Development of Complex Curricula for Molecular Bionics and Infobionics Programs within a consortial* framework**

Consortium leader

PETER PAZMANY CATHOLIC UNIVERSITY

Consortium members

SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER

The Project has been realised with the support of the European Union and has been co-financed by the European Social Fund ***

**Molekuláris bionika és Infobionika Szakok tananyagának komplex fejlesztése konzorciumi keretben

***A projekt az Európai Unió támogatásával, az Európai Szociális Alap társfinanszírozásával valósul meg.

BIOMEDICAL IMAGING

(Orvosbiológiai képalkotás)

Functional Magnetic Resonance Imaging (fMRI) - the BOLD method

(Funkcionális Mágneses Rezonancia- a BOLD módszer)

ISTVÁN KÓBOR, VIKTOR GÁL

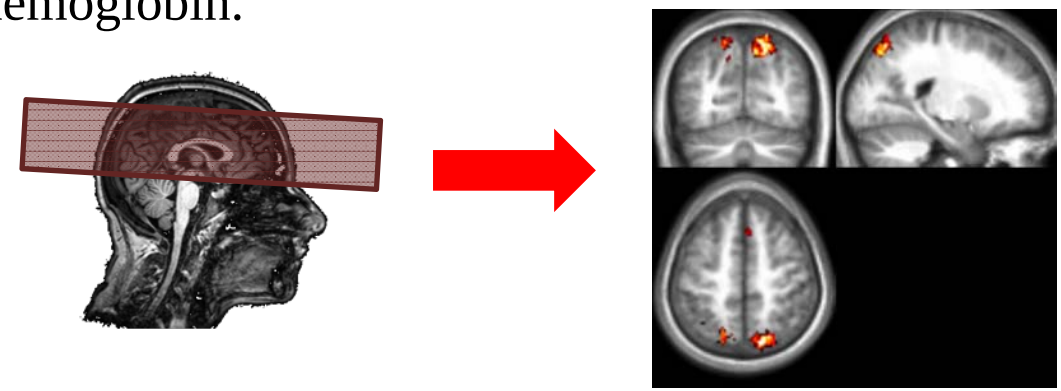
Functional Magnetic Resonance Imaging

Functional Magnetic Resonance Imaging (**fMRI**) refers to different types of specialized MRI scans with a common goal:

➢to measure the dynamics of **local neural activity** in the brain or spinal cord of humans or other animals.

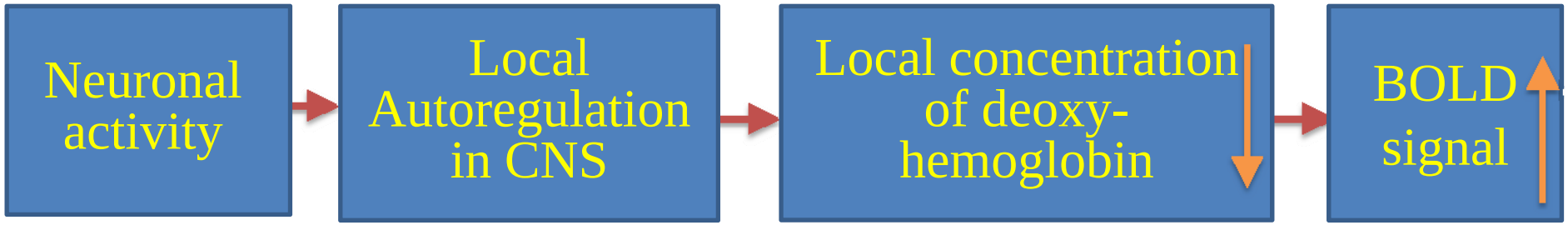
➢**methods:** endogenous or exogenous contrast agents can be used to directly or indirectly detect neural action.

- Blood-oxygen-level dependent imaging (**BOLD**) is the most frequently used technique, where the contrast agent is the blood deoxyhemoglobin.



Sources of the BOLD signal

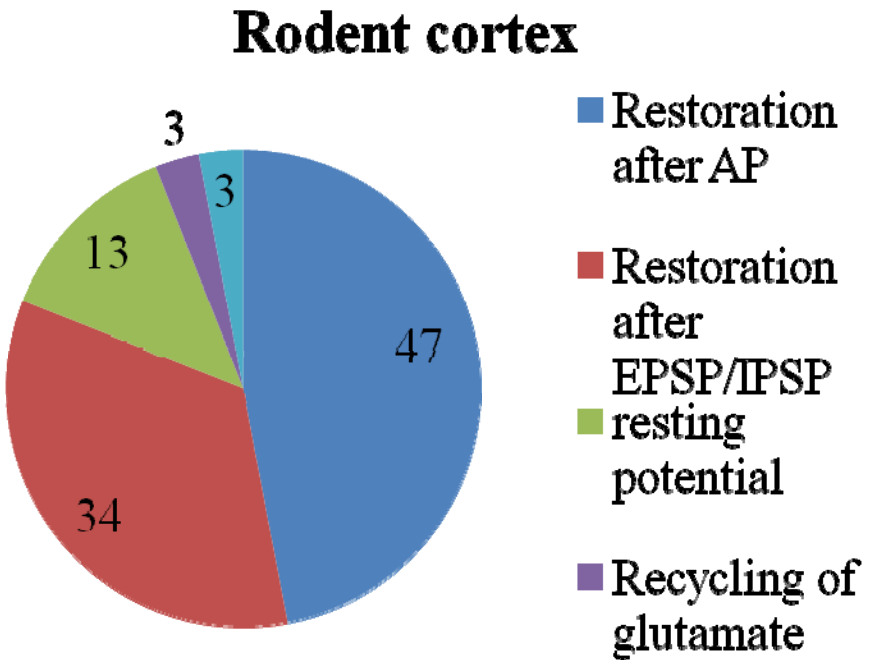
- Auto(vaso)regulation in CNS controls the local oxygen supply according to the local activity.
- Changes in the hemoglobin (oxygen carrier molecule) concentration can be detected by MRI.

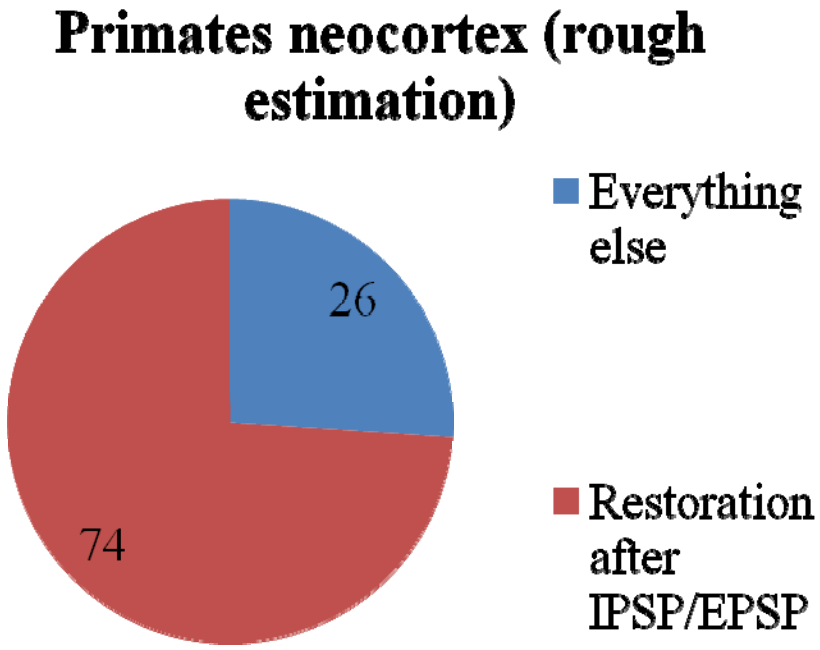


Metabolic requirements of neural activity

- Neural mechanisms require external sources of energy (glucose) and oxygen to support metabolic processes (e.g. restoration of the concentration gradients following changes in membrane potential).
- Direct source of energy at the cell level are the ATP molecules (adenosin-triphosphate). ATP is produced via oxidation of glucose (glycolysis) in the cell
  - When oxygen supply is appropriate: aerobic glycolysis (90%)
  - When oxygen supply is inadequate: anaerobic glycolysis (very fast, 10%)
- Iron-containing Hemoglobin (Hb) in the blood is what transports oxygen from the lungs to the rest of the body (i.e. the tissues), where it releases the oxygen for cell use. 2 forms depending on O_2 binding:
  - oxyhemoglobin (oxyHb) is saturated with O_2
  - deoxyhemoglobin (deoxyHb) binds no O_2
- For imaging purposes, the main vasculature concerned are the capillaries networks – where glucose and oxygen exchanges happen

Metabolic rates of the different components of neuronal activity





Attwell and Laughlin *J of Cerebral Blood Flow & Metabolism* (2001)

How does the brain cope with the increased metabolic demands?

- Activity dependent changes in CBF & CMRO2: autoregulation
- Cerebral Blood Flow (CBF) and Cerebral Metabolic Rate of Oxygen ($CMRO_2$) are coupled under baseline conditions
  - PET measures CBF well, $CMRO_2$ poorly
  - fMRI measures $CMRO_2$ well, CBF poorly

- CBF about .5 ml/g/min under baseline conditions
  - Increases to max of about .7-.8 ml/g/min under activation conditions

- $CMRO_2$ only increases slightly with activation
  - Note: A large CBF change may be needed to support a small change in $CMRO_2$

Energy Consumption and blood supply

- O_2 consumption: 20% of the total body (Brain tissue is 2-3% of body weight)
- Most of the energy is spent maintaining action potentials and in post-synaptic signaling: post-synaptic activity probably dominates in human
- Inhibitory synapses use less energy than excitatory ones
- Neural activity use locally available glucose and Hb bound O_2
  - Glucose, oxyHb
  - deoxyHb, pH, CO_2

Autoregulation: Energy Consumption Theory

- Increased CBF provides higher concentration of glucose and Hb bound O_2:
  - Glucose, oxyHb ↑
  - deoxyHb, pH, CO_2 ↓
- CBF Increases to max of about .7-.8 ml/g/min under activation conditions
- Initial thoughts were that increase of **blood flow is directly linked to** the elevated metabolic rate (and thus increase in energy and **O_2 requirements)** of the active tissue. Candidate signal substrates:
  - Lactate, pH, CO_2, O_2,

But this is not true!

Autoregulation of the blood flow

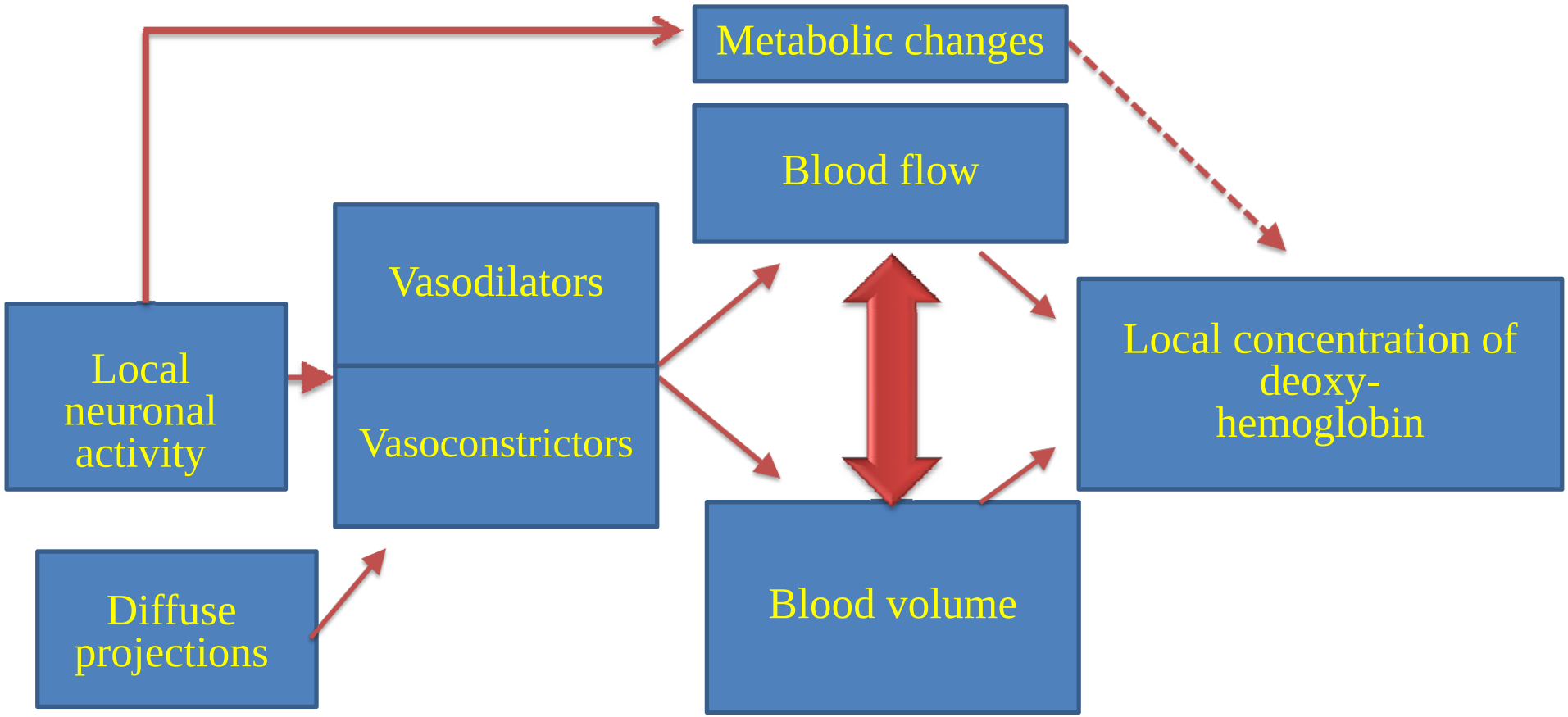
Then how does the brain cope with the increase in glucose and O_2 demands?

- ***Glutamate***-generated Calcium influx at post-synaptic level releases potent vasodilators:
  - Nitric Oxide
  - Adenosine
  - Arachidonic Acid metabolites
- Blood flow is increased over an area larger than the one with elevated neural activity
- Global blood flow changes also associated with dopamine, noradrenaline and serotonin
  - Not related with regional energy utilisation at all!!

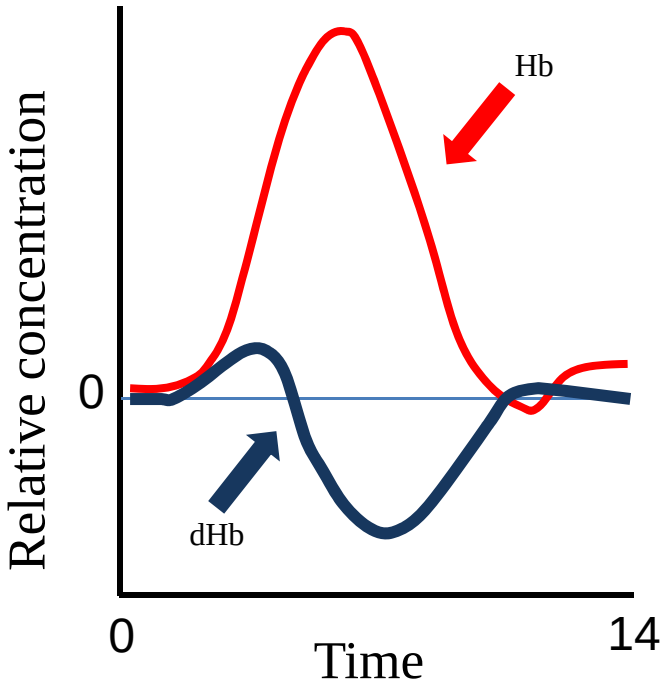
Energy utilisation and increase in blood flow are processes that occur in parallel and are not causally related

Attwell, D. , Iadecola, C. 2002. "The neural basis of functional brain imaging signals". *Trends in Neuroscience*. 25 (12) 621-625

Factors defining local deoxyhemoglobin-concentration



Activity dependent changes in deoxy- and oxyhemoglobin levels



- Quite distinct changes in oxygenated(Hb) and deoxygenated hemoglobin(dHb) following neuronal activation.
- Unlike weak deoxygenated hemoglobin signal spatial pattern of oxygenated hemoglobin does not reflect the pattern of neuronal activity

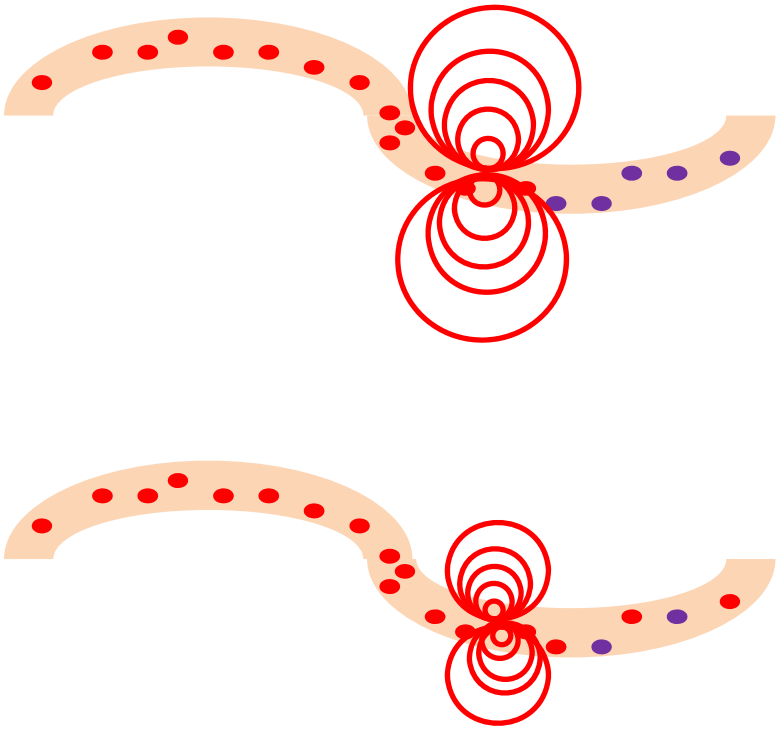
Oxygen and Field homogeneity

Depending on blood oxygen level:

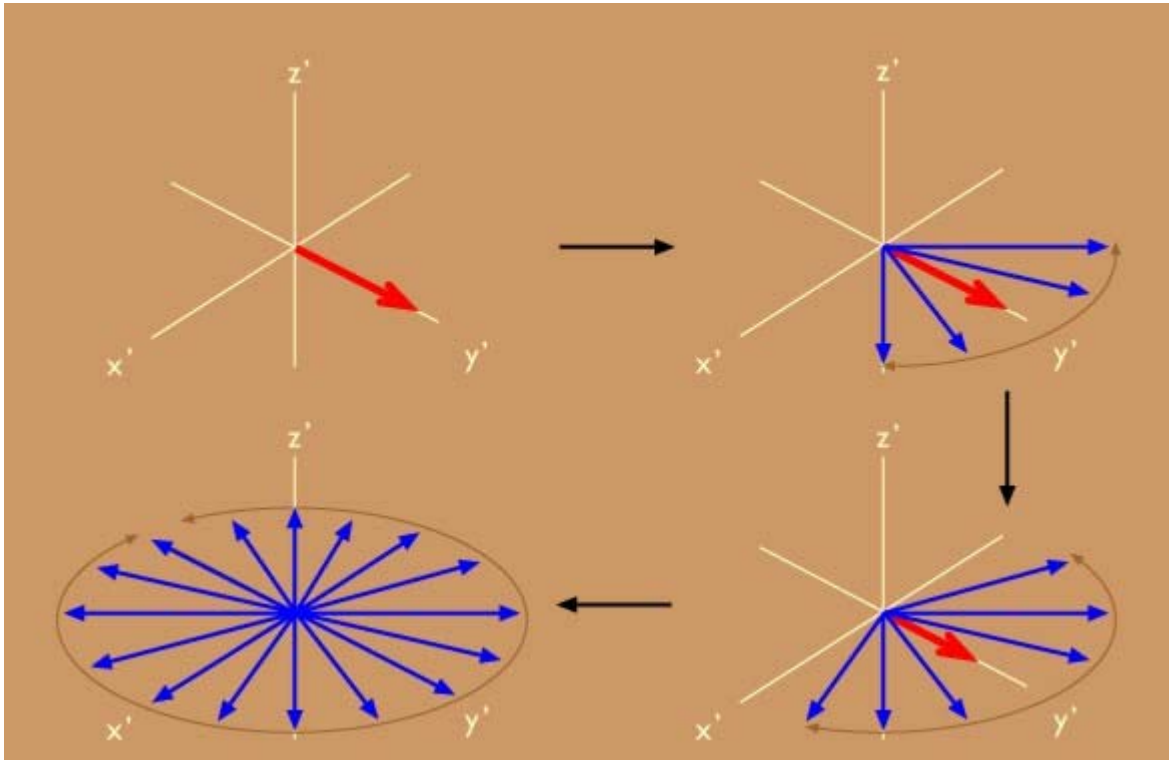
deoxyHb is paramagnetic, increases local inhomogeneity of magnetic field

oxyHb diamagnetic

- local homogeneity of magnetic field increased

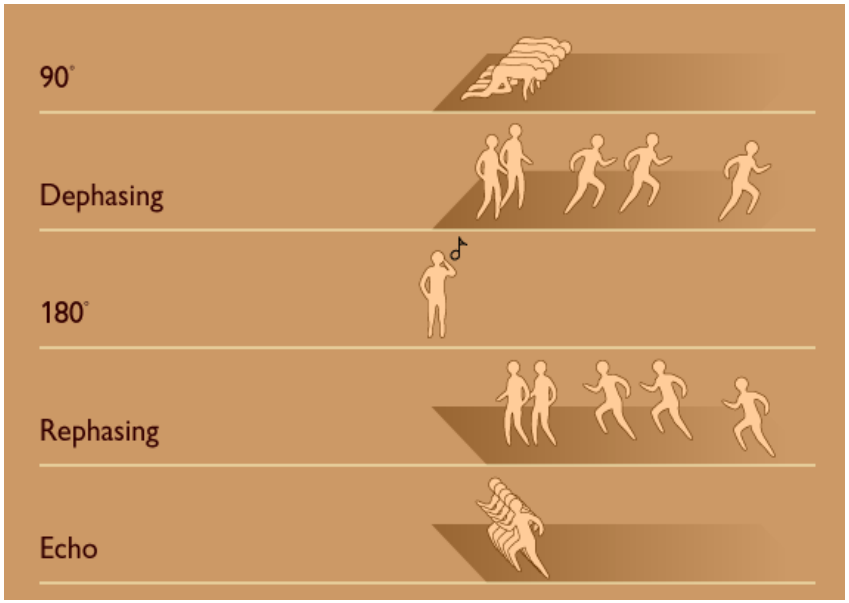


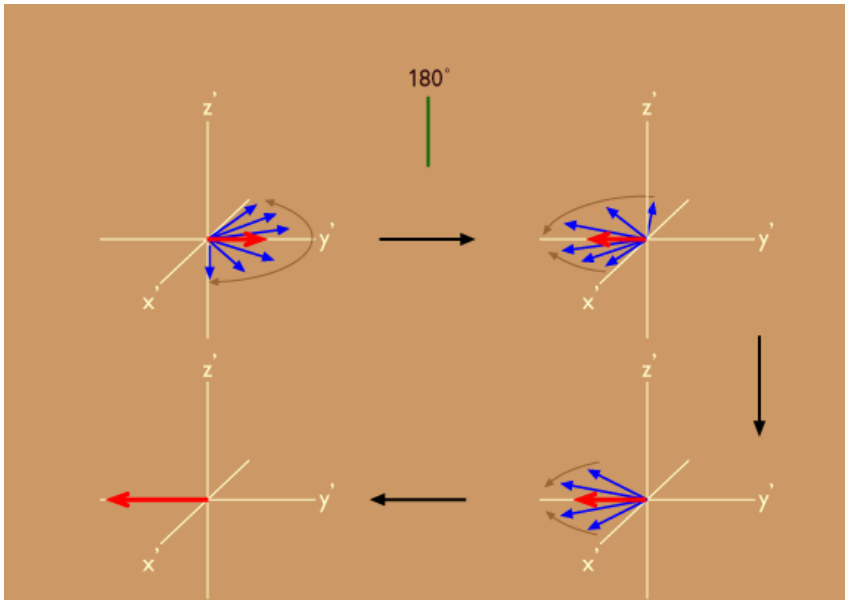
Impact of local inhomogeneity: attenuation of MR signal



Reversible+irreversible, origin: spin-spin (molecular) interaction and **within-voxel inhomogeneities of the magnetic field**

Biomedical Imaging: fMRI - the BOLD method

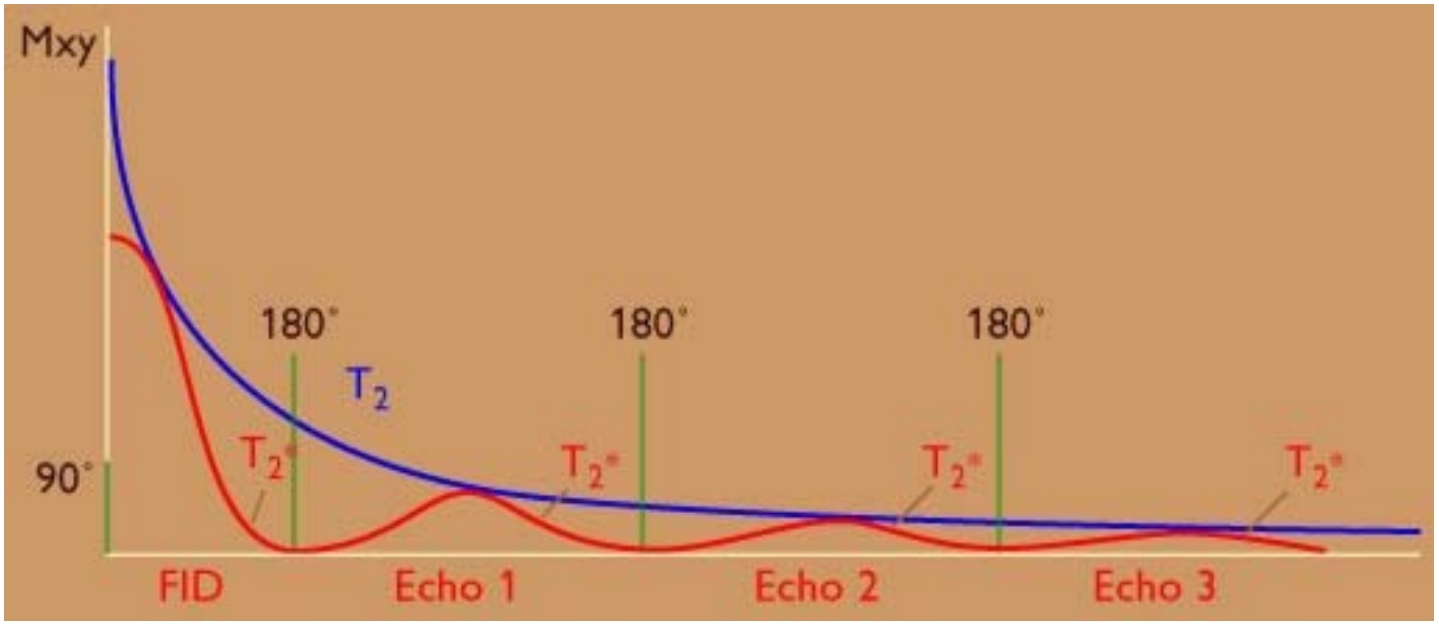




Irreversible: dynamically changing difference in frequency/dephasing of the spin precessions –dephasing is not constant. Source: molecular motion and spin-spin interaction.

Reversible: constant difference in frequency (within one slice acquisition), dephasing speed is not changing, refocusing RF pulse can recover phase coherence. Origin: local magnetic field non-uniformities.

Impact of local inhomogeneity on T_2*



T2 relaxation time: irreversible dephasing, molecular interaction

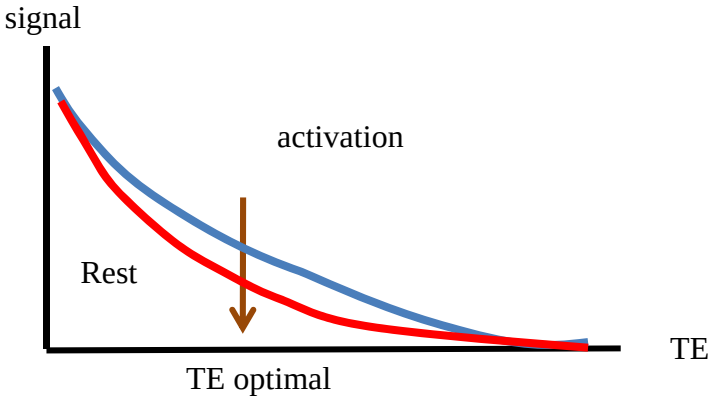
T2* relaxation time: MR signal attenuation due to irreversible+reversible dephasing. Local magnetic field non-uniformity is a major component of the effect: it correlates with local deoxyHb concentration.

How to detect BOLD contrast

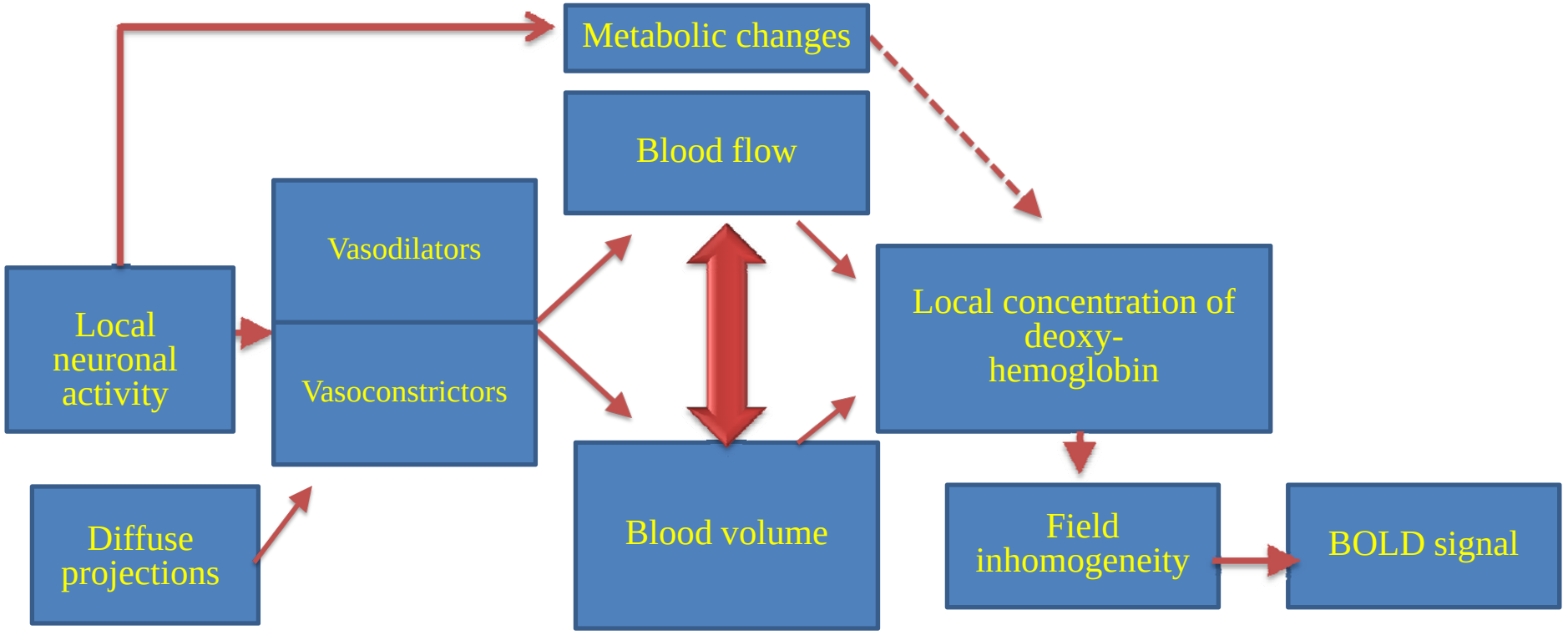
- Signal decay is sensitive to magnetic field inhomogeneities =>
  - Sensitive to signal difference based on deoxyHB concentration

Optimal read-out time:

- When signal difference is highest between different deoxyHB levels
  - TE=25-35ms at 3Tesla (depends on anatomical region as well)



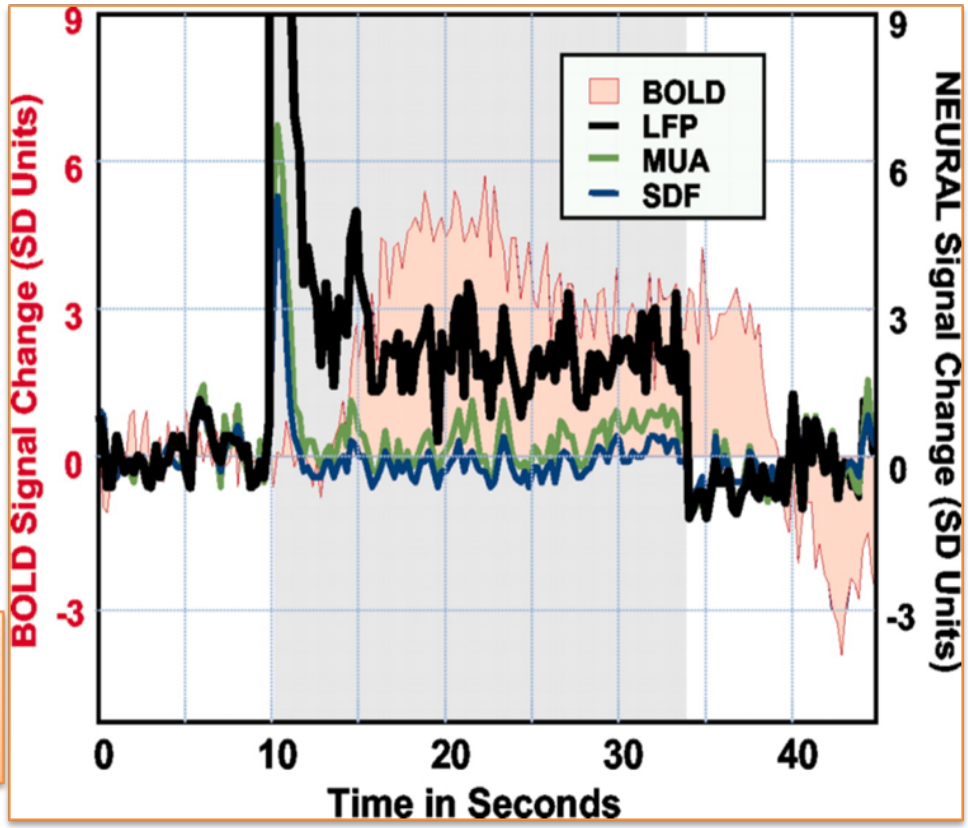
Link between BOLD and neural activity: Neurovascular coupling



Neuronal Origins of BOLD: proof of concept

•BOLD response correlates primarily with Local Field Potential that reflects activity in the neuropil(dendritic activity)

•Increased neuronal activity results in increased MR (T2*) signal



LFP: Local Field Potential
MUA: Multi-Unit Activity
SDF: Spike-Density Function

Logothetis Journal of Neuroscience, 2003,

Gradient EPI: benefits

- Most frequently used sequence in fMRI:
  - Gradient Echo Planar Imaging (gradient EPI)

Why Gradient?

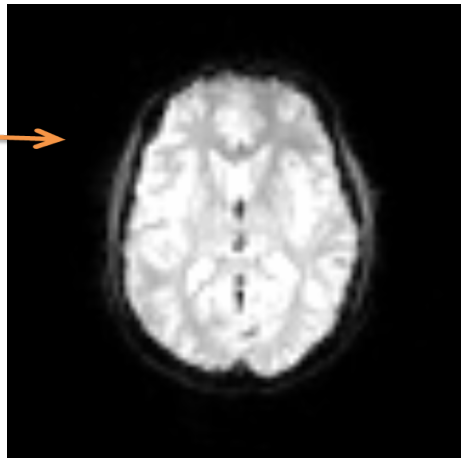
- Requires relatively long read-out time =>
  - Very sensitive to magnetic field inhomogeneities =>
    - Sensitive to signal difference based on deoxyHB concentration
- Signal decay is characterized by T2* relaxation

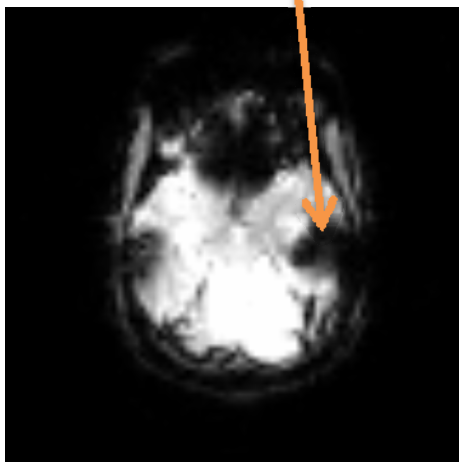
Why EPI?

- Relatively high temporal resolution: required time for a whole brain acquisition typically 2-3sec
- At higher magnetic fields (4.5T, 7T, 9.4T) can be combined with spin-echo sequence

Gradient EPI: disadvantages

- Low contrast and spatial resolution
- Serious distortions near to air/tissue borders (e.g. amygdala/inner ear)
- High water-fat shift
- Signal instability over time





Spatial Resolution and specificity of BOLD response

- In general: high spatial resolution because changes in BOLD response rely on changes in perfusion of *capillaries* (ø 5-10µm)
- Influencing factors:
- Voxel size (depending on region to scan 1-5mm)

  - attention! reduced voxel size → reduced signal compared with noise and increased acquisition time, but less diversity in tissue content
- Concordance of neural activity and vascular response
  - Arteries are fully oxygenated
  - Venous blood has increased proportion of dHb
  - Difference between Hb and dHb states is greater for veins
  - Therefore BOLD is the result of venous blood changes

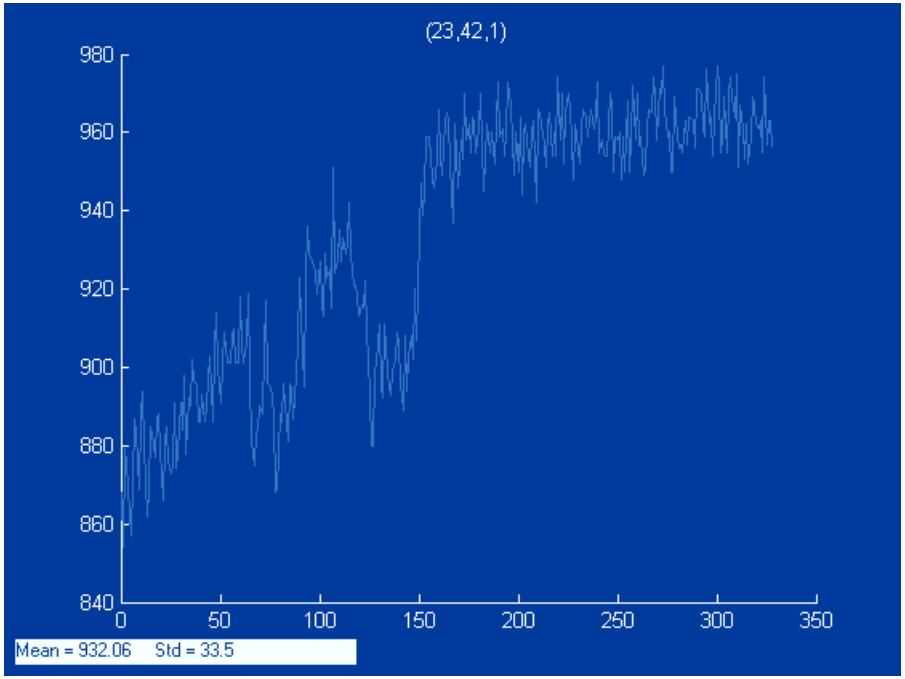
Signal can arise from larger and more distant blood vessels!!!

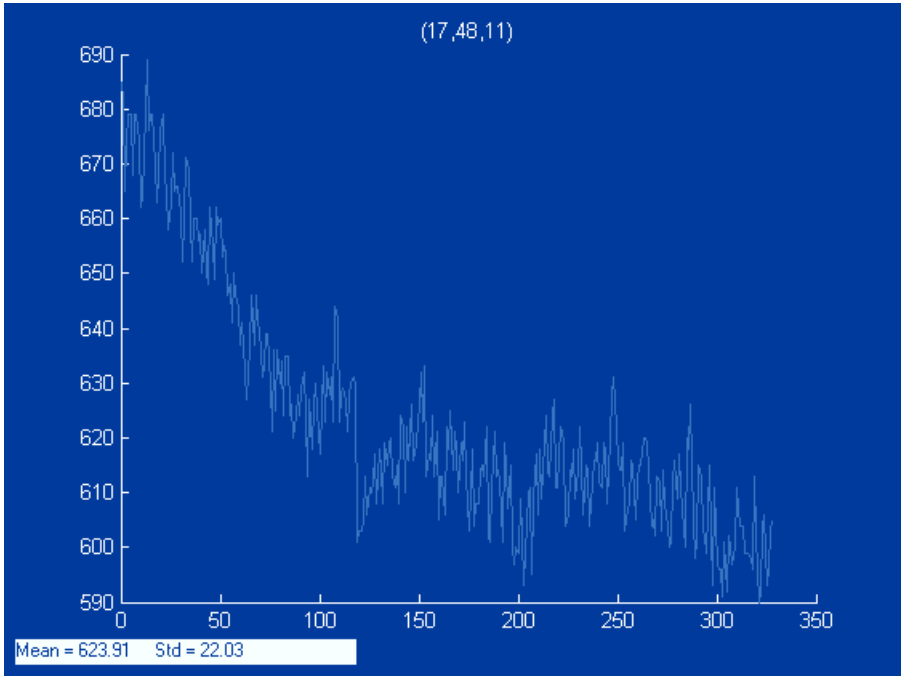
Temporal resolution of fMRI

- Typical sampling time of a volume: 2-3sec
- Temporal resolution is inversely related to
  - Spatial resolution
  - Imaging volume size
  - TE (sensitivity to BOLD)
- Stimuli can be detected:
  - Minimum duration : < 16 ms
  - Minimum onset diff: 100 ms to 2 sec
    - Above 2 sec, linear summation of responses
    - Below 2 sec: nonlinear interactions

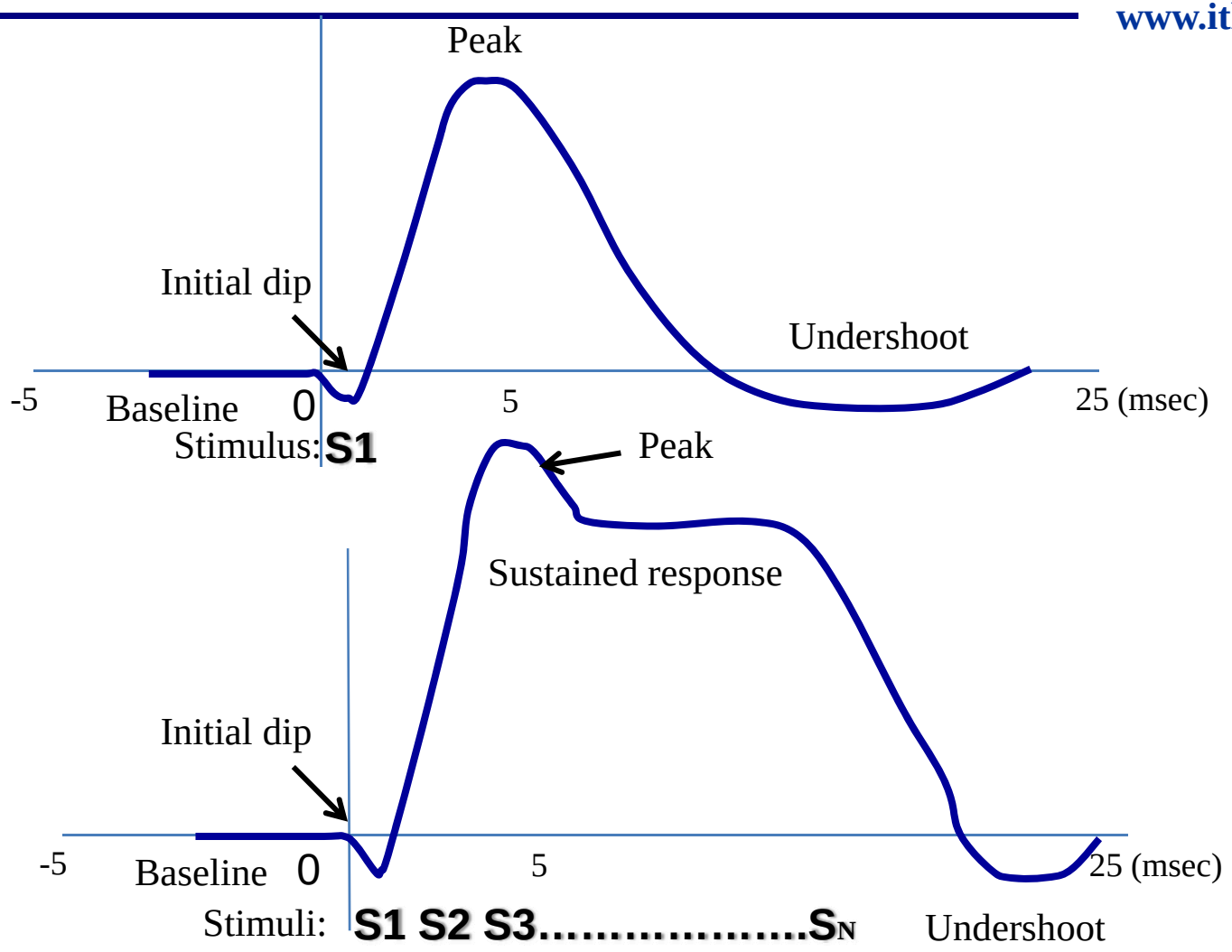
Stability of the BOLD signal

- Low frequency drifts and temporal autocorrelation is an inherent characteristic





Biomedical Imaging: fMRI - the BOLD method



Initial Dip (Hypo-oxic Phase)

- Initial Dip (1-2sec) may result from initial oxygen extraction before later over compensatory response
- Transient increase in oxygen consumption, before change in blood flow
  - Menon et al., 1995; Hu, et al., 1997
- Shown by optical imaging studies
  - Malonek & Grinvald, 1996
- Smaller amplitude than main BOLD signal
  - 10% of peak amplitude (e.g., 0.1% signal change)
- Potentially more spatially specific
  - Oxygen utilization may be more closely associated with neuronal activity than perfusion response

Rise (Hyperoxic Phase)

- Results from vasodilation of arterioles, resulting in a large increase in cerebral blood flow
- Inflection point can be used to index onset of processing

Peak – Overshoot

- Over-compensatory response
  - More pronounced in BOLD signal measures than flow measures
- Overshoot found in blocked designs with extended intervals
  - Signal saturates after ~10s of stimulation

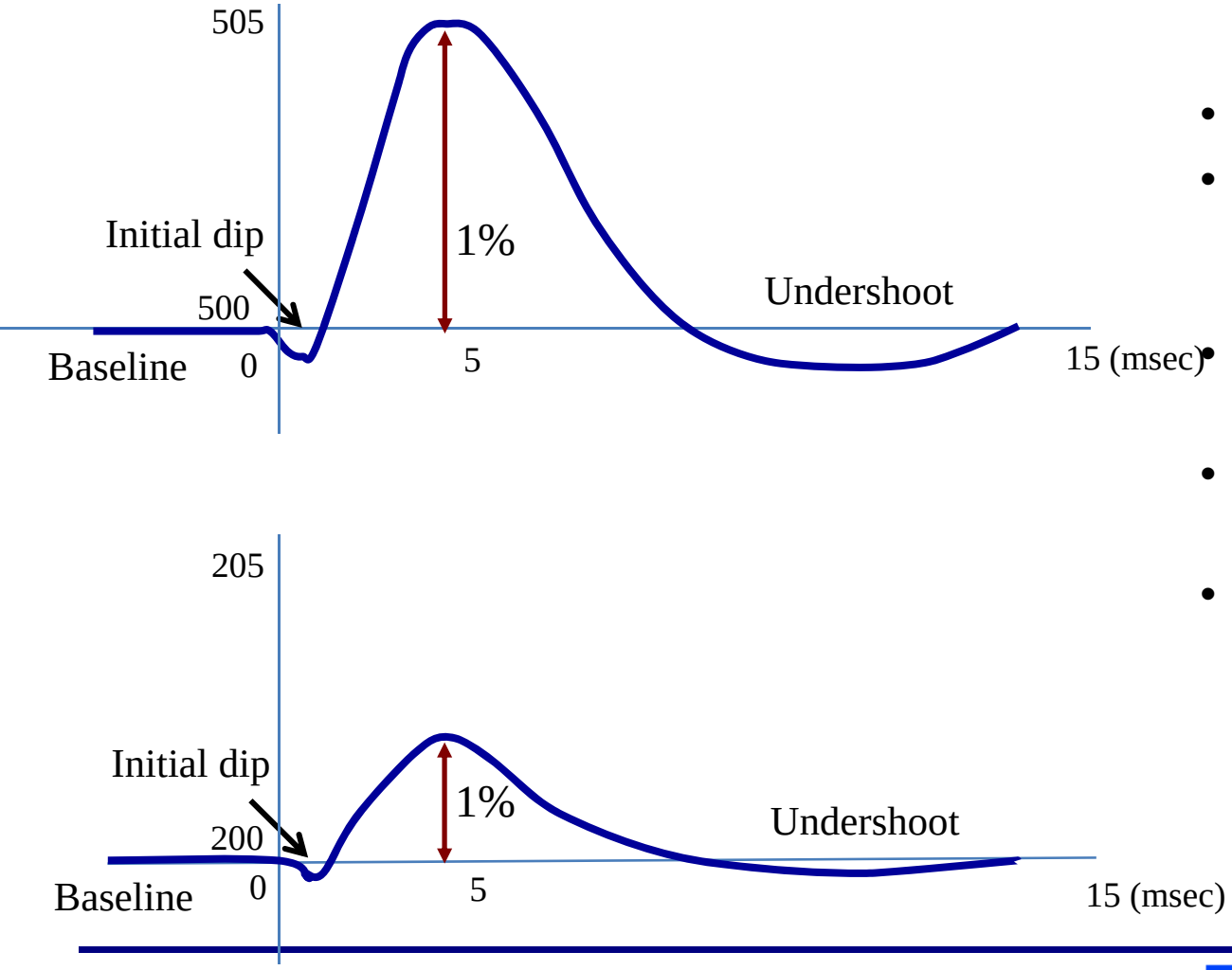
Sustained Response

- Blocked design analyses rest upon presence of sustained response
  - Comparison of sustained activity vs. baseline
  - Statistically simple, powerful
- Problems
  - Difficulty in identifying magnitude of activation
  - Little ability to describe form of hemodynamic response
  - May require detrending of raw time course

Undershoot

- Cerebral blood flow more locked to stimuli than cerebral blood volume
  - Increased blood volume with baseline flow leads to decrease in MR signal
- More frequently observed for longer-duration stimuli (>10s)
  - Short duration stimuli may not evidence
  - May remain for 10s of seconds

Normalization of responses: Percent Signal Change



- Peak / mean(baseline)
- Basic assumption: signal is proportional to mean baseline.
- Question: mean baseline depends on what?
- Amplitude variable across subjects, age groups, etc.
- Peak signal change dependent on:
  - Brain region
  - activation parameters
  - Voxel size
  - Field Strength

Issues: what are we actually measuring?

- Inputs or Outputs?
  - BOLD responses correspond to intra-cortical processing and inputs, not outputs
  - Aligned with previous findings related to high activity and energy expenditure in processing and modulation
- Excitation or inhibition circuits?
  - Excitation increases blood flow, but inhibition might too – ambiguous data
  - Neuronal deactivation is associated with vasoconstriction and reduction in blood flow (hence reduction in BOLD signal)
- And what about the awake, but resting brain?
  - Challenges in interpreting BOLD signal
  - Presence of the signal without neuronal spiking

Issues: what are we actually measuring?

90.000 to 100.000 neurons per $1mm^3$ of brain tissue

10^9 synapses, depending on cortical thickness

What is in a Voxel?

Volume of $55mm^3$

- Using a 9-16 mm^2 plane resolution and slice thickness of 5-7 mm

Only 3% of vessels and the rest are….(be prepared!!)

- 5.5 million neurons
- 2.2-5.5 x 10^{10} synapses
- 22km of dendrites
- 220km of axons

Relative vs. Absolute Measures

- BOLD fMRI provides relative change over time
  - Signal measured in “arbitrary MR units”
  - Percent signal change over baseline
  - Direct longitudinal or intersubject comparisons are impossible
  - within subject interregional (different cortical areas)

  comparisons : only qualitative or indirect
- Arterial spin labeling (another type of fMRI method discussed later) or PET provides absolute signal
  - Measures biological quantity in real units
    - CBF: cerebral blood flow
    - CMRGlc: Cerebral Metabolic Rate of Glucose
    - $CMRO_2$: Cerebral Metabolic Rate of Oxygen
    - CBV: Cerebral Blood Volume

Why the Growth of fMRI?

- Powerful
  - Improved ability to understand cognition
  - Better spatial resolution than PET
  - Allows new forms of analysis
- High benefit/risk ratio
  - Non-invasive (no contrast agents)
  - Repeated studies (multisession, longitudinal)
- Accessible
  - Uses clinically prevalent equipment
  - No isotopes required
  - Little special training for personnel

What fMRI Can Do

Help in understanding healthy brain organization

- map networks involved with specific behavior, stimulus, or performance
- characterize changes over time (seconds to years)
- determine correlates of behavior (response accuracy, etc…)

Current Clinical Applications

- presurgical mapping
- better understanding mechanism of pathology for focused therapy
- drug effect assessment
- assessment of therapy progress, biofeedback
- epileptic foci mapping
- neurovascular physiology assessment

Current Clinical Research

- assessment of recovery and plasticity
- clinical population characterization with probe task or resting state

What fMRI Can't Do

- Too low SNR for routine clinical use (takes too long)
- Requires patient cooperation (too sensitive to motion)
- Too low spatial resolution (each voxel has several million neurons)
- Too low temporal resolution (hemodynamics are variable and sluggish)
- Too indirectly related to neuronal activity
- Too many physiologic variables influence signal
- Requires a task (BOLD cannot look at baseline maps)
- Too confined space and high acoustic noise.