fMRI Physics, Tasks Design, and its Clinical Applications

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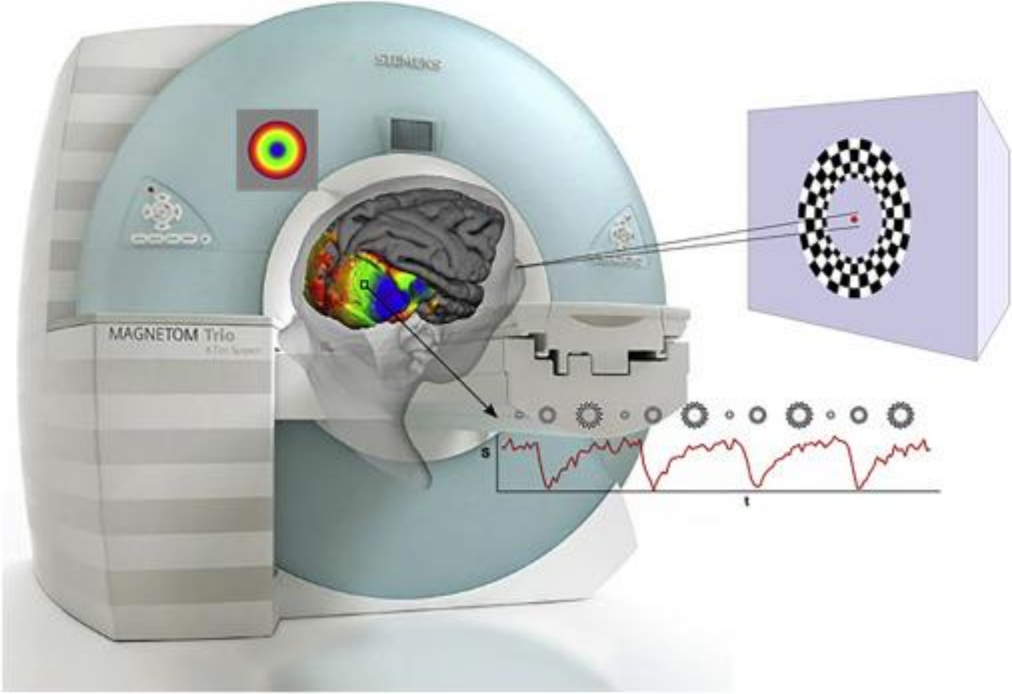
fMRI Physics, Tasks Design, and its Clinical Applications

- **fMRI Physics, Image Formation and Processing**
- **Tasks designs**
- **fMRI Clinical Applications**

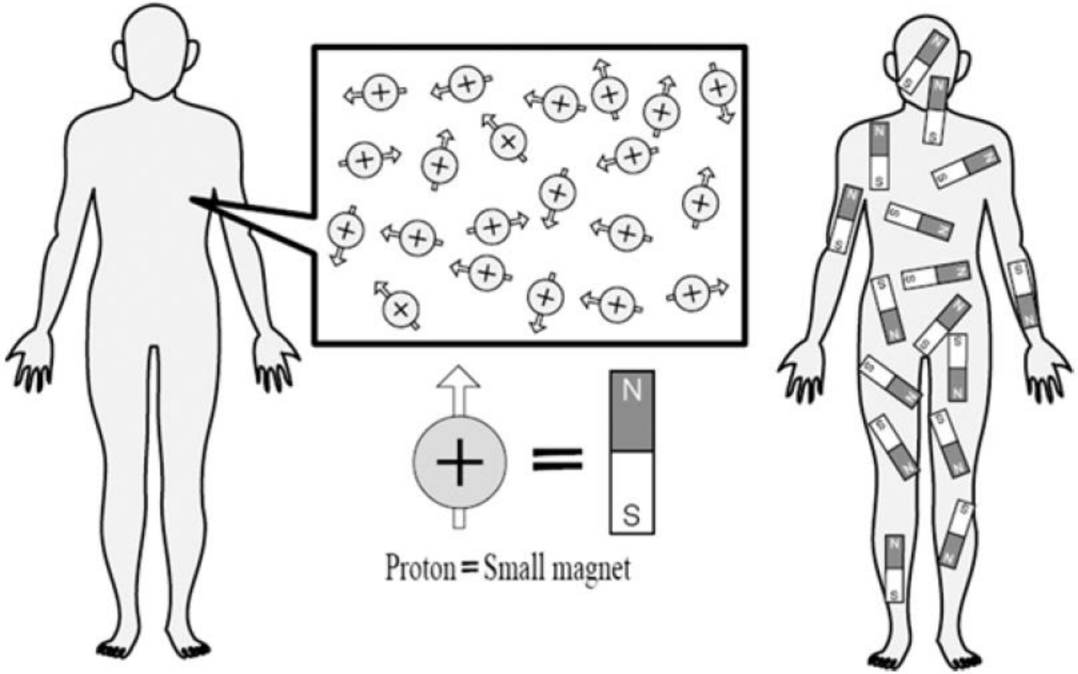


MRI Active Nuclei

- H1
- C13
- N15
- O17
- P31

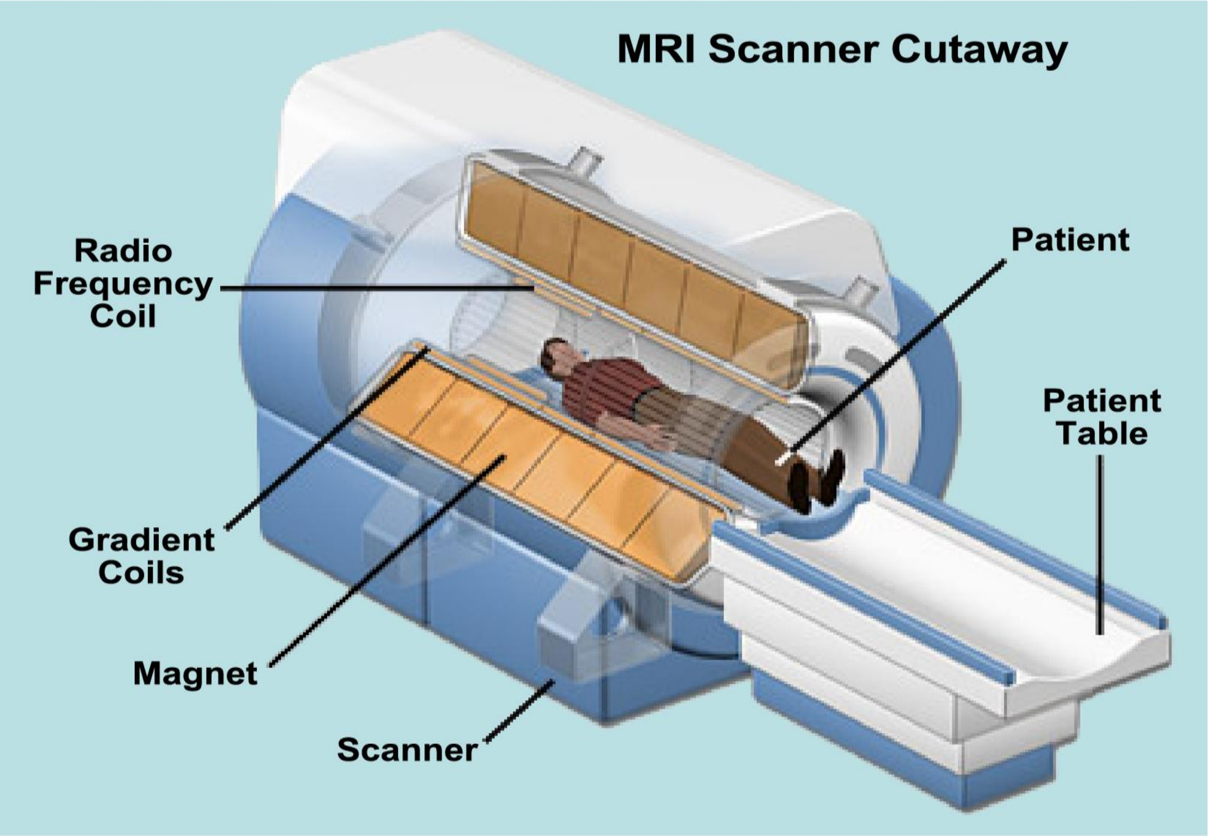
➤ Due to unpaired protons acts as tiny magnets

Nuclei Directions in Body



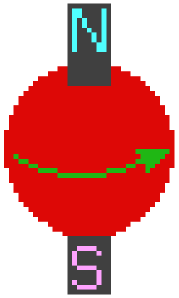
Protons have a random direction when no external magnetic field is applied.

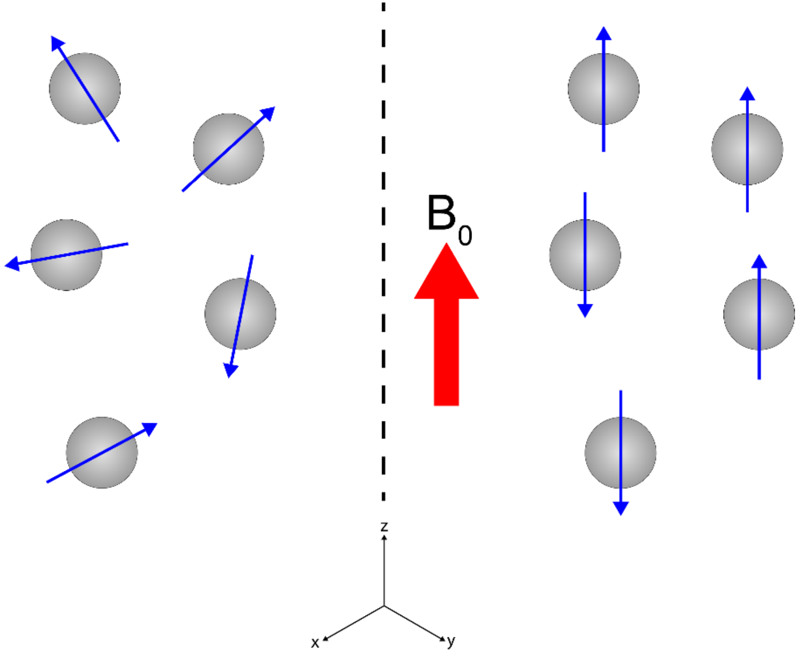
Basics of MRI Equipment



Gyromagnetic ratio

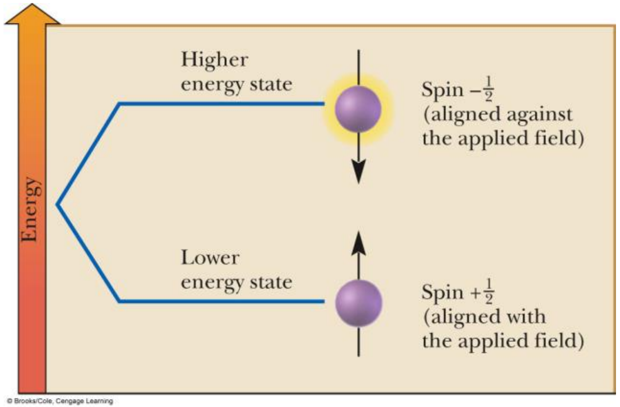
$$\gamma = Q/2m$$



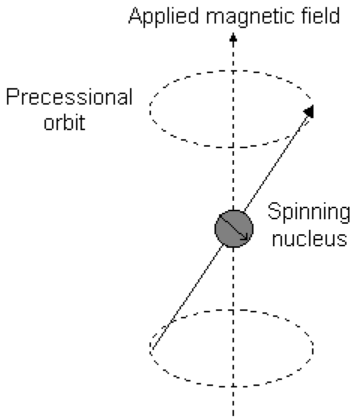


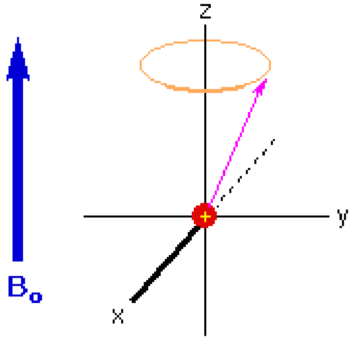
- The gyromagnetic ratio (denoted as γ) is a fundamental property that governs the behavior of atomic nuclei in a magnetic field. Specifically, it relates the magnetic moment of a particle to its angular momentum.
- It determines the precession frequency of protons (hydrogen nuclei) within a magnetic field.
- This precession frequency is essential for creating the signals detected during MRI scans.

Precession



$$\gamma = Q/2m$$
$$\omega = \gamma B_0$$

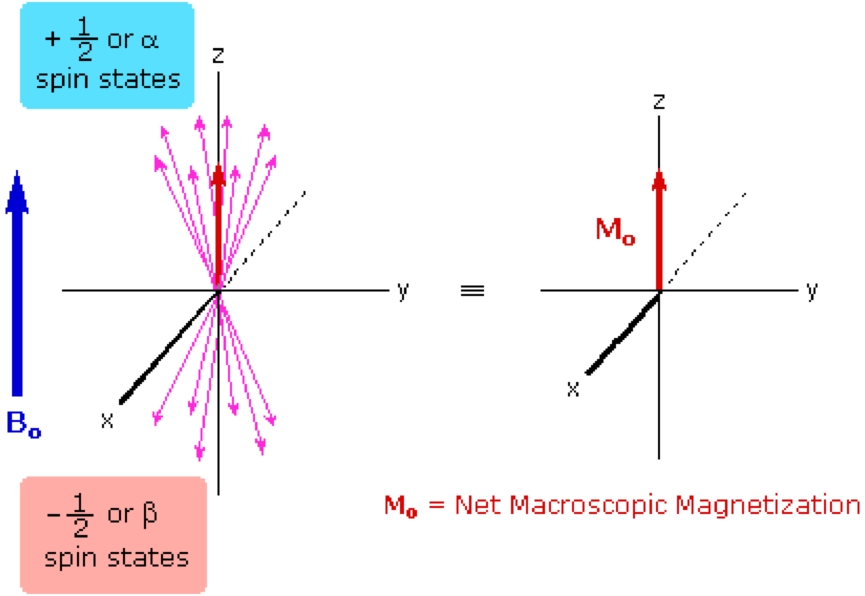


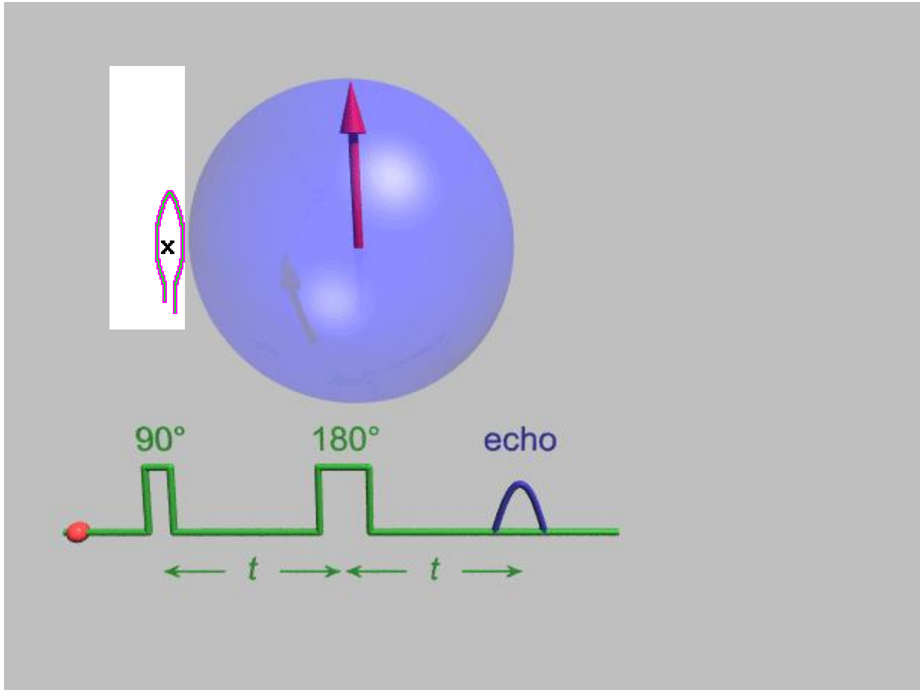


Precession refers to the circular motion of atomic nuclei (such as protons) within a magnetic field.

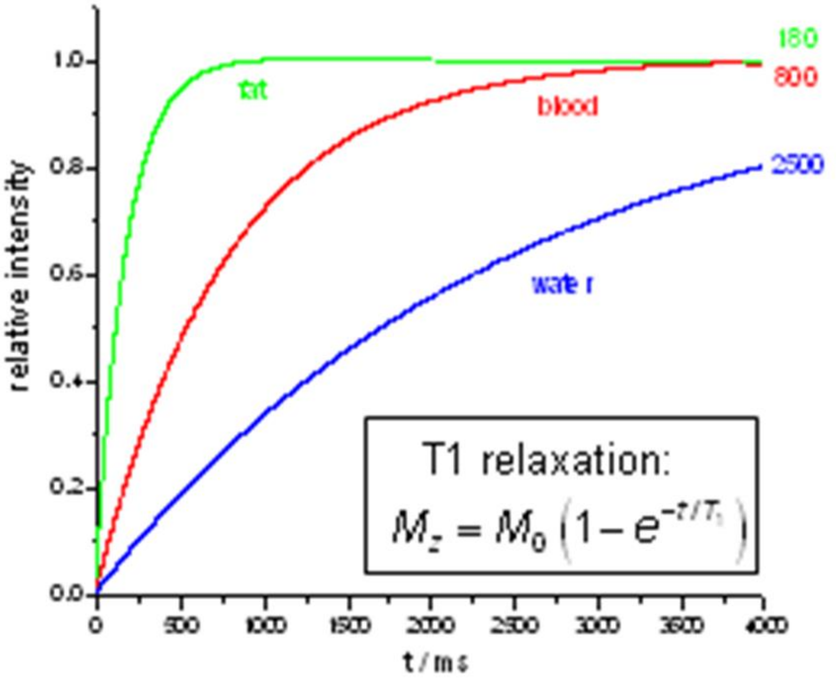
- The precession rate is quantified by the Larmor frequency (also called the precessional frequency).
- The strength of the magnetic field directly influences the Larmor frequency.

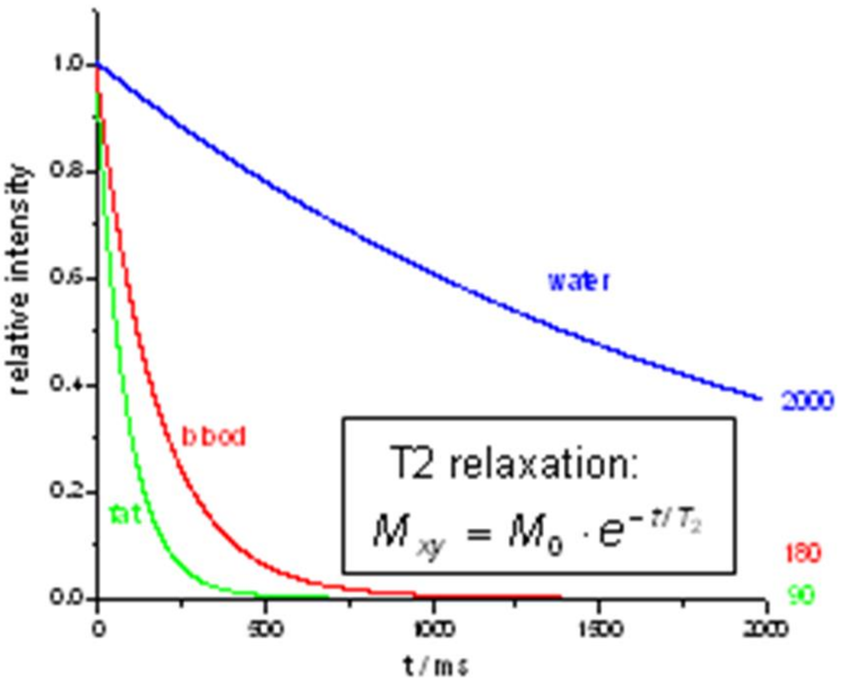
Spin echo sequence



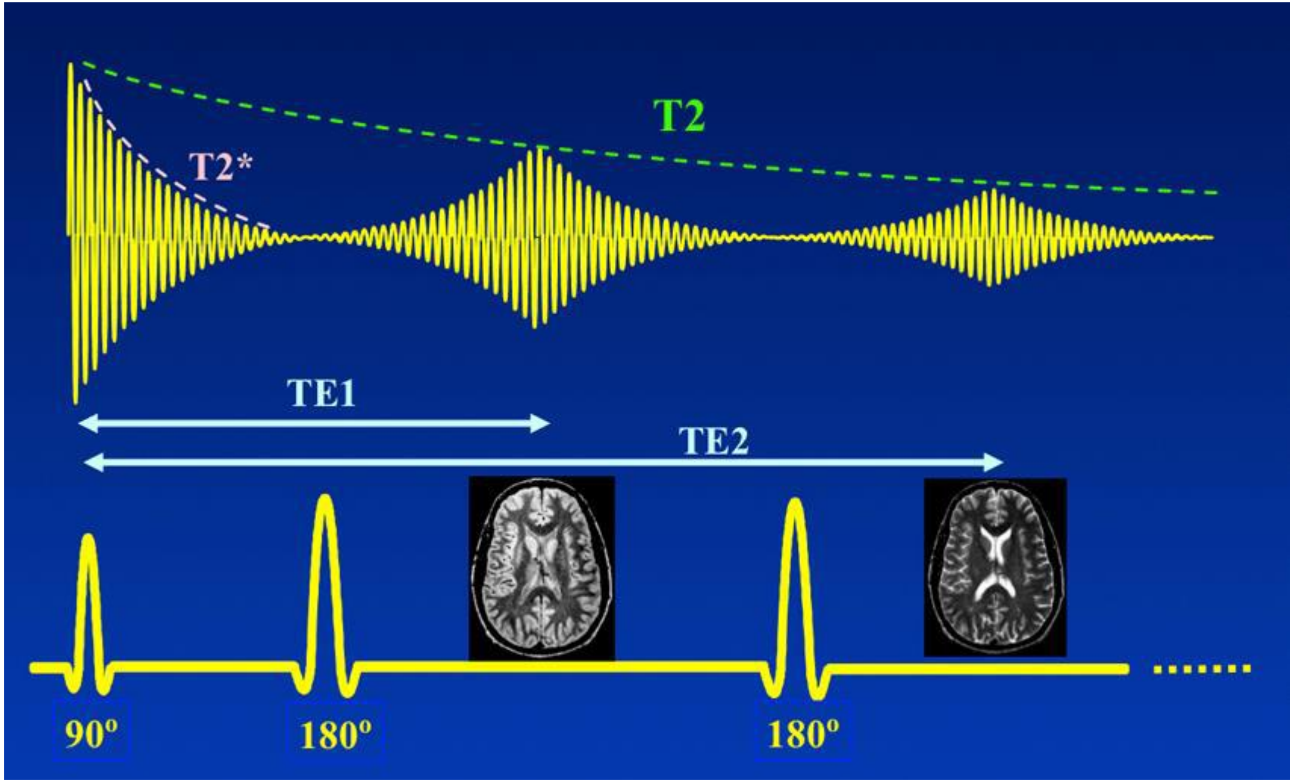


T1 vs T2

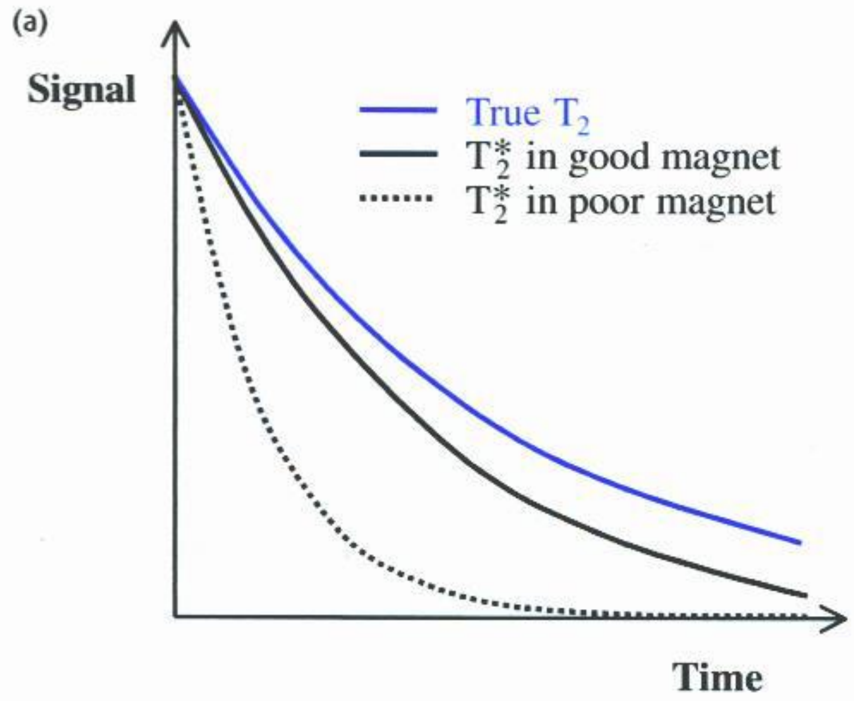

T1 relaxation:
$M_z = M_0 \left(1 - e^{-t/T_1}\right)$
relative intensity
t / ms
fat
blood
water
180
800
2500


T2 relaxation:
$M_{xy} = M_0 \cdot e^{-t/T_2}$
relative intensity
t / ms
water
fat
2000
180
90

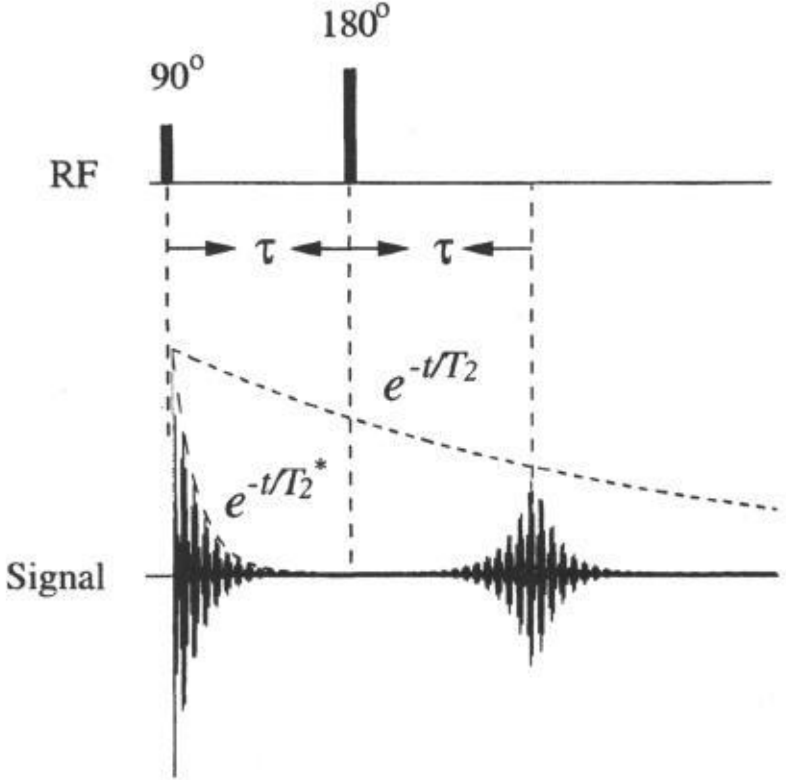
T2 Vs T2*

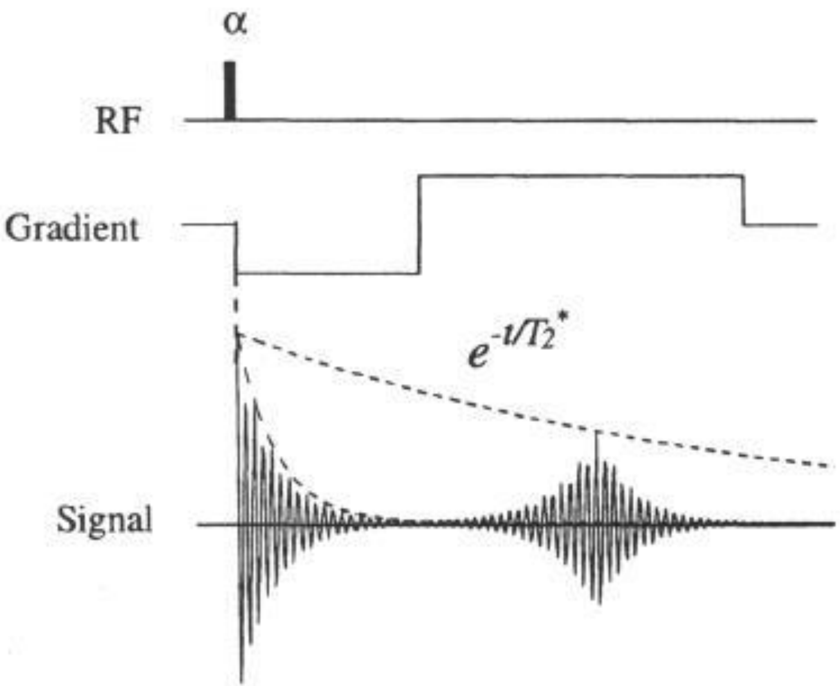


T2 * (GE) vs T2(SE)

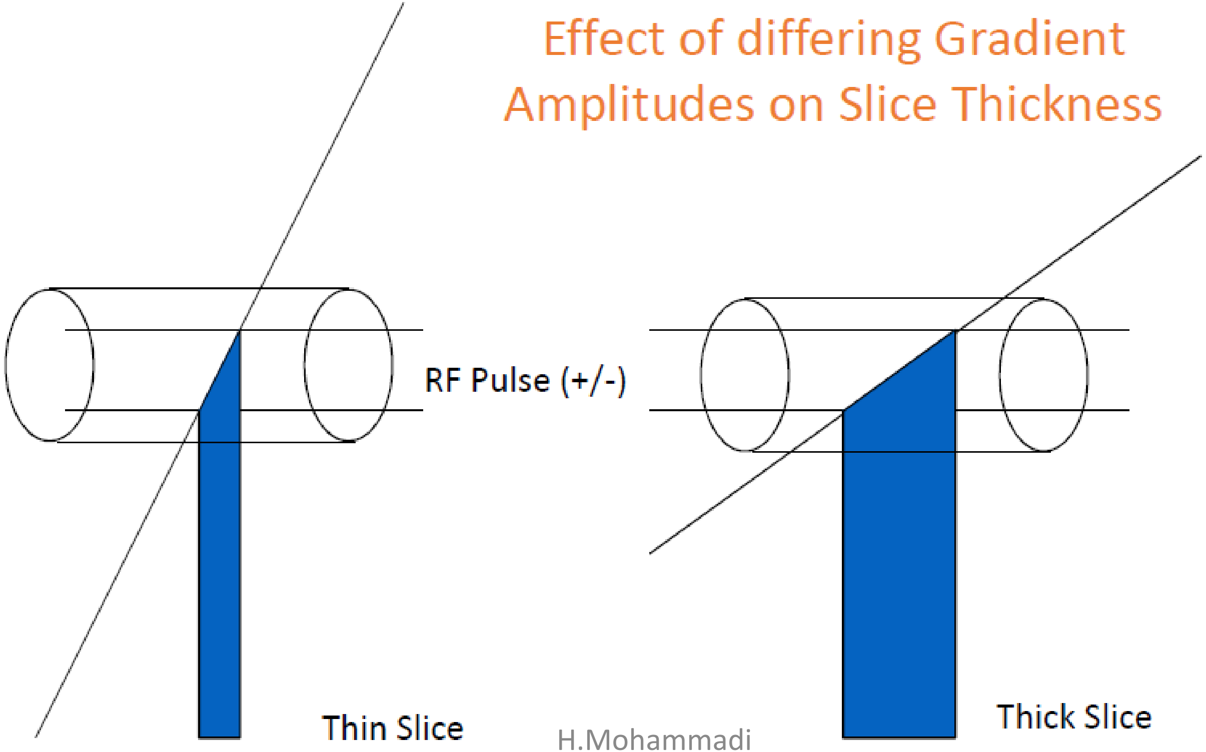


Spin Echo vs Gradient Echo



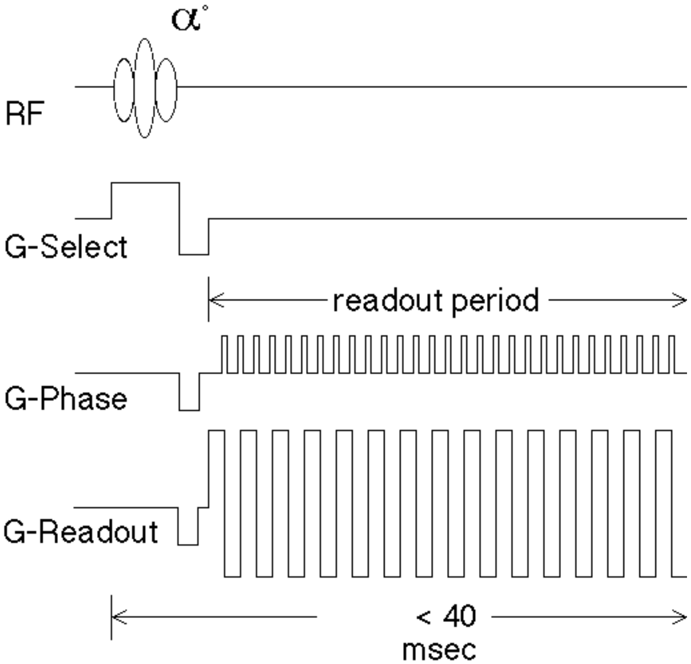


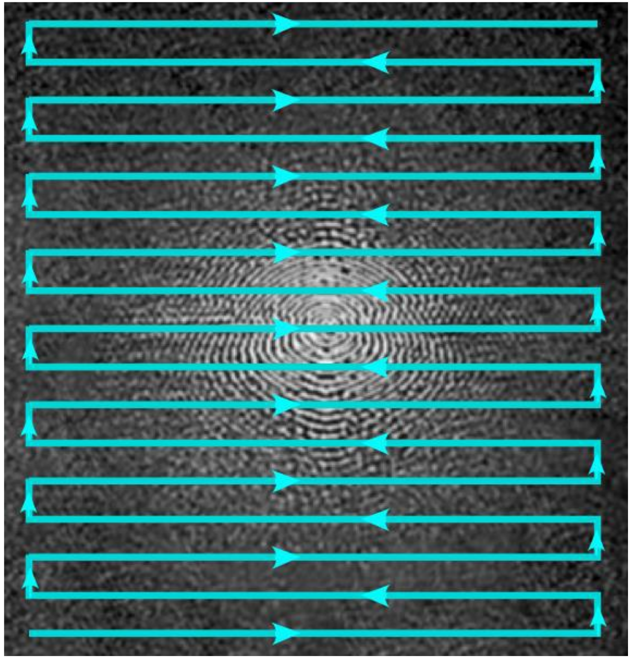
Effect of differing Gradient Amplitudes on Slice Thickness



EPI Sequence

EPI refers to a sequence in which data from all of k-space was collected following a single RF excitation pulse (single shot)





fMRI: Physiology and Physics

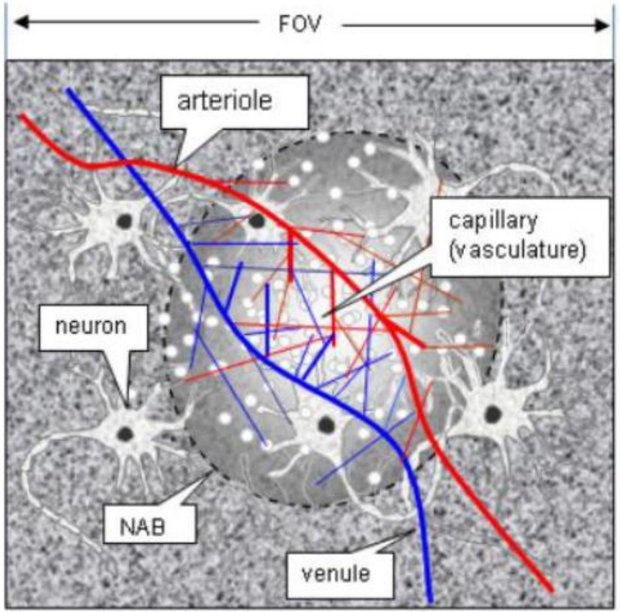
Neural Activity

PHYSIOLOGY ↓

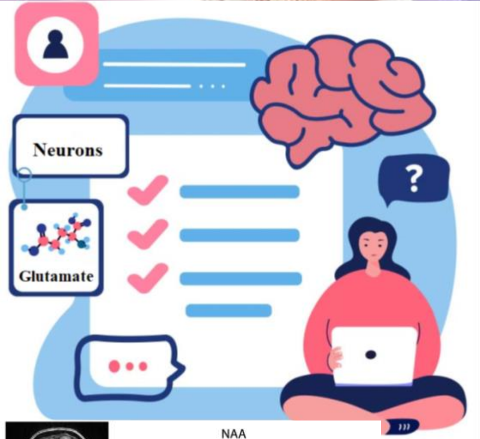
Hemodynamic Response

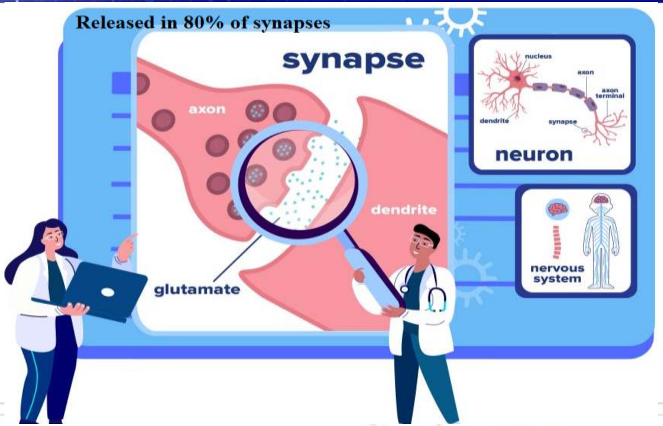
PHYSICS ↓

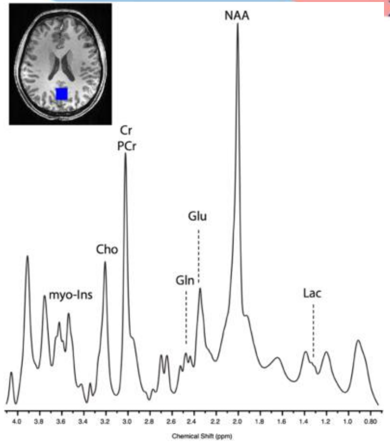
MRI Contrast

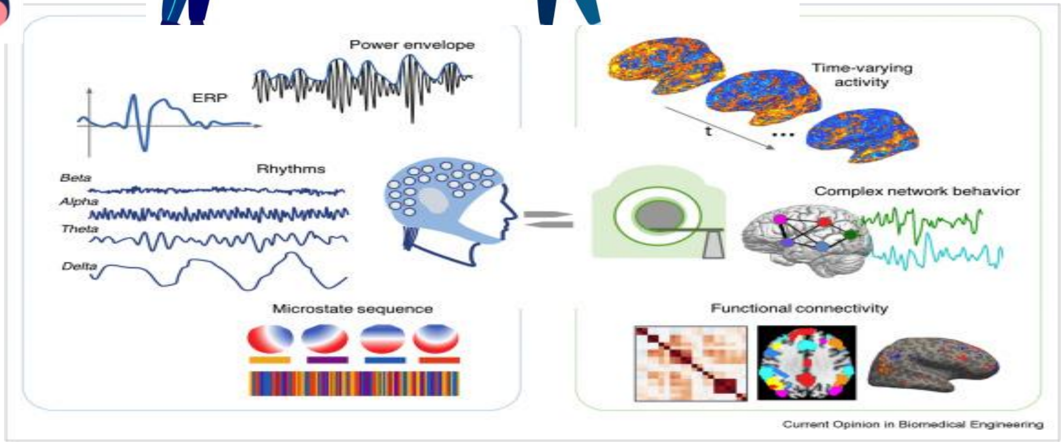


Simultaneous Metabolic, Electrophysiologic, and Hemodynamic Functions of the Brain

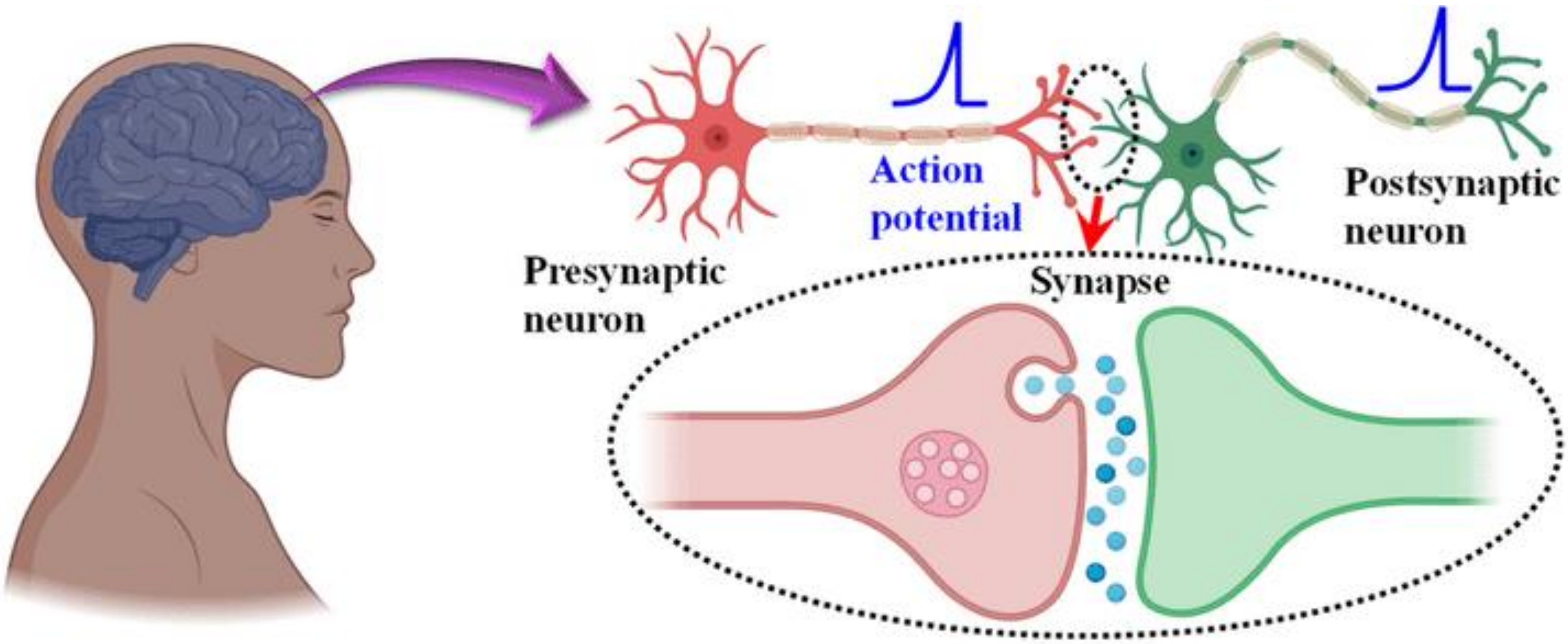




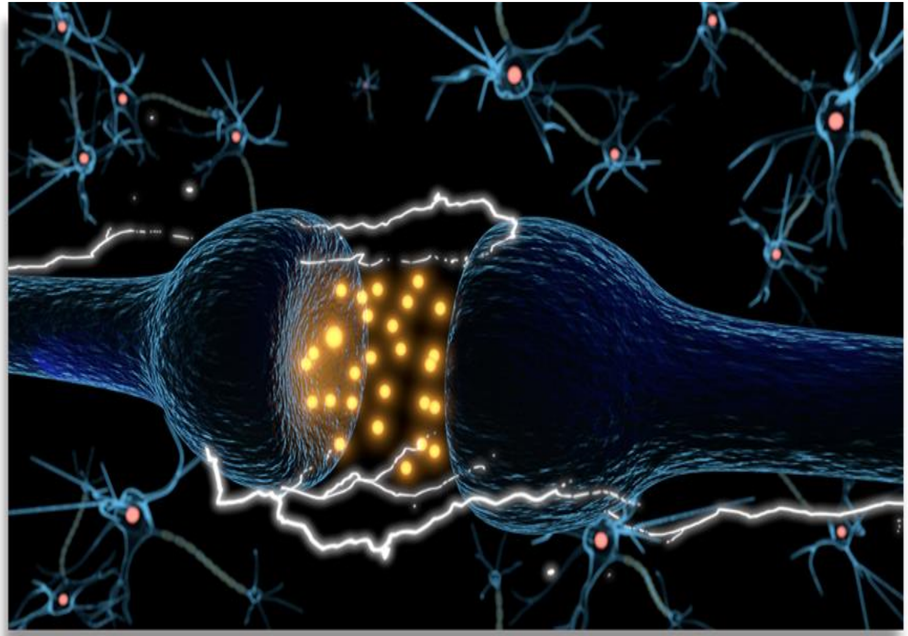


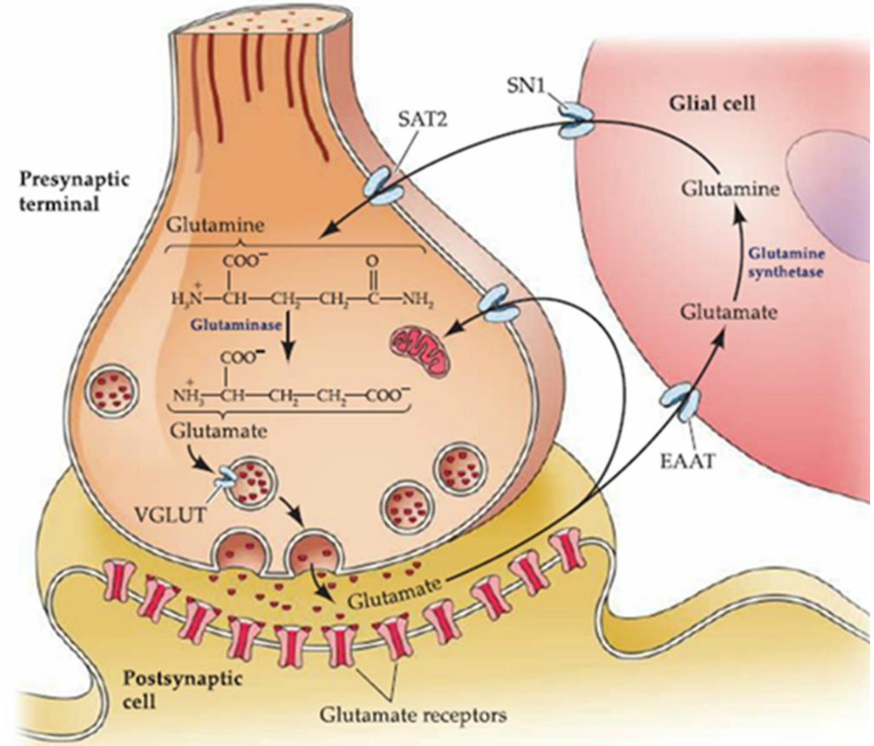


Physiology of Neuron Activation



Physiology of Neuron Activation

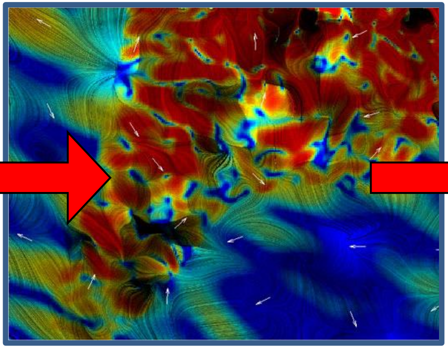




Hemoglobin magnetic properties

DeoxyHb paramagnetic

strong field inhomogeneities

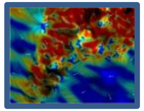


Fast dephasing

Fast T2*

OxyHb diamagnetic

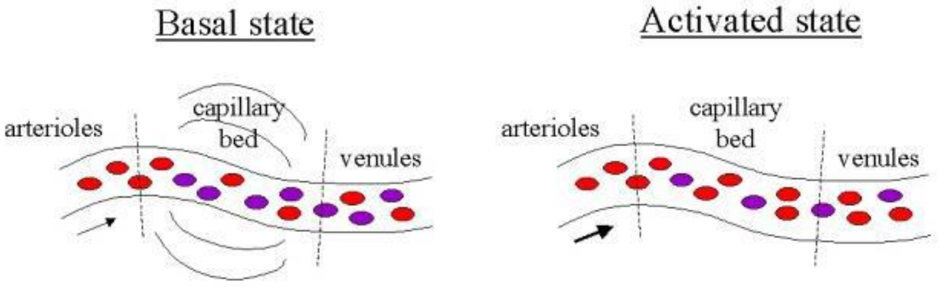
weak field inhomogeneities



Slower dephasing

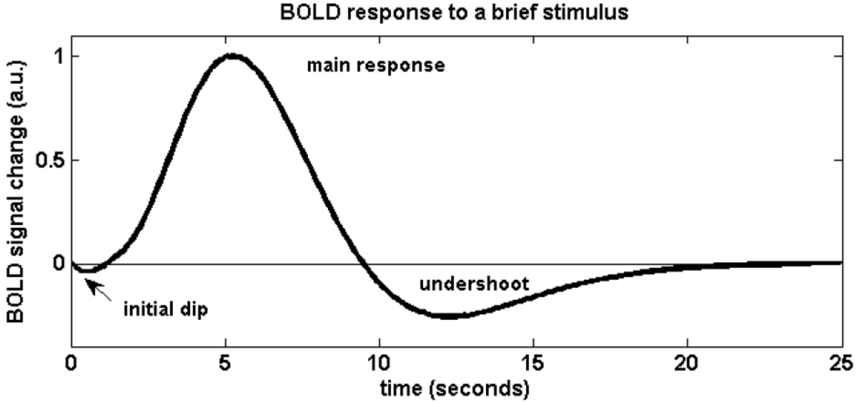
slower T2*

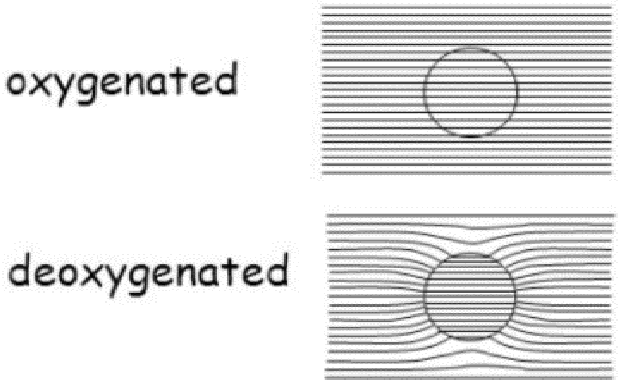
BOLD Effect & HRF



- normal flow
- basal level [Hbr]
- basal CBV
- normal MRI signal

- increased flow
- decreased [Hbr] (*lower field gradients around vessels*)
- increased CBV
- increased MRI signal (*from lower field gradients*)





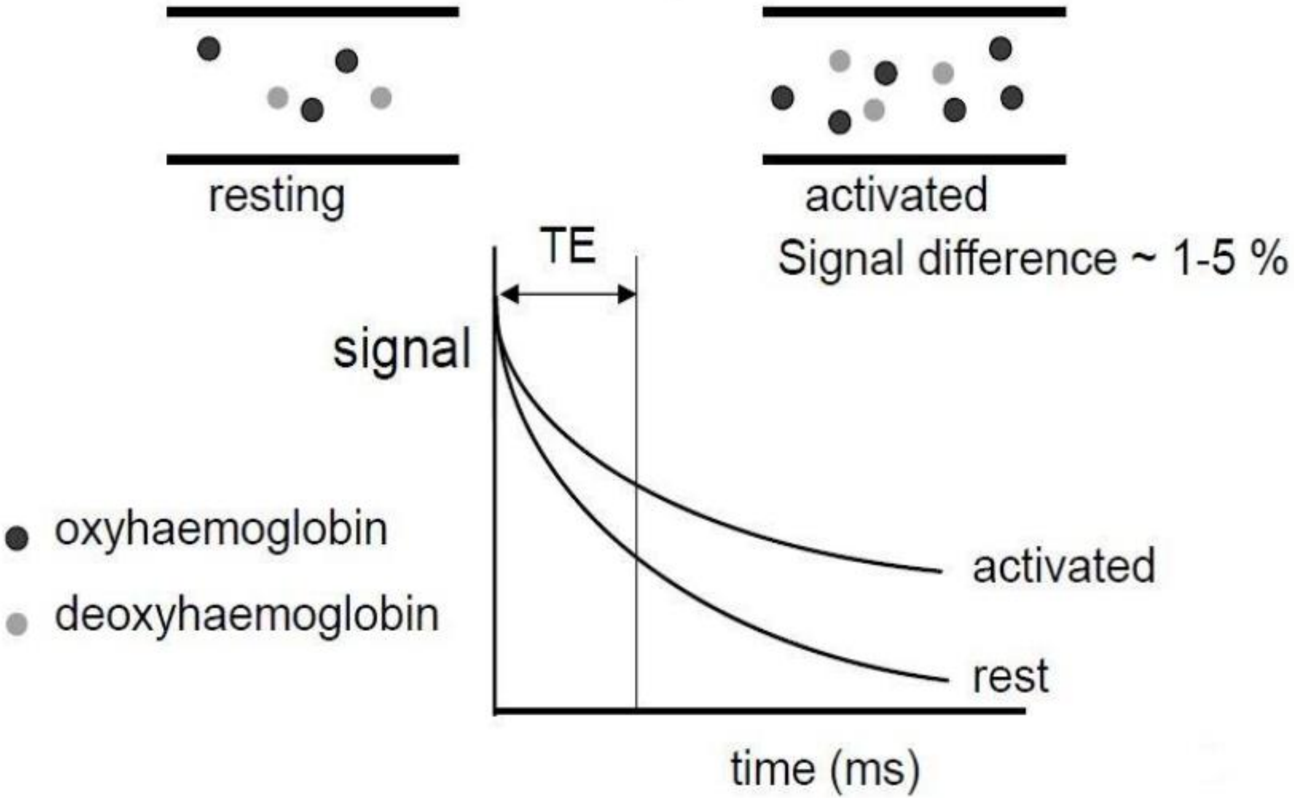
fMRI Contrast

DeoxyHb paramagnetic

strong field inhomogeneities

OxyHb diamagnetic

weak field inhomogeneities



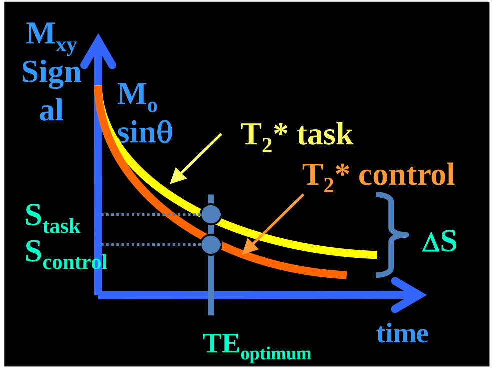
How does this relate to neural activity?

- T2* decay is quicker in presence of other magnetic material (e.g. dHb)

- In active brain → there is an increase in O_2 and HbO (during main signal phase)

  Less magnetic particles present because therefore → T2* relaxation is relatively slower

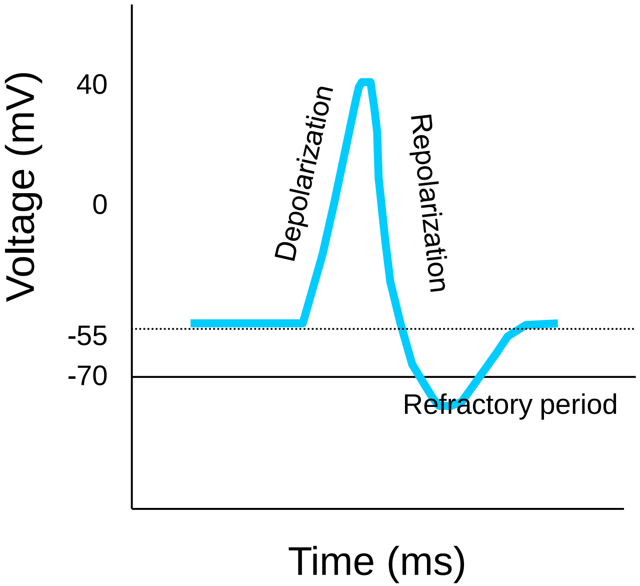
- Inhomogeneities in the field due to Δ O_2 → signal

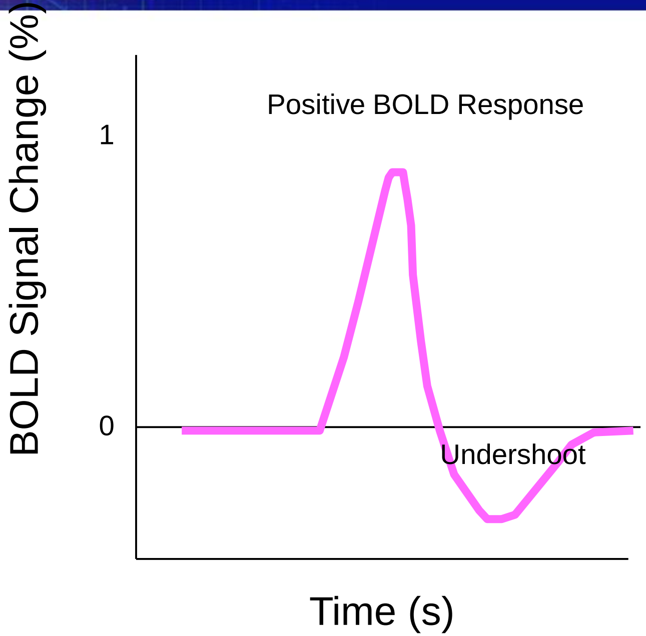


Take-home message:

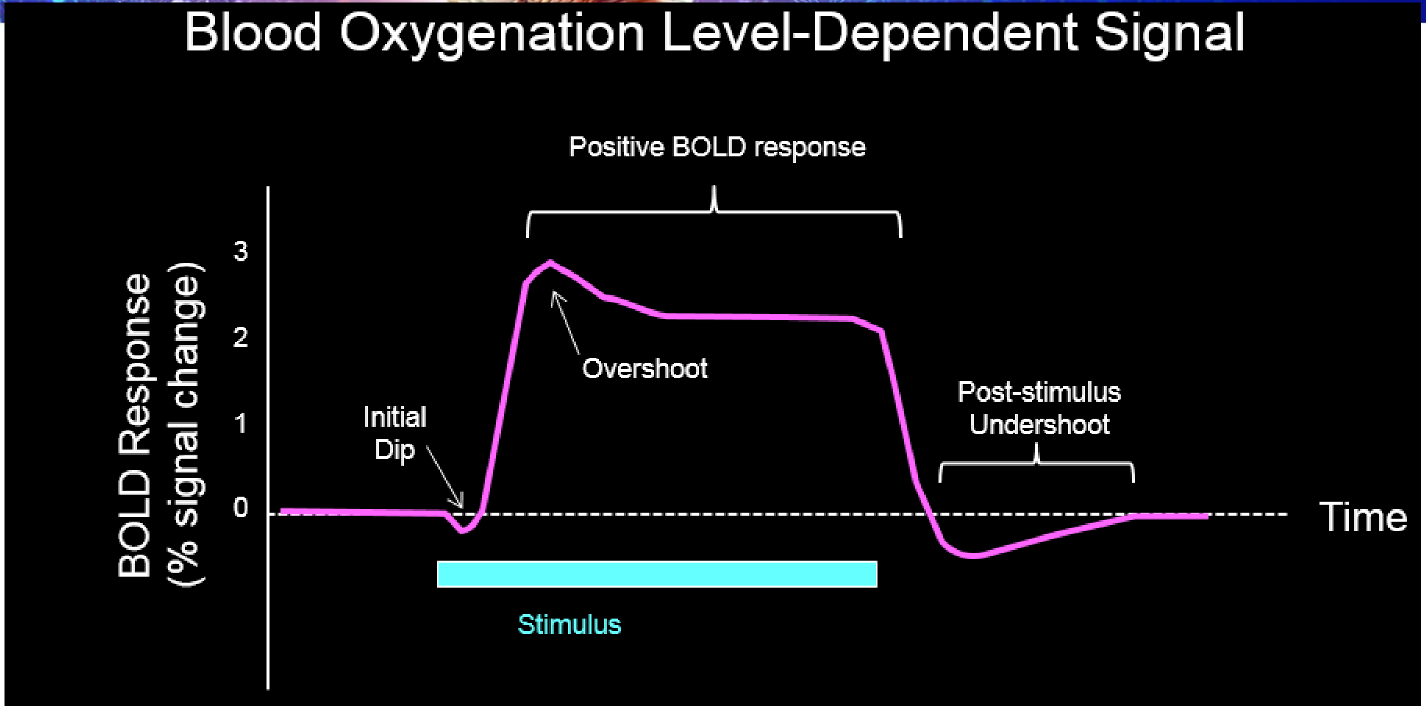
- BOLD is a T2*-weighted contrast
- We are measuring a signal from hydrogen but the signal we get from hydrogen atoms is weaker when less oxygen (Oxyheamoglobin) is present

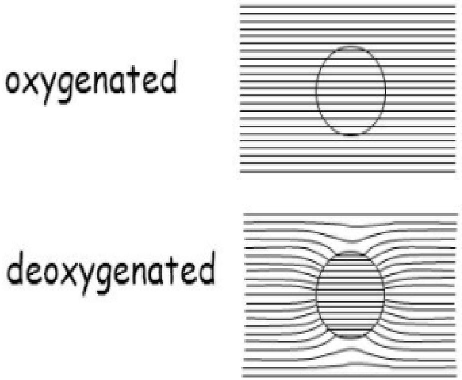
From Neurons to BOLD





Hemodynamic Response Function

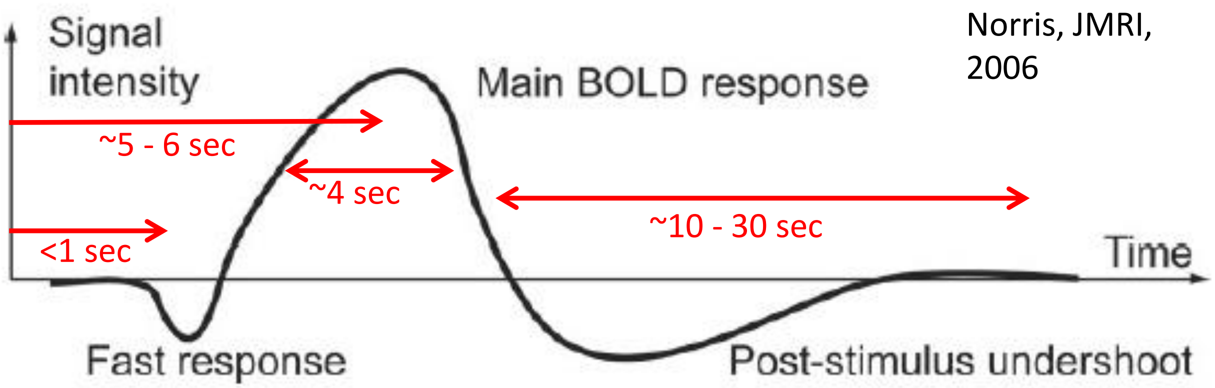




The Hemodynamic Response HDR: The change in MR signal on **T2*** images following local neuronal activity. The hemodynamic response results from a decrease in the amount of deoxygenated hemoglobin present within a voxel.

Neurophysiology

Typical hemodynamic response to single short stimulus

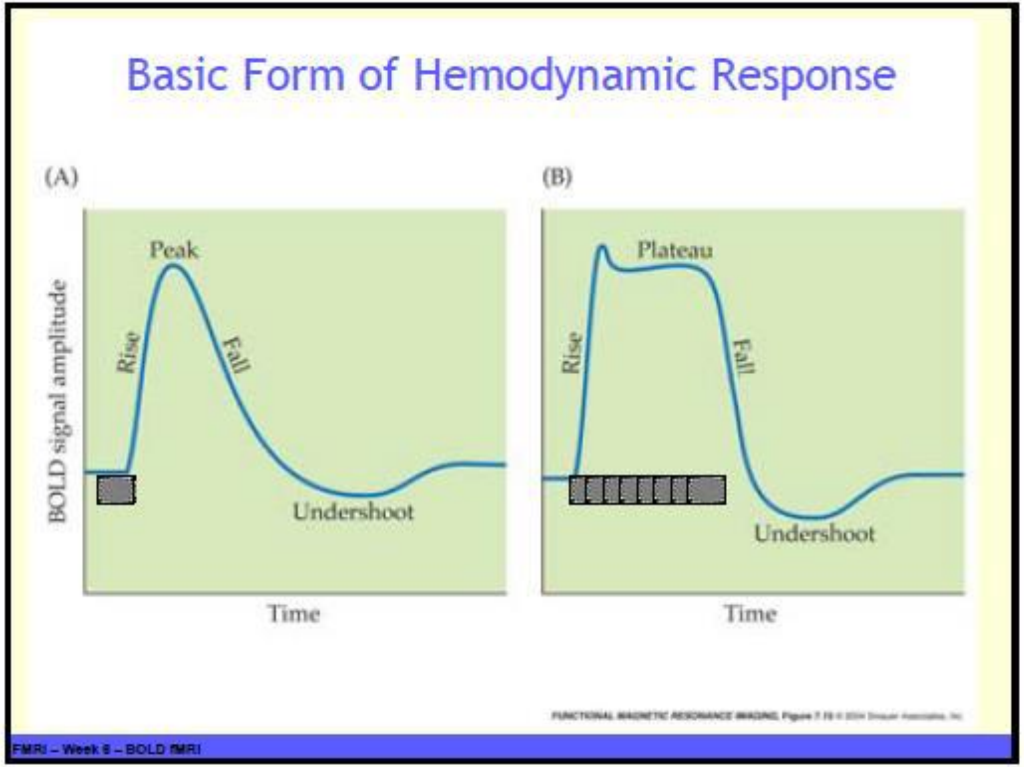


Norris, JMRI, 2006

Fast response: increase in metabolic consumption

Main BOLD response: increased local blood flow

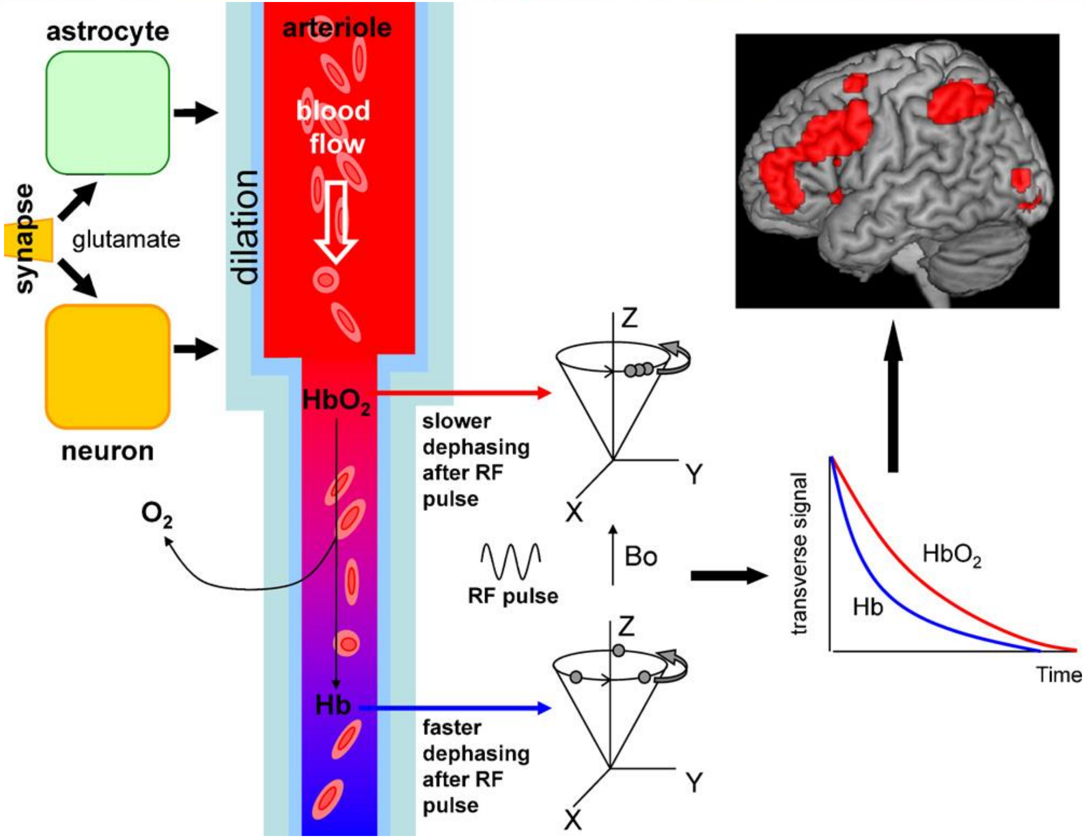
Post-stimulus undershoot: metabolic consumption remains elevated after blood flow subsides



its shape varies with the properties of the stimulus and, presumably, with the underlying neuronal activity.

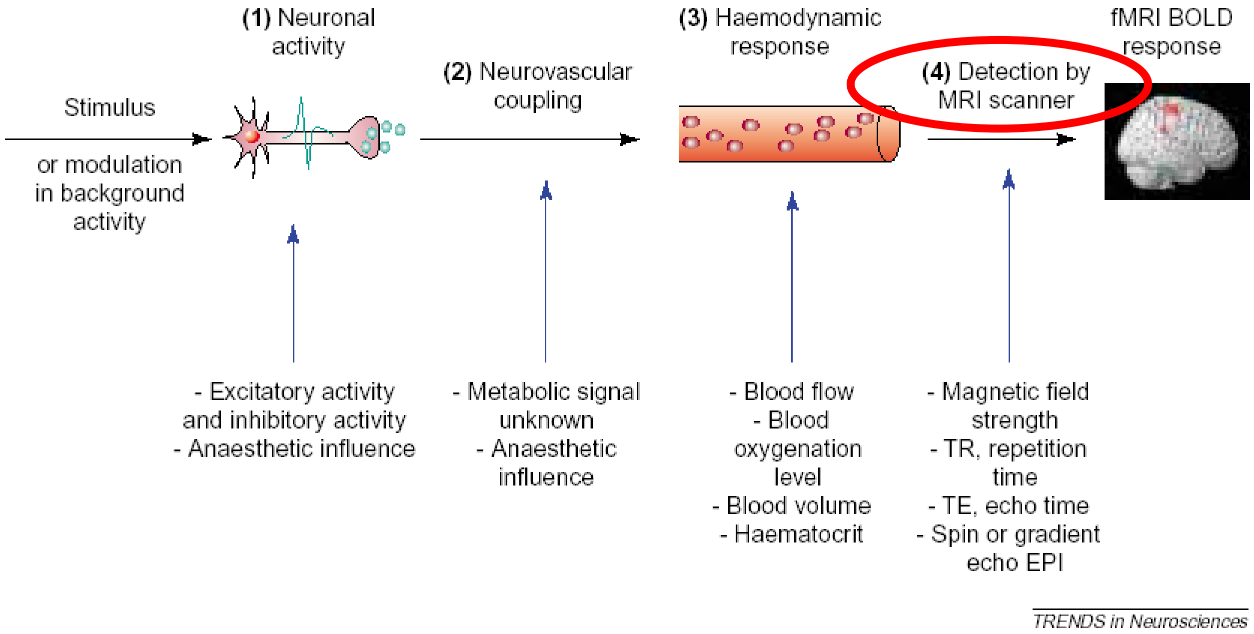
increasing the duration of neuronal activity would increase the width of the hemodynamic response(as seen in the figure)

Hemodynamic Function



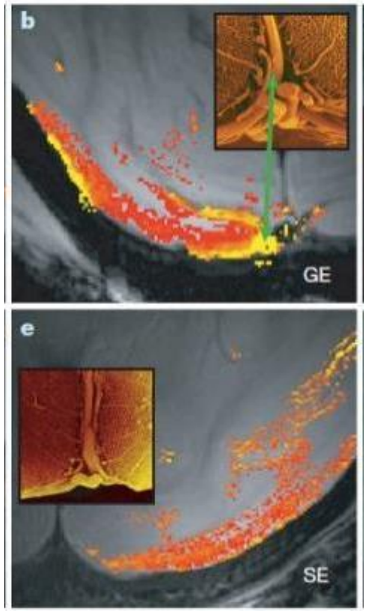
Schematic diagram showing the different stages of how BOLD signals are generated, from neurobiology through physics to data analysis. On the left, neuronal activity releases transmitters (glutamate) which act via neuronal and astrocytic signaling systems to trigger an increase of local blood flow. Neuronal activity also leads to O2 consumption and generation of paramagnetic deoxygenated hemoglobin (Hb) from diamagnetic oxygenated hemoglobin (HbO2). The blood flow increase brings in fresh oxygenated blood which (in adults) lowers the local concentration of Hb. This decreases the non-homogenizing effect that Hb has on the local magnetic field which protons in H2O experience. As a result, after a radiofrequency (RF) pulse is applied transverse to the magnetic field used to align the proton spins (Bo), the synchronized spin precession in the transverse plane dephases more slowly (graph on right). The difference in decay time between the red (HbO2) and blue (Hb) curves in the graph generates the increased MRI signal from protons in areas where neurons are active, which is represented as the red spots superimposed on a structural image of the brain at the top right.

Stimulus to BOLD



Source: Arthurs & Boniface, 2002, *Trends in Neurosciences*

Gradient Echo vs. Spin Echo

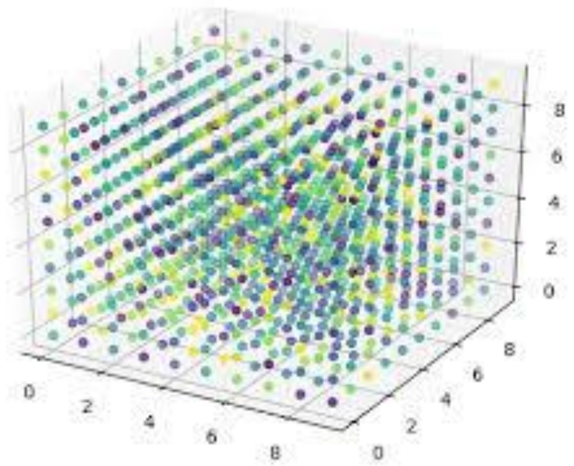


Gradient Echo
- high SNR
- strong contribution of vessels

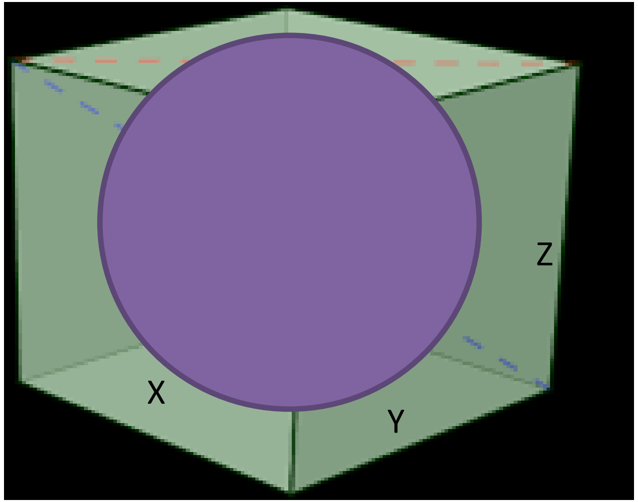
Spin Echo
- lower SNR
- weaker contribution of vessels

Source: Logothetis, 2008, Nature

fMRI Image Formation and Processing



Digital images

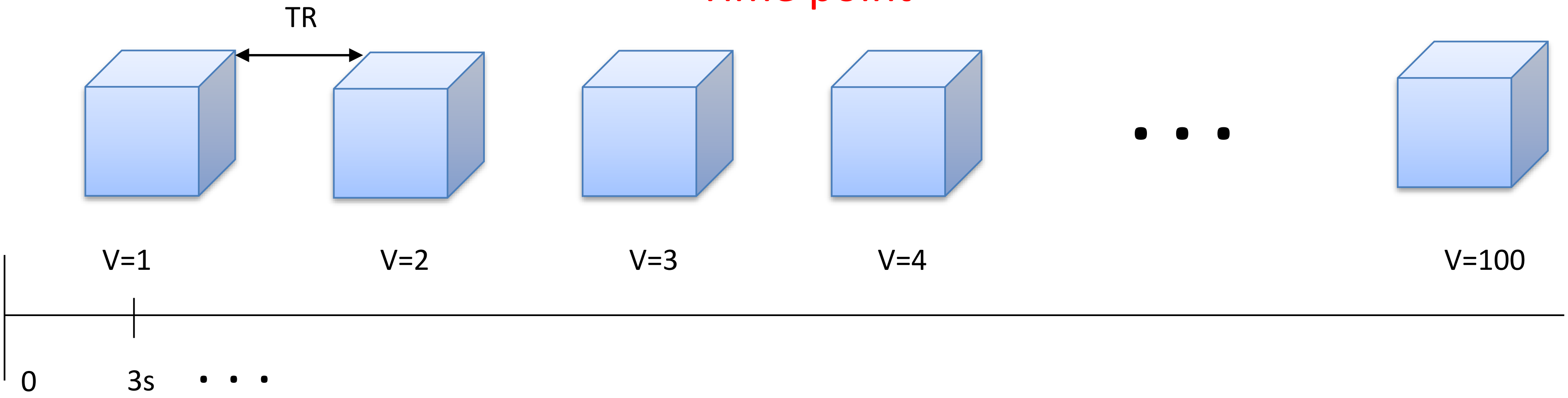


50 × 50 × 40

Volume

Measurement

Time point

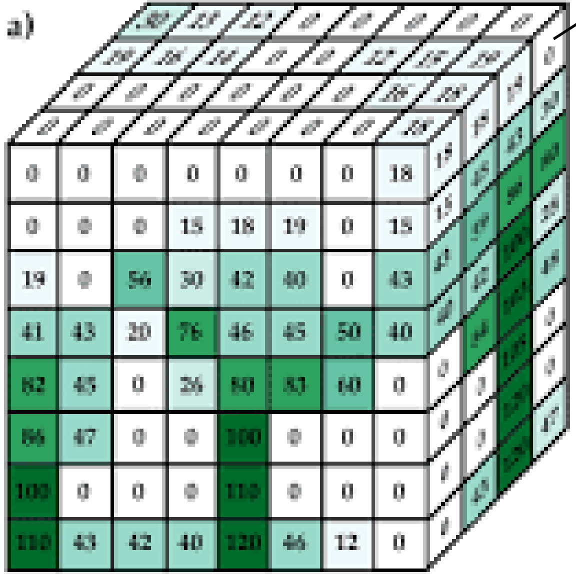


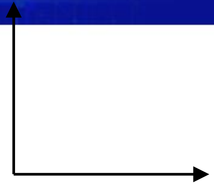
TR=2.5 - 3s

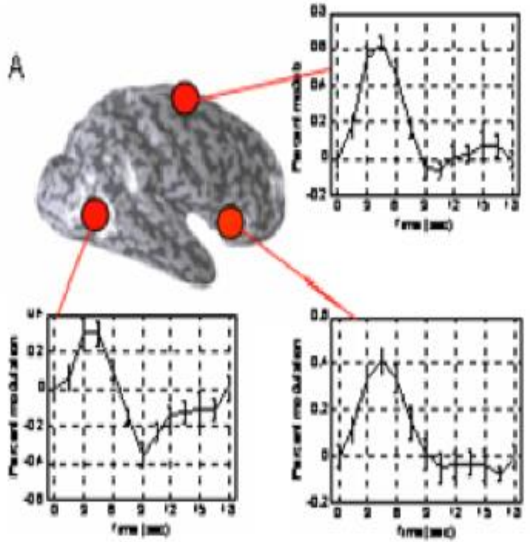
f=1/TR, f=1/3=0.4Hz

- **fMRI signal**

50 × 50 × 40 = 100 000 voxels

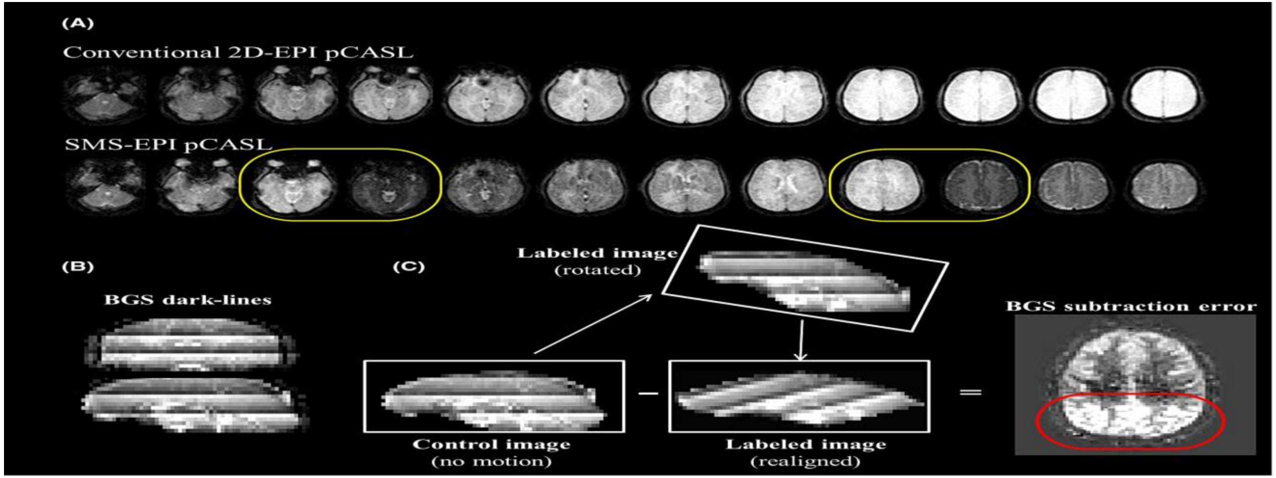




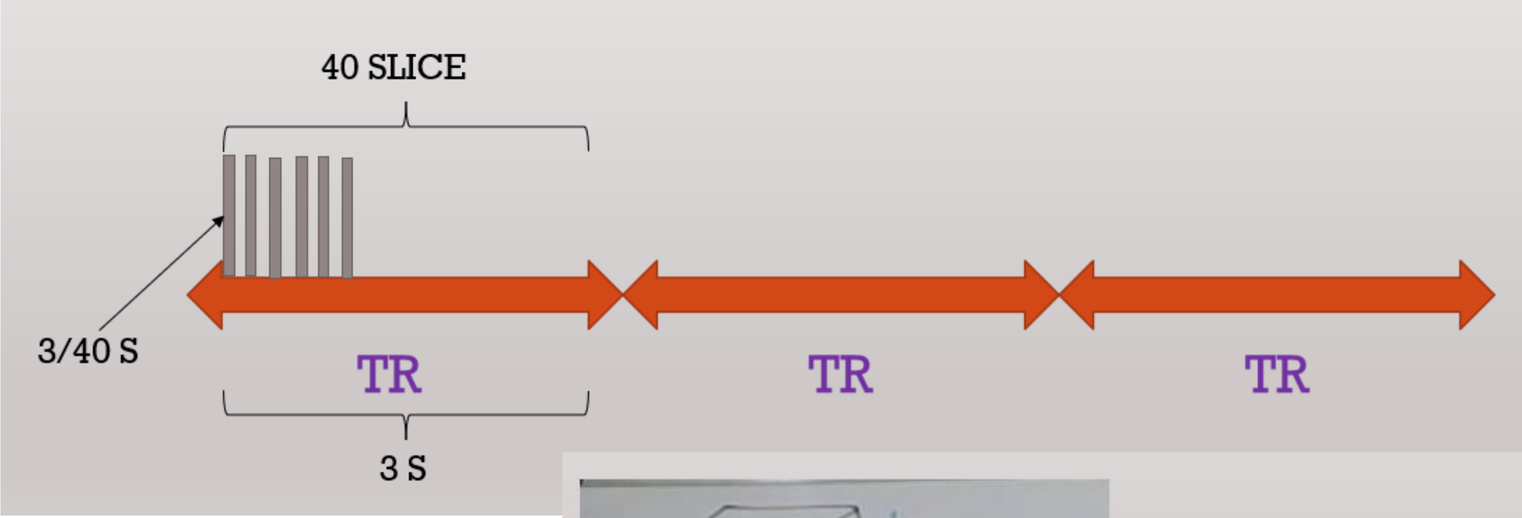


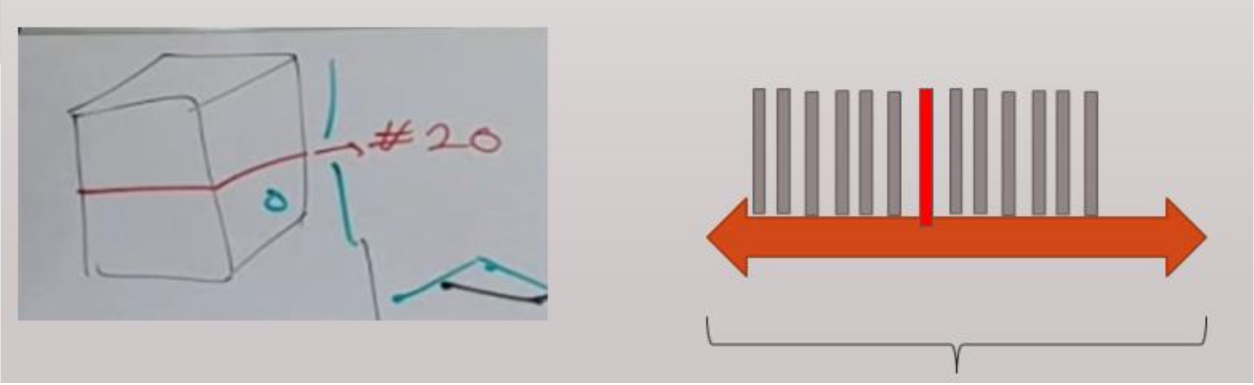
Some Image Processing Steps

1- Slice Timing
2- Motion Correction (Realignment**)**
3- Normalization (Registering the brain images of different people together)
4- Coregistration (Registering of functional and structural images)



SLICE TIMING CORRECTION





Motion Correction

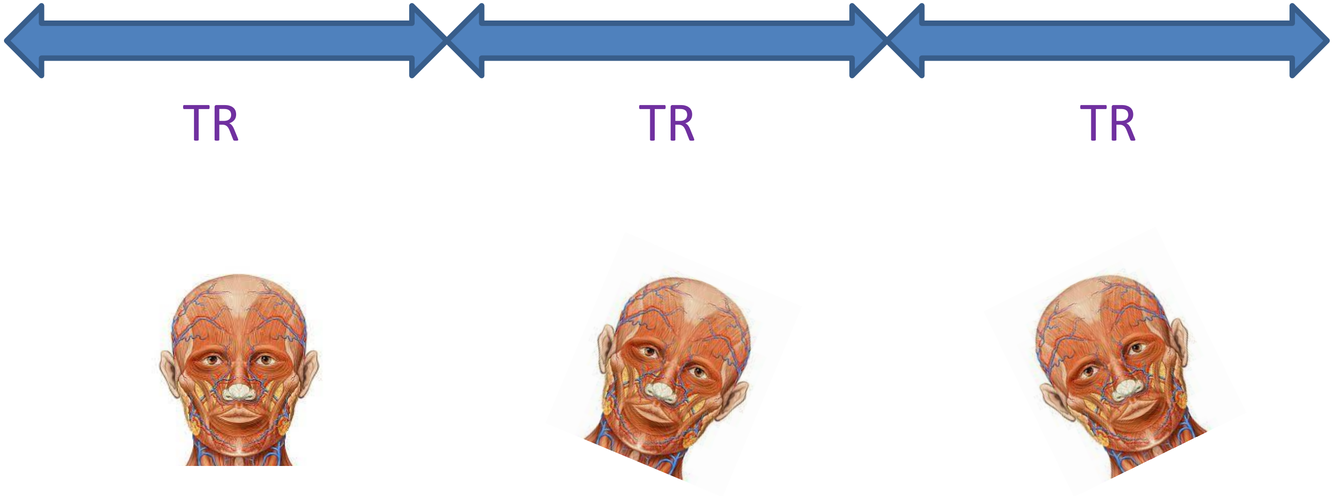
Prevalence of motion in fMRI images (even in the best participants)

In general, two types of motion may occur in imaging:

The first mode is related to a movement that has a very long period of time, that is, the period of time that the person's head is moving or rotating is relatively long, that is, from the first time that the head starts to move, the data may still be there, for example, a minute later, be in motion.

Motion Correction

- Rigid Body Transformation
- Reference or standard volume



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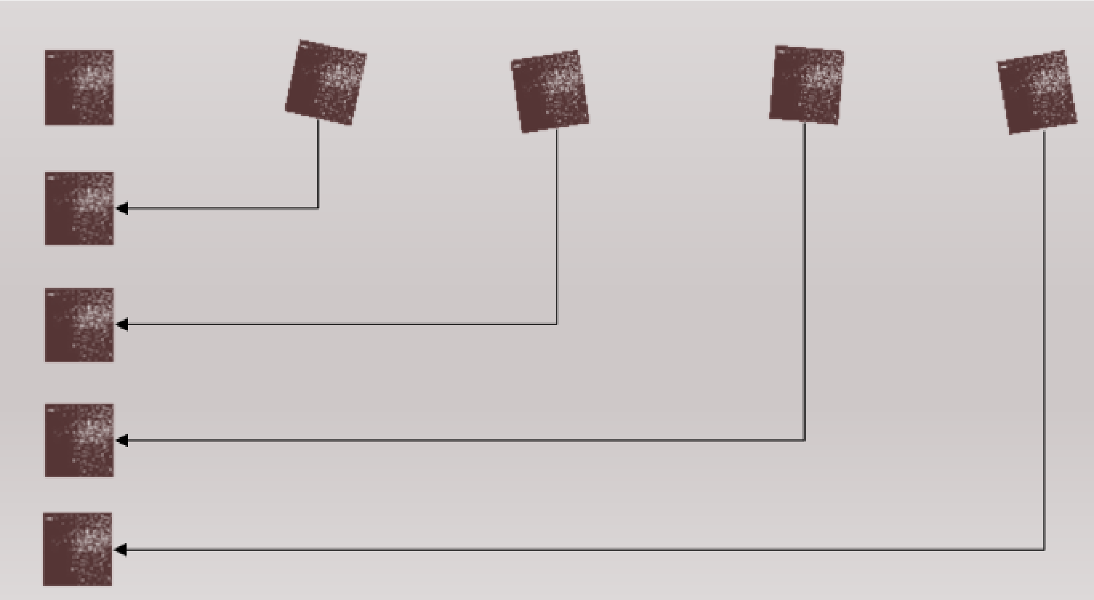
Motion Correction

-It is called **realignment**: This name is because, after motion correction, all volumes of MRI data are aligned and coincide.

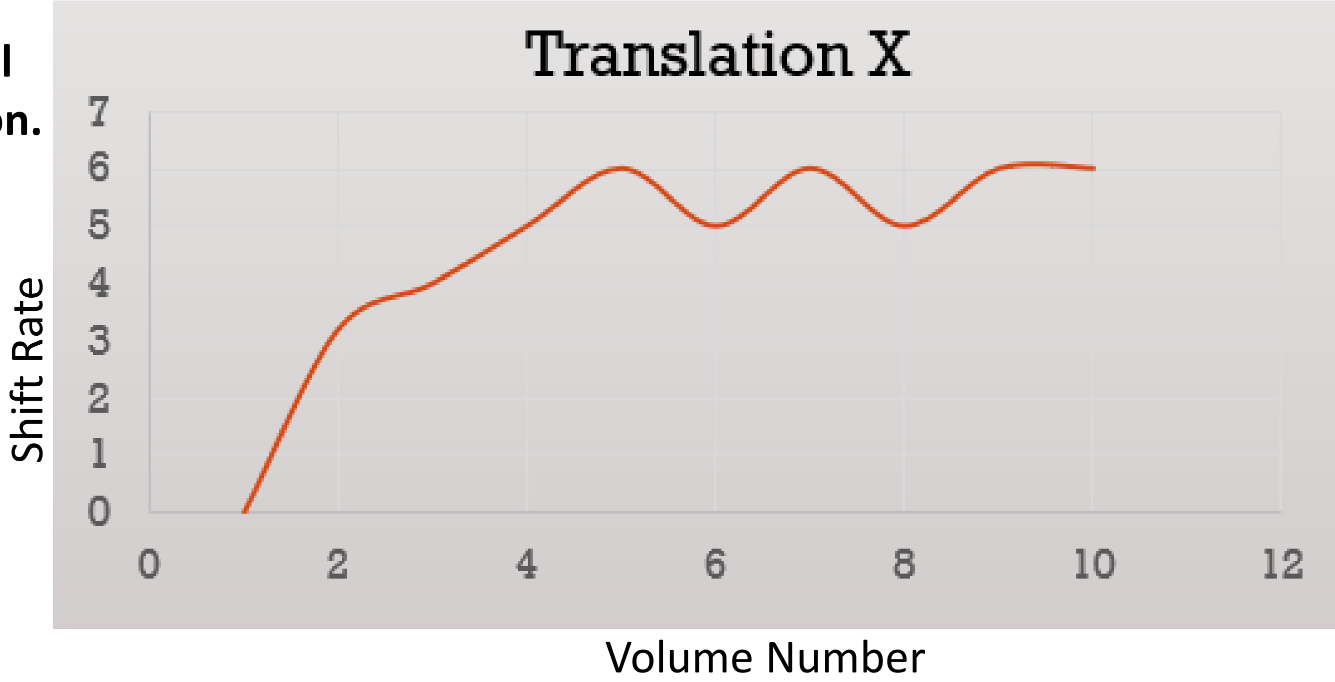
-Six degrees of freedom:
Translation (X, Y, Z)
Rotation (X, Y, Z)

If only 6 degrees of freedom are sufficient to transfer and align two images together, that image transfer method is called a **Rigid** method.

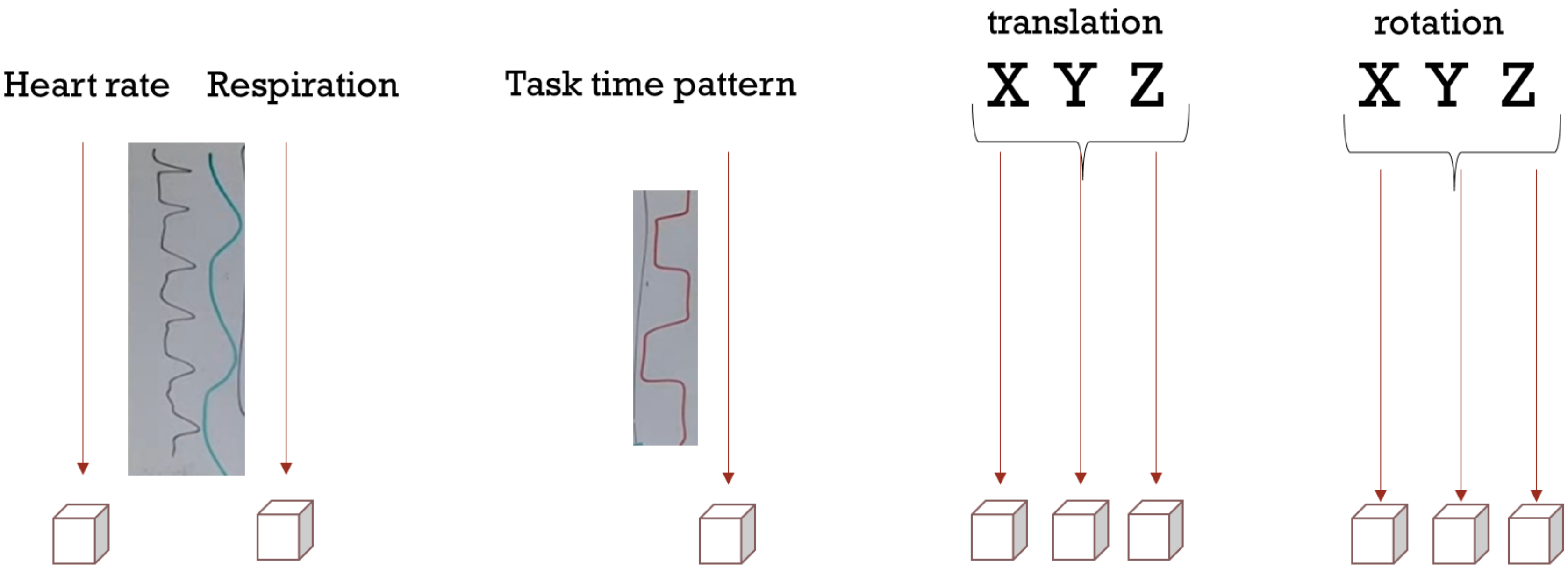


Motion Correction

Remove single volume or all volumes due to extra motion.

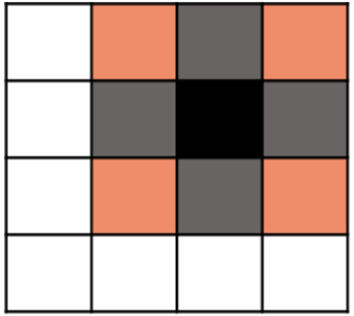


General Linear Model (GLM) Analysis



Spatial Smoothing

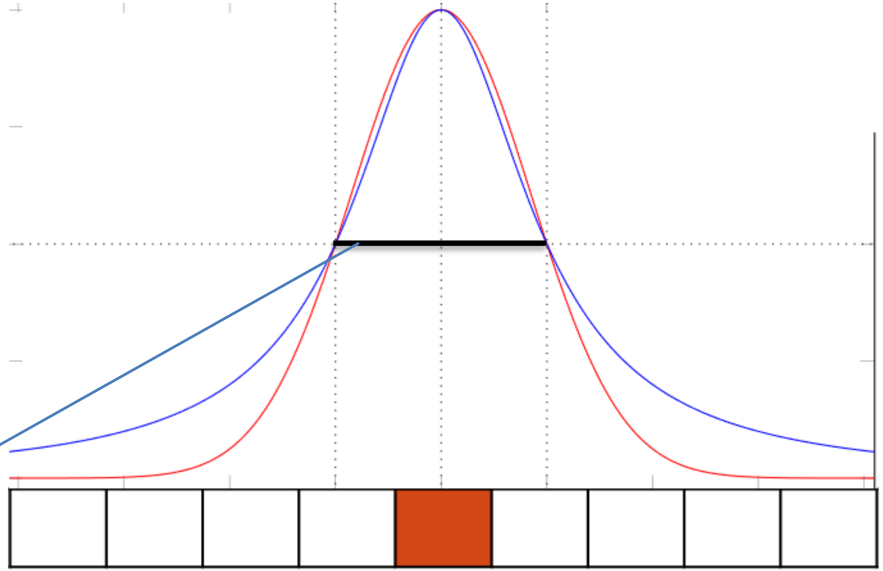
Increases SNR



Common surface = 1

Common side = $1/\sqrt{2}$

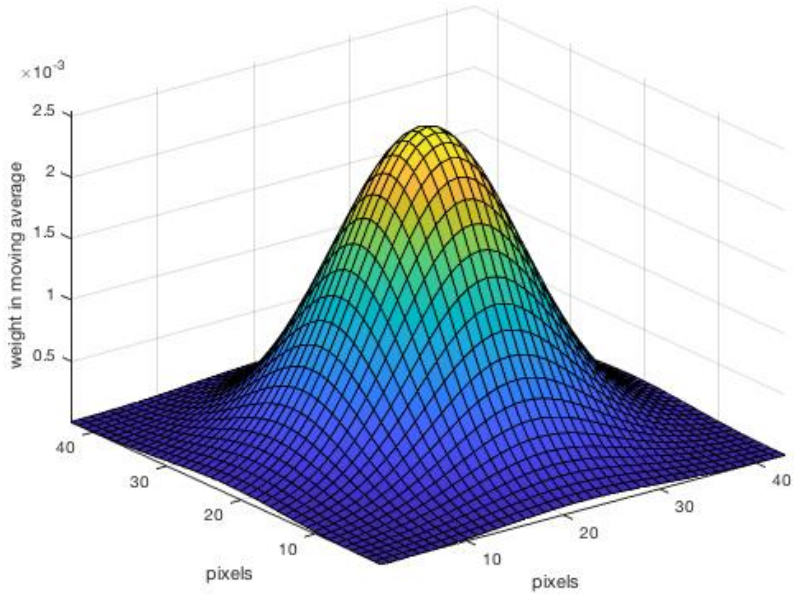
Common corner = $1/\sqrt{3}$



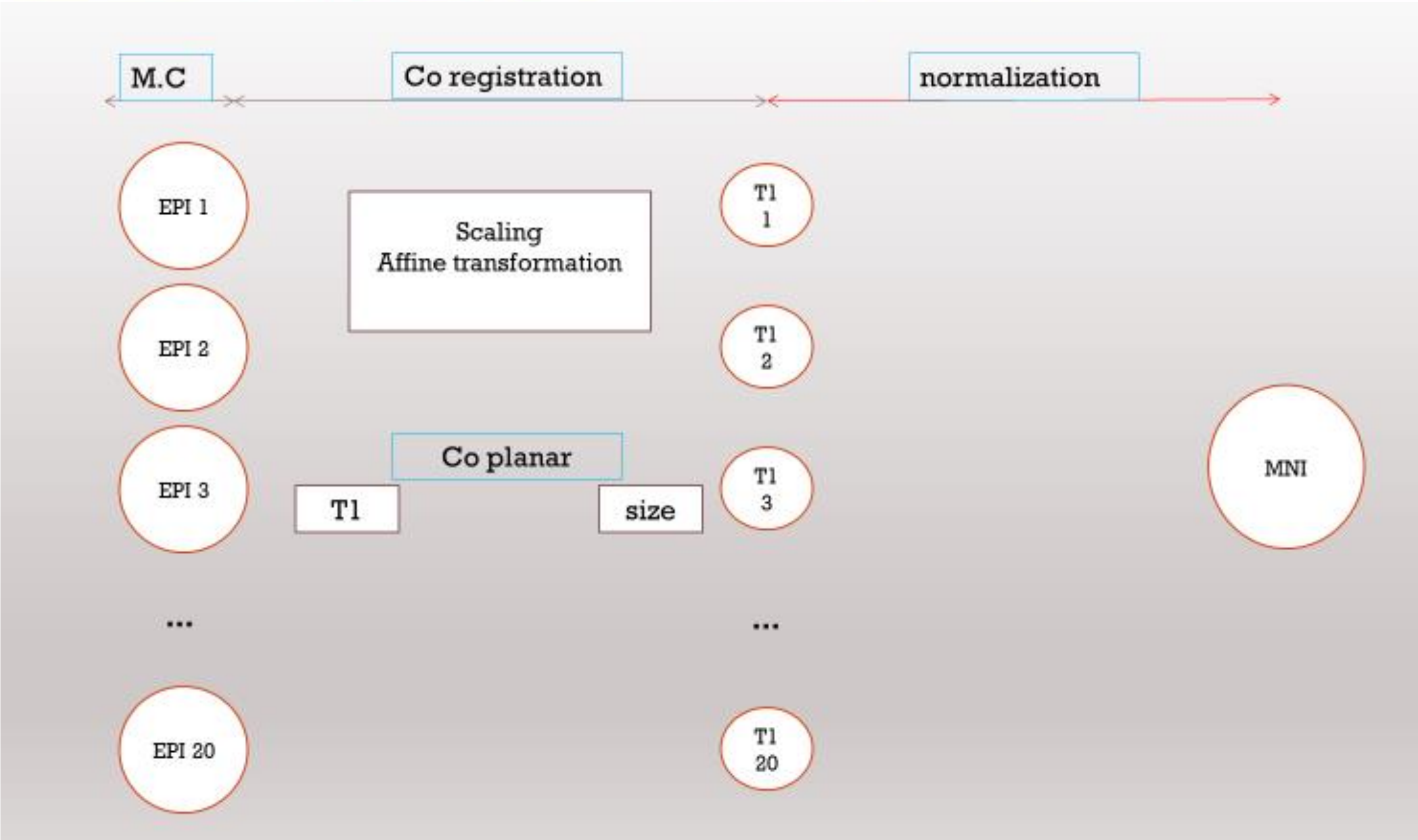
The optimum amount of Full-Width at Half Maximum (FWHM) is 1-3 pixels

Spatial Smoothing

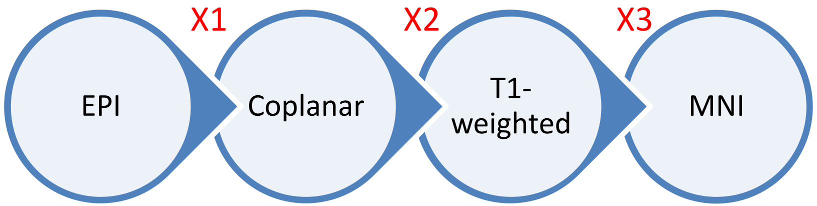
In practice and in reality, we will have a 3D Gaussian function applied to 3D data.
for each voxel to 26 adjacent neighboring voxels on a level, on an edge, or in a corner

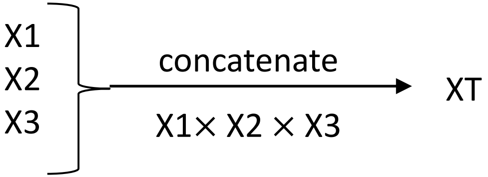


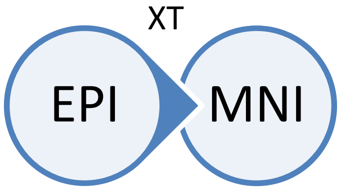
Coregistration and Normalization



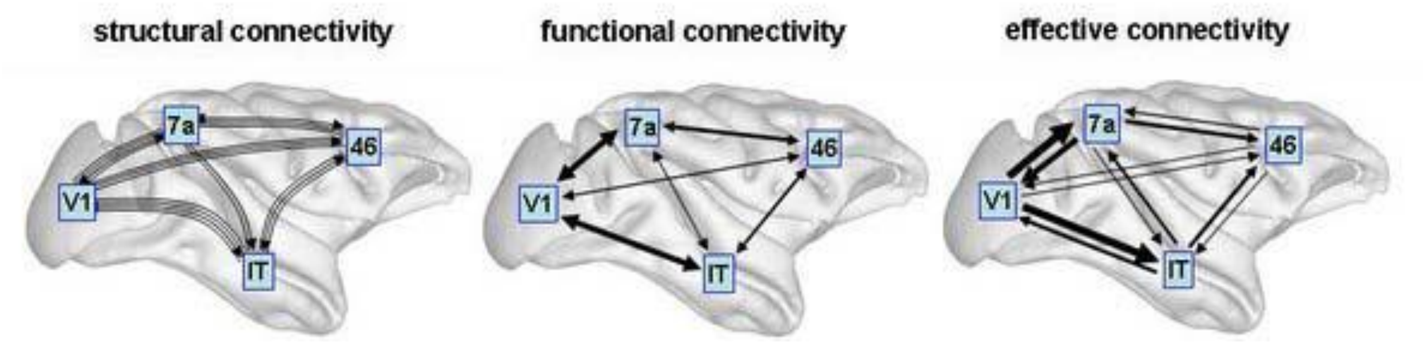
Coregistration and Normalization







Functional Connectivity Vs Effective Connectivity



- **anatomical/structural connectivity** = presence of axonal connections
- **functional connectivity** = statistical dependencies between regional time series
- **effective connectivity** = causal (directed) influences between neurons or neuronal populations

fMRI Tasks designs

Some Questions to Ask

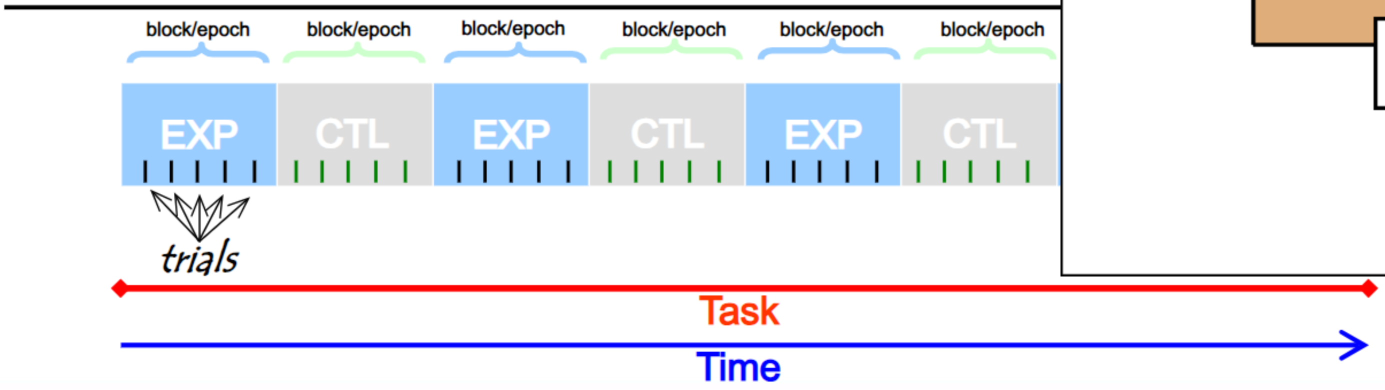
- Does the task tap (e.g., angry faces) or induce (e.g., hard math questions) the process of interest?
- Are the component processes of the task known? (e.g., attention, memory, emotion, executive)
- Does the task have a good control condition (s)?
- Is the task appropriate for the population of interest?

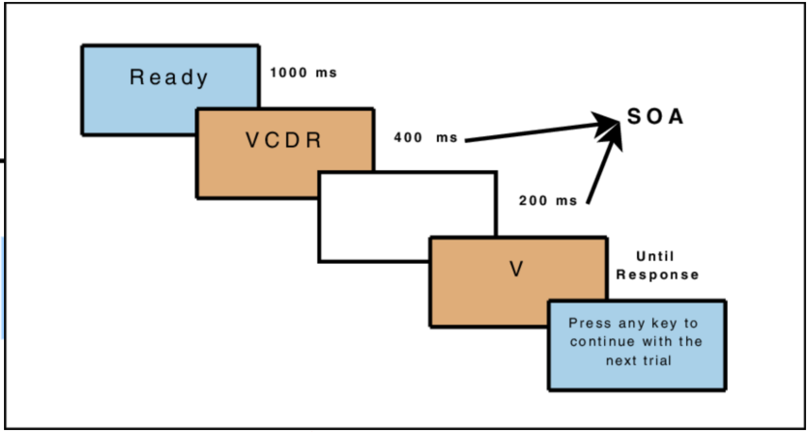
Terminology

Task: A task (includes experimental and control conditions)

Block or epoch: A time interval containing trials from one condition

Trial: A specific single event in a task





Design Types

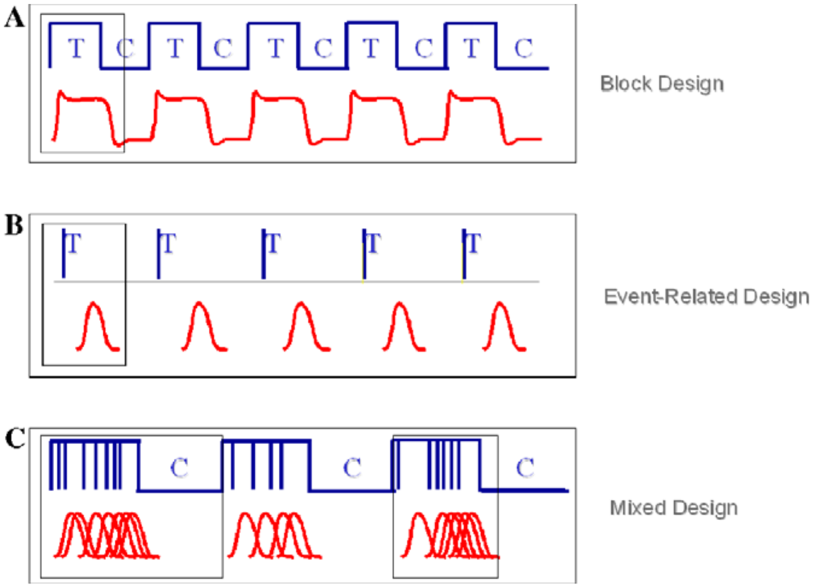
Three main fMRI task design types:

- blocked
- event-related (ER)
- mixed

Each design type has advantages and disadvantages

Choice can depend on:

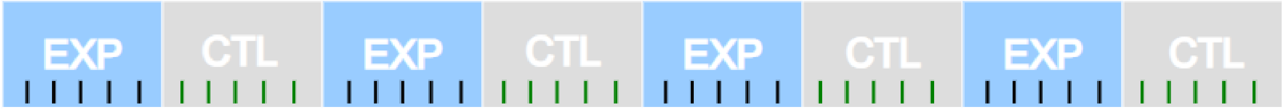
- nature of task (is it amenable to an ER design?)
- experimental hypothesis (e.g., transient response: ER)
- expected brain response (e.g., long HDR recovery, Bloc

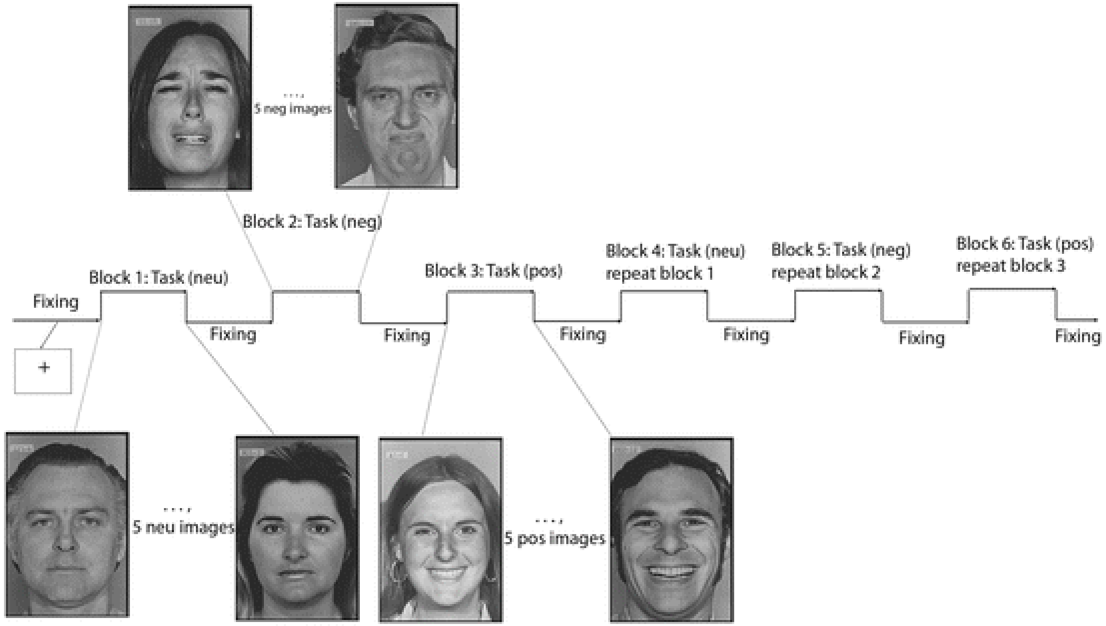


Blocked Design

The simplest and first of the design types

Two or more conditions (experimental or control)





Blocked Design Considerations

- Simple alternating design (Task – CTL – Task – CTL) great to find condition differences, but can't tell if any activation in both or just one condition
- Null-Task blocks (i.e., resting) can be used to find activation common to conditions or specific to a condition
- Duration of task may affect task difficulty
  - consider fatigue and practice effects
  - duration of epoch may impact task difficulty (e.g., WM)

Blocked Design Considerations

- Epochs should be of equal length, especially if only 2 conditions

- If more than 2 conditions, and want to combine conditions, then condition 3 may need more trials/greater duration to be comparable (e.g., combine task 1 and task 2 compared to null epochs, 1 3 2 3 2 3 1 3 2 3)

- More but shorter (not too short) epochs may be better than less but longer epochs

  - Potentially get rid of epochs with too much artifact (e.g., motion)

  - ↓ length + ↑ task frequency = ↓ noise = Increase BOLD Signal

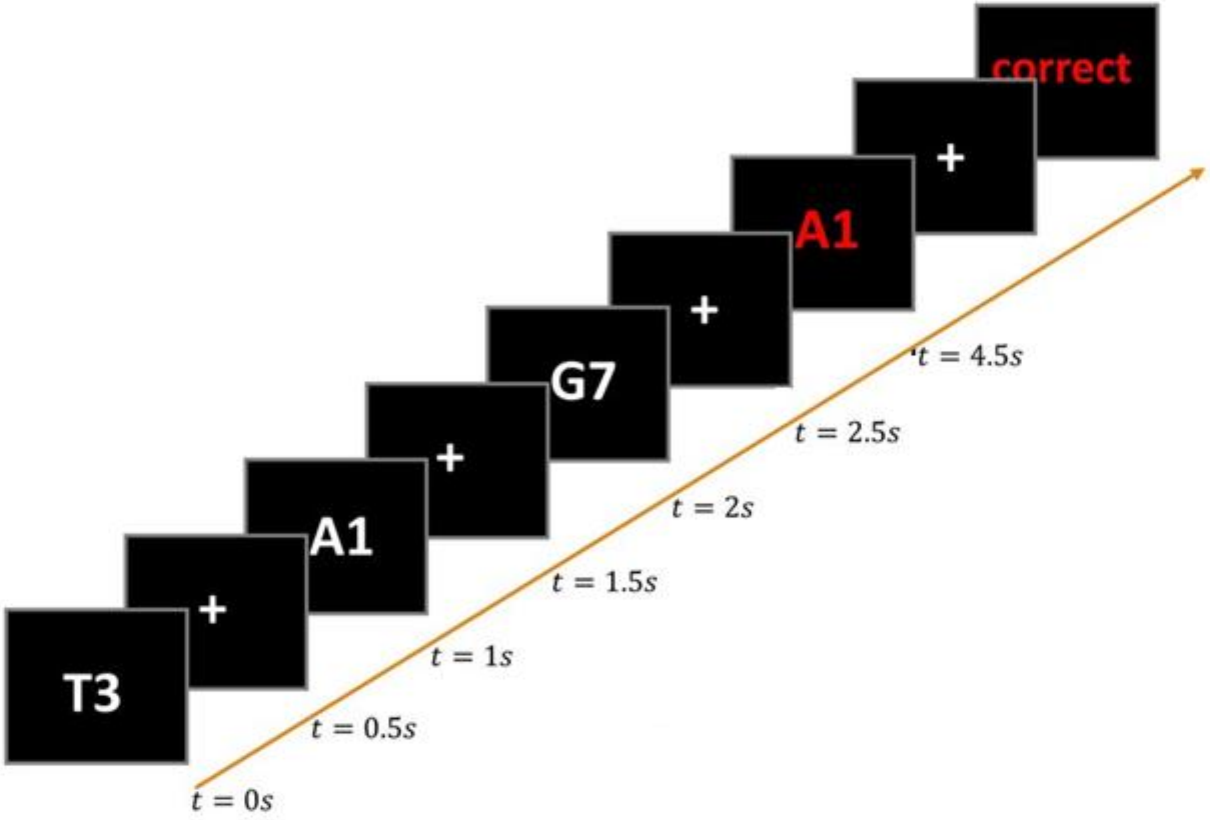
  - Greater frequency of epochs also reduces impact of scanner drift associated with hardware (e.g., slight changes in magnetic field)

Blocked Design: Good or Bad

Very good at detection BOLD signal of effect if present, regardless of shape of HDR

But, relatively insensitive to shape of HDR and can’t estimate time course of activation in voxels (because of superposition, the summation of HDR to each stimulus

Event Related Design



Event Related Design Considerations

- Based on assumption that neutral activity occurs in short and discrete intervals
- Epoch in ER design refers to time segment usually time locked to stimulus or around stimulus for a single trial
- Randomized order to stimuli helps reduce expectation and can increase BOLD even at short ISI
- Faster ISI gives more trials so more variance thus more power, but too fast not good to estimate time course of individual trials (signal saturates early on)

Event Related Design: Pros and Cons

- Good for estimation shape and timing of HDR, helps infer timing of neural activity, discriminate between component processes (e.g., encoding, maintenance and recall in WM task)

- ER designs more flexible than blocked, can be analyzed in more ways (e.g., stimulus- or response- locked, accurate versus inaccurate recall)

- Major con is less power than blocked design

Mixed Designs

- Stimuli presented in discrete blocks, but each block has multiple event types.

- Allows analysis of “blocks” to measure steady-state responses (i.e., assumed sustained activity across stimuli, like attention).

- Also can look at “item related processes” as in an ER analysis

Additional Considerations

- Get as large sample size as possible
- Arrange timing of stimuli to maximally evoke process of interest (e.g., continual engagement of a process)
- Arrange timing intervals so that processes are minimally correlated (variable ISI and ITI timing can help)
- Collect behavioral data whenever possible (shows subject is attending, test models, etc.)

Additional Considerations

- Careful in selection of control conditions (minimize confounds):
  - Understand what process you are trying to isolate.
  - Stimulus characteristics (color, brightness, size, etc.)
  - Control for correlated but not necessarily of interest variables (e.g., familiarity with stimuli, difficulty level)
  - If you don’t know expected effect size, collect as much data from subjects as possible.

- Rapid succession of events increases HDR
- Occurrence of one stimulus does not predict (correlated) with the occurrence of another, so better estimate shape of HDR better.
- Better sampling of HDR
- Reduces subject ability to predict what will occur (which could induce unwanted strategy use, reduce expectancy and outcome processing effects desired)

Population of Interest

Is the task appropriate for the population studied?

- Sensory and motor demands (e.g., visual WM stimuli for patients with MS and optic neuritis)
- Complexity of task requirements (e.g., instructions very complex, too much shifting set)
- Duration of task (e.g., in ADHD kids too long may confound attention with other process of interest)
- Age appropriate (consider developmental stage)

Clinical Applications of fMRI

Since its discovery, fMRI has been applied to the study and treatment of a wide range of neurologic disorders. Functional MRI has shown great utility in identifying the anatomic location corresponding with specific motor, somatosensory, language, and cognitive processes.

Clinical Applications of fMRI

- **Presurgical Localization:** fMRI is used to locate critical functional regions before surgery, making neurosurgery safer and more comfortable. This includes hemispheric lateralisation of language and memory functions prior to temporal lobe epilepsy surgery and the localisation of eloquent cortex to guide focal excisions.
- **Evaluation of Therapeutic Strategies:** fMRI is used in the evaluation of new therapeutic strategies, especially in neurorehabilitation.
- **Drug Development:** Pharmacological fMRI (phMRI) may be an important future area. It can be used for human target validation, defining potentially efficacious dose ranges for new drug candidates, and for the differentiation of new medicines.
- **Neurodegenerative Diseases:** Research applications of fMRI and PET are extending the role of imaging in the early detection of neurodegenerative diseases, particularly Alzheimer's disease, differentiation of dementia subtypes, and detection of pre-clinical Parkinson's disease.

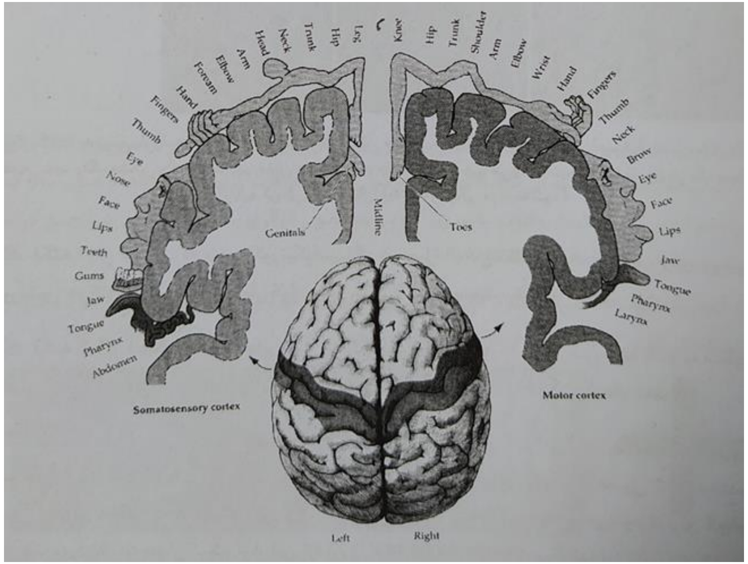
Presurgical planning

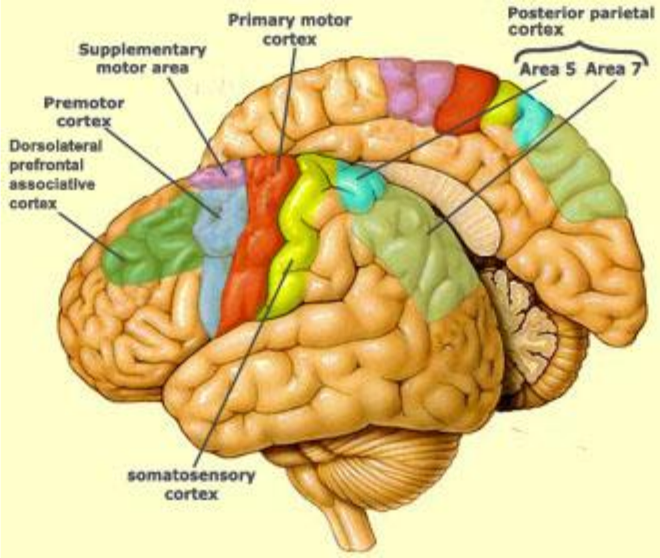
Surgeries performed for Rolandic area lesions may result in serious impairments in sensory and motor function.

To prevent this case and to minimize the damage caused to people, functional imaging is used to perform motor or sensory tasks.

The purpose of this work is to detect and localize the primary motor cortex, which is the lesion around the Rolandic sulcus.

The primary motor cortex is located in front of the Rolandic groove (Central Sulcus). Different parts of this cortex are related to the movement of different parts of the body. According to the spread of the tumor, different tests can be chosen to evaluate and localize the primary motor cortex.





Movement tests that are performed to localize the movement of the cortex include hand movement, leg movement, lip movement, and tongue movement.

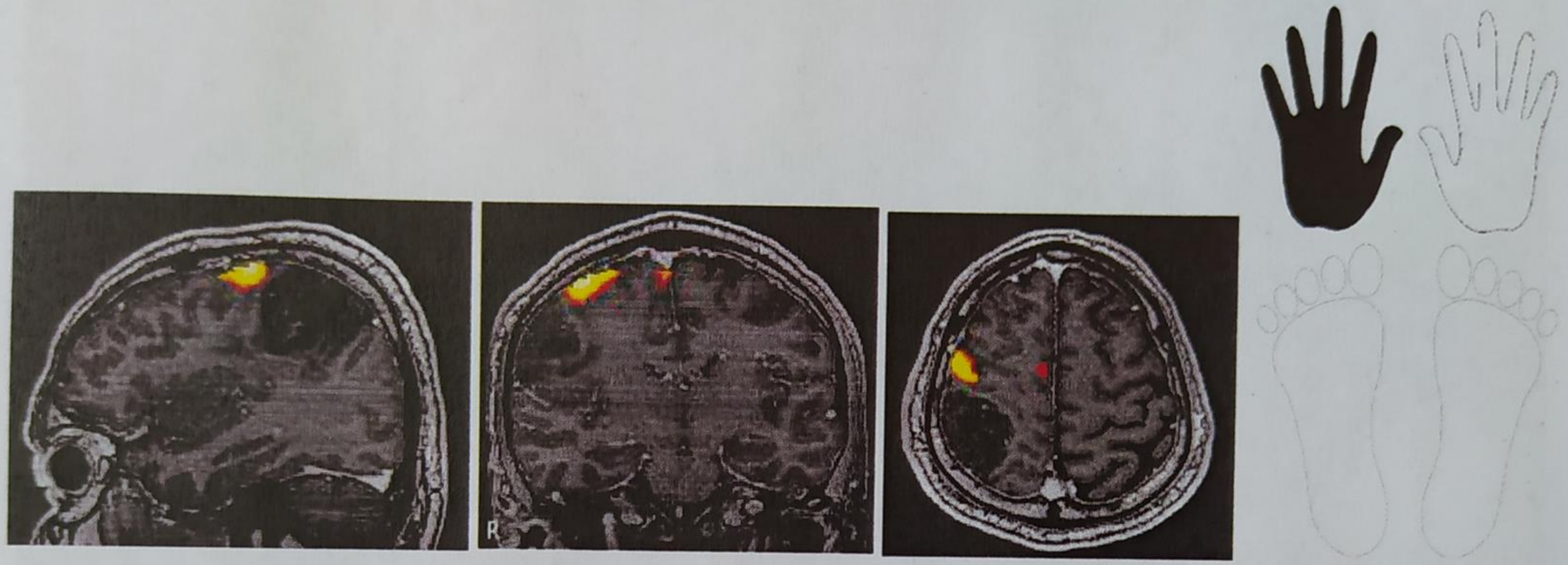
Hand movement test

If we divide the motor cortex on the outer surface of the brain into 3 areas, the middle part is related to hand movement.

The space related to the movement of the thumb is larger than other fingers and the neurons in this area have a lower stimulation threshold for the movement of the thumb.

Therefore, in the movement test to localize the movement area of the hand, the patient is asked to bend and open his thumb when he sees the image of the hand.

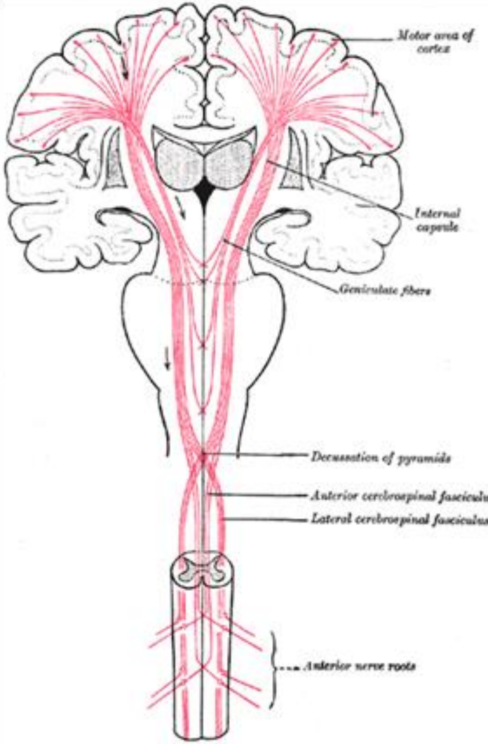
Hand movement test



Note 1: Since the corticospinal pathway intersects in the medulla, the patient is asked to move the opposite hand to check the motor cortex of each hemisphere.

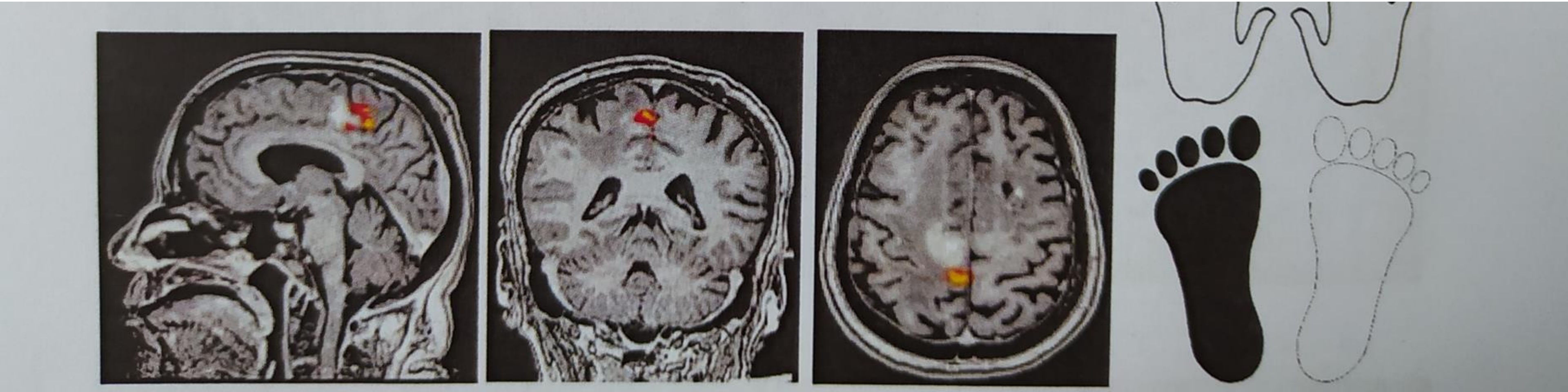
Note 2: If the lesion has caused excessive displacement or destruction of the motor cortex, the patient is asked to perform the test on both hands at the same time in order to compare with the opposite side.

Note 3: If the patient is unable to move the hand, which can be due to the compressive effect of the lesion, the destruction of the functional area due to the lesion, or the destruction and compressive effect on the nerve fibers transmitting the movement command: In order to distinguish between these factors, the patient's companion is asked to help the patient perform the desired movement, this test is called passive motor task.



Foot movement test

The motor cortex related to the foot is located on the inner side of the hemispheres.
In order to localize the movement area of the feet, the patient is asked to bend and open the toes in accordance with the test and observing the image of the foot.
In the movement of the legs, to check each hemisphere, the leg movement of the opposite side is done.



Lips movement test

The motor vertex for the lips is located in the lower parts of the motor cortex.
In the desired test for the movement of the lips, the patient is asked to move his lips according to the training he has received before while viewing the stimulus image and then to Open smile.

Since the facial motor fibers are also called from the motor cortex to the hemisphere, in the analysis of this movement we expect that the lip motor cortex will be activated in both hemispheres.

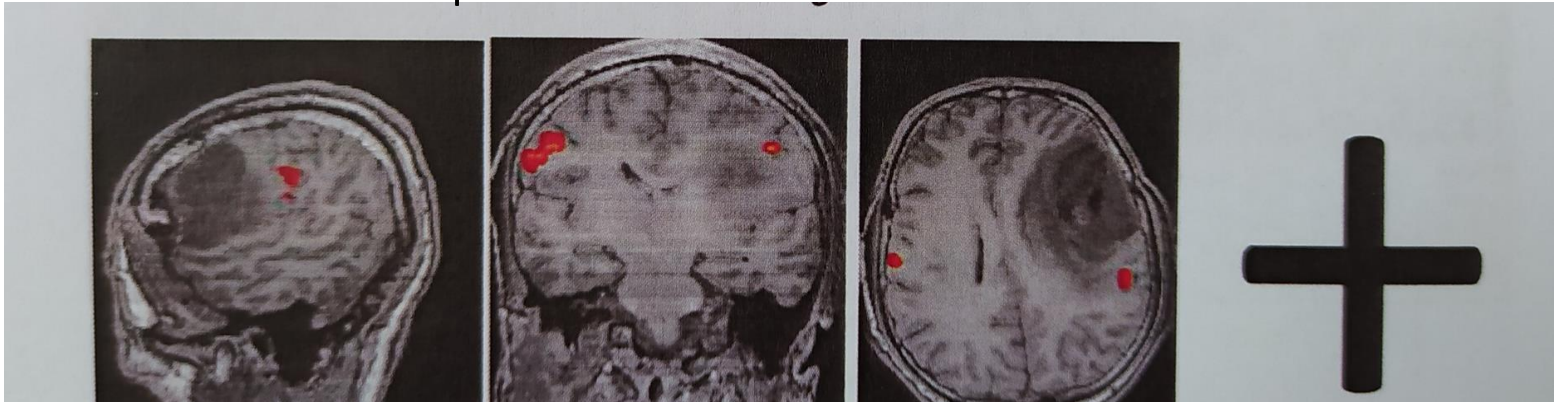
Tongue movement test

The language motor cortex is located in the lowest part of the motor cortex.

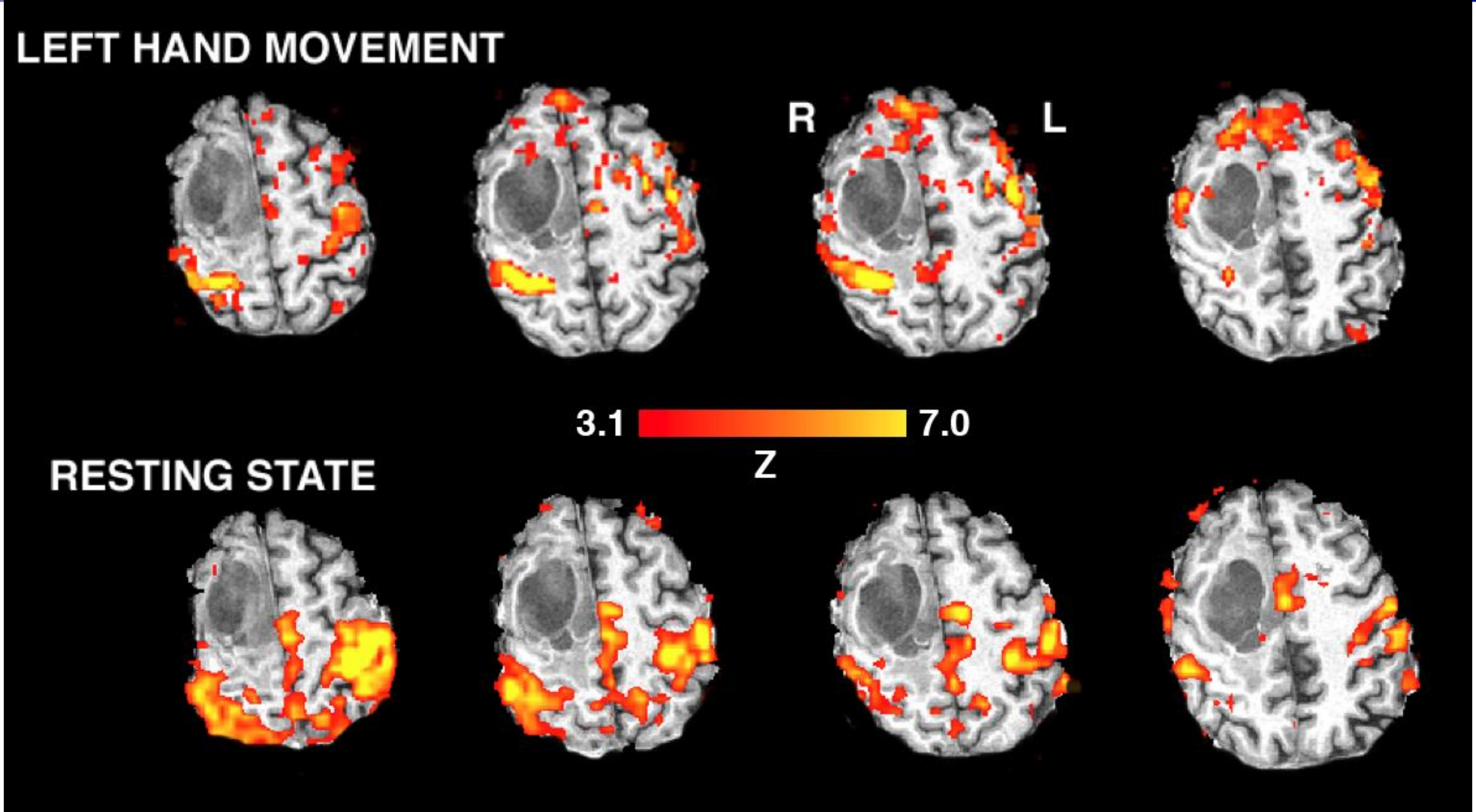
To activate this cortex, the patient is asked to stick his tongue to the roof of his mouth and then lower it while viewing the stimulus.

Because the areas of lip and tongue activity are close to each other, the patient should perform this movement with closed lips and try not to move the lips.

The motor fibers of the tongue are also called from the motor cortex of the tongue area to the hemisphere, so in the analysis of this movement, we expect the motor cortex of the tongue to be activated in both hemispheres.



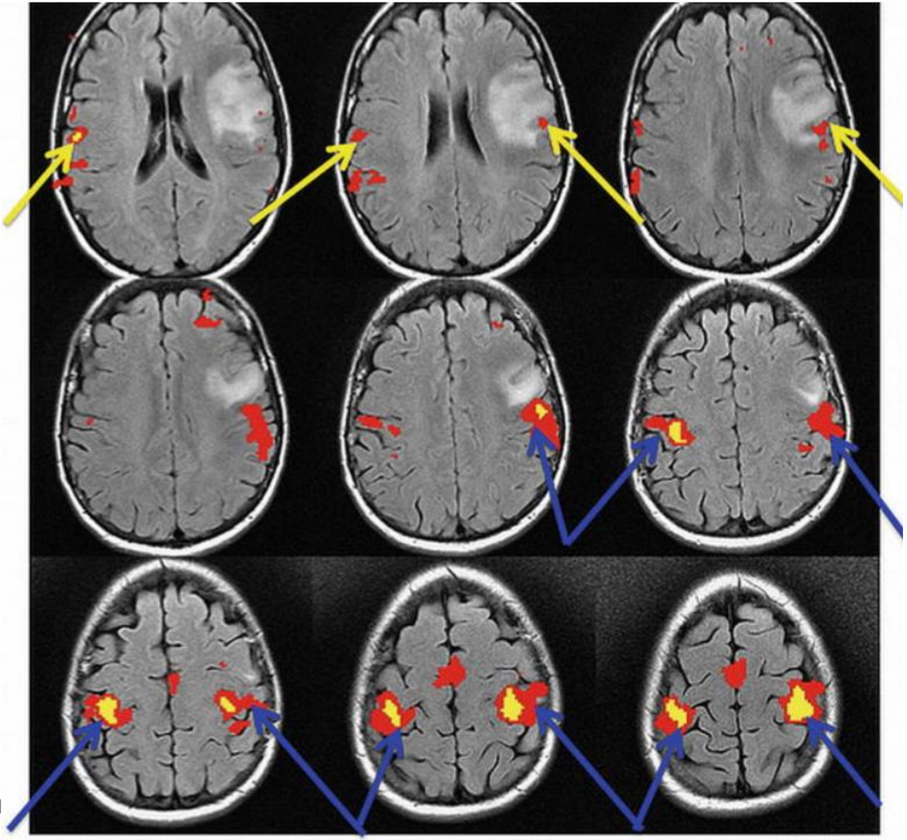
Presurgical Localization



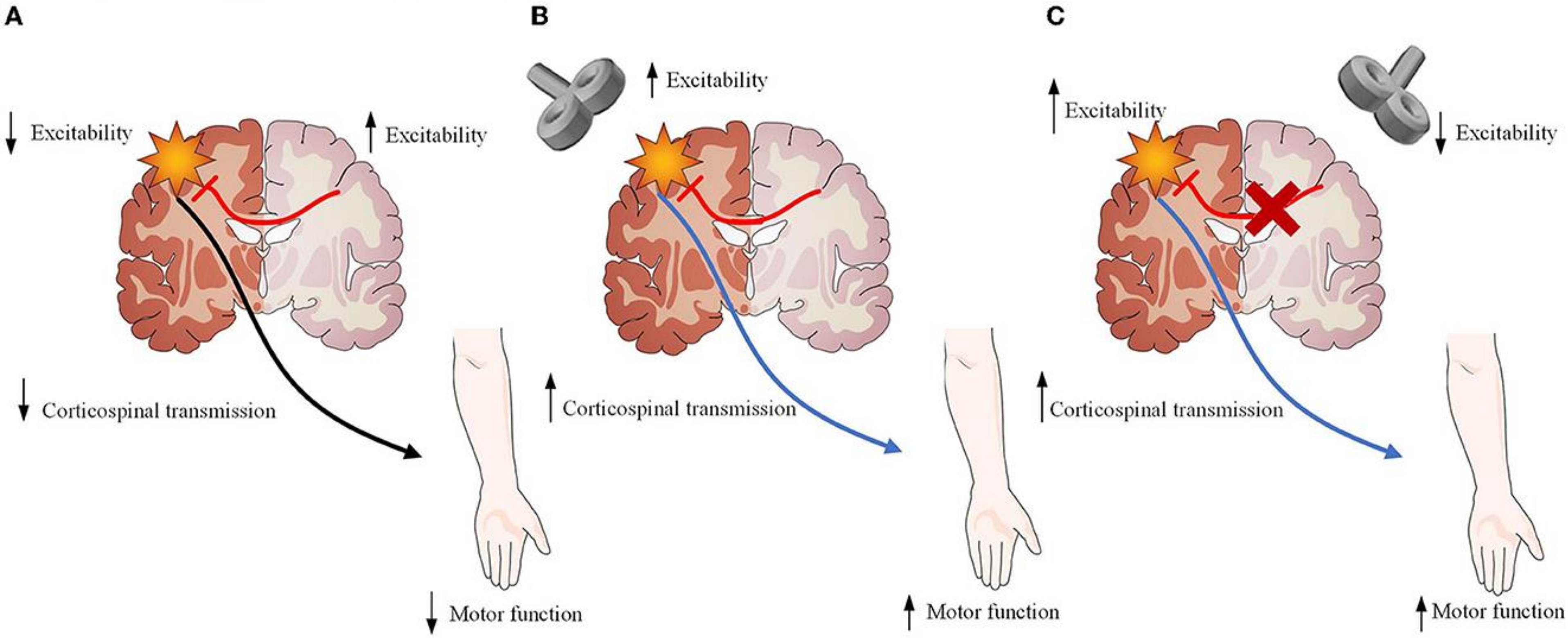
Presurgical Localization

Position of the hand (blue arrow) and tongue (yellow arrow). fMRI signals in the primary motor gyrus

Another way in which fMRI contributes significantly to motor gyrus localization is in the foot motor region. The foot motor region is located most medially just over the interhemispheric fissure. This region is often localized medial and slightly posterior to the hand motor region in the axial plane. Direct cortical stimulation (the surgeon's intraoperative gold standard for functional mapping) of this region is difficult because the sagittal sinus makes the cortex difficult to access. Therefore, fMRI localization of the foot motor region is valuable for presurgical planning.



Evaluation of Therapeutic Strategies



In a review in a previous issue of Alzheimer's Research & Therapy, Vemuri and colleagues [10] point out that the most consistent finding across previous resting-state fMRI studies of AD is decreased functional connectivity in AD patients versus healthy older controls in a posterior default mode network region composed of the precuneus and posterior cingulate cortex.

Thank you

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