MRI Lecture 9

Functional MRI (fMRI)

November 11, 2016

Overview

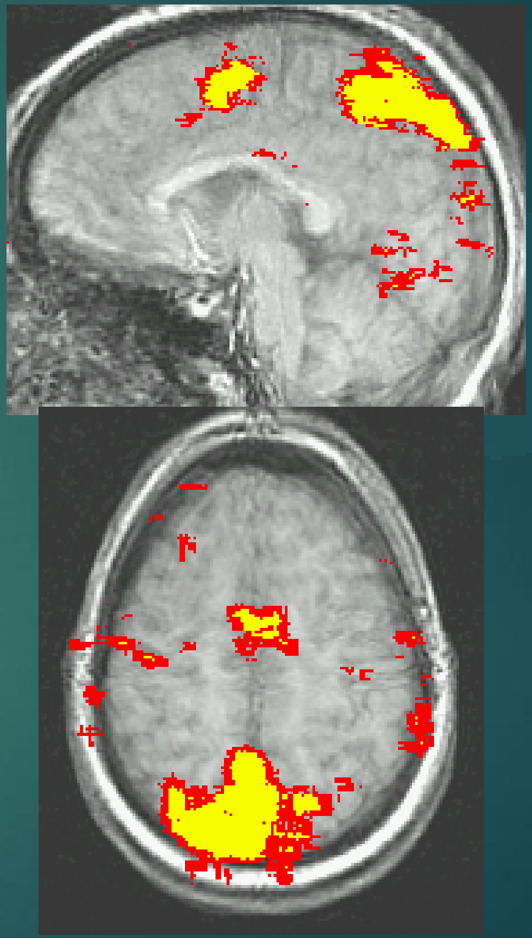
- Overview/History of fMRI
- How it Works /Basic Principles

  - The Blood Oxygen-Level Dependent Signal (BOLD)

  - How the BOLD signal is measured
- Design of experiments
- How to analyze the data
- Group analysis
- Limitations and problems

Overview of fMRI

- Developed in 1991
- Uses MR to detect changes in blood flow across functional states
- Blood oxygen level dependent (BOLD) response
- Good spatial and temporal resolution
- Completely non-invasive
- Studies are easy to implement
- Numerous applications



Activation in response to a visual inhibition task

History of fMRI

- 1990: Ogawa observes BOLD effect with T2*, blood vessels became more visible as blood oxygen decreased

- 1991: Belliveau observes first functional images using a contrast agent

- 1992: Ogawa et al, and Kwong, et al. publish first functional images using BOLD signal


Ogawa

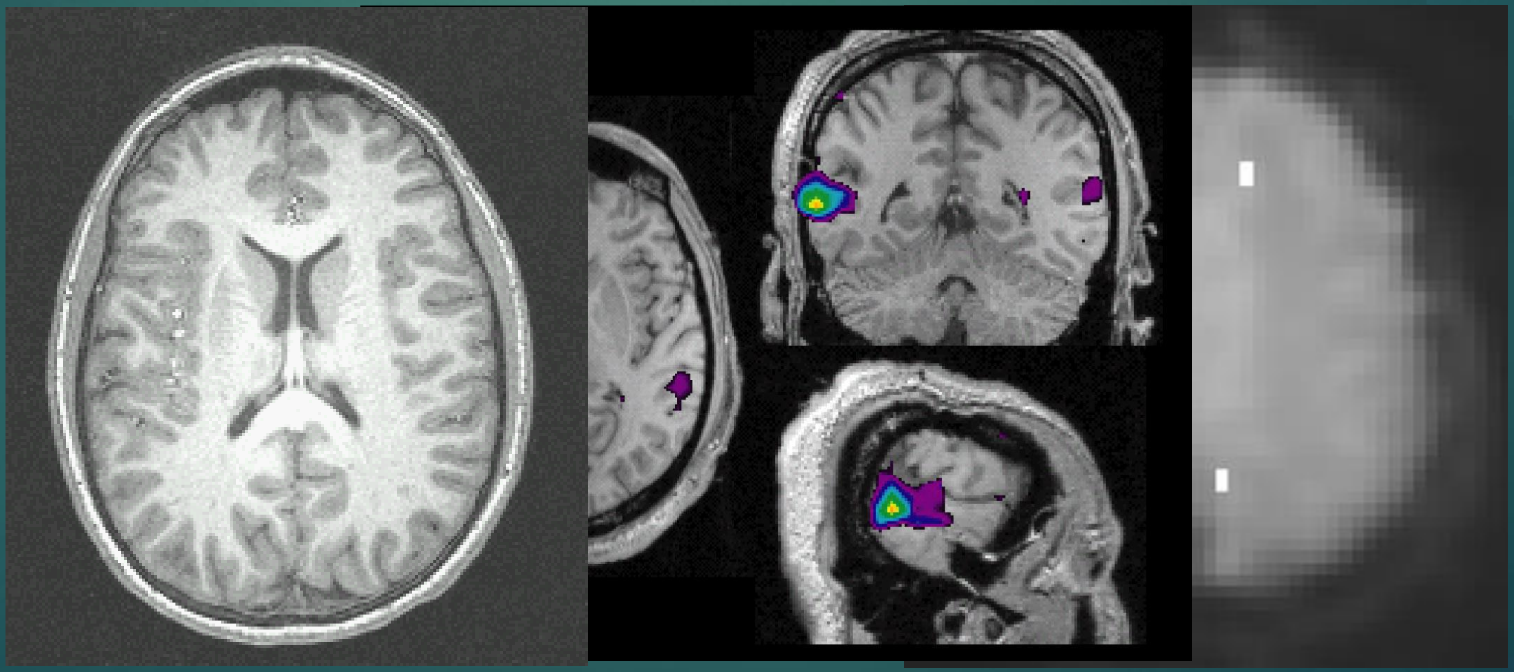
MRI

- For structure
- Signal from H+ ions (in water)
- Irrelevant functional state

fMRI

- For function
- BOLD signal
- Requires two states

From Johnson and Becker's Whole Brain Atlas 'www.med.harvard.edu/AANLIB'



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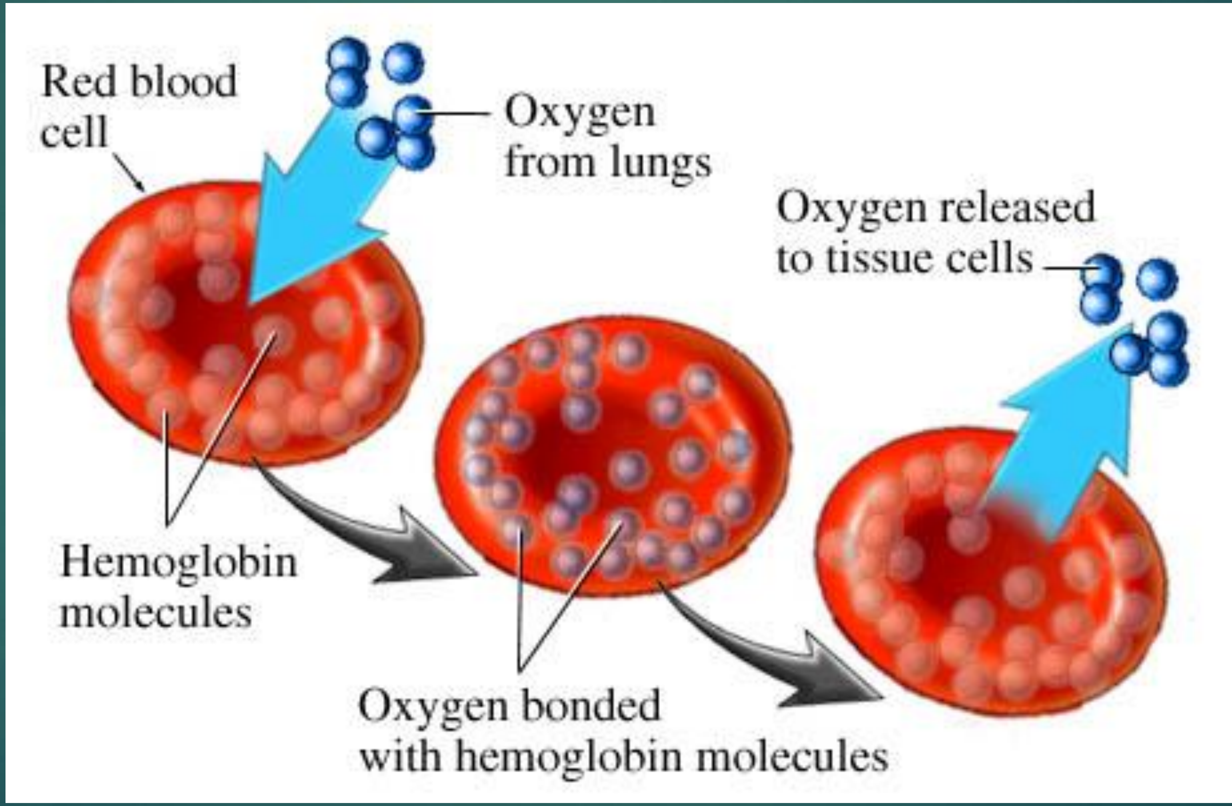
What Happens When We Think?

1. Neurons fire
2. Metabolic demand increases
3. Cerebral blood flow increases
4. Decrease in local amounts of deoxygenated blood

Oxyhemoglobin vs. Deoxyhemoglobin

diamagnetic

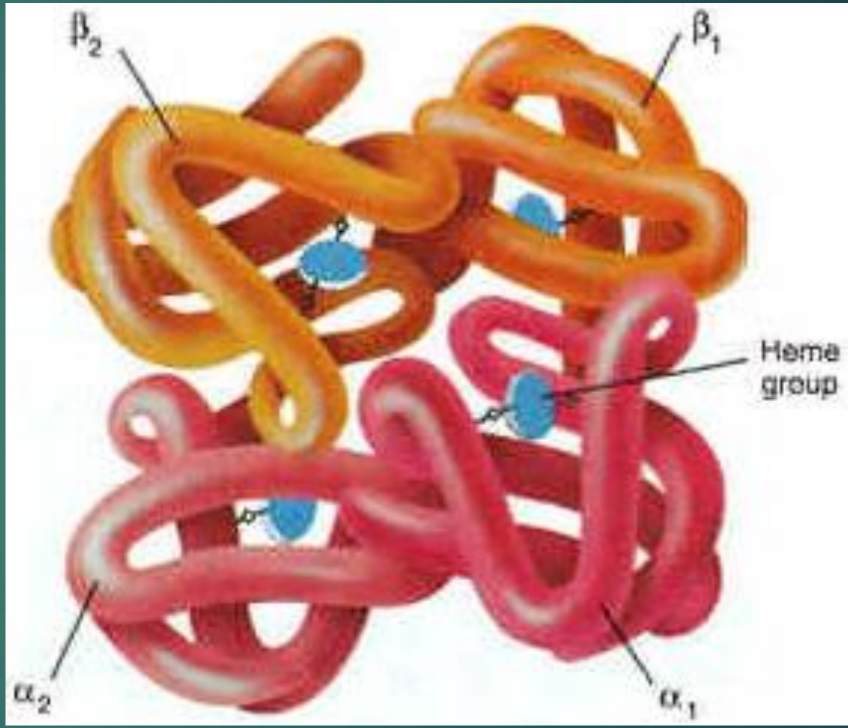
paramagnetic



http://health.yahoo.com/media/healthwise/n5551170.jpg

Deoxyhemoglobin is Paramagnetic

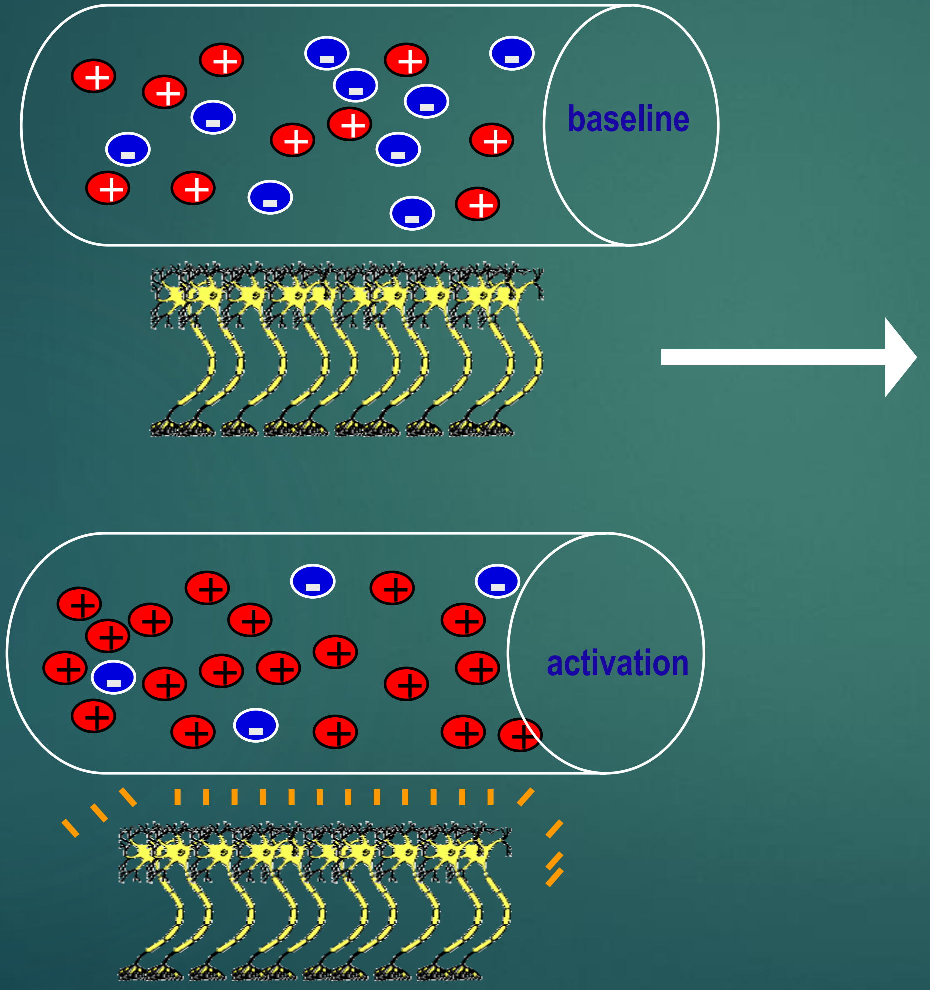
- A hemoglobin molecule consists of a porphyrin ring with a central iron atom (heme), hooked to a clump of protein called globin.
- Decreases in amounts of local deoxyhemoglobin reduce local magnetic field gradients between the blood in the capillary bed and the tissue
- Values of T2 and T2* increase locally for these "activated" regions of the brain

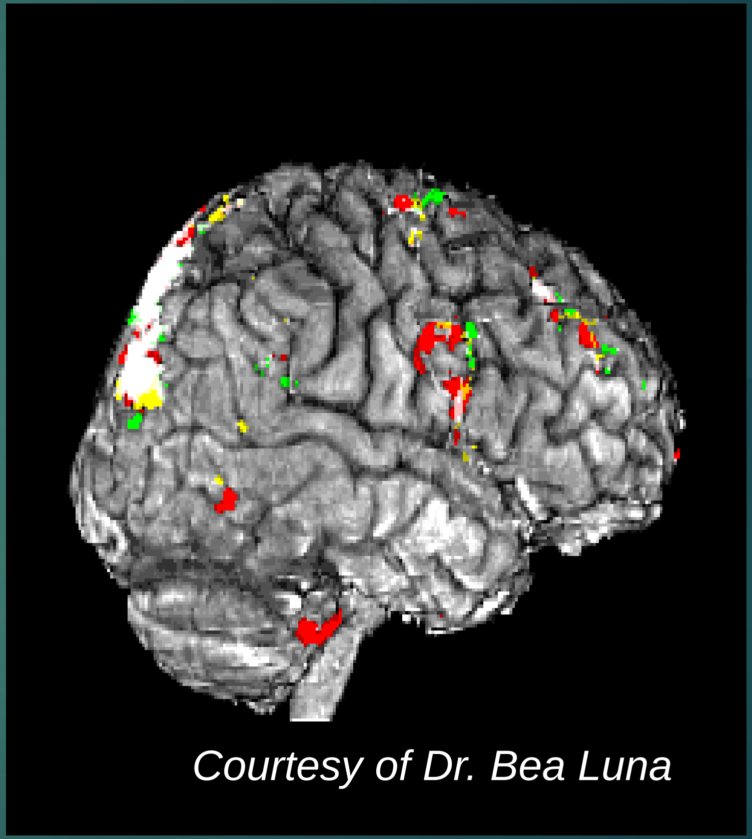


http://www.daviddarling.info/encyclopedia/H/hemoglobin.html

Blood Oxygen Level Dependent (BOLD) Signal

Neuronal Capillary Bed

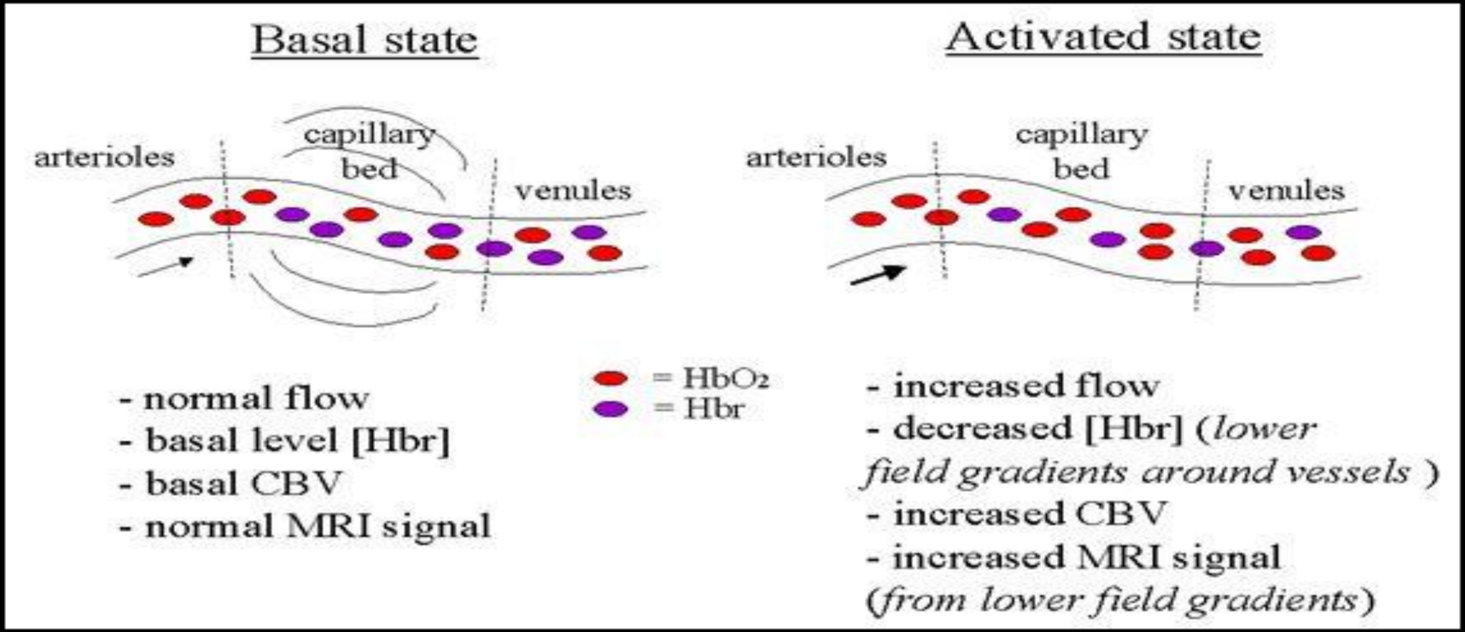


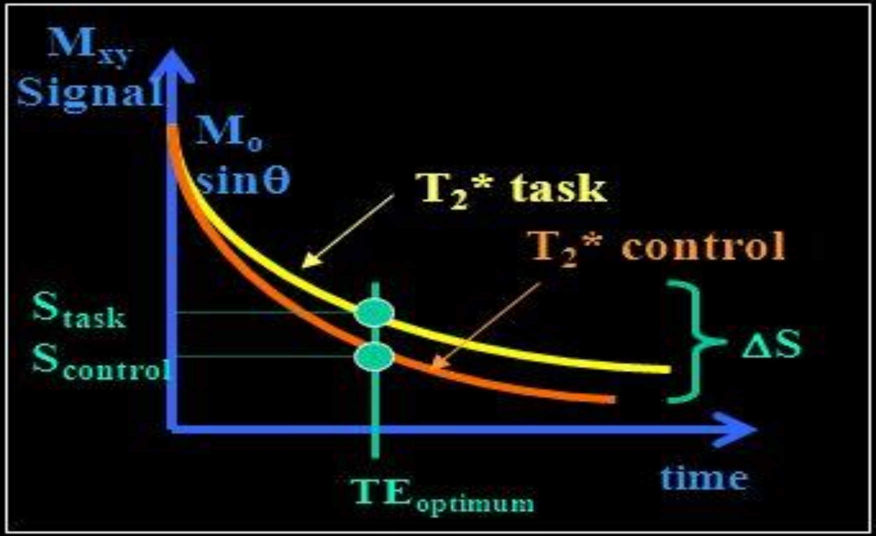


BOLD signal

Blood Oxygen Level Dependent signal

–neural activity ➔ ↑ blood flow ➔ ↑ oxyhemoglobin ➔ ↑ T2* ➔ ↑ MR signal



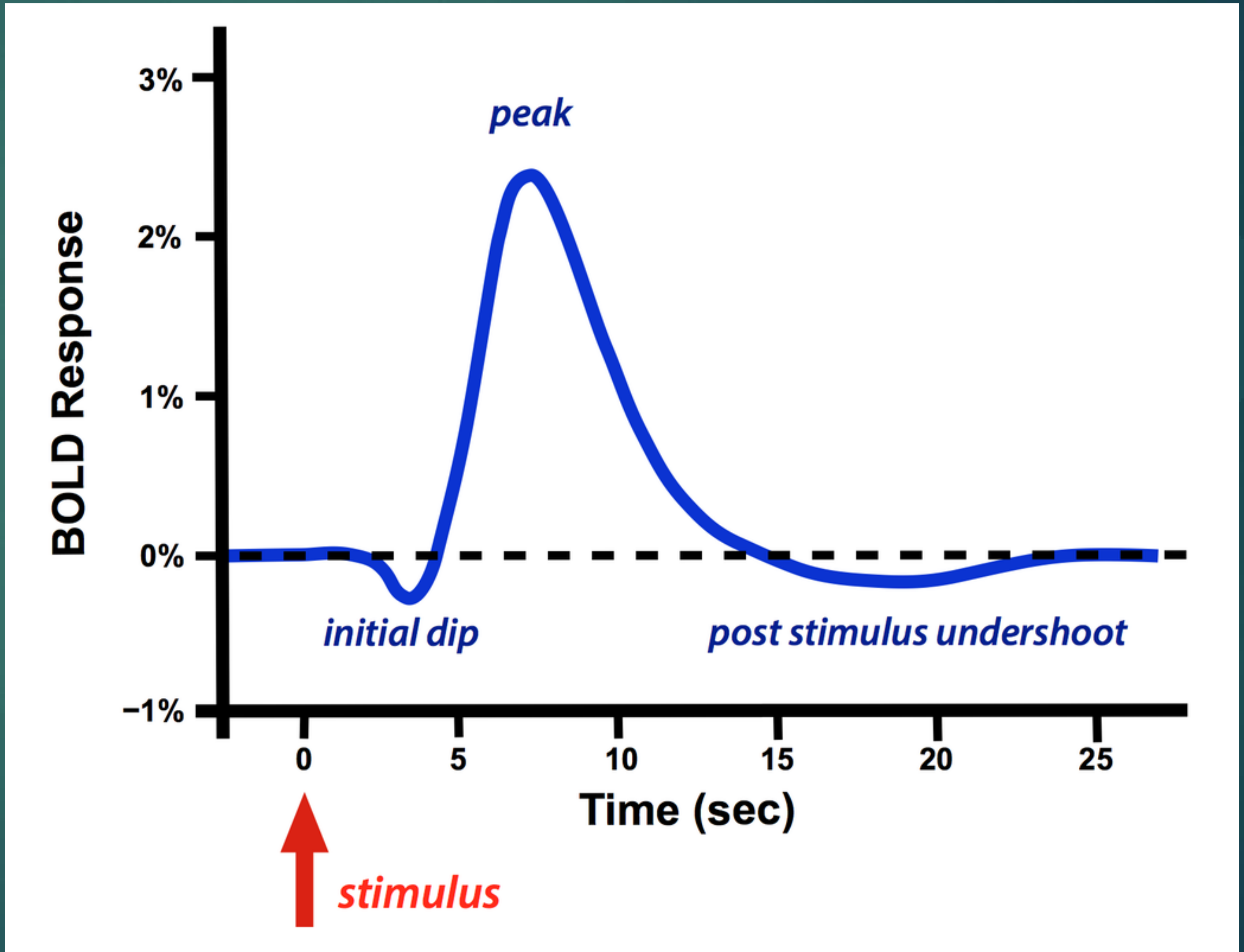


Source: Brief Introduction to fMRI by Irene Tracey

Source: Jorge Jovicich

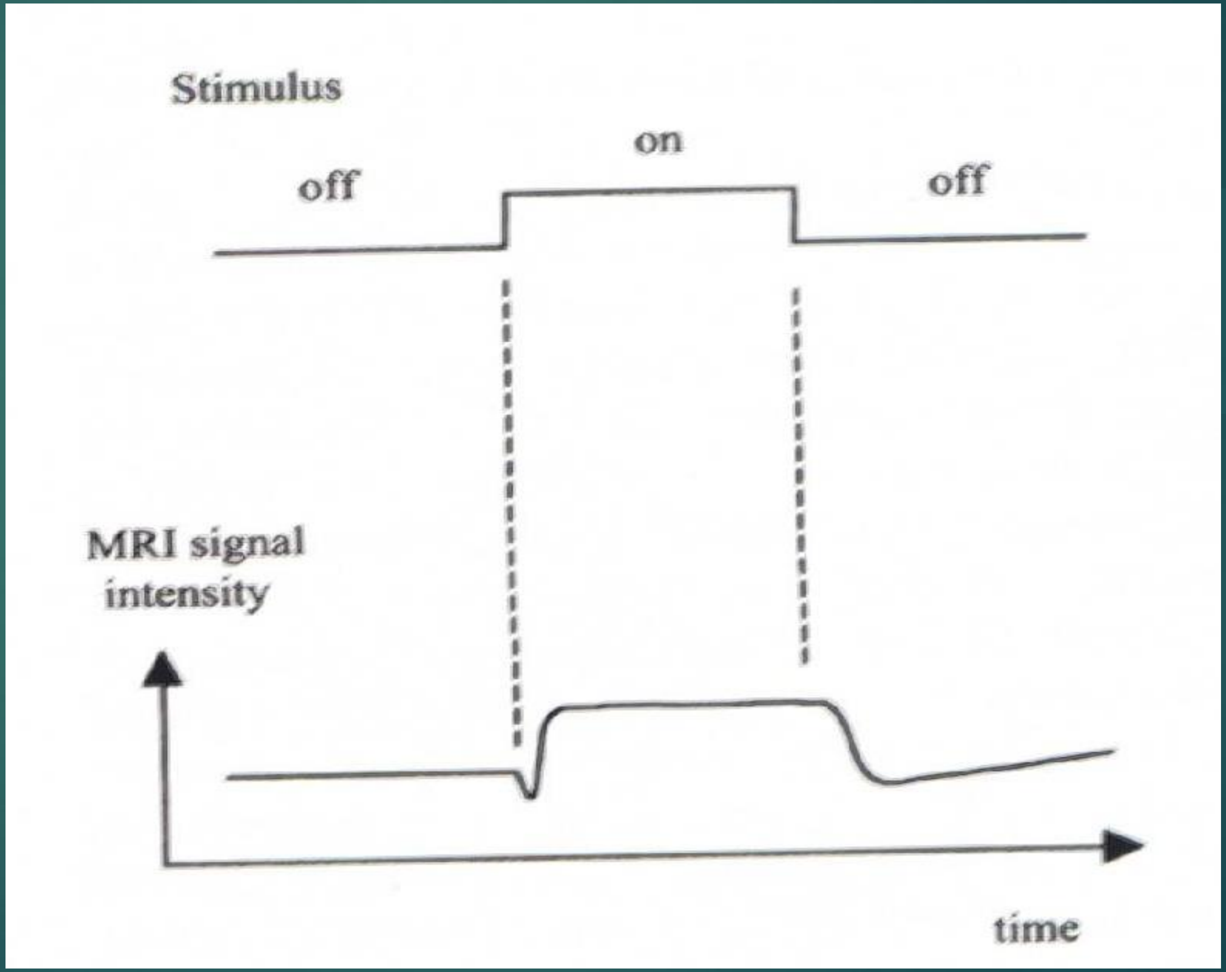
The BOLD Signal (hemodynamic response function (HRF))

A slow response

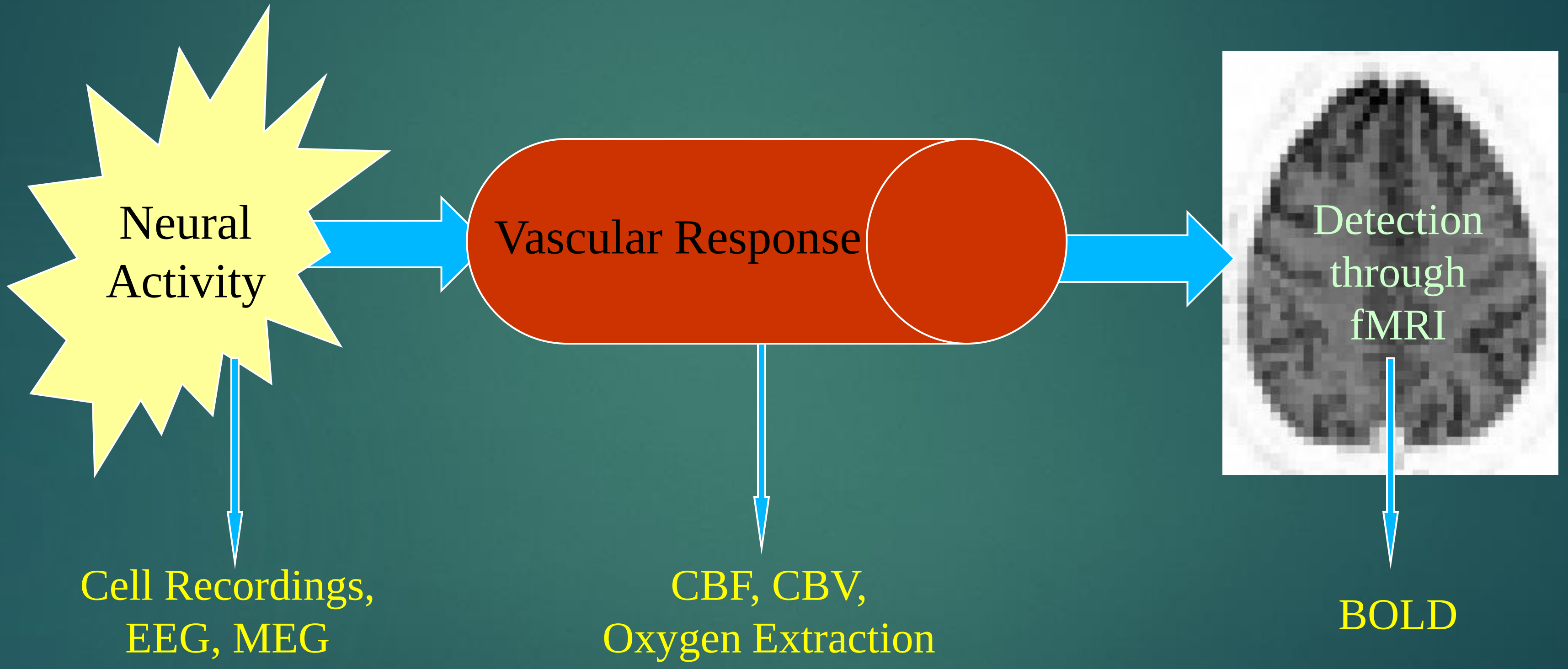


The BOLD Signal (HRF)

Activity within one voxel of tissue



An **Indirect** Measure of Neural Activity



What is the Underlying "Neural Activity"

- From both excitatory and inhibitory neurons
  - Spiking activity
  - Subthreshold Activation
  - Synaptic Currents

- Directory proportional to neural firing? (Heeger et al, 2000: Rees et al 2000)
- Intracortical processing (Viswanathan and Freeman, 2007, Rauch et al. 2008)

Front Neurosci. 2016; 10: 185.
Published online 2016 Apr 29. doi: 10.3389/fnins.2016.00185

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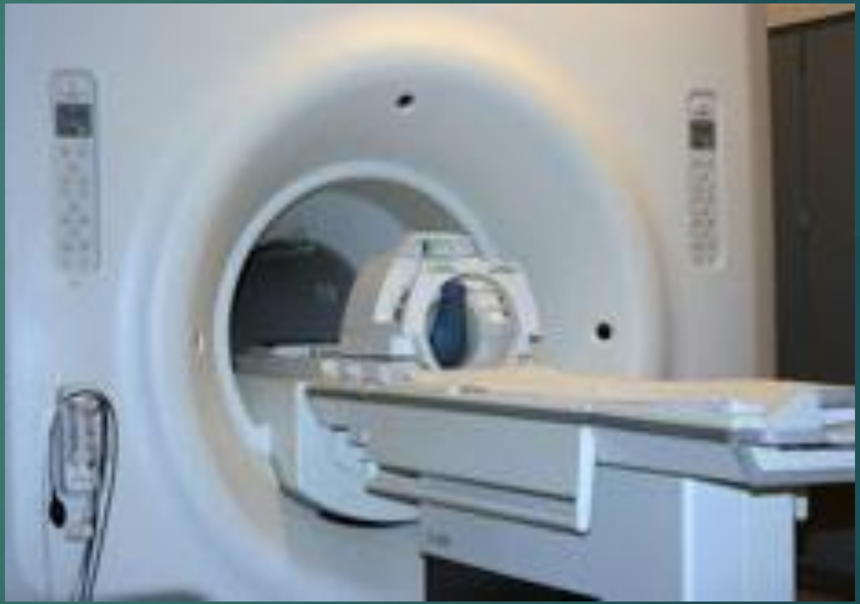
Scan Preparation

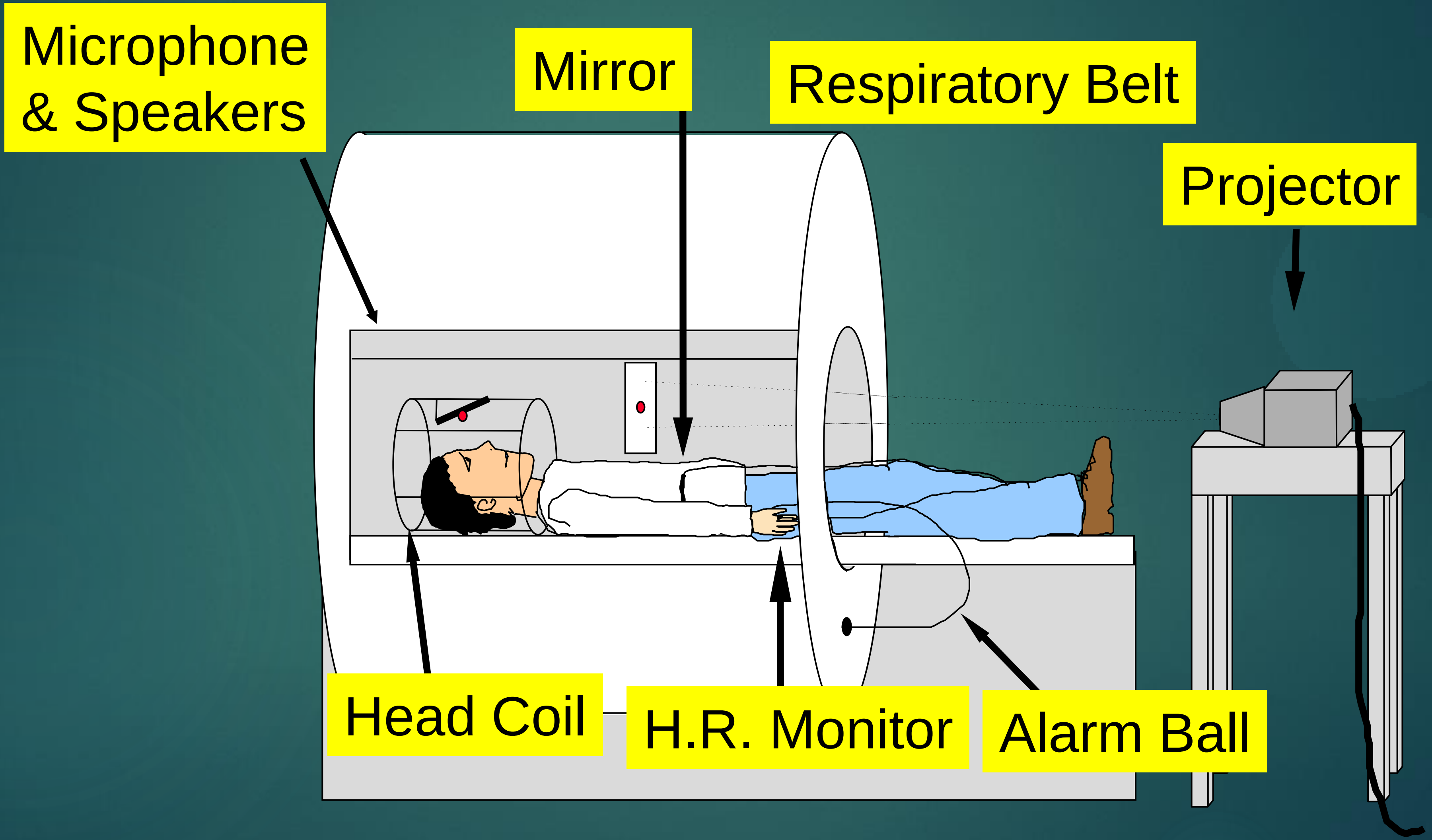
MRRC UPMC University of Pittsburgh Medical Center
Magnetic Resonance Research Center

- Screened by nurse
- Pregnancy test (females)
- Undergo simulation
- Trained on cognitive tasks



Siemens Trio 3T Scanner

The Scanning Environment

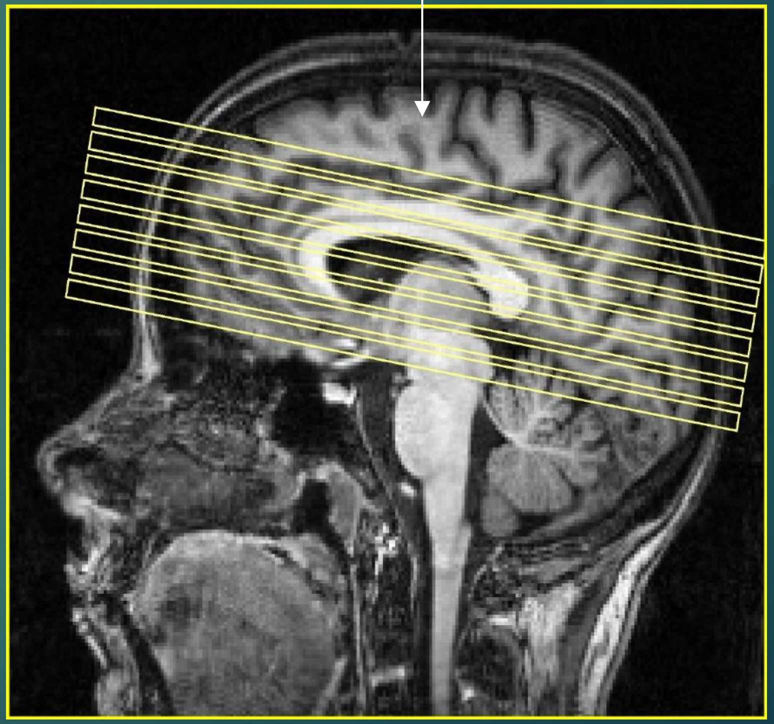


Courtesy of Dr. Bea Luna

BOLD Signal – How Do We Measure It?

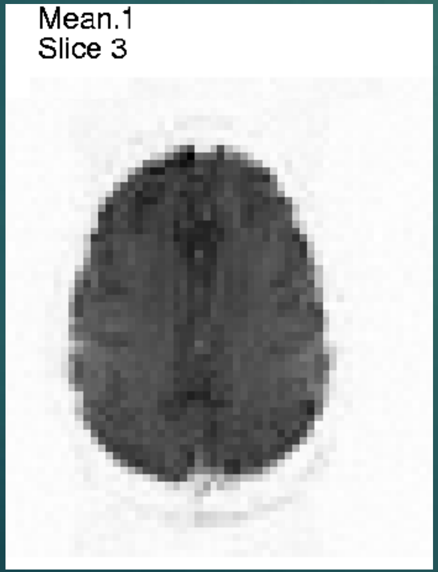
- Subject alternates between two cognitive conditions
- Rapidly and repeatedly record images
- Compare images across conditions to detect BOLD signal

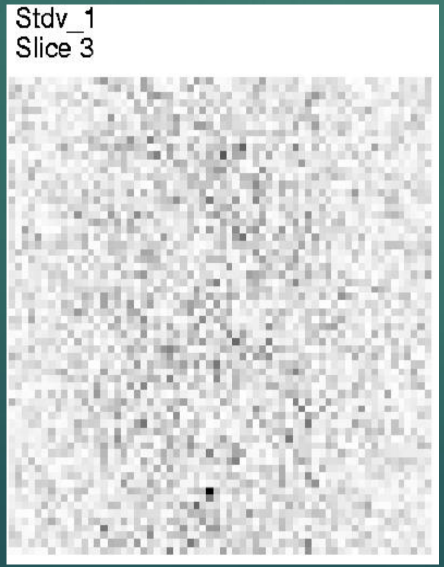
Select slices based on area you are interested in "seeing"

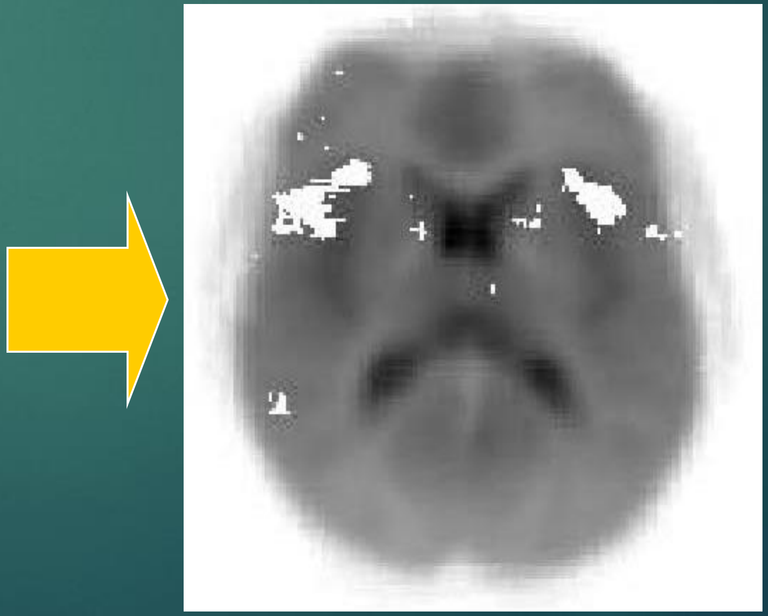


Apply Statistics to Find Activation

- Changes in intensity due to the BOLD effect are SMALL (3-5% at 1.5T)
- To detect these, average images over time across cognitive conditions or states
- Apply statistical test to find intensity differences



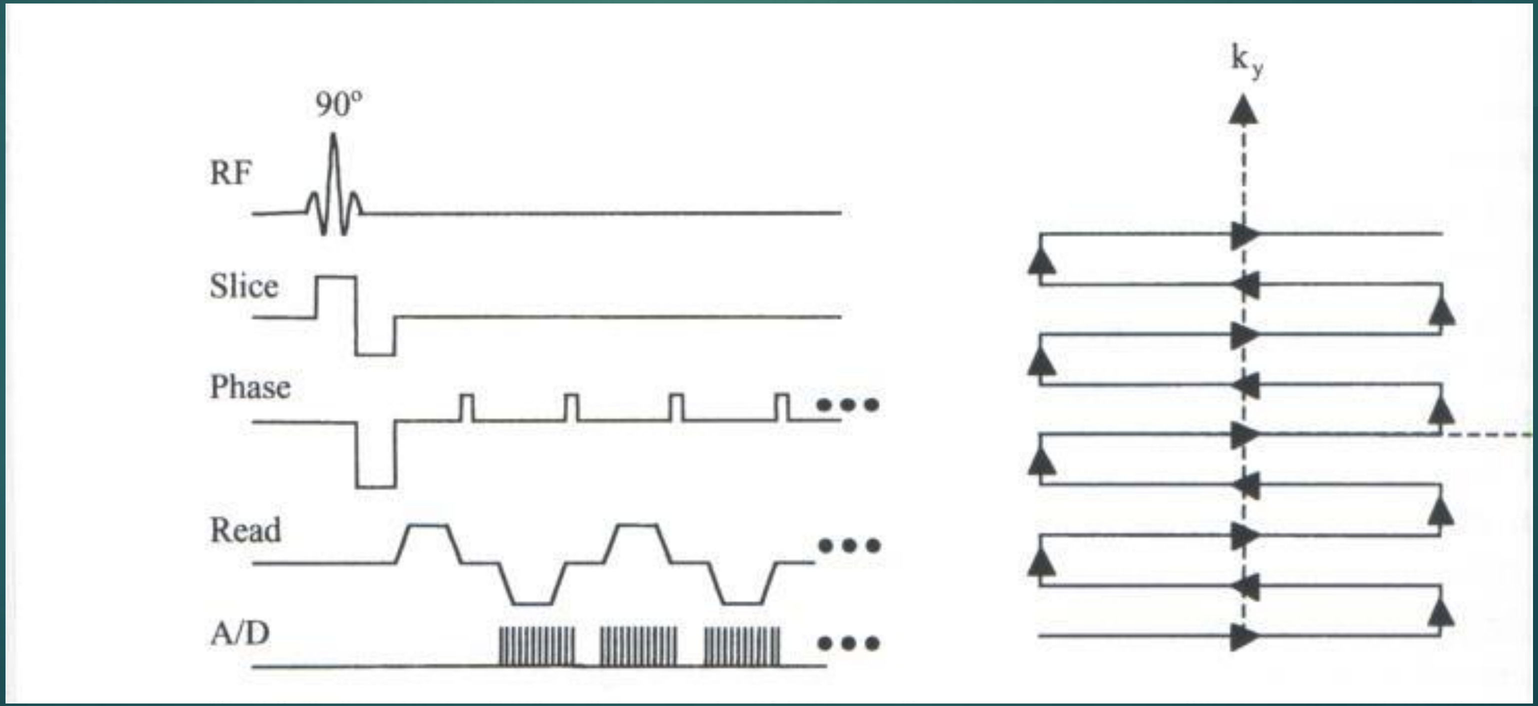




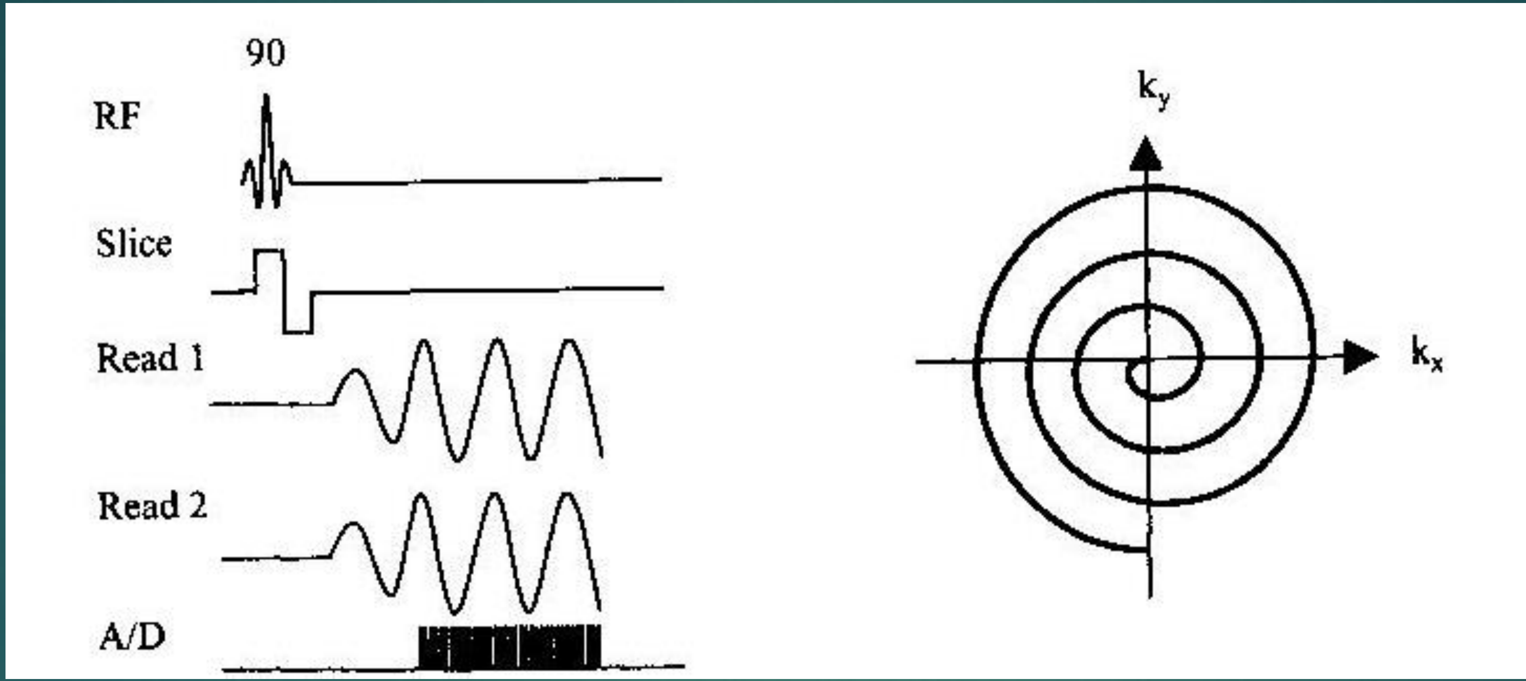
Pulse Sequences - EPI

-Must be extremely fast

-Echo Planar Imaging Sequence (EPI) – scan entire k-space slice for each RF pulse



Pulse Sequences - Spiral



-Again, entire k-space slice for one RF pulse

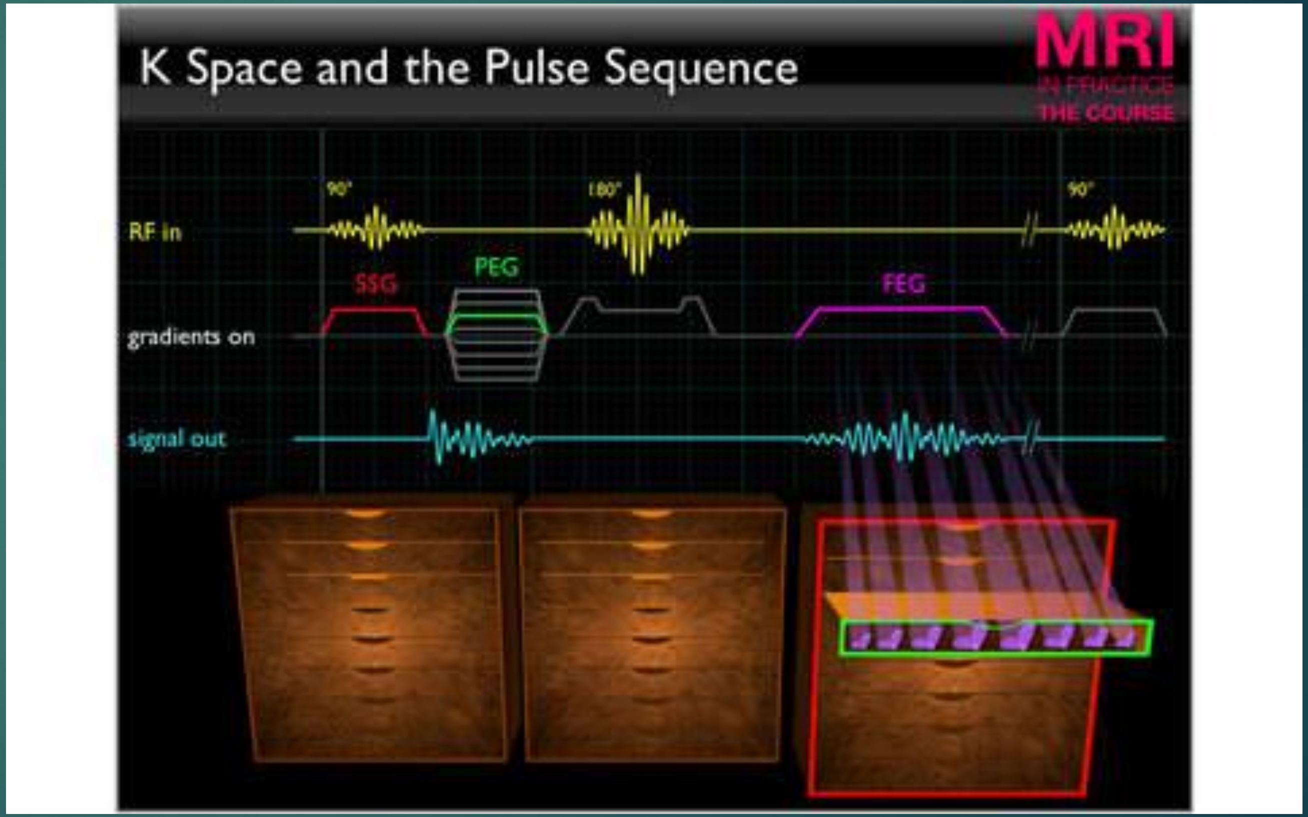
-Collecting low frequencies of k-space first

-Depending on shape of spiral, can sample the low frequencies more densely

-Can generally be faster than EPI

Collecting Data in K-space

- K-space is a frequency space for 2 dimensional spatial frequencies
- To create an image, use the 2D Fourier Transform



K-space to Image Space

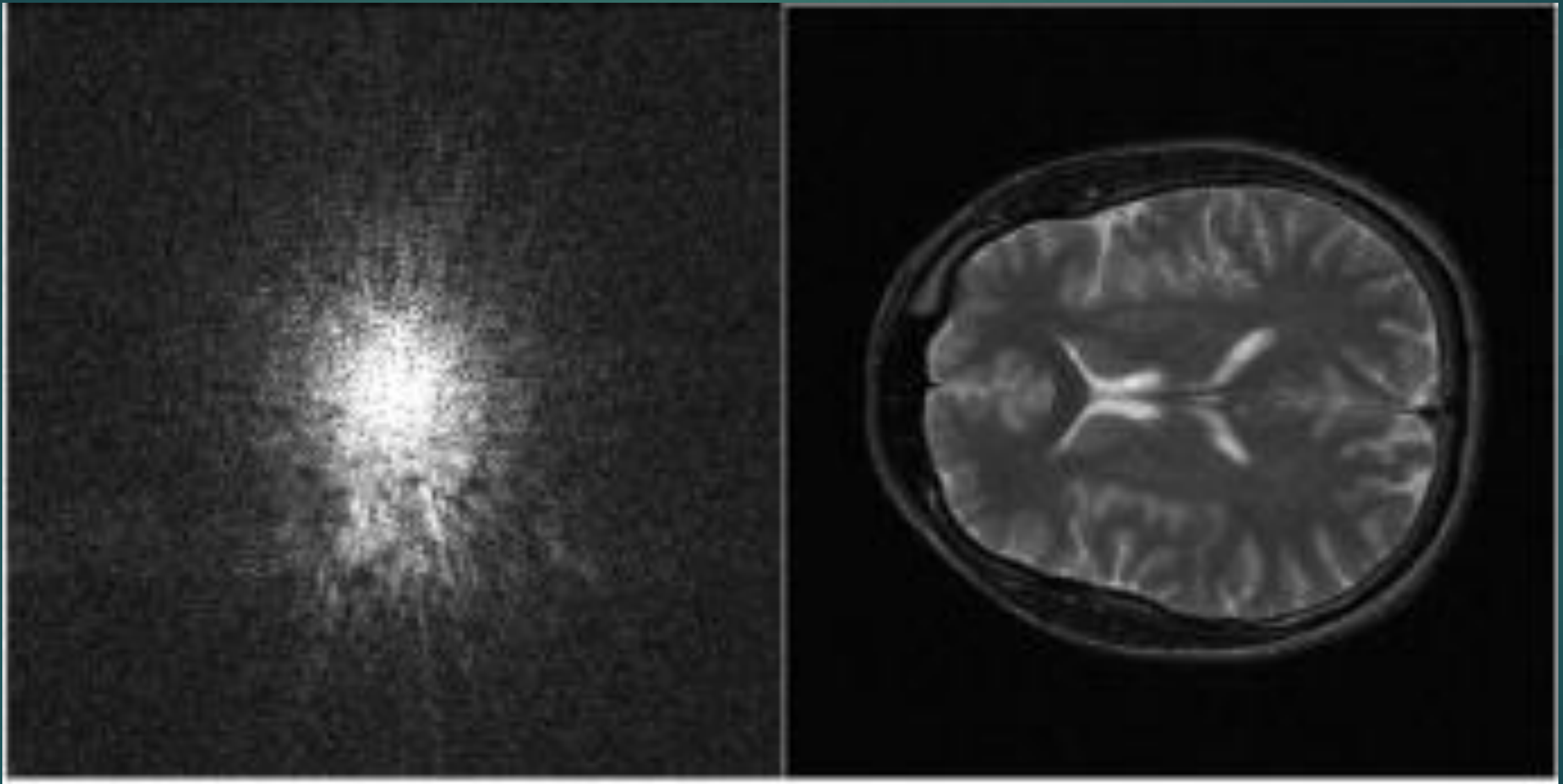
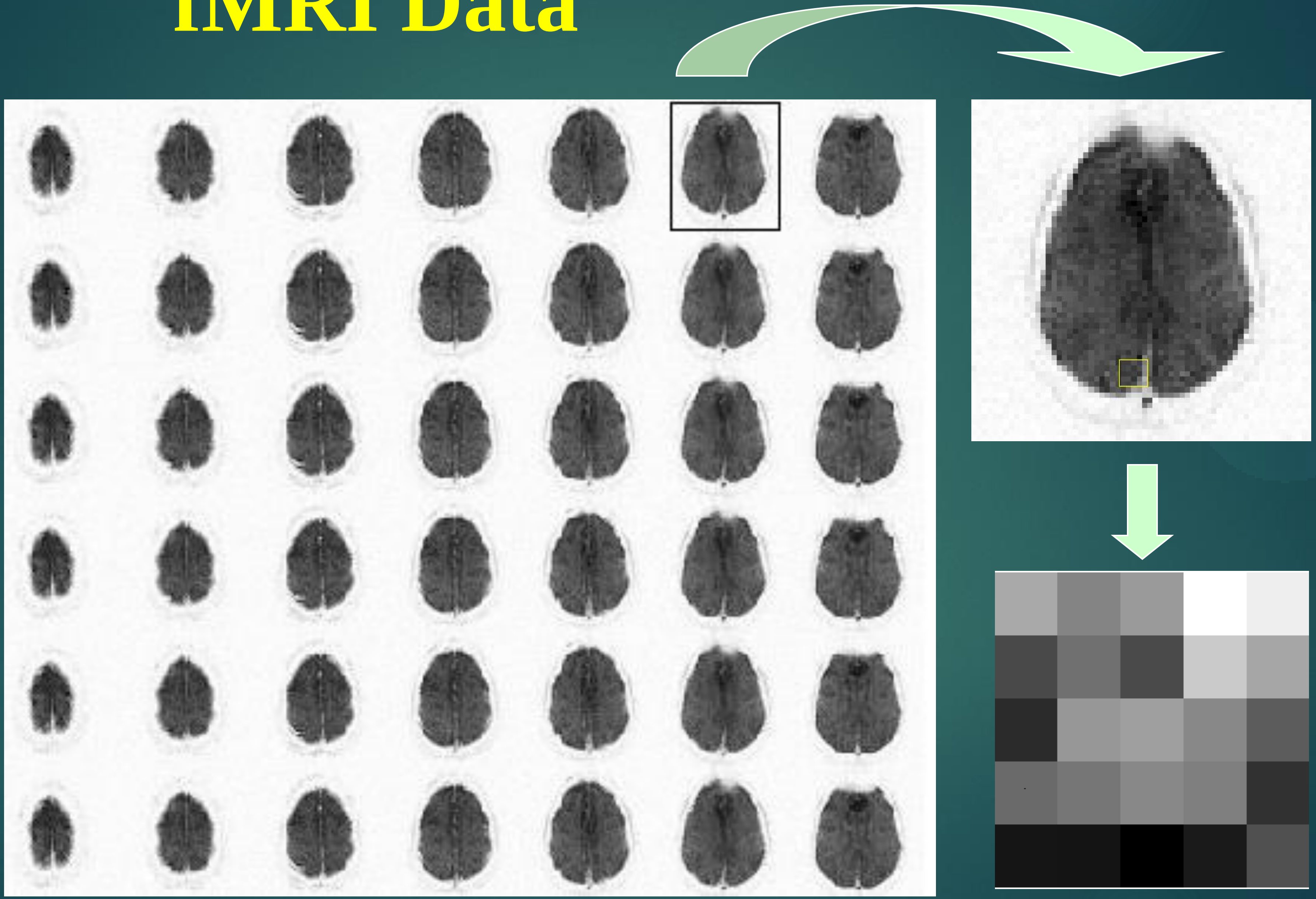


Figure 1: K-space data (left) and resulting brain image after 2D-FT (right)

fMRI Data



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Types of Cognitive Studies

- **Motor studies** -finger tapping, eye movements
- **Working memory studies** - n-back
- **Inhibition studies** - Go-NoGo Task, Stop Task, eye movement inhibition
- **Language and reading studies**
- **Drug use and craving studies**
- **Emotion Studies** – match facial expressions

- ***Generally alternate two VERY SIMILAR conditions***

Designing Experiments

- Something simple that a person can do in the scanner
- Try to limit the amount of subject movement, especially in the head
- Limited by the loud noise of the machine
- Consider experiment design in terms of timing (multiple runs of same thing?)
- Statistically “see” where the activation is
- Keep tract of a performance measure to ensure that person is doing the experiment (behavioral data)

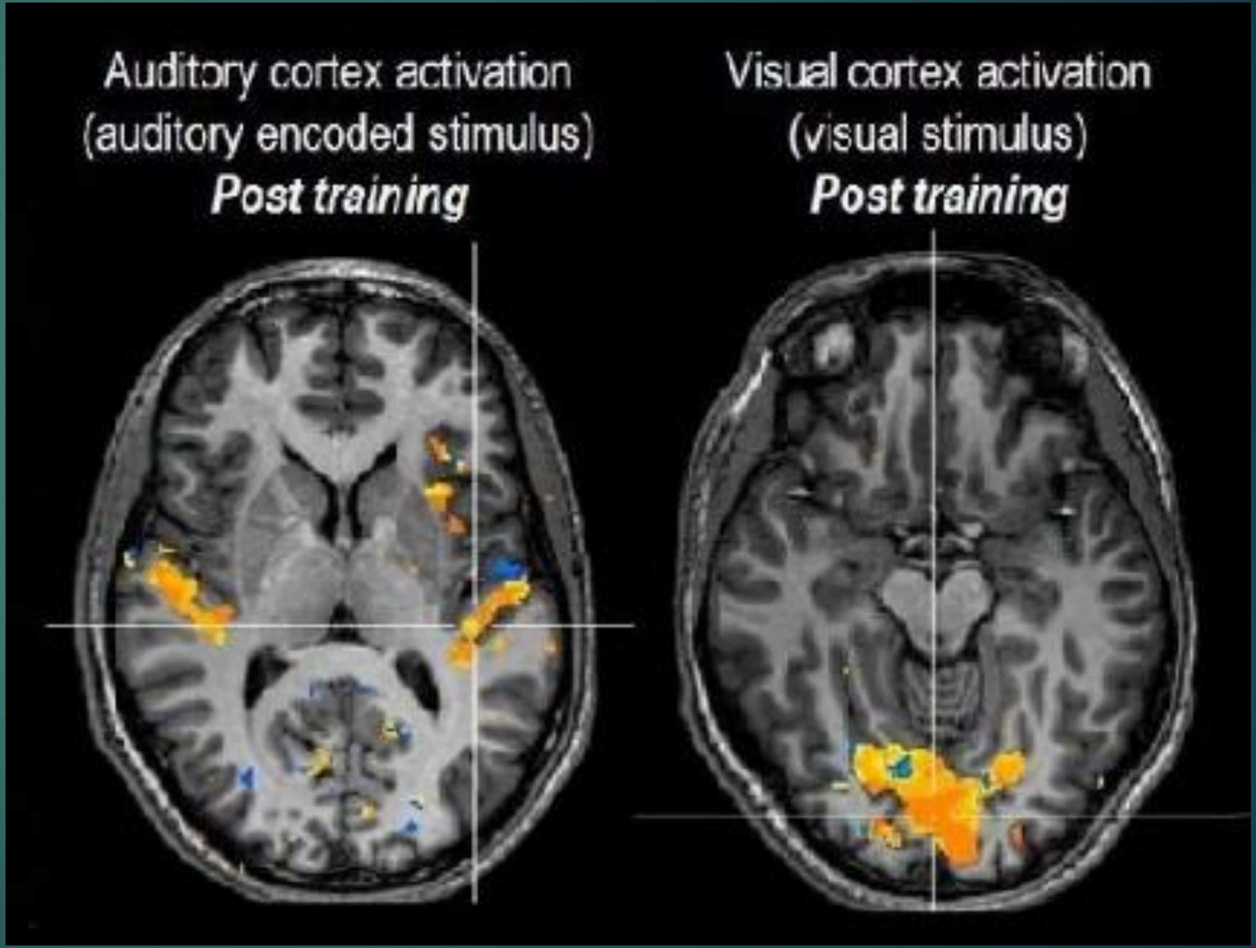
Designing Experiments (continued)

Design a task that alternates to a small extent so that brain areas that activation changes are attributable to a small change

- Finger tapping vs non-finger tapping
- Looking at faces versus looking at blocks
- Reading sentences versus non-sentences
- Looking at violent pictures versus neutral pictures

Activation Differences

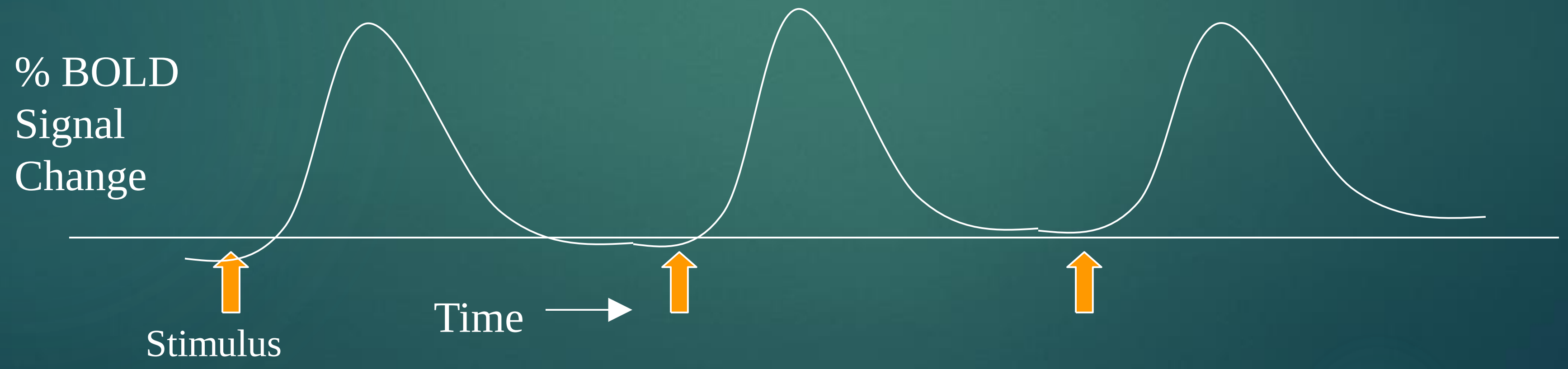
- Activation maps are generated by looking at DIFFERENCES between to cognitive states
- Want main activation regions to subtract out with analysis



Typical fMRI Task Paradigms (timing)

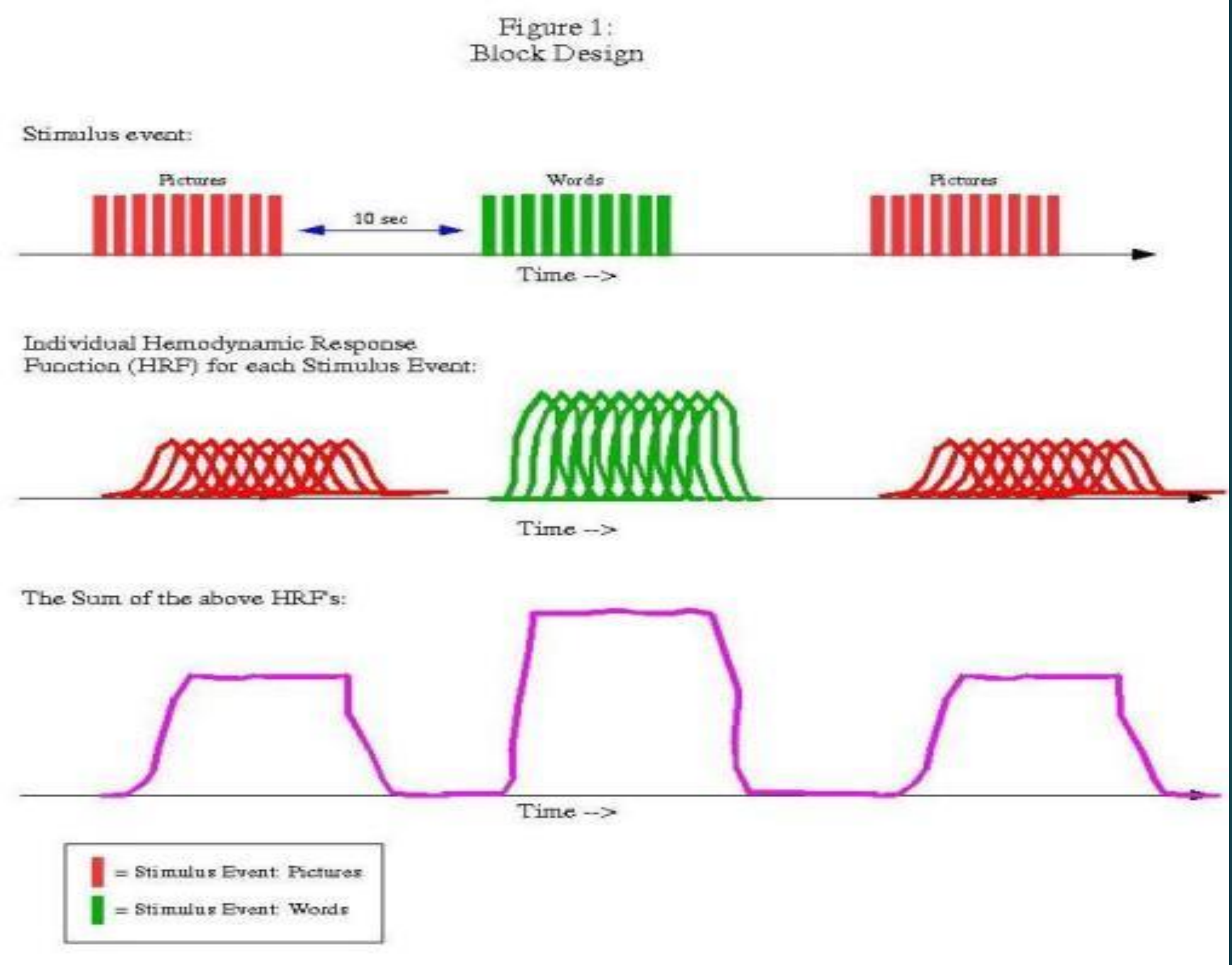
Assumption of BOLD signal in a block design -

Assumption of BOLD signal in an event-related design -



Block Design Experiment

- Perform the same task repeatedly for a block of time
- BOLD signal rises and stays high
- Allow time between for BOLD signal to return to baseline



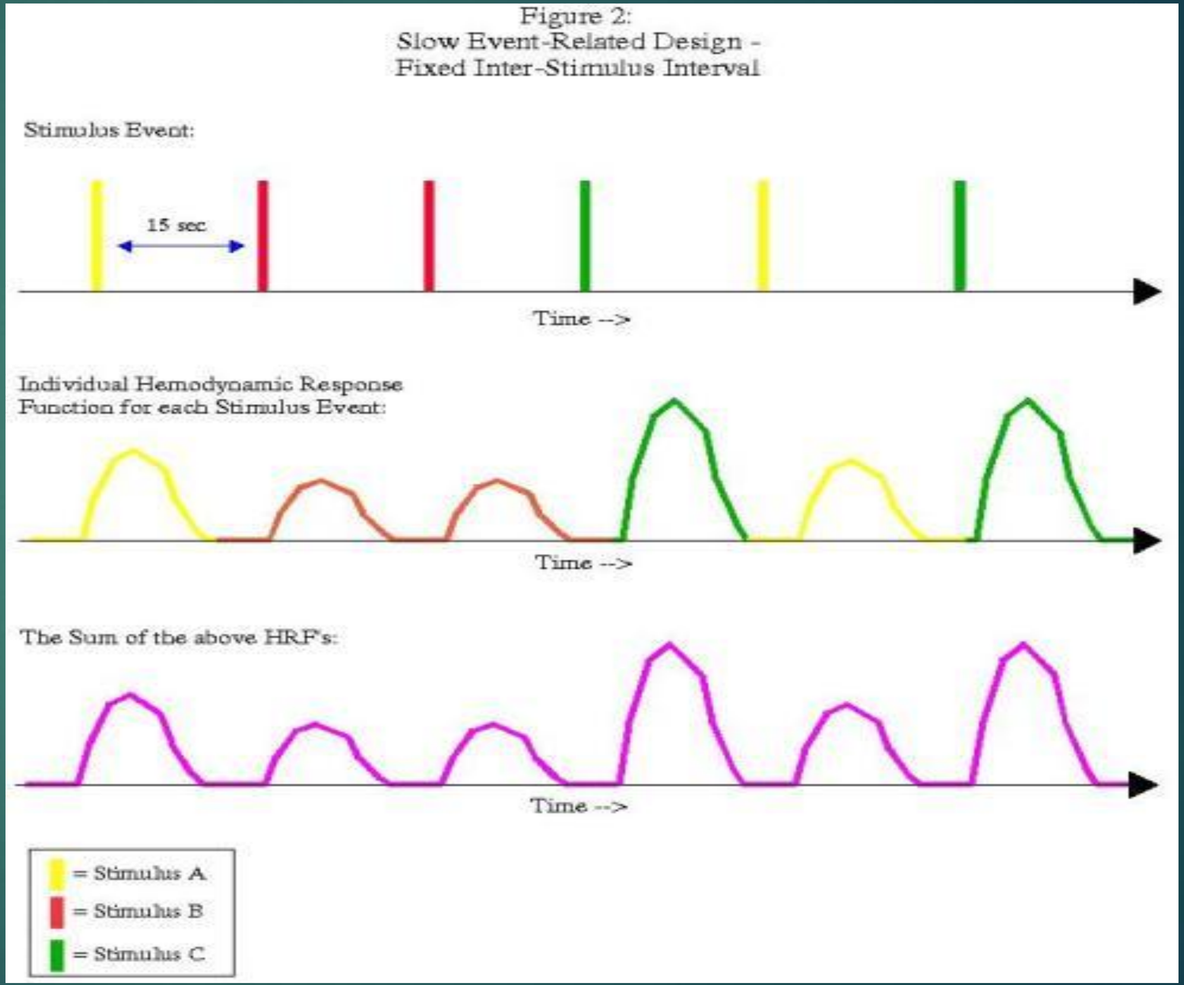
https://afni.nimh.nih.gov/pub/dist/HOWTO/howto/ht03_stim/html/stim_background.html

Block Design

- Advantages
  - Simple, great for exploratory studies
  - Allow for experimental flexibility
  - Statistically powerful
- Disadvantages
  - Predictable and boring for subject
  - Difficult to control specific cognitive design for long time (ex. rest)
  - Time response information is lost
  - BOLD signal may not remain constant throughout block

Event Related Design (Slow)

- Perform the task as a single event
- BOLD signal rises and falls
- Allow time between for BOLD signal to return to baseline (about 15-20 seconds)
- Wait time is called the inter-stimulus interval (ISI)



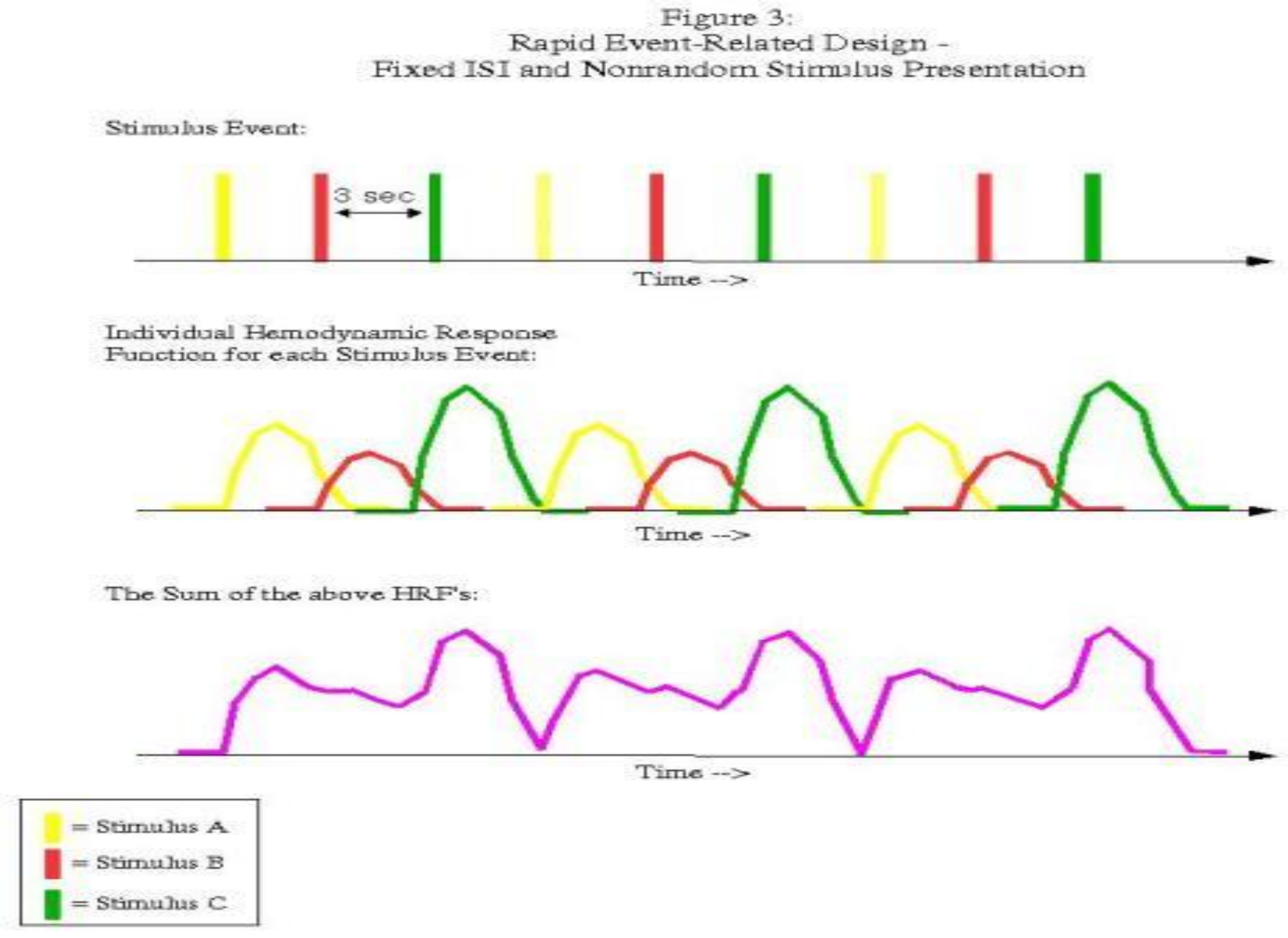
https://afni.nimh.nih.gov/pub/dist/HOWTO/howto/ht03_stim/html/stim_background.html

Problem with Slow Experiments

- Difficult for participant to remain focused and awake
- Time inefficient, spending lots of time waiting for BOLD signal to return to baseline
- Disproportionate time at baseline compared to events
- Signal to noise is lower than block designs (can increase number of trials per condition, but this also increases experimental duration)

Rapid Event-Related Design

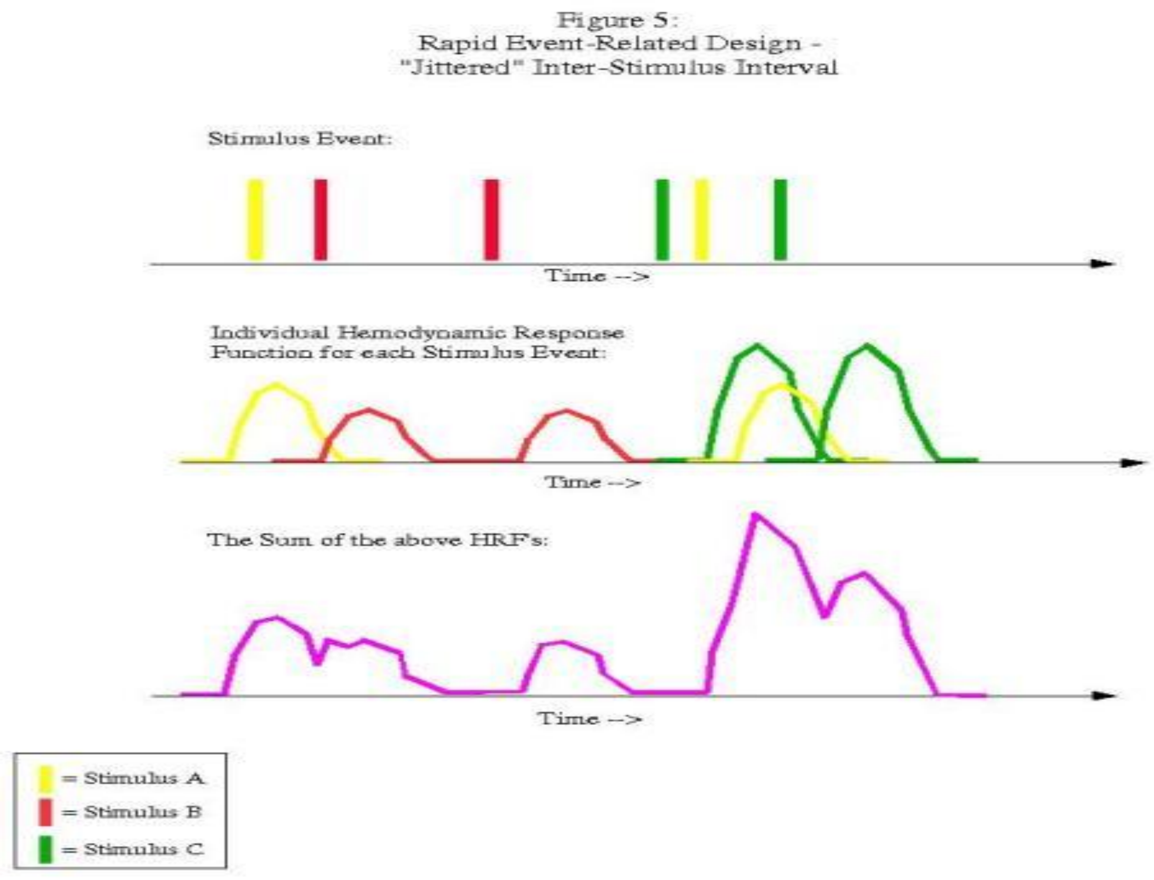
- Short, Fixed ISI, Non-randomized presentation
- Problem that we cannot differentiate which event to which response (ambiguous signal)
- Multicollinearity, a mathematical problem
- NOT A GOOD STUDY DESIGN



https://afni.nimh.nih.gov/pub/dist/HOWTO/howto/ht03_stim/html/stim_background.html

Rapid ER – Jittered ISI and Random Stimulus Presentation

- Advantages: Differential HRF overlap
- More overall randomness
- Easier to fit the HRF to this data



https://afni.nimh.nih.gov/pub/dist/HOWTO/howto/ht03_stim/html/stim_background.html

Example Study Designs

Example Experiments

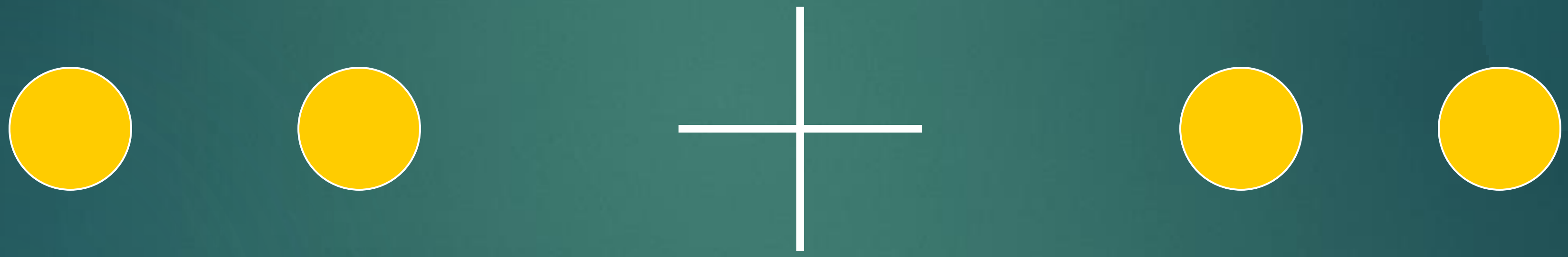
- Antisaccade task (cognitive inhibition)
- Faces task (implicit emotional processing)
- Reward task (Guessing game)

Antisaccade Task

- Designed to activate sensorimotor and inhibitory areas
- Instructions
  - Fixate on the cross hair
  - If you see it turn green, move your eyes horizontally toward the dot that follows
  - If you see it turn red, move your eyes away from the dot that follows to the opposite horizontal location

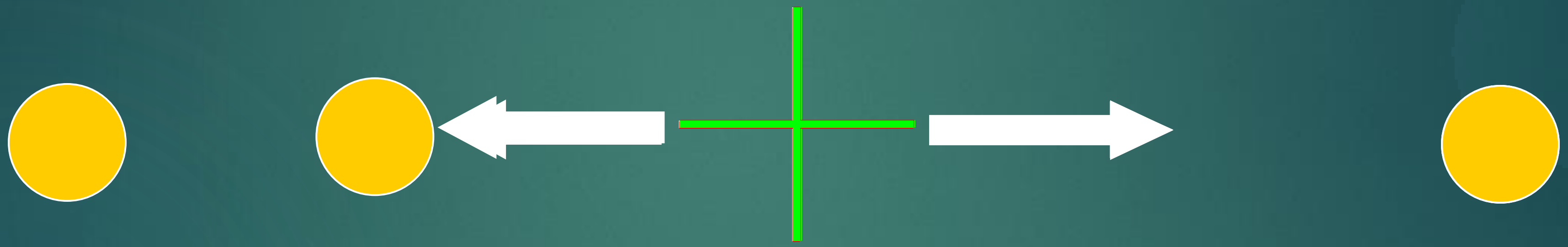
Sensorimotor Task

Great Job!



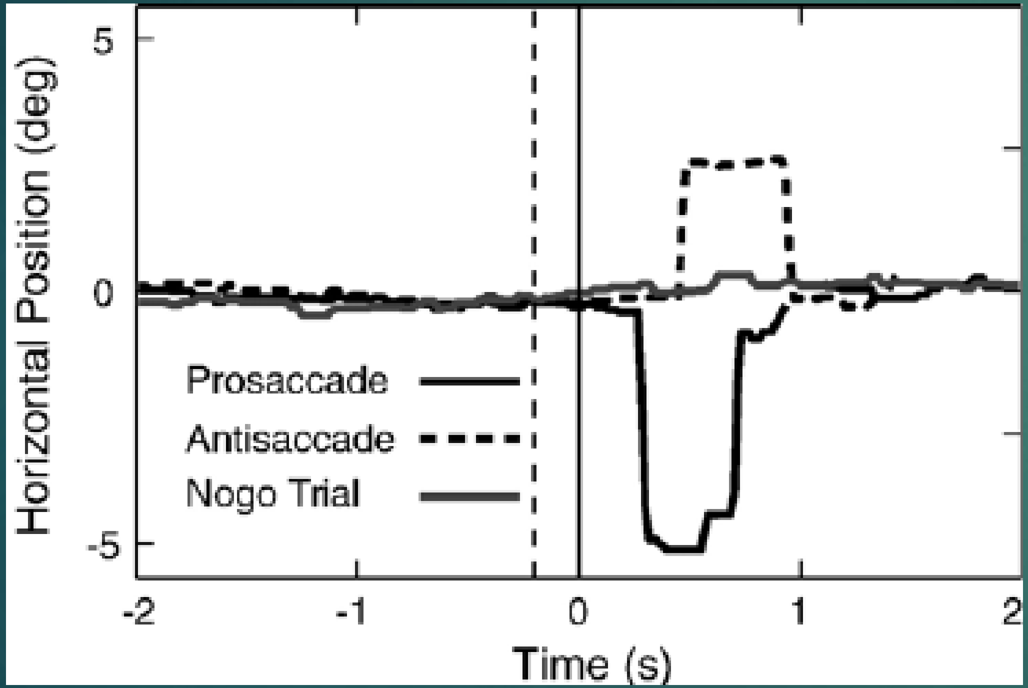
Cognitive Inhibition Task

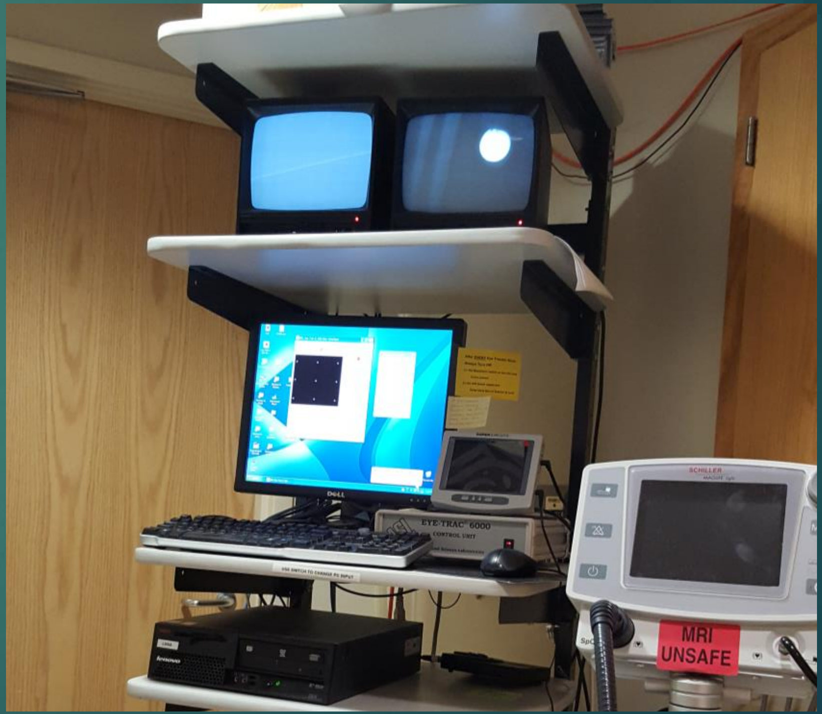
Great Job!



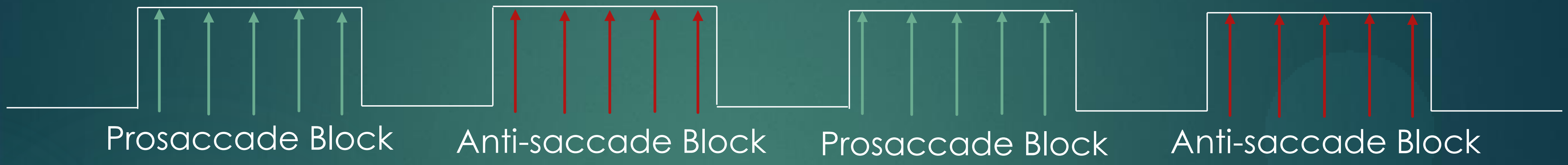
Antisaccade Behavioral Measure

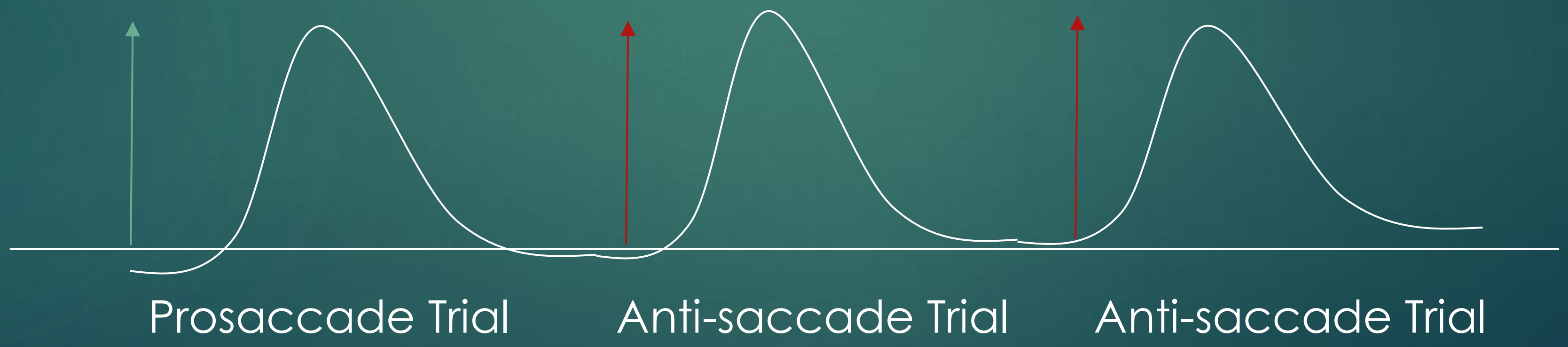
- Need eye tracking to ensure task is performed correctly





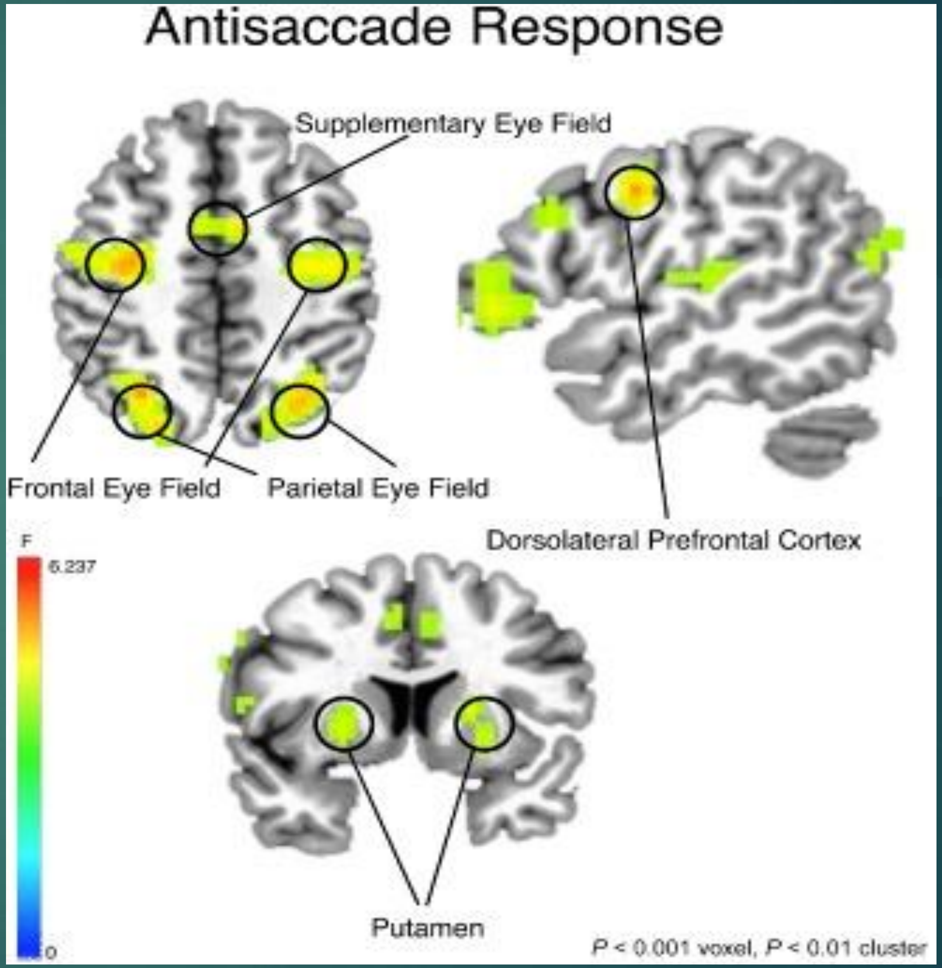
Block Design or Event-Related?





Cognitive Inhibition (Antisaccade Task)

- Activating visual areas
- Activation of inhibitory areas
- Activation of frontal eye fields, dorsolateral prefrontal cortex



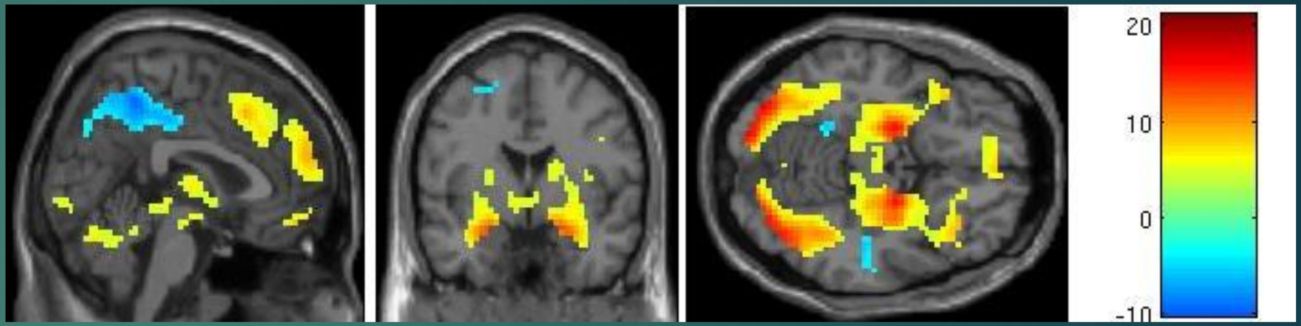
https://www.researchgate.net/figure/267984357_fig4_Figure-5-Activation-map-for-main-effect-of-time-during-anti-saccade-AS-response-epoch

Faces Task – Implicit Emotion Processing

- Implicit = they are not attending to the emotion (designed to activation background emotion processing)
- Instructions:
  - Pay attention and respond as fast as you can
  - If you see a picture of a male, press your middle finger
  - If you see a picture of a female, press your index finger

Implicit Emotion Processing (Faces Task)

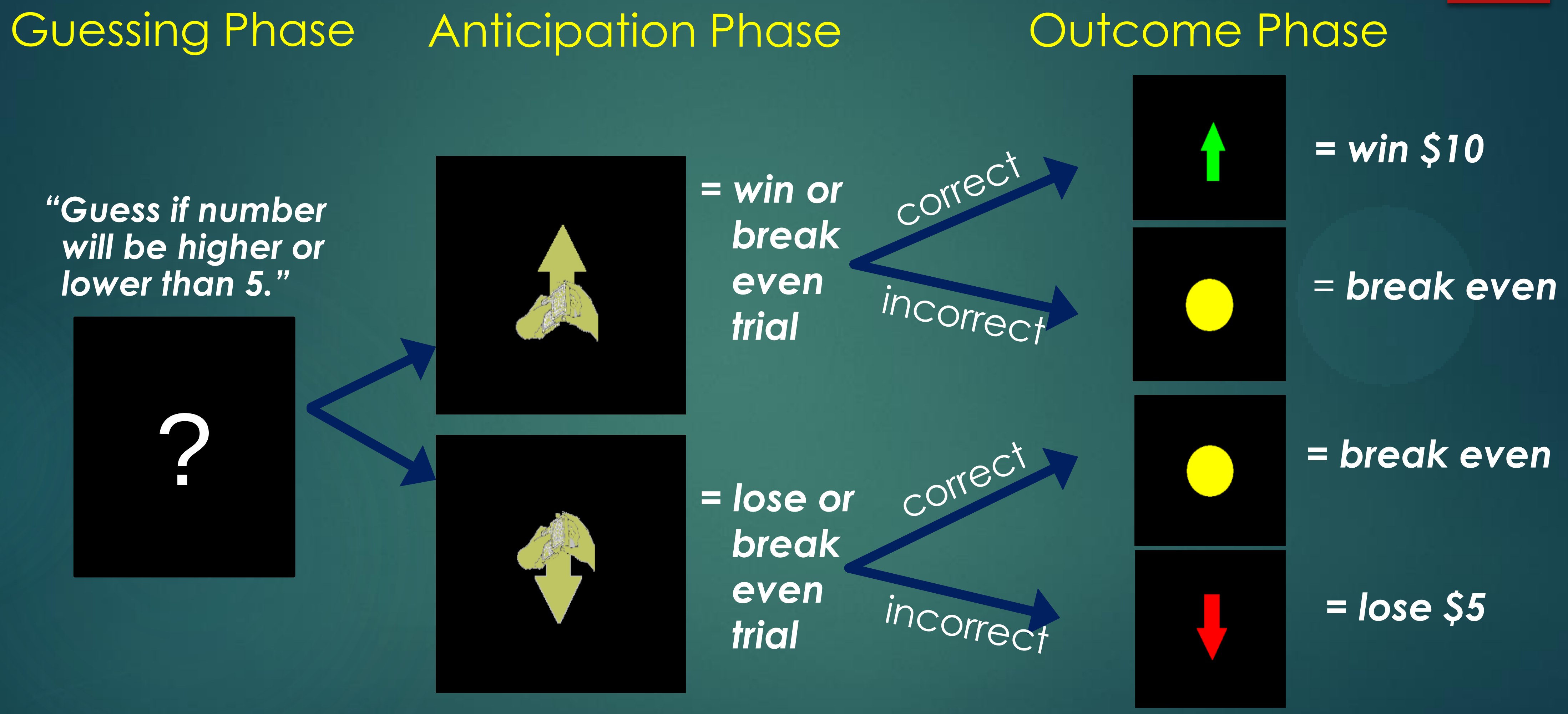
- Activation of visual areas
- Strong activation of amygdala and emotion processing areas
- Activation of dorsal ACC and orbital frontal areas



Reward/Guessing Task

- Designed to activate reward and loss centers in the brain for both anticipation and outcome

- Instructions:
  - When you see the question mark, guess if a number on the screen will be higher than or lower than five
  - If you see the shuffling hand up, you could win or break even
  - If you see the shuffling hand down, you could lose or break even
  - You will see the actual number then either an arrow telling you if you win or lose, or a yellow circle indicating that you broke even

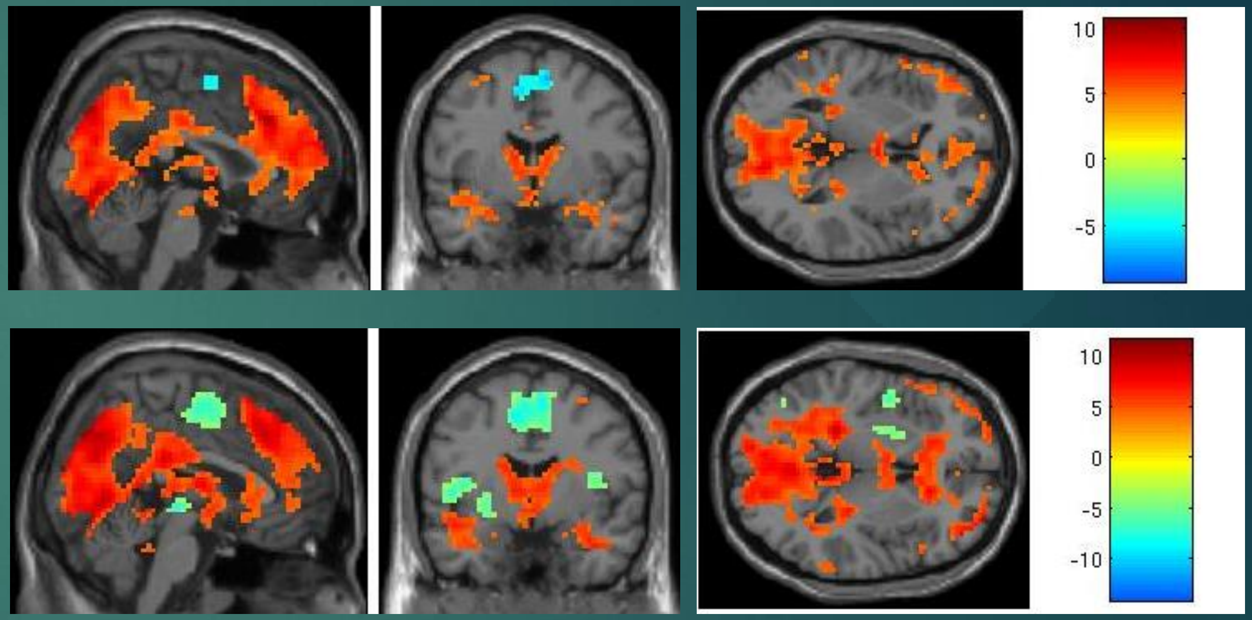

Guessing Phase
Anticipation Phase
Outcome Phase
"Guess if number will be higher or lower than 5."
?
= win or break even trial
= lose or break even trial
correct
incorrect
correct
incorrect
= win $10
= break even
= break even
= lose $5

Reward/Guessing Task

- Activates caudate, putamen, dopamine rich areas
- Activations visual cortex, frontal areas dorsal ACC
- De-activation, especially during loss

Winning

Losing



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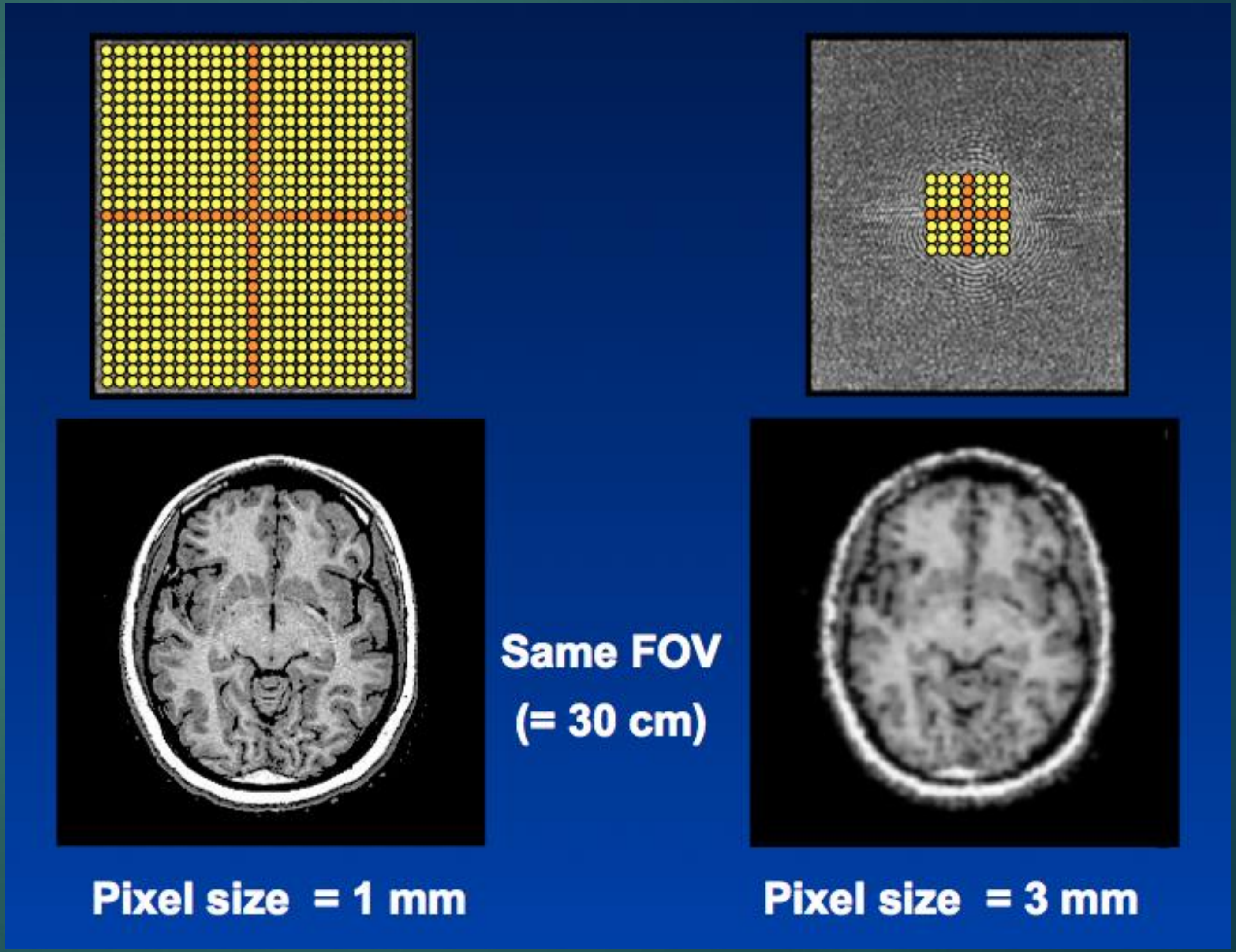
K-space to Image Space

- When designing the experiment, make sure you pick your parameters to get best resolution
- The more of k-space that is sampled, the better
- FFT is mostly done automatically by the scanner now-a-days



fMRI Data Analysis Steps

Process data to remove noise

↓

Normalize brains into a common space

↓

Statistical analysis of individual subjects (t-maps, F-maps, time series analysis)

↓

Create group maps

Convert Dicom Files to Image Files

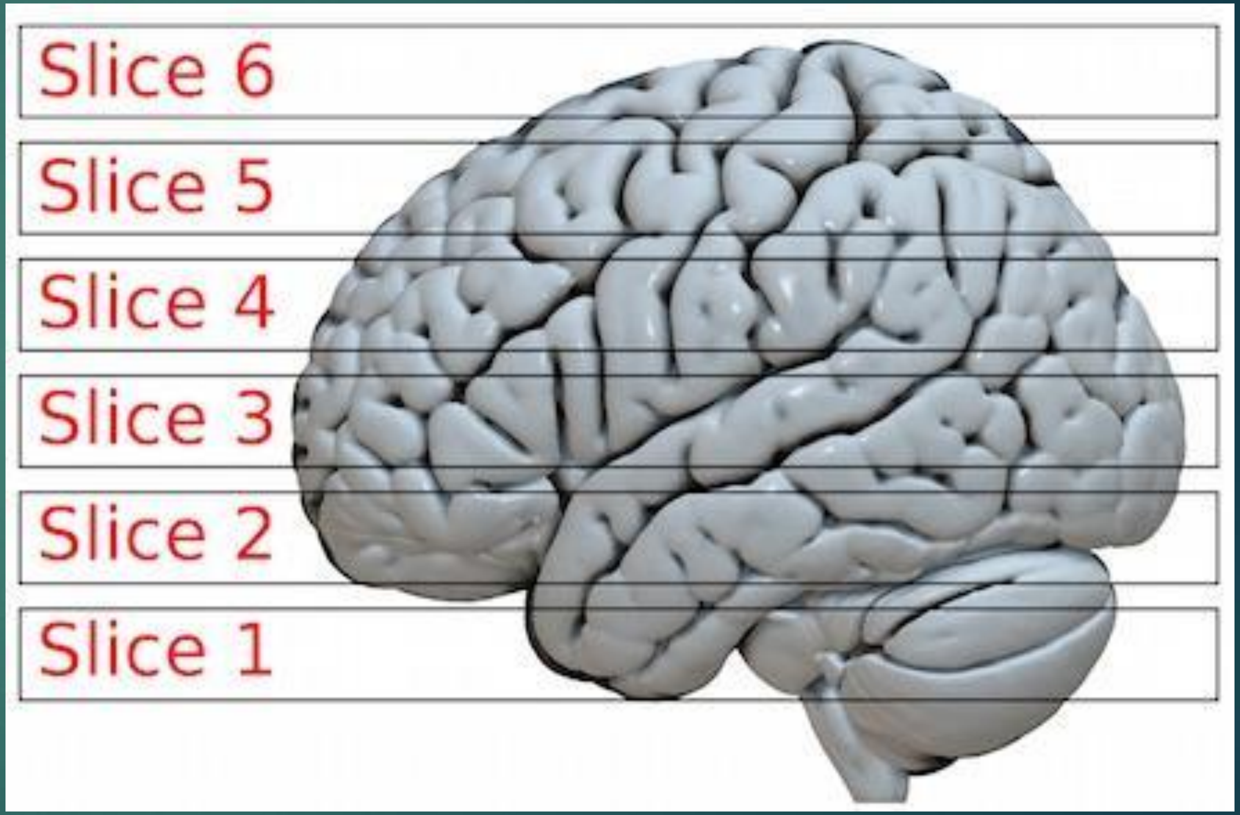
- DICOM files are the raw files that are received directly from the scanner
- DICOM = Digial Imaging and Communications in Medicine
- Standard for handling, storing, printing, and transmitting information in medical imaging
- Includes a file format and a network communications protocol
- Developed by the National Electrical Manufacturers Association (NEMA)
- Time and date imbedded in the file name

Dicom to Image Format (continued)

- Image files –
  - Analyze files – two separate files containing the header information (.hdr) and the image information (.img)
  - NIFTI files – similar to analyze but one files (.nii)
  - AFNI file format – two separate files containing the header information (.HDR) and the image information (.BRIK)
  - Many others, depends on processing software

Preprocessing: Slice timing correction

- Only for event-related study designs
- TR is the time it takes to collect all slices in the brain
- Each slice is collected at slightly different times
- Acquisition is usually interleaved to prevent bleeding of signal from adjacent slices



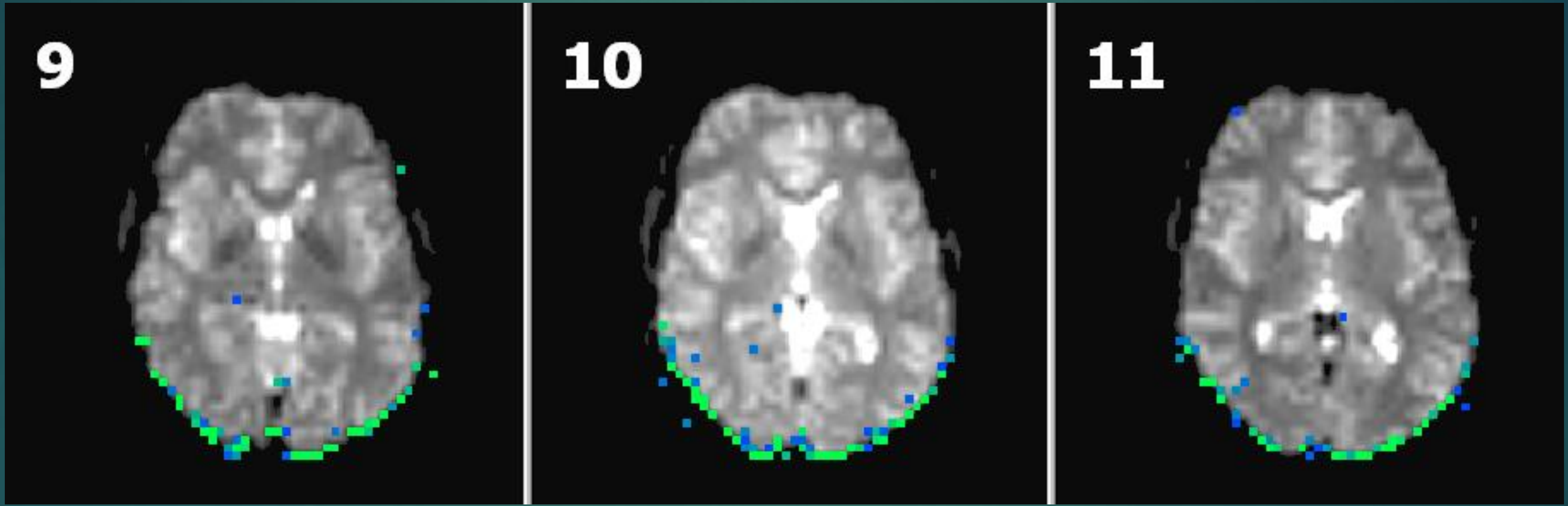
Slice Timing

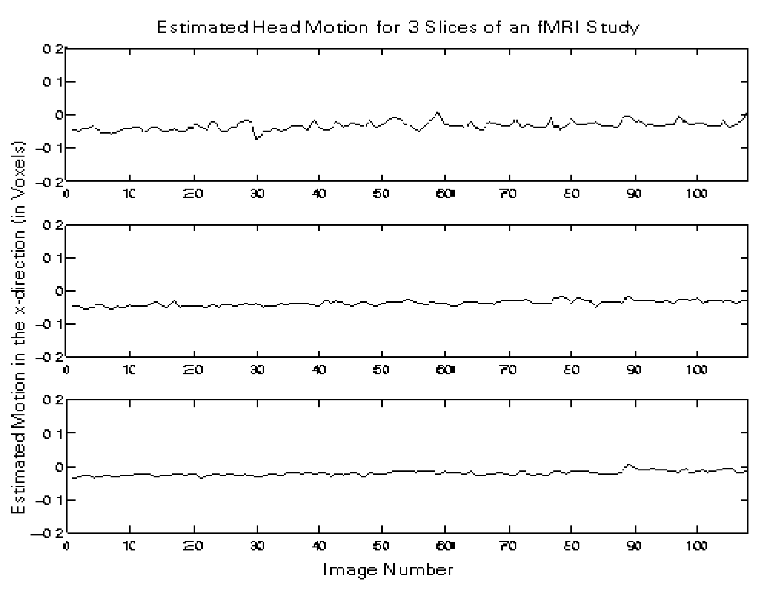
- IF TR (time of repetition = 2 seconds and have 6 slices:
  - Slice 1 is collected at t = 0 seconds
  - Slice 2 is collected at t = 2/6 seconds = 0.33 sec
  - Slice 3 is collected at t = 4/6 seconds = 0.67 sec
  - Slice 4 is collected at t = 6/6 seconds = 1.00 sec
  - Slice 5 is collected at t = 8/6 seconds = 1.33 sec
  - Slice 6 is collected at t = 10/6 seconds = 1.67 sec
- Back to slice 1 at t = 2 seconds
- Don't need to worry about this with Block Designs

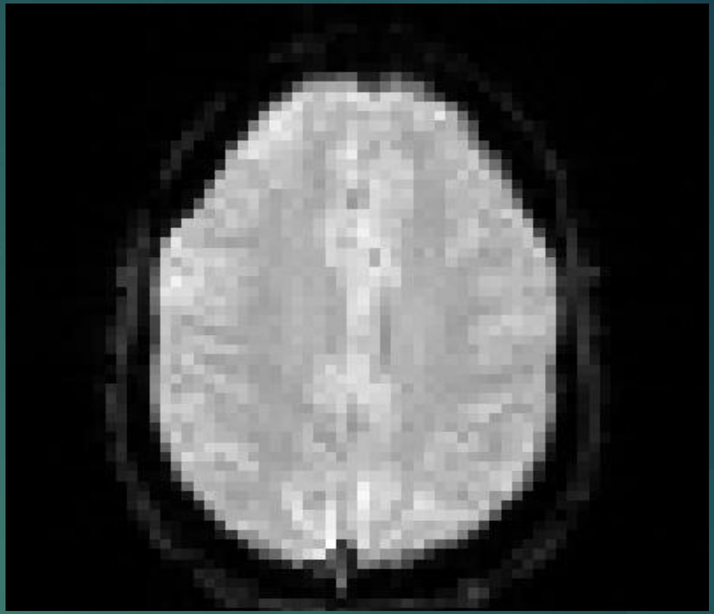
Motion Correction

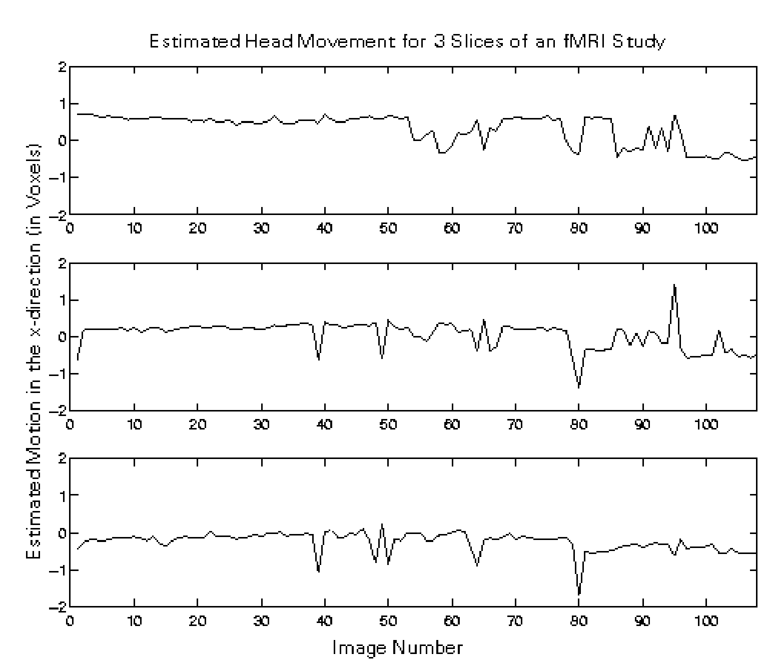
- Especially problematic with fMRI because looking at series of images over time
- If we model one voxel over time and the position changes, no longer looking at the same piece of tissue
- We are looking at intensity changes over time, if the signal intensity changes due to motion, we get as false "activation" signal (correlated with the task)
- How do we correct for this?
  - During the scan
  - After the scan
- How much motion can be tolerated?

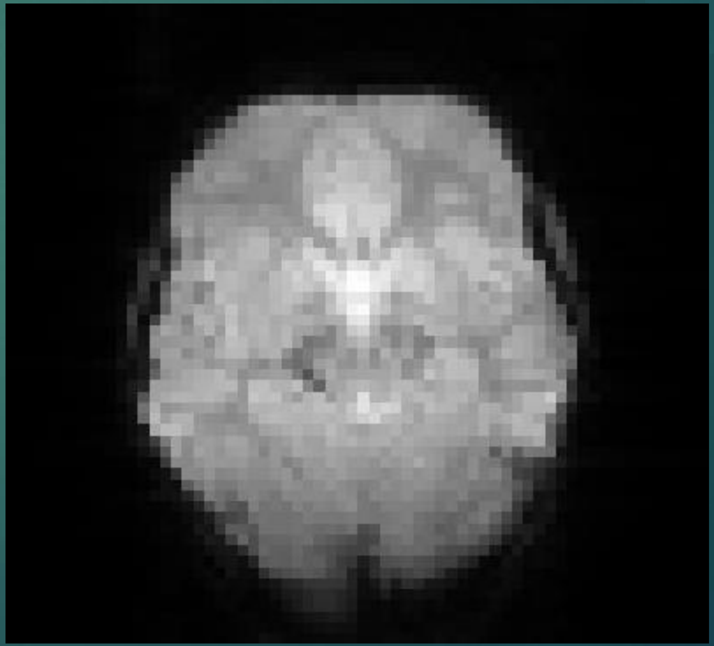
Motion Artifact Example




Estimated Head Motion for 3 Slices of an fMRI Study
Estimated Motion in the x-direction (in Voxels)
Image Number



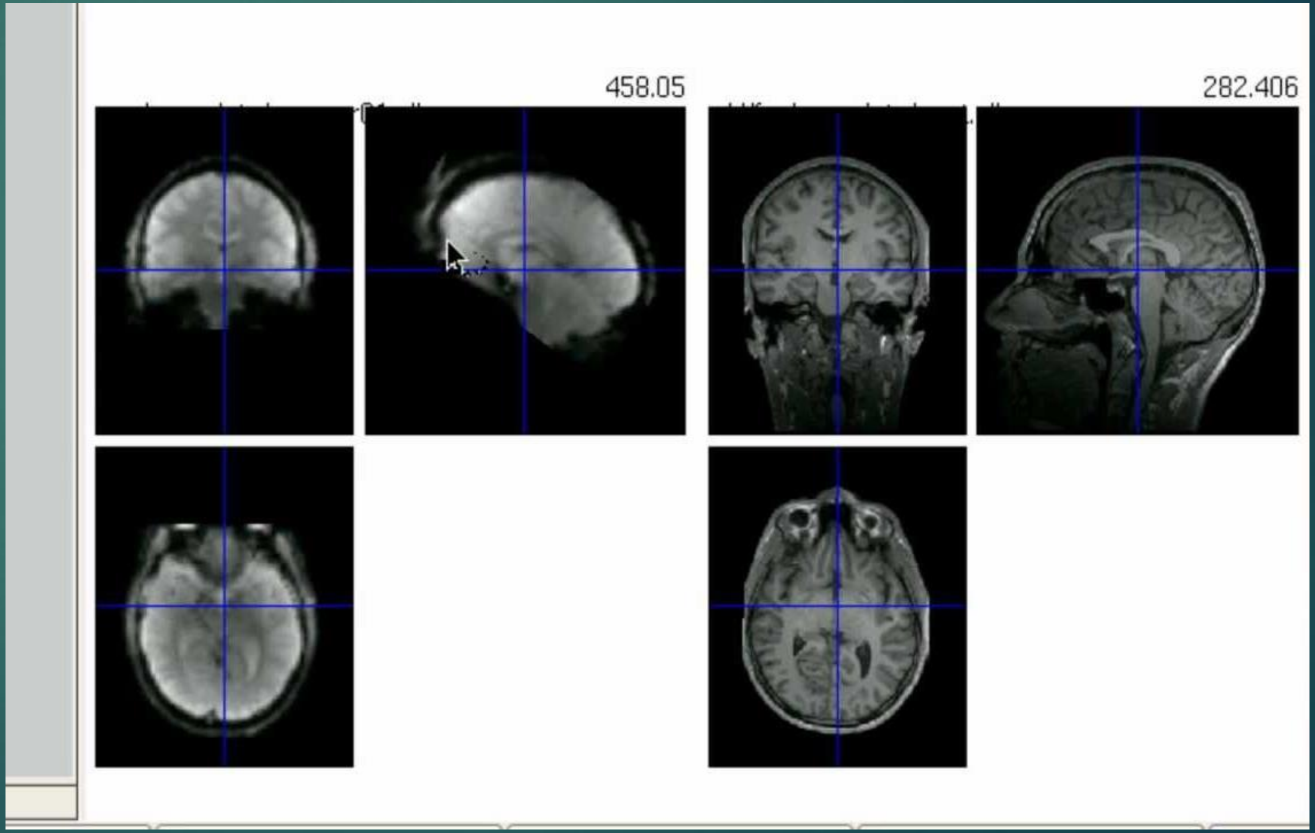

Estimated Head Movement for 3 Slices of an fMRI Study
Estimated Motion in the x-direction (in Voxels)
Image Number



Coregistration between Anatomical and Functional Images

- Need to line up the person's anatomical and functional images to determine where the activation is anatomically

- So important that anatomical images are often collected before the functional scans



fMRI Data Analysis Steps

Process data to remove noise

↓

Normalize brains into a common space

↓

Statistical analysis of individual subjects
(t-maps, F-maps, time series analysis)

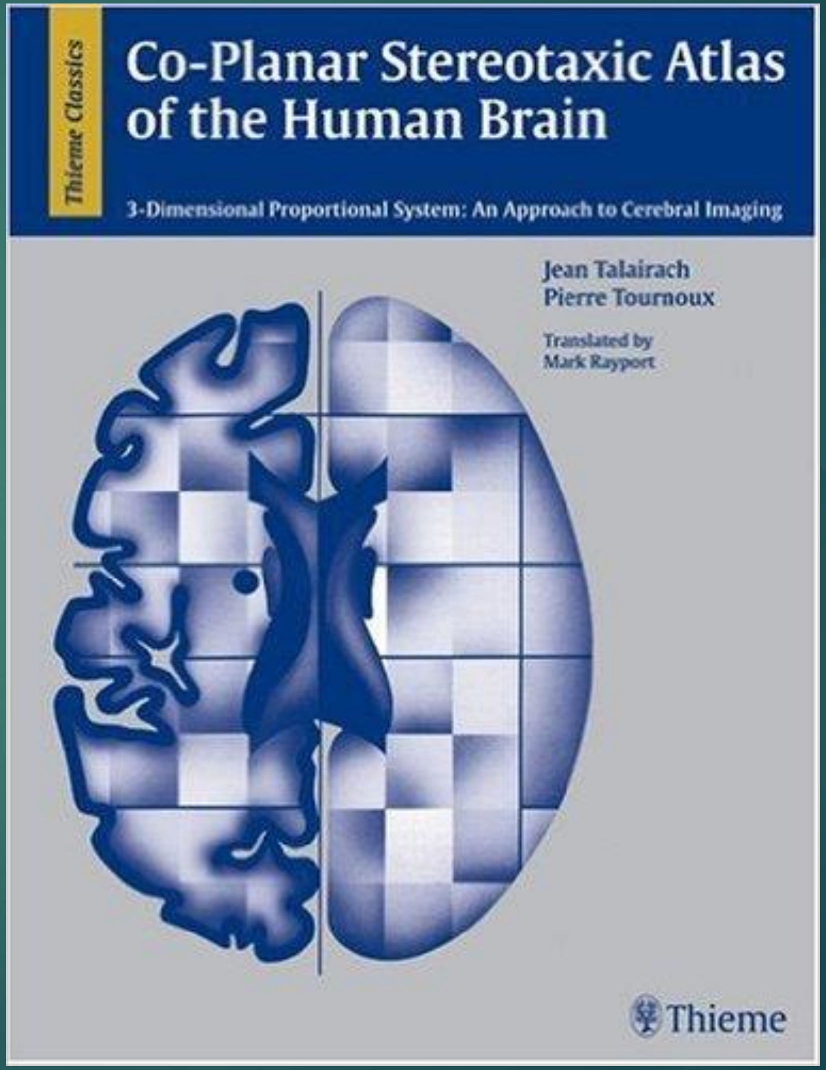
↓

Create group maps

Normalization to a Common Brain Space

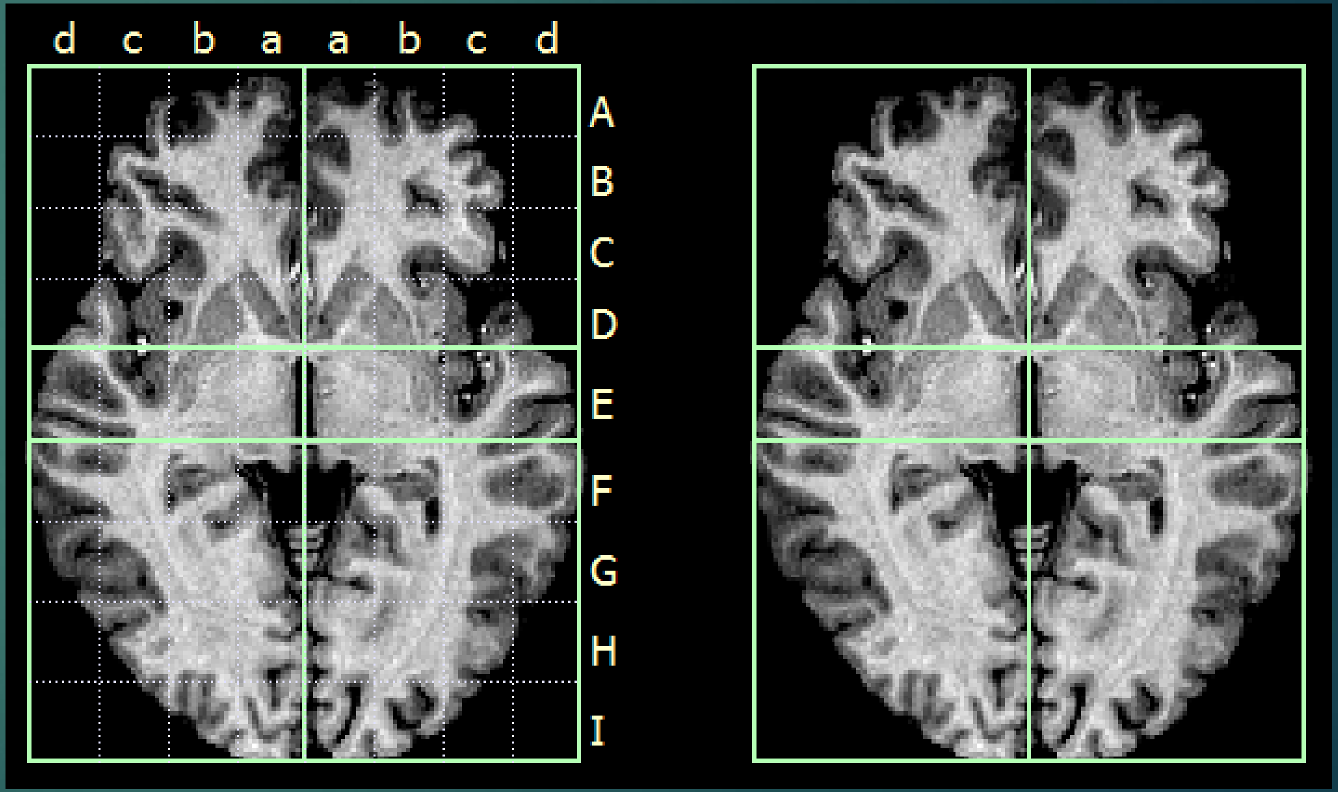
- For group analysis, how can we compare two different brains
  - Different shapes
  - Different sizes
  - Variation in features (CSF volume in ventricles)

- Need a standard brain template to normalize to



Talairach Brain / Coordinates

- Stereotactic system = 3D coordinate system
- Developed by Jean Talairach in 1967 defining a standard coordinate system for neurosurgeons
- New version in 1988 co-authored by Tournoux
- Talairach/Tournoux Atlas
- Original normalization space used in fMRI

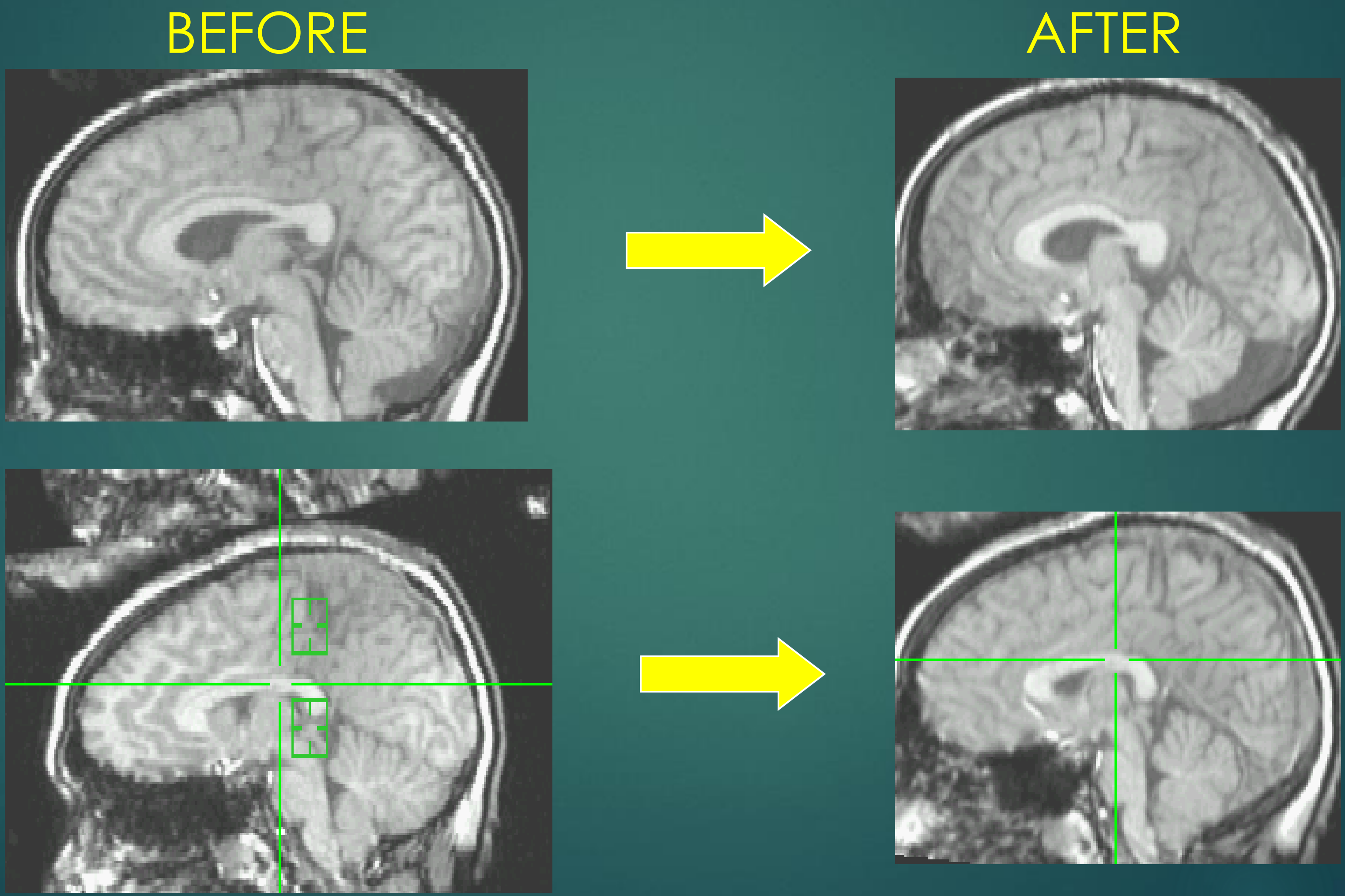


J. Talairach and P. Tournoux, "Co-planar Stereotaxic Atlas of the Human Brain: 3-Dimensional Proportional System - an Approach to Cerebral Imaging", Thieme Medical Publishers, New York, NY, 1988

Talairach Atlas

- Originally used to for surgical planning for deep subcortical structures in the brain (e.g. basal ganglion, thalamus, etc.)
- Based on the brain of 69 YO French female
- Numerous stories about the preparation of this woman's brain for sectioning

“Talairaching” of Brains



Disadvantages of Talairach

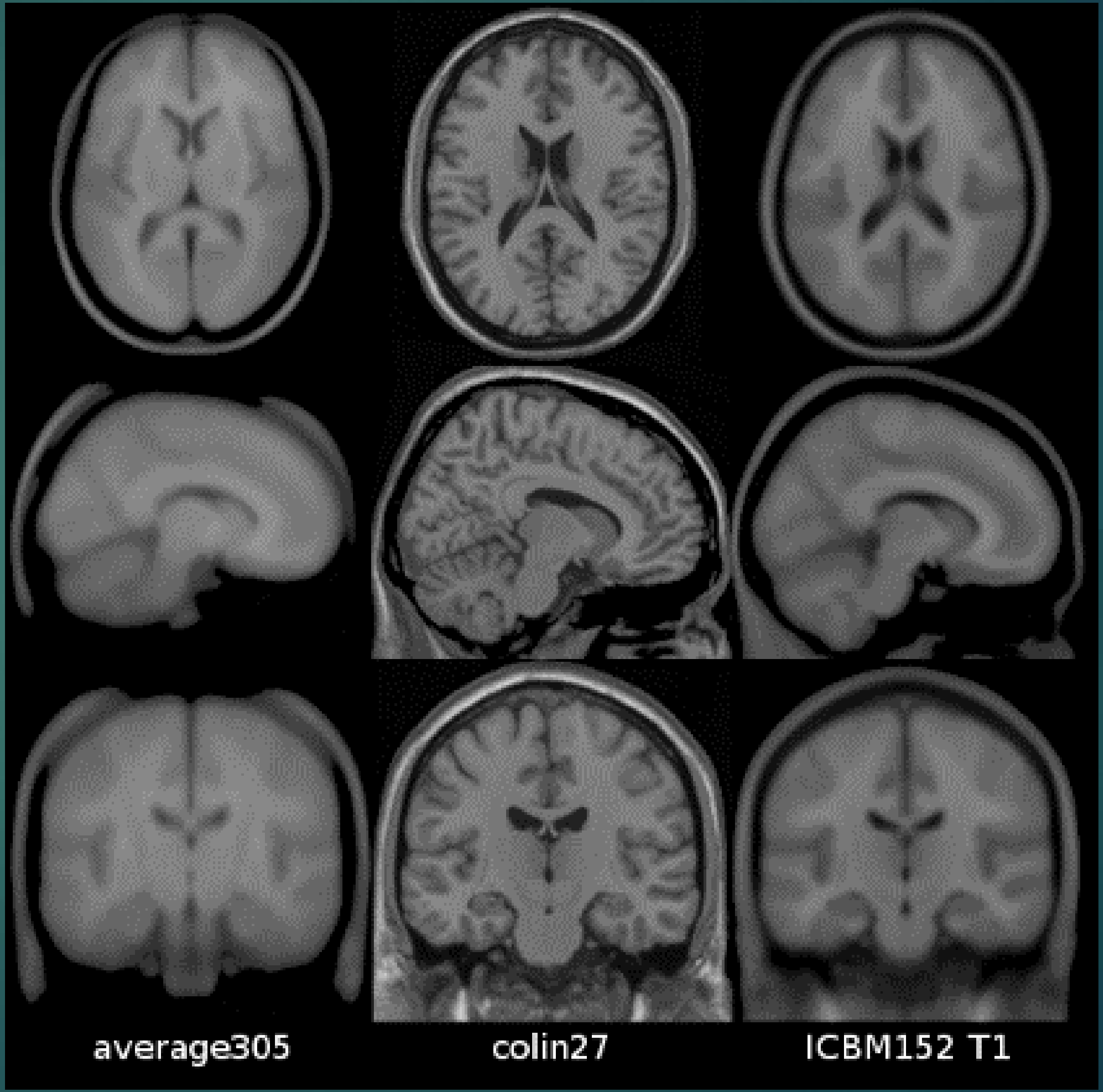
- Based on a single cadaver brain and not representative of younger living brains
- Left-Right hemispheric differences are ignored (assumed symmetric for spatial normalization)
- Cerebellum completely ignored
- Notorious problems (e.g. occipital lobe is much smaller in atlas than most brains)
- Non-European brains (e.g. Asian) do not fit well within the Talairach space

Newer Template was Developed (Montreal Neurological Institute (MNI) Brain

- Wanted a standard brain more representative of the population
- Approximately matched to Talairach
- Took 241 normal brains and manually defined landmarks to equivalent positions on Talairach atlas
- Took 305 normal MRI scans and matched them to the brains lined to Talairach atlas
- Averaged the 305 brains (MNI305 brain)
- Also have ICBM152 (average of 152 normal MRIs)
- Colin Holmes, scanned 27 times and registered each MRI to created a detailed single-subject brain set

A. C. Evans and D. L. Collins and S. R. Mills and E. D. Brown and R. L. Kelly and T. M. Peters, "3D statistical neuroanatomical models from 305 MRI volumes", Proc. IEEE-Nuclear Science Symposium and Medical Imaging Conference, 1813-1817, 1993.

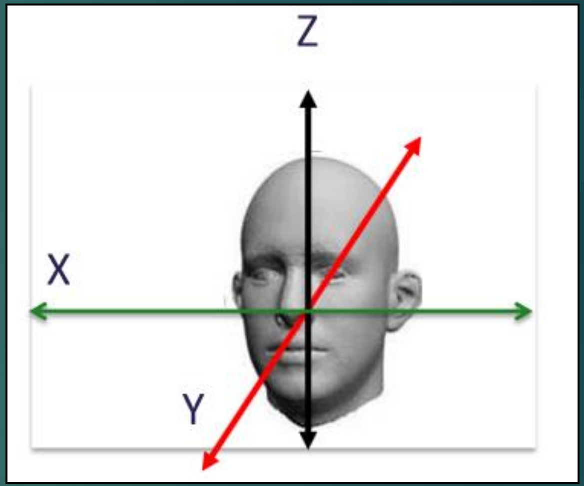
Famous Brains

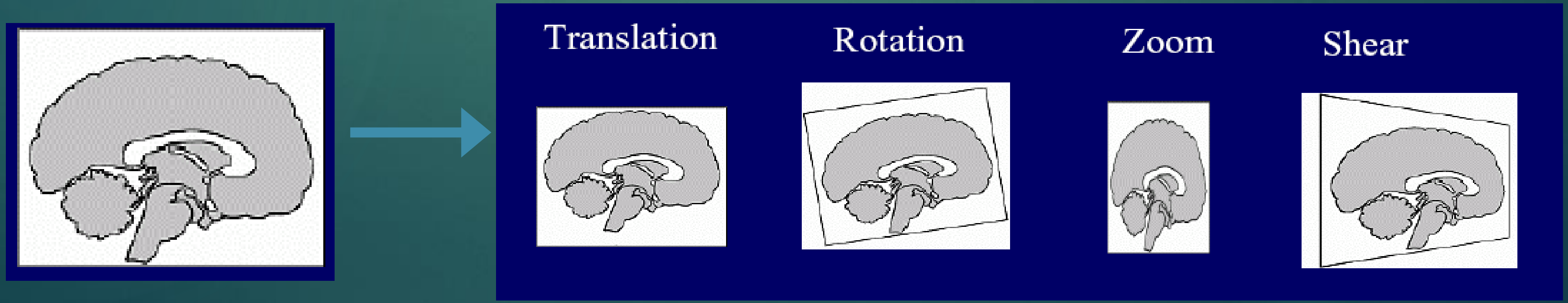


Normalization

Normalization: Procedure (12 degrees of freedom (dof))

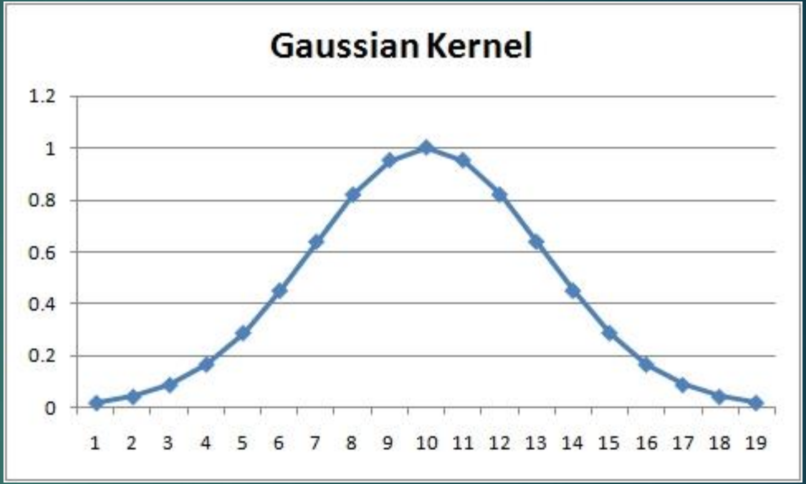
1. Translations across axes (3 dof)
2. Rotations around axes (3 dof)
3. Scaling or Zooming (3 dof)
4. Shearing or Skewing (3 dof)





Spatial Smoothing

- Blurs out residual anatomical differences and registration errors
- Data becomes more normally distributed
- Increases sensitivity to effect of similar scale kernel function (BOLD or HRF signal)
- Each voxel is replaces by the weighted average of itself and its neighboring voxels



Problems of Spatial Smoothing

- Reduction of spatial resolution of the data
- Edge Artifacts
- Merging
- Mislocalization of activation peaks