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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

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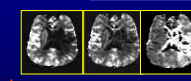
Functional MRI

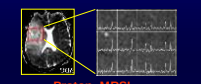


Diffusion-Weighted Image
CBV
CBF
MTT

MR Parametric Image

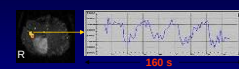
MR Spectroscopic Image

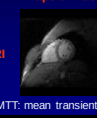
MR label / contrast agent

MR Kinematics


Proton- MRSI


Maps of Background Gradient


160 s
Blood-oxygen-level-dependence FMRI of left hand grasping


Snap-shot cardiac MR

CBF: cerebral blood flow; CBV: cerebral blood volume; MTT: mean transient time; MRSI:MR spectroscopic imaging

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Molecular and Cellular Functional MRI of Brain

Electric activation – elastography*, direct electro-magnetic effect*
Calcium dynamics - Mn
Neurotransmitter release - MRS* (e.g. glutamine/glutamate, GABA)
Activation of receptor – pharmacological MRI*, receptor molecular image
Metabolism-hemodynamics – H1-C13 flux*, BOLD*, CBF*, CBV*
Cell signaling - c-AMP, calmodulin, kinase mapping, proteinase
Gene expression - beta-gal mapping (smart particle)
Synatpic 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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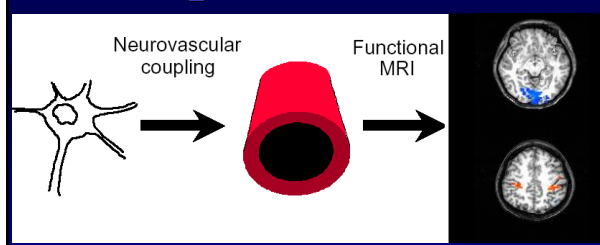
What do your brain behave during a following fMRI task?

Visuo-motor task



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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

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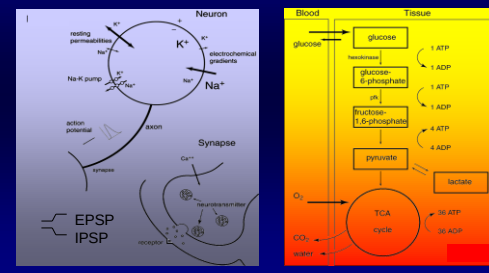
Mechanisms

Metabolism - Hemodynamics



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

Adapted from Buxton's Chapter1

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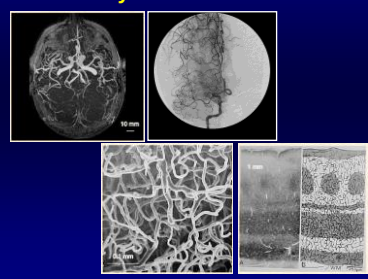
Mechanisms

Metabolism - Hemodynamics



Adapted from Buxton's Chapter1

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Mechanisms

Neural activation leads to

Brain Activity → f(x, t)	Electromagnetic response → e(f(x, t))	'Functional' image → d(e(f(x, t)))	e.g. EEG, MEG
Brain Activity → f(x, t)	Metabolic response → g(f(x, t))	'Functional' image → h(g(f(x, t)))	e.g. Glu-PET, MRS
Brain Activity → f(x, t)	Vascular response → i(f(x, t))	'Functional' image → k(i(f(x, t)))	e.g. BOLD-fMRI, Perfusion MR, H2O-PET, NIR(S)

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Mechanisms

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!!

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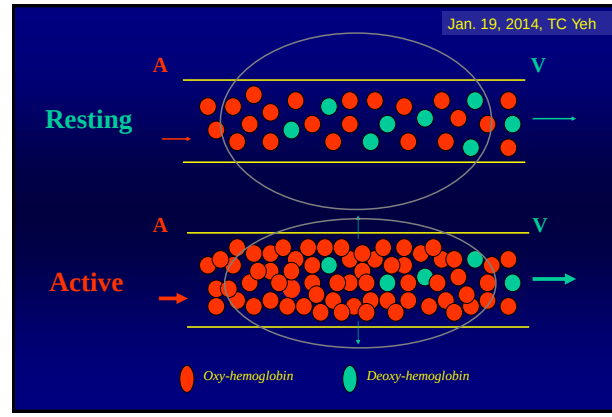

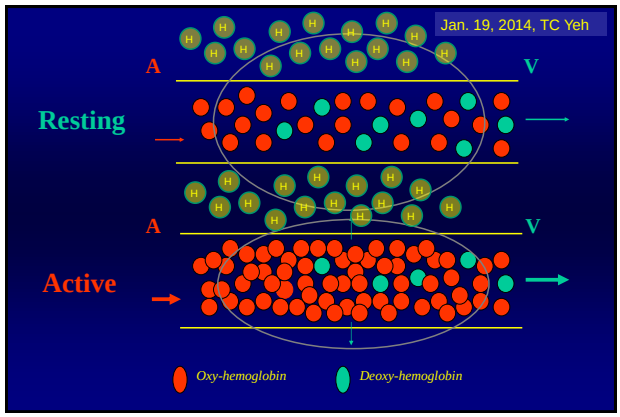
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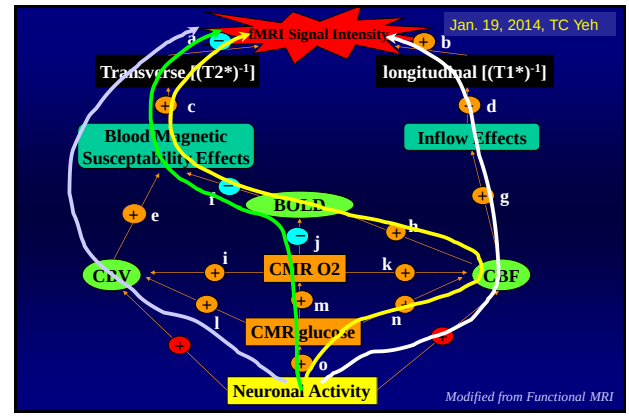
Resting
Active
A
V
A
V
Oxy-hemoglobin
Deoxy-hemoglobin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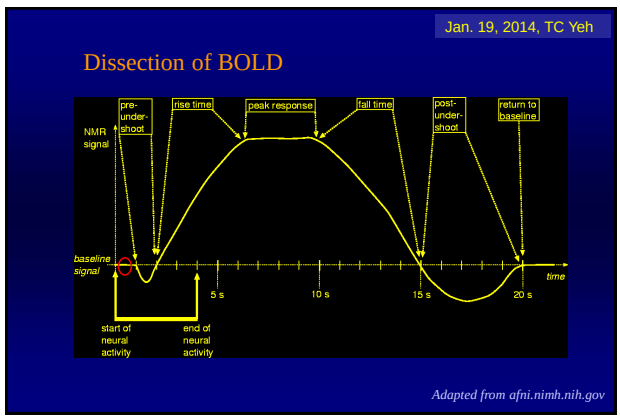
fMRI Signal Intensity
Transverse [(T2*)-1]
longitudinal [(T1*)-1]
Blood Magnetic Susceptability Effects
Inflow Effects
BOLD
CBV
CMR O2
CBF
CMR glucose
Neuronal Activity
Modified from Functional MRI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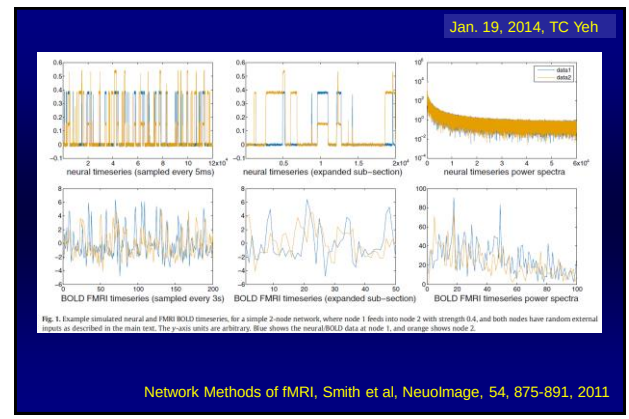
Dissection of BOLD
pre-undershoot
rise time
peak response
fall time
post-undershoot
return to baseline
NMR signal
baseline signal
time
5 s
10 s
15 s
20 s
start of neural activity
end of neural activity
Adapted from afni.nimh.nih.gov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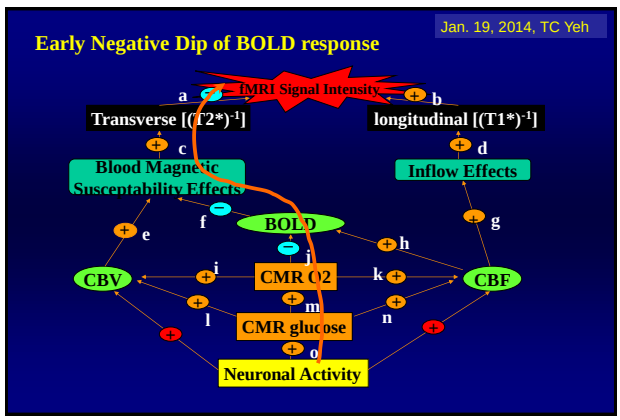
neural timeseries (sampled every 5ms)
neural timeseries (expanded sub-section)
neural timeseries power spectra
BOLD FMRI timeseries (sampled every 3s)
BOLD FMRI timeseries (expanded sub-section)
BOLD FMRI timeseries power spectra
Network Methods of fMRI, Smith et al, NeuoImage, 54, 875-891, 2011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Early Negative Dip of BOLD response
fMRI Signal Intensity
Transverse [(T2*)-1]
longitudinal [(T1*)-1]
Blood Magnetic Susceptability Effects
Inflow Effects
BOLD
CBV
CMR O2
CBF
CMR glucose
Neuronal Activity

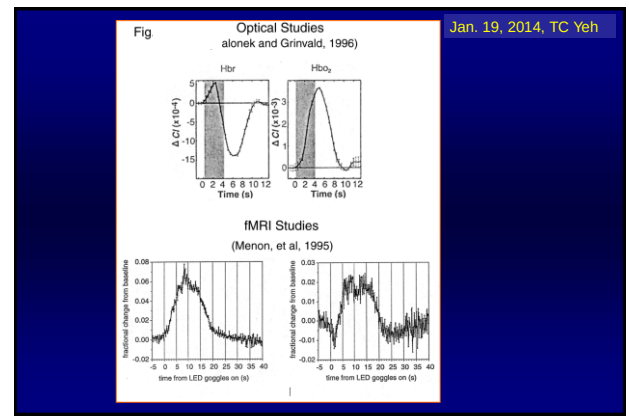
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Fig.
Optical Studies
alonek and Grinvald, 1996)
Hbr
Hbo2
Time (s)
fMRI Studies
(Menon, et al, 1995)
time from LED goggles on (s)

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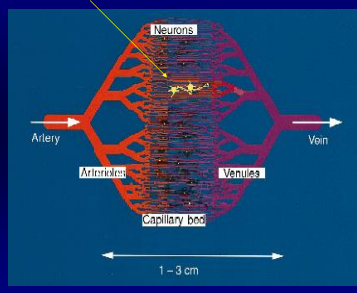
Neuronal Activation



fMR Spatial Limits

Limit of Spatial Resolution

- Effect of Drained Venules and Veins
- Effect of Garden Watering (hemodynamic autoregulation)

Adapted from Trends in Cognitive Sciences 3, 1999

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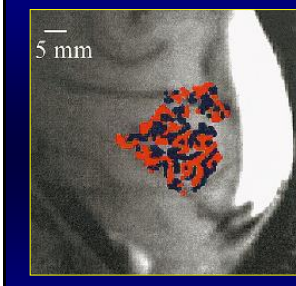

fMR Spatial Limits

Visual Columnar Presentation

Midline sagittal fMRI map and image of the right bank of the occipital pole of a normal volunteer showing ocular dominance stripes, cor-responding to the left and right eye inputs.

: Left Eye

: Right Eye

Adapted from Trends in Cognitive Sciences 3, 1999

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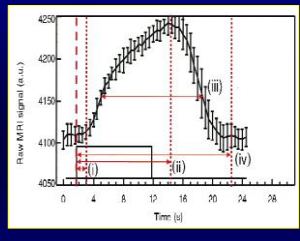

time course of fMRI signal change in visual cortex in response to a visual stimulus

fMR Temporal Limits

Limit of Temporal Resolution

- Delay of Hemodynamic Coupling
- Early Dip
- Post-stimulation Undershoot
- Non-linear Response
- Stimulation Saturation (Block-design v.s Event type study)

Adapted from Trends in Cognitive Sciences 3, 1999

Linear and Non-linear BOLD Response

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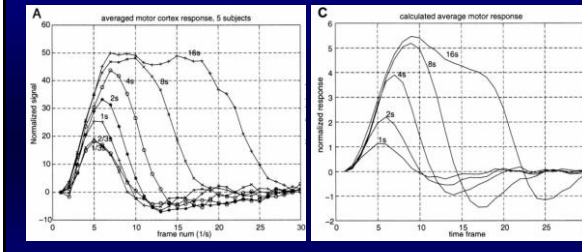
3-Hz finger tapping by visual or auditory cues



Prediction of BOLD responses was based on 1-sec measured BOLD signal as the impulse function for convolution.

Deconvolution of Impulse Response in Event-Related BOLD fMRI, NeuroImage 9, 416–429, 1999

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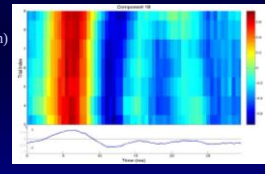
General Information of BOLD



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

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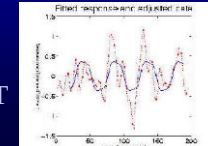
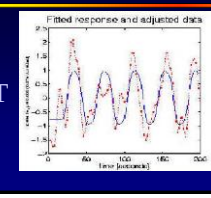
Field Dependence of BOLD Contrast

1.5T



3.0T



Data of VGHTPE

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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)

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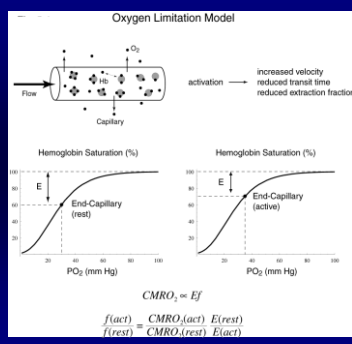

Adapted from Buxton's Chapter16

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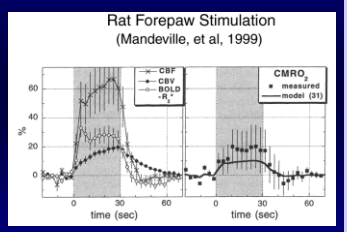

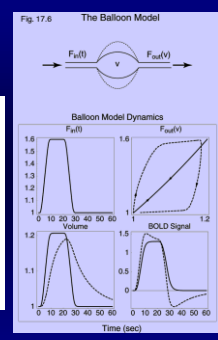

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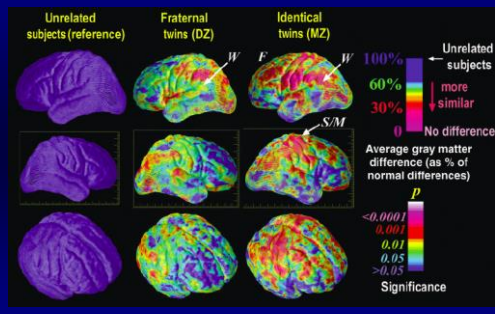
Structural Variability



Nature Neuroscience, 4, 12, 2001

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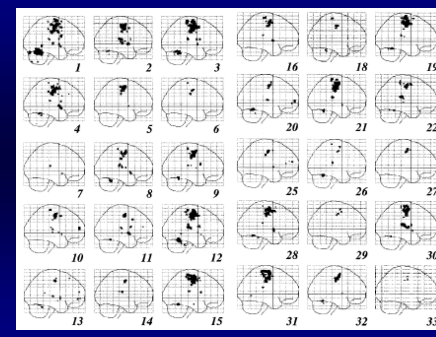
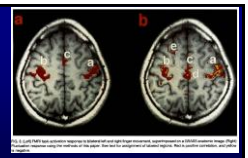
Functional Variability

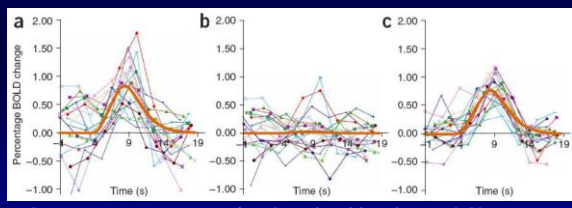


Variability in fMRI: An Examination of Intersession Differences, NeuroImage 11, 708–734, 2002

Functional Variability or Consistency



Mag. Reson. Med. 34 735, 1995



Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses. Nat Neurosci 9:23–25, 2005

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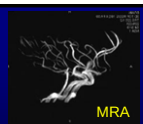
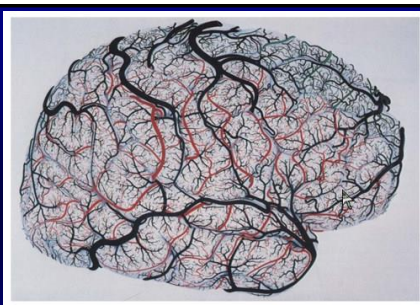


: artery
: vein



Duvernoy et al., Brain Res Bull 1981

Innervation of EXTRA-cerebral vessels by peripheral nerve system

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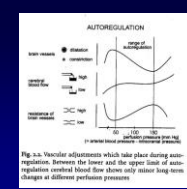
Mechanism of autoregulation

1. Autonomic tone (sympathetic/parasympathetic)
2. Renin-angiotensin (hormonal)
3. Metabolic
4. Myogenic
5. Endothelial (CO_2, PDGF, NO)



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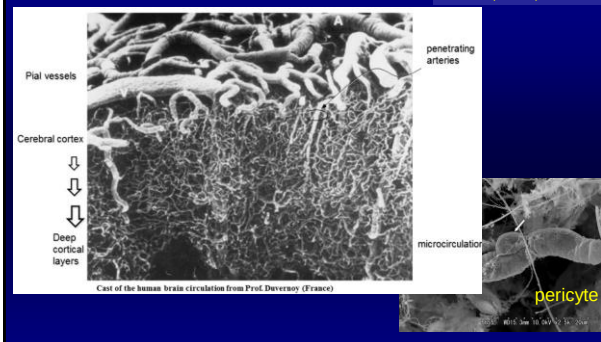

Innervation of INTRA-cerebral vessels by intrinsic neurons

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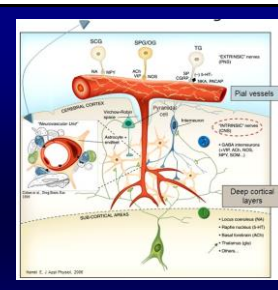

superior cervical (SCG), sphenopalatine (SPG), otic (OG) or trigeminal (TG) ganglia

ACh, acetylcholine; CGRP, calcitonin gene-related peptide; GABA, -aminobutyric acid; NA, norepinephrine; NKA, neurokinin A; NOS, nitric oxide synthase; NPY, neuropeptide Y; PACAP, pituitary adenylate-cyclase activating polypeptide; SOM, somatostatin; SP, substance P; VIP, vasoactive intestinal polypeptide; 5-HT, serotonin.

The "extrinsic" nerves to cerebral blood vessels at the surface of the brain come from the peripheral nervous system (PNS) and originate either in the SCG, SPG, OC 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 NA, 5-HT, ACh, or GABAergic afferents from either subcortical neurons from the locus coeruleus, raphe nucleus, basal forebrain, or local cortical interneurons.

Edith Hamel, MNI

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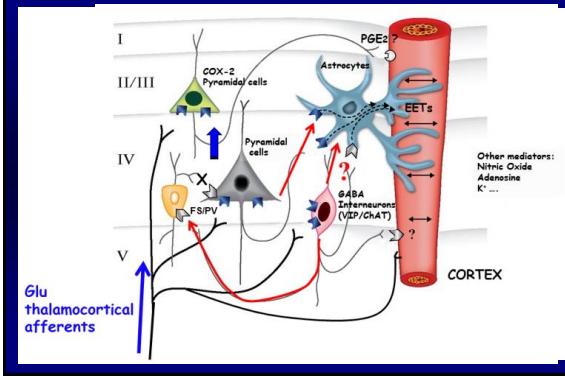

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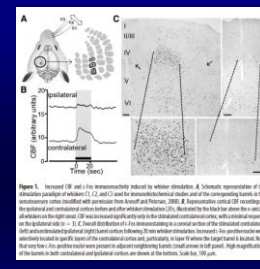
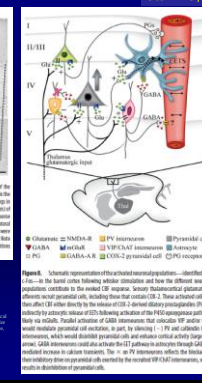


Pyramidal Neurons Are "Neurogenic Hubs" in the Neuvascular Coupling Response to Whisker Stimulation

- The Journal of Neuroscience, July 6, 2011 - 31(27):9836 –9847



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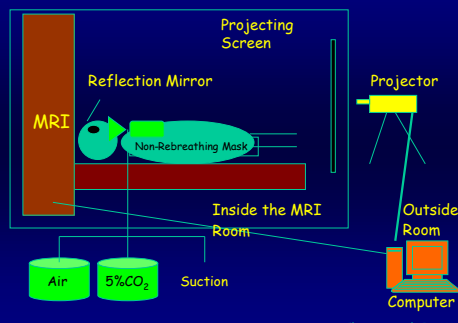
Playing Brain by Driving Auto-regulation or Neuro-glio-vascular circuitry



Cheng et al, ISMRM 2006, p456

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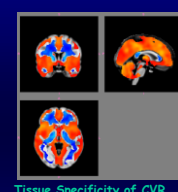
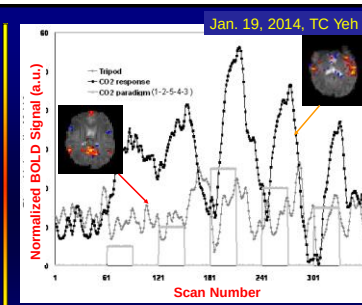
Cerebrovascular Reserve (CVR) based on Carbogen-modulated MRI



Tissue Specificity of CVR (Cerebro-vascular Reservoir)

GM:8.17 ± 5.09 (mean ± 1 SD)
WM:5.99 ± 4.21 (mean ± 1 SD)



Carbogen 1% 2% 5% 4% 3%

Yeh et al, ISMRM 2006, p1095

Linear or near-linear modulation of BOLD signal was achieved by carbogen inhalation in the range of 1–5%. ICA (independent component analyses) detected the delayed response of PaCO2 during carbogen inhalation (left figure). MRI mapping by carbogen CVR (right figure) may provide quantitative analysis of cerebro-vascular auto-regulation which plays the important roles in the patho-physiological mechanisms of cerebrovascular diseases and BOLD-based fMRI studies.

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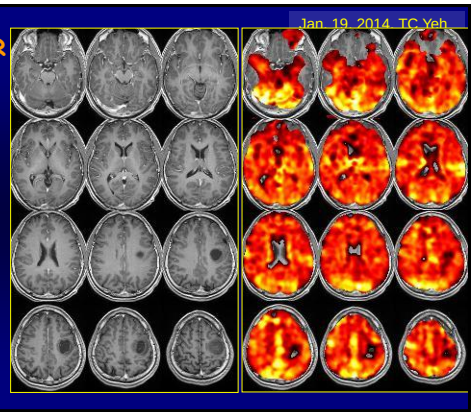
A 38 year-old male had a mixed-graded glioma with mild perifocal edema at left prefrontal region.

Cerebral vascular reserve (CVR), measured by graded CO2, showed deteriorated CVR in tumor and peri-tumor regions.

Pt. code : 090212



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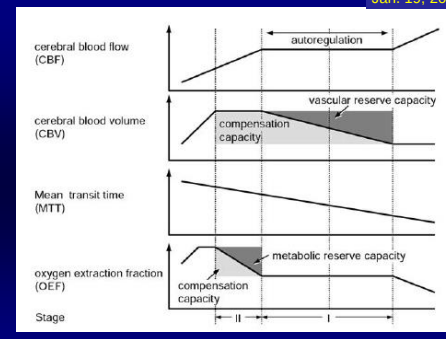

Physiological responses to focal cerebral ischemia in humans
William J. Powers, Robert L. Grubb Jr, Marcus E. Raichle
Annals of Neurology, 1984; 16, 546–552, November 1984

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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 (Kastrup, 1999)

Pathological condition (Hamzei, 2003)

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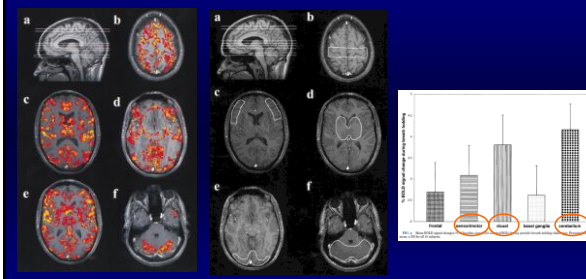
Method : breath-holding



Regional Variability of Cerebral Blood Oxygenation Response to Hypercapnia, NeuroImage 10, 675–681 (1999)

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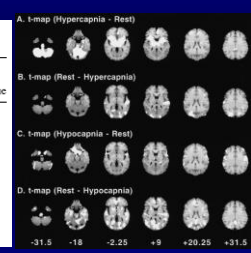
Method : inhalation hyper-capnia or hypo-capnia

Rest

TABLE 3. *Coordinates of the pixels in which significant relative CBF changes were identified*

Region	Coordinate x	y	z	*t* value
Hypercapnia minus rest				
Pons	4	−20	−31.5	3.7
Cerebellum				
(right)	32	−56	−31.5	6.9
(left)	−22	−60	−31.5	7.7
Thalamus				
(right)	8	−8	9	6.8
(left)	−6	−14	9	7.2
Putamen				
(right)	24	2	2.25	5.0
(left)	−22	−2	2.25	5.4



Changes in Human Cerebral Blood Flow and Cerebral Blood Volume During Hypercapnia and Hypocapnia Measured by Positron Emission Tomography, J CBF& Metabolsim,23, 665-670 (2003)

Jan. 19, 2014, TC Yeh

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- anterior and posterior circulation (Karstrup, 1999)

Pathological condition (Hamzei, 2003)

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Pathological De-coupling

Pathologic state / Drug	Reference
Carotid occlusion	Röther et al. 2002
Transient global ischemia	Schmitz et al. 1998
Penumbra of cerebral ischemia	Mies et al. 1993, Wolf et al. 1997
Subarachnoid hemorrhage	Dreier et al. 2000
Trauma	Richards et al. 2001
Epilepsy	Fink et al. 1996, Brühl et al. 1998, von Pannwitz et al. 2002
Alzheimer´s disease	Hock et al. 1996, Niwa et al. 2000
Theophylline	Ko et al. 1990, Dirnagl et al. 1994
Scopolamine	Tsukada et al. 1998

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Question or Idea !!

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