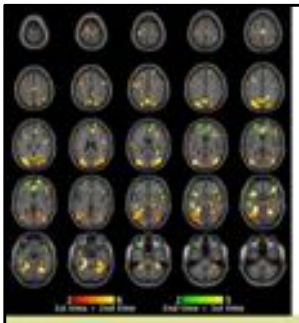
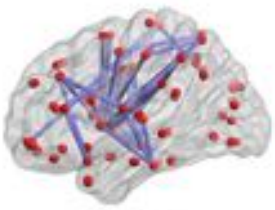
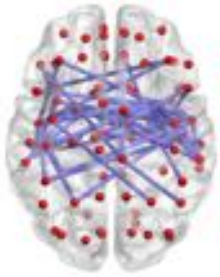




Side View



Top View

Functional MRI

Dr. Peter Van Schuerbeek

Universitair Ziekenhuis Brussel

VUB

Software needed for the practicum

- Matlab
- SPM12 (https://www.fil.ion.ucl.ac.uk/spm/)
- Example data ("Individual Data")

Data and software is available on: Neural Signal Processing 2023

- For the part of the fMRI data analysis, we will analyze step by step some example data in SPM12

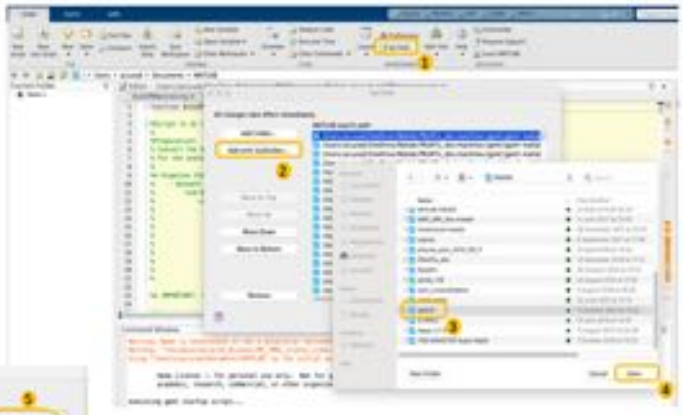
- SPM12 is downloadable from https://vub-my.sharepoint.com/:f:/g/personal/peter_van_schuerbeek_vub_be/EtHhJnMHUx9Dvonba5EsiZ4Bxr5mKiuvzoBYKHL-32paJQ?e=cKNeWG
- The data isavailable on https://vub-my.sharepoint.com/:f:/g/personal/peter_van_schuerbeek_vub_be/Ep4_-78poSxFgVfgT4lMmKgBqaCKFvcI9-pVQ8_dRMt9xw?e=icGKLx

- Installation of SPM12
    - Copy SPM12 to your computer
    - Open Matlab
    - In Matlab: add SPM path to the Matlab search path list -> Set Path

- Save and unzip the example data to your computer

Add the spm12 folder to your Matlab path

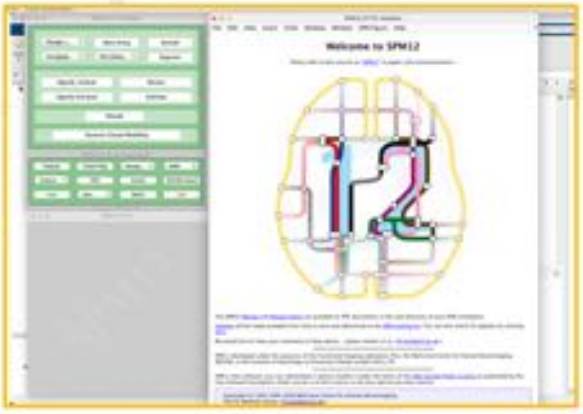
1. Select "Set path"
2. Select "Add with Subfolders"
3. Select your spm12 folder
4. Select "Open" or "Save"
5. You should see the spm12 folders in the list
6. Select "Save"
7. Select "Close"



Test of spm12

1. Type "spm fmri" in the Command Window
2. SPM should open

(after some output in the Command Window)

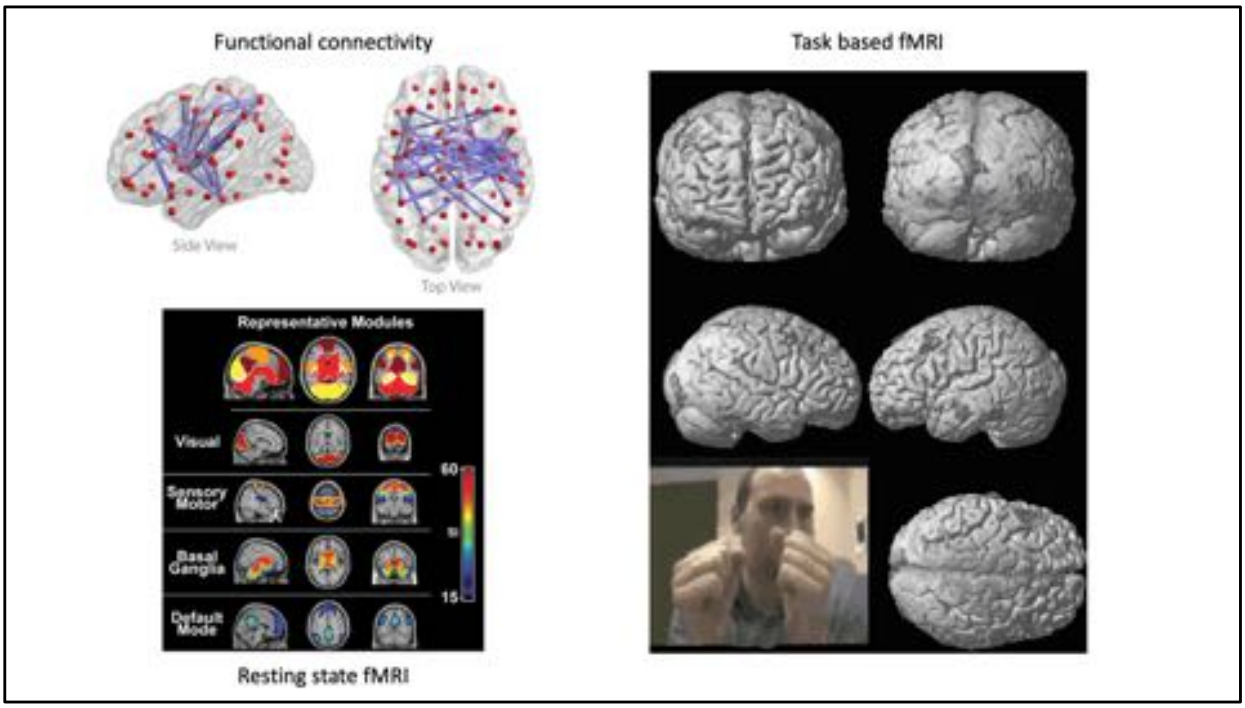


Introduction

Universitair Ziekenhuis Brussel

VUB

- Functional Magnetic Resonance Imaging (fMRI) is done using standard MRI scanners as used in the daily clinic or in special MRI scanners optimized for advanced neuro applications (stronger and faster gradients, smaller scanner bore (60cm) -> faster scanning, higher resolutions, better SNR)
- fMRI is mostly used
    - In research: to study normal and pathological brain functions and to evaluate treatments
    - In the clinic: to locate the motor or language areas in preparation for churgery
- Most partients and study participants know the MRI scanners as
    - Big machines with a very small tunel -> gives the feeling of claustrophobia
    - A lot of noise during the scanning (up to 120 dB)
    - An fMRI exam takes a long time (up to 1h in experimental studies, mostly 30 minutes in clinical exams)
    - You may not enter the scanner room with metal objects or electronic devises (coins, GSM, …) due to the presence of a very strong magnetic field
- Golden rule in fMRI: the higher the field strength of the MRI scanner the better
    - 1.5T as experimental or clinical scanner: only if no other scanner is available
    - 3T as experimental or clinical scanner: most used today
    - 7T only as experimental scanner



- In general, with fMRI we study normal and abnormal brain functions

- More specific we try to
    - Localize task-related neural activity (right) -> task fMRI
    - Find functional networks with interacting brain areas (top left) -> functional connectivity
    - Study the default (ongoing) activity in the brain during rest (bottom left) -> resting state fMRI

- With fMRI we can answer questions and hypotheses about
    - Normal brain functions
    - The effect of individual related factors that affect normal brain functions (education, personality, skills, experiences, …)
    - The alteration in brain functioning due to neuropathologies
    - The effects of medication and treatment
    - …

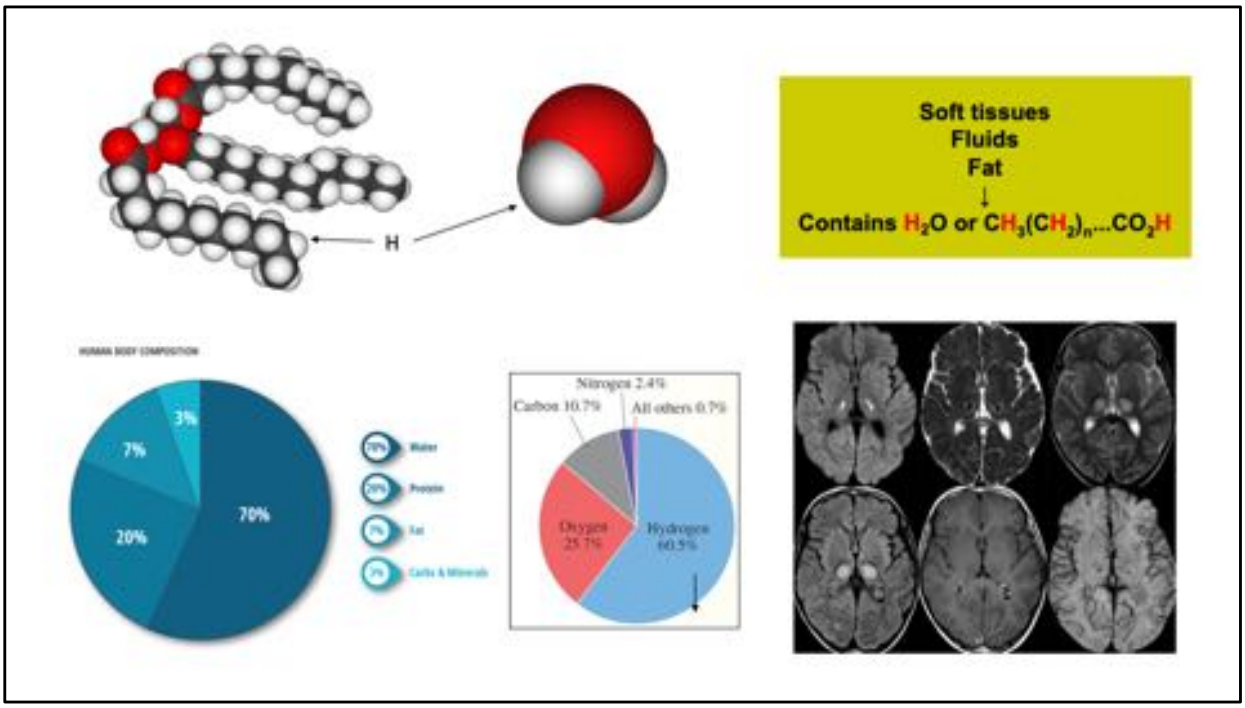
NMR = Nuclear Magnetic Resonance = quantum mechanics theory

MRI = Magnetic Resonance Imaging = medical imaging technique based on NMR

fMRI = Functional Magnetic Resonance Imaging

Interesting sides about the physics of MRI:

- mri-q.com
- mri-physics.net
- cis.rit.edu/htbooks/mri/
- www.mritutor.org
- revisemri.com
- https://radiopaedia.org
- https://www.imaios.com/en/e-Courses/e-MRI



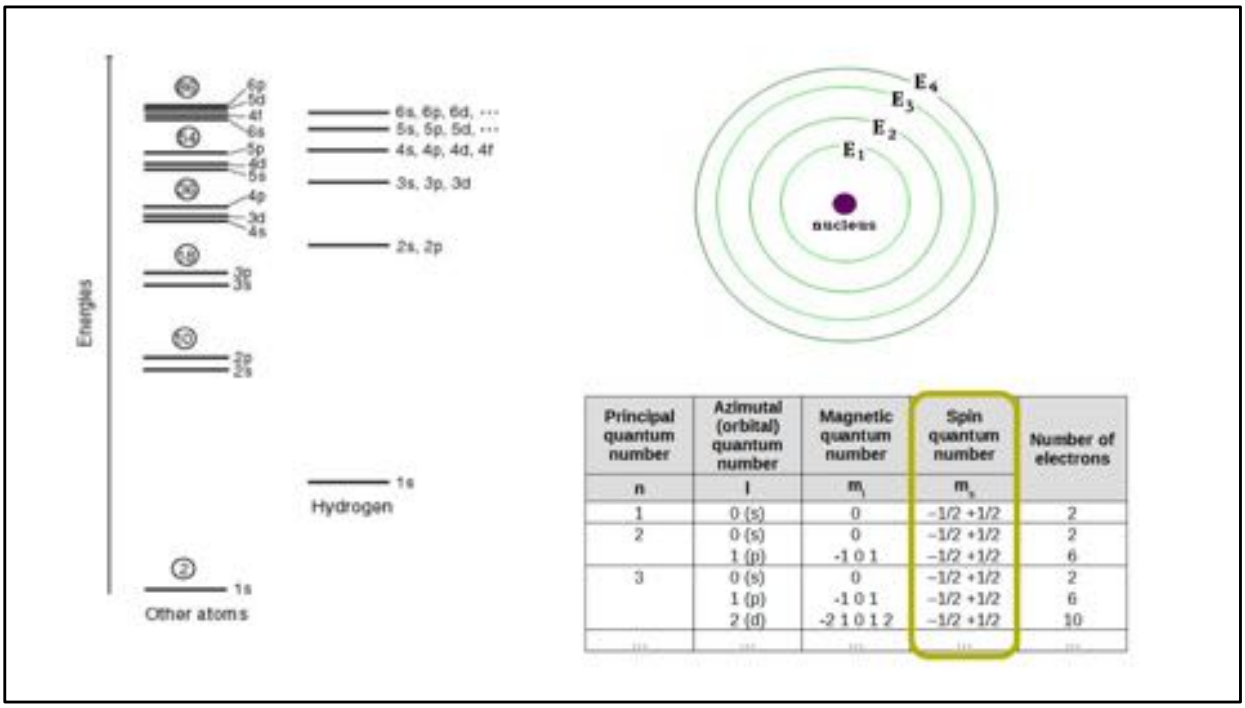
- At MRI, many different image contrasts are possible to obtain
    - The same tissue can appear dark, gray or white in different images depending on the scan technique used
    - Tissue signals can be saturated (suppressed)
- The source of the signals is independent of the used MRI technique
    - Despite the various contrasts, the source of the signals is always the same
    - All measured signals come from the H-ions from the water and lipid molecules
- Visible tissues:
    - Soft tissues -> contains H_2O
    - Fluids -> contains H_2O
    - Fat -> contains lipids
- Not visible
    - Air and bone

- Hydrogen is by far the most common atom in a human body -> gives the strongest signal
- Molecules containing H
    - Water: present in fluids and the cellular interstitial space -> high mobility -> good NMR properties
    - Fat: present In adipose tissues, skeletal muscle and bone marrow -> restricted mobility but good NMR properties
    - Macromolecules: proteins -> highly restricted mobility -> poor NMR properties -> no NMR signal

- Small organic molecules: amino acids, sugars, organic acids, … -> good NMR properties but concentration is to low (-> signals are overpowered by the water signal) -> target for in vivo MR spectroscopy (MRS)

See also

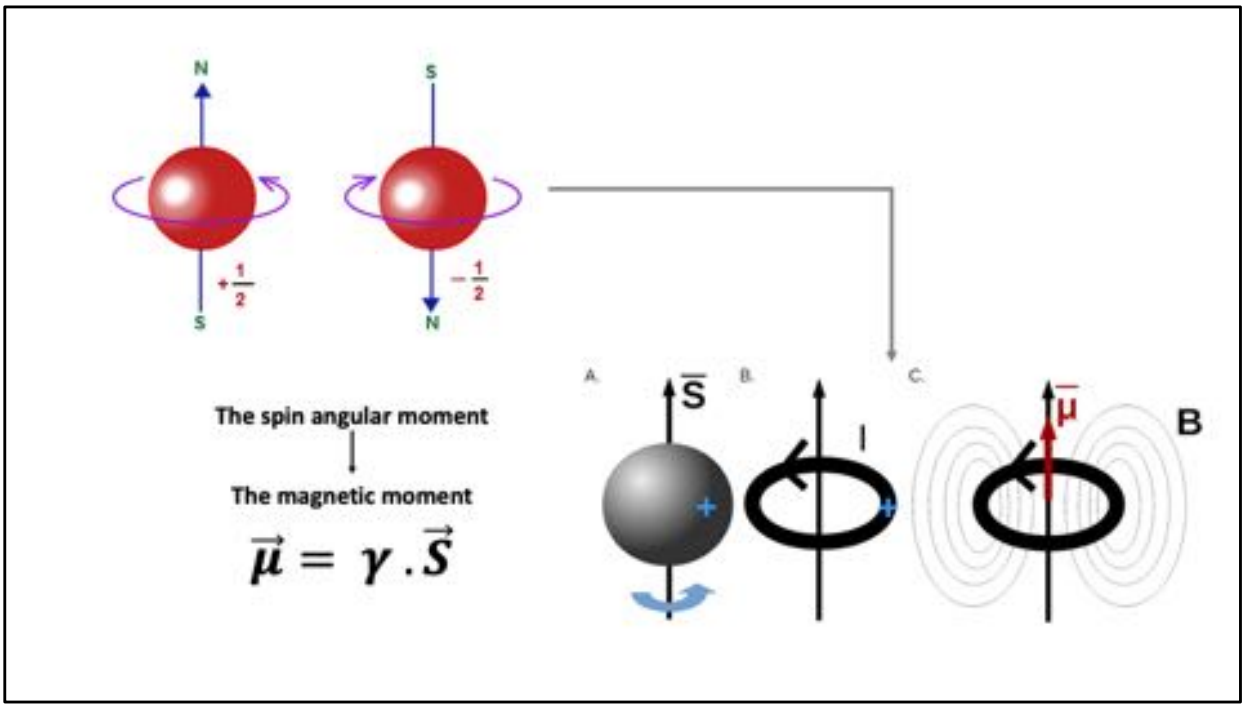
http://mri-q.com/which-hs-produce-signal.html



Principal quantum number	Azimutal (orbital) quantum number	Magnetic quantum number	Spin quantum number	Number of electrons
n	l	m_l	m_s	
1	0 (s)	0	−1/2 +1/2	2
2	0 (s)	0	−1/2 +1/2	2
	1 (p)	-1 0 1	−1/2 +1/2	6
3	0 (s)	0	−1/2 +1/2	2
	1 (p)	-1 0 1	−1/2 +1/2	6
	2 (d)	-2 1 0 1 2	−1/2 +1/2	10
...	...	...	...	...

- Beginning 20th century: development of quantum mechanics
    - Subatomic particles can only be in quantum states (discrete energetic states) -> described by quantum numbers
    - Interactions between subatomic particles and radiation happens by a transition of one state to the other by exchanging energy
        - Absorption of energy -> transition to a higher energy state
        - Transmission of energy (radiation) -> transition to a lower energy state
    - Interactions between particles and radiation only possible if the absorbed or transmitted energy corresponds to the energy difference between two states
- 1913: Bhor's model of the atom
    - Central in the atom is the nucleus containing protons and neutrons
    - The electrons are ordered in quantitated orbitals surrounding the nucleus defined by quantum numbers
        - Principal quantum number: main orbital shell
        - Azimutal quantum number: orbital's subshell
        - Magnetic quantum number: orientation of the subshell
        - **Spin quantum number: spin of the electron**

See also
https://en.wikipedia.org/wiki/Bohr_model
https://en.wikipedia.org/wiki/Quantum_number
https://en.wikipedia.org/wiki/Quantum_mechanics
https://en.wikipedia.org/wiki/Introduction_to_quantum_mechanics



The spin quantum number

- Electrons rotate around their own axis -> spinning motion
- Only 2 possible rotations possible:
  - Counterclockwise
  - Clockwise
- 2 rotation states described by the spin quantum number
  - +1/2: spin up
  - -1/2: spin down
- The rotation motion is defined by an angular moment (**S**)
- The angular moment of charged particles generate a magnetic dipole field (**B**)
  A. Electrons are rotating around their own axis (spinning motion) -> rotation defined by an angular moment **S**
  B. A rotating electric charge -> modeled as an electric current I
  C. According to Ampère's law: I induces a magnetic dipole field **B** defined by its magnetic moment **μ**

Relation between μ and S: μ = γ . S with γ the gyromagnetic ratio

-> only 2 possible states for the magnetic moment

The nucleus:

- Protons -> positive charge
- Neutrons -> no charge

Since all subatomic particles do have a spin quantum state

=> Protons and neutrons are spinning

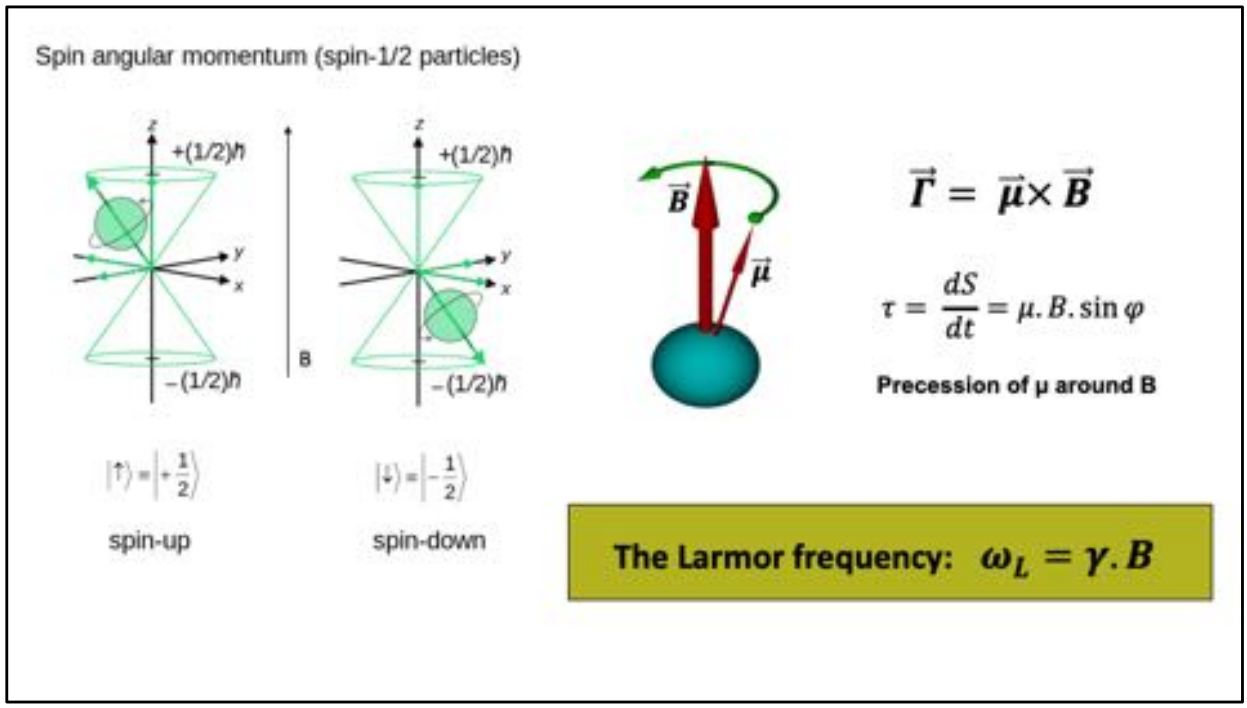
=> Protons and neutrons do have a spin angular moment **S**

=> The total nuclear moment of a nucleus is the net result of the individual protons and neutrons

Due to the positive charge of the protons in the neuclei

=> nuclei do have a magnetic moment $\vec{\mu} = \gamma . \vec{S}$

See also http://mri-q.com/what-is-spin.html
http://mri-q.com/gyromagnetic-ratio-gamma.html



For nuclei with a angular moment 1/2 in an external magnetic field B:

- The spins tries to align with B but …
  - Only two states are allowed
  - These states are not exactly aligned with B

  ⇒ **There is an angle between the magnetiec moment μ and B**

- Theory of a spinning electron in a magnetic field -> similar to the theory of the spinning top in a gravitation field

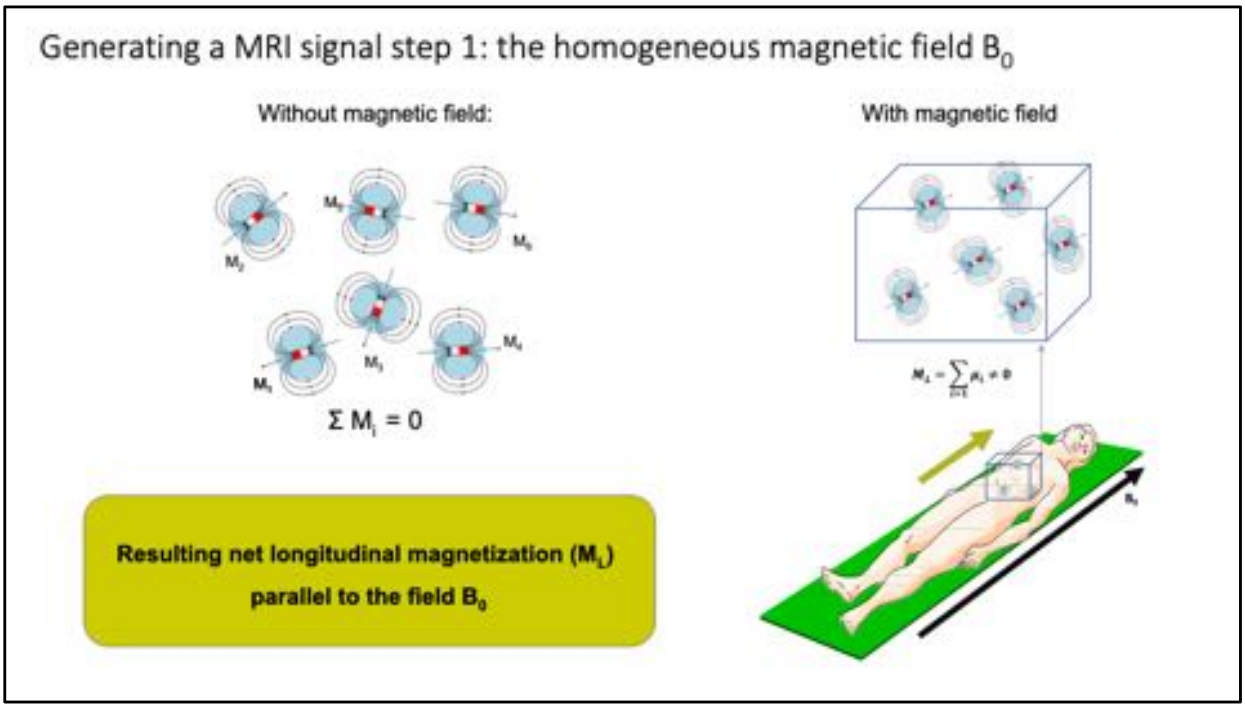
  - Torque from B to μ: $\vec{\tau} = \vec{\mu}\ x\ \vec{B} = \gamma . \vec{S}\ x\ \vec{B}$ -> $\tau = \frac{dS}{dt} = \gamma . S . B . \sin\varphi$ (the torque determines the rate of change of the angular momentum)

    -> μ starts a precession motion around B

  - Frequency of the precession motion = the Larmor frequency

See also:
https://en.wikipedia.org/wiki/Larmor_precession
http://mri-q.com/why-precession.html
http://mri-q.com/who-was-larmor.html

Repeating of the gyroscopic precession: https://www.youtube.com/watch?v=yO-af0ZN74s



Hydrogen nuclei = proton = spin in MRI nomenclature

The human body contains a lot of protons and all of these protons do have a magnetic moment

Without an external magnetic field present

- Each magnetic moment is oriented ad random
- No net magnetization

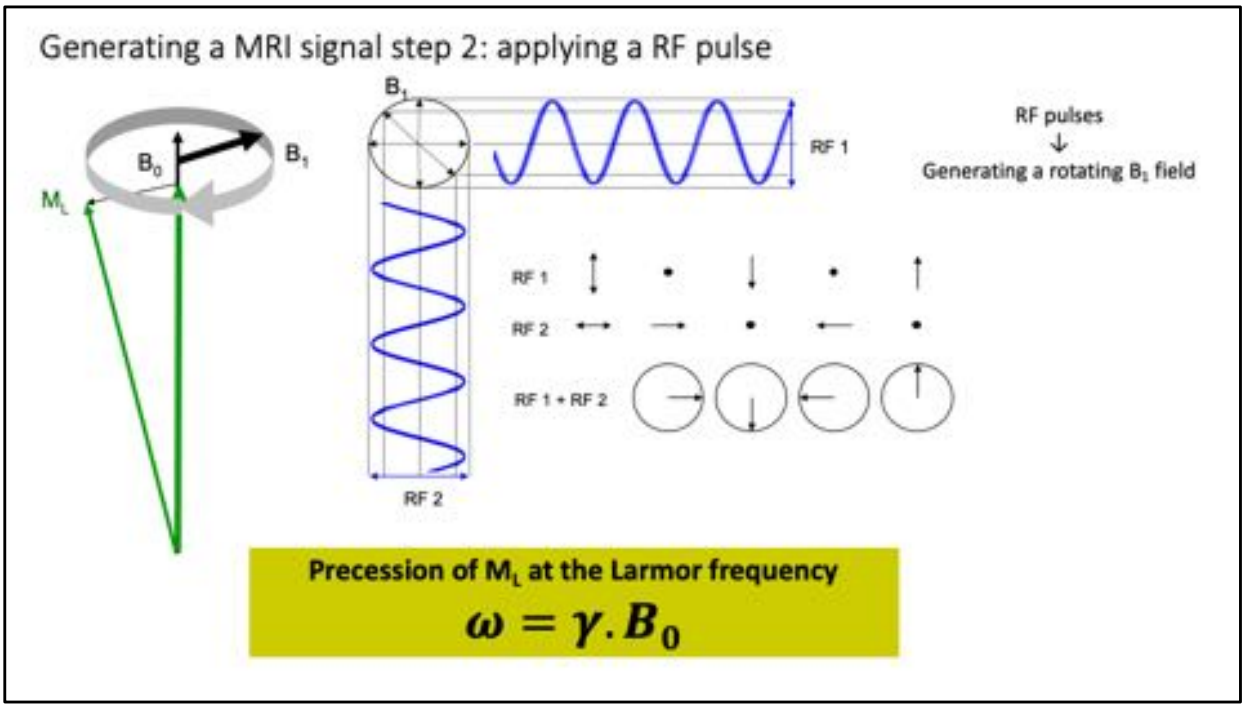
With an external magnetic field B_0 present

- Each magnetic moment tries to align with B_0 (spin up -> parallel, spin down -> anti-parallel)
- **Since more spins are in the up state than there are in the down state, a net magnetization M_L will be generated**
  - M_L parallel with B_0 -> Longitudinal magnetization

As M_L is static -> no signal will be generated in a detection coil!

We need to force M_L to rotate to generate a measurable signal

See also http://mri-q.com/net-magnetization-m.html
http://mri-q.com/does-m-also-precess.html
http://mri-q.com/fall-to-lowest-state.html
http://mri-q.com/quantum-reality.html



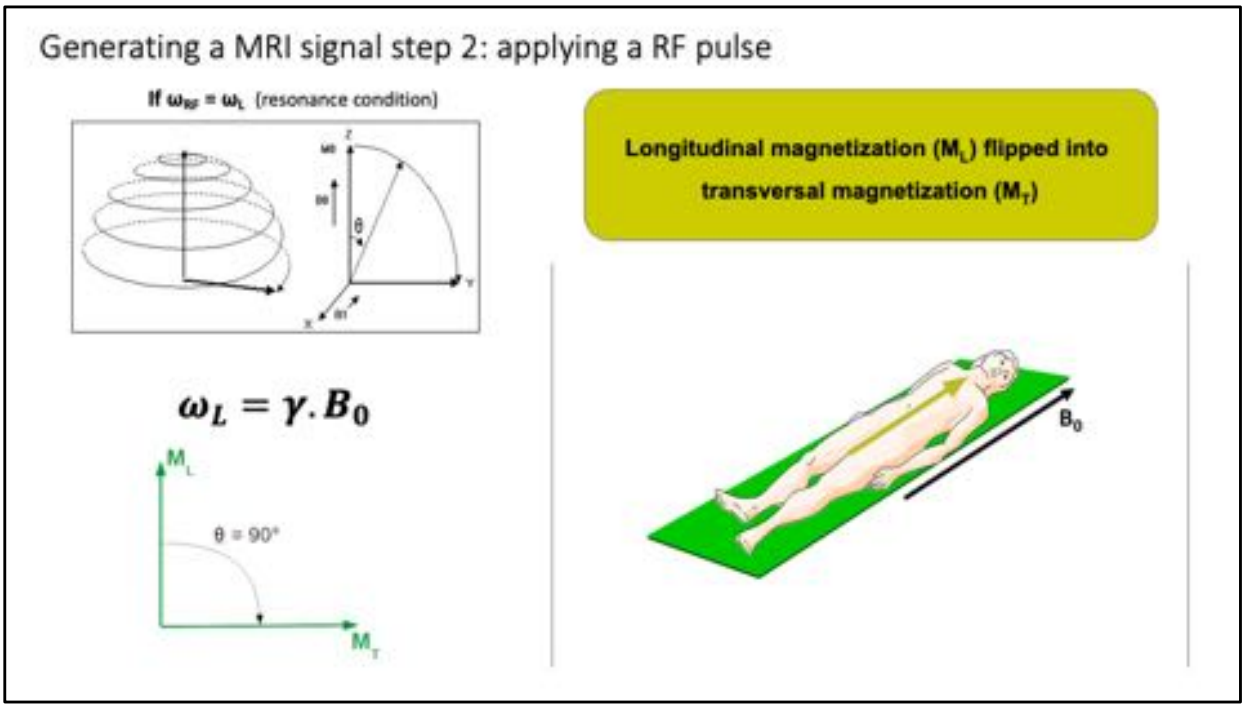
Generating a MRI signal step 2: applying a rotating B_1-field

A rotating B_1-field

- A combination of 2 linear changing RF fields (RF 1 and RF 2)
  - At the same frequency: ω_{RF}
  - 90° out of phase
- Rotating frequency of the B_1-field: ω_{RF}
- Perpendicular to B_0

Remarque: The B_1-field is mostly called the RF pulse

$\Rightarrow$ Disturbance of the alignment of M_L with B_0
$\Rightarrow$ Torque from B_0 to M_L
$\Rightarrow$ **Precession of M_L at the Larmor frequency**



Secondly we apply a excitation (RF pulse). As a result M_L start to flip down. As soon as M_L is not alligned with B_0 it will start to precess around B_0 at the Larmor frequency $\boldsymbol{\omega_L = \gamma . B_0}$

With $\boldsymbol{\gamma}$ the gyromagnetic ratiio of hydrogen (42MHw/T). To continue to flip down ML, the frequency of our RF pulse should be equal to $\boldsymbol{\omega_L}$ to stay iin tune with the precession motion of M_L.

If $\omega_{RF} = \omega_L$ -> resonance condition

$\Rightarrow$ **Flipping of M_L into M_T**

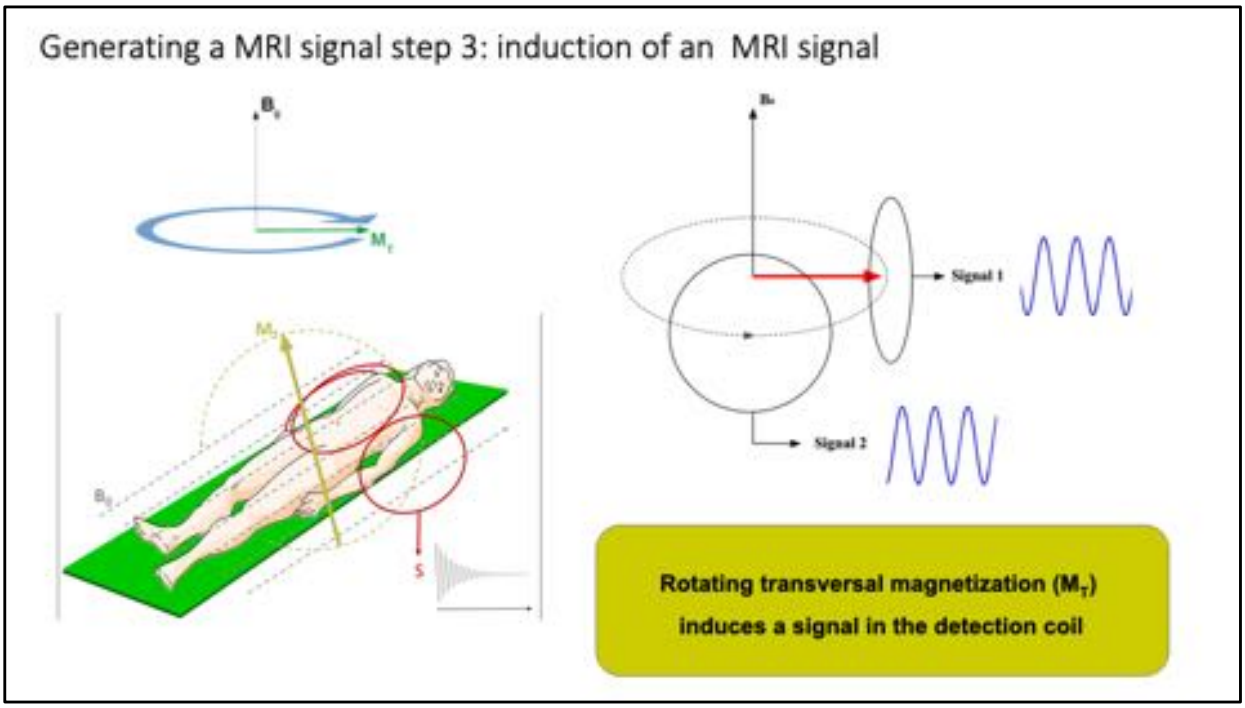
The longitudinal magnetization gets flipped into transverse magnetization perpendicular to B_0

See also

http://mri-q.com/how-does-b1-tip-m.html

http://mri-q.com/why-at-larmor-frequency.html

http://mri-q.com/what-is-flip-angle.html

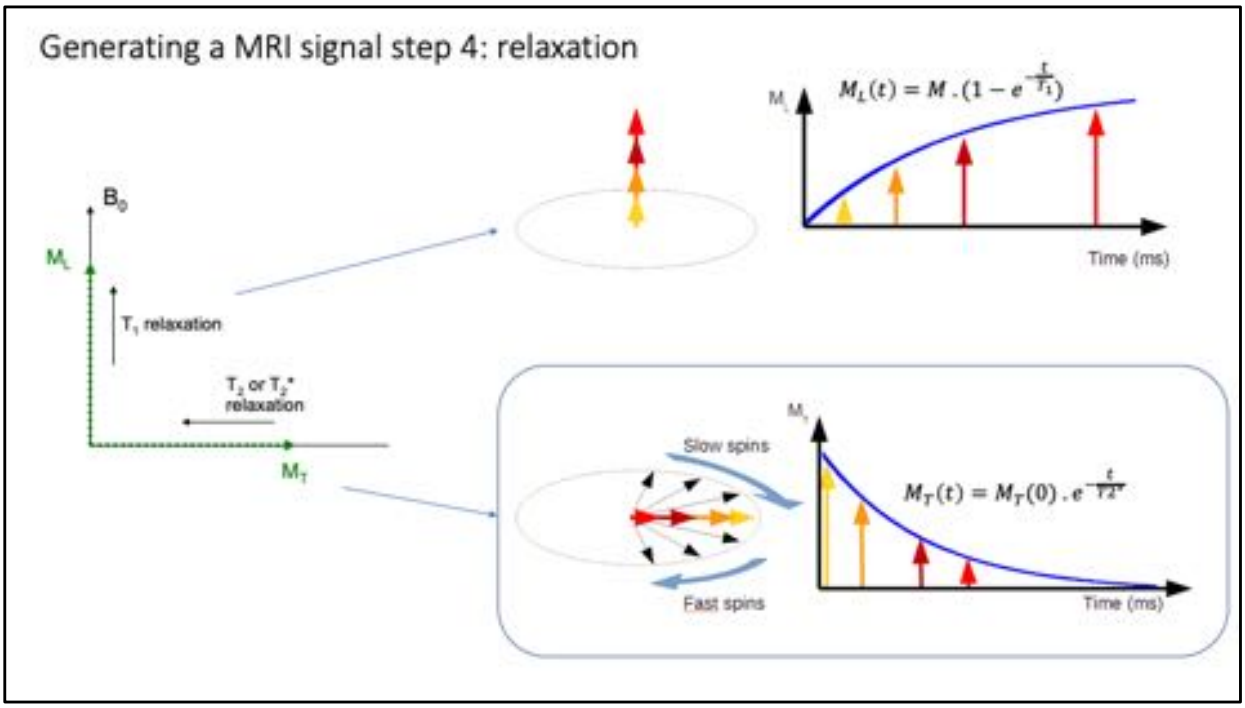


Generating a MRI signal step 3: after the RF-pulse

- If there is still a M_L
    - M_L is aligned with B_0 -> remains stationary
    - Will not induce a signal

- The generated M_T
    - Perpendicular to B_0 -> **M_T start to precess around B0 at the Larmor frequency**

- According to Faray's induction law:
    - The rotating transverse magnetization induces a signal in a detection coil ("circular" antenna)
    - Properties of the induced signal:
        - Magnitude M_T -> Magnitude S
        - Rotation frequency M_T -> Frequency S (Larmor frequency)
        - Phase M_T -> Phase S



Generating a MRI signal step 4: Relaxation

After switching of B_1

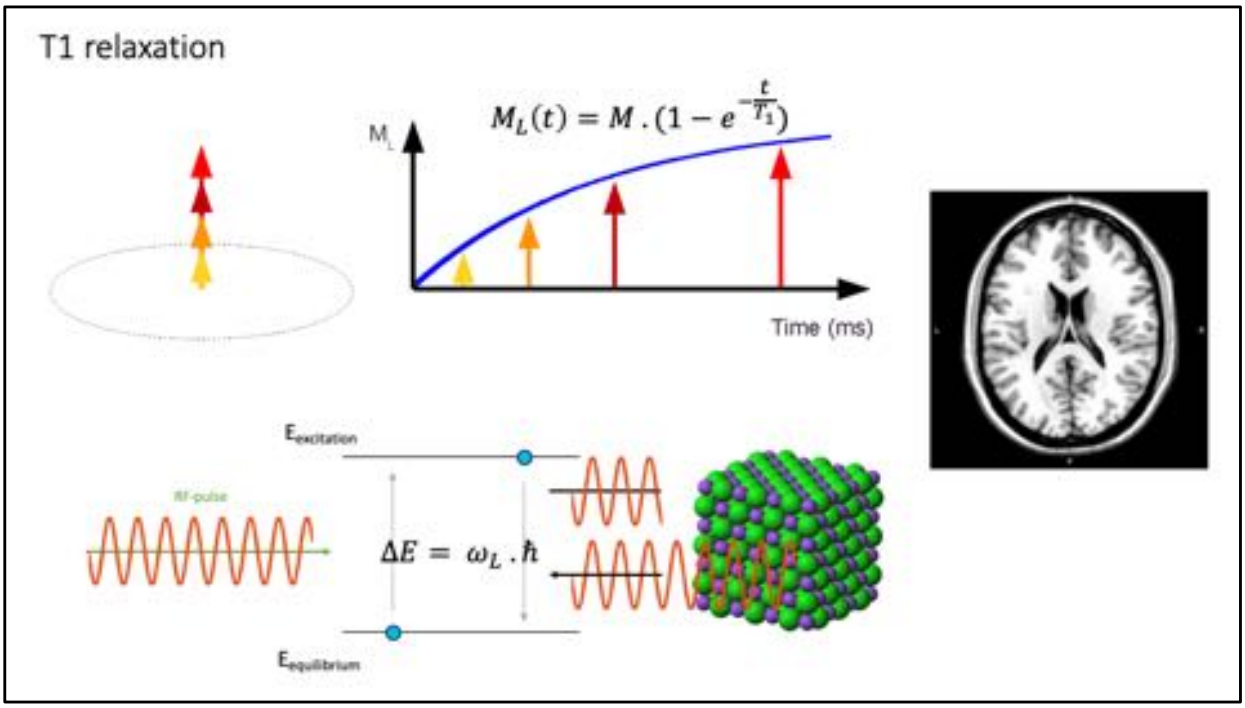
- Only B_0 is present
- All spins will align back with B_0

⇒ **M_L will recover back to its full magnitude (longitudinal relaxation)**
⇒ **M_T will decay to 0 (transverse relaxation)**

But:

- Longitudinal and transverse relaxation are independent from each other -> different relaxation mechanism
- Characteristic relaxation time longitudinal relaxation: T1
- Characteristic relaxation time transverse relaxation : T2(*)
- T1 >> T2 > T2*

For an animation see: https://www.youtube.com/watch?v=0YBUSOrH0Iw
See also http://mri-q.com/free-induction-decay.html



- Before the excitation (RF) pulse
  - All spins aligned with B0 -> The ground state (lowest energy level)

- After the excitation (RF) pulse
  - All spins perpendicular to B0 -> Excitation state (higher energy level)

    ⇒ **The absorbed RF-energy to go from a low to a higher energy state:** $\Delta \boldsymbol{E} = \boldsymbol{\omega_L} \cdot \hbar$

  - The excitation state is also a stationary state
    - ⇒ No spontaneous falling back to the ground state -> no spontaneous emission of the absorbed energy
    - ⇒ Only stimulated transitions from the high to the low energy state -> stimulated emission of the absorbed energy

- Stimulated emission (similar to the physics of laser light amplification)
  - A RF wave with a frequency equal to the Larmor frequency is absorbed by the spin and forces the spin to fall back to the ground state
  - By falling back to the ground state the spin emit all of the absorbed energy
    - ⇒ Transmission of a RF wave at the Larmor frequency

  - **Important to note: stimulated emission is only possible if the frequency of the incident RF wave equals the Larmor frequency!**

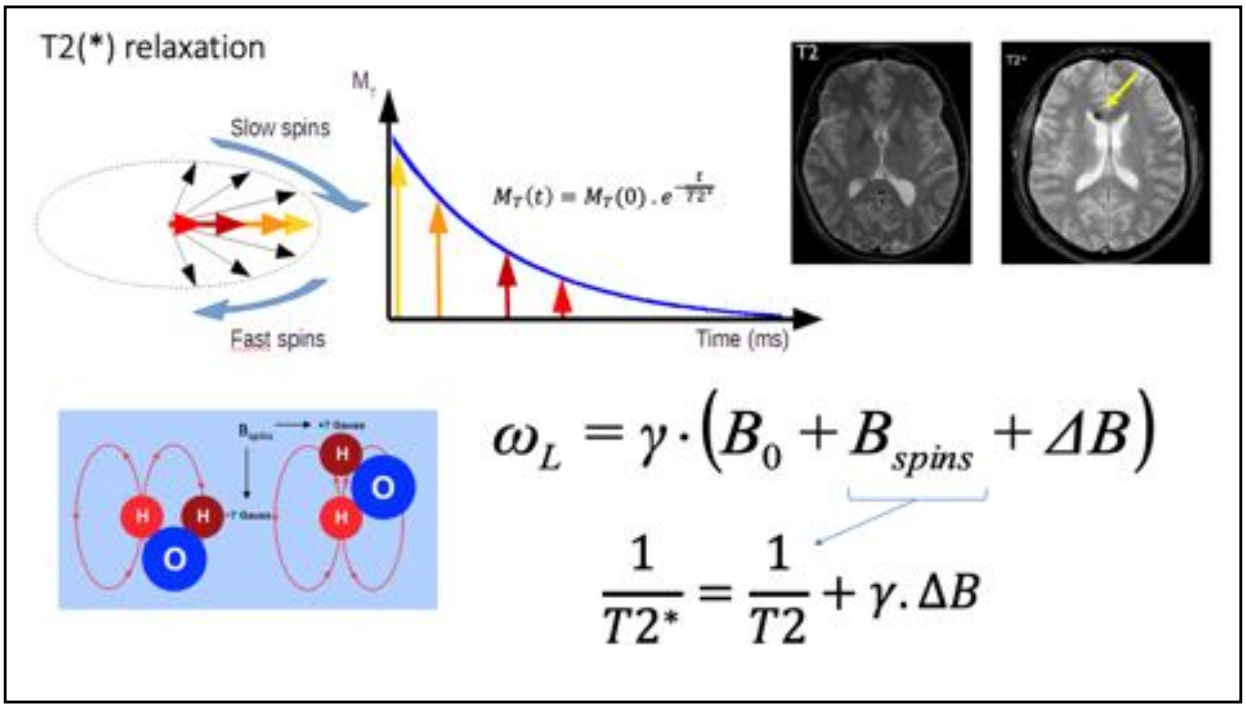
- The spin-lattice interaction -> T1 relaxation
    - The tissue particles ("the lattice") are at body temperature
        $\Rightarrow$ Are in thermal energy states
        $\Rightarrow$ The particles are vibrating and rotating
    - According to Ampére's law: the ions in the lattice produce a magnetic field (moving electric charges) -> the lattice field
    - The lattice field contains a whole spectrum of frequencies depending on the tissue properties (thermal spectrum)

    - **If one of the frequencies of the lattice field = the Larmor frequency -> stimulated transition of the spins from the excited to the ground state**

    - When spins are back in the ground state -> realignment with B_0
        => Recovery of M_L to its original size (M -> from before the excitation pulse)
    - The recovery curve of M_L is an increasing exponential curve
    - The relaxation (-> recovery) of M_L happens at a characteristic time T1 (time it takes for 63% of the spins to relax)

- T1 relaxation is tissue dependent and can be used to make T1 weighted MRI images (e.g. for high resolution anatomical images)

See also:
https://en.wikipedia.org/wiki/Spin-lattice_relaxation
https://en.wikipedia.org/wiki/Stimulated_emission
http://mri-q.com/what-is-t1.html



- T2(*) relaxation = decay of the transverse magnetization M_T

- The local magnetic field strength at the level of the protons depends on
    - The strength of the magnetic field of the MRI scanner (B_0)
    - The spin-spin interactions (B_{spins}) (random fluctuating)
        - Depends on the location from the neighboring spins

        -> tissue dependent -> T2

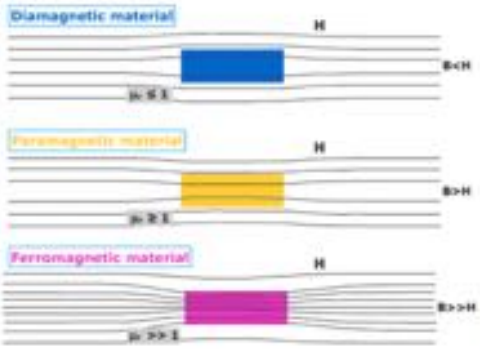
    - Local magnetic field distortions (ΔB)
        - Inhomogeneity of the main magnetic field B_0 -> susceptibility effects
        - Presence of feromagnetic material (e.g. from implants)
        - Presence of feromagnetic atoms/molecules (e.g. from a contrast agent)
        - Sudden changes in the permeability of the “tissue” for magnetic fields (e.g. at air-tissue borders)

- Due to the susceptibility effects -> faster dephasing of the spins - > faster decay of M_T -> T2*

- T2: tissue characteristic relaxation time due to spin-spin interactions only -> tissue dependent -> can be used to make T2 weighted MRI scans
- T2*: tissue characteristic relaxation time combining the effects of the spin-spin interactions (T2) and the magnetic field distortions (ΔB)
- The contrast in T2* weighted images is similar to the contrast in T2 weighted images, but is a local magnetic field distortion exist (e.g. due to the in hemoglobin in an old bleeding), the image contrast lowers.

See also

http://mri-q.com/what-is-t2.html
http://mri-q.com/t2-vs-t2.html
http://mri-q.com/what-is-susceptibility.html



Example:

- diamagnetism: human tissues
- Paramagnetism: air
- Ferromagnetism: iron objects

Magnetic **susceptibility** (χ)= a measure of how much a material will become magnetized in an applied magnetic field.

Permeability ($\mu_r = (1 + \chi)$) = the measure of magnetization that a material obtains in response to an applied magnetic field.
(μ_r the relative permeability of a tissue, μ_0 the permeability of free space)

The magnetic induction (B) is linked to the magnetic field strength (H) by $B = \mu_r.H = \mu_0(1 + \chi)H$

In diamagnetic and paramagnetic materials: $\mu_r \approx 1$

↓

No distortion of the magnetic field -> $\Delta B = 0$ -> $T_2^* = T_2$

In ferromagnetic materials: $\mu_r \gg 1$

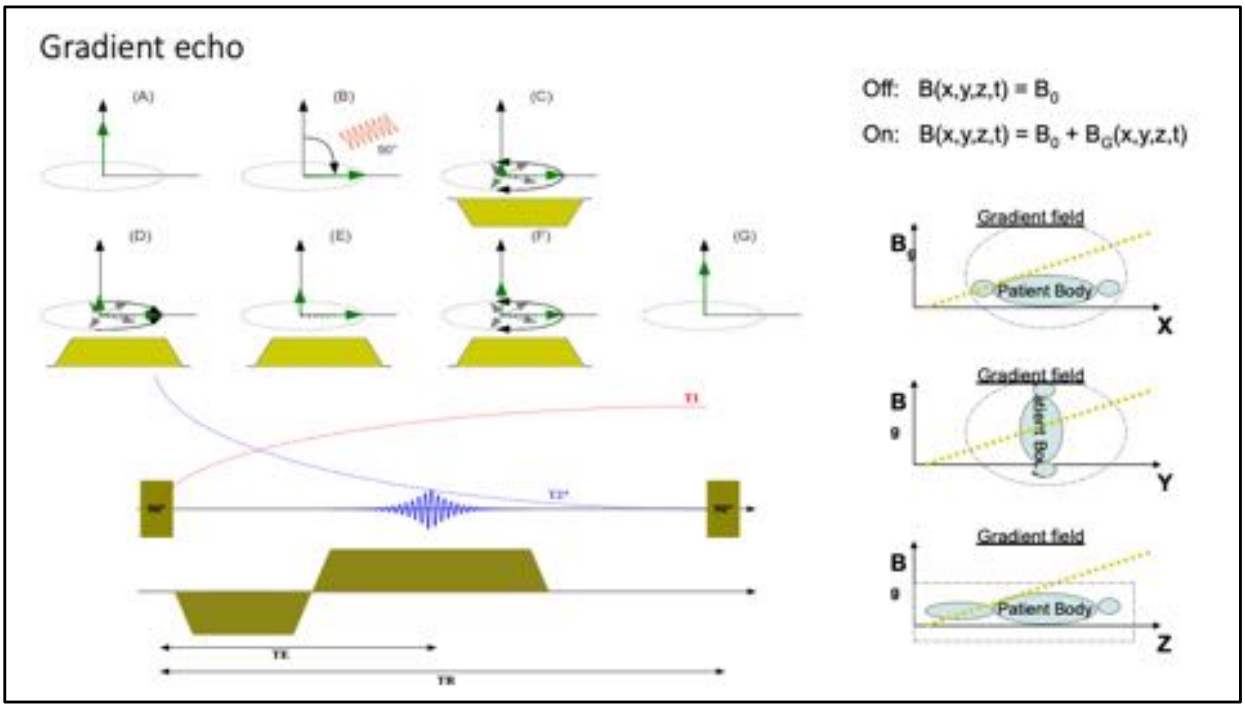
↓

Strong distortion of the magnetic field -> $\Delta B > 0$ -> $T_2^* < T_2$

See also
https://mriquestions.com/what-is-susceptibility.html

If the local field inhomogeneity increases

a. T2* will increase
b. T2* will decrease
c. T2* will not be affected



Interlude: **gradient magnetic fields (B_G) = linear varying magnetic fields in space**

3 main gradient directions present in an MRI scanner:

- X: left -> right
- Y: anterior -> posterior
- Z: feet -> head

By combining the main gradients: a gradient field in any direction can be created

Presence of gradient fields:

- While not scanning: switched off (only B0 present)
- During scanning: switched on and off as defined in the sequence

->applied magnetic field in the scanner at position (x,y,z) at time t:

$B(x,y,z,t) = B0 + B_G(x,y,z,t)$

See also http://mri-q.com/what-is-a-gradient.html

Technique to generate an echo: **Gradient echo (GE)**

A. Equilibrium state: all spins are aligned with B_0 -> M_L
B. Applying a 90° RF pulse: M_L is flipped into M_T
C. Forced decaying of the spins by applying a **gradient field**: $\omega_L = \gamma . (B0+B_{spins}+\Delta B-B_G(x,y,z,t))$
D. Forced rephasing of the spins by applying the **reversed gradient field**: $\omega_L = \gamma .$

($B0+B_{spins}+\Delta B+B_G(x,y,z,t)$)

- Faster spins before the reversing of the gradient becomes the slower spins after the reversing
- Slower spins before the reversing of the gradient becomes the faster spins after the reversing

A. All spins are in phase again
B. Forced decaying of the spins by applying a gradient field: $\omega_L = \gamma . (B0+B_{spins}+\Delta B+B_G(x,y,z,t))$
C. After some time the equilibrium time is restored due to T2* decay and T1 recovery

From D -> F: an echo signal is created

Maximal amplitude of the measured gradient echo:

- Initial amplitude of the FID (amplitude of M_L at time 0)
- Solely rephasing of the dephasing caused by the applied gradient field B_G

  -> no rephasing of the dephasing caused by B_{spins} and ΔB

  -> T2* decay

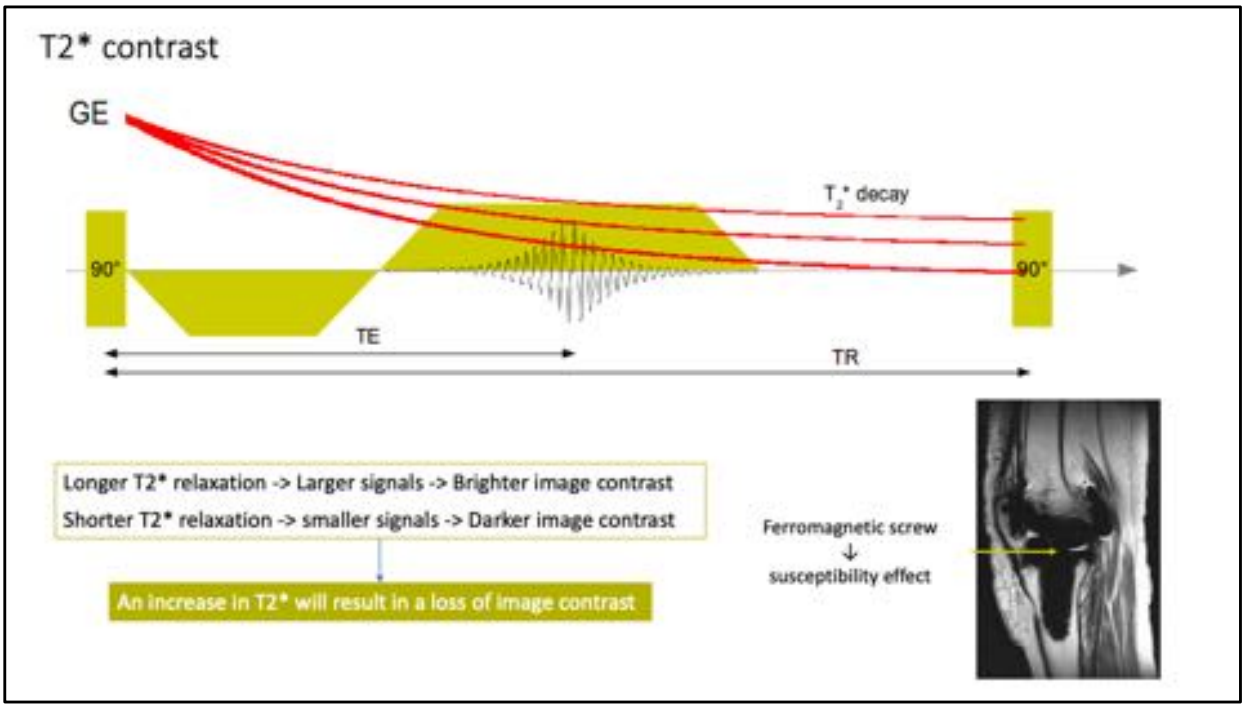
Basic cell of a SE sequence (= order and timing of hardware actions):

- At time 0: 90° RF pulse
- From time 0 till TE/2: negative gradient field
- From time TE/2 till 3*TE/2: positive (or reversed) gradient field

Timings of importance:

- **TE (echo time) -> time from the 90° RF pulse to the maximum of the measured echo**
- **TR (repetition time) -> time between two repetitions of the basic cell of the GE sequence (between 2 successive RF pulses)**

See also http://mri-q.com/gradient-echo1.htm



The amount of T2* weighting in an image is defined by TE.

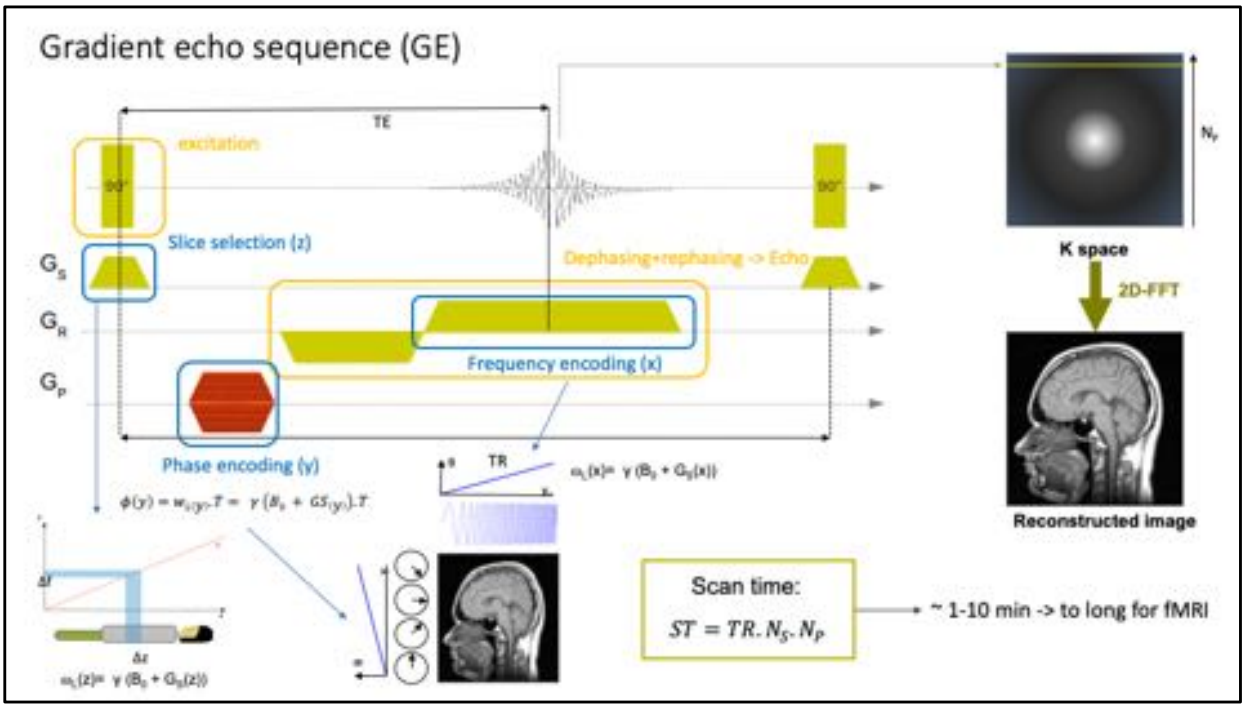
If TE is long (e.g. 30ms)

- Longer T2* relaxation -> Larger signals -> Brighter image contrast
- Shorter T2* relaxation -> smaller signals -> Darker image contrast

As a result, an increase in T2* will result in a loss of image contrast.

If the local field inhomogeneity increases

a. The image contrast will increase
b. The image contrast will decrease
c. The image will not be affected



In MRI, imaging is done by using a sequence

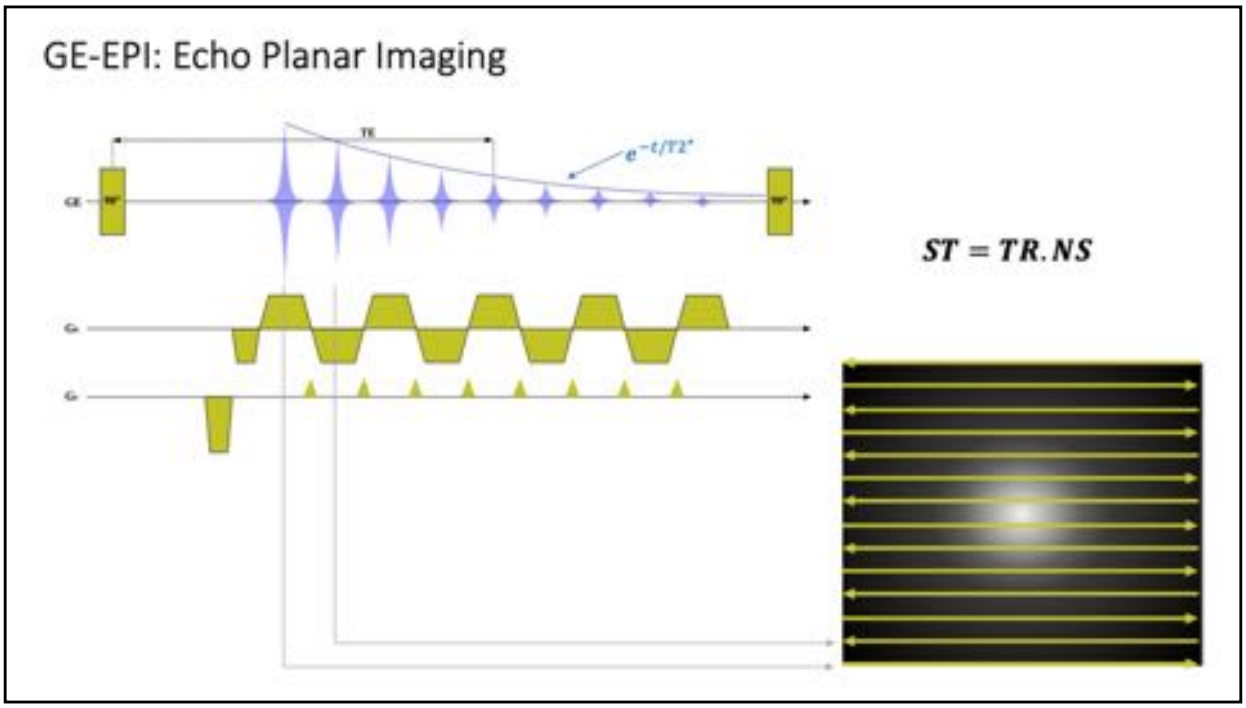
- Timeline that describes the different hardware actions done during the MRI scan
- We have a line describing the RF pulses given and the measured RF signal
- We have multiple lines describing the gradient fields (linearly changing magnetic fields) used for the image encoding (encoding the measured signal by the position of the protons in the body (e.g. the left versus the right side of the brain))
- Gradient echo (GE):
    - Excitation of the longitudinal magnetization into transverse magnetization
    - the measured echo is created by the bipolar read gradient (G_R)
        - Negative lobe: dephasing of the spin magnetizations
        - Positive lobe: rephasing of the spin magnetizations -> echo signal is formed
    - The position encoding of the spins by applying slice, phase and frequency encoding
- The measured echo is saved in the K-space (1 line/echo)
- The basic cell of the sequence is as many times repeated as the number of lines needed to scan the full K-space (e.g. 256)
- The time between 2 repetitions of the basic cell is called the repetition time (TR)
- The time between the excitation pulse and the center of the echo is called the echo time (TE)
- From the measured K-space, the image can be reconstructed by applying a 2D Fourier Transformation

The scan time is defined by

- TR: the duration of the basic cell of the sequence

- N_P: the number of phase encoding steps (lines) measured to have the full K-space of a slice
- N_S: the number of slices

- Typically, an MRI scan takes several minutes -> to slow for fMRI were we need a temporal resolution of <3s



- Echo Planar Imaging (EPI)
    - Basic idea: all phase encoding steps are done within 1 TR -> Shorten the scan time to ST=TR.N_S (N_S = number of slices)
    - After each RF excitation pulse a train of echoes is measured
    - The successive echoes are induced by iteratively inversing the frequency encoding gradient
    - The phase encoding is done by short blip gradients in between 2 echo measurements
- Sampling the K-space in EPI

- The first negative phase and read gradients are used to go to the left bottom of the K space
- Blipped phase encoding gradients
    - K space is sampled alternating from left to right and from right to left
    - The blip phase gradient is used to jump to the next line

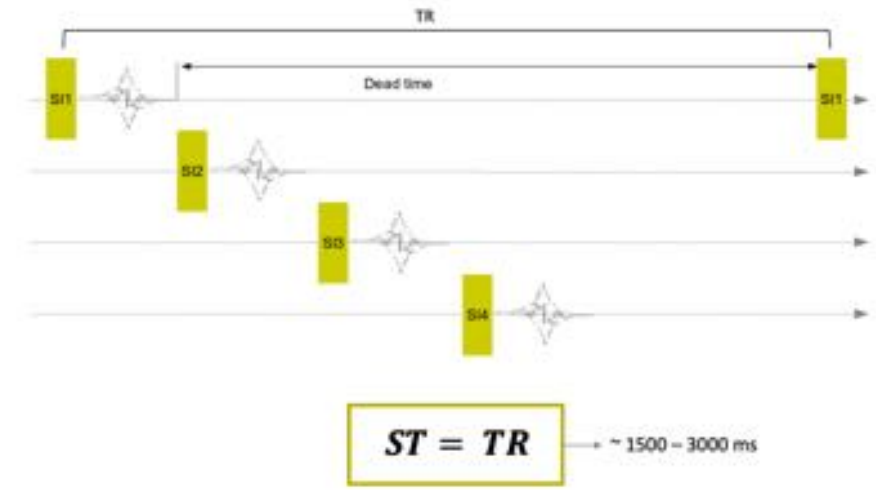
    -> **180° phase shift between the even and odd lines**

- The amplitude of the echo at time TE (central echo) is T2* weighted in GE-EPI -> successive gradient echoes

- The echo train length or EPI factor is limited due to the T2* relaxation of the signal

See also
http://www.revisemri.com/questions/pulse_sequences/epi
http://mri-q.com/echo-planar-imaging.html

Multi slice imaging



$$ST = TR$$ ~ 1500 – 3000 ms

- TR >> time needed to create and measure an echo signal -> dead time between the echo measurement and the next excitation pulse
- Excitation pulses are slice selective -> Spins at other slice positions are not affected by the RF pulse

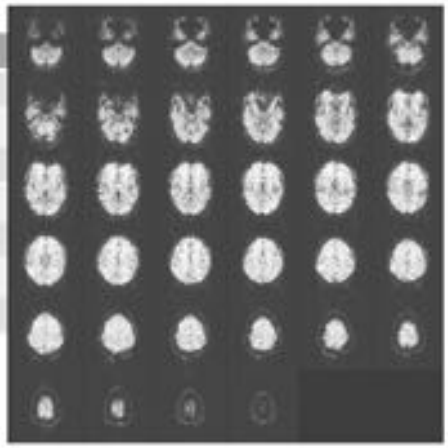
- Multi slice imaging within 1 TR
    - After the measurement of the echo of the first slice the spins from the second slice are excited
    - After the measurement of the echo of the second slice the spins from the third slice are excited
    - …

- If all slices are scanned within 1 TR, ST reduces to $\boldsymbol{ST = TR}$

See also http://mri-q.com/mixing-of-slices.html

Example of fMRI GE-EPI settings

TR	2000 ms
TE	30 ms
Number of slices	36
Slice thickness	3 mm
Slice gap	0 mm
FOV	240 x 240 mm^2
Scan matrix	80 x 80
EPI factor	80

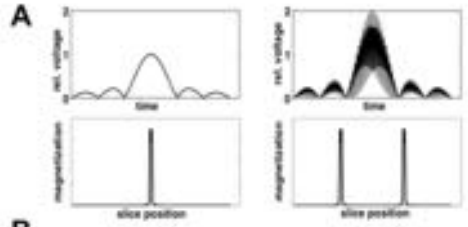


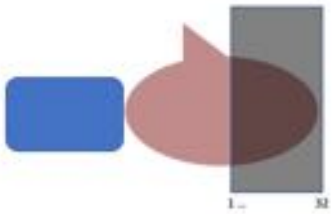
Scan time: 2s

Scan resolution: 3 x 3 x 3 mm^3

- With this sequence we are able to scan the entire brain in 3s, but at a cost of a low image resolution
- In fMRI, the whole brain is scanned every 0.5-3 s

Simultaneous Multi-Slice (SMS) / MultiBand/ HyperBand





Without SMS: 1, 3, 5... 31, 2, 4, ... 32 (interleaved order)

↓

32 individual slices to measure

With SMS: (1, 5, 9, ... 29) , (3,7,11,...31), (2,6,10,...30), (4,8,12,...32)

↓

Only 4 slice packages with 8 slices each to measure

$$RF(t) = A(t).\sum_{N} e^{i.\omega_n.t+\varphi_n}$$

- Simultaneous multi-slice (SMS), MultiBand (MB) or Hyperband imaging, uses RF pulses that are a composite of multiple RF pulse varying in frequency and phase
    - A left: single barn RF pulse: $\boldsymbol{RF(t) = A(t).e^{i.\omega.t+\varphi}}$
    - A right: composite RF pulse = the sum of N=2 single band RF pulses: $\boldsymbol{RF(t) = A(t).\sum_N e^{i.\omega_n.t+\varphi_n}}$

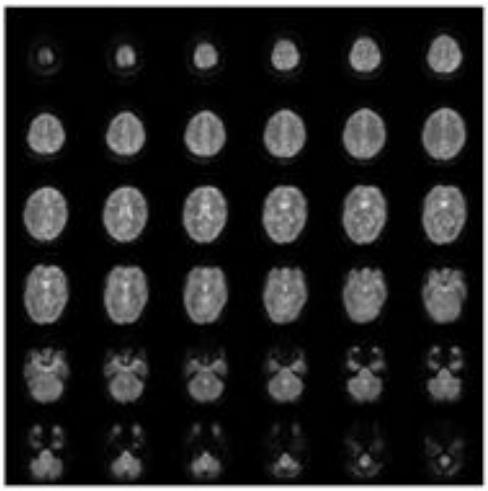
- Each frequency in the RF pulse select a single slice at a different position
- The acquired signals come from all selected slices -> is split during the image reconstruction

- The SMS technique helps to increase the spatial resolution while shortening the temporal resolution

See also
http://mriquestions.com/simultaneous-slices.html
http://mriquestions.com/simultaneous-multi-slice.html
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4915494/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3830622/

Current HCP fMRI scan protocol

TR	720 ms
TE	33 ms
Flip angle	52 deg
Number of slices	72
Slice thickness	2 mm
Slice gap	0 mm
FOV	208 x 180 mm^2
Scan matrix	104 x 90 (2x2 mm)
EPI factor	90
HyperBand factor	8



Temporal resolution = 720 ms

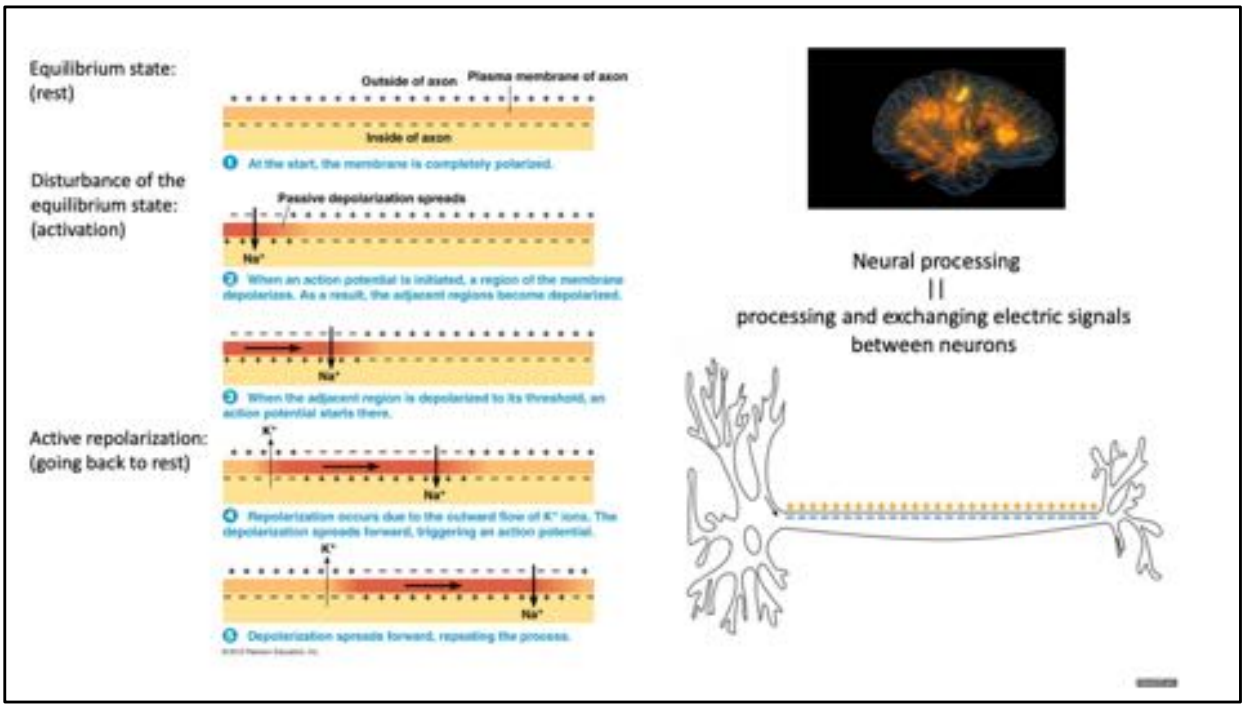
Spatial resolution is 2 mm isotroppic

These are the standard scan parameters proposed by the Human Connectome Project (HCP: http://protocols.humanconnectome.org/HCP/3T/imaging-protocols.html) for fMRI experiments

The hemodynamic response

Universitair Ziekenhuis Brussel

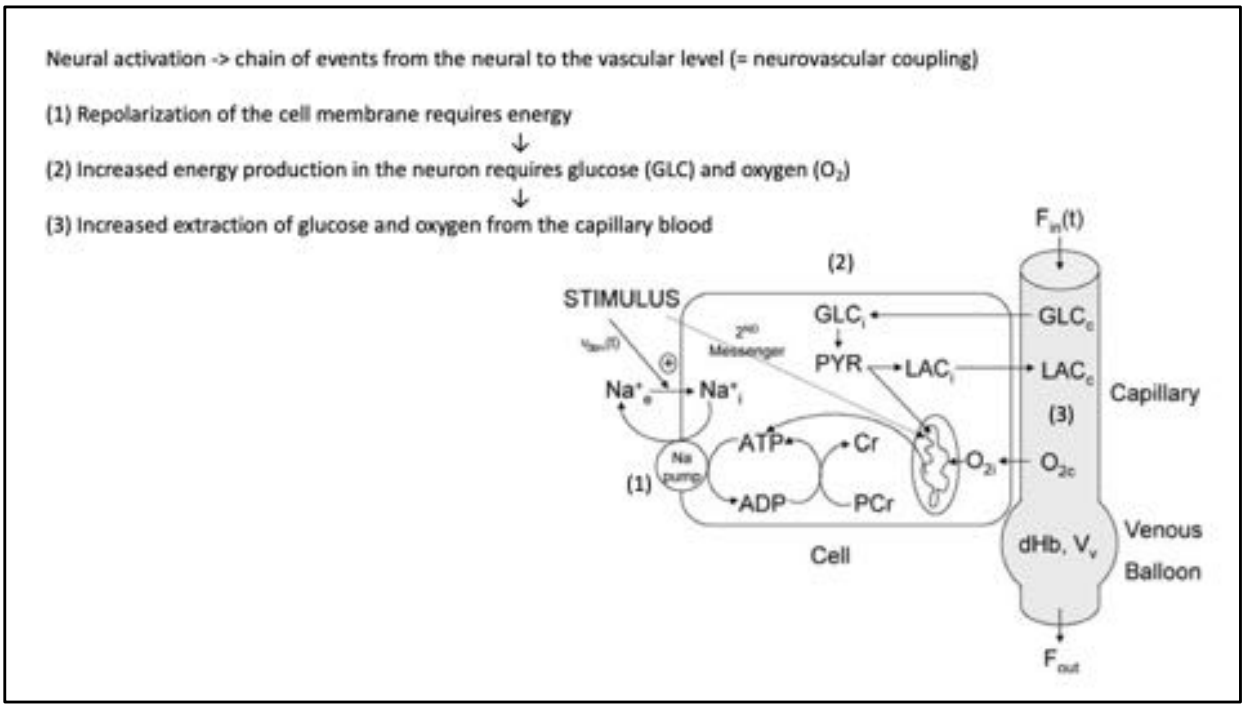
VUB



- Neural processing is based on the activation of neurons and the exchange of signals between neurons

- These signals are
    - Electric pulses traveling along the axon of the neuron
        - Dynamic depolarization and repolarization of the membrane by a change in the ion (Na^+ and K^+) concentrations inside the axon
    - Neurotransmitters exchanged at the synapse from one neuron to the other

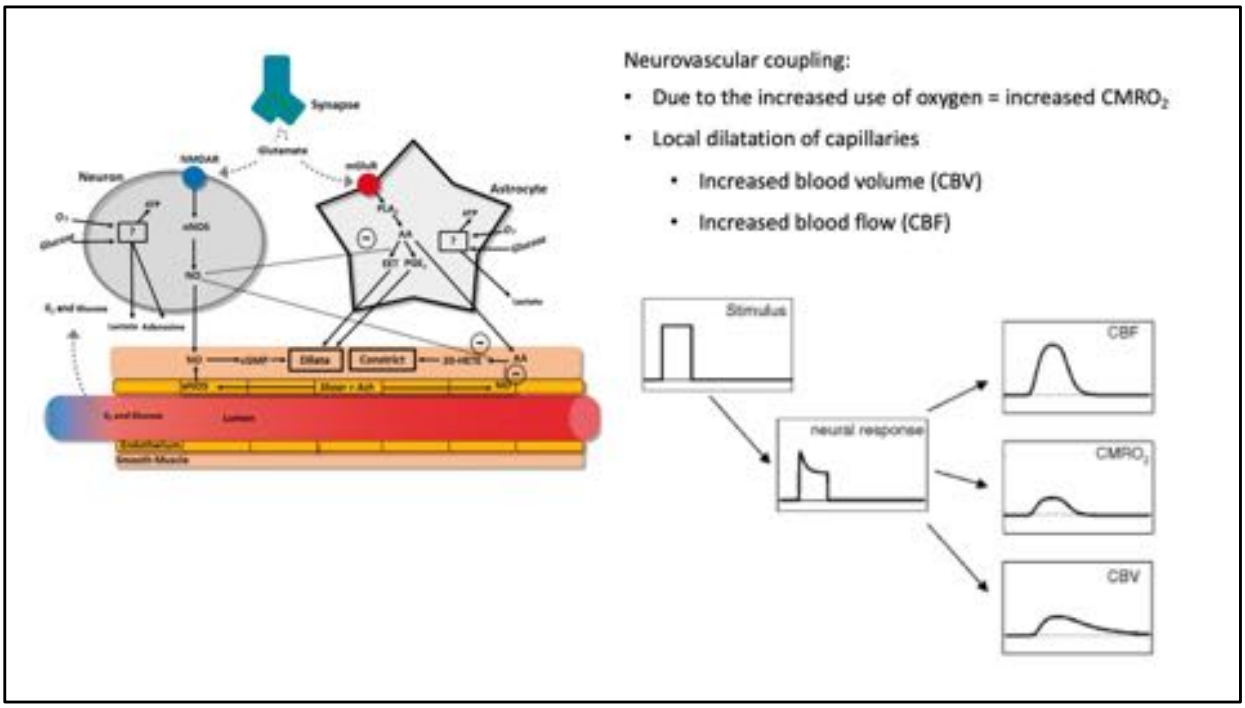
- Steps:
    - The neurotransmitter depolarizes membrane of the neuron at its dendrite -> inflow of Na+
    - If the activation threshold is met -> depolarization of the neighboring axonal membrane -> traveling of an electric pulse
    - Repolarizing of the membrane happens by active exchange of ions between the intercellular and extracellular space through the membrane (pumping)



- The active transport (pumping) of ions through the axonal membrane requires energy to restore the rest action potential -> energy consuming (ATP ⇋ ADP)

- Secondary to the dynamic change in the electric potential, there are dynamic changes in the processes generating metabolic energy
- Sequence of complex processes:
    - 1: Depolarization of the cell membrane
    - 2: Spontaneous inflow of Na^+ -> increased Na^+ concentration intracellular
    - 3: Activation of the Na-pump (Na^+, K^+ -ATPase)
    - 4: Increased synthesis of ATP -> mainly from oxidative glucose metabolism -> increased need for oxygen (O_2) and glucose (GLC)
    - 5: Dynamic changes in the capillary oxygenated (OHb) and deoxygenated (dHb) hemoglobin, blood flow (CBF) and blood volume (CBV) -> neurovascular coupling

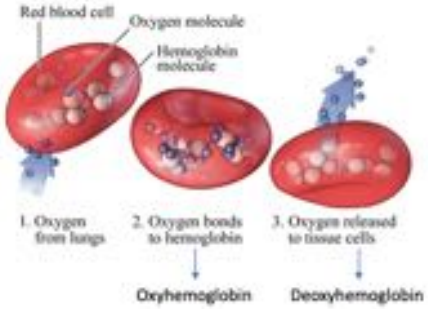
See also
Wong-Riley. 2012. Energy metabolism of the visual system. Eye Brain 2:99-116
Aubert and Costalat 2002. A model of the coupling between brain electrical activity, metabolism, and hemodynamics: application to the interpretation of functional neuroimaging. NeuroImage 17:1162-1181
https://nl.wikipedia.org/wiki/Natrium-kaliumpomp
https://en.wikipedia.org/wiki/Na%2B/K%2B-ATPase
https://en.wikipedia.org/wiki/Adenosine_triphosphate

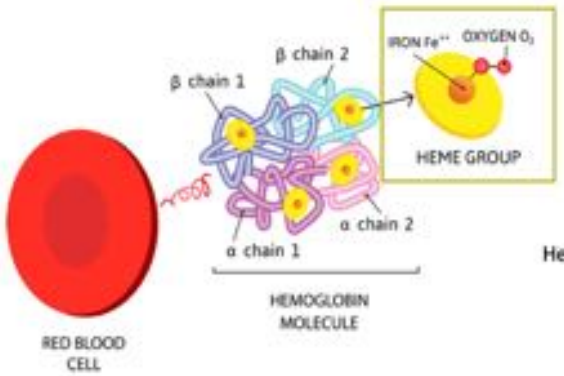


- **Neurovascular coupling** refers to the relationship between local neural activity and subsequent changes in cerebral blood flow (CBF)
- Neurons are activated by the availability of neurotransmitters at their synapse (e.g. glutamate binds at the glutamatergic receptors at the neuron and astrocytes) -> cascade of metabolic reactions
    - Some of the metabolites relax the smooth vascular muscle -> vasodilation -> increased CBF
- Factors driving the neurovascular coupling
    - Neuron activation (depolarization and repolarization) -> replenishing of used GLC and 0_2
    - Neurotransmitter recycling (glutamate)
- The vascular response is
    - Slow: 5-6 seconds after the neural response
    - In balance with the increased glucose consumption
    - Overcompensates the increased oxygen consumption

See also
http://www.scholarpedia.org/article/Neurovascular_coupling
http://mriquestions.com/does-boldbrain-activity.html
Philips 2016. Neurovascular coupling in humans: physiology, methodological advances and clinical implications. J. Cereb. Blood Flow Metab. 36(4):647-664
Attwell et al. 2010. Glial and neuronal control of blood flow. Nature 468(7321):232-243

Oxygen in the blood is transported by the hemoglobin molecule in the red blood cells



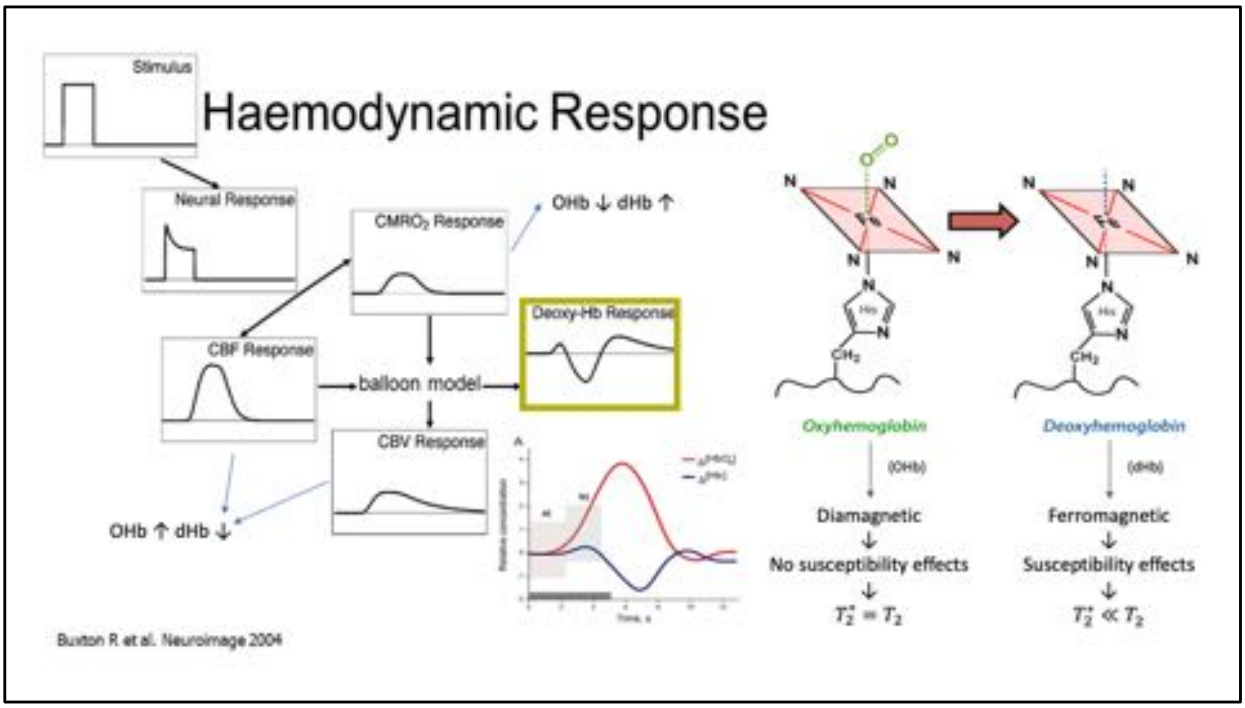


Hemoglobin = 4 chains with a heme group containing Fe^{++}

↓

Deoxyhemoglobin (no oxygen bound to Fe) -> Fe^{++}

Oxyhemoglobin (oxygen bound to Fe) -> FeO_2

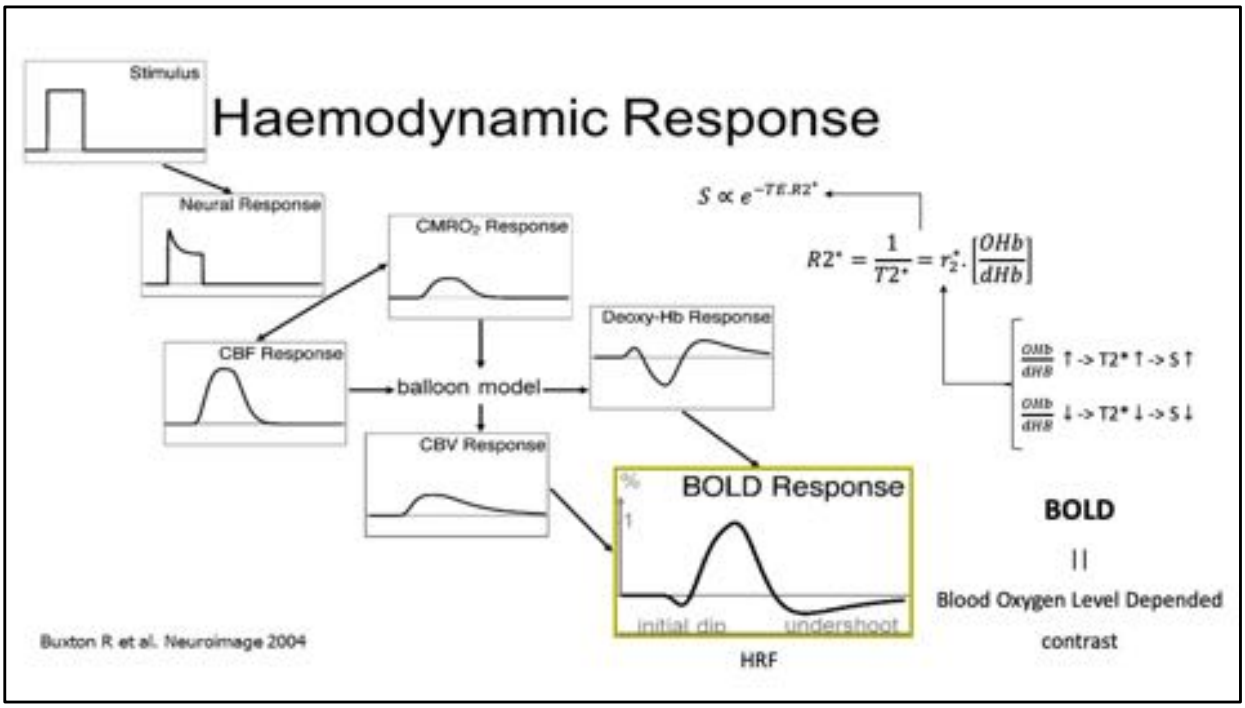


- The neurovascular coupling is of importance, since it changes the ration of oxygenated and deoxygenated hemoglobin
- Oxygenated and deoxygenated hemoglobin have different magnetic properties

- Hemoglobin
    - Macromolecule containing 4 subunits each consisting of a non-protein heme with an iron ion (Fe^{2+})
    - The free iron ion can bind other molecules (e.g. oxygen (0_2) -> oxyhemoglobin)

- The magnetic properties of hemoglobin depends on the presence or absence of a molecule bound to Fe^{2+}
    - No molecular binding: Fe^{2+} -> deoxyhemoglobin: ferromagnetic
    - Molecular binding (e.g. with O_2): X-Fe-0_2 -> oxyhemoglobin: diamagnetic

See also
http://mriquestions.com/types-of-hemoglobin.html

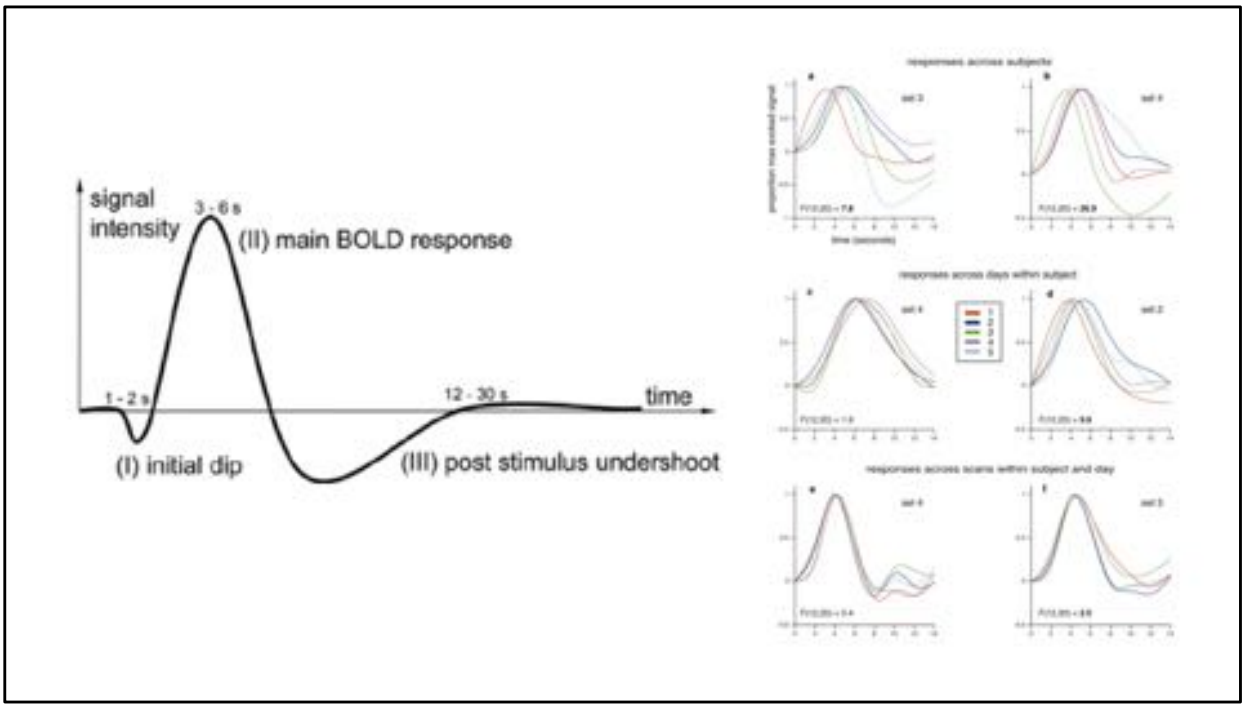


- BOLD: Blood Oxygen Level Dependent

- The presence of ferromagnetic deoxyhemoglobin (dHb) in the blood causes a magnetic field gradient around the vessel (capillary or veins) -> susceptibility effect
- The strength of the susceptibility effect depends on the ratio oxyhemoglobin/deoxyhemoglobin (OHb/dHB): $R2^* = \frac{1}{T2^*} = r_2^*.\left[\frac{OHb}{dHb}\right]$ (r2* the relaxivity = the rate at which the relaxation rate changes as a function of concentration)

- As a consequence: a change in the ratio (OHb/dHB)
    - Changes the strength of the susceptibility effect (T2*)
    - Changes the contrast (S)
        - Increased (OHb/dHb) -> increased signal
        - Decreased (OHb/dHb) -> decreased signal

See also
http://mriquestions.com/bold-contrast.html
http://mri-q.com/what-is-relaxivity.html



- The Hemodynamic Response Function (HRF)
    - The initial dip
        - Hypothesis 1: to originate from an early CMRO2 change with no change in CBF -> increased dHb concentration
        - Hypothesis 2: the result from a change in the arterial CBV
        - Most likely: a combination of multiple factors -> still a matter of ongoing debate
        - The initial dip is mostly not visible in fMR data at 1.5T or 3T
    - The main BOLD response
        - Overcompensation of $CMRO_2$ by CBF -> increased OHb concentration (inflow) + decreased dHb concentration (outflow) -> increased OHb/dHb
    - The post stimulus undershoot
        - Still not fully understood
        - Hypothesis 1: the result from a slow CMRO2 recovery
        - Hypothesis 2: the result from a CBF undershoot combined with a slow recovery of the venous CBV

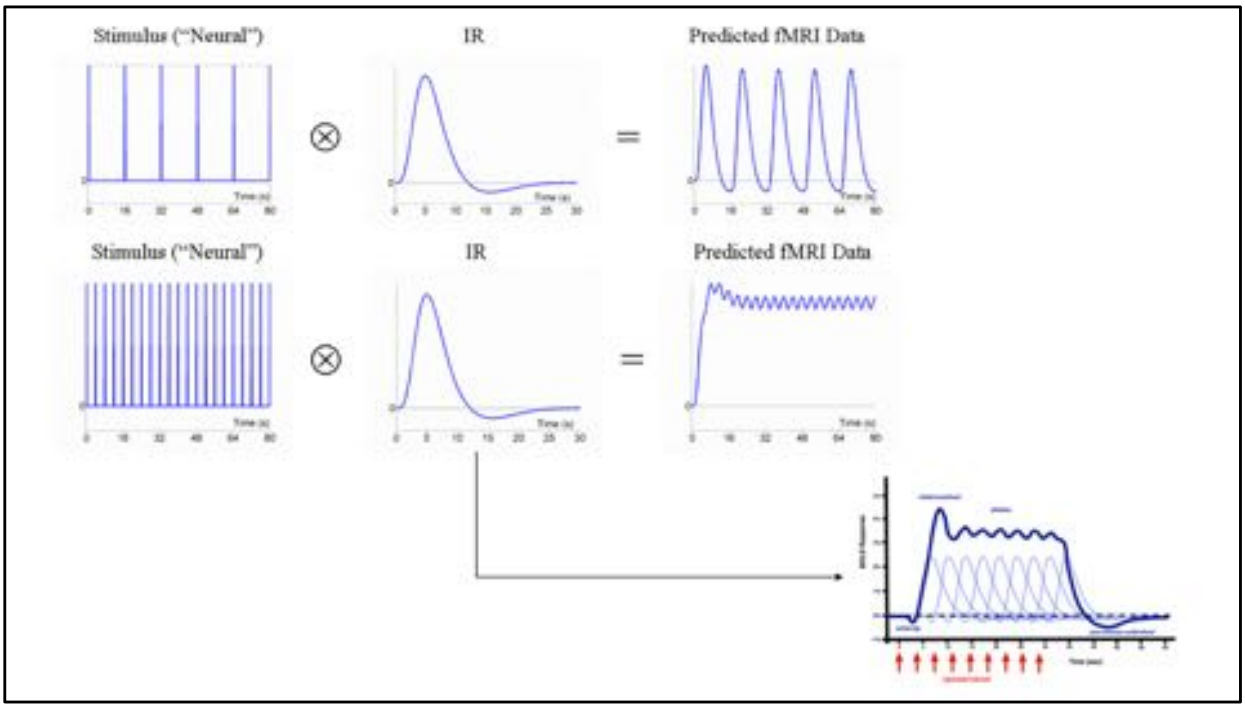
- The HRF varies
    - In the same area between subjects
    - Between brain areas within the same subject
    - In the same subject and brain area, between scans (affected by factors as nutrients used (alcohol, coffee, …), fatigue,…)

- The HRF varies
    - In lineshape
    - Delay of the peak maximum
    - Width of the peak

- Duration of the HRF

See also

Buxton 2012. Dynamic models of BOLD contrast. NeuroImage 62(2):953-961
Van Zijl 2012. The BOLD post-stimulus undershoot, one of the most debated issues in fMRI. NeuroImage 62(2):1092-1102
Aguirre et al. 1998. The variability of human, BOLD hemodynamic response. NeuroImage 369(8):360-369
Handwerker et al. 2004. Variations of BOLD hemodynamic responses acros subjects and brain regions and their effects on statistical analysis. NeuroImage 21(4):1639-1651



- Each stimuli generate a BOLD response

- If stimuli are repeated faster than the duration of the individual BOLD response (less than 4-5s), their BOLD responses overlap and are "added" to each other
    - After an initial overshoot, the signal reach a plateau -> Prolonged period (block) of increased signal
    - The increase in the hemodynamic responses and the increase in BOLD signal is non-linear

See also
http://mriquestions.com/does-boldbrain-activity.html
http://imaging.mrc-cbu.cam.ac.uk/imaging/DesignEfficiency

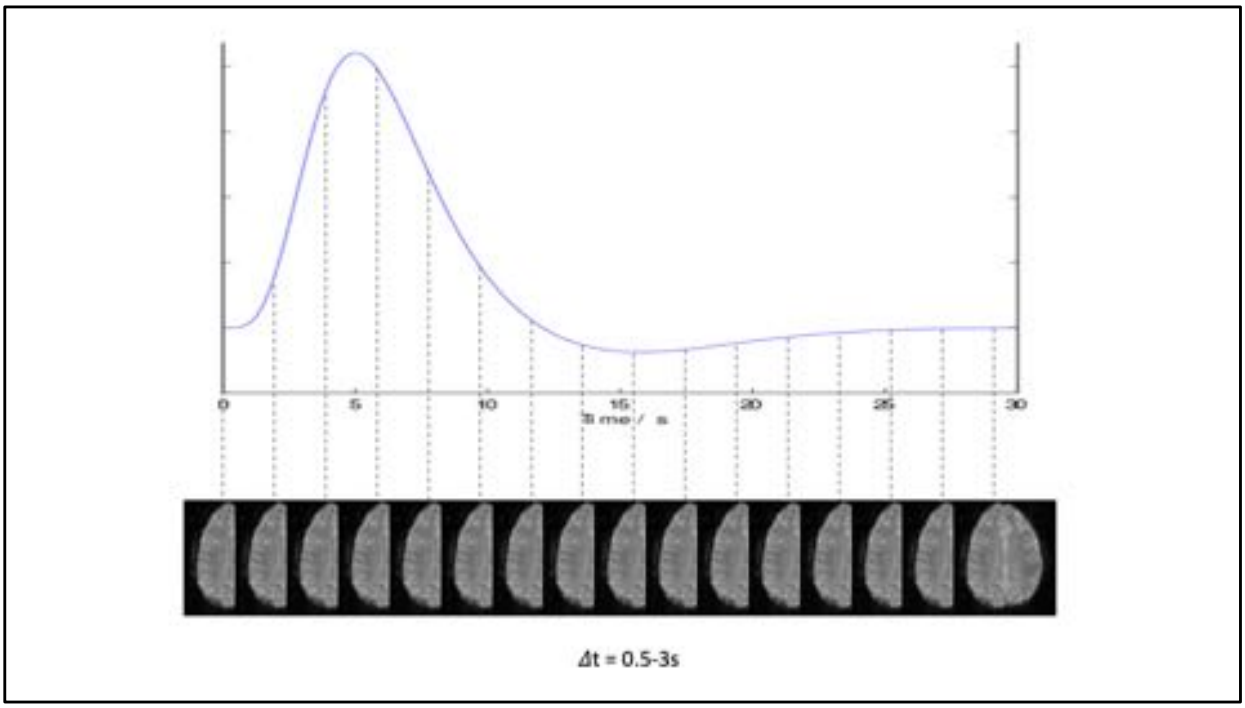
When neurons are constantly activated (constant neural activity)

a. The image contrast will increase
b. The image contrast will decrease
c. The image will remain constant

fMRI scan techniques

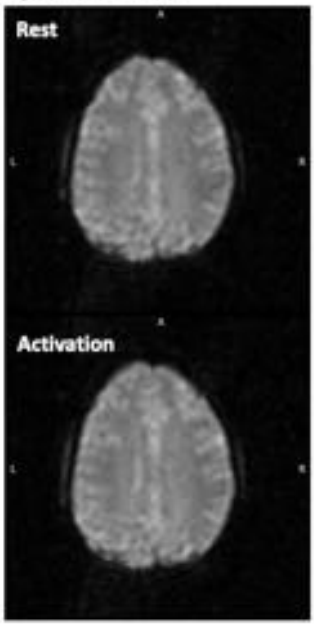
Universitair Ziekenhuis Brussel

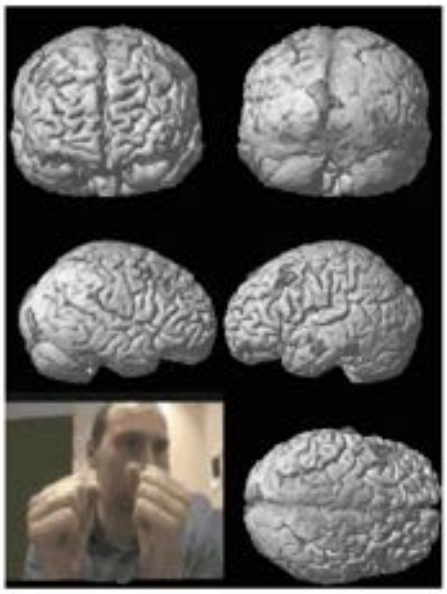
VUB



To scan the dynamic changes in BOLD signal, we need a dynamic scan with a temporal resolution of 0.5 to 3s. -> EPI sequence!

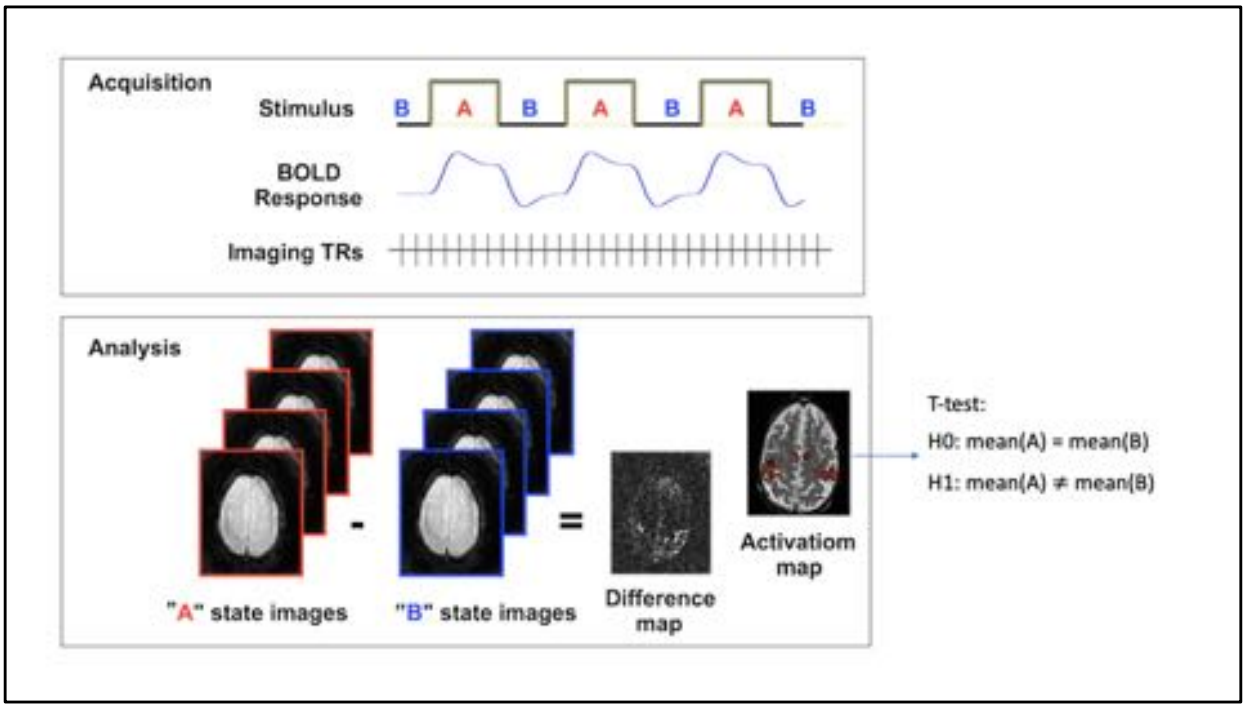
Statistical problem





- Main problem in fMRI: signal changes due to BOLD are much smaller compared to the noise -> not possible to see any difference between rest and activation -> no real time monitoring of the brain activity as shown in the movie

- Solution:
    - Repeated measures of brain states during different conditions (e.g. motor task versus rest)
    - Statistical methods to analyze the data -> all fMRI results do have a statistical uncertainty



- To increase the sensitivity to detect contrast differences between task states, every 0.5-3s a full brain scan is taken while the participant/patient performs a task consisting of different conditions/states for at least 5 minutes

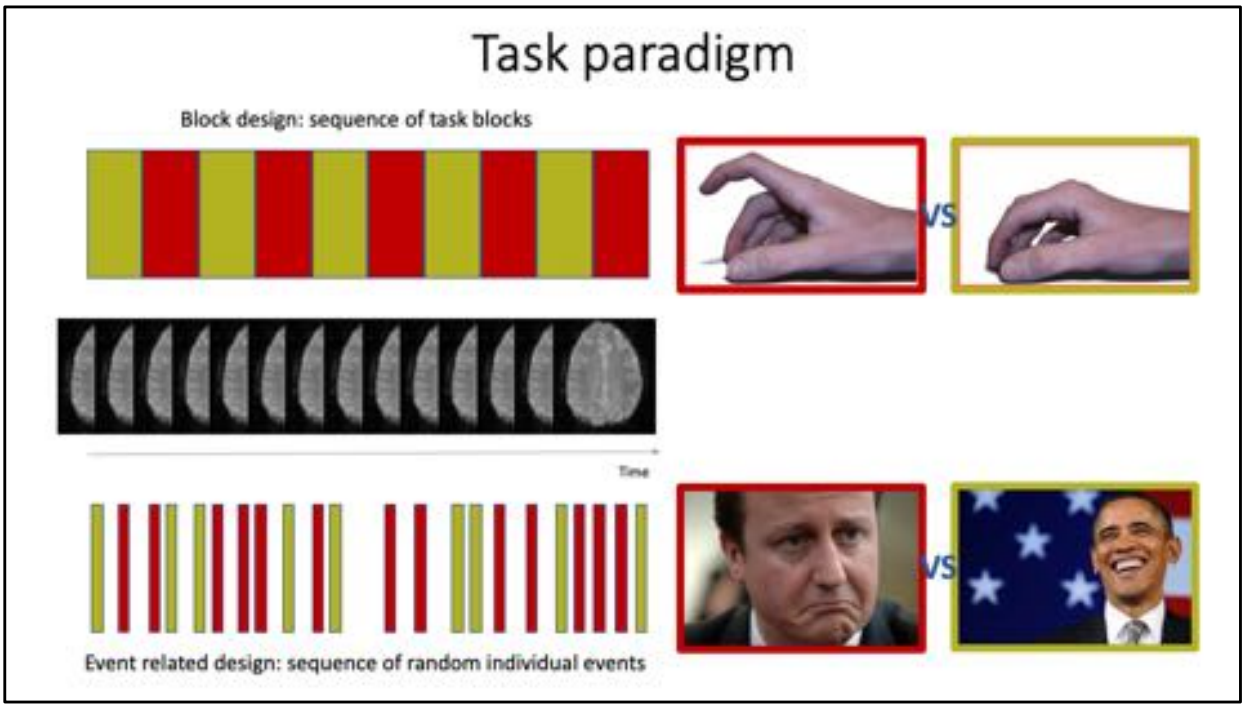
- During the analysis, the mean scans taken during the various task conditions are compared to come to activation maps (t-tests).

See also
Chen JE, Glover GH. Functional magnetic imaging methods. Neuropsychol Rev 2015; 25:289-313.
http://mriquestions.com/bold-pulse-sequences.html

Task paradigm

Universitair Ziekenhuis Brussel

VUB



- Paradigm: timeline describing the timings of the various conditions in the task during the fMRI experiment

- Examples of various task conditions
    - Rest versus motor task (e.g. finger tapping)
    - Stimuli eliciting happy feelings (e.g. laughing faces) versus stimuli eliciting sad feelings (e.g. sad faces)

- Temporal characteristics of the fMRI scan
    - Temporal resolution: maximal 0.5-3 s
    - Total duration > 4 minutes

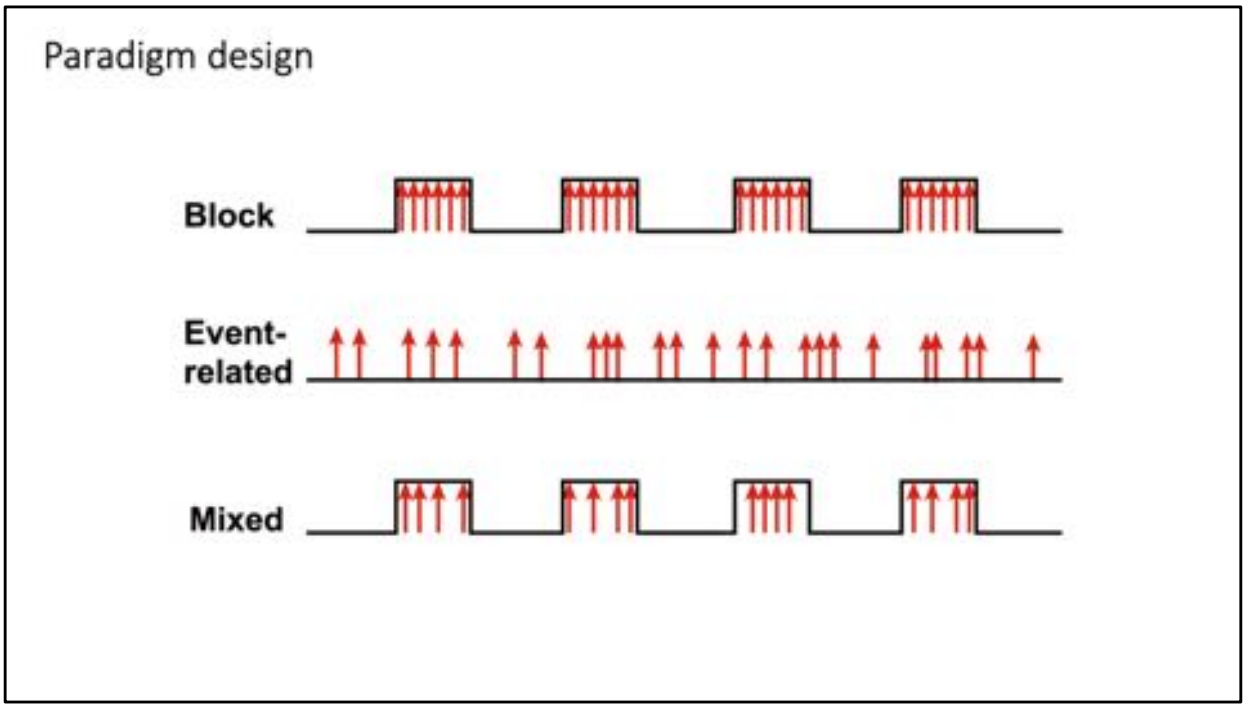
- Stimuli can be given as
    - A block -> prolonged period (10-30 s) of a task condition
    - An individual event -> ”0 s” duration

- Paradigm design types
    - Block design
        - The various task conditions (epochs) are given as continuous blocks
        - “on-off design”: repeated blocks of various states
        - Order and duration of the blocks are fixed
        - Ideal duration of a block: 10-30 s
    - Event-related design
        - The stimuli (trials) are given as individual events
        - Order and inter-stimulus time are randomized (jittered)
    - Mixed design
        - Mix of a block and an event related design
        - Fixed blocks with only 1 stimulus condition but within a block the

timing between the stimuli is jittered

- Number of different task conditions in a paradigm
    - Minimal: 2
    - Maximal: not defined but
        - The more conditions the more complex the task and the final analysis and interpretation of the results
        - The more conditions the longer the fMRI study should take to get sufficient statistics
    - Preferable maximal 3

See also
http://mriquestions.com/fmri-paradigm-design.html
Amaro and Barker 2006. Study design in fMRI: Basic principles. Brain and Cogn. 60:220-232



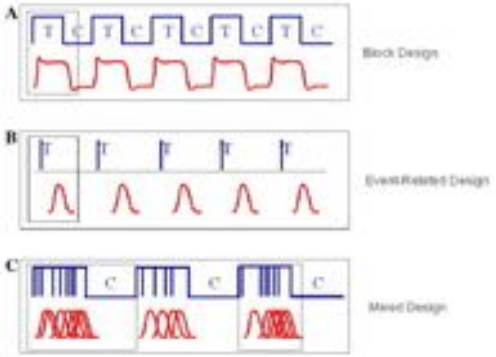
- Paradigm design types
    - Block design
        - The various task conditions (epochs) are given as continuous blocks
        - “on-off design”: repeated blocks of various states
        - Order and duration of the blocks is fixed
        - Ideal duration of a block: 10-30 s
    - Event-related design
        - The stimuli (trials) are given as individual events
        - Order and inter-stimulus time is randomized (jittered)
    - Mixed design
        - Mix of a block and an event related design
        - Fixed blocks with inly 1 stimulus condition but within a block the timing between the stimuli is jittered

- Number of different task condition in a paradigm
    - Minimal: 2
    - Maximal: not defined but
        - The more conditions the more complex the task and the final analysis and interpretation of the results
        - The more conditions the longer the fMRI study should take to get sufficient statistics
    - Preferable less than 3

See also
http://mriquestions.com/fmri-paradigm-design.html
Amaro and Barker 2006. Study design in fMRI: Basic principles. Brain and Cogn. 60:220-232

Comparison between paradigm designs

	Block	Event-related	Mixed
Detection power	High	Low	High
Estimation efficiency	Low	High	High
Predictability	High	Low	Medium
SNR	High	Low	Medium



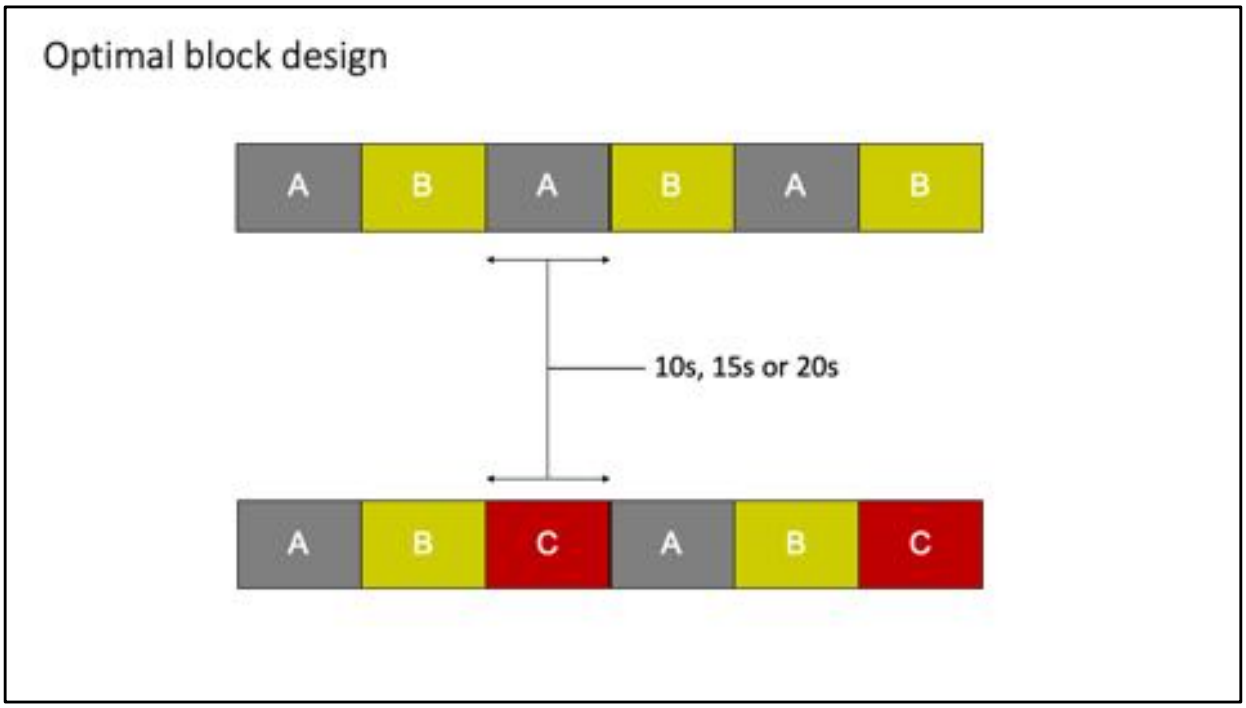
- Detection power: ability of a design to detect activity
- Estimation efficiency: ability of a design to characterize the shape of the HRF
- Predictability: ability to predict the timing and condition of the next stimulus in the test
- SNR: difference between activation and rest state (additivity of the HRF)

- To increase the SNR and the detection power in event-related studies the "randomized" order and inter-stimuli periods are optimized to create an overlap between the HRF (addition of individual HRFs) while preserving the unpredictability and the estimation efficiency.

- Preferred choices
    - Motor tasks e.g. finger tapping): block design
    - Sensory tasks (e.g. visual stimulation): block design
    - Cognitive tasks (e.g. Stroop (matched and unmatched color words and word colors (e.g. Blue written in red))): event-related
    - Memory tasks (e.g. familiar and unfamiliar faces): event-related
    - Emotional task (e.g. happy versus sad stimuli): event-related

- To increase the SNR and the detection power in event-related studies the "randomized" order and inter-stimuli periods are optimized to create an overlap between the HRF (addition of individual HRFs) while preserving the unpredictability and the estimation efficiency.

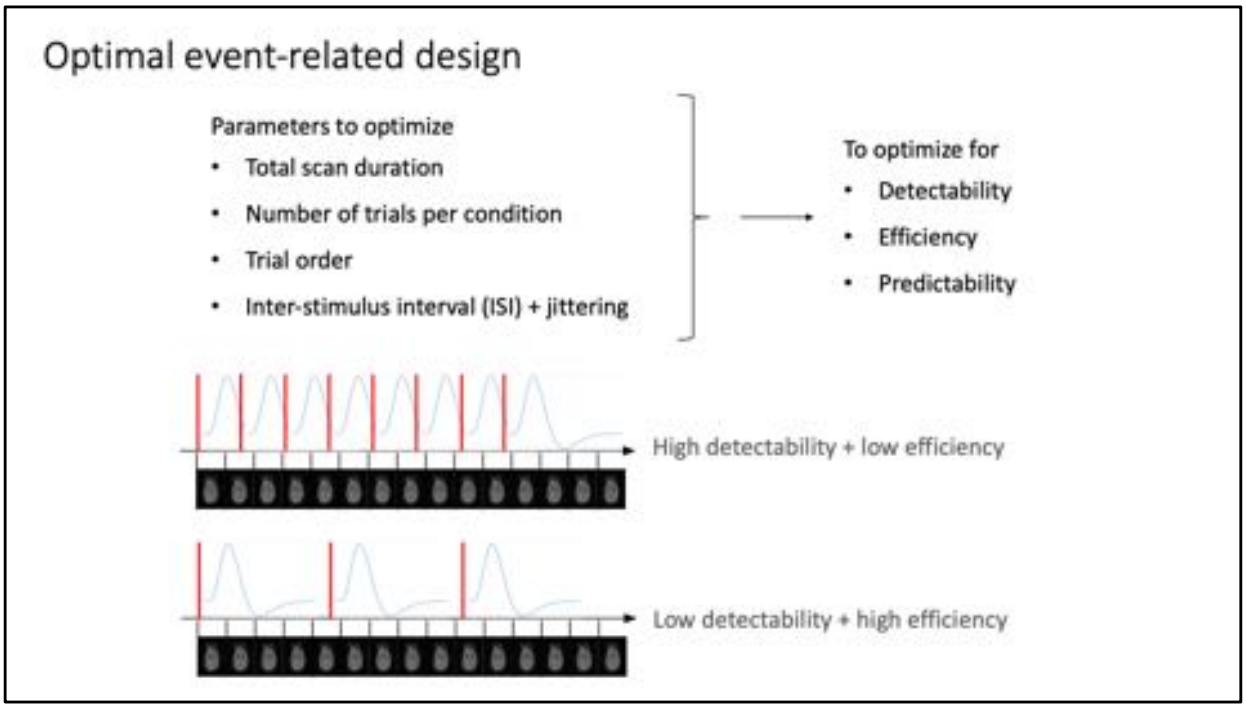
See also
http://mriquestions.com/fmri-paradigm-design.html
Amaro and Barker 2006. Study design in fMRI: Basic principles. Brain and Cogn. 60:220-232



- An optimal block design is maximized for its detectability -> highest power to find the neural activity
- Block designs always have a limited sensitivity -> not possible to estimate the shape of the HRF

- Optimal settings
    - Block order: ABAB (for 2 conditions A and B) or ABCABC (for 3 conditions A, B and C)
    - Rest blocks should be avoided, if you are only interested in the difference between 2 active conditions A and B
    - Block length: 10s, 15s or 20s
    - Total duration of an experiment > 4 minutes

See also
Maus B, Van Breukelen GJP, Goebel R, Berger MPF. Optimization of blocked designs in fMRI studies. Psychometrika 2010; 75:373-390.



- Event-related designs can be optimized for
    - Detection power (DP) -> power to detect a hemodynamic response
    - Efficiency (E) -> power to determine the shape of the individual HRF
    - Predictability (P) -> probability of a stimulus occurrence

- There is a trade-off between DP, E and P
    - Not possible to optimize a design for all 3 parameters
    - Need to make a balance between DP, E and P, depending on the experimental question by
        - Searching for the optimal trial order
        - Searching for the optimal inter-stimulus interval (ISI)
        - Including jittering -> randomized ISI
    - As a rule of thump
        - Optimizing for DP is at a cost of E and P -> your design evolves toward a block design (additivity of the HRF)
        - Optimizing for E is at a of DP -> your design evolves toward well separated individual trials

- Parameters to optimize for your design for a given DP, E and P
    - Total duration of the experiment
    - Number of trials per condition
    - Order of the trials
    - ISIs

- Optimization can be done using software tools based on simulation and iterative algorithms
    - Genetic Algorithm: http://psych.colorado.edu/~tor/Software.htm
    - NeuroDesign: http://www.neuropowertools.org

- Optseq: https://en.wikibooks.org/wiki/SPM/Design_efficiency

See also

Liu TT, Frank LR, Wong EC, Buxton RB. Detection power, estimation efficiency, and predicability in event-related fMRI. NeuroImage 2001; 13:759-773.

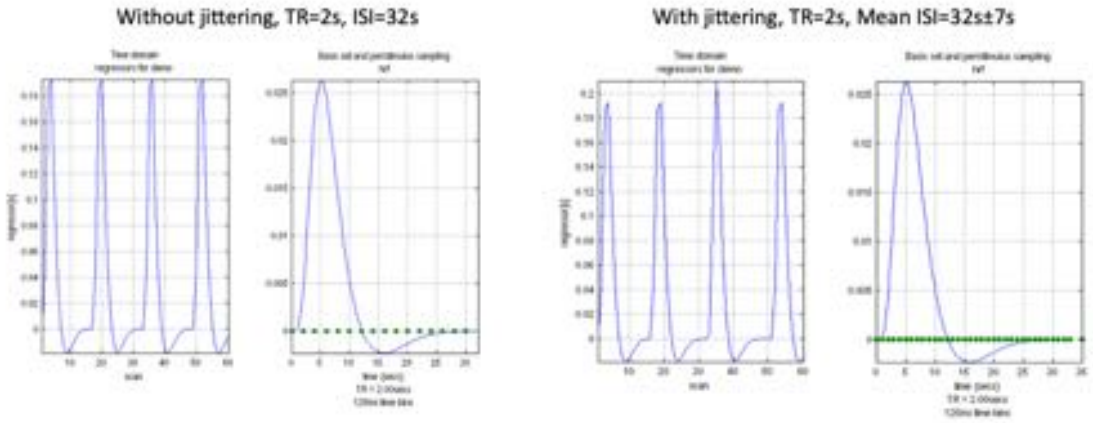
Maus B, Van Breukelen GJP, Goebel R, Berger MPF. Optimization of blocked designs in fMRI studies. Psychometrika 2010; 75:373-390.

Bim et al. 2002. Detection versus estimation in event-related fMRI: choosing the optimal stimulus timing. NeuroImage 15(1):252-264

Mehelli et al. 2003 Estimation efficiency a priori: a comparison of blocked and randomized designs. NeuroImage 18:798-805

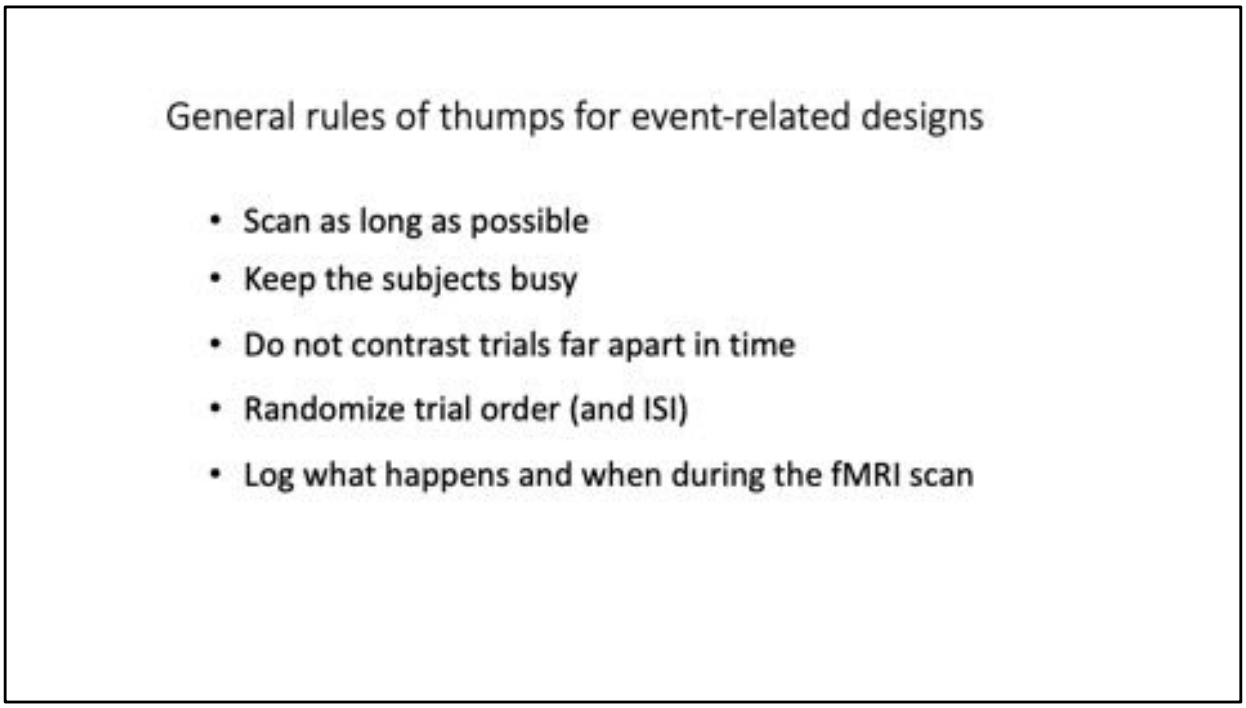
Wager and Nichols 2003. Optimization of experimental design in fMRI: a general framework using a genetic algorithm. NeuroImage 18:293-309

Jitter



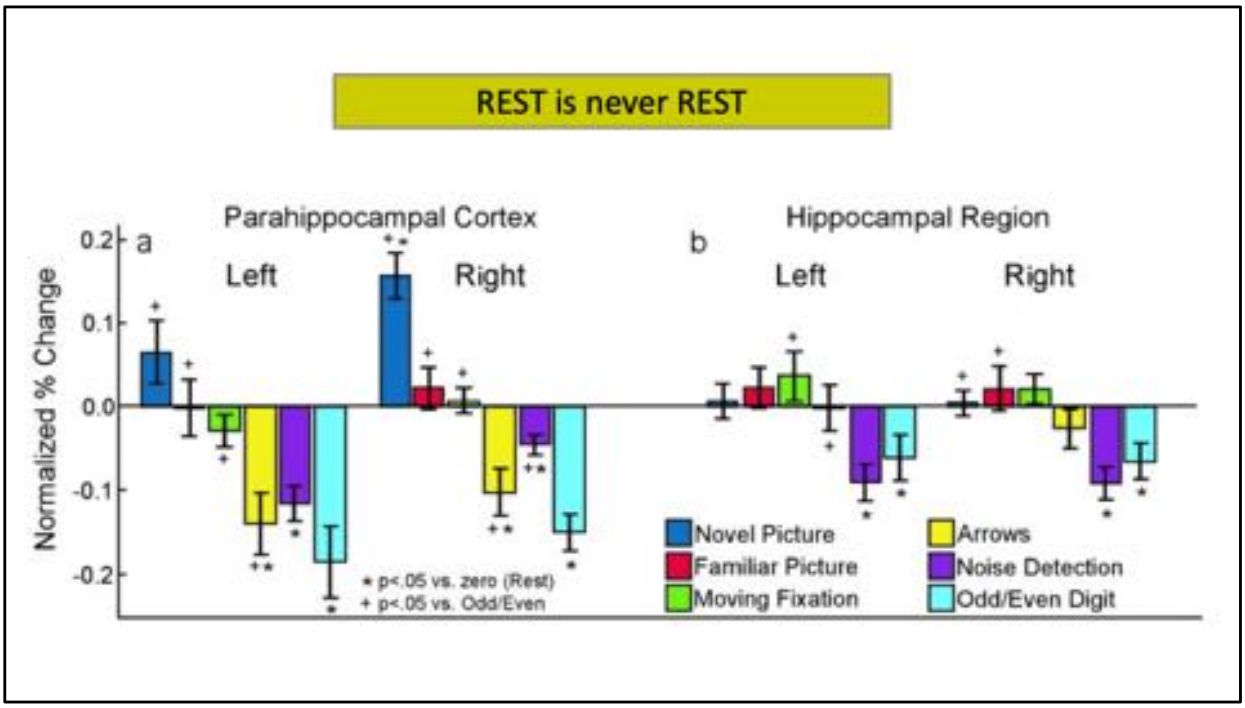
- Why jittering to optimize for E?
    - HRF shape is stable in a brain area in an individual + fMRI scan frequency is fixed (f=0.5 Hz or f= 0.33 Hz)
    - Without jittering: fixed sampling of the HRF -> one sample every 2-3 s
    - With jittering: random sampling of the HRF -> higher sample frequency -> increased detectability / increased efficiency

- In practice
    - Short ISI -> only sampling of the HRF peak
    - Long ISI -> sampling of the whole HRF
    - Best ISI long enough to sample the whole peak -> peak maximum included for maximal detectability



- Scan as long as possible: more scans / more events (trials) -> more statistics -> more detection power
- Keep the subjects busy
    - More attention -> stronger activations
    - Short ISI -> increased HRF -> more power
    - E.g. passive looking at pictures = boring -> loss of attention = poor task performance -> less brain activity
    - pictures = increased attention -> better task performance -> better fMRI results
- Do not contrast trials far apart in time -> problem of low-frequency noise
    - Dynamic fMRI data contains low-frequency signal changes (noise) (e.g. from regular pulsations in CBF due to heart beating)
    - In the analysis, a high-pass filter is used to remove the low-frequency noise
    - Contrasting trials far apart in time, means searching for signal variations at low-frequencies -> are removed by the high-pass filter
- Randomize trial order
    - Reduce predictability -> requires more attention
    - Increases the ISI while keeping the subject busy -> better sampling of the HRF peak
- Log what happens and when during the fMRI scan
    - Trials timings, subject responses
    - Will be used afterwards during the fMRI analysis

See also
http://imaging.mrc-cbu.cam.ac.uk/imaging/DesignEfficiency



- REST condition = not processing any stimulus nor performing any task -> brain is supposed to be at rest
    - Subject is awake -> sleep is a different condition with its own neural activity
    - Eyes closed -> to eliminate the visual input

- During the fMRI analysis, we contrast the neural activity measured during various task conditions
    - Contrast 1: Activation (A) versus rest (R) => A-R -> periods with REST condition are needed
    - Contrast 2: Condition 1 (C1) versus condition 2 (C2) => (C1-R)-(C2-R)=(C1-C2) -> periods with REST are not needed

- But REST is never REST
    - Analyzing a stimulus is the result of multiple complex processes (e.g. visual features (colors, shapes, face detection, …), emotional, attentional shifting, memory, …)
        - A-R result in all brain areas involved in analyzing the stimuli = the sum of all underlying processes
        - A well chosen baseline condition could help to separate a specific process (e.g. processing emotion in faces by contrasting happy faces with neutral looking faces)
    - Even at rest, a lot of neural processes are going on
        - A-R means contrasting the contrast during performing the task or processing the stimuli relative to the ongoing activity during rest
        - The sensitivity to detect condition related activity is reduced in areas with a lot of ongoing brain activity during rest
        - Negative neural activations (deactivations) can be found -> less neural activity during the active condition compared to the ongoing activity

during rest

- Picture in the slide: activation comparison during various visual detection tasks compared to various baseline and rest conditions

See also
Stark CEL, Squire LR. When zero is not zero: the problem of ambiguous baseline conditions in fMRI. Proc Natl Acad Sci USA 2001; 98:12760-12766. (Shows that the brain is active during periods of rest, confounding both block and event-related design experiments).

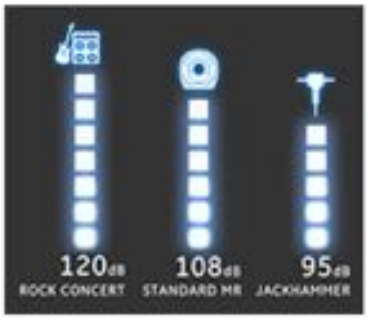
The power of an fMRI study depends on

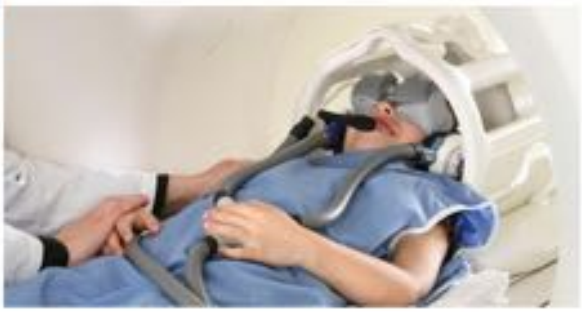
a. The difference between the active and rest task conditions
b. The number of trials (events)
c. The duration of the trials (events)
d. The total length of the experiment
e. The TR of the fMRI scan

Examples of fMRI paradigms

Universitair Ziekenhuis Brussel

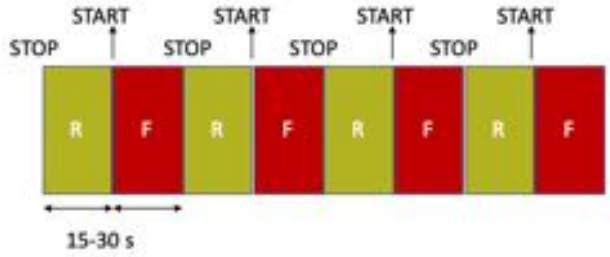
VUB

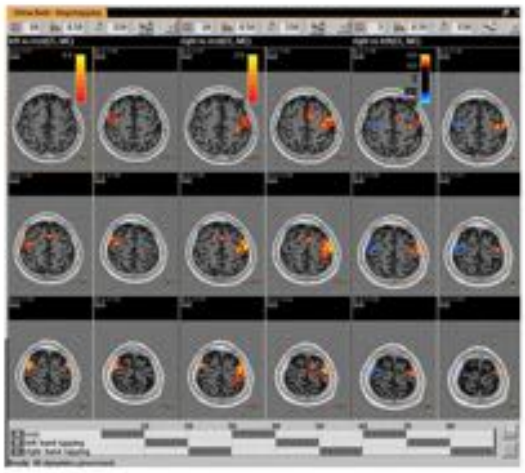




- Except for motoric tasks, visual and/or auditive stimuli are presented to the subject in the scanner
- Common problems and challenges to deliver a stimulus to a subject in the scanner and to record their responses
    - The presence of a strong magnetic field -> all devices in the scanner room may not contain ferromagnetic components
    - The need for shielding the scanner room (to avoid RF artifacts in the images from signal pick-up from outside the scanner room) -> all cables going into the scanner room should be shielded or pass through a RF filter
    - Limited space in the scanner bore
    - Loud noise from the scanner (up to 120 dB for an EPI sequence) -> huge problem for auditory stimulation
- Stimuli delivering solutions
    - Visual -> problem of subjects wearing glasses (MRI compatible glasses mostly not at hand)
        - Projection on a projection screen or using a MRI compatible television -> visible for the subject in the scanner using a mirror system
        - MRI compatible goggles
    - Auditory
        - MRI compatible head phones with active noise cancelation
        - Building silent periods in the sequence (e.g. scan a volume in 2s and wait 1 more second for the start of the next dynamic)
    - Sensory
        - Touch or pricks given manually
        - MRI compatible heat devices
- MRI compatible response devices are available on the market (response boxes, trackballs, tablet, …)

Example 1: finger tapping -> motor cortex





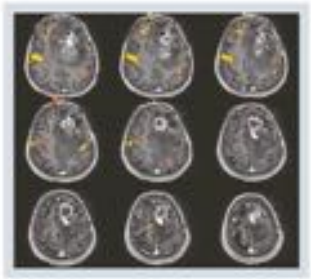
- To improve patient's recovery after surgery, a pre-operative fMRI scan using a finger tapping task is often done.

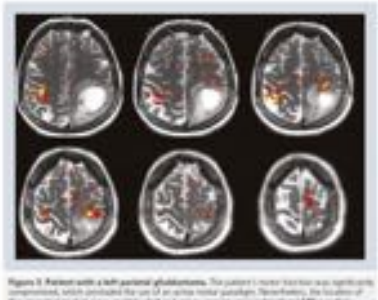
- Task paradigm:
    - Start and stop instructions given auditory
    - Block design with 2 alternating conditions: finger tapping (F) and rest (R)
    - Duration of 1 block: 15-30 s
    - Temporal resolution of the fMRI scan: 2-3 s
    - Total scan duration: 4-5 min

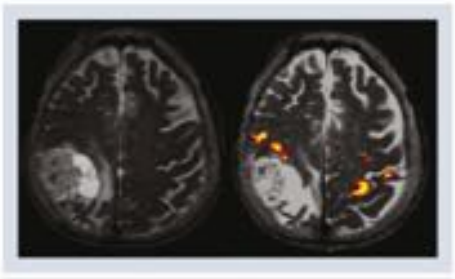
- The finger tapping task is an easy task to do and motoric activity in the brain is very strong and well described in the literature -> finger tapping is often used a the "gold standard" to test an fMRI sequence

See also
http://mriquestions.com/motor-paradigms.html

Stathopoulos et al. Preoperative functional MRI of motor and sensory cortices: how imaging can save vital functions. Review Article - Imaging in Medicine (2012) Volume 4, Issue 1





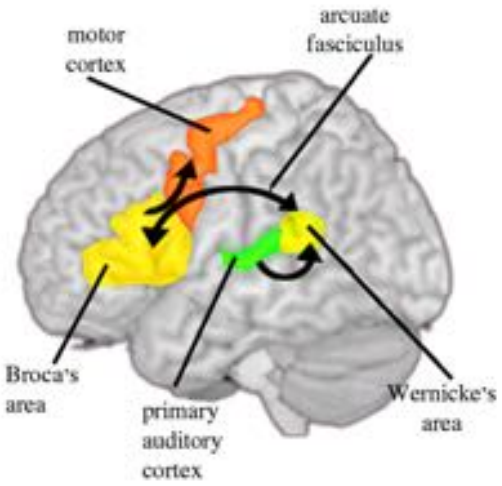


https://www.openaccessjournals.com/articles/preoperative-functional-mri-of-motor-and-sensory-cortices-how-imaging-can-save-vital-functions.html

Example 2: Language -> Broca and Wernicke areas

- Rest
- Non-existing words

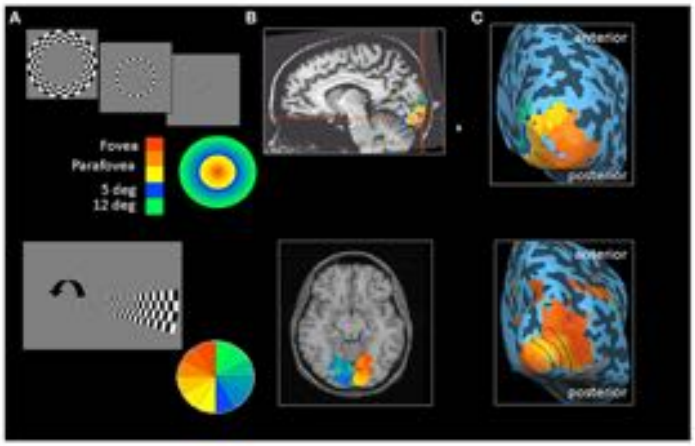
- Categories -> instruction: "Sports"
- Sentences -> instruction: "Tool used for writing"
- Words -> instruction: "Ball"

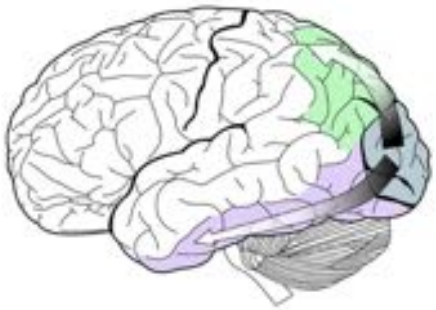


- Besides finger tapping, surgeons are regularly interested to locate the language centers in the brain
    - Broca area: speech production
    - Wernicke area: speech comprehension
- Task paradigm
    - Auditory stimulation
    - Block design with 2 conditions:
        - Categories: give examples from a specified category (e.g. sports -> football, judo, running, …)
        - Sentences: give the right word for the given definition (e.g. Tool used for writing -> a pen)
        - Words: make a sentence with the given words (e.g. ball -> The children are playing with a ball)
        - Letters: make words starting with the given letter (e.g. A -> auto, agent, agenda, …)
    - Baseline:
        - Listening to non-existing words (e.g. Hfgkhqgfk)
    - Duration of 1 block: 15-30 s
    - Temporal resolution of the fMRI scan: 2-3 s
    - Total scan duration: 4-5 min
- Not all language areas, evenly activate the Wernicke and Broca area
    - Focus on speech production -> Broca activated
    - Focus on speech comprehension -> Wernicke activated

See also
http://mriquestions.com/language.html

Example 3: The visual cortex





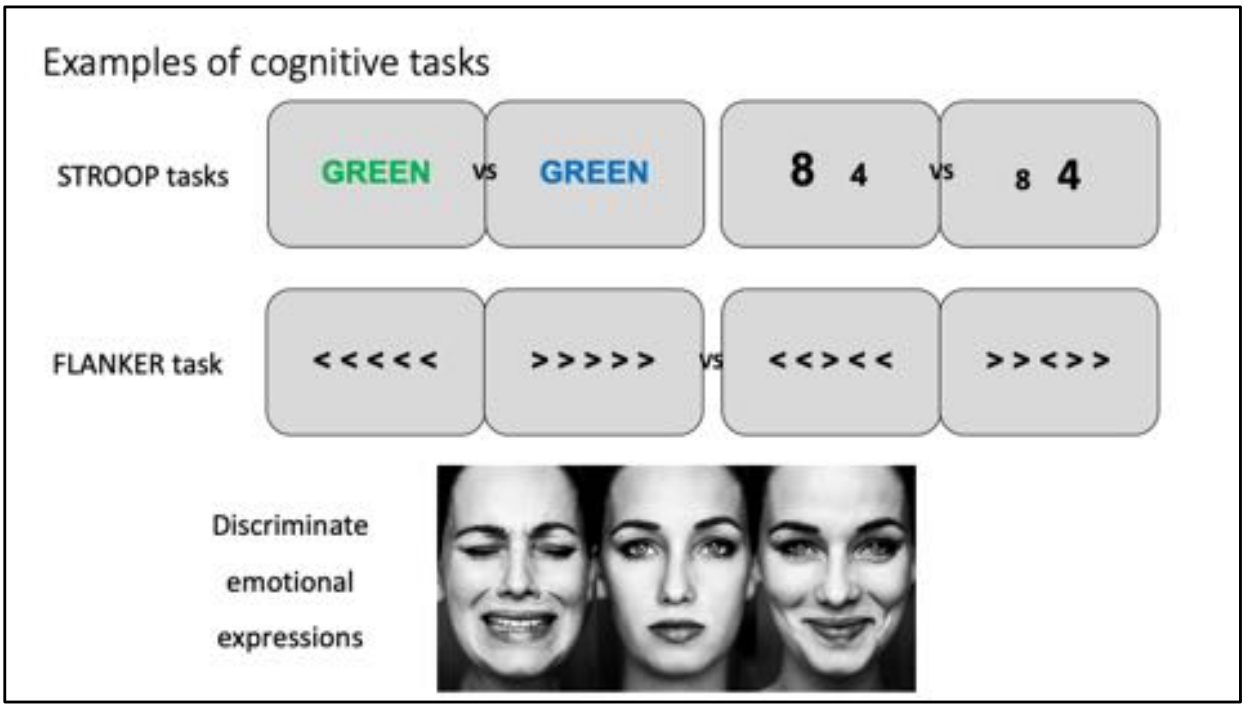
- All visual processing starts in the occipital cortex (grey) and extend dorsally (spatial location and motion) and ventrally (object recognition)

- Provoking a visual response without activating other processes (memory, emotion, …) can easily be done using a checkerboard patern
    - Black-white pattern flikkering from positive to negative 4-5 times per second
    - Provokes a general activation of the visual cortex

- More detailed analysis of the visual cortex can be induced by using more complex checkerboard patters (rotating wedge, expanding ring,…)

- Main problem for visual stimulation
    - The visual stimulus should fill the visual field -> preventing other visual information to be processed
    - Rest should be darkness

See also
http://mriquestions.com/visual.html
Raz and Levin 2014. Cortical and white matter mapping in the visual system-more than meets the eye: on the importance of functional imaging to understand visual system pathologies. Front. Integr. Neurosci. 8:68



- The Stroop test is a classic test to test for the processing of conflicting information
    - Color naming
        - Congruent trials: the color word is written in the right color -> no conflict
        - Incongruent trials: the color word is written in a different color -> conflict
    - Numerical fond size -> select the number presented in the largest fond
        - Congruent trials: the biggest number is the number in the largest fond -> no conflict
        - Incongruent trials: the smallest number is in the largest fond -> conflict
- Flanker task: Respond with the button at the side indicated by the middle arrow
    - Congruent: other arrows point in the same direction (no conflict)
    - Incongruent: other arrows point in the opposite direction (conflict)
- Emotional task: discriminate the emotional expression in the face
- In all these task, predictability of the trials affect the study performance -> use event-related study paradigms

See also
https://en.wikipedia.org/wiki/Stroop_effect
Leung et al. 2000. An event-related functional MRI study of the stroop color word interference task. Cereb. Cortex 10(6):552-560
Natu and O'Toole 2011. The neural processing of familiar and unfamiliar faces: a review and synopsis. Br. J. Psychol. 102(4):726-747

fMRI processing tutorial:

Audiovisual Valence Congruence

Universitair Ziekenhuis Brussel

VUB

Task paradigm: Audiovisual Valence Congruence

What you see has the same valence (emotion) as what you hear (congruent)
Versus
What you see has the opposite valence (emotion) as what you hear (incongruent)
for positive versus negative stimuli
↓
2x2 design: (congruent - incongruent) x (positive - negative)

Visual stimuli (video) + Auditory stimuli (music)
Stimulation as individual events (3s long)
4 conditions:
1. Visual positive + Auditory positive
2. Visual positive + Auditory Negative — Congruent trials
3. Visual negative + Auditory positive — Incongruent trials
4. Visual negative + Auditory negative

12 trials / run / condition -> 48 trials / run
8 catch trials (no stimulus, but responses recorded -> attention test)
20 subjects (all healthy adult volunteers)

Positive valence

Negative valence

Gao, C., Weber, C. E., Wedell, D. H., & Shinkareva, S. V. (2020). An fMRI study of affective congruence across visual and auditory modalities. Journal of cognitive neuroscience, 32(7), 1251-1262
Chuanji Gao and Christine E. Weber and Douglas H. Wedell and Svetlana V. Shinkareva (2021). fMRI: Audiovisual Valence Congruence. OpenNeuro. [Dataset] doi: 10.18112/openneuro.ds003507.v1.0.1

We will process 1 individual fMRI run for 1 participant

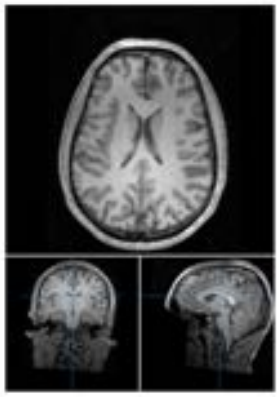
We will perform group analyses based on the preprocessed group data

Task: indicate that the emotion in the music is the same or not as in the video by button presses

Catch trial = a trial within an experiment in which a stimulus is not present but the participants' responses nonetheless are recorded. For example, in an experiment in which participants identify auditory signals, catch trials are those in which no signal is given. The use of a catch trial may help to estimate the level at which a participant is guessing when no stimulus is present

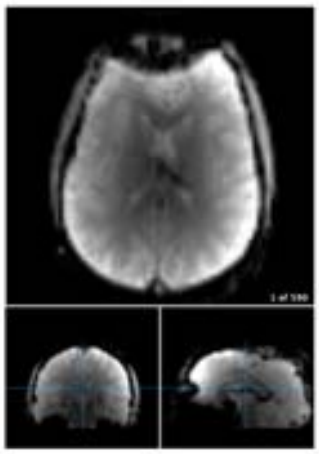
Scan protocol (Siemens 3T)

T1 weighted anatomical scan
- 3D TGE (MPRAGE) (sagittal slices)
- Scan volume: 192 x 256 x 256 mm
- Matrix: 192 x 256 x 256
- Voxel dimensions: 1 x 1 x 1 mm



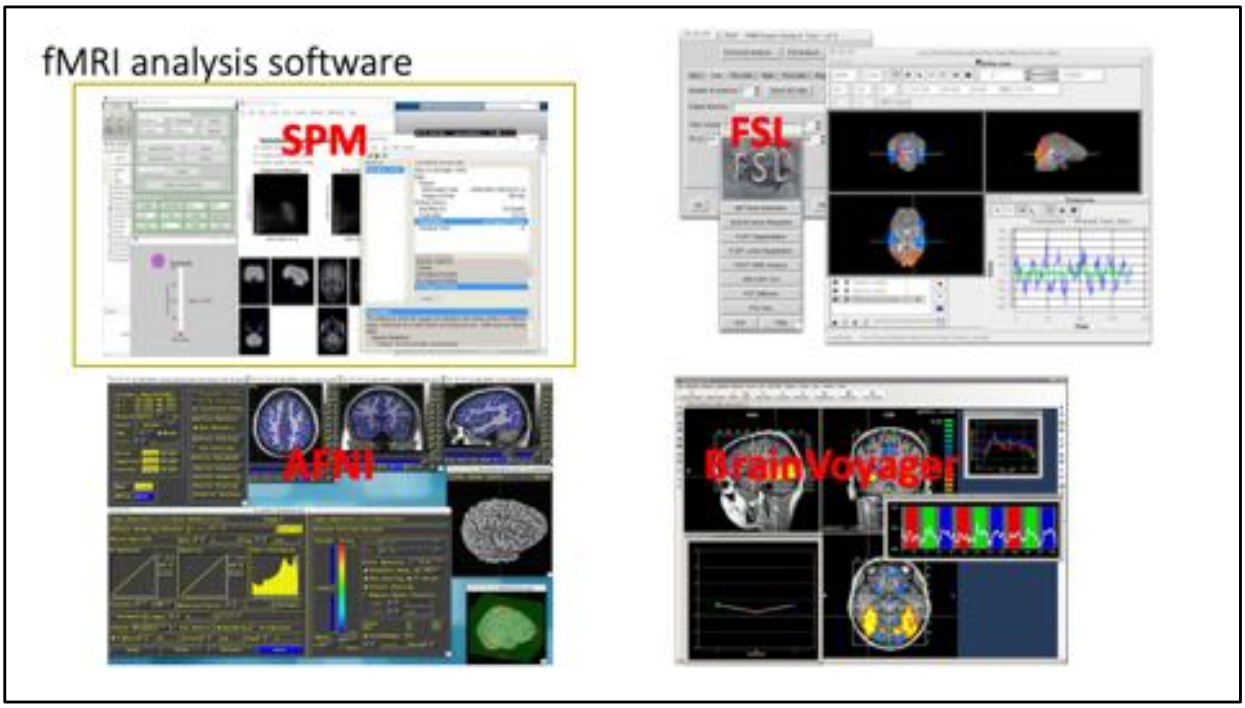
fMRI scan
- GE-EPI (axial slices)
- Scan volume: 202 x 256 x 256 mm
- Matrix: 70 x 70 x 40
- Voxel dimensions: 3 x 3 x 3 mm
- Temporal resolution: 1s
- 590 dynamics
- HyperBand: 4

Fieldmap scan
- 2x GE-EPI (axial slices)
- Scan volume: 202 x 256 x 256 mm
- Matrix: 70 x 70 x 40
- Voxel dimensions: 3 x 3 x 3 mm
- HyperBand: 4
- Phase encoding direction scan 1: AP
- Phase encoding direction scan 2: PA



Gao, C., Weber, C. E., Wedell, D. H., & Shinkareva, S. V. (2020). An fMRI study of affective congruence across visual and auditory modalities. Journal of cognitive neuroscience, 32(7), 1251-1262

Chuanji Gao and Christine E. Weber and Douglas H. Wedell and Svetlana V. Shinkareva (2021). fMRI: Audiovisual Valence Congruence. OpenNeuro. [Dataset] doi: 10.18112/openneuro.ds003507.v1.0.1



- SPM (http://www.fil.ion.ucl.ac.uk/spm/)
  - Free but uses Matlab
  - Works on Windows, Mac and Linux
  - Easy to extend SPM with your own tools (open source)
  - Easy to create batch scripts
- FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/)
  - Free
  - Works on Mac and Linux, but not on Windows (except when using a virtual Linux machine)
  - Possible to add own scripts (open source)
  - Some tools are not reachable from the widget but can only be used from the command line
- AFNI (https://afni.nimh.nih.gov)
  - Free
  - Works on Mac and Linux, but not on Windows (except when using a virtual Linux machine)
  - Possible to add own scripts (open source)
- BrainVoyager (http://www.brainvoyager.com)
  - Not free
  - Works on Windows, Mac and Linux
  - Not open source
- Many Python toolboxes
  - Nipype to automate the SPM, FSL and AFNI processing of the data (the original software (e.g. SPM) should be installed and working!)
  - Nilearn, fmriprep, brainiak, …

- Works on Mac and Linux, but not on Windows (except when using a virtual Linux machine)

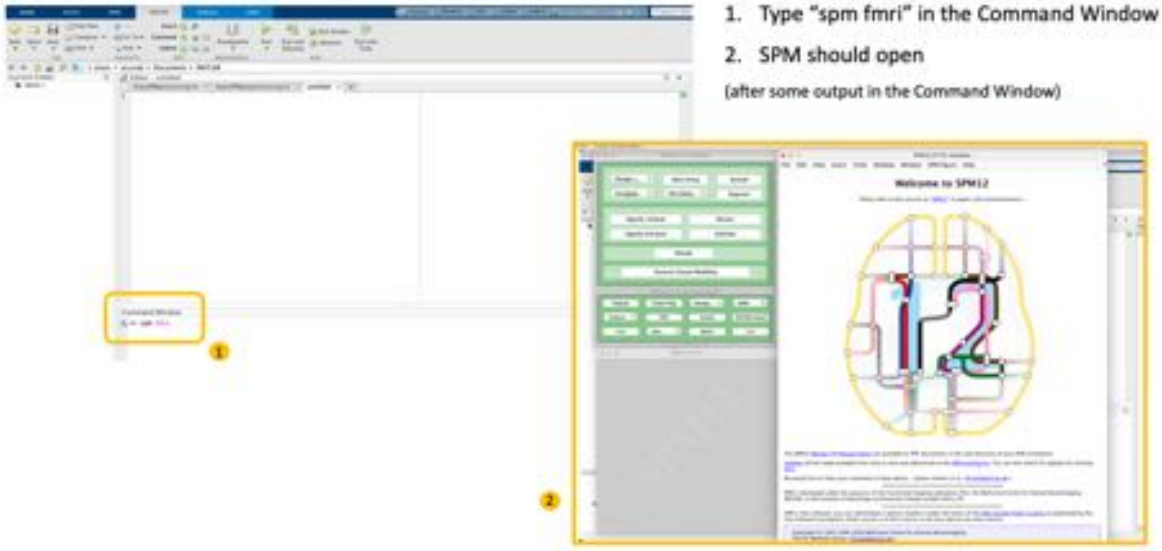
See also
https://en.wikipedia.org/wiki/List_of_neuroimaging_software
http://mriquestions.com/best-fmri-software.html

Starting SPM12

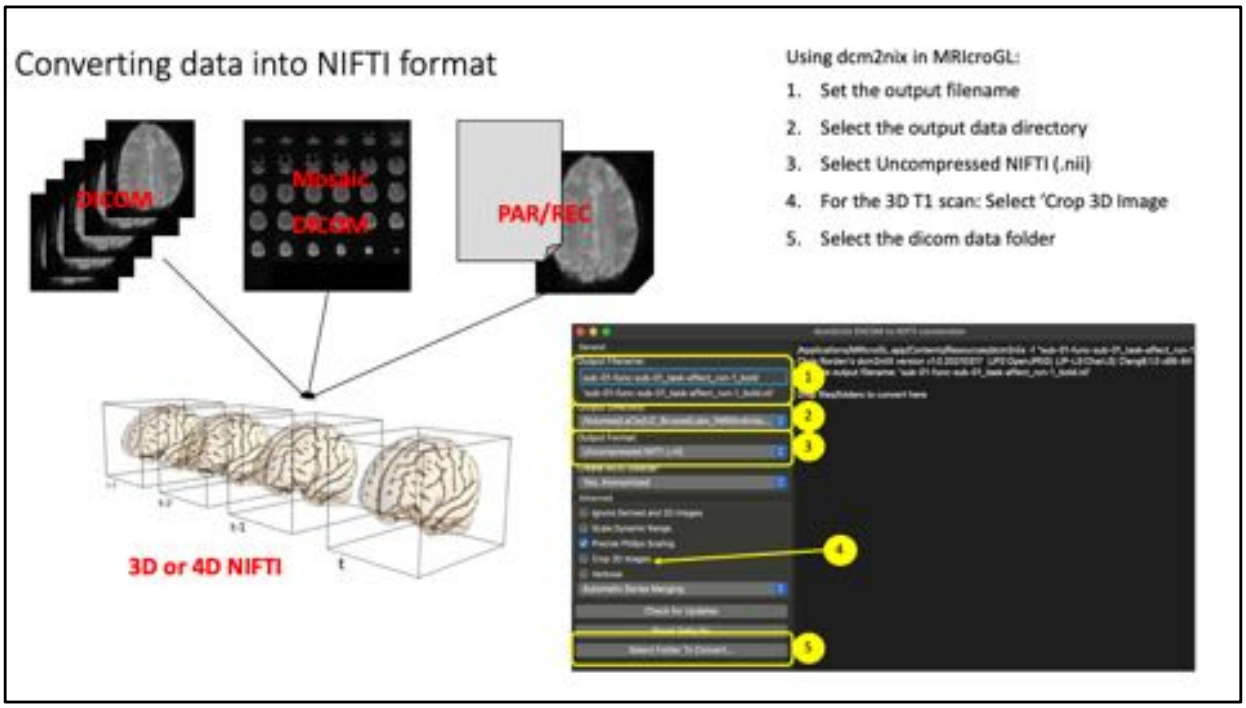
In Matlab

1. Type "spm fmri" in the Command Window
2. SPM should open

(after some output in the Command Window)



Preparing the fMRI data

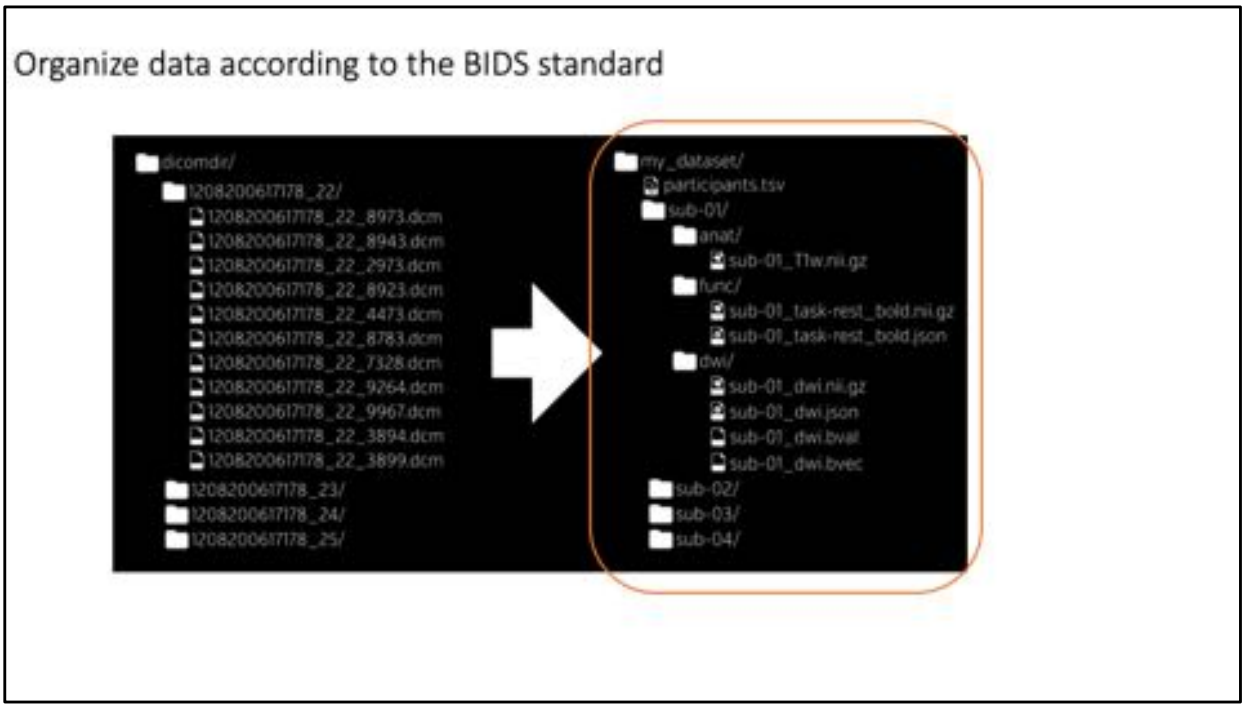


- Data coming from the scanner are in
    - DICOM format (GE) -> 1 slice per DICOM file
    - Mosaic DICOM (Siemens) -> all slices from 1 dynamic combined in a mosaic image
    - PAR/REC (Philips) -> the scan information is written in a header file (PAR) while all data stored is in the REC file

- Data format used by the analysis software:
    - 3D NIFTI (SPM): one file per dynamic
    - (compressed) 4D NIFTI (FSL): all fMRI data in one file with 4 dimensions (x,y,z,t)

- Data from the scanners can be transformed into NIFTI format using dcm2niix in MRIcroGL(https://www.nitrc.org/projects/mricrogl/)

- This conversion is already done for the tutorial data!



- Organize the NIFTI data according to the Brain Imaging Data Structure (BIDS) standard
    - International standard to organize brain imaging data from fMRI, DWI, DTI, EEG, MEG studies
    - Dataset organized in a fixed folder structure
        - Study folder -> sub-ii -> ses-jj -> anat -> sub-ii_T1w.nii
        - Study folder -> sub-ii -> ses-jj -> func -> sub-ii_task_..._bold.nii
        - …
    - Fixed naming convention of the files
    - Information about the participants and fMRI task is saved in text files (.tsv files)
        - In the main study folder if it applies to all subjects
        - In the subject folder if it applies only to that subject
        - The sequence parameters are saved in .json files
        - For diffusion scans, the .bvec and .bval files contain the information about the diffusion directions
    - For reference see: https://bids.neuroimaging.io
    - The advantage is that processing can be automatized by Python or Matlab scripts

- This step can be done together with the DICOM to nifti conversion

The individual data for subject 1

T1 weighted anatomical scan

Fieldmap scans

fMRI scan

.json file = text file with the fMRI scan parameters

.nii file = the actual image data

Events.tsv file = text file with the onsets and duration of the task conditions

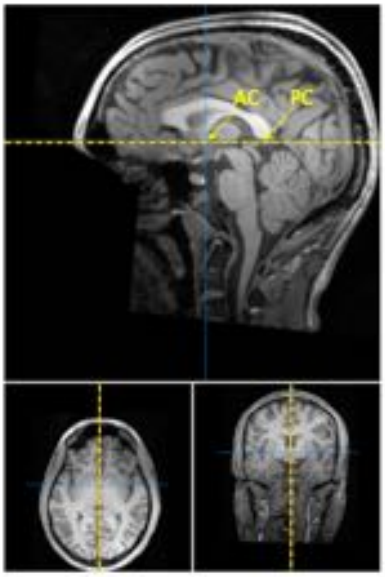
Preprocessing the data

Step 1: setting the image origin and orientation

To improve the image registration, segmentation and normalization steps, all scans should be set with the origin in the anterior commissure (AC) and oriented to put the head straight in all orientations.

Reference axes:

1. AC-PC line
2. Space between the left and rights hemispheres



Step 1: setting the image origin and orientation

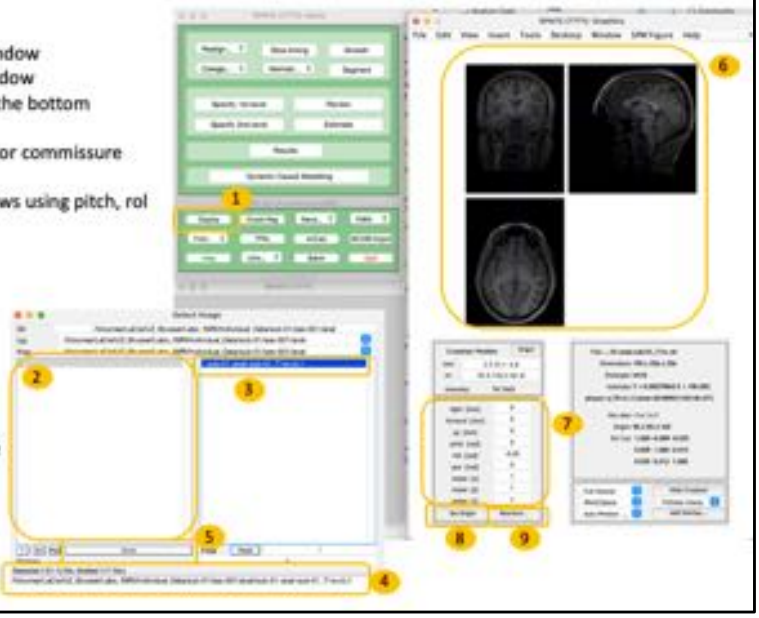
1. In SPM Menu: click "Display"
2. In Select Image: go to the data folder in the left window
3. In Select Image: select the nifty file in the right window
4. In Select Image: the selected file should appear at the bottom
5. In Select Image: click "Done"
6. In Graphics Window: set the crosshair at the anterior commissure (AC)
7. In Graphics Window: set the head straight in all views using pitch, rol and yaw

(Step 7 and 8 are done interactively)

If the crosshair is at the AC and all orientations are ok:

8. In Graphics Window: click "Set Origin"
9. In Graphic Window: click "Reorient"
10. In Image(s) to reorient: deselect all files and click "Done"
8. In Save Matrix: click "Yes" and save the reorient.mat files inn the folder of the nifty file

This step should be done separately for the anatomical scan, the fieldmap scans and the fMRI scan



It is advisable to set your Matlab path to your data. It make the data selection easier.

For the anatomical scan, it is advisable to use the cropped 3D (sub-…_T1w_Crop_1.nii) image.

Step 1: setting the image origin and orientation for the 3D T1 scan

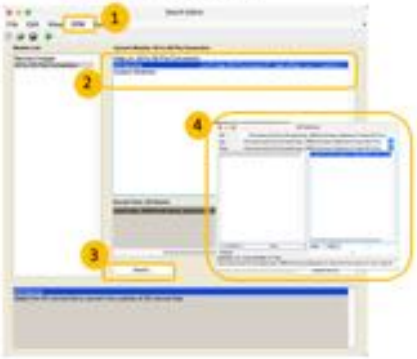
Open the Batch Editor

1. In the top Menus: select SPM -> Util -> Reorient Images
2. Select Images to reorient
3. Click "Specify"
4. In the data selection window: select the anatomical scan (advisable the cropped version)
5. Reorient by: select 'Saved reorientation matrix'
6. Saved reorientation matrix: select the reorient.mat file for the anatomical scan

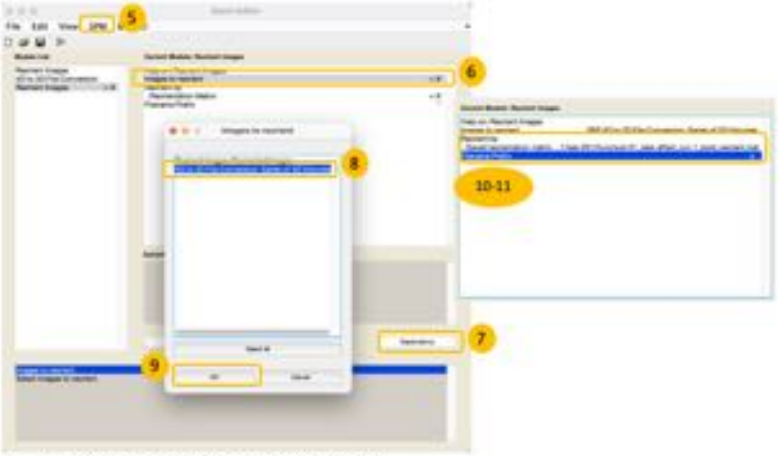
7. Optionally:
The orientation of the data will only change the orientation information in the header of the nifty file. Consequently, repeating the data processing multiple times can lead to wrong results. To overcome the overwriting of the original nifty file, an Filename Prefix for the reoriented data can be specified.

Step 1: setting the image origin and orientation for the func and fmap scans

4D to 3D conversion

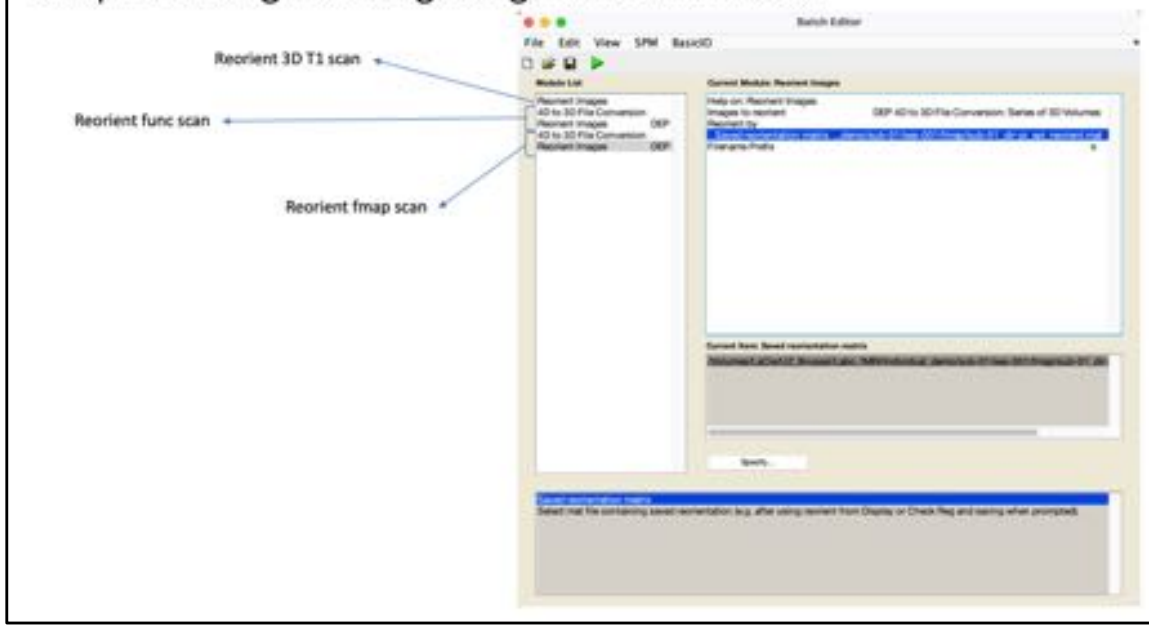


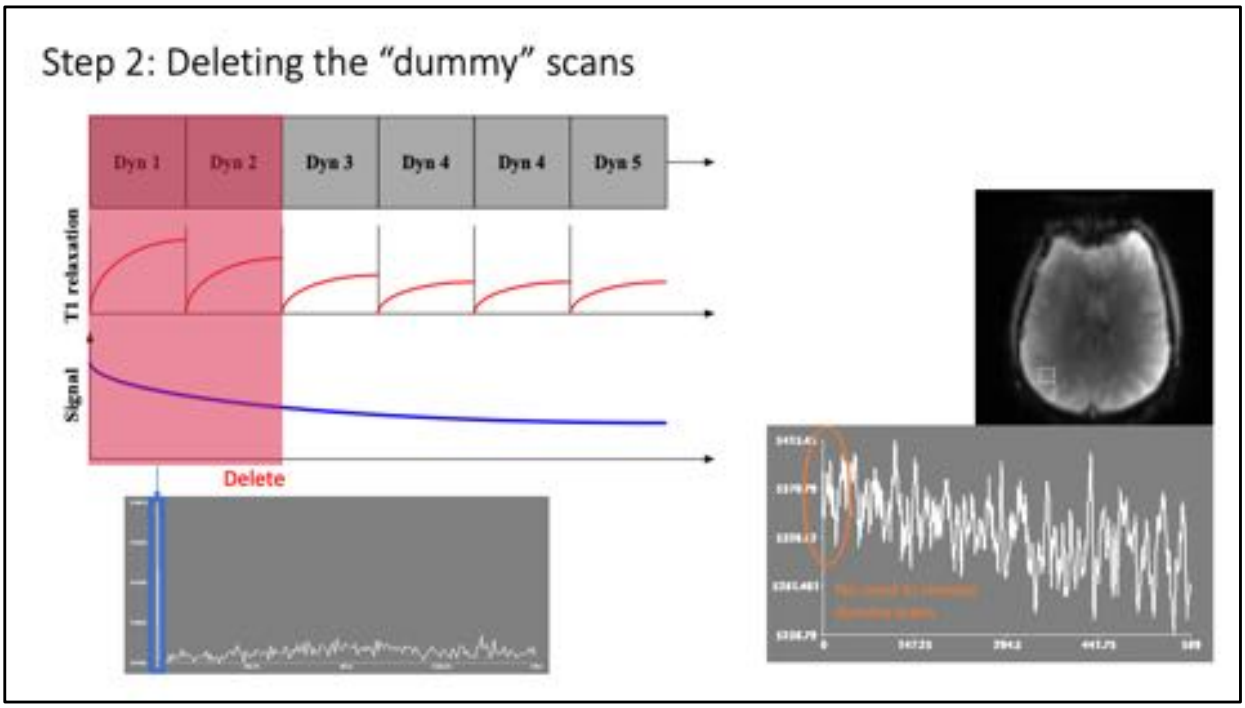
1. In the top Menus: select SPM -> Util -> 4D to 3D File Conversion
2. Select "4D Volume"
3. Click "Specify"
4. In the data selection window: select the fMRI scan



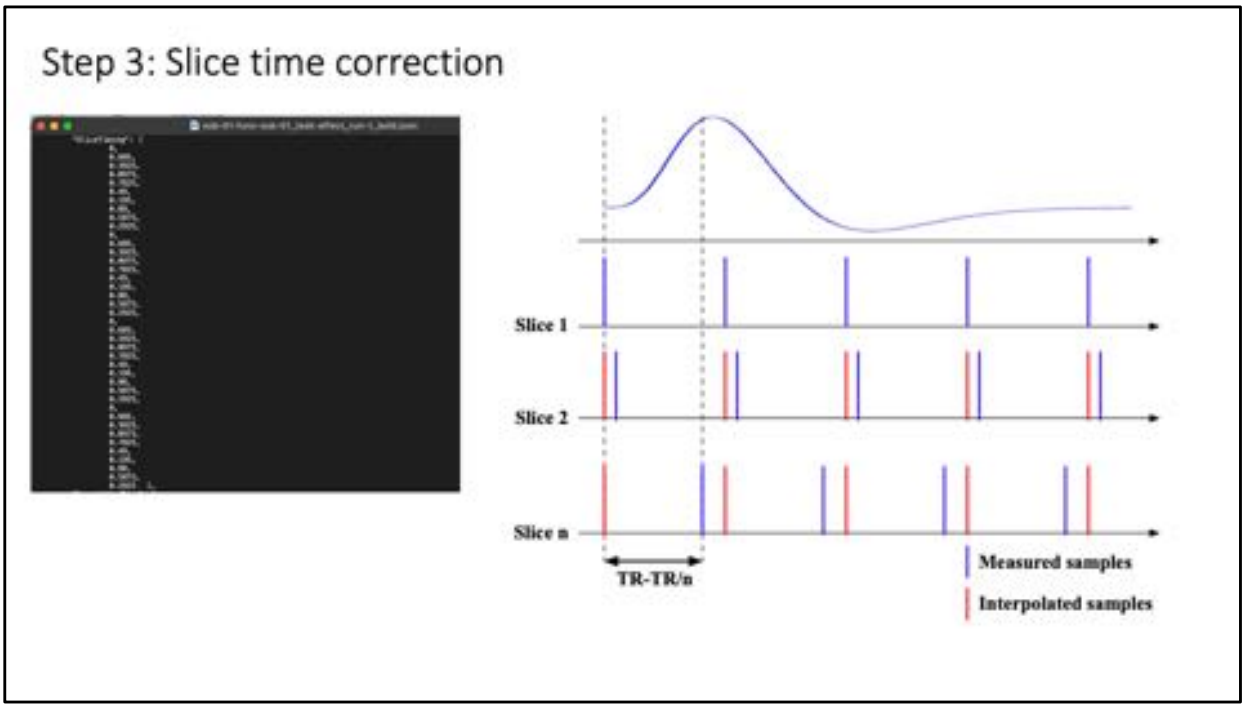
5. In the top Menus: select SPM -> Util -> Reorient Images
6. Select Images to reorient
7. Click "Dependency"
8. In the "Image to orient" window: select '4D to 3D Conversion: Series of 3D Volumes'
9. Click 'Ok'
10. Reorient by: select 'Saved reorientation matrix'
11. Saved reorientation matrix: select the reorient.mat file for the func/fmap scan

Step 1: setting the image origin and orientation





- Due to the short TR, an incomplete T1 relaxation the fMRI signal will partially saturate during the first dynamics
- After 2-5 dynamics, the signal stabilize to a steady state level
- Correction
    - During the scan: 2-5 dummy scans (fMRI dynamics without echo read out -> no images from) are added prior to the fMRI series -> not possible on all scanners
    - During the processing of the data: the first 2-5 scans are deleted
- In our tutorial experiment:
    - The signal in a ROI shows no signal saturation in the first few dynamics
    - No need to delete any dynamic



- Slice acquisition in the EPI sequence
    - A whole slice is scanned in 1 EPI train -> takes a few milliseconds
    - All slices are scanned one after the other -> time offset error of almost 2-3 s between the first and last slice scanned: $\text{last} - first\ slice = TR - \frac{TR}{number\ of\ slices}$

- Due to the large time offset error in the synchronization of the HRF and the scanning of the slices, a slice dependent bias can be induced in the results

- Slice time can be corrected by slice time correction
    - Sinc-interpolation to shift the signals to the right timings
    - Mostly, the first slice timings are used as the reference timings
    - Take care of the slice order
        - Ascending (1,2,3,4,…)
        - Descending (30,29,28,…)
        - Interleaved (1,3,5,…,2,4,6,…)
        - Reversed interleaved (2,4,6,…,1,3,5,…)

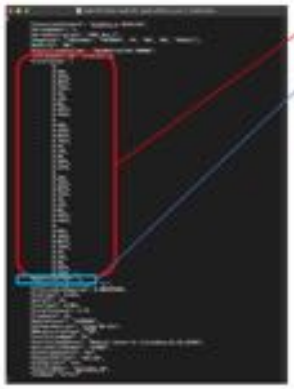
- Be aware that when using simultaeous multi-slice/MultiBand/HyperBand, the slice order and timings much more complex due to the fact that several slices are measured together. The correct slice timings can be found in the .json file accompanieing the nifti file.

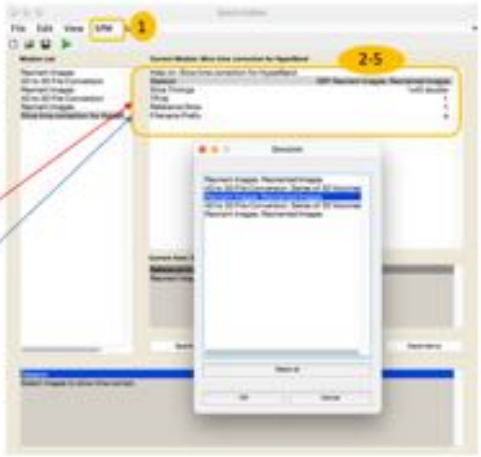
See also
Sladky et al. 2011. Slice-time effects and their correction in functional MRI. NeuroImage 58(2-2):588-594
https://en.wikibooks.org/wiki/Neuroimaging_Data_Processing/Slice_Timing

Step 3: Slice time correction

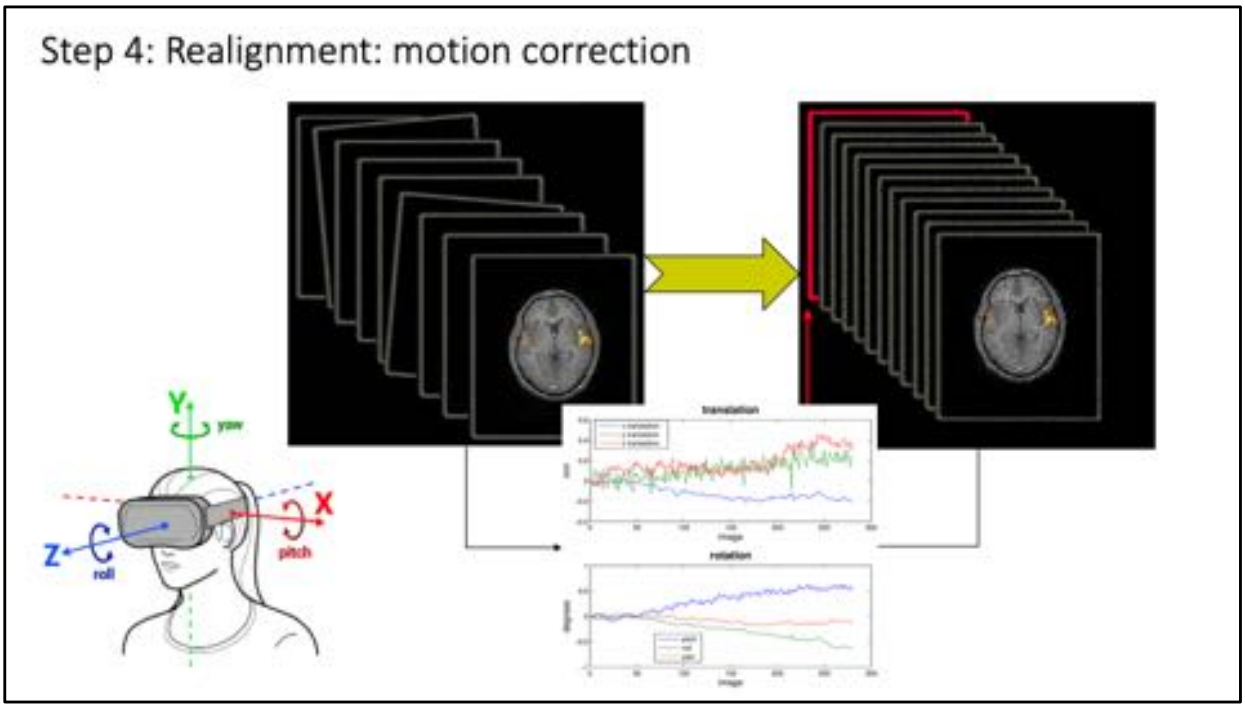
The standard slice time correction doesn't work for data scanned with HyperBand! Use my modified function*!

1. In the top Menus: select SPM -> Tools -> Multi echo & HyperBand -> Slice time correction for HyperBand
2. Session(using Dependency): Reoriented Images: Reoriented Images (from the func series!)
3. Slice Timings: copy/paste the slice timings from the func.json file
4. TR (s): look up in the func.json file
5. Reference Slice: 1 (first slice)





* Code available at https://github.com/P-VS/MEHBfMRI



- fMRI scans last for several minutes
    - Hard for subjects not to move at all
    - The brain is moving due to the pulsating flow in the carotids

- During the analysis
    - We look for signal changes within a voxel -> assuming a voxel corresponds consistently to the same position in the brain
    - Movements of the brain lead to inconsistencies between a voxel and the corresponding position in the brain -> risk for an erroneous analysis

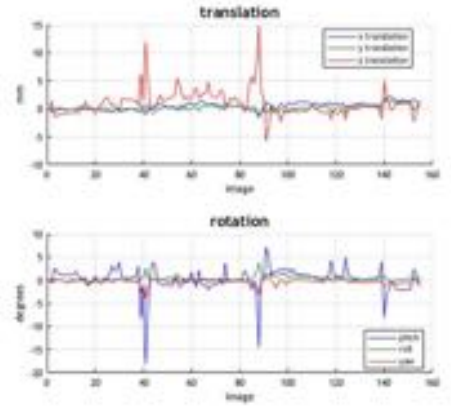
- Any movement of the head can be described by the combination of 6 transformations
    - Head shifts in X, Y and Z (3 transformations)
    - Rolls around the X, Y and Z axis (3 transformations)

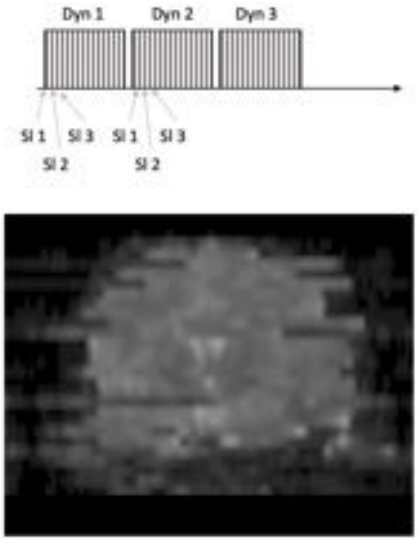
- Image realignment:
    - Determining the 6 rigid body transformations needed to map each dynamic onto a reference scan (the first dynamic or the mean image)
    - Resampling each dynamic according to the determined transformation parameters -> includes interpolation

- As a rule of thump: movements of less than 1.5mm and rotations of less than 1.5º are acceptable.

See also
https://en.wikibooks.org/wiki/Neuroimaging_Data_Processing/Realignment

But … if motion is too much …





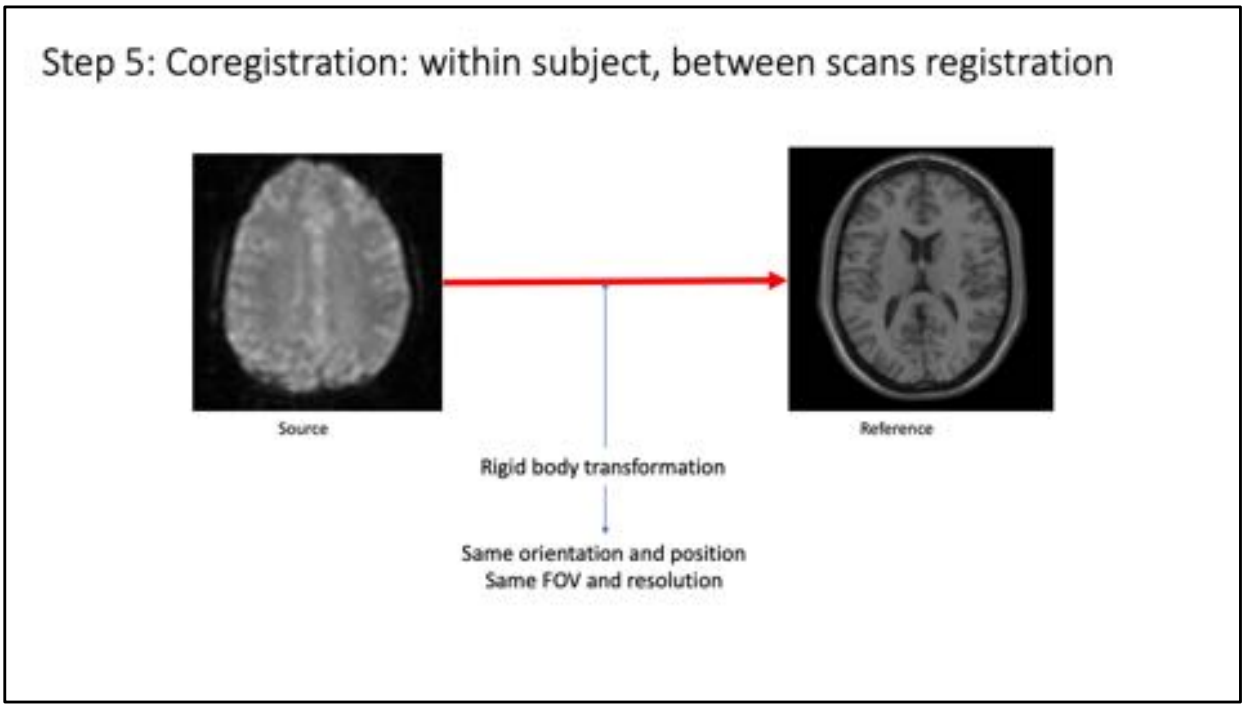
- If motion is too much
    - Not perfect correctable by realignment
    - High risk for false positive and negative results
    - Better to not include this data for further analysis

- General rule of thump
    - Maximum translation < 1mm
    - Maximum rotation < 1°

- Be aware, realignment does only correct for motion between successive dynamics but does not correct for motion between slices

Step 4: Realignment: motion correction

1. In the top menus: SPM -> Spatial -> Realign -> Realign: Estimate & Reslice
2. Data -> New: Session
3. Session: (using Dependency) -> Slice time correction for HyperBand: Slice time correction files

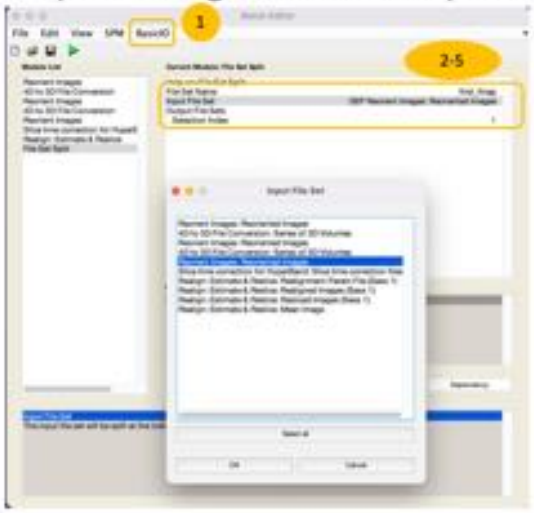


Coregistration = mapping of 2 scans with different contrast weightings but from the same patient on each other

- Rigid body transformation with 6 parameters (translation along X, Y and Z direction, rotation around the X,Y and Z axis)
- The source is the image that is rotated and translated to match the reference scan
- The reference is the image to which the other is coregistrered to

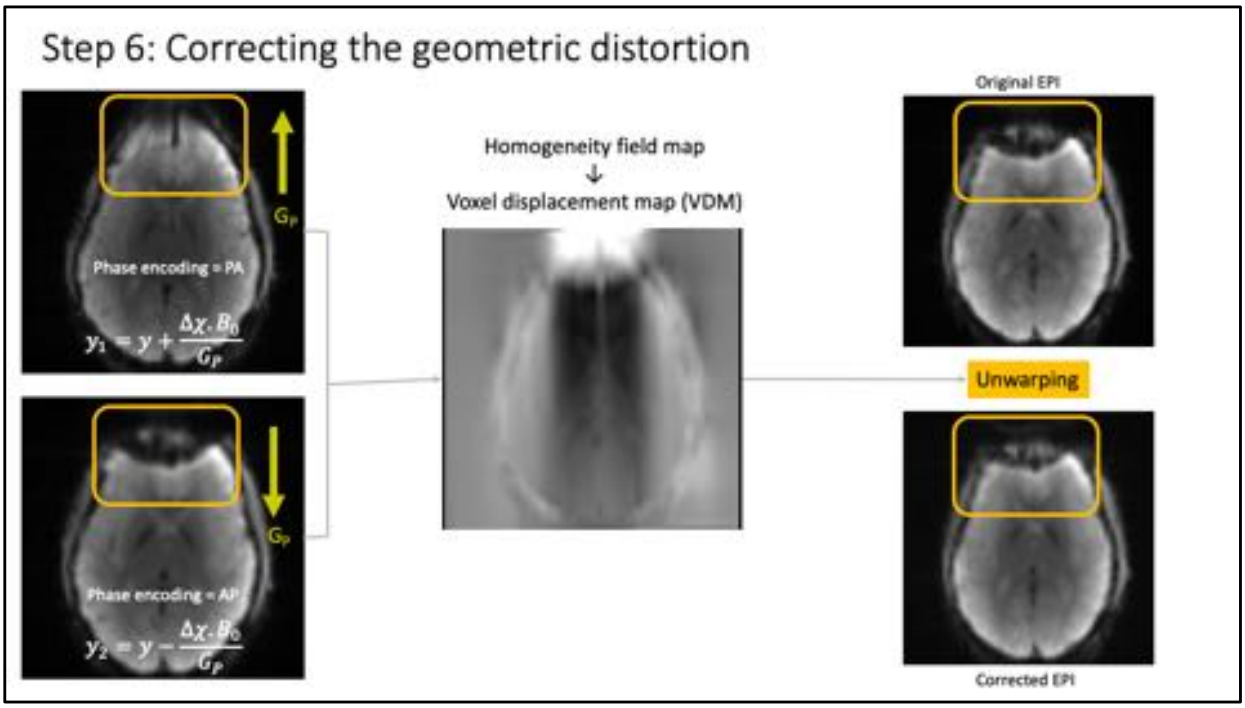
We will use this step to coregistrer the anatomical scan and the segmentation maps to the fMRI scan

Step 5: Coregistration: fmap to func



1. In the top Menus: select BasicIO -> File/Dir operations -> File Operations -> File Set Split
2. File Set Name: first_fmap
3. Input File Set: (using Dependency) Reorient Images: Reoriented Images (for the fmap data!)
4. Output File Sets: New: Selection Index
5. Selection Index: 1

6. In the top Menus: select SPM -> Spatial -> Coregister -> Coregister: Estimate & Reslice
7. Reference Image: (using Dependency) Realign: Estimate & Reslice: Mean Image
8. Source Image: (using Dependency) File Set Split: flist_fmap (1)
9. Other Images: (using Dependency) File Set Split: flist_fmap (1)



- In EPI, the susceptibility artifact leads to geometric distortion of the image (signal displacement)
    - Inherent in the frontal and temporal brain areas due to the nearness of the nose and ear cavities to the brain
    - The field inhomogeneity introduced by the susceptibility effect leads to a shift of the signal in the phase encoding direction

- The direction of the geometric distortion depends on the polarity of the gradient used along the phase encoding direction (Y-dimension in this example)
    - Reversing the polarity of the gradient -> geometric distortion goes in the opposite direction

- Using a reference image, measured with the read gradient reversed, a displacement field map can be calculated iteratively:
    - 2 scans needed with the same scan parameters
        - Reversed-gradient scan
        - The fMRI scan (with forward gradient)
    - Voxel displacement map (VDM) are determined: maps the displacement of the signals from the geometric distorted to the geometric undistorted image
    - Iterative calculation
        - A displacement field is calculated and applied and compared to a smoothed version of the forward and reversed-phase images
        - Based on the error, the displacement field is optimized and compared to a less smoothed version of the original images
    - Final result: image at minimal distance from the phase-reversed and the original EPI scan ($x = \frac{x_1+x_2}{2}$) -> corrected or at least reduced geometric

distortion

- The correction will never be perfect
- Susceptibility effects also leads to signal loss. The lost signal can never be corrected

See also
Morgan et al. 2004. Correction of spatial distortion in EPI due to inhomogeneous static magnetic fields using the reversed gradient method. J. Magn. Res. Imaging 19:499-507
Andersson et al. 2003. How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. NeuroImage 20(2):870-888
Jezzard 2012. Correction of geometric distortion in fMRI data. NeuroImage 62(2):648-651
https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FUGUE#Fieldmap_Acquisition
https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/topup
http://www.fil.ion.ucl.ac.uk/spm/toolbox/fieldmap/
Jezzard 2012. Correction of geometric distortion in fMRI data. NeuroImage 62(2):648-651
http://mri-q.com/data-pre-processing.html

Step 6: Correcting the geometric distortion

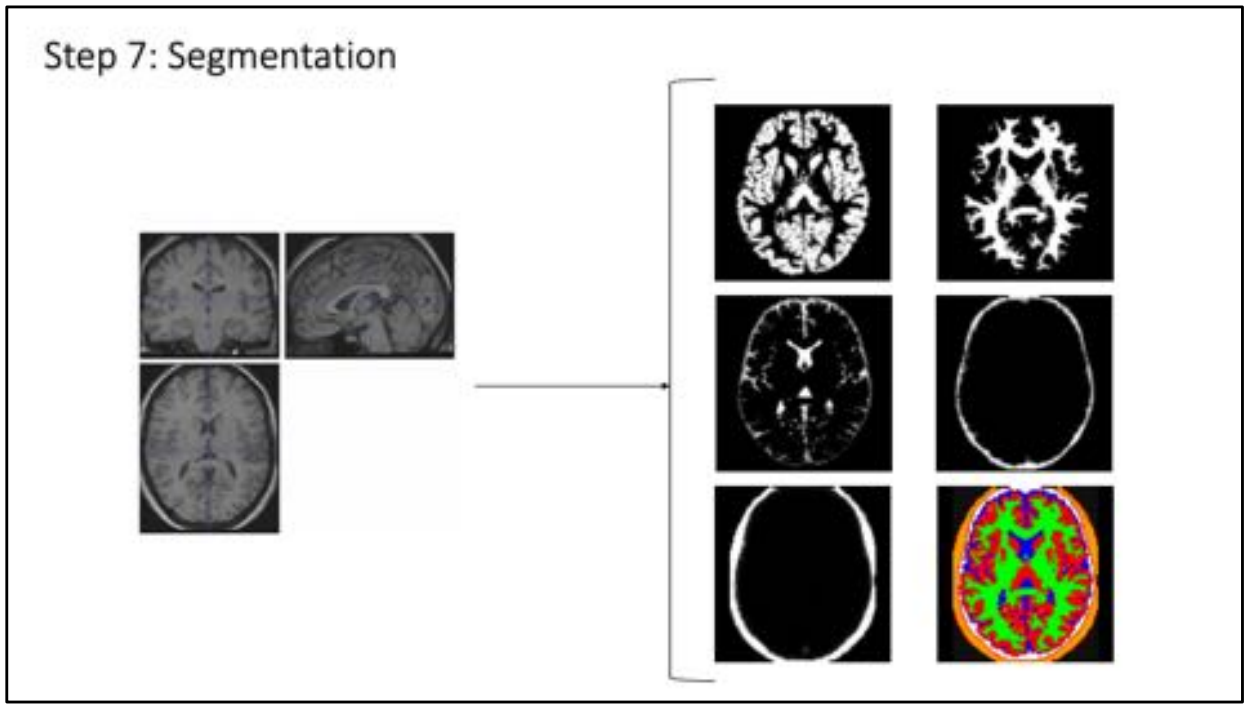
Determine homogeneity map

Apply to the func data

1. In the top Menus: select SPM -> Tools -> ACID Toolbox -> Pre-processing -> Choose HySCO options -> HySCO
2. Blip-up image (using Dependency): Coregister: Estimate & Resliced Images
3. Blip-down image (using Dependency): Realign: Estimate & Reslice: Mean Image

In the json file (for func and fmap):
"PhaseEncodingDirection": "j-" -> blip down
"PhaseEncodingDirection": "j" -> blip up

4. In the top Menus: select SPM -> Tools -> ACID Toolbox -> Pre-processing -> Choose HySCO options -> Write HySCO corrected images
5. Reference blip-up image: (using dependency) Coregister: Estimate & Resliced Images
6. Other blip-down images: (using dependency) Realign: Estimate & Reslice: Resliced Images (Sess 1)
7. Inhomogeneity field (or done for none): (Using dependency) HyCO: Inhomogeneity field



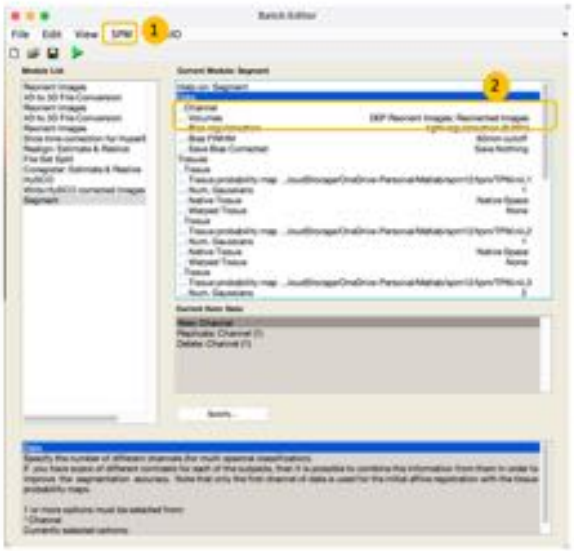
- In the high resolution anatomical scan the signal is supposed to be a weighted sum of the signals of the various tissues (gray matter (GM), white matter (WM), CSF, and non-brain (NB) tissues).
- Based on anatomical tissue maps a model is fitted in all voxels of the anatomical scan:
    - Signal = t_1 .GM + t_2 . WM + t_3 . CSF + t_4 . NB_1 + t_5 . NB_2 + $\boldsymbol{\varepsilon}$
        - With t_i the fitting parameters expressing the voxel fraction for the respective tissue
        - $\boldsymbol{\varepsilon}$ a noise term

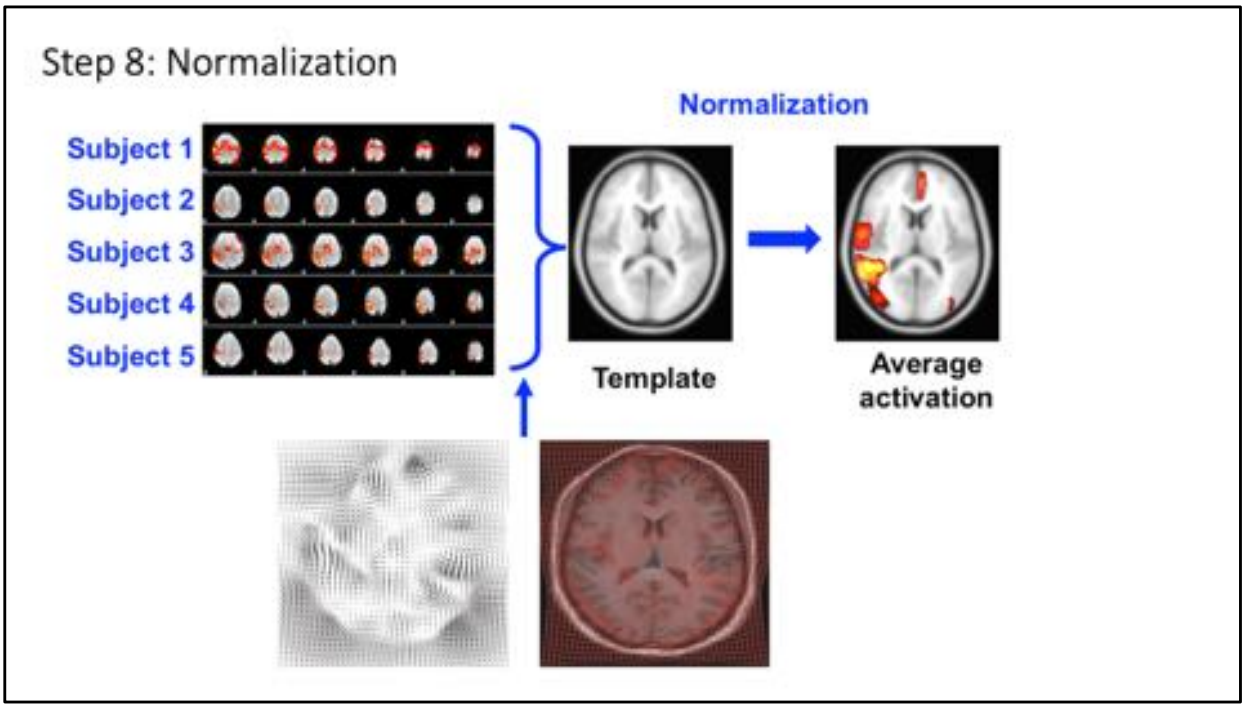
- The segmentation step result in 5 tissue fraction (probability) maps

- To improve the segmentation, it is advisable to manually set the origin in the anterior comisor and to reorient the scan according to the axial, coronal and sagittal planes.

Step 7: Segmentation

1. In the top Menus: select SPM -> Spatial -> Segment
2. Volumes (using Dependency): Reorient Images: Reoriented Images (from the anatomical scan)



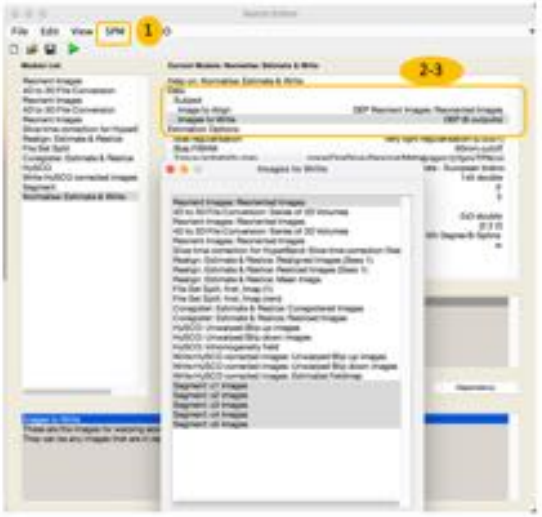


- Normalization = coregistration of a subject's scan to a standard template (in SPM: ICBM template)
    - Iterative determination of the non-linear transformation parameters (3 translations, 3 rotations, scaling, stretching and shearing)
    - The normalization is done by normalizing the anatomical scan and applying the determined transformation parameters to the fMRI scan
    - After the normalization, the size and shape of the individual's brain correspond to the size and shape of the template
- Useful for
    - Linking a voxel position (defined by its x, y and z coordinates) in the brain to an anatomical label defined in an neuroanatomical atlas (MNI atlas, Broadman atlas, …)
    - Performing second level analyses (within or between groups analyses) -> all voxels in all individuals need to correspond to exact the same position -> need to remove the difference in shape and size of individual brains
- Normalization is not done in clinical fMRIs for surgery -> coherence in positions, distances and angles in the brain between the fMRI scan and the real anatomy should be preserved

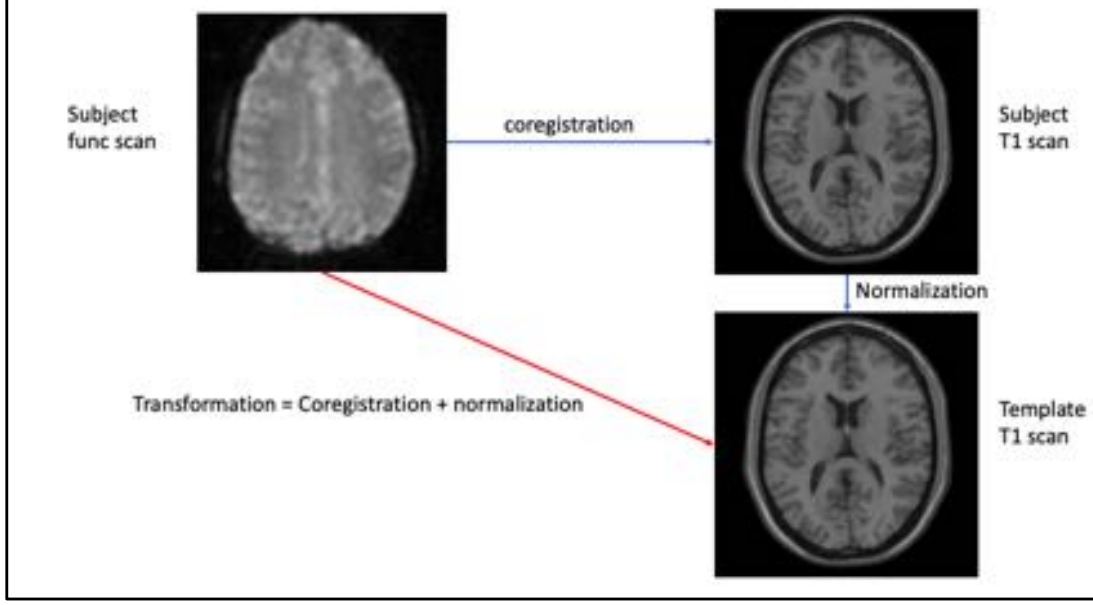
See also
https://en.wikibooks.org/wiki/Neuroimaging_Data_Processing/Coregistration_and_Normalization
https://en.wikipedia.org/wiki/Spatial_normalization
http://www.fil.ion.ucl.ac.uk/spm/doc/books/hbf2/pdfs/Ch3.pdf
http://mriquestions.com/registrationnormalization.html

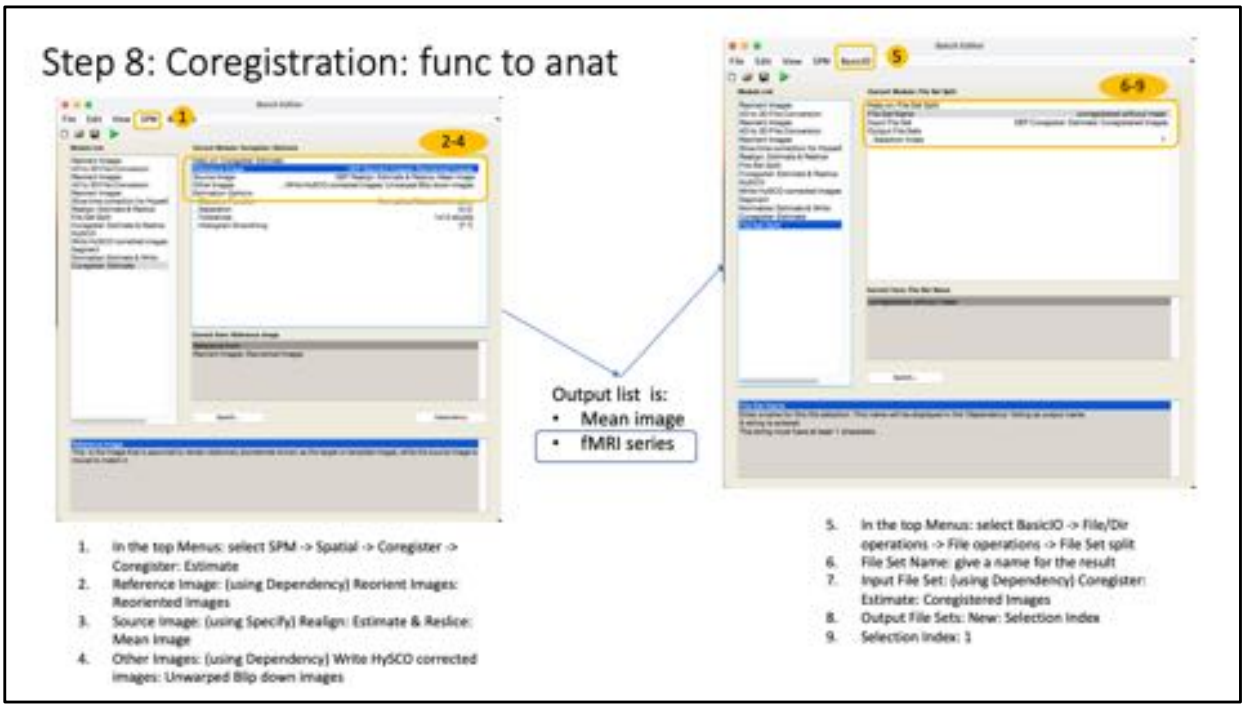
Step 8: Normalization: The anatomical scan and segmentation maps

1. In the top Menus: select SPM -> Spatial -> Normalise -> Normalise: Estimate & Write
2. Image to align: (using Dependency) Reorient Images: Reoriented Images (from anat scan!)
3. Images to write: (using Dependency) Reorient Images: Reoriented Images (from anat scan!) + Segment: c1 – c5 Images



Step 8: Normalization: The fMRI scan

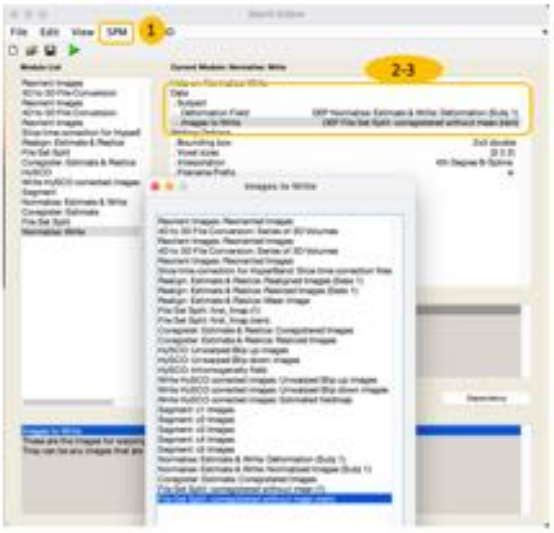




If we don’t do the file set split step than in the last step, when make a 4D file from all the output, we would have 1 extra dynamic (591 instead of 590).

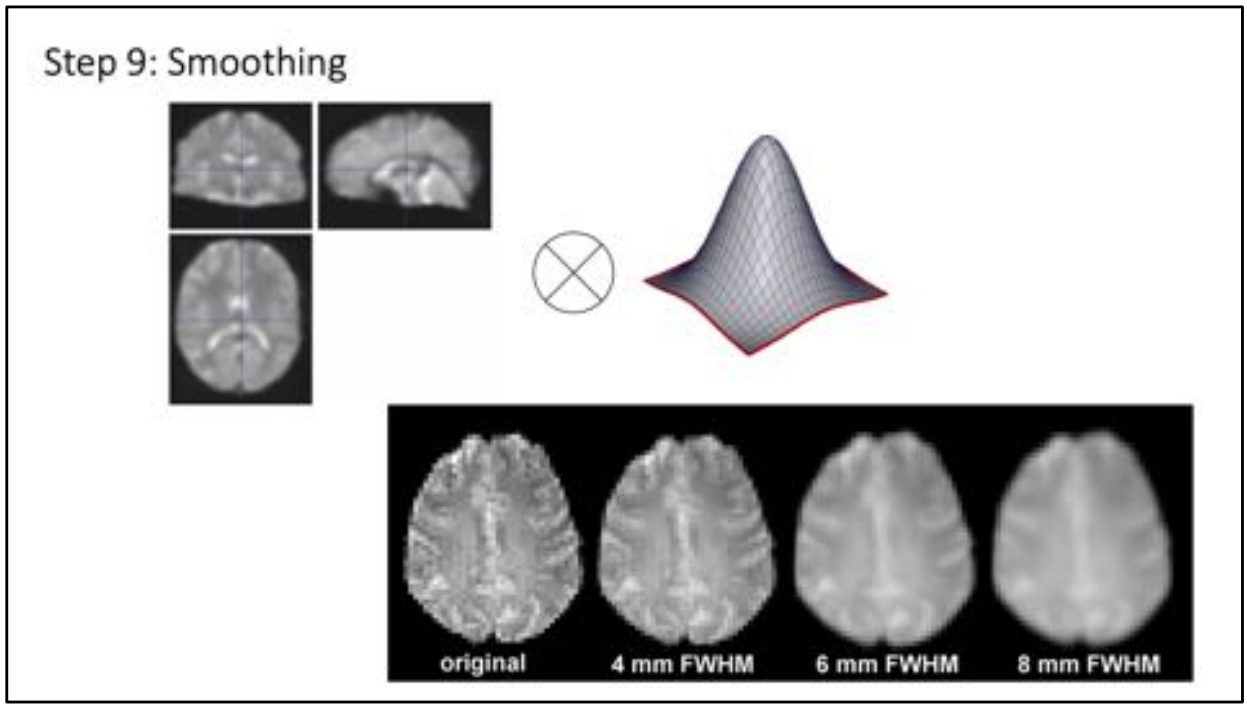
Step 8: Normalization: The fMRI data

1. In the top Menus: select SPM -> Spatial -> Normalise -> Normalise: Write
2. Deformation Field: (using Dependency) Normalise: Estimate & Write: Deformation (Subj 1)
3. Images to write: (using Dependency) File Set Split: your_given_name (rem)



The deformation field = the normalization transformation as determined during the normalization of the coregistrered anatomical scan.

We use the normalization parameters stored in the deformation file to do the normalization of the functional scan.



- Why smoothing?
    - Even after normalization, small anatomical differences between subject still exist
    - The signal-to-noise (SNR) ratio in fMRI series is low

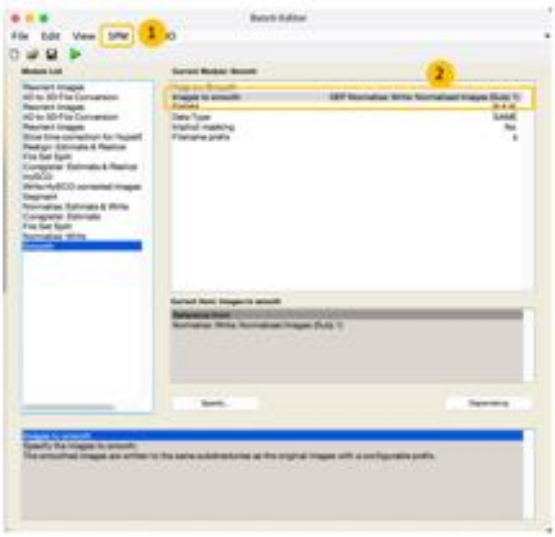
    -> smoothing improves the statistical power

- Smoothing is done by the convolution of the 3D fMRI volumes with a 3D Gaussian filter
    - Larger smoothing kernels: less noisy data
    - Smaller smoothing kernels: better spatial resolution
    - Standard used in SPM: FWHM=8x8x8 mm^3

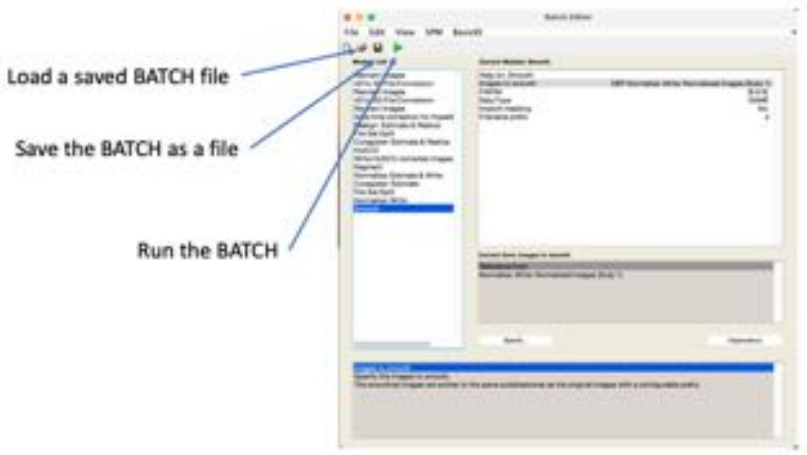
See also
https://en.wikibooks.org/wiki/Neuroimaging_Data_Processing/Smoothing
https://en.wikibooks.org/wiki/SPM/Spatial_smoothing
Mikl et al. 2008. Effects of spatial smoothing on fMRI group inferences

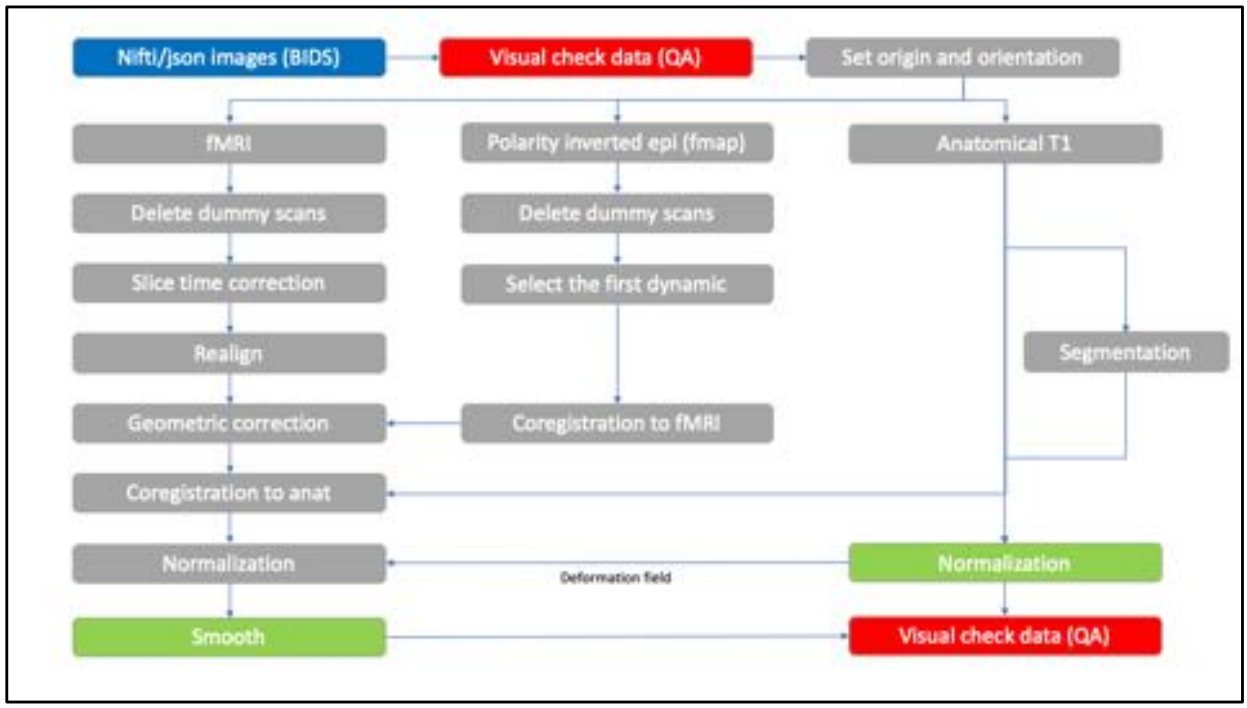
Step 9: Smoothing

1. In the top Menus: select SPM -> Spatial -> Smooth
2. Images to smooth: (using Dependency) Normalise: Write: Normalised Images (Subj 1)

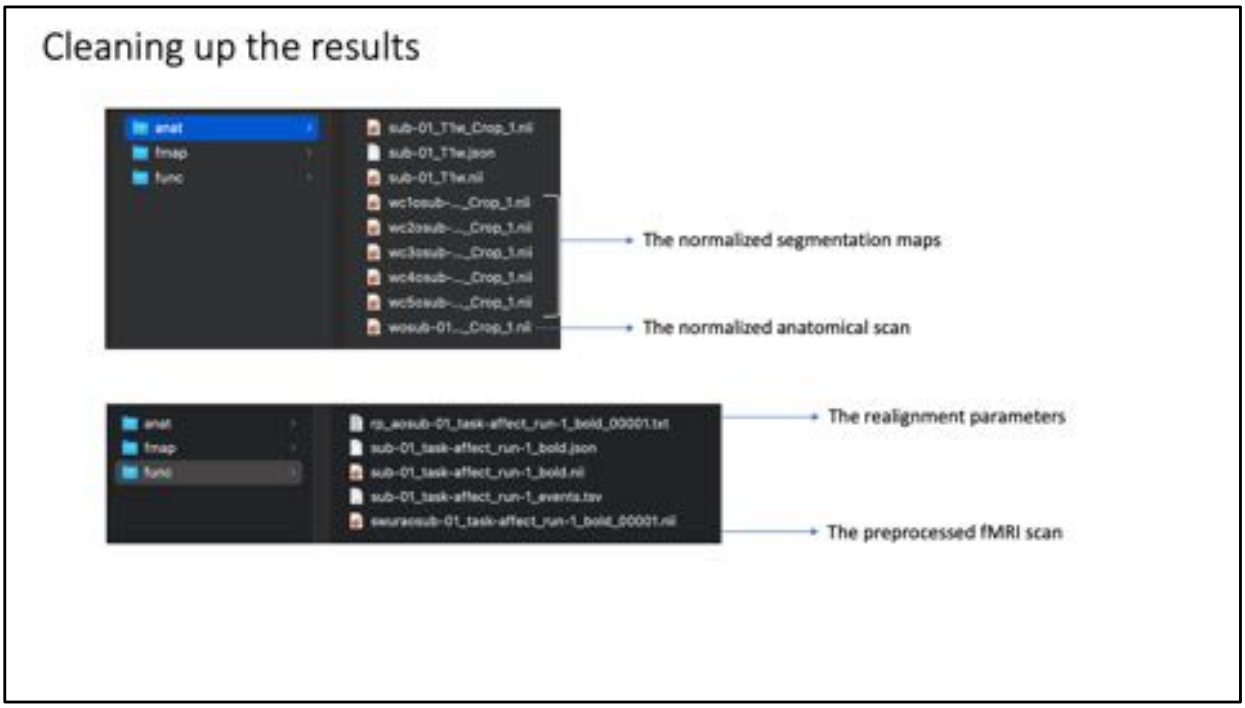


Run the batch (at home)





Deformation field: contains the information for the non-linear transformation from subjects space to normalized (MNI) space

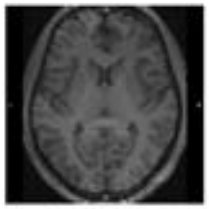


During the preprocessing of the fMRI data, each step will generate a new time series -> lots of files and lots of gigabits

Intermediate files that are no longer of use will be cleaned up to save space and ease further processing

- Transforming the output of the smoothing step (a series of 3D .nii files) into 1 4D nifty file
- Delete all unnecessary files
- Files to keep
    - Normalized T1 scan
    - Normalized segmentation maps
    - 4D smoothed fMRI data
    - The text file with the realignment parameters (translations and rotations motion of the head during the fMRI scan)
- Do not select files that are not created, that appear twice or that are already deleted! This will cause errors.

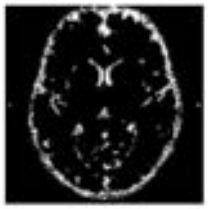
The preprocessing results



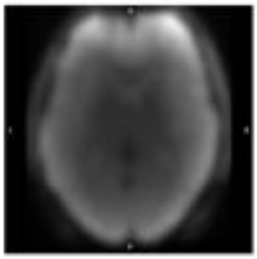
wosub-01_T1w

wc1osub-01_T1w

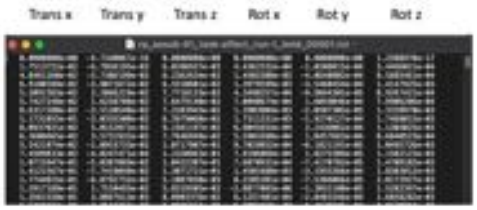
wc2osub-01_T1w



wc3osub-01_T1w



swuraosub-01_..._bold



Realignment parameters

DANK U - THANK YOU

Universitair
Ziekenhuis
Brussel

VUB