decreases with larger voxels
  - There is a limit of course; specificity is ultimately limited by spatial coarseness of hemodynamic response
- Typical parameters at 3T:
  - 24 slices, 64x64 matrix, voxel size = 3.5x3.5x3.5 mm^3, BW = 2998 Hz, TE = 40 ms, TR = 2000 ms
- Take that with a grain of salt! It all depends on the question *you* want to ask! Will explore this more during Experimental Design Block

117

Part 2:
Beyond BOLD: Novel techniques for imaging activation

118

Why BOLD?

- Highest CNR and sensitivity compared to all other functional MRI techniques
- High temporal resolution (compared to speed of response)
- High spatial resolution possible, but not with standard approaches
- Feasible on nearly all MRI scanners (including clinical machines) without special hardware or software
- BOLD has been one of the largest success stories in the past decade!

119

Why *not* BOLD?

- As we've learned, there are fundamental spatial and temporal limitations in BOLD fMRI
- Temporal:
  - Considerable delay and dispersion after stimulus onset and cessation
  - Response lags stimulus and neuronal response by seconds
- Spatial:
  - BOLD not exclusively sensitive to microvasculature; difficult to separate larger vein effects (*brain versus vein*).
  - Fundamental limitation of hemodynamic response; *watering garden* analogy…

120

Why *not* BOLD?

- Remember that BOLD is a *relative* technique; moreover, it is not a real physiological parameter
- No direct knowledge of any absolute physiological parameters like CBF, CBV, $CMRO_2$, etc.
- BOLD relative change often depends on baseline state, which can vary from scan to scan, person to person
- Results can be highly variable
  - Same person, same task, different day: different results
  - Can lose statistical power over course of study

121

Novel approaches

- CBF: Arterial Spin Labeling
- Calibrated BOLD (relative $CMRO_2$)
- CBV: Vascular Space Occupancy

122

Arterial Spin Labeling (ASL)

- Non-contrast MR technique used to image CBF directly, i.e. tissue perfusion (microvascular flow)
- Involves creating a “magnetic” bolus by using RF energy to invert proton spins of water in arterial blood
- Inverted spins act as an endogenous contrast agent
- Imaging spins as they traverse the vascular tree generates perfusion maps
- *CBF quantification in absolute units, ml/ (mg-min)*

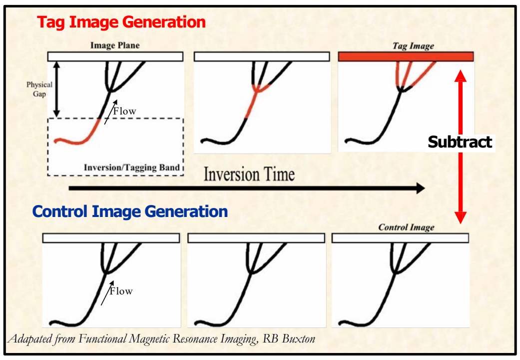
123

ASL: Advantages over BOLD

- More stable than BOLD time course signal
- *Absolute* technique; can quantify absolute CBF; calibrate changes with baseline CBF
- Is sensitive to arterial/ capillary flow; should be more tightly localized to site of neuronal activity
- Ideal for longitudinal studies
- Simultaneous BOLD/ ASL; BOLD is free!
- CBF is a fundamental, clinically meaningful physiological parameter

124

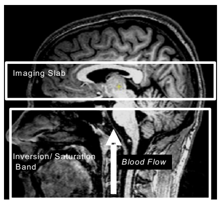
ASL: General Pulsed Approach

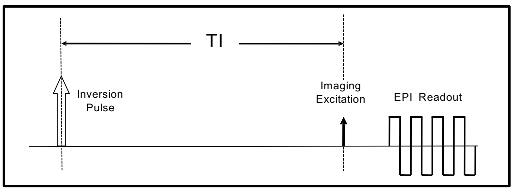


Adapated from Functional Magnetic Resonance Imaging, RB Buxton

125

Pulsed ASL Anatomical Diagram & Pulse Sequence Timing





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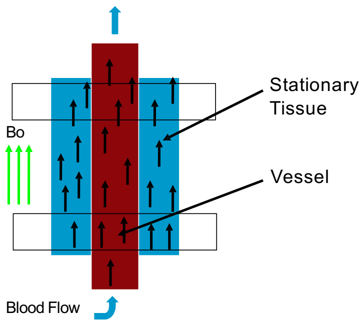

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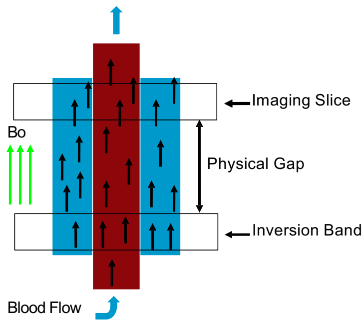

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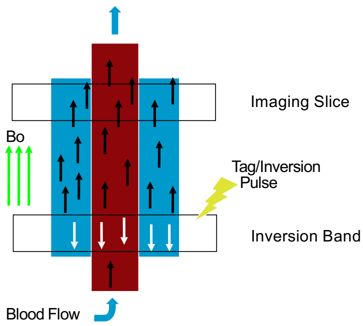

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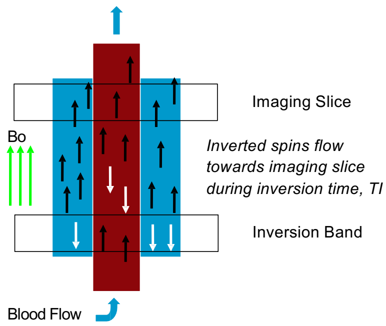

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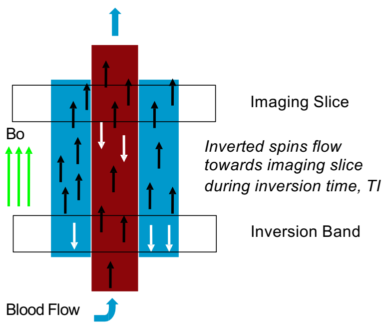

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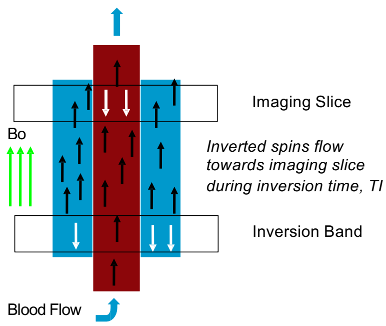

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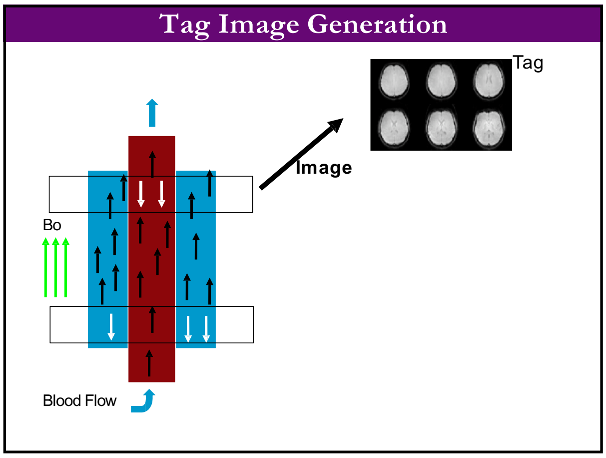

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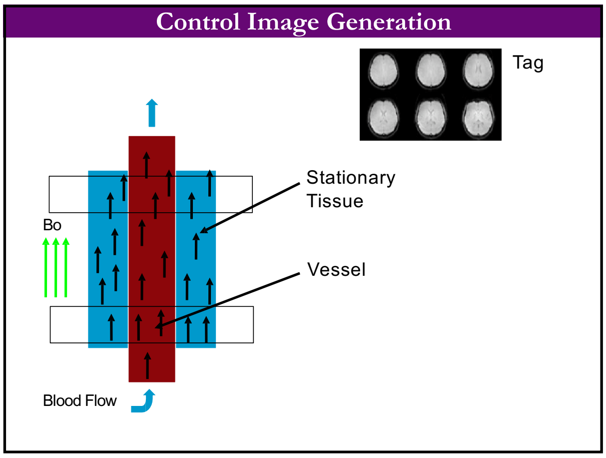

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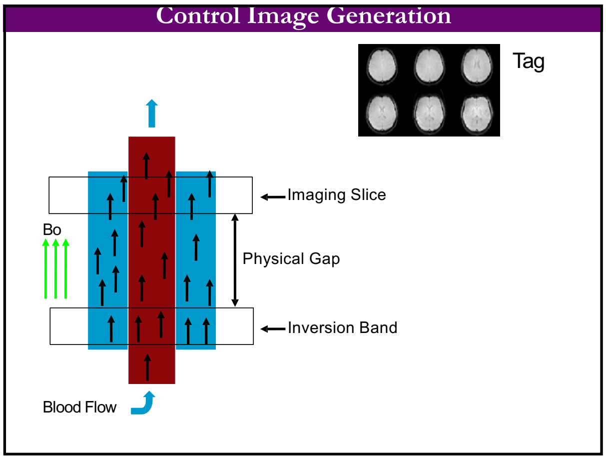

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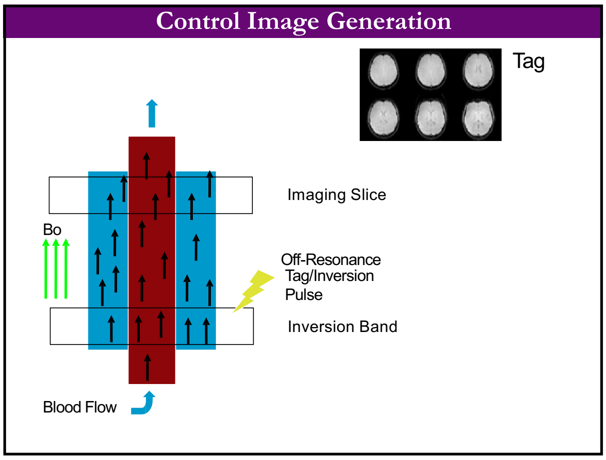

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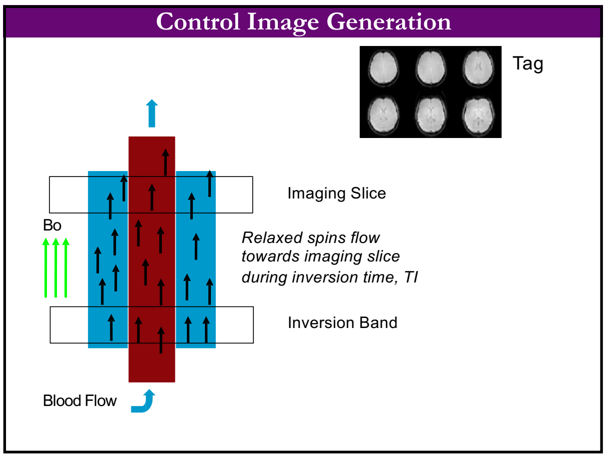

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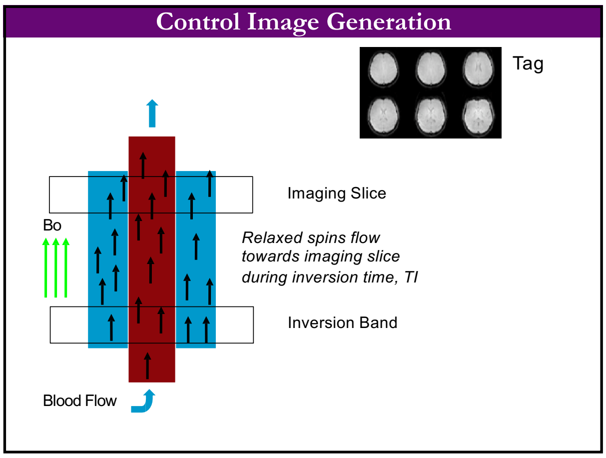

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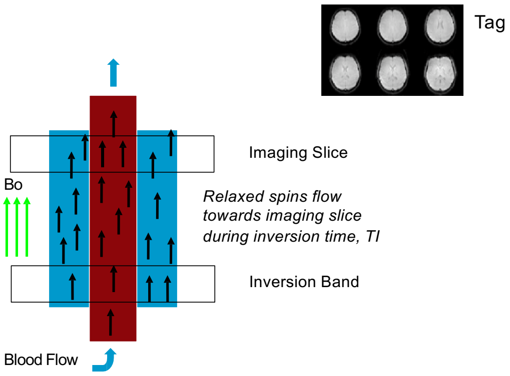
Control Image Generation



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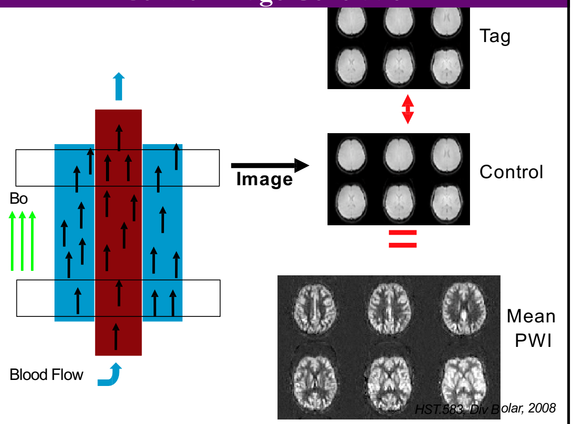
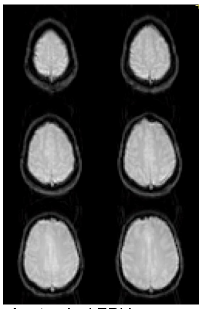
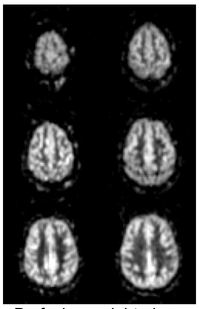


140

ASL: EPI & Perfusion Images


Anatomical EPI images


Perfusion-weighted images (averaged and smoothed)

141

ASL: CBF Quantification

- CBF is calculated by simply dividing the volume of inverted spins delivered (V_{ASL}) , by the delivery time (|)*
- Volume of spins delivered (V_{ASL}) proportional to perfusion map signal intensity
- Delivery time (|) equal to inversion time, TI
- An additional 10 sec calibration scan is required for final conversion of SI in arbitrary units to CBF in ml/(g of tissue – min)

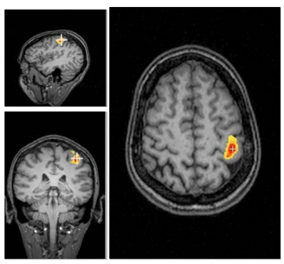
142

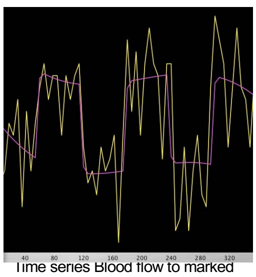
Limitations of ASL

- Low signal-to-noise ratio (SNR); activation change is ~1% of total signal (versus BOLD which is 3-5%)
  - Perfusion map from single-subtraction takes ~4 seconds; mean perfusion map requires ~6 min (90 averages)
  - Limited to low-resolution and few-slice acquisitions
  - ***Considerably less sensitive than BOLD!***
- Tricky technique! Requires careful parameter optimization

143

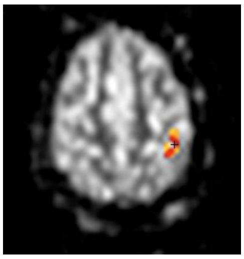
ASL: Motor Cortex Activation


Overlay on anatomical T1-weighted image – Primary Motor Cortex –

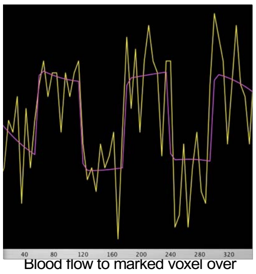

Time series Blood flow to marked voxel over time

144

ASL: Motor Cortex Activation



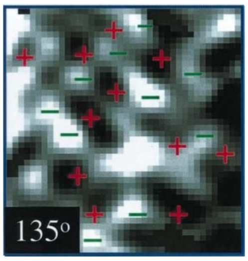
Overlay on perfusion-weighted image



Blood flow to marked voxel over time

145

ASL: Highly specific to activation



- Duong and colleagues used CBF-mapping MRI (ASL) to delineate orientation columns in cat visual cortex
- Showed that hemodynamic-based fMRI could indeed be used to individual functional columns
- ASL not prone to BOLD venous large-vessel contribution

146

ASL: Summary

- Becoming a popular addition to BOLD, especially as imaging hardware improves (and alleviates SNR limitations)
- Can be done simultaneously with BOLD, to *calibrate* BOLD signal
- Major MR scanner manufacturers now offer ASL as a produce sequence

147

Calibrated BOLD

- Use BOLD-ASL to calculate *relative CMRO2* changes during activation (Davis, PNAS, 1998, Hoge, PNAS/MRM, 1999)
- Based on the derivable equation:

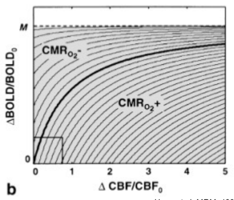
$$\frac{CMR_{O_2}}{CMR_{O_2}|_0} = \left(1 - \frac{\left(\frac{\Delta BOLD}{BOLD_0}\right)}{M}\right)^{1/\beta} \left(\frac{CBF}{CBF_0}\right)^{1-\alpha/\beta}$$

- If we know relative change in BOLD and CBF, we can compute relative change in $CMRO_2$
- Assume alpha, beta, need to calculate ***M***

148

Calibrated BOLD

- ***M*** represents the maximum possible BOLD change



Hoge et al, MRM, 1999

- At the limit, CBF will increase so much that *ALL dHb gets washed out!* ***Beyond this point, any additional increase in CBF will not change dHb content or BOLD signal!***

149

Calibrated BOLD

- To calculate ***M*** from CBF and BOLD, we need to make relative $CMRO_2$ change *zero*

$$\frac{\Delta BOLD}{BOLD_0} = M\left(1 - \cancel{\left(\frac{CMR_{O_2}}{CMR_{O_2}|_0}\right)^{\beta}} \left(\frac{CBF}{CBF_0}\right)^{\alpha-\beta}\right).$$

- We can do this by inducing ***hypercapnia***; i.e. inhalation of CO_2 causes CBF/ BOLD change via vasodilation, but no $CMRO_2$ change*

150

Summary: Calibrated BOLD

- Theoretically, only one grade of hypercapnia is needed to define ***M***, $CMRO_2$ isocontours
- Even without hypercapnia, can simply assume ***M***
- Using coupling index (n) as actvation measure may reduce intrasubject and intersubject variability of BOLD/CBF signal
  - For example, given the same task in different sessions, the calibrated change will be less variable
  - Could increase power of your study (i.e. via group statistics, etc.)

151

Acquisition Options

- Field of view / Matrix size / Resolution
- Slice orientation
- Echo time (TE)
- Bandwidth (Readout Speed)
- Parallel Imaging (PAT factor)
- Repetition time (TR)
- Number of repetitions
- Field-map

Signal dropout

Image distortion

BOLD sensitivity

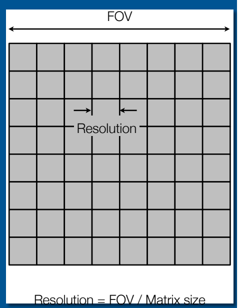
Signal-to-noise ratio (SNR)

152

Image Resolution

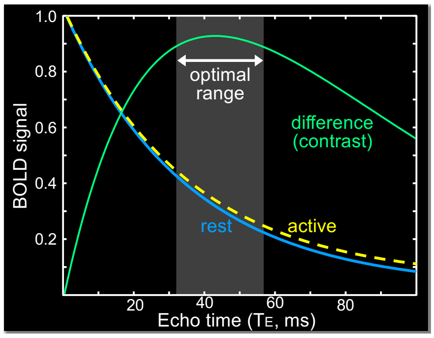
44

- SNR increases with voxel size
  - Bigger voxels → Higher SNR
- Increasing matrix size
  - Higher resolution, but increases imaging time
- Reducing field-of-view can cause wrap-around artefacts



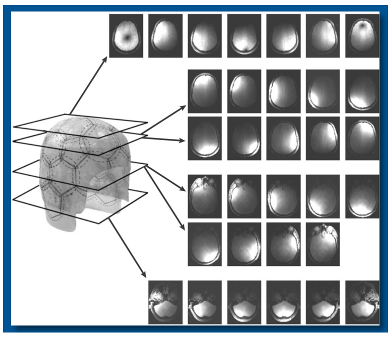
153

Optimal BOLD Echo Time



154

- Parallel Imaging (PAT factor)

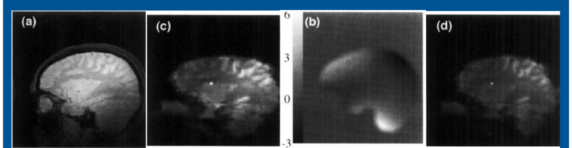


155

Removing Distortion

42

- Reduce imaging time by:
  - Reducing matrix size (resolution or field-of-view)
  - Increasing bandwidth (at the cost of reduced SNR)
  - Using parallel imaging to accelerate (adds noise)
- Correct distortion using a collected field-map



Jezzard P et al., MRM 1995

156

Typical Parameters

45

Parameter	Typical value at 3T	
Echo Time (TE)	30 ms	Determines BOLD contrast
Repetition Time (TR)	1 - 4 s	Determines temporal resolution
Matrix Size/Resolution	64 x 64 / 2–3 mm	Limited by imaging time, distortion, SNR
Scan Duration	2 - 10 mins	Lower limit: sensitivity

157

Multi-Band Accelerated EPI Pulse Sequences

Multi-banded RF pulses can be used to accelerate volume coverage along the slice direction by simultaneously exciting and acquiring multiple slices and subsequently unaliasing them using parallel imaging principles and the spatial information available in multi-channel RF array coils. This allows for a direct reduction in the volume TR by the number of simultaneously excited slices (i.e., the multiband (MB) factor or the slice acceleration factor).

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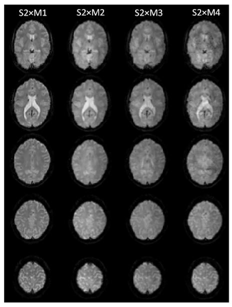
Center for Magnetic Resonance Research, Department of Radiology



158

Overview of Imaging Physiology Block

- Lecture 6:
  - Brain at baseline: neural activity, energy metabolism, and cerebral blood flow
  - "Activated" brain: changes in brain physiology in response to external stimuli, and Introduction to BOLD fMRI

159

Overview of Imaging Physiology Block

- Lecture 7:
  - BOLD fMRI in-depth
  - Beyond BOLD: state-of-the art fMRI techniques to directly image physiological parameters

160

感谢各位同学！

敬请批评指正！

161