UNIVERSITÀ DI TRENTO

CIMeC Center for Mind/Brain Sciences

Brain Functional MRI Introduction

Louvain-la-Neuve - Neuroimaging Workshop 2019

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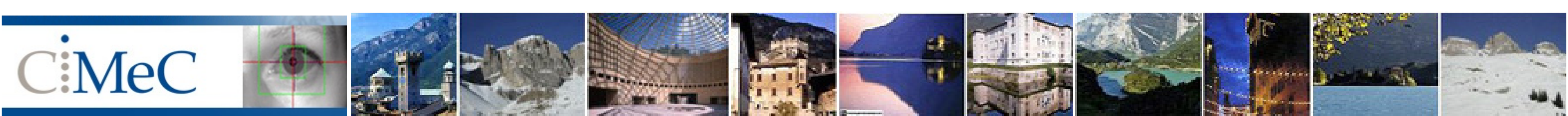
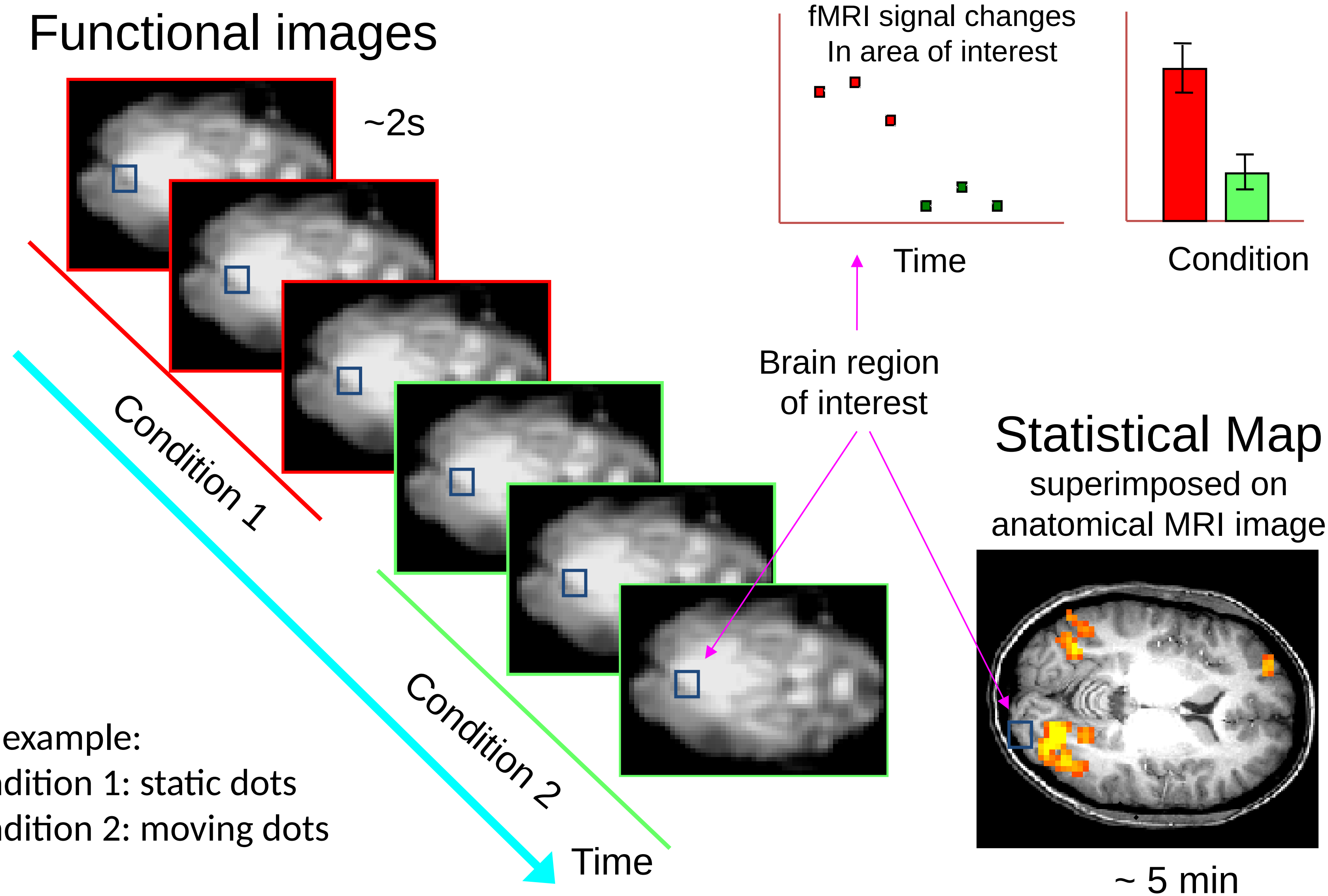


Functional MRI: Why?



For example:
Condition 1: static dots
Condition 2: moving dots

Modified from Jody Culham's fMRI Newbies web site

Lecture 4 outline

Brain functional MRI:

- We want functional contrast:
  - Blood Oxygenation Level Dependent (BOLD)
- We want to measure signal fluctuations
  - Fast MRI: Echo Planar Imaging
- We want “clean” data for modeling & analysis
  - Pre-processing

Brain Functional MRI Contrasts

Options:

- **Invasive**
  - Vascular volume (gadolinium)

- **Non-invasive**
  - Blood Oxygenation Level Dependent (BOLD)
  - Perfusion (CBF: cerebral blood flow)
  - CMRO2 (Cerebral metabolic rate O2 consumption)
  - Vascular volume changes (VASO)
  - … ongoing research (currents, diffusion, etc.)

standard

research

Blood Oxygenation Level Dependent (BOLD) contrast

BOLD contrast is the net result of two separate effects:

- Hemodynamic response
- Magnetic properties of the hemoglobin molecules

Energy brain metabolism

Neural function relates to oxygen consumption

- **Inhaled air**
  - 78% nitrogen
  - **21% oxygen**
  - 1% inert gases (argon)
  - **0.04% carbon dioxide**

- **Exhaled air**
  - 78% nitrogen
  - **16% oxygen**
  - 1% inert gases (argon)
  - **4% carbon dioxide**
  - **Water vapour**

What happened?

C_6 H_12 O_6 + 6O_2
→ 6CO_2 + 6H_2 O + Energy released

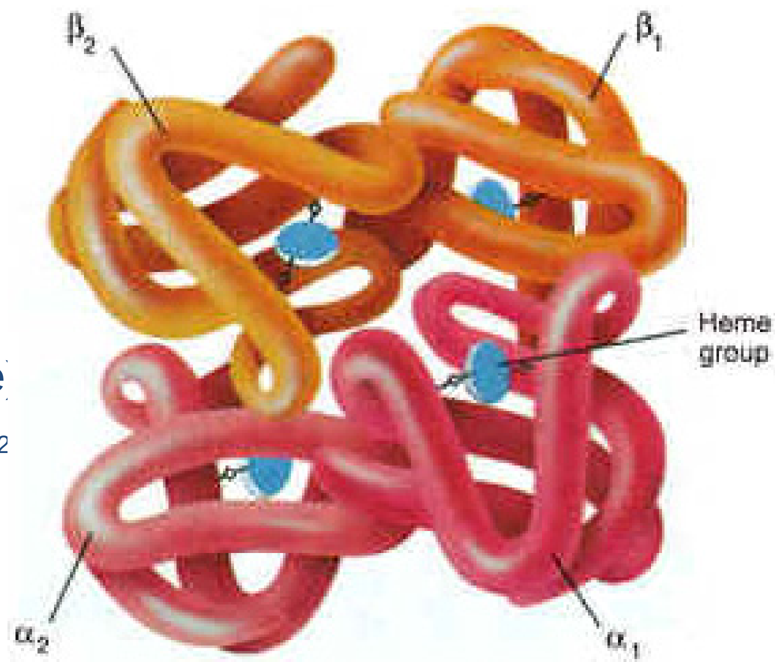
Glucose + Oxygen
→ Carbon dioxide + water + Energy

Oxygen oxydized glucose to produce energy

Energy taxi: hemoglobin (Hb)

- Each red blood cell: about 250 million Hb molecules

- Function: transport of ‘goods’ and ‘wastes’
  - carries O_2 to tissue and CO_2 away from tissue
  - one Hb molecule can carry up to 4 atoms of O_2

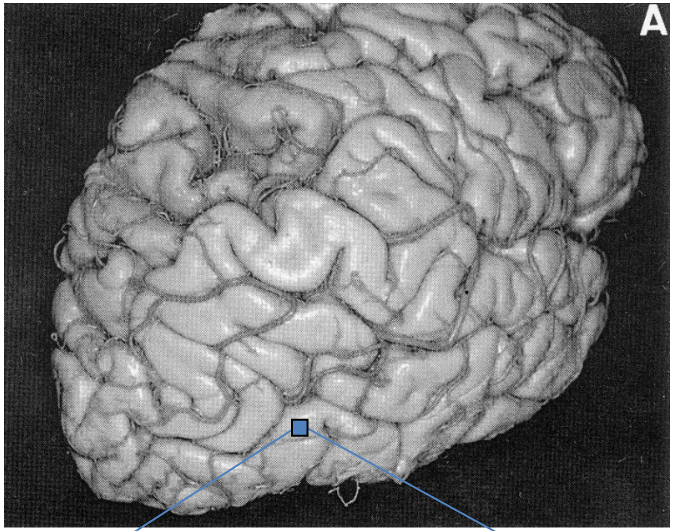


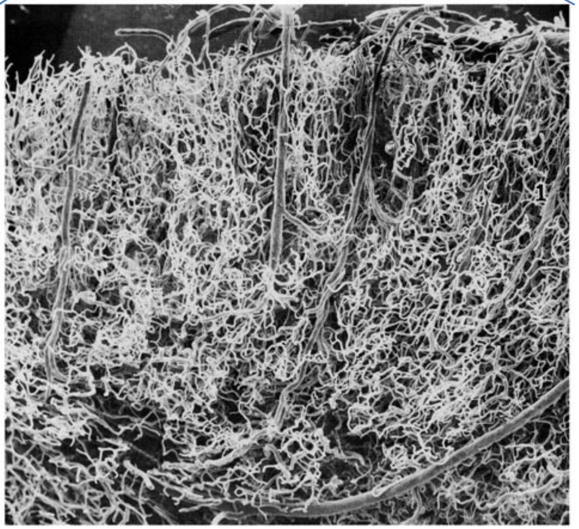
- Hemoglobin molecule structure:
  - four protein globin chains
  - each globin chain contains a heme group
  - at center of each heme group is an iron atom (Fe)
  - each heme group can attach an oxygen atom (O_2

- Hemoglobin molecule states
  - Oxy-hemoglogbin
  - Deoxy-hemoglobin

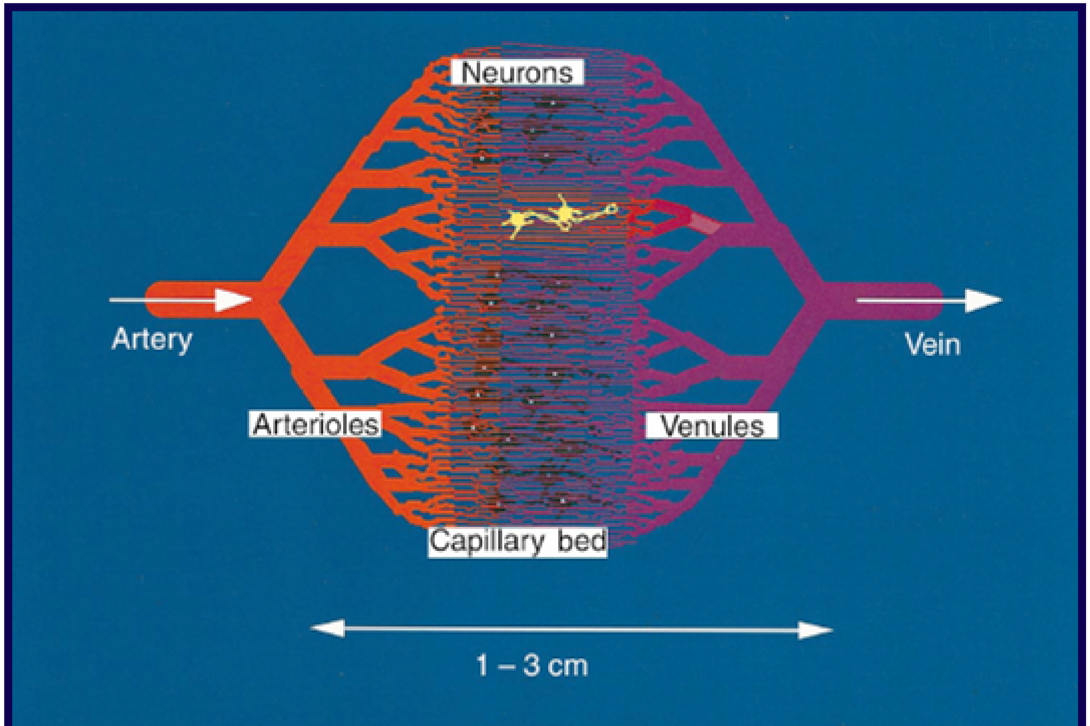
: http://wsrv.clas.virginia.edu/~rjh9u/hemoglob.html,

Brain vasculature & hemodynamic response



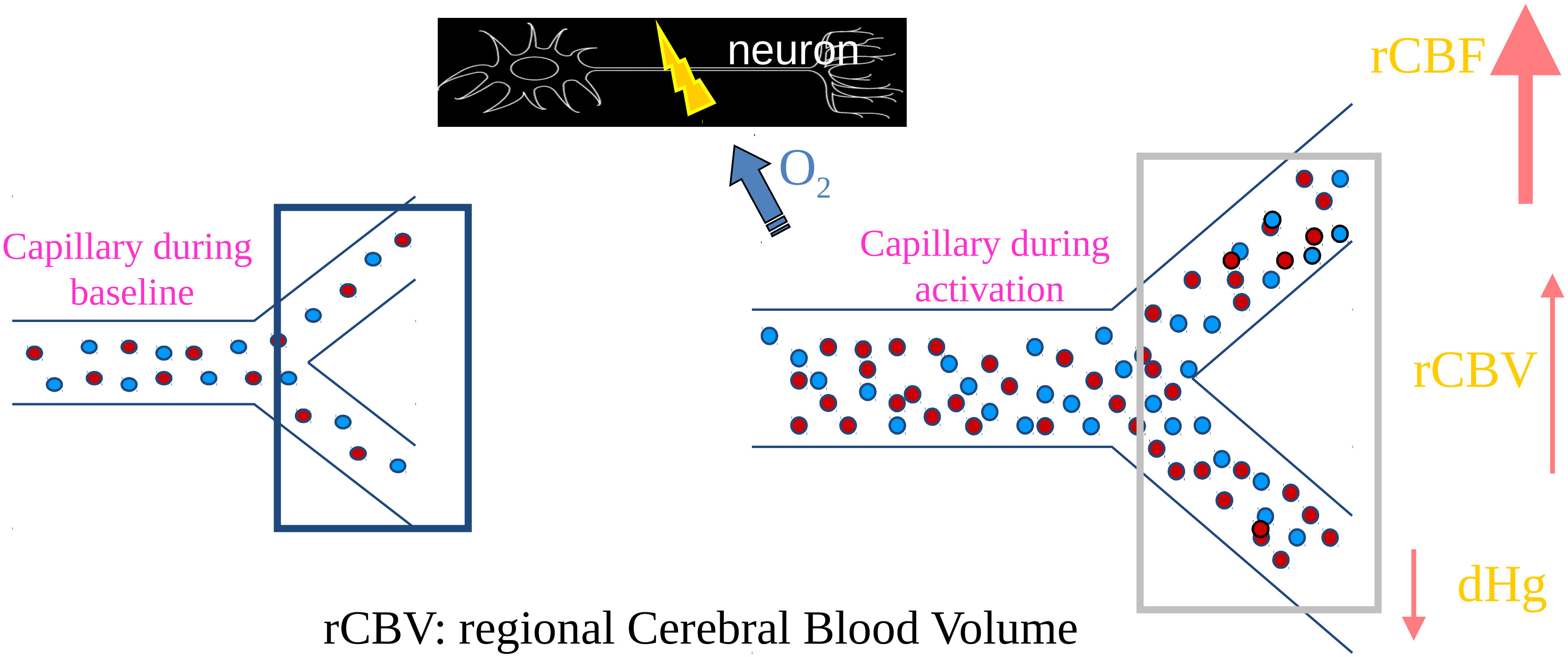


- Brain weight: 2% of body weight
- Brain energy budget: ~20% of body
- Very efficient irrigation system



Source: Menon & Kim, TICS

Brain hemodynamic response



rCBV: regional Cerebral Blood Volume

rCBF: regional Cerebral Blood Flow

dHg: deoxygenated Hemoglobin ●

Hg: oxygenated Hemoglobin ●

Blood Oxygenation Level Dependent (BOLD) contrast

BOLD contrast is the net result of two separate effects:

- Hemodynamic response
  - Concentration of oxygenated hemoglobin changes with neural activation
  - Changes are «local» to brain activation areas
  - There is a quick decreas in oxy-Hg shortly after activation starts
  - After a few seconds a local excess of oxy-Hg in active area is observed

- Magnetic properties of the hemoglobin molecules

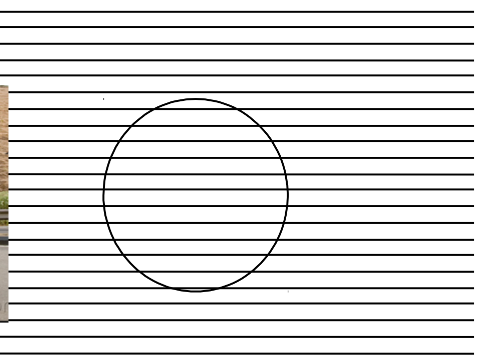
Magnetic properties of hemoglobin (Hb)

Oxygenation states give rise to different magnetic states

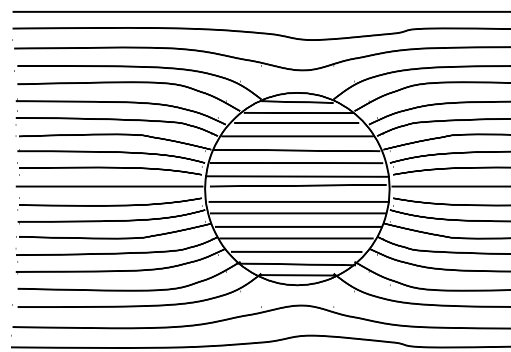
- **Oxygenated-Hb**
  - Isomagnetic with respect to the surrounding tissue, no net magnetization, paired electrons
- **Deoxygenated-Hb**
  - Paramagnetic with respect to the surrounding tissue, net magnetization, unpaired electrons
- Pauling & Coryell, PNAS 1936.

Blood test tube inside an external magnetic field B0

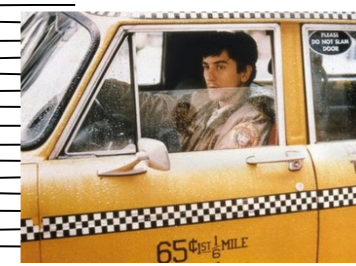
Full taxi



Oxygenated Hg

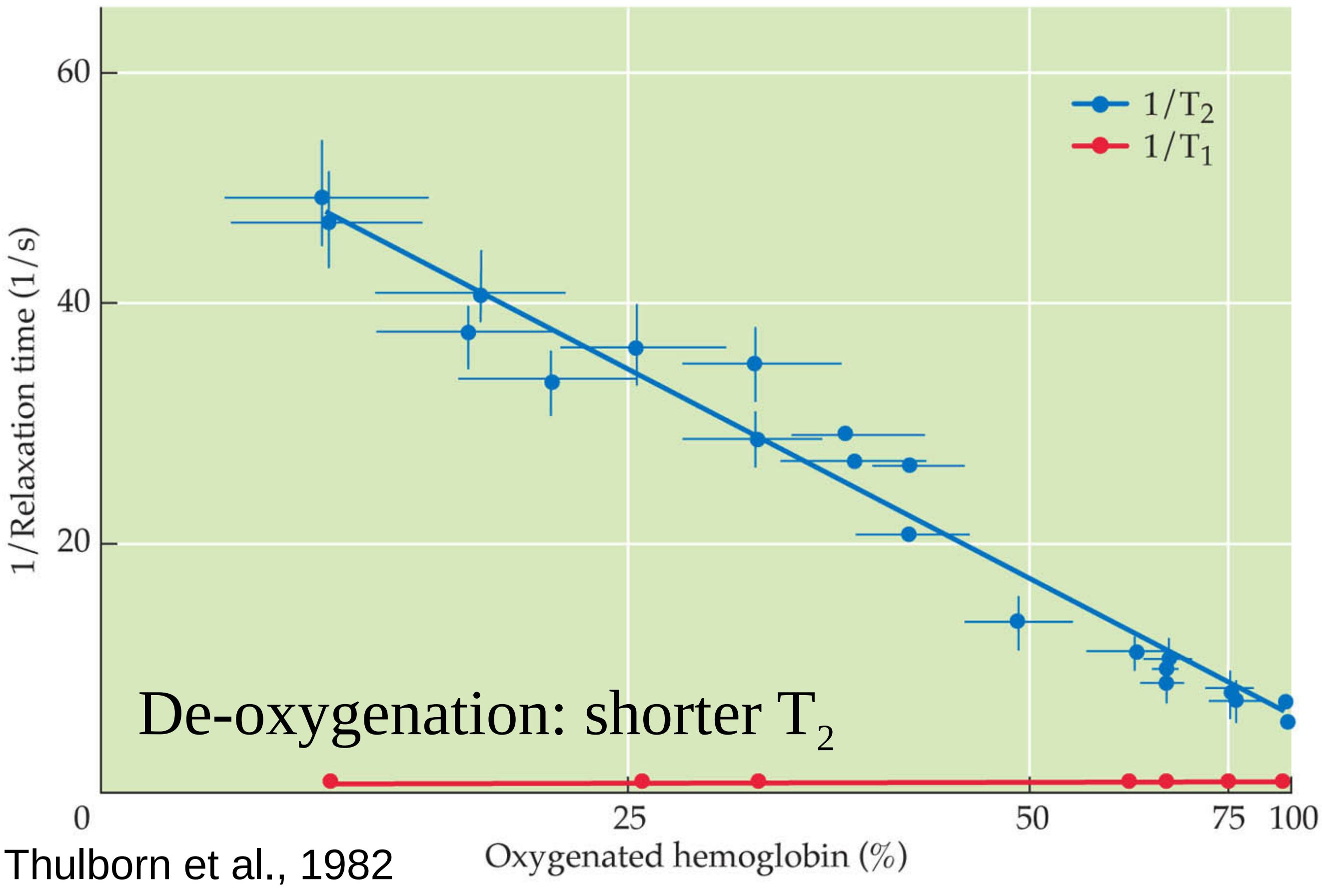


Deoxygenated Hg



No passengers

Hemoglobin oxygenation and the MRI signal



Thulborn et al., 1982

T1: no effects

T2: clear effects

Hemoglobin oxygenation and the MRI signal

Spin Echo

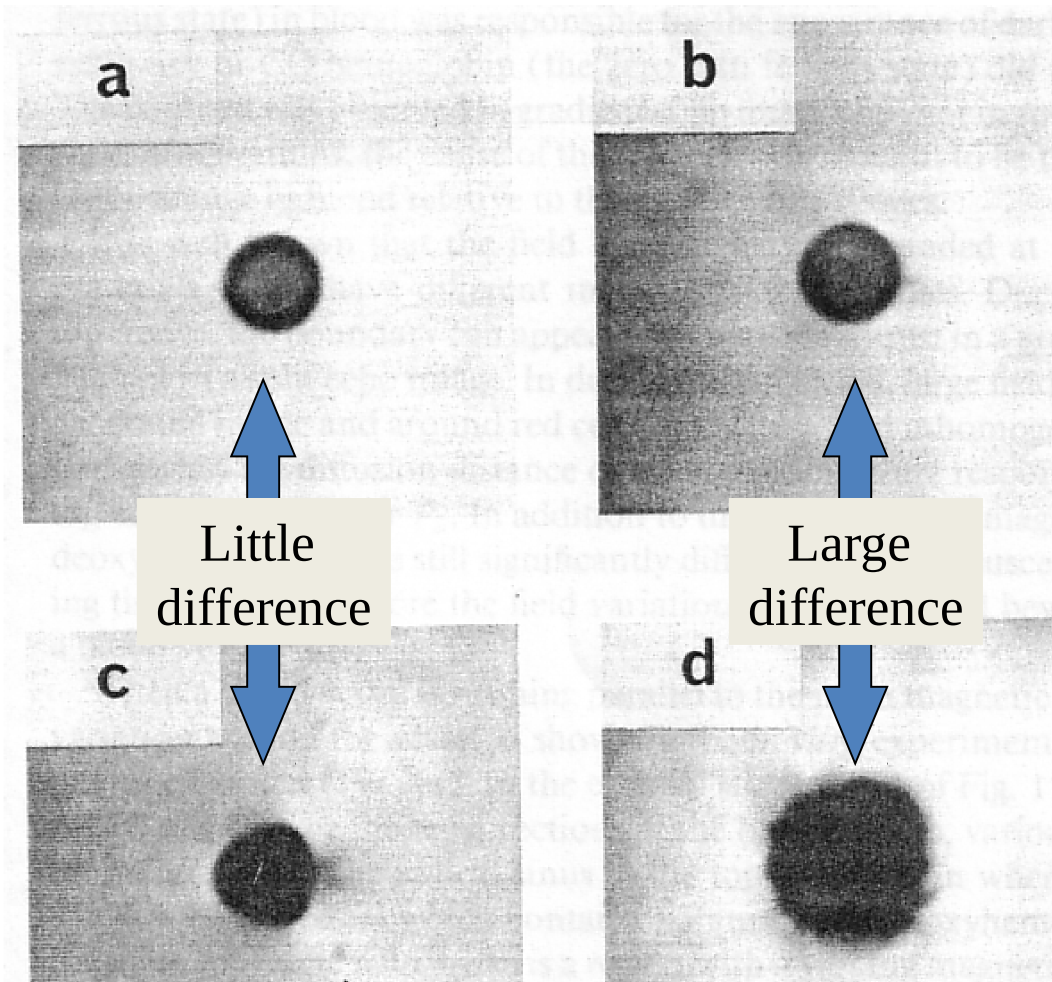
T_2 changes

Gradient Echo

T_2^* changes

Oxyhemoglobin

Deoxyhemoglobin

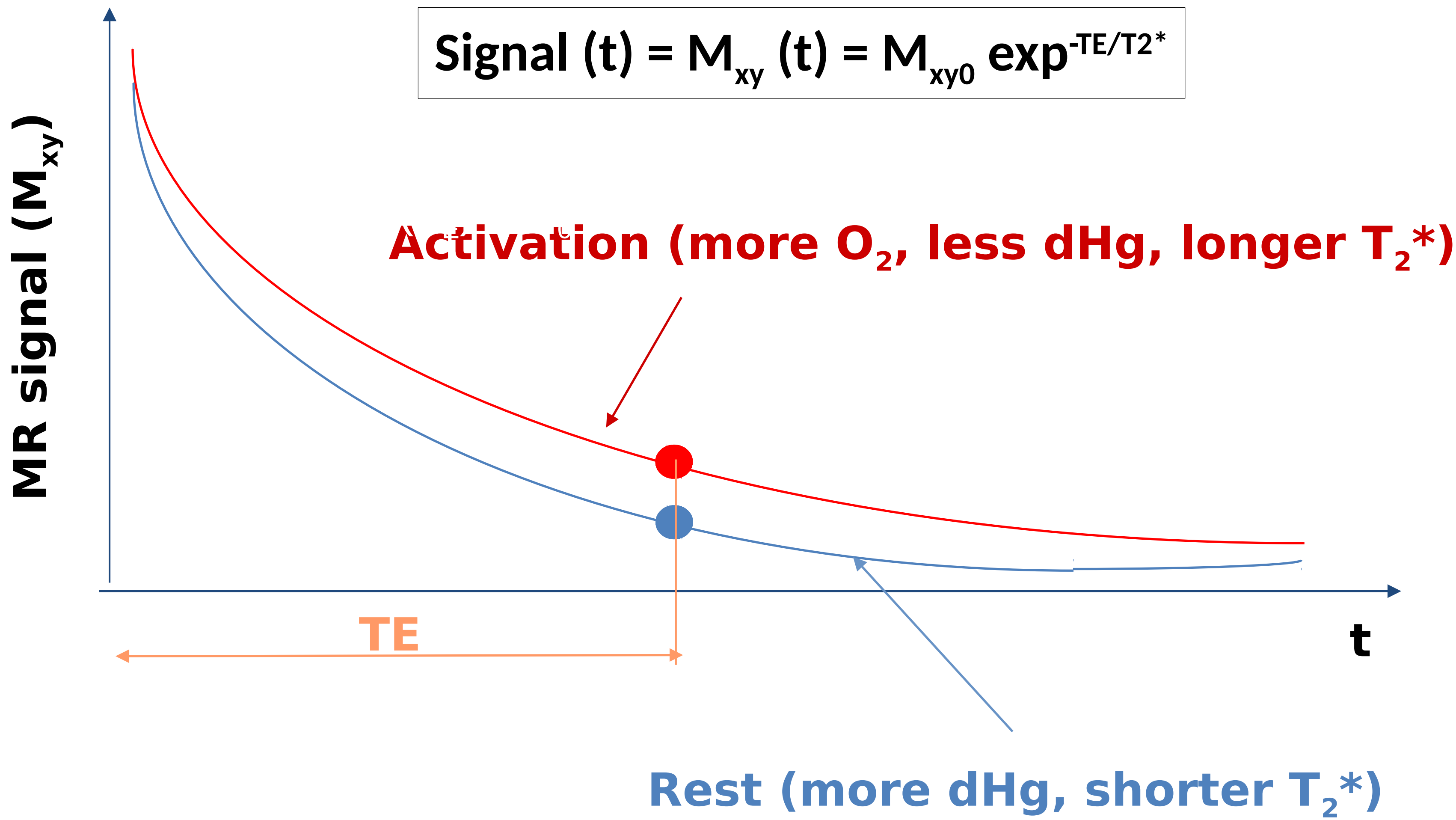


Test tubes, Ogawa 1990b

With fast T2*-weighted image, we can measure oxygenation changes in blood!

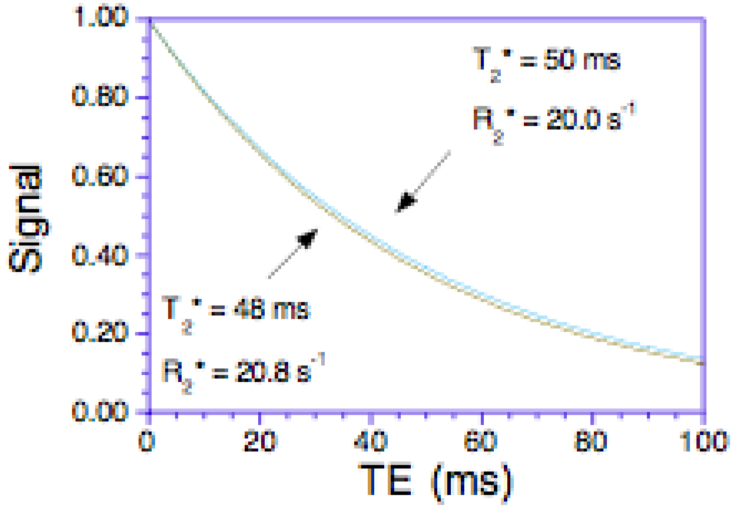
Maybe we can use blood oxygenation changes specific to brain function?

BOLD sensitivity: T_2* and TE

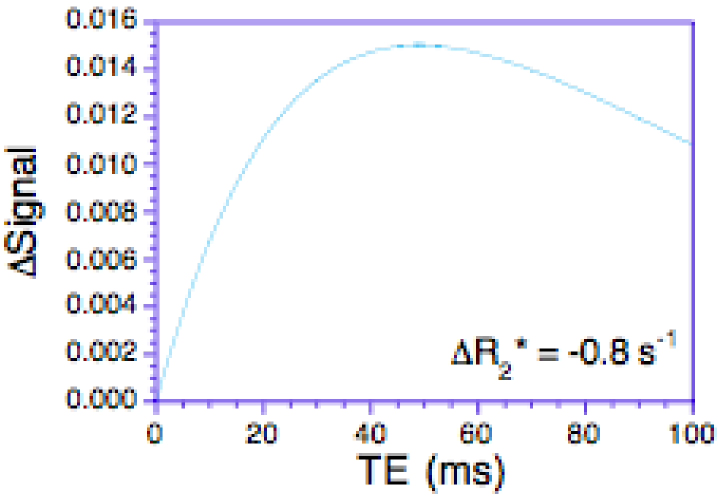


BOLD sensitivity: T_2* and TE

Gray matter T_2* changes are relatively small between activation states.



The difference in T_2* shows an optimum TE choice for the maximum sensitivity to detect changes of T_2*



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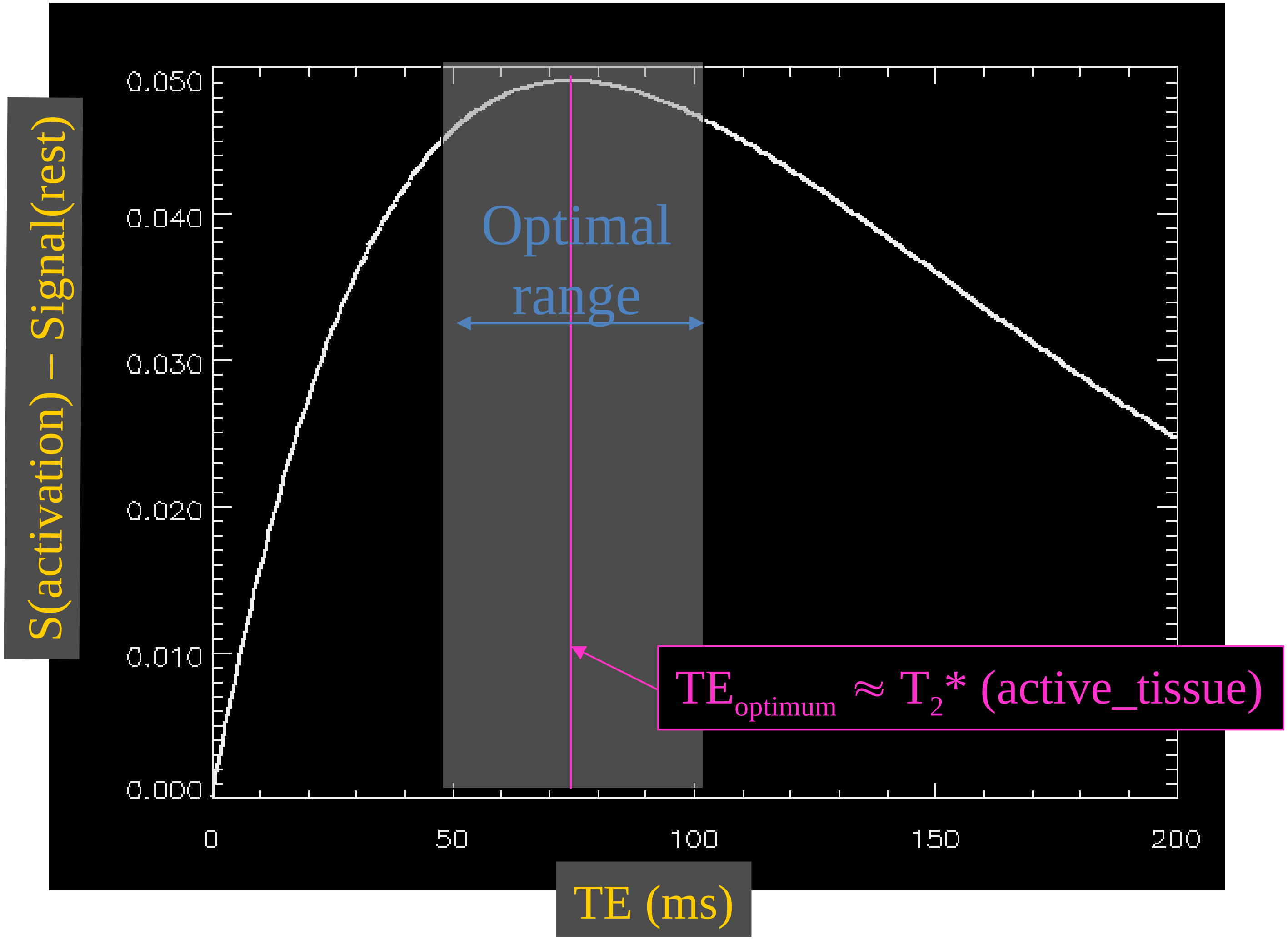
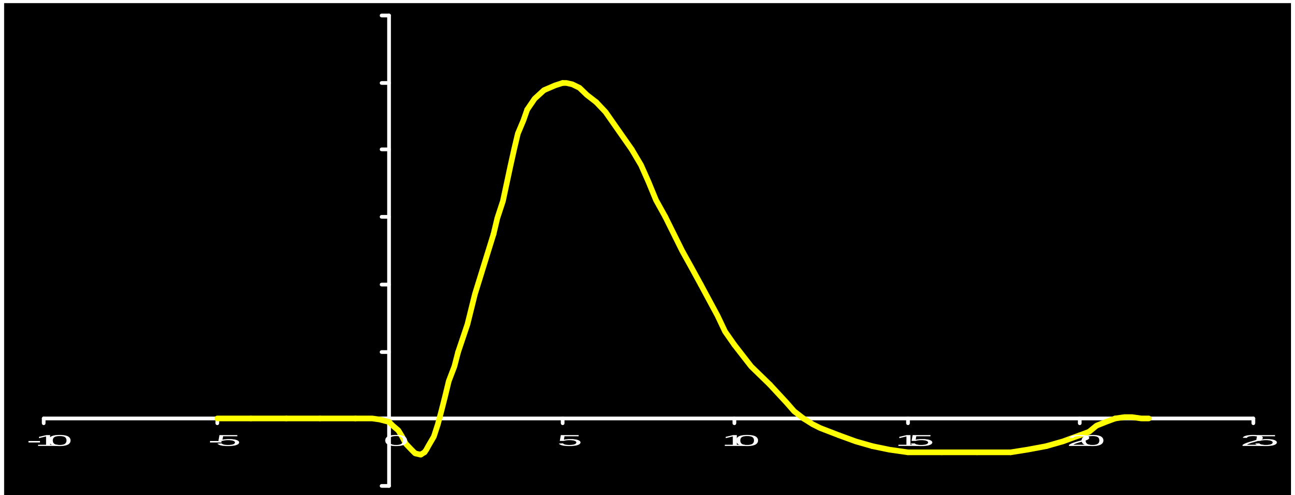
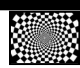


MRI measure of the hemodynamic response

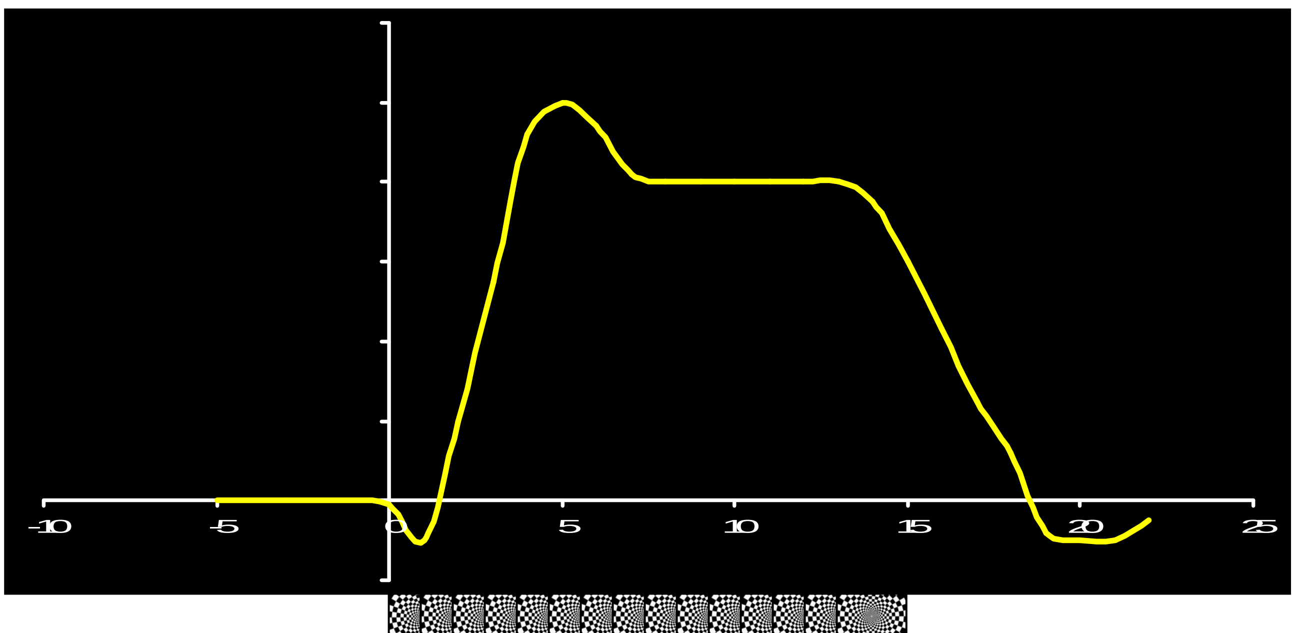




t (seconds after stimulation)

If [dHb]↑ ⇒ MR signal↓

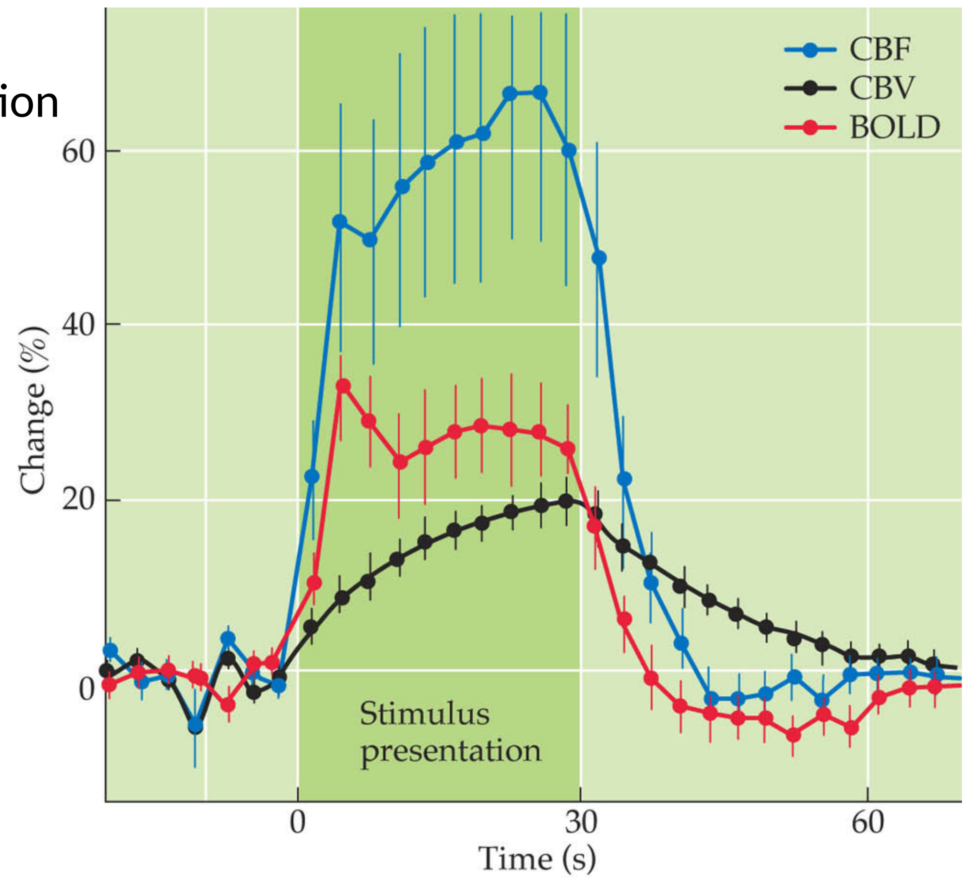
If [dHb]↓ ⇒ MR signal ↑



BOLD specificity: suboptimal

Brain activity responses to whisker stimulation in mice with contrast agent

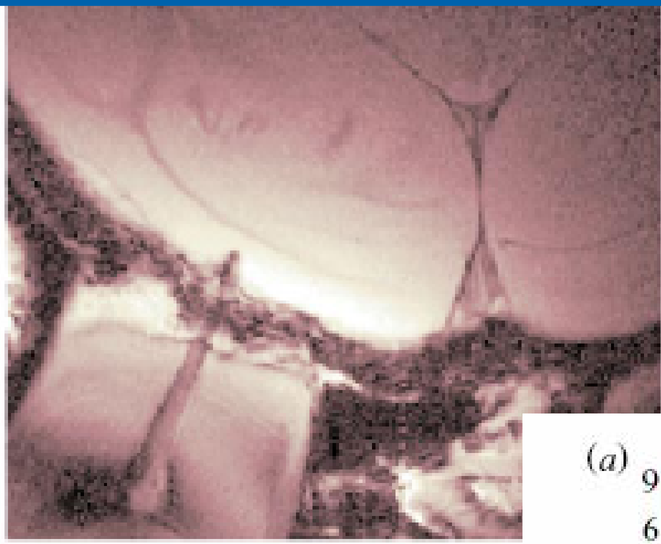
- deoxy-Hb can change because:
  - Metabolism to support neuronal activation
  - Blood flow changes
  - Blood volume changes
- BOLD measures the combined effect

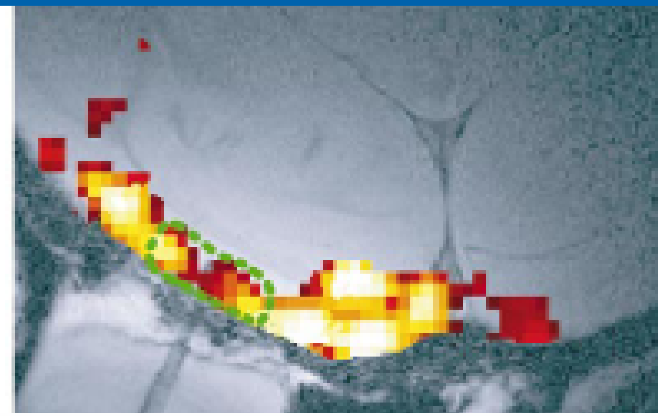


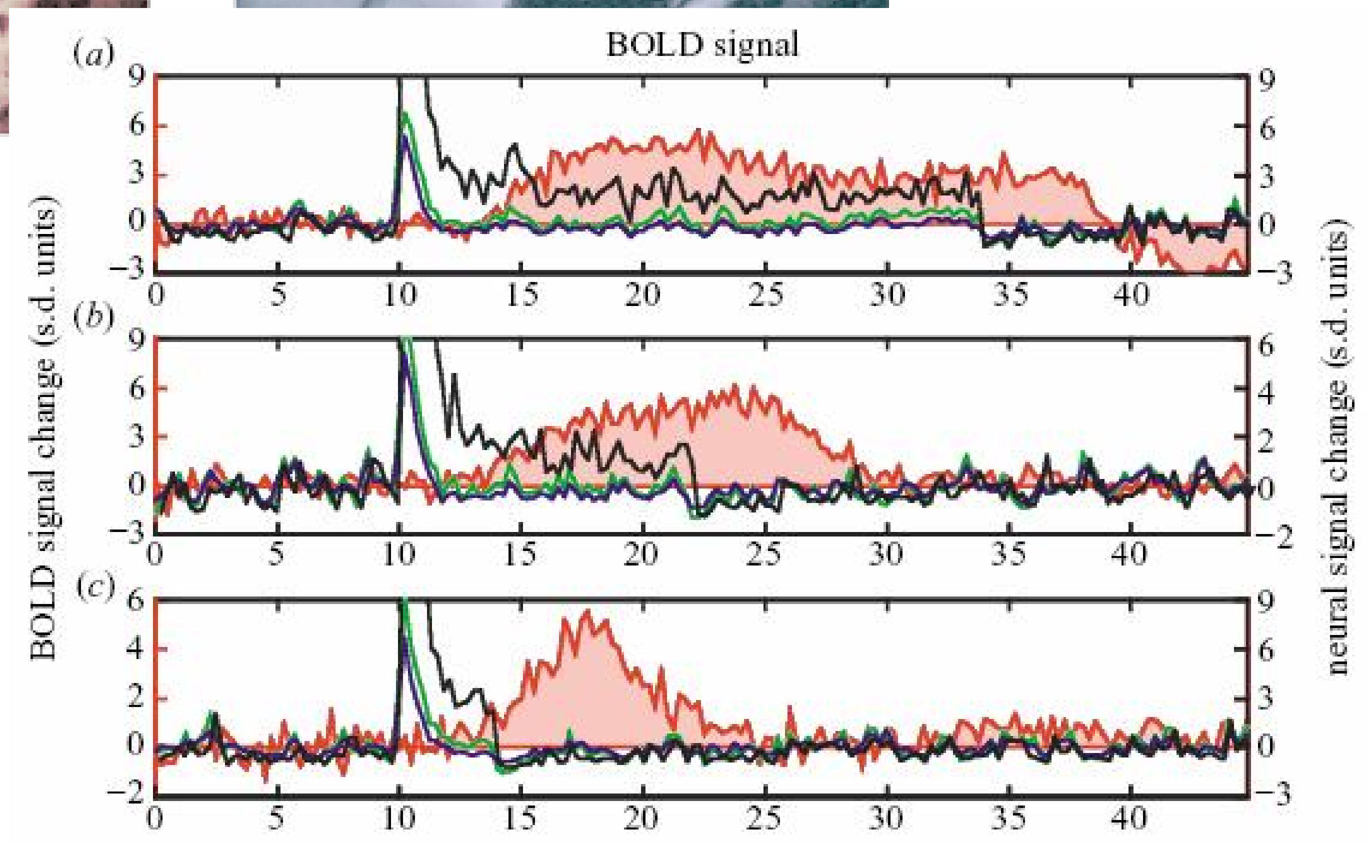
CBF: Cerebral Blood Flow
CBV: Cerebral Blood Volume
BOLD: Blood Oxygenation Level Dependent

From Huettel, Song and McCarthy

BOLD specificity: there is hope







Evidence that BOLD response reflects pooled local field potential activity (Logothetis 2001)

Lecture 4 outline

Brain functional MRI:

- **We want functional contrast:**
  - **Blood Oxygenation Level Dependent (BOLD)**
- **We want to measure signal fluctuations**
  - **Fast MRI: Echo Planar Imaging**
- **We want "clean" data for modeling & analysis**
  - **Pre-processing**

What sequence would we like for fMRI?

- High Functional sensitivity
  - T_2* gives the strongest BOLD effects
- High Speed
  - Fast acquisition to follow signal dynamics
- High Spatial resolution
  - To understand anatomical location of activity
- High Functional specificity
  - To correctly interpret signal fluctuations

Echo Planar Imaging (EPI)

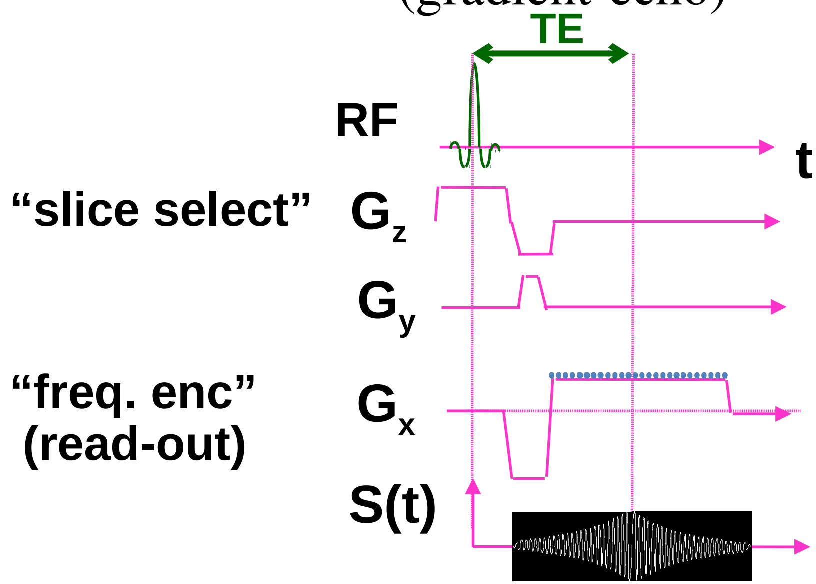
- EPI: standard imaging sequence for fast MRI
  (brain fMRI, diffusion, perfusion, etc.)

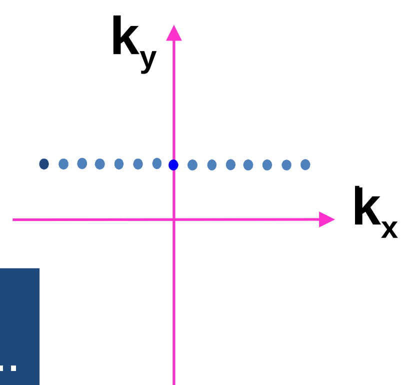
- EPI advantages for brain fMRI
  - Nowadays easily available
  - Dominant contrast is T_2^* (BOLD)
    - Spin-echo EPI can have T_2 & T_2^*
  - Typically allows full brain coverage in ~1sec (or less!) with 2 mm isotropic voxels (or less!)

- EPI limitations:
  - High sensitivity to local magnetic field inhomogeneities
    - Signal loss and image distortions
  - Gradient switching: Nyquist ghost
  - Loud
  - Signal decay during acquisition limits spatial resolution

Structural versus EPI MRI

Conventional MRI
(gradient-echo)

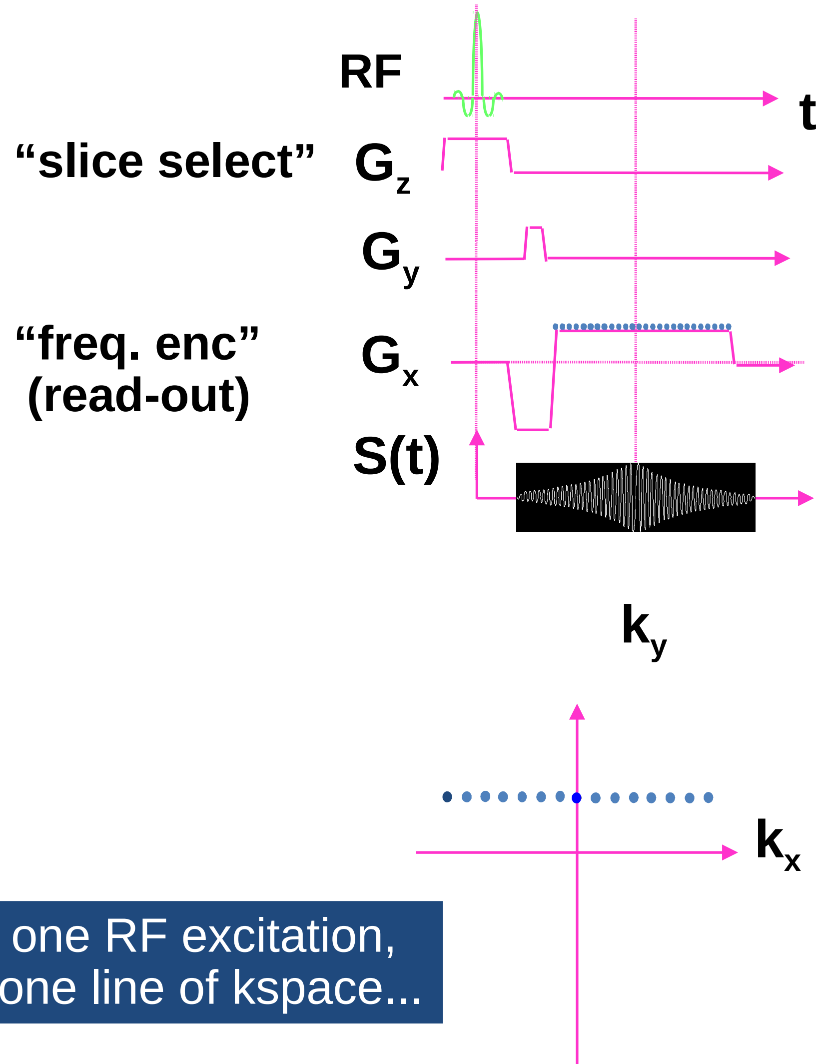




one RF excitation,
one line of kspace...

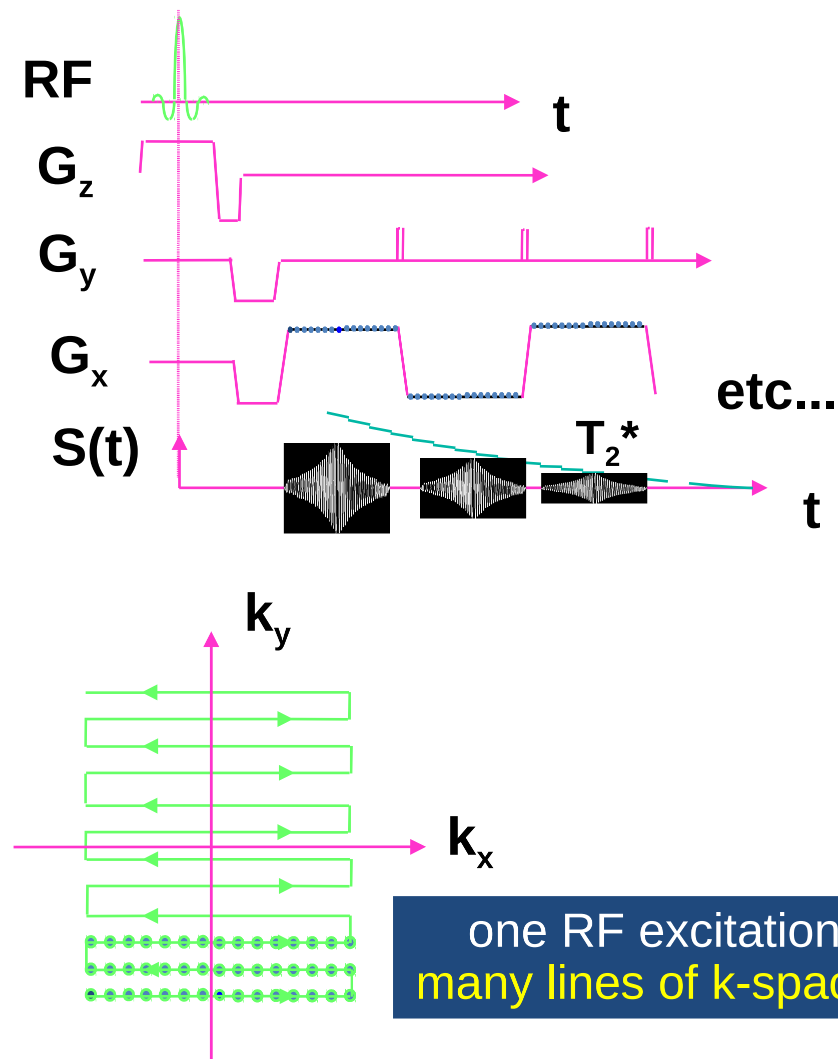
What sequence would we like for fMRI?

Conventional MRI
(gradient-echo)



one RF excitation,
one line of kspace...

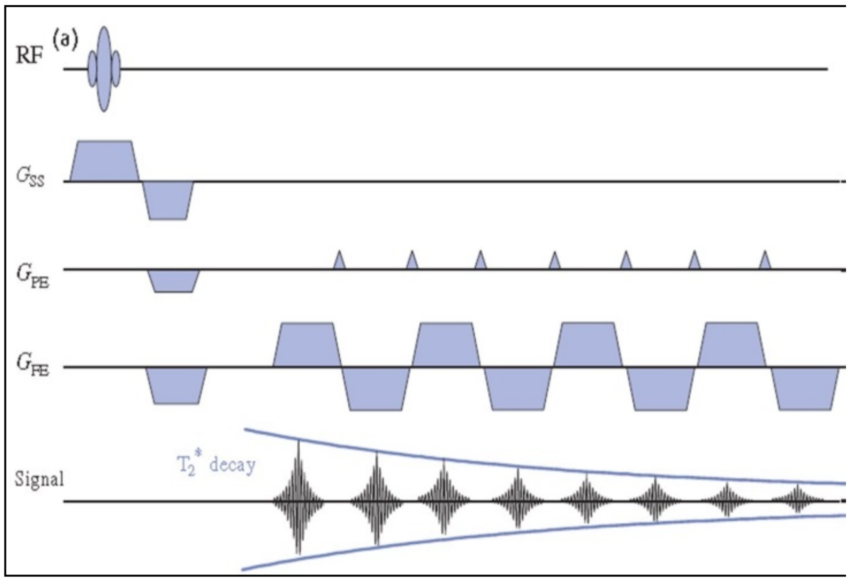
Echo-planar imaging
(gradient-echo)



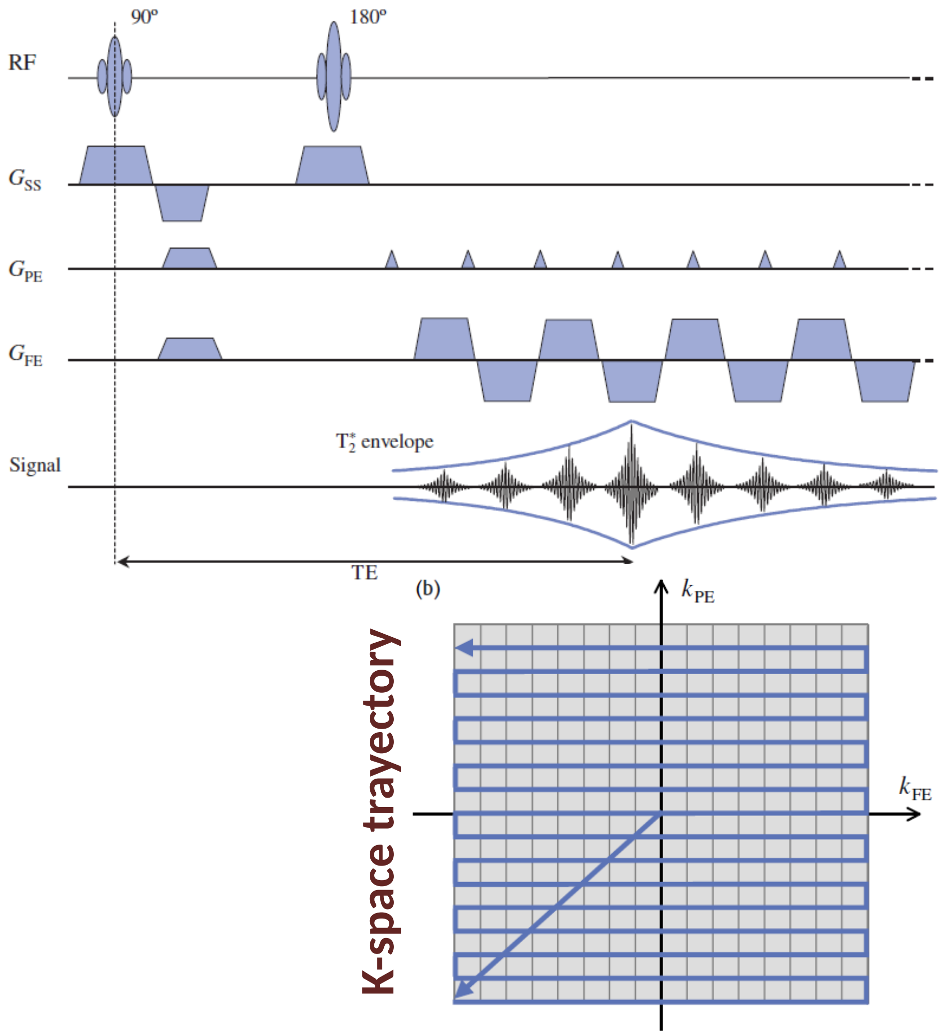
one RF excitation,
many lines of k-space...

Standard EPI

Gradient-echo EPI (T2*)



Spin-echo EPI (T2 and T2*)

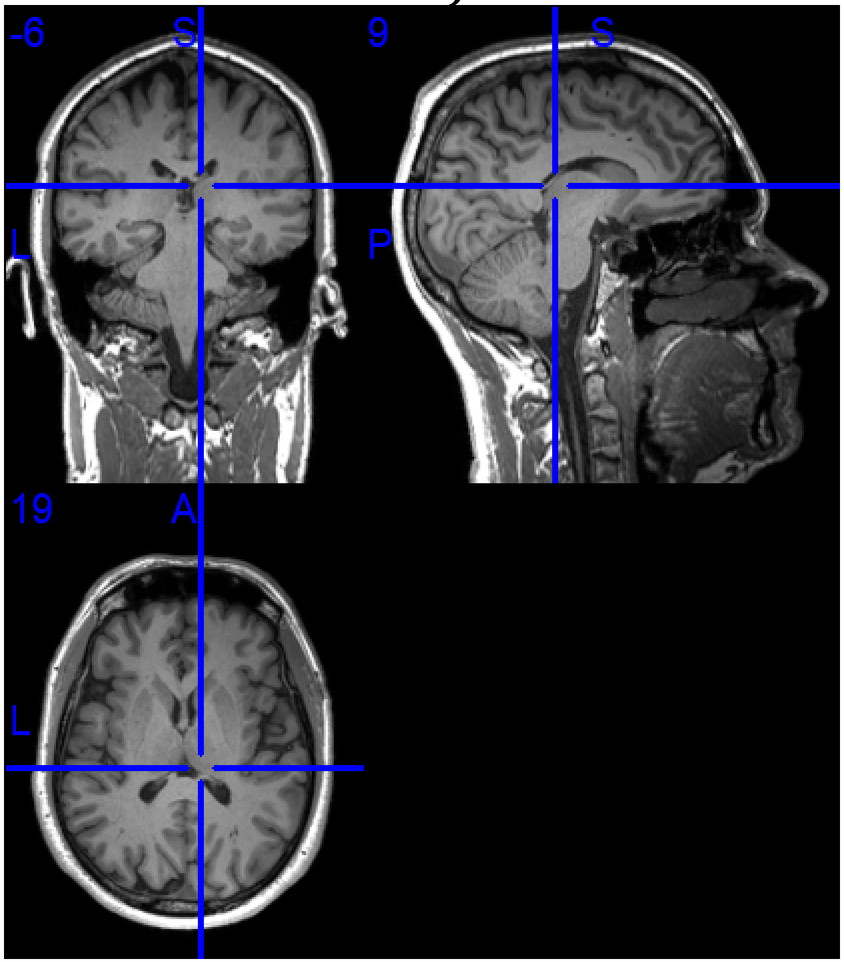


$$S_{(TE)} = S_0\, e^{-TE/T_2^*}$$

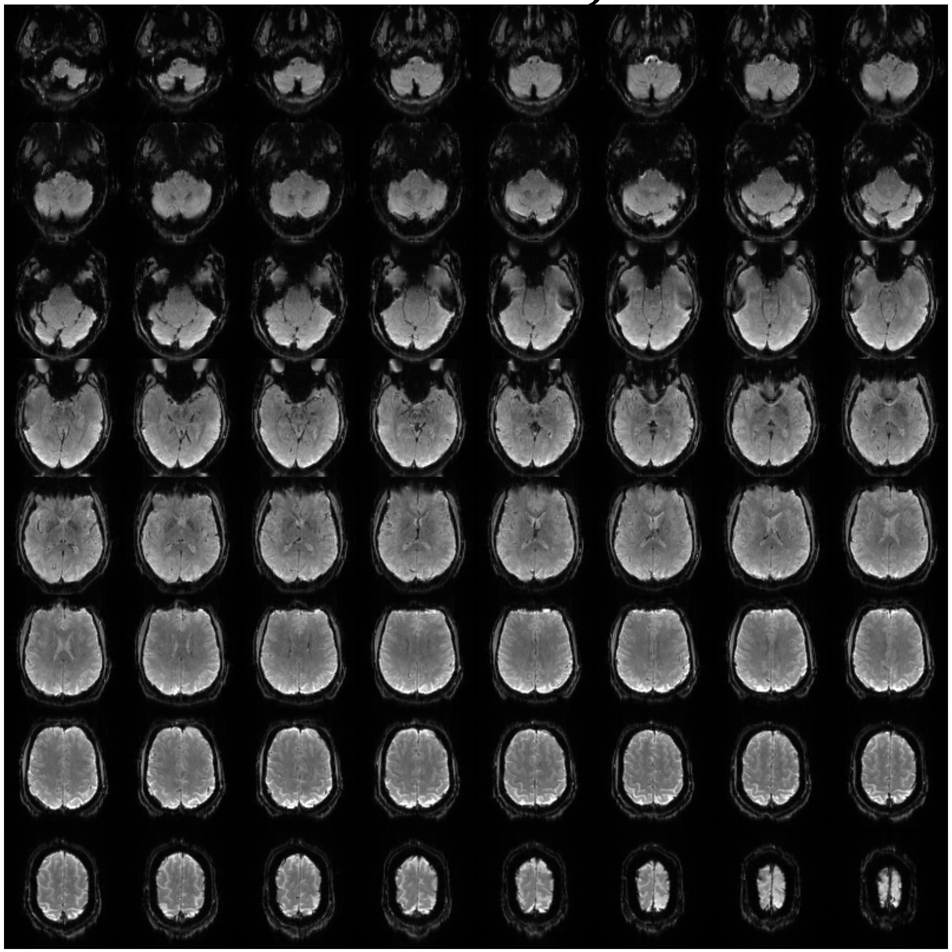
$$\frac{1}{T_2*} = \frac{1}{T_2} + \gamma \frac{\Delta B}{2}$$

Example

Structural MRI (T1-weighted)
1x1x1 mm^3, 328 s



Functional MRI (T2*-weighted)
2x2x2 mm^3, 1 s



3T Prisma Siemens, 64 head/neck channel coil

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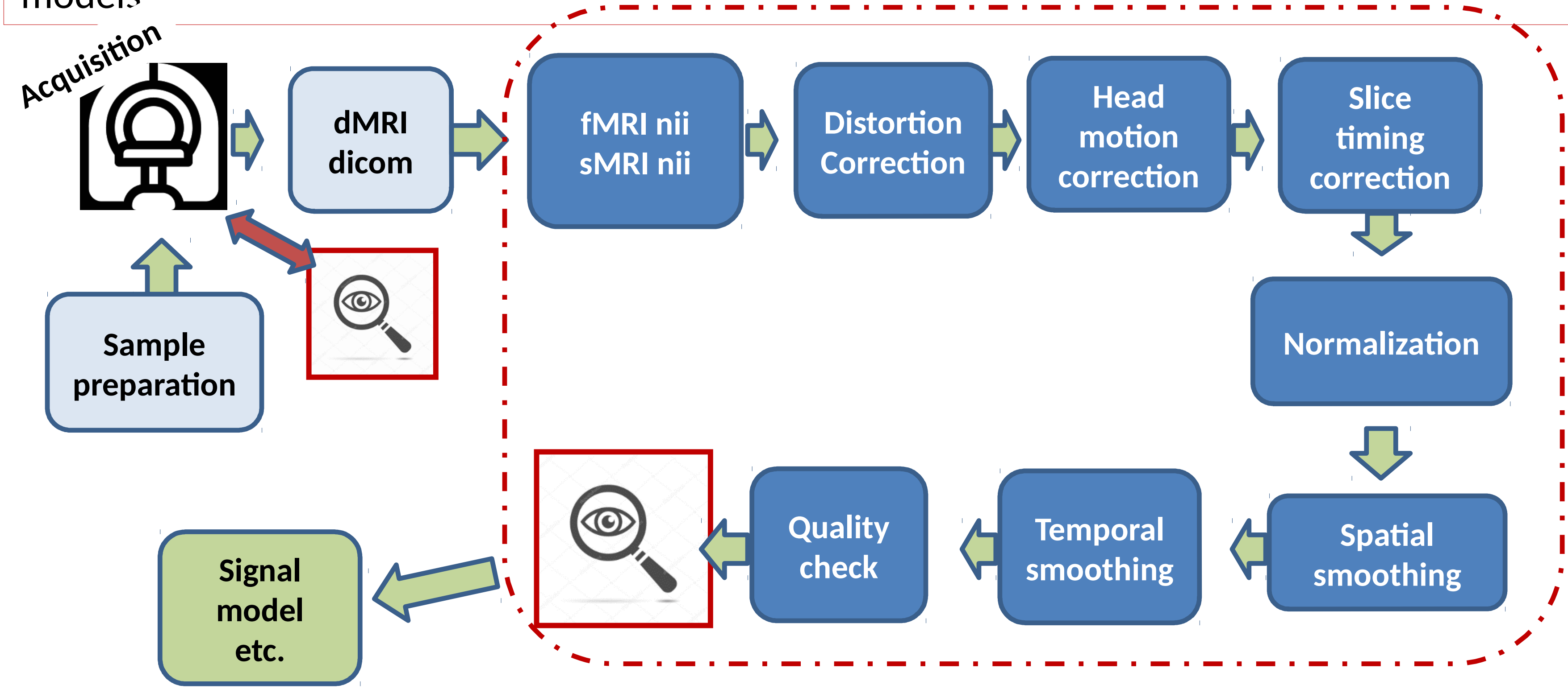
fMRI MRI pre-processing

Pre-processing: analyses steps to minimize noise, artifacts to get the «cleanest» data for models



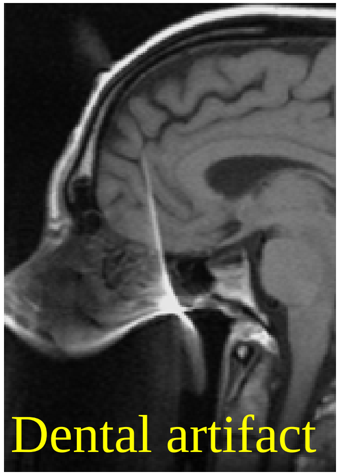
This is a generic example
Jury out for optimal details

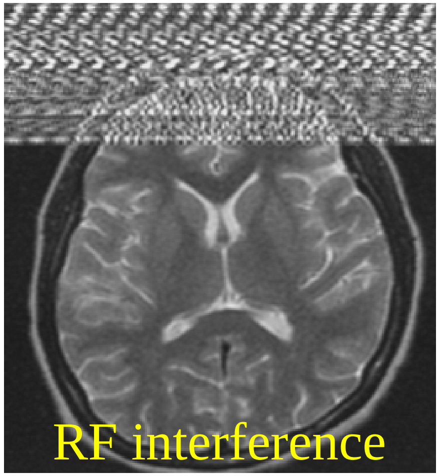
Various pre-processing tools available:

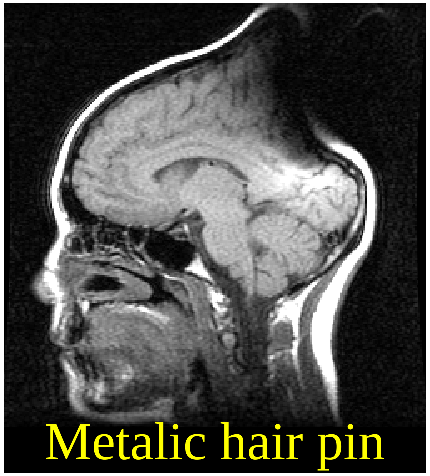
- https://www.fil.ion.ucl.ac.uk/spm/
- https://fsl.fmrib.ox.ac.uk/fsl
- https://afni.nimh.nih.gov/
- …

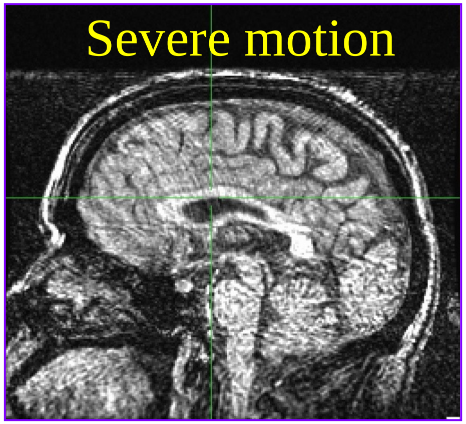
LOOK at the data DURING the experiment

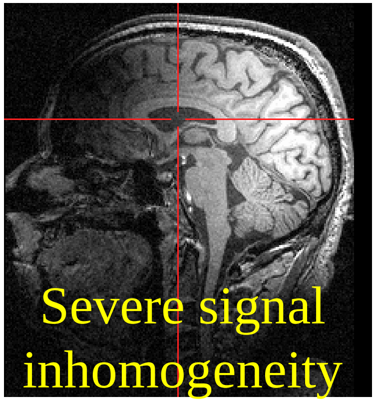
Look for problems, for example:

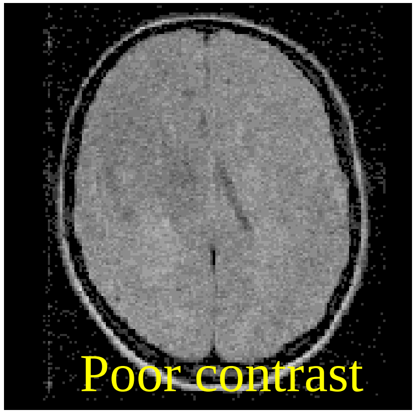


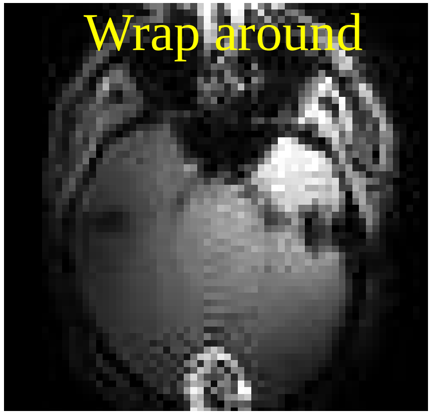


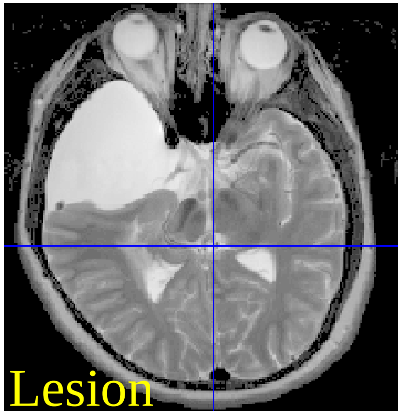












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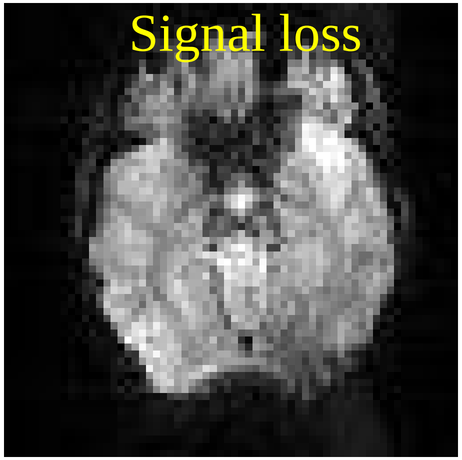

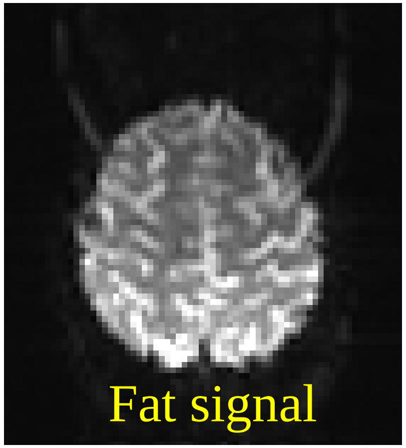

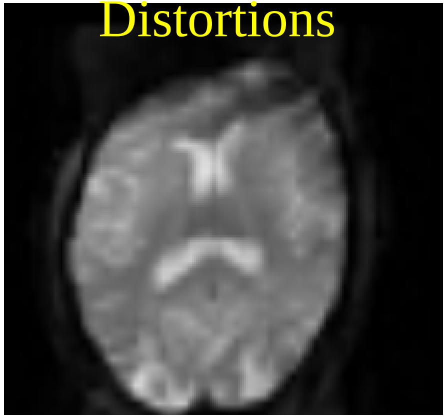

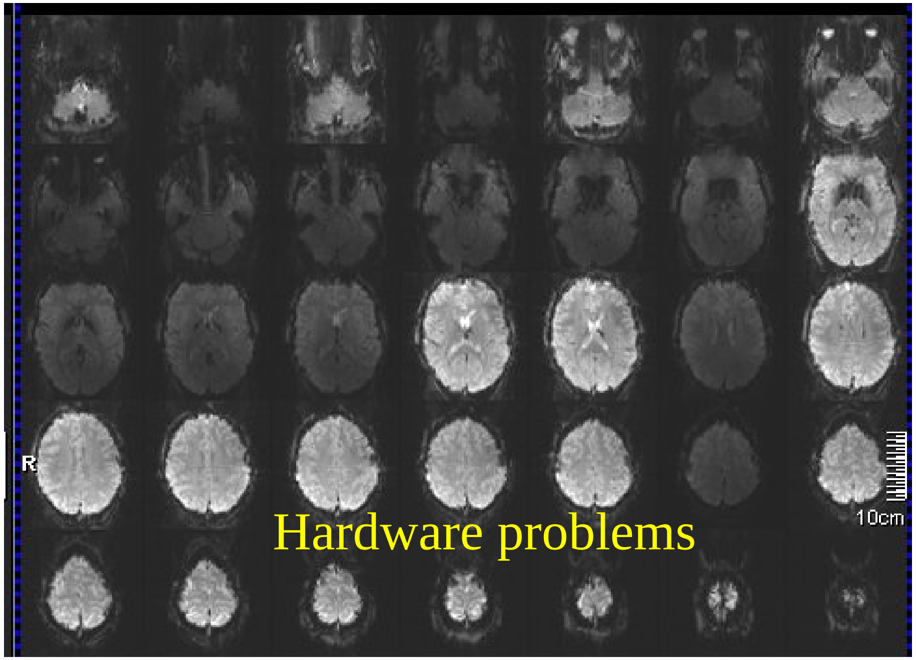

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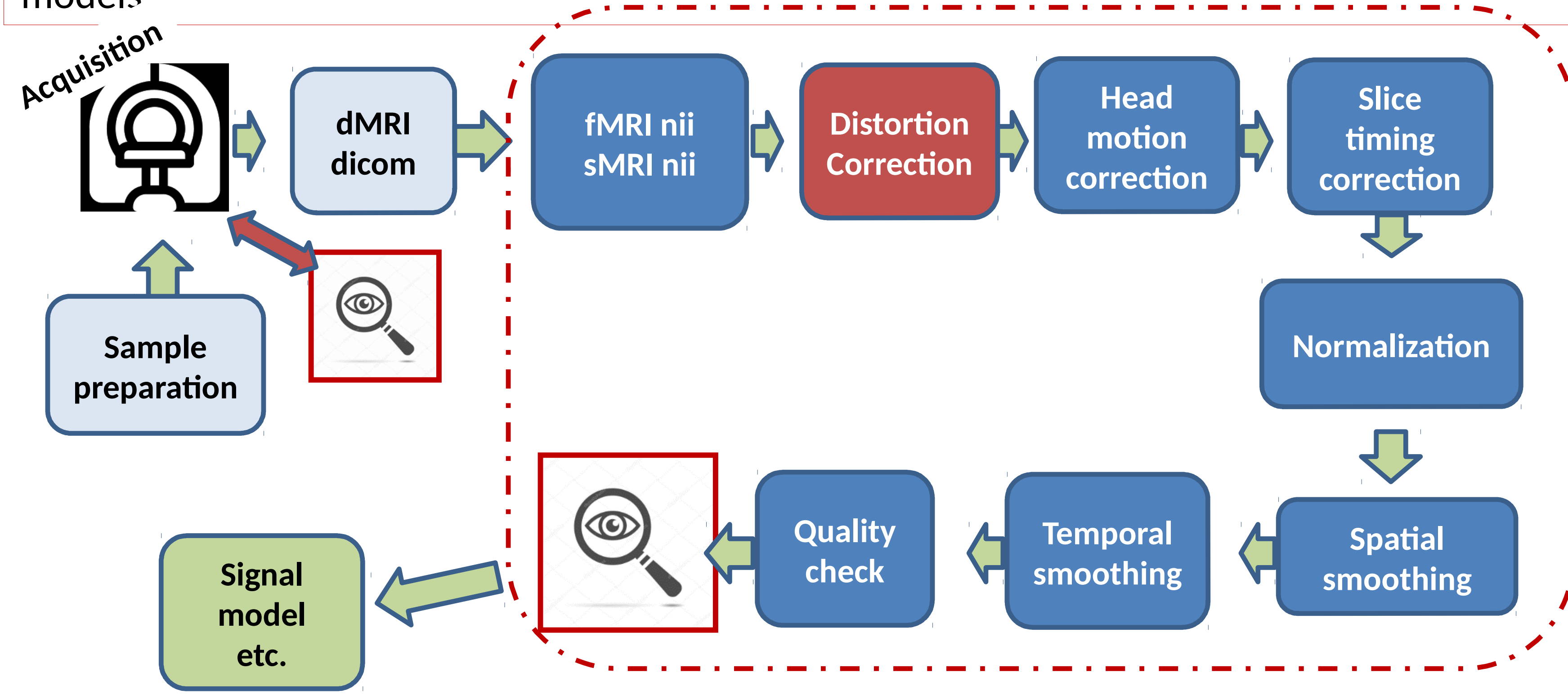

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- https://afni.nimh.nih.gov/
- …

Geometric distortions in EPI

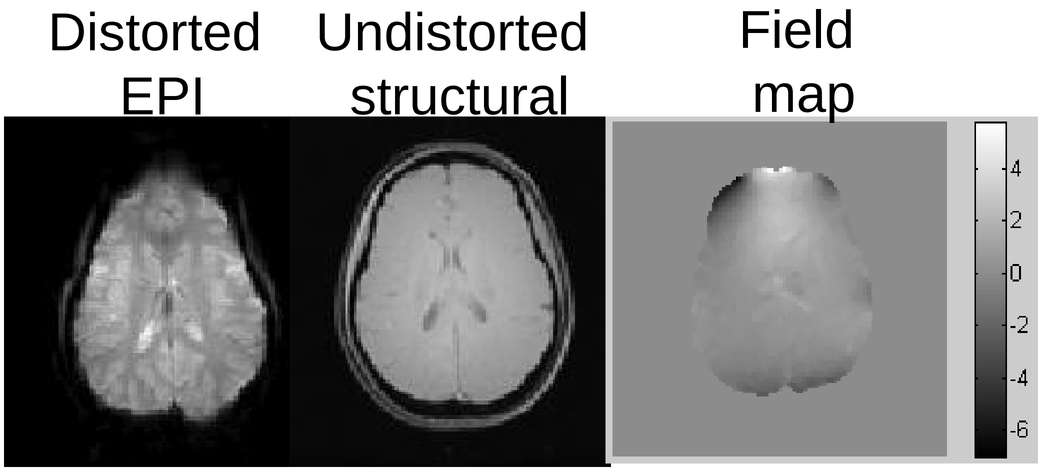
- The problem:
  - Image reconstruction assumes uniform B_0 in the sample
  - In reality this is not true: $B(\bar{r}) = B_0 + \Delta B(\bar{r})$
  - As a result, EPI shows:
    - areas with signal loss (where T2*<<TE): nothing to do!
    - areas with geometric distortions: something to do!

$$\Delta x = \gamma \cdot \Delta B(\bar{r}) \cdot FOVx \cdot \Delta tx$$
$$\Delta y = \gamma \cdot \Delta B(\bar{r}) \cdot FOVy \cdot \Delta ty$$

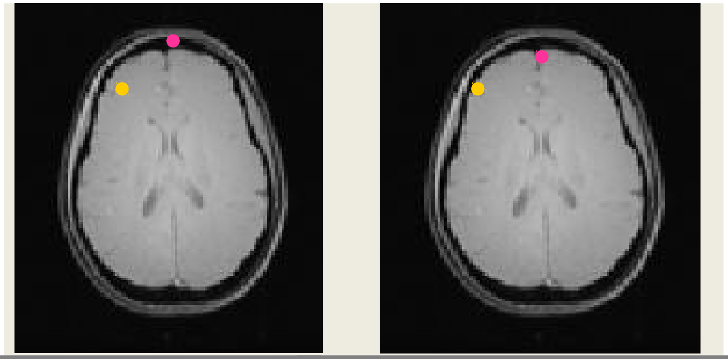
Voxel shifts relative to true voxel location.
So:
If ΔB is measured
we can shift back voxel

Δx, Δy : amounts of shift (misplacement) in x, y directions in mm
FOVx, FOVy : field of view in x, y direction in mm
Δtx, Δty : sampling interval in x, y direction ($\propto$ 1/sampling rate)

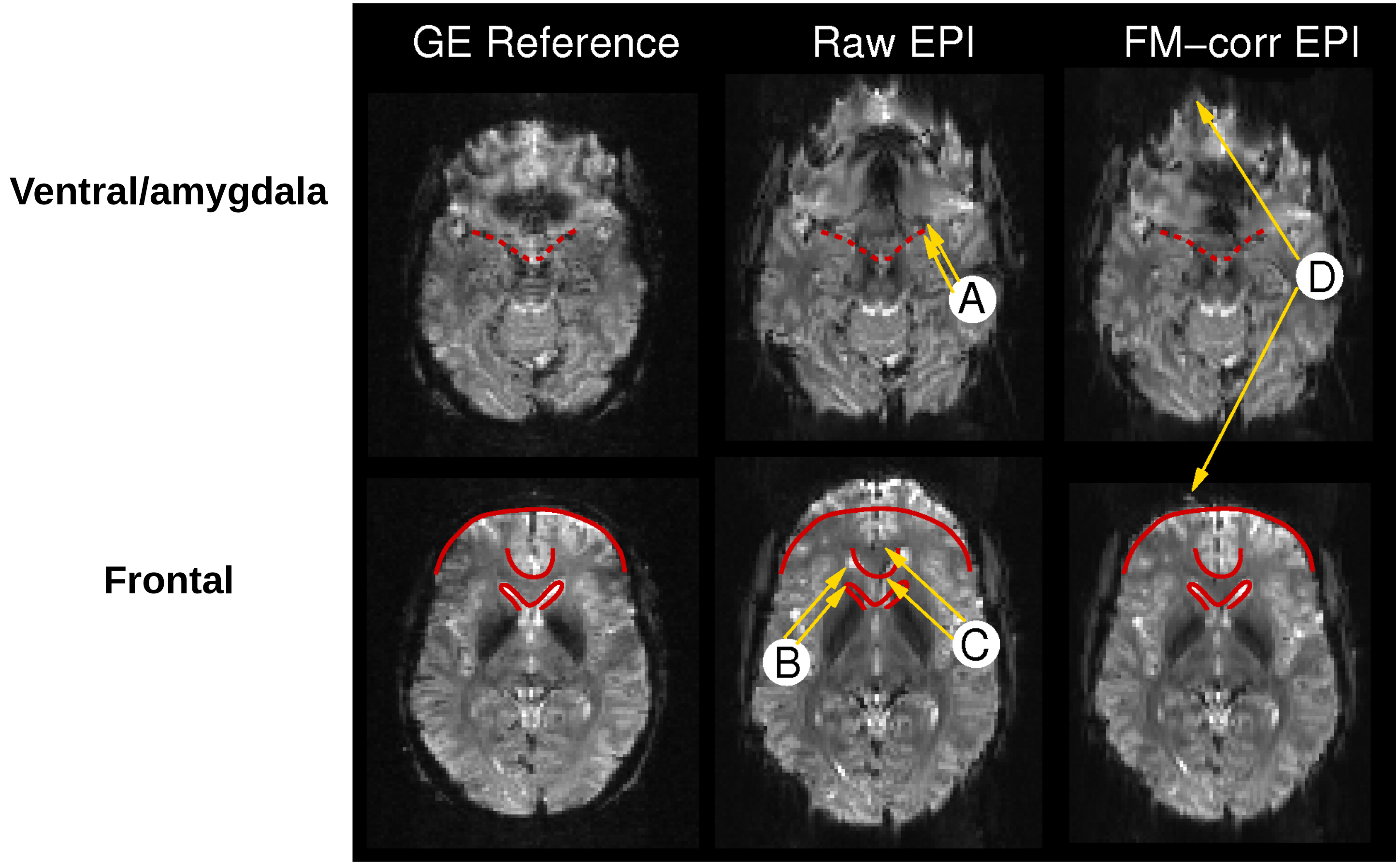
Geometric distortions in EPI



- **Significance**
  - Misregistration of EPI and Anatomical image
    - ⇒ Incorrect mapping of region of interest(ROI)
    - ⇒ Need to be corrected using **Fieldmap**



EPI geometric distortions and correction



A) ~ 2 mm distortions close to the amygdala

B) 11 mm distortions at the ventricles

C) 14 mm distortions ant grey matter

D) Small residual field map errors

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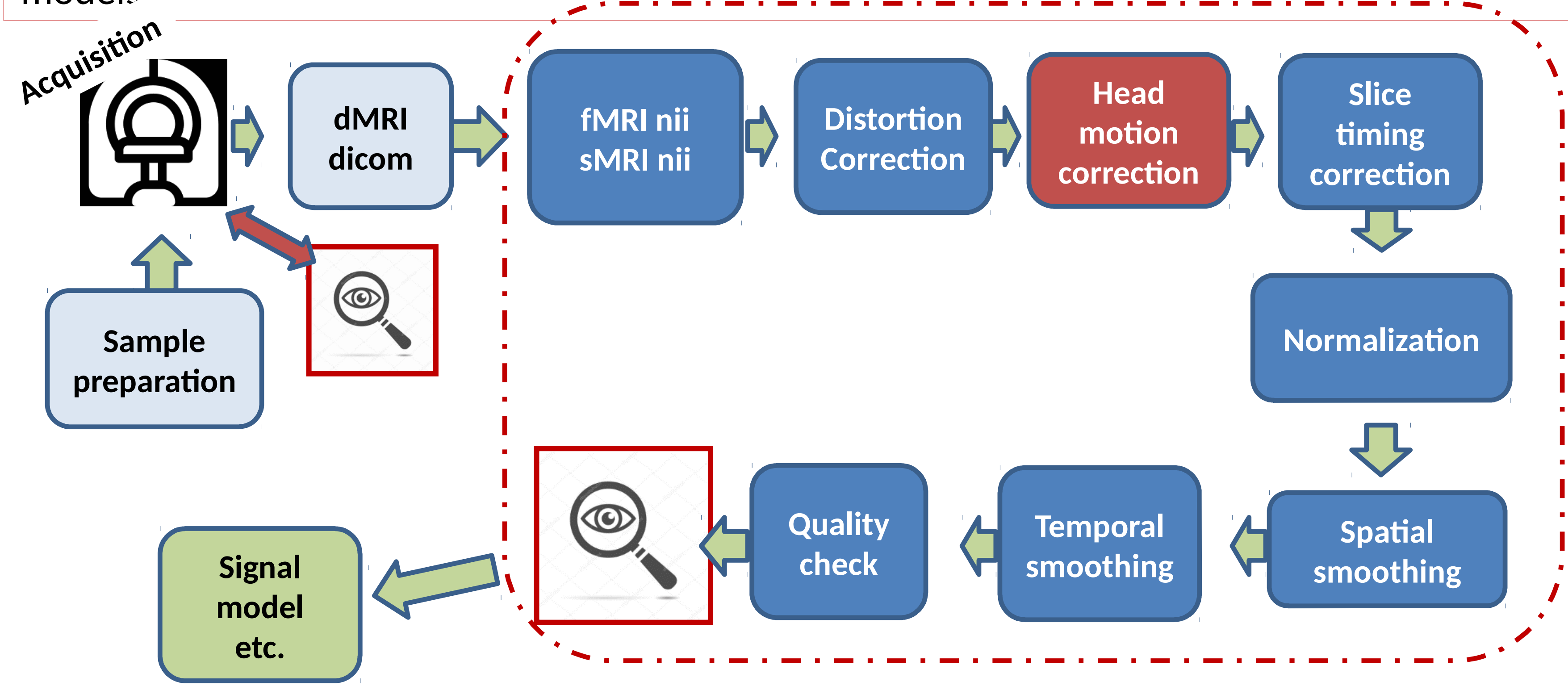

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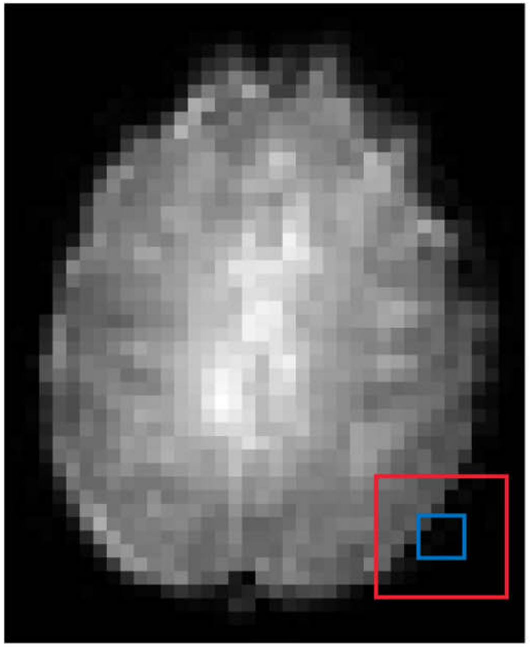
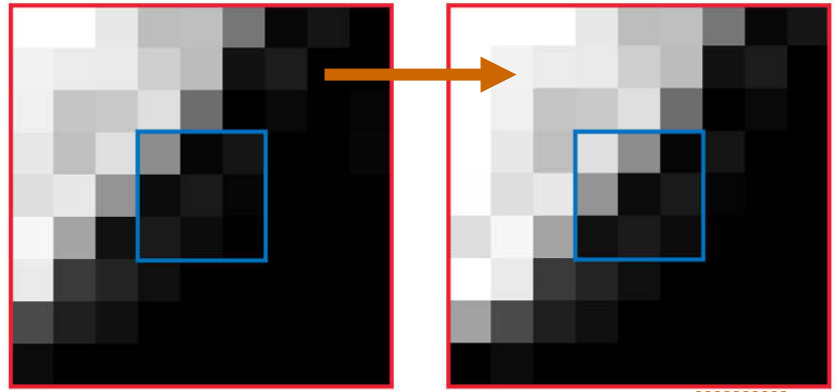
- …

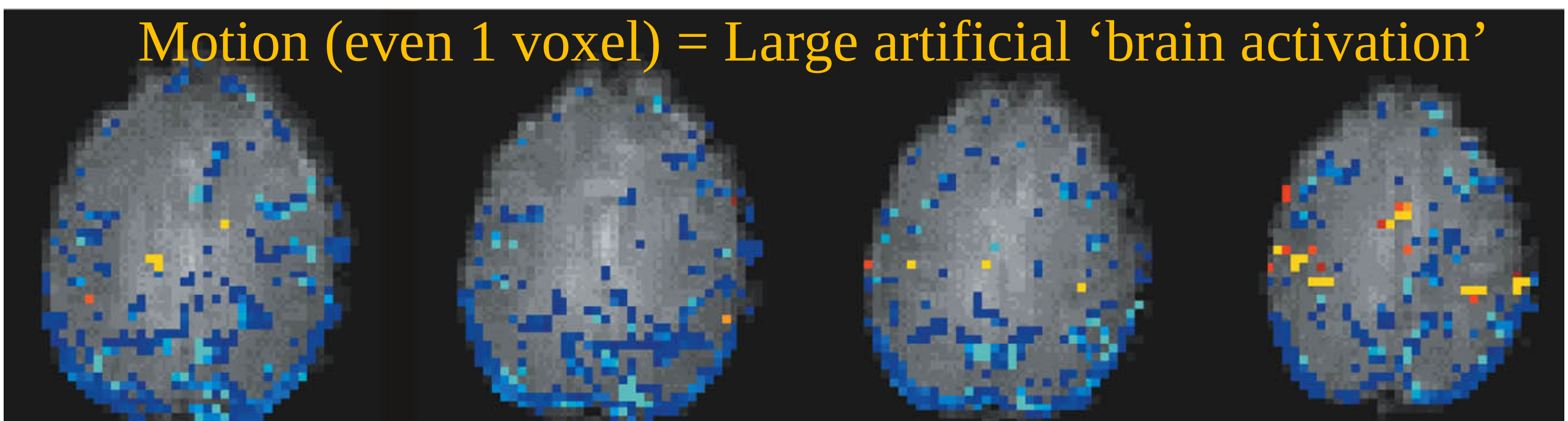
Head motion effects





507	89	154
119	171	83
179	117	53

663	507	89
520	119	171
137	179	117



Motion correction: co-registration to reference

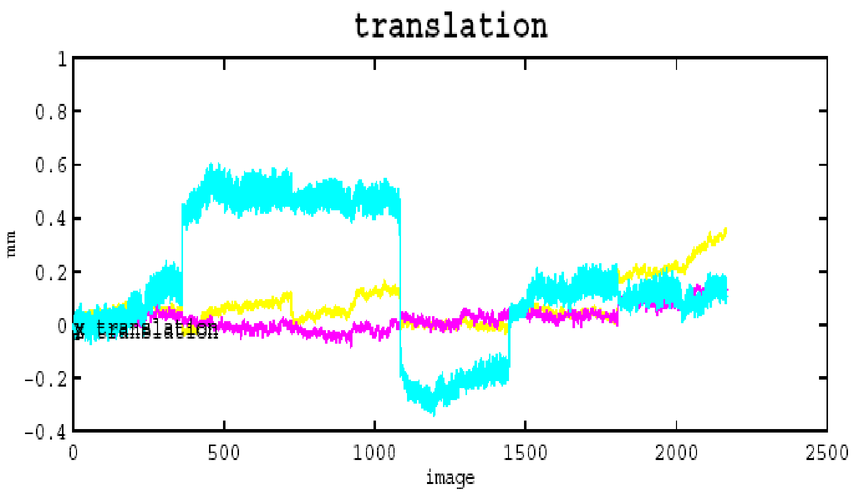
- Define a reference image from the EPI time series
- Iteratively co-register (minimize a cost function) each EPI to reference
  - Determine the rigid body transformation that minimizes
  - For each corrected EPI the transformation is defined by

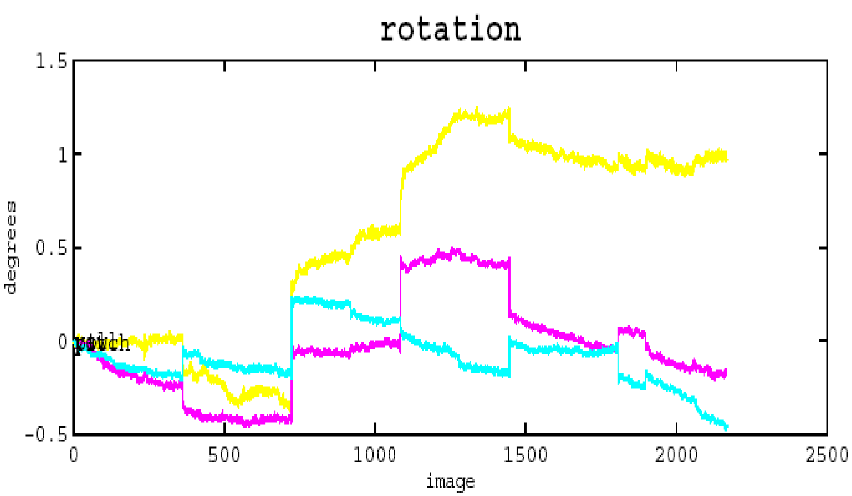
    3 translations - in X, Y & Z directions.

    3 rotations - about X, Y & Z axes.

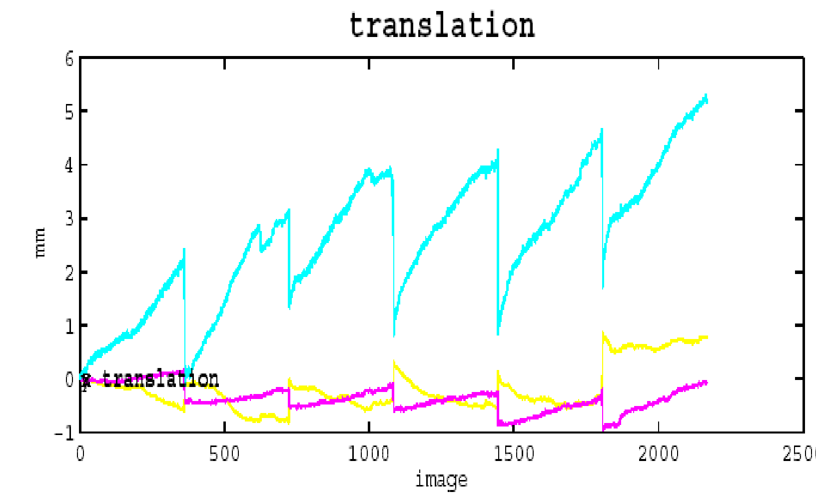
Motion correction results

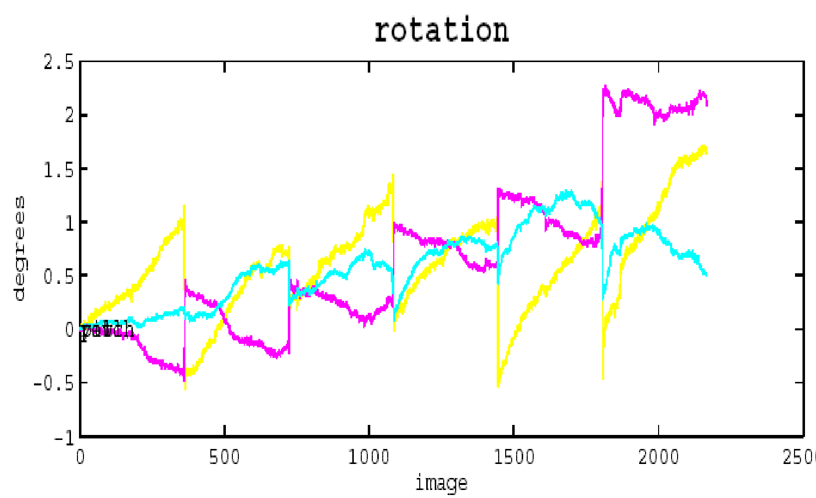
Could be acceptable motion





Too much motion (>> 1mm)

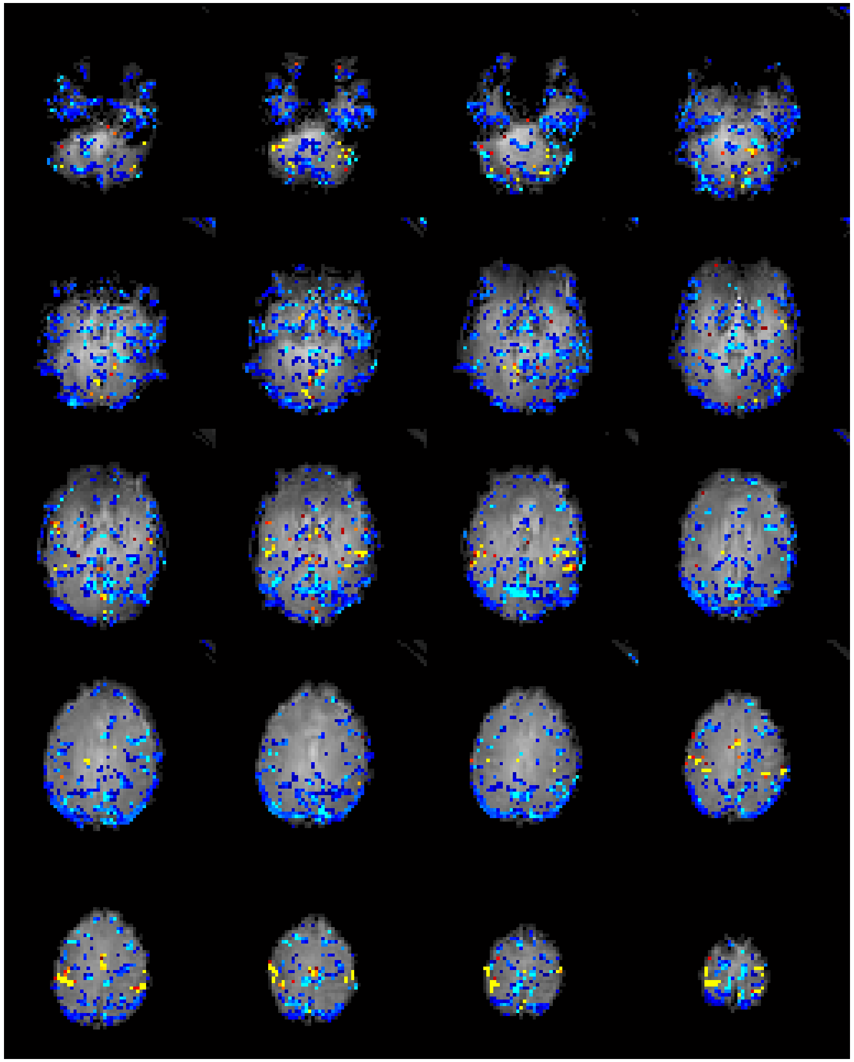




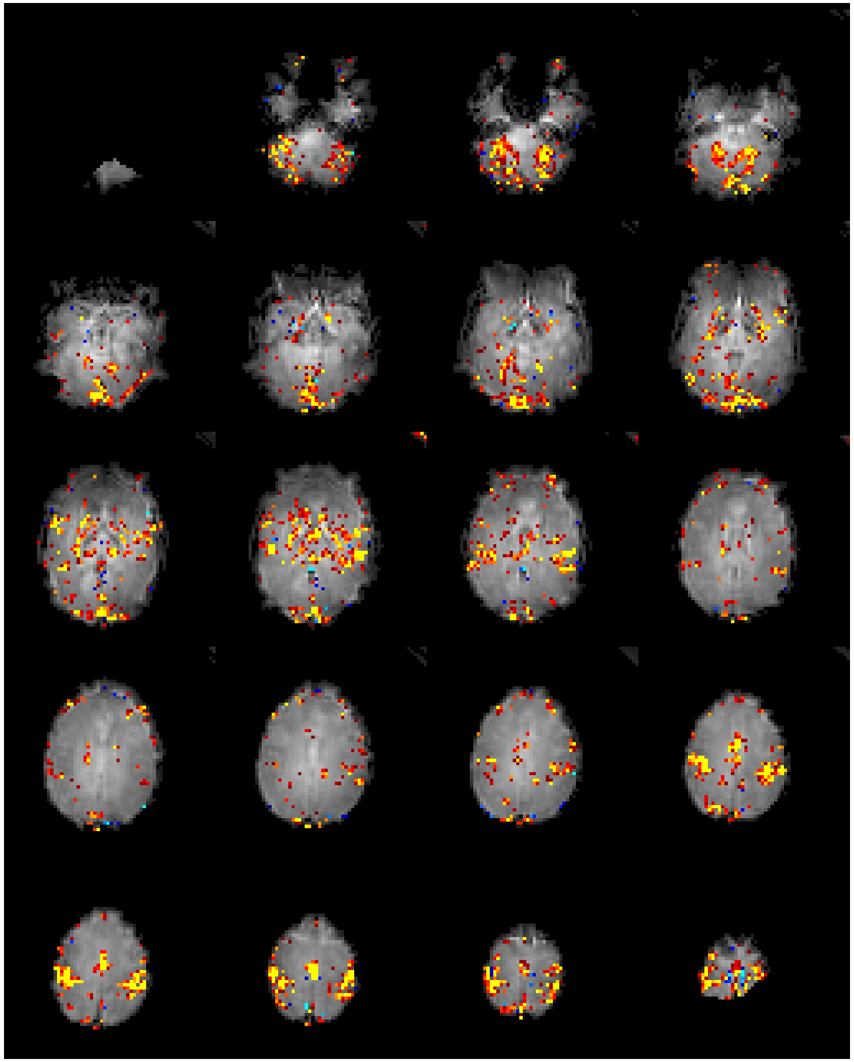
Modified from Source: Huettel S.A., Song A.W., McCarthy G.

Motor fMRI without/with motion correction

Uncorrected

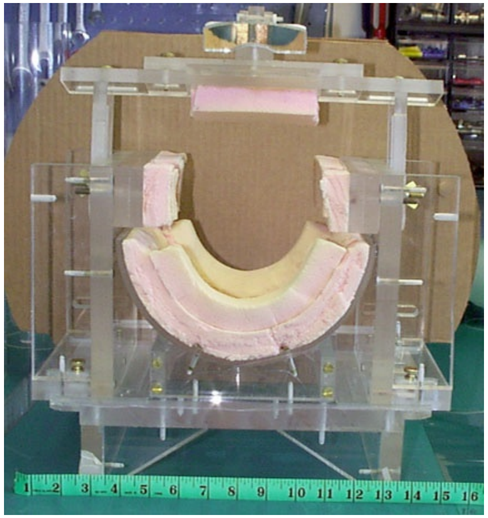


Corrected



Modified from Source: Huettel S.A., Song A.W., McCarthy G.

Reducing head motion



Head Vise
(more comfortable than it sounds!)

Bite Bar

Vacuum Pack

Thermoplastic mask

Often collaboration and foam padding works as well as anything

Reducing motion: Prevention best remedy

- Tell your subjects how to be good subjects
  - "Don't move" is too vague

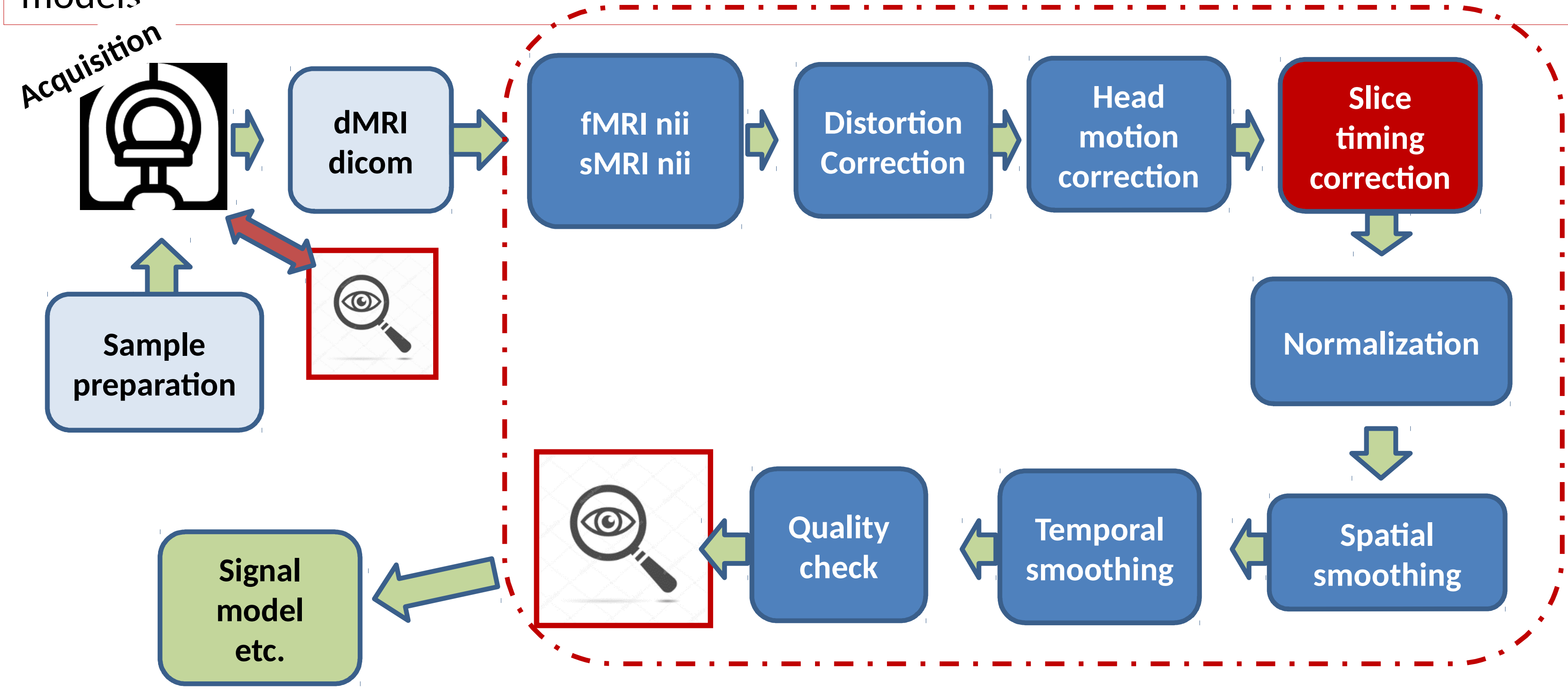
- Make sure the subject is comfy going in
  - avoid "princess and the pea" phenomenon
- Emphasize importance of not moving at all during beeping
  - do not change posture
  - if possible, do not swallow
  - do not change posture
  - do not change mouth position
  - do not tense up at start of scan
- Discourage any movements that would displace the head between scans
- Do not use compressible head support

- Example of info for first-time subjects:
  http://defiant.ssc.uwo.ca/Jody_web/Subject_Info/firsttime_subjects.htm

Source: Jody Culham

fMRI MRI pre-processing

Pre-processing: analyses steps to minimize noise, artifacts to get the «cleanest» data for models



This is a generic example
Jury out for optimal details

Various pre-processing tools available:

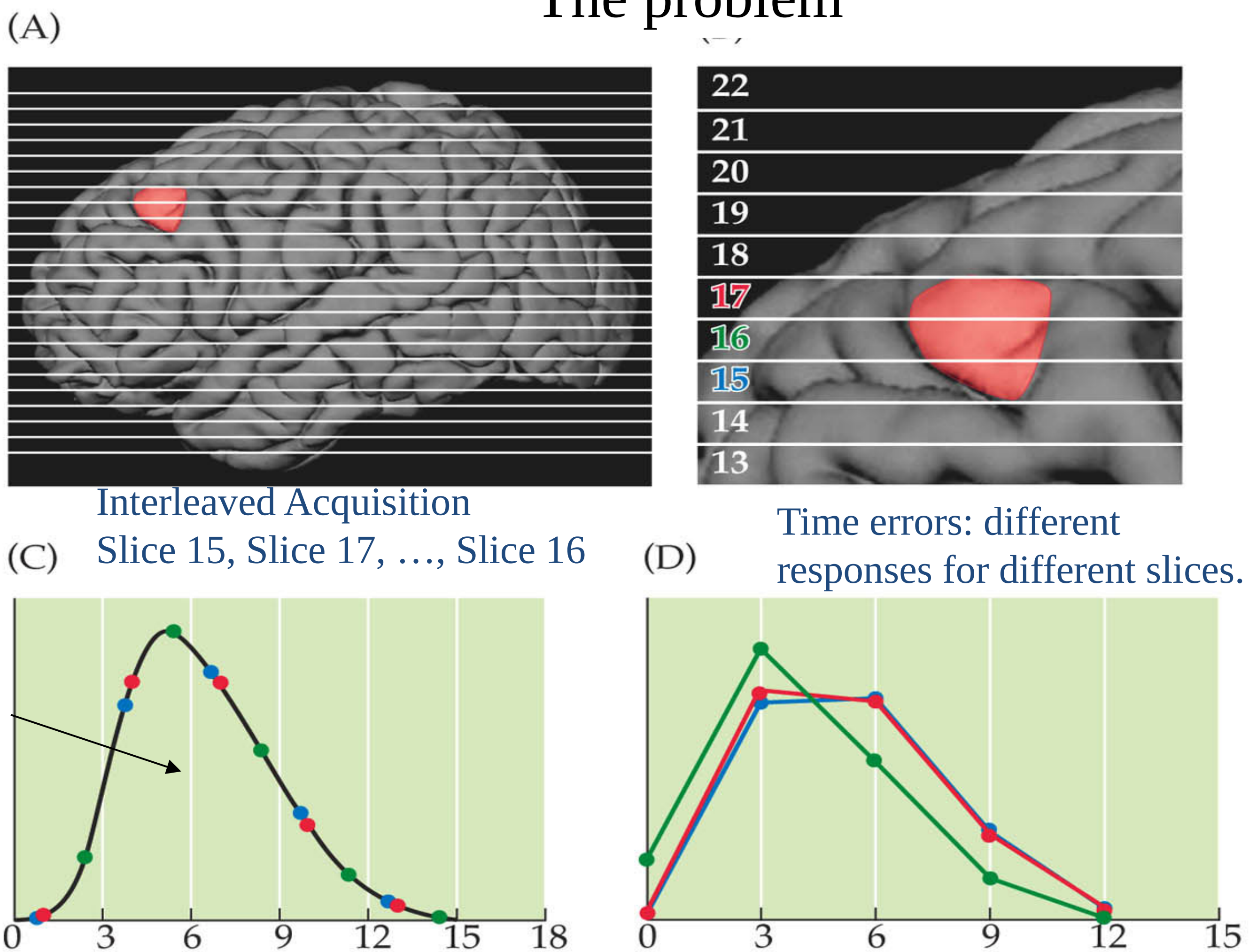
https://www.fil.ion.ucl.ac.uk/spm/
https://fsl.fmrib.ox.ac.uk/fsl
https://afni.nimh.nih.gov/
...

Slice acquisition timing correction

- The problem:
  - Ideally
    - Each brain volume is acquired instantaneously
    - Each volume time point represents the cognitve state of the whole brain related to that time point
  - In reality
    - Echo image slice is acquired at a different time
      - Sequential slice acquisition
      - Interleaved slice acquisition
  - Consequence:
    - inacurrate representation of hemodynamic response
- Solutions:
  - Reduce the time for whole-brain sampling
  - Postprocessing: temporal interpolation

Slice acquisition timing correction

The problem

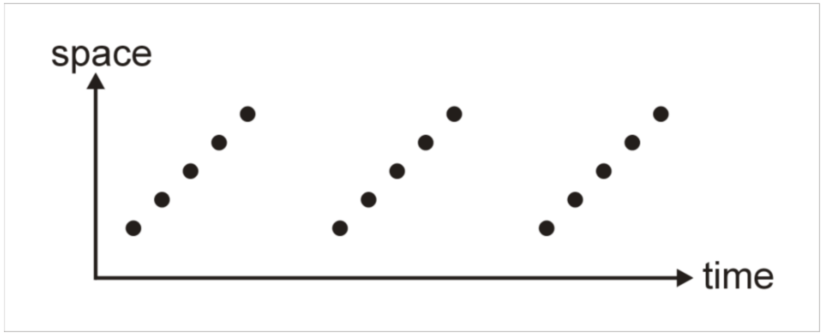


Ideal hemodynamic response for the active area: same for all slices

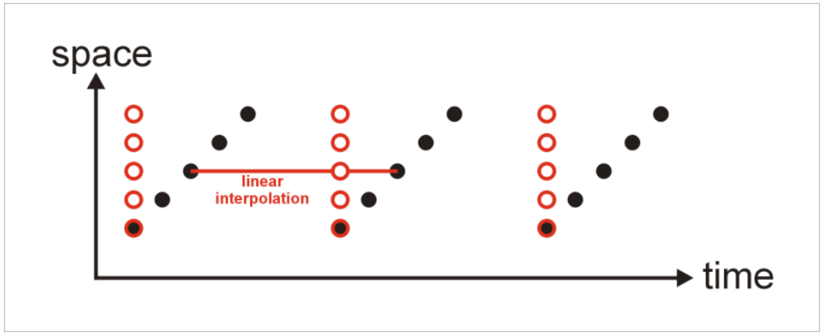
Modified from Source: Huettel S.A., Song A.W., McCarthy G.

Slice acquisition timing correction

- Estimate for each voxel, the signal intensity that would have corresponded to a time shift that aligns all slices to a reference acquisition time.



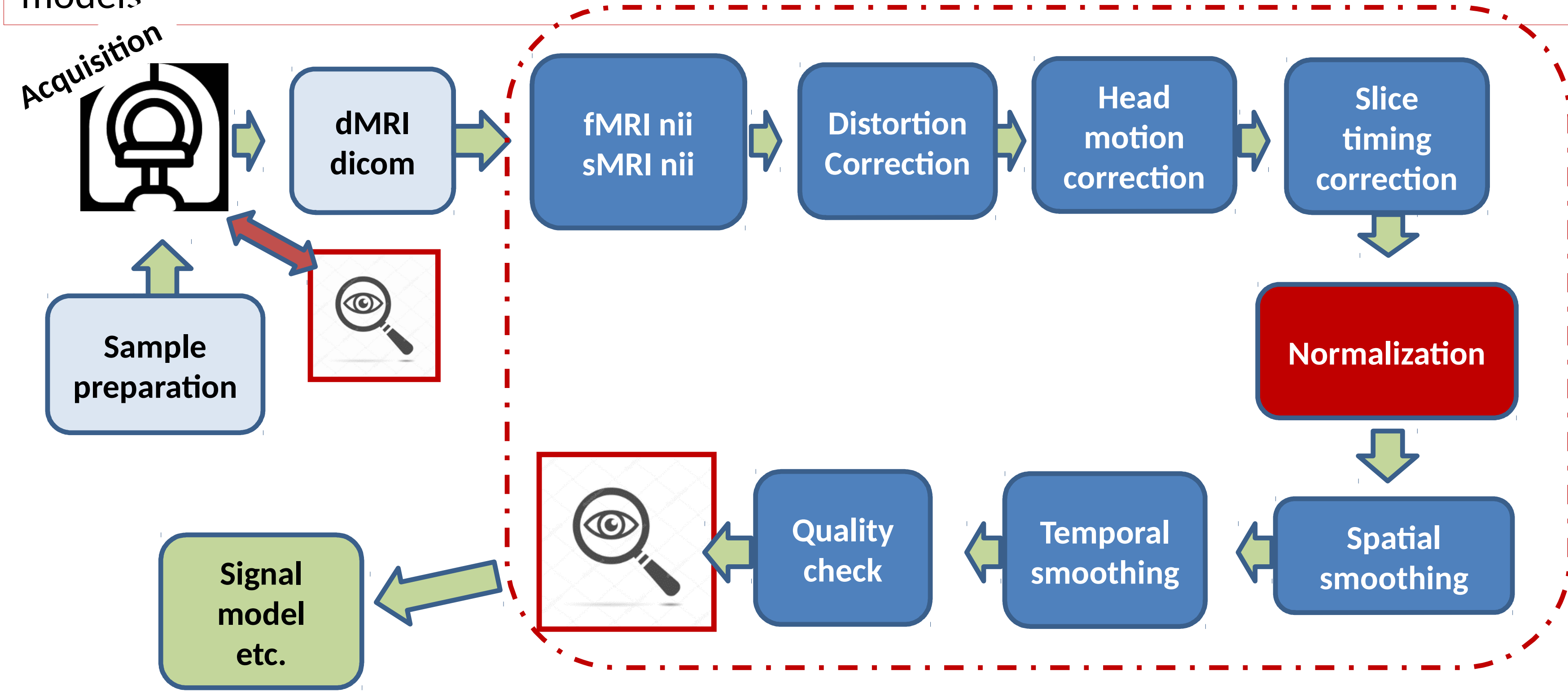
SEQUENTIAL slice acquisition: functional volume are shifted in time



This is corrected by sinc (or linear) interpolation in time

fMRI MRI pre-processing

Pre-processing: analyses steps to minimize noise, artifacts to get the «cleanest» data for models



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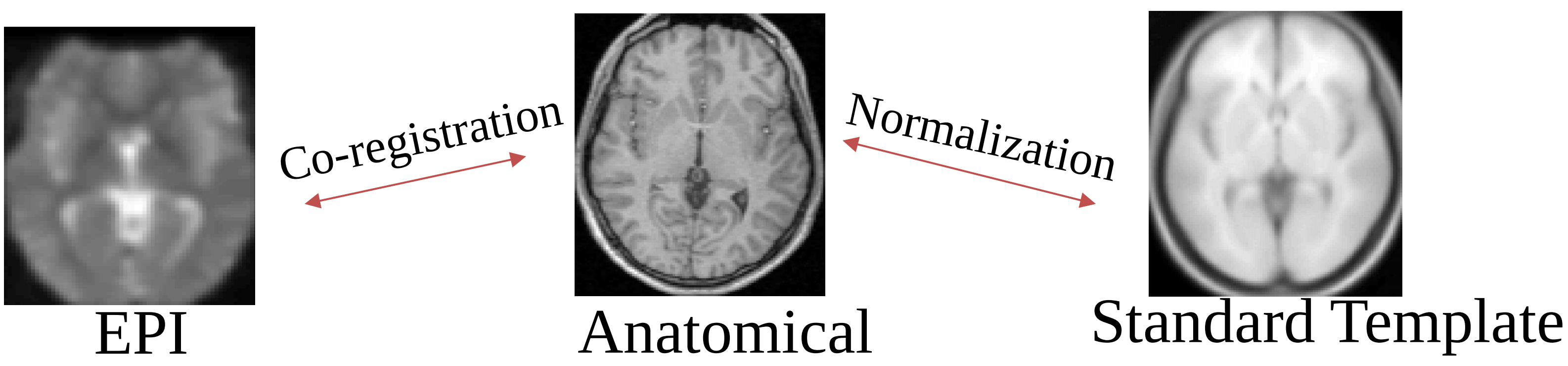
https://afni.nimh.nih.gov/
...

Co-registrations and Normalization

- Single subject or group analyses:
  - For each subject:
    - Co-registration between fMRI and anatomical scans
      - Rigid body transformation (cost function minimized)
      - This adds an interpolation step (smoothing)
    - Co-registration (normalization) of both (now aligned) to standard atlas
      - For spatial reference
      - Talairach space, or probabilistic atlases, cortical surface based
      - This adds an interpolation step (smoothing)
      - Caveats: normalization space may not represent all subjects



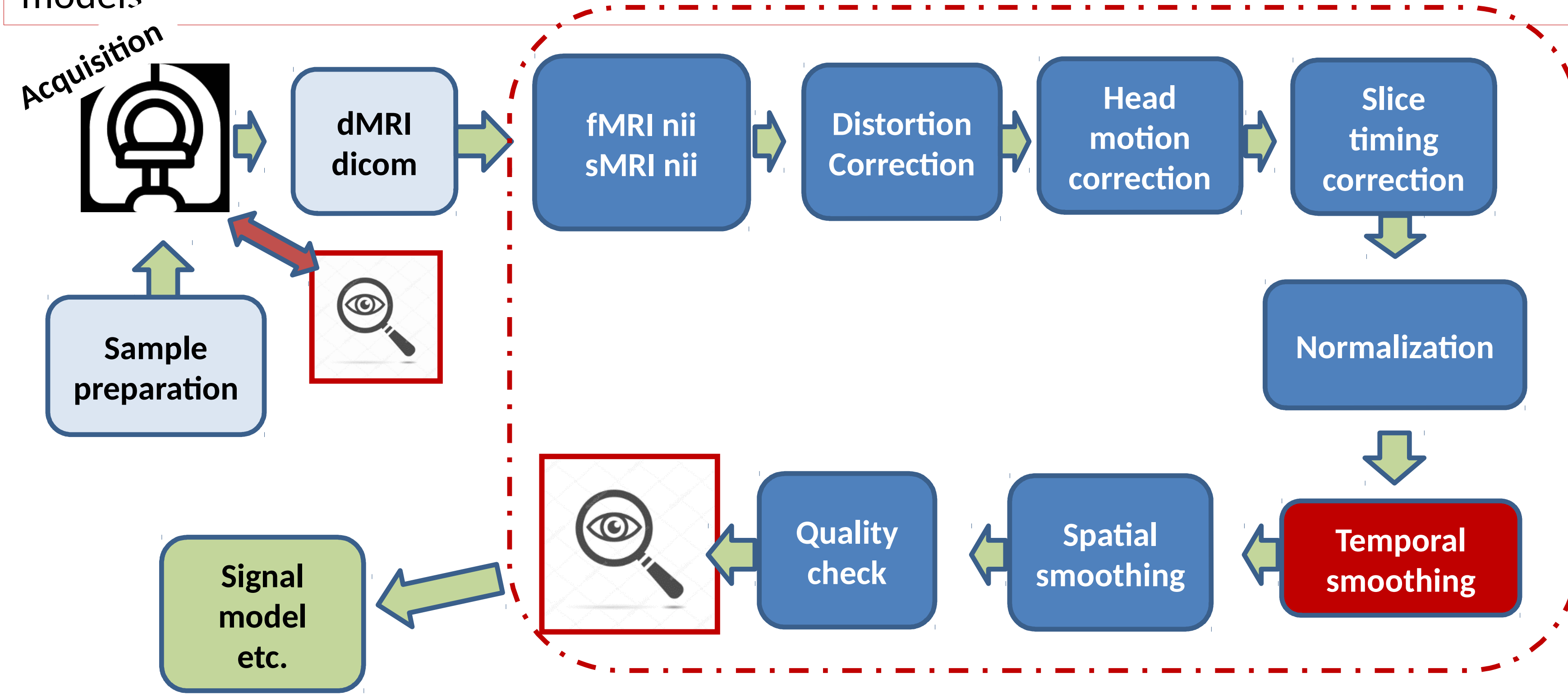
Standardized spaces (brain atlas)

- **Talairach space** (proportional grid system)
  - From atlas of Talairach and Tournoux (1988)
  - Based on single subject (60y, Female, Cadaver)
  - Single hemisphere
  - Related to Brodmann coordinates

- **Montreal Neurological Institute** (MNI) space
  - Combination of many MRI scans on normal controls
    - All right-handed subjects
  - Approximated to Talaraich space
    - Slightly larger
    - Taller from AC to top by 5mm; deeper from AC to bottom by 10mm
  - Used by SPM, National fMRI Database, International Consortium for Brain Mapping

fMRI MRI pre-processing

Pre-processing: analyses steps to minimize noise, artifacts to get the «cleanest» data for models



This is a generic example
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https://fsl.fmrib.ox.ac.uk/fsl

https://afni.nimh.nih.gov/

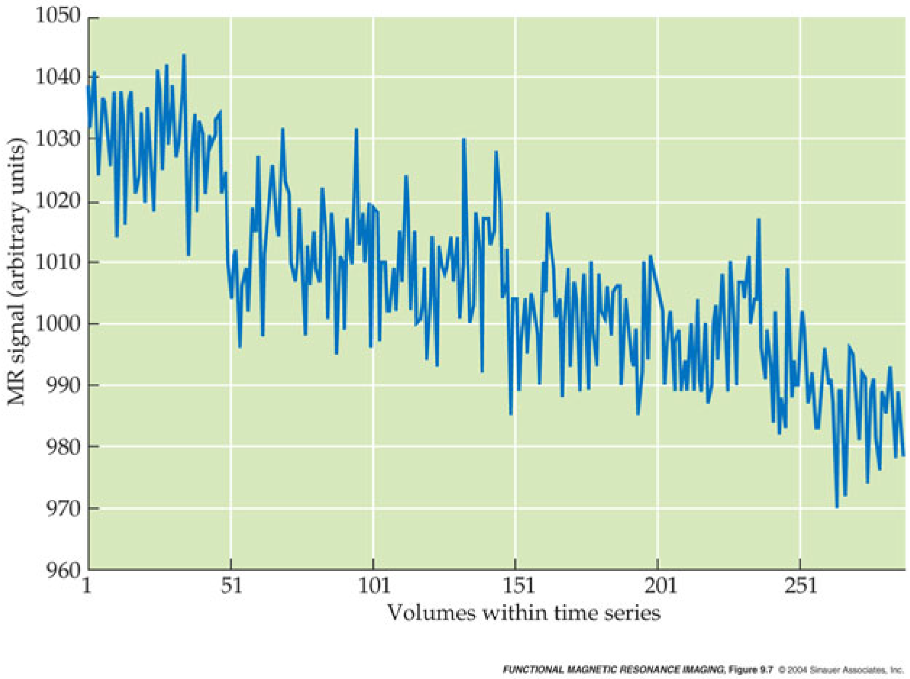
…

Temporal filtering fMRI data

- Goal: remove fluctuations that may be attributed to sources of no interest
- Identify unwanted frequency variation
  - Drift (low-frequency)
  - Physiology: cardiac (1-1.5 Hz), respiratory (0.2-0.3 Hz)
  - Task overlap (high-frequency)
- Reduce power around those frequencies through application of filters
- Potential problem: removal of frequencies composing response of interest

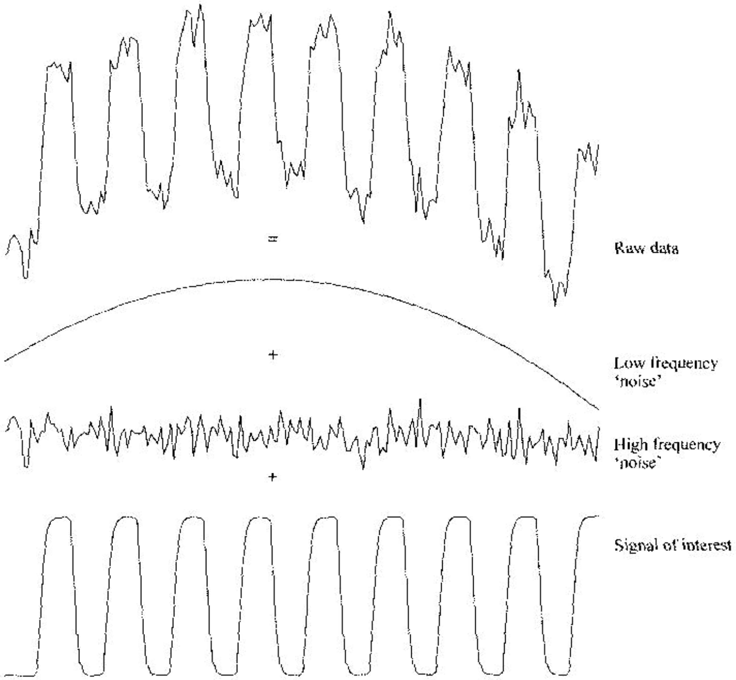
Temporal filtering fMRI data

Signal drifts from hardware instabilities



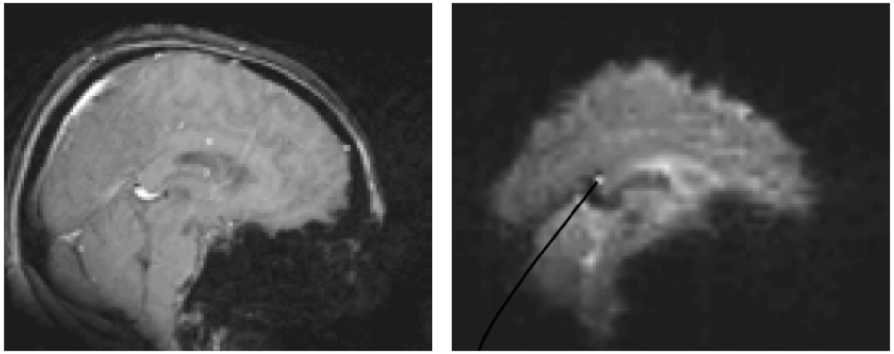
Huettel, Song & McCarthy, 2004,
Functional Magnetic Resonance Imaging

Drift on an activation time course

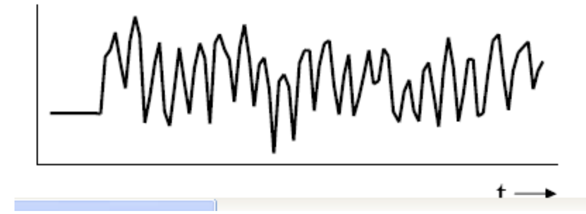


Source: Smith chapter in Functional MRI: An Introduction to Methods

Temporal filtering fMRI data



http://www.fil.ion.ucl.ac.uk/spm/course/



Respiration

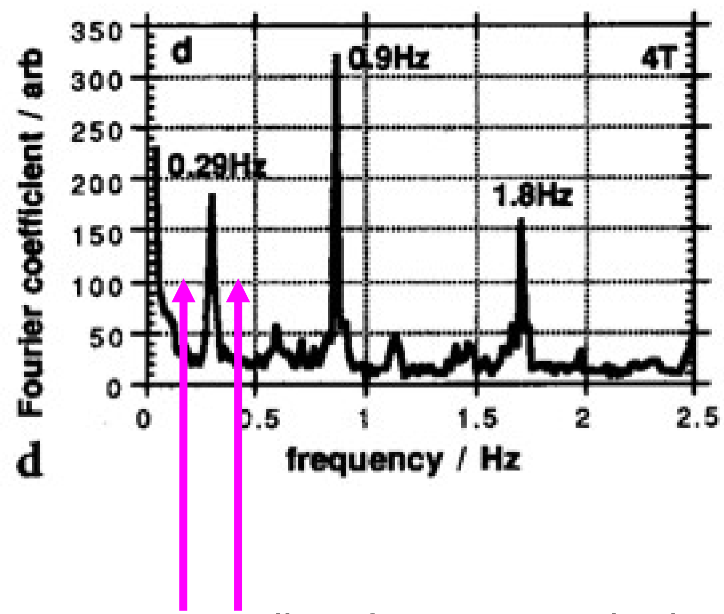
- Every 4-10 sec (0.3 Hz)
- Moving chest distorts susceptibility

Cardiac Cycle

- Every ~1 sec (0.9 Hz)
- Pulsing motion, blood changes

Solutions

- Gating
- Filter AND avoiding paradigms at those frequencies

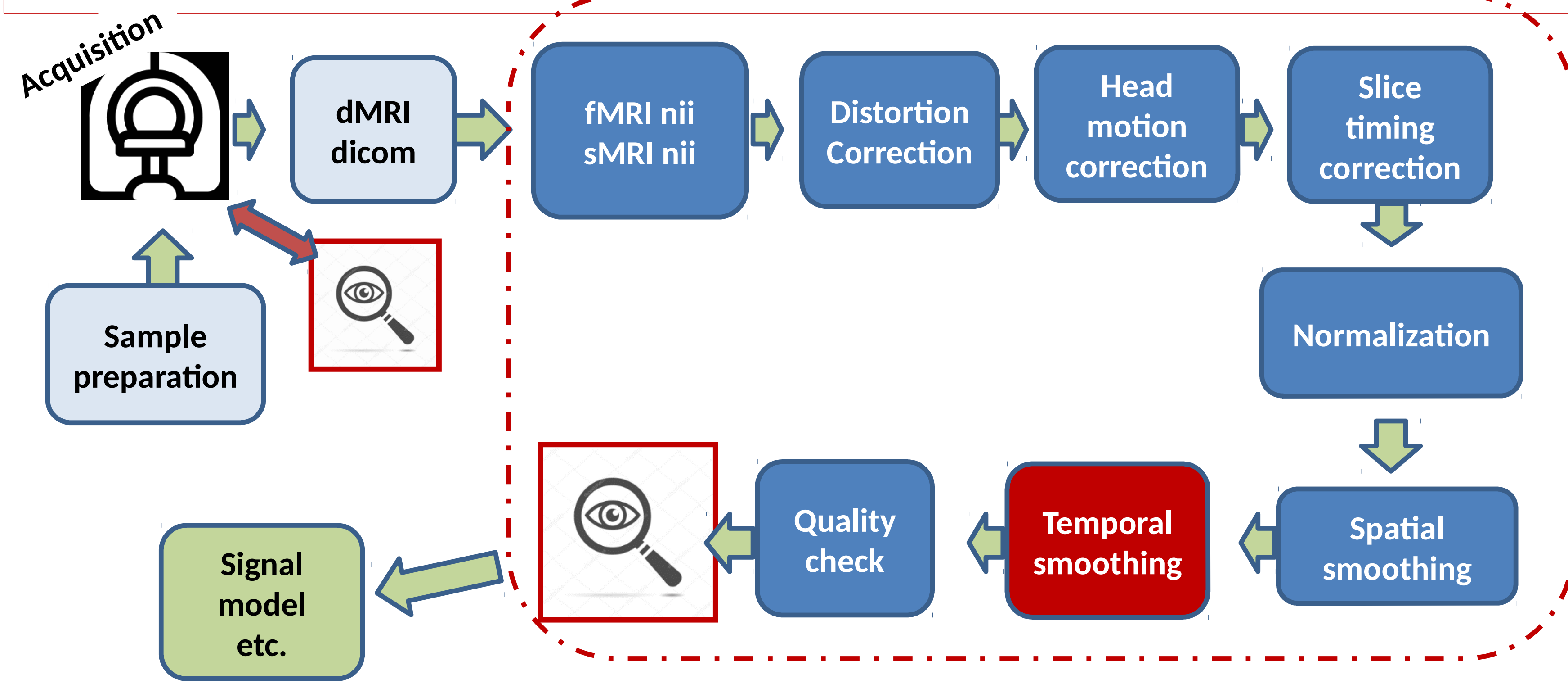


You want your paradigm frequency to be in a “sweet spot” away from the noise

Source: Jody Culham

fMRI MRI pre-processing

Pre-processing: analyses steps to minimize noise, artifacts to get the «cleanest» data for models



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https://afni.nimh.nih.gov/
...

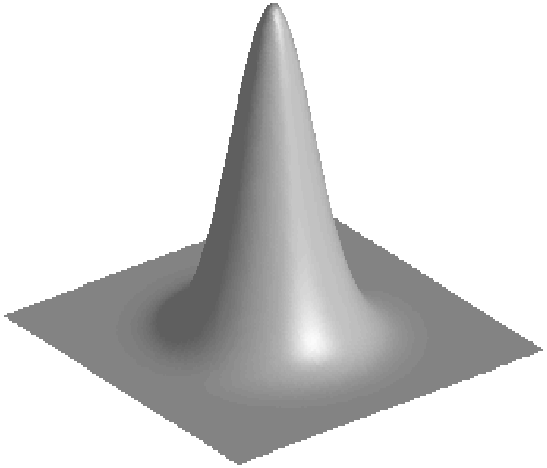
Spatial smoothing

Spatial smoothing essentially 'blurs' your functional data.

Why would you ever want to reduce the spatial resolution of your data?

Spatial smoothing may often be required when averaging data across several subjects due to the individual variations in brain anatomy and functional organization.

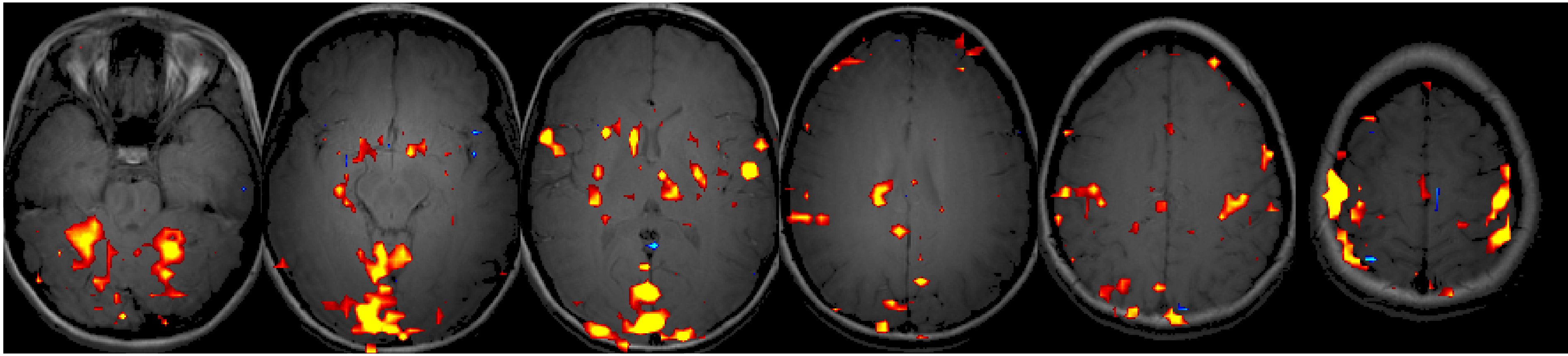
Increased degrees of smoothing (FWHM)



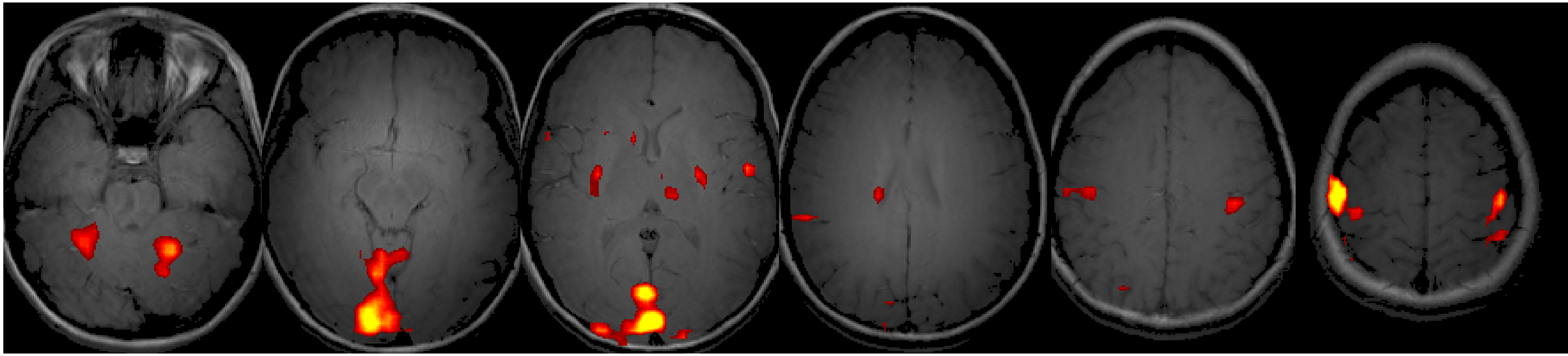
Gaussian smoothing kernel

Spatial smoothing: reducing false positives

Unsmoothed Data

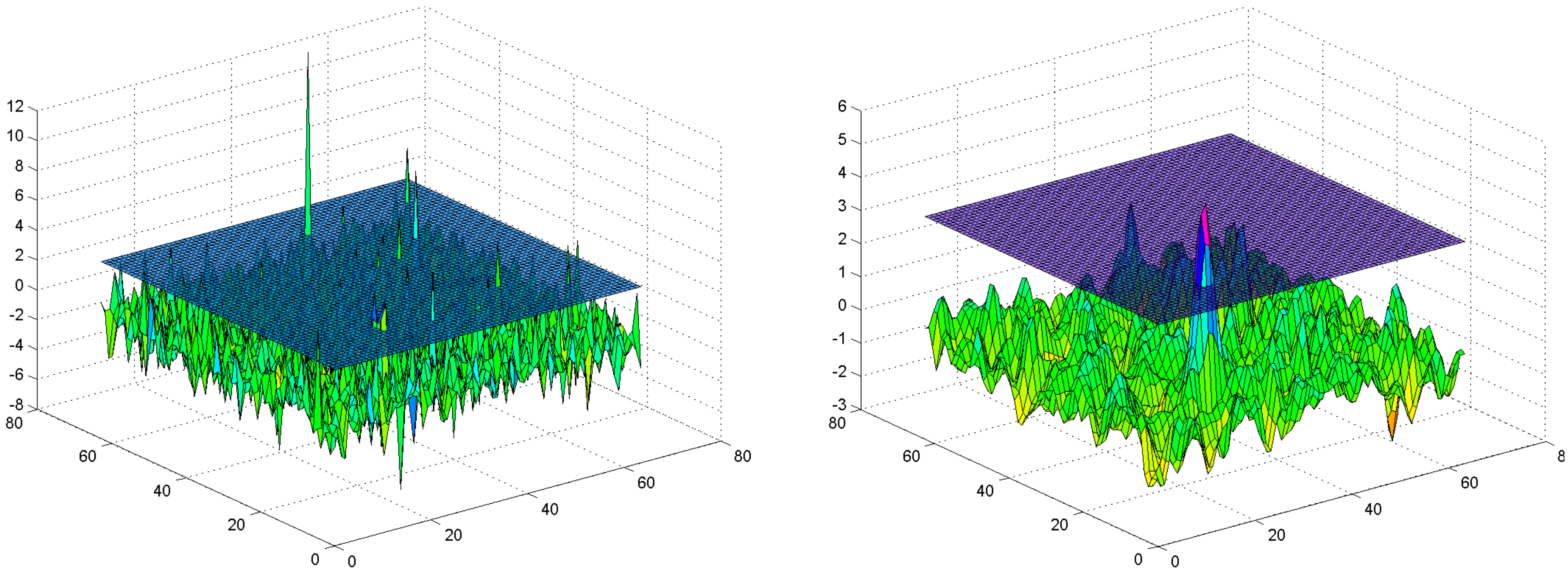


Smoothed Data (kernel width 5 voxels)



Modified from Source: Huettel S.A., Song A.W., McCarthy G.

Spatial smoothing: reducing false positives



Modified from Source: Huettel S.A., Song A.W., McCarthy G.

Spatial smoothing

- Advantages
  - Increases Signal to Noise Ratio (SNR)
    - Matched Filter Theorem: Maximum increase in SNR by filter with same shape/size as signal
  - Reduces number of comparisons
    - Allows application of Gaussian Field Theory
  - May improve comparisons across subjects
    - Signal may be spread widely across cortex, due to intersubject variability

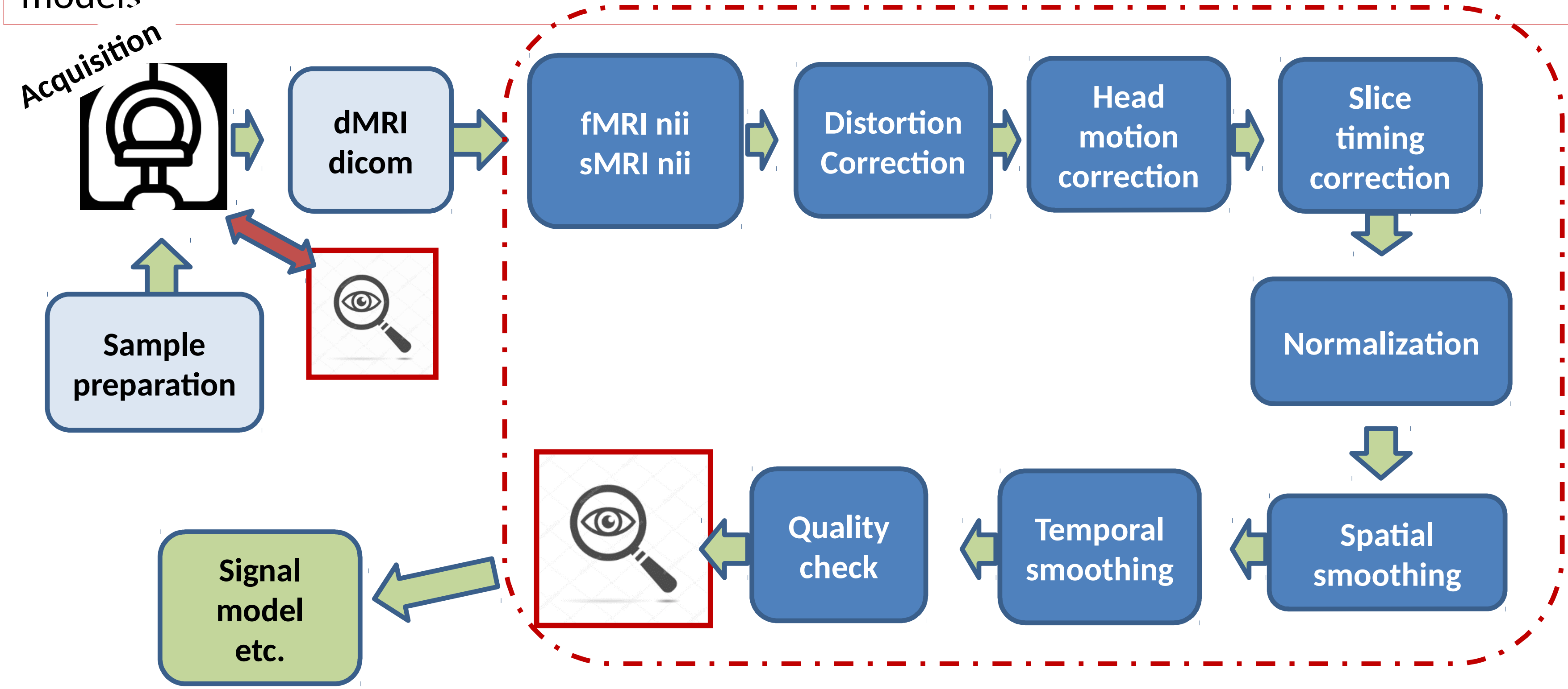
- Disadvantages
  - Reduces spatial resolution
  - Challenging to smooth accurately if size/shape of signal is not known

Notes:

- Often used in general linear model analysis
- Often not used in layer fMRI

fMRI MRI pre-processing

Pre-processing: analyses steps to minimize noise, artifacts to get the «cleanest» data for models



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- https://fsl.fmrib.ox.ac.uk/fsl
- https://afni.nimh.nih.gov/
- …

Literature recommendations include

.

Collection of overview papers from various leaders in the field

- 20 years of fMRI
- Reproducibility in Neuroimaging
- MRI of cortical layers
- Cleaning up fMRI time series

Web materials:

- https://practicalfmri.blogspot.com/
- http://www.fmri4newbies.com/
- OHBM Educacional Series: https://www.pathlms.com/ohbm/courses/ (tons of stuff!)
- ISMRM Educational Series: https://www.ismrm.org/education/
    - https://www.ismrm.org/online-education-program/diffusion-perfusion-fmri-videos/
- https://gate.nmr.mgh.harvard.edu/wiki/whynhow/

Concept map for lectures

Lecture 1

MR Image & Contrast

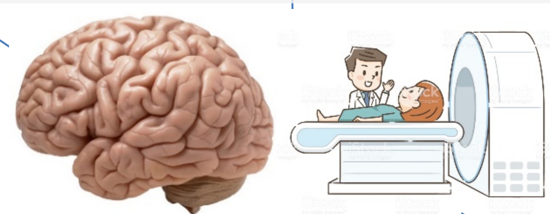
- Spatial encoding
- Magnetic gradients
- Pulse sequences

NMR Signal origin

- Powerful magnet
- Radio frequency
- Magnetic field gradients

MR Safety

- Powerful magnet
- Radio frequency
- Magnetic field gradients



Lecture 2

Structural MRI

- Contrast, important parameters
- Sequences & artifacts
- Analyses & applications

Lecture 3

Diffusion MRI

- Contrast, important parameters
- Sequences & artifacts
- Analyses & applications

Lecture 4

Functional MRI

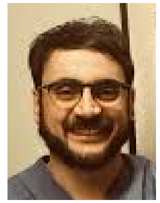
- Contrast, important parameters
- Sequences & artifacts
- Pre-processing

Acknowledgements

Collaborators include


Moira Marizzoni


Giovanni Frisoni

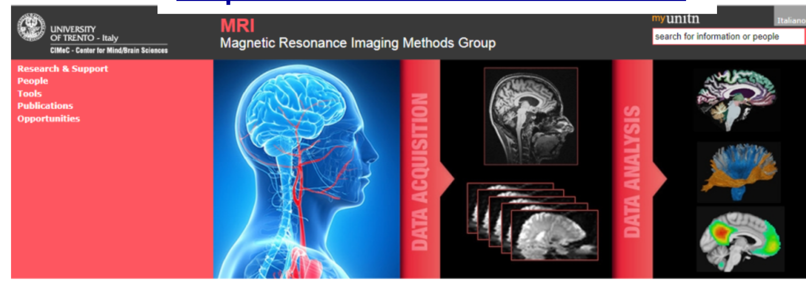

Silvio Sarubbo

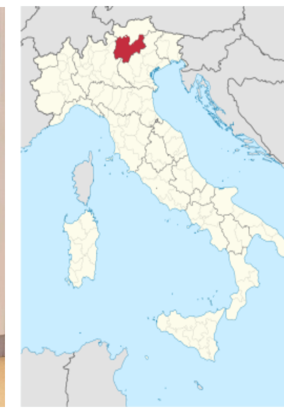

Olivier Collignon


Valeria d. Maggiore


Flor Jacobacci

http://r.unitn.it/en/cimec/mri



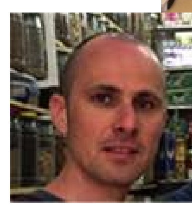


Current /recent lab include


D. Zacà

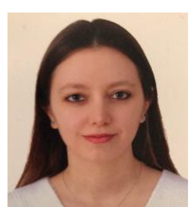

C. Maffei


V. Iacovella


N. Pace


L. Novello


F. Saviola


M. Akinci


S. Tambalo

TONIGHT (http://www.milonga.be)

TANGO BAR
21:30 - 02:00

Rue de Dublin 13, 1050 Ixelles, Belgium
MILONGA BRUSSELS