A Challenging FMRI Issue: Neuronal Activity and Metabolic-Hemodynamic Coupling

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MR Neuroimaging:

A. Structural neuroimaging & neuroinformatics
1. Morphometry (morphological measurements)
2. Connectivity by diffusion tensor image (DTI) / diffusion spectral image (DSI)

B. Functional neuroimaging & neuroinformatics
1. The measurement of biophysical or physiological parameters, such as molecular diffusion, pH, tissue perfusion, blood flow, temperature, blood oxygenation (e.g., blood oxygenation level dependent, BOLD contrast), electric current;
2. Identification of the distribution of specific molecules of biomedical interest by spectroscopic MRI or chemical shift imaging (CSI);
3. Utilization of MR label or tracer to investigate the normal cellular function or pathological processes of specific organ;
4. Kinematics study using the fast MRI techniques;
5. Multimodality integrated neuroimaging; and
6. MR-based molecular imaging

Molecular and Cellular Functional MRI of Brain

Electric activation – elastography*, direct electro-magnetic effect*
Neurotransmitter release - MRS* (e.g. glutamine/glutamate, GABA)*
Activation of receptor - pharmacological MRI*, receptor molecular imaging
Metabolism-hemodynamics – H1-C13 flux*, BOLD*, CBV*, CBF*
Cell signaling – c-AMP, calmodulin, kinase mapping, proteinase
Gene expression – bio-gal mapping (smart particle)
Synaptic strength & Synaptic connection – DTI/DSI*, signals of resting brain*
Cell volume change – diffusion (apparent diffusion coefficient) change*

* present technique applicable for human study
DTI/DSI: diffusion tensor image/diffusion spectral image

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Functional MRI

MRS: magnetic resonance spectroscopy; BOLD: blood oxygenation level dependent; DTI: diffusion tensor imaging; DSI: diffusion spectral imaging; CBF: cerebral blood flow; CBV: cerebral blood volume; MTT: mean transit time; MRSI: MR spectroscopic imaging

What do your brain behave during a following fMRI task?

Visuo-motor task
Neurovascular coupling
Functional MRI

CBF: cerebral blood flow; CBV: cerebral blood volume; MTT: mean transit time; MRSI: MR spectroscopic imaging
Definition of Neuronal Activation?

Invasive recording:
Membrane electrical potential or field, e.g. intracellular recording, field potential, intra-operative neural monitoring (IONM), etc

Noninvasive
- electrophysiological change
- metabolic/vascular response

Mechanisms

Metabolism - Hemodynamics

Neural activation leads to
- Increased glucose consumption
- Increased oxygen consumption
- Increased cerebral blood flow (CBF) ↑
- Oxygen extraction ↓
- Increased cerebral blood volume (CBV) ↑
- Increased oxy-hemoglobin
- Decreased deoxy-hemoglobin

Less signal loss ❌ Signal increase!!

Mechanisms

Metabolism - Hemodynamics

EPSP: excitatory post-synaptic potential; IPSP: inhibitory PSP

Adapted from Buxton's Chapter 1

Mechanisms

Neural activation leads to
- Functional image
  - f(x, t)
  - g(f(x, t))
  - h(g(f(x, t)))
  - e(f(x, t))
  - d(e(f(x, t)))

E.g. EEG, MEG
E.g. Glu-PET, MRS
E.g. BOLD-fMRI, Perfusion MR, H2O-PET, NIR(S)

Mechanisms

Resting

Active

Oxy-hemoglobin
Deoxy-hemoglobin
Dissection of BOLD

Early Negative Dip of BOLD response

Network Methods of fMRI, Smith et al, NeuroImage, 54, 875-891, 2011

Modified from Functional MRI

Adapted from afni.nimh.nih.gov
Neuronal Activation

fMR Spatial Limits
Limit of Spatial Resolution
- Effect of Drained Venules and Vains
- Effect of Garden Watering (hemodynamic autoregulation)

fMR Temporal Limits
Limit of Temporal Resolution
- Delay of Hemodynamic Coupling
- Early Dip
- Post-stimulation Undershoot
- Non-linear Response
- Stimulation Saturation (block design vs event type study)

General Information of BOLD
Hemodynamic response
Signal change: 1~15% (depending on the task involved and field strength)
@ 1.5T: 2~4%
Rise time to maximum ~ 6 s
Recover to baseline ~ 20 s
Not easily quantifiable

Field Dependence of BOLD Contrast
1.5T
3.0T
Data of VGHTPE
Physiological Heterogeneity of BOLD Mechanisms

Mismatching of neuronal metabolism and physiological response
- limited oxygen model

Mismatching of CBF and CBV
- balloon model

Individual difference
- structural variation
- functional variation
- age-dependence

Auto-regulation or Neuro-glio-vascular circuitry
- PaCO2 effect of 4% CO2, Corfield, 2001; and 6% CO2, Lythgoe, 1999

Regional difference of vasomotor response
- anterior and posterior circulation (Karstrup, 1999)

Pathological condition (Hamzei, 2003)

Adapted from Buxton’s Chapter 16
**Structural Variability**

Nature Neuroscience, 4, 12, 2001

**Functional Variability or Consistency**

Mag. Reson. Med. 34, 735, 1995


**Physiological Heterogeneity of BOLD Mechanisms**

Mismatching of neuronal metabolism and physiological response
- Limited oxygen model
- Mismatching of CBF and CBV
- Balloon model
- Individual difference
- Structural variation
- Functional variation
- Auto-regulation

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**Mechanism of autoregulation**

1. Autonomic tone (sympathetic/parasympathetic)
2. Renin-angiotensin (hormonal)
3. Metabolic
4. Myogenic
5. Endothelial (CO2, PDGF, NO)
Innervation of INTRA-cerebral vessels by intrinsic neurons

Edith Hamel, MNI

Glu, thalamo-cortical afferents

Playing Brain by Driving Auto-regulation or Neuro-glio-vascular circuitry

Cheng et al, ISMRM 2006, p456

Cerebrovascular Reserve (CVR) based on Carbogen-mediated MRI

Yeh et al, ISMRM 2006, p1095

superior cervical (SCG); sphenopalatine (SPG); otic (OG) or trigeminal (TG) ganglia ACh, acetylcholine; DGPR, calcitonin gene-related peptide; GABA, -aminobutyric acid; NA, norepinephrine; NKA, neuropeptide K; NOS, nitric oxide synthase; NPY, neuropeptide Y; PACAP, pituitary adenylate cyclase-activating polypeptide; SOM, somatostatin; SP, substance P; VIP, vasoactive intestinal polypeptide; SHT, serotonin.

The "extrinsic" nerves to cerebral blood vessels at the surface of the brain come from the peripheral nervous system (PNS) and originate from the SCG, SPG, OG, or TG.

Blood vessels located within the brain parenchyma, or the microcirculation, are innervated by "intrinsic" nerve pathways that find their origin in the central nervous system (CNS). For cortical microvessels, anatomical and/or functional evidence indicate that they receive NMT, 5-HT, ACh, or GABAergic afferents from either subcortical neurons from the locus coeruleus, raphe nucleus, basal forebrain, or local cortical interneurons.

Normalized BOLD Signal (a.u.)

Scan Number

Carbogen 1% 2% 3% 4% 5% 3% Yeh et al, ISMRM 2006, p1095

Linear or non-linear modulation of BOLD signal was achieved by carbogen inhalation in the range of 1-5%.ICA (Independent Component Analysis) decomposition analysis revealed the existence of a population of vasodilator components, depending on the carbogen 5% signal that may provide qualitative analysis of cerebral vascular auto-regulation which plays the dominant role in the pathophysiological mechanisms of cardiovascular disease and stroke.
A 38 year-old male had a mixed-grade glioma with mild perifocal edema at left prefrontal region. Cerebral vascular reserve (CVR), measured by graded CO2, showed deteriorated CVR in tumor and peri-tumor regions.

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  - PaCO2 of 4% CO2, Corfield, 2001; and 6% CO2, Lythgoe, 1999
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  - Anterior and posterior circulations (Kastrup, 1999)
- Pathological condition (Hamzei, 2003)

**Method:** inhalation hyper-capnia or hypo-capnia

<table>
<thead>
<tr>
<th>Region</th>
<th>Cond.</th>
<th>t</th>
<th>z</th>
<th>p value</th>
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<tbody>
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<td>Basal</td>
<td>left</td>
<td>4</td>
<td>-27</td>
<td>-3.5</td>
</tr>
<tr>
<td>Control (right)</td>
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<td>-56</td>
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<td>Thalamus (right)</td>
<td>8</td>
<td>-4</td>
<td>9</td>
<td>0.02</td>
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**Method:** breath-holding


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<table>
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<tr>
<th>Pathological state / Drug</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Cardiac arrest</td>
<td>Röhrer et al. 2002</td>
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<tr>
<td>Transient global ischemia</td>
<td>Schenck et al. 1999</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>Dreier et al. 2000</td>
</tr>
<tr>
<td>Trauma</td>
<td>Richards et al. 2001</td>
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<td>Epilepsia</td>
<td>Fink et al. 1998, Boé et al. 1998, von Parnitz et al. 2002</td>
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<td>Theophylline</td>
<td>Ko et al. 1990, Dimgol et al. 1994</td>
</tr>
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<td>Scopolamine</td>
<td>Tsukada et al. 1988</td>
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Question or Idea!!

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