Methods of Investigation, Part I: Behavioral/neuropsychological testing & MRI

H-126 Typical and Atypical Neurodevelopment
September 11, 2017

Overview

- Neuropsychology and behavioral testing
- MRI: The physics behind it
- Structural versus functional MRI
- Diffusion tensor imaging
- What are we measuring in fMRI? The BOLD effect
- The subtraction logic
- fMRI analysis or 'Where do the colored blobs come from'?
- Challenges of designing an fMRI experiment
- Pediatric Imaging: Special considerations

Brief history of Neuropsychology: Trepanation

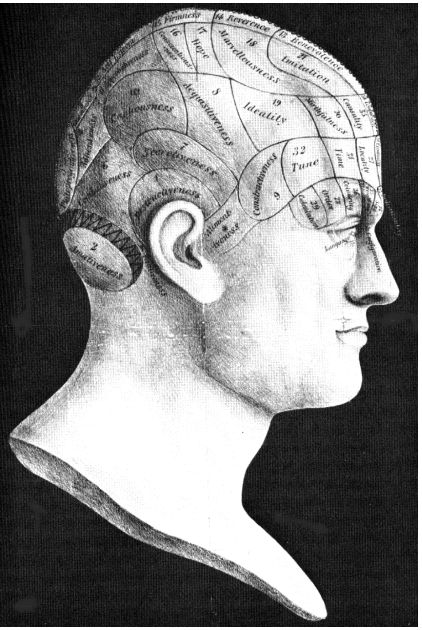
The trepanned skull of Chios

FIG. 1. The trepanned skull of Chios. The *arrow* points to the healed linear fracture associated with the bur hole. Copyright Hellenic Ministry of Education and Religious Affairs, Cultural Sector, 20th Ephorate of Prehistoric & Classical Antiquities, Archaeological Museum of Chios. Published with permission.

- Oldest known example: 2200-1720 BC in Crete
- Archeological evidence for trepanation found all over the world
- Broca suggested it was to "release deamons"
- Used to treat brain injury at least in Ancient Greece (e.g., by Hippocrates & followers)

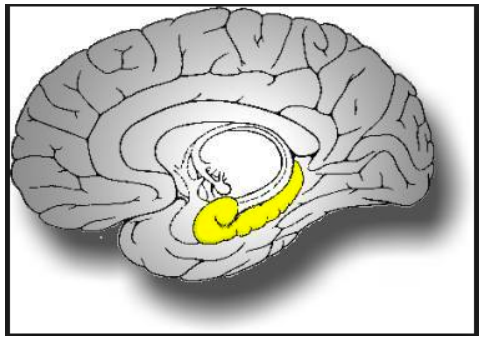
Tsermoulas, G., Aidonis, A., & Flint, G. (2014). *Journal of Neurosurgery*, *121*(2), 328–332

Brief history of Neuropsychology: Phrenology (around 1810-1840) Franz Joseph Gall



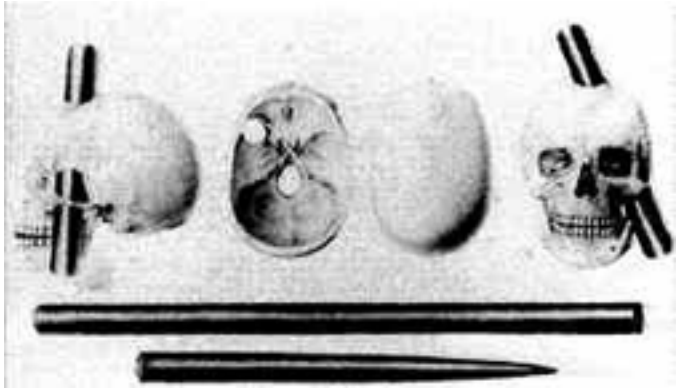
By late 19th century – Neurology

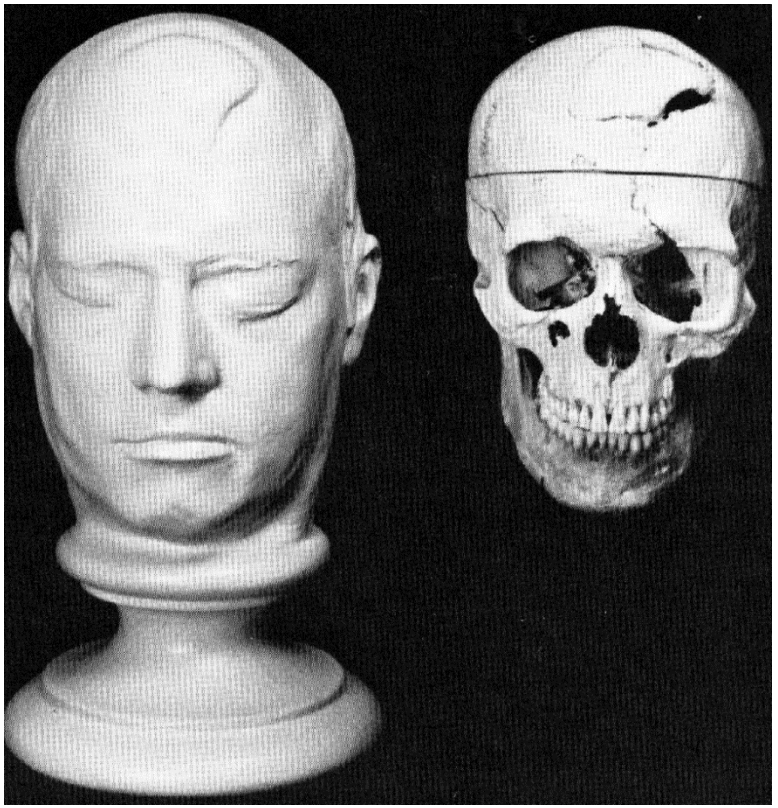
- Scientists began linking specific brain lesions with cognitive functions
- The names of these scientists are all over the modern brain, as are their (sometimes fanciful) ideas



CASE STUDIES

We have learned a lot about the brain from individuals who have had major brain injuries. One such, is Phineas Gage (accident 1848).





The main injury to Gage's skull was at the exit, where the tamping iron created an irregular area of damage about 3.5 inches long and 2 inches wide. You can see from this bust the large scar left on Phineus' head & his oddly healed eye socket & skull.

Broca and Wernicke Aphasia

In 1861 Broca reports "Mr. Tan" (Leborgne)
Patient can only produce "tantan"
but understands language
→ Broca aphasia

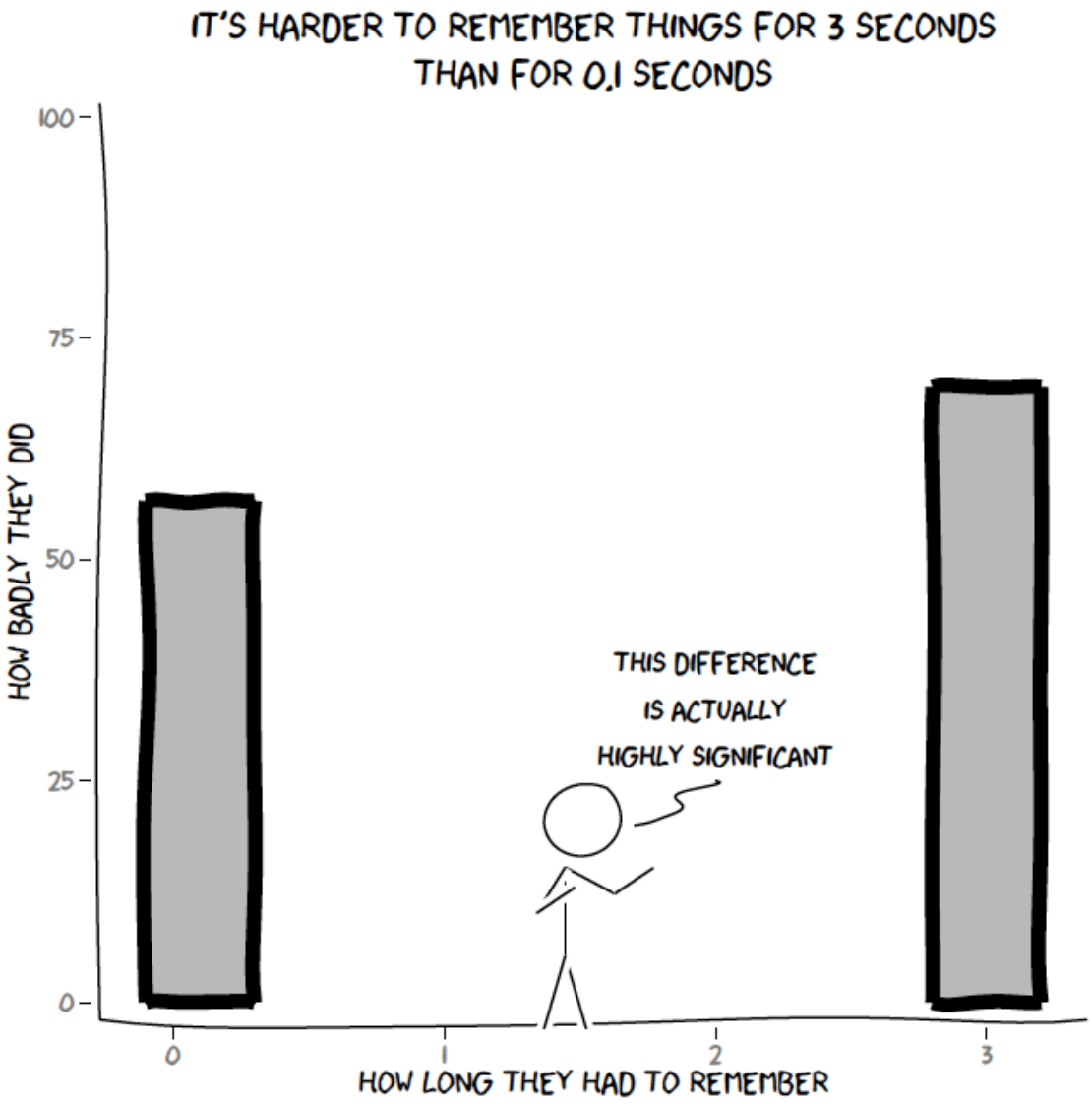
In 1874 Wernicke presents
10 patients who cannot understand language
but can still produce it
→ Wernicke aphasia

- Wernicke proposes that there are 2 language areas: one for production (Broca's area) & one for meaning (Wernicke's area) & that these are connected
- Disruption of the 'meaning area' or 'motor area' or it's connections would result in different disruptions.

Birth of Neuropsychology

- The case of aphasia highlights a related and important point: testing 'speech' is not enough
- In addition, neurological deficits are often subtle
- More and more sophisticated tests were created to specifically test aspects of behavior that were linked with the function of neural structures in an attempt to tell what kind of damage someone had incurred following a brain injury.

Developing Neuropsycholgical Tests



Standardization

- What does it mean if a 27-year-old gets 5 questions right on an IQ test and a 6-year-old shows the same performance?
- How do you compare two 6-year-olds who get 5 versus 8 questions right?

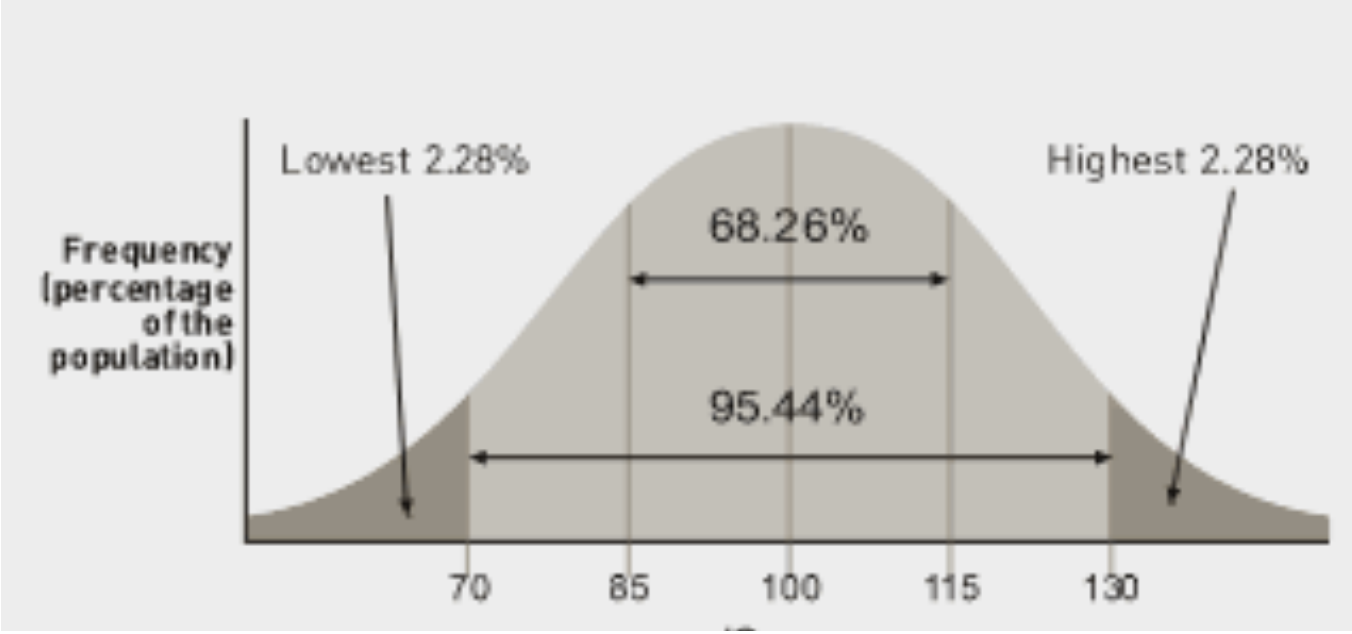
Raw Score: (generally) number of items answered correctly

Standard Score (SS): derived from Raw Score and age/grade; reflects how far the score lies from the norm group's mean according to standard deviation

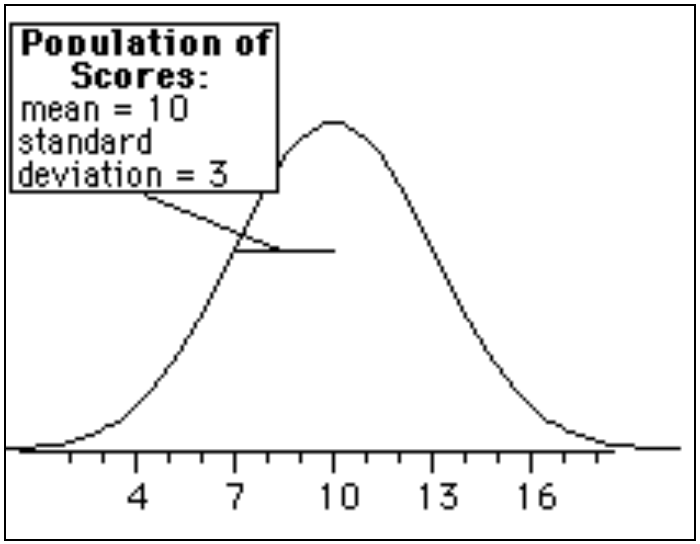
Percentile Rank: derived from SS; tells the percentage of people that age/grade that the individual scored better than

Age- and Grade-Equivalents: the average score of norm-group children at a particular age or grade

Normal distribution



Mean = 100
SD = 15



Mean = 10
SD = 3

Reliability

1. If this test were re-administered to the same child, would he/she get the same result?

   → test-retest reliability

2. If a different tester administered this, would the child get the same result?

   → inter-rater reliability

3. If this test were administered twice to the same child, would the result be the same?

   → test-retest reliability

4. If the question were asked another way, would the result be the same?

   → alternate form reliability, internal reliability

Validity (examples)

- Do (all) the items represent the domain that the test is supposed to measure?

  → Content validity

- Are the test scores related to a concurrent or future criterion?

  → Predictive validity

- Does the test assess a psychological construct or trait?

  → Construct validity

- Did knowledge of test results lead to constructive change in examinee's life?

  → Treatment validity

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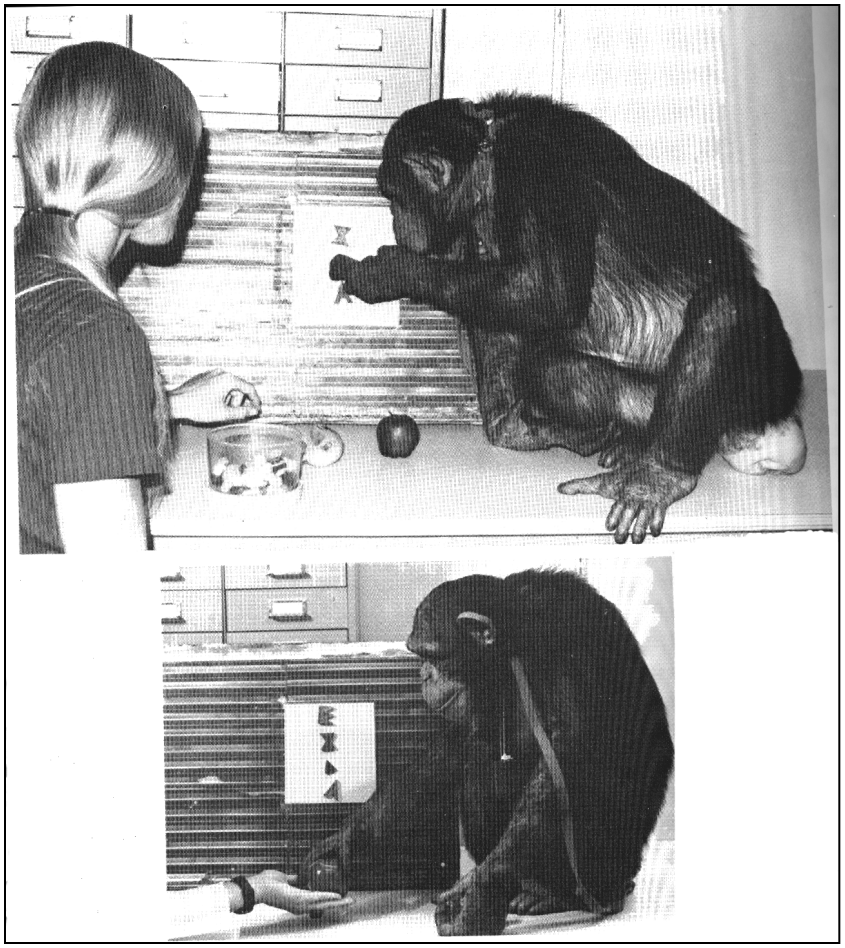
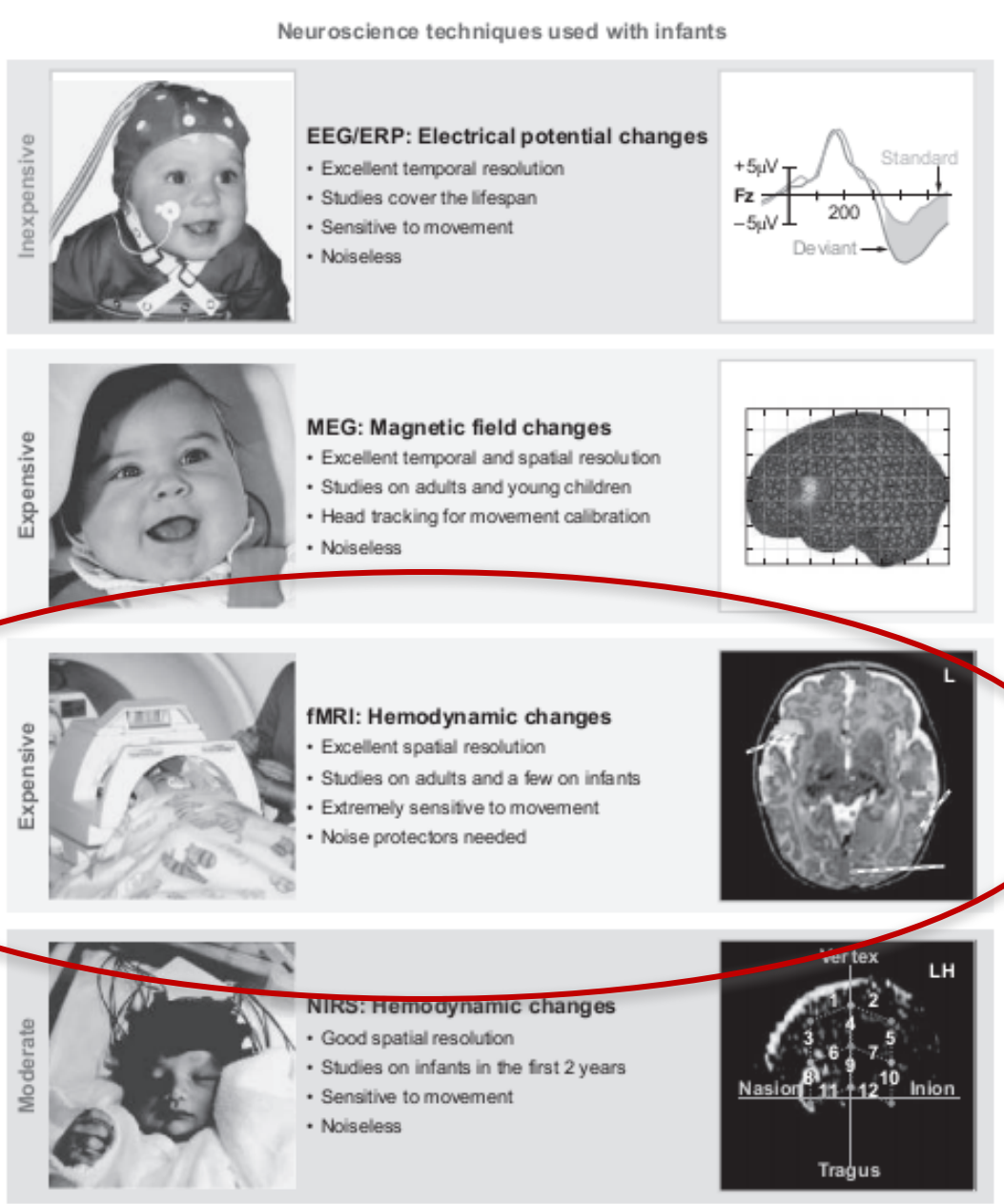
How do we study the brain?

- Trepanation?
- Phrenology?
- Lesions?
- Neurospychology?
- Animal Studies?



Neuroscience techniques



Source: Kuhl & Rivera-Gaxiola (2008), Institute for Learning & Brain Sciences, University of Washington

(Image: Hoff/Language Development)

MRI physics…

- MRI uses magnetic fields to create images of biological tissues

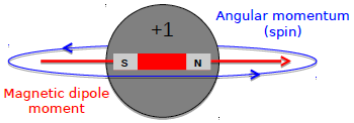
MRI magnet ~ 3Tesla (T)

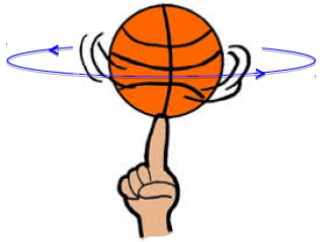
Earths magnetic field ~ .00003T

- Typically, when we talk about MRI, we are referring to a signal that comes from hydrogen atoms within water molecules in our body.

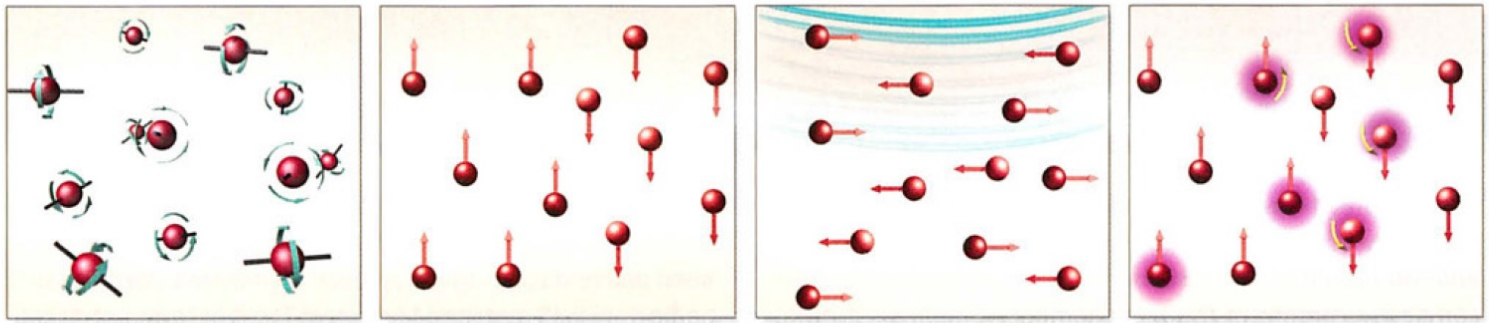
Spinning protons…

- The hydrogen atom is the most abundant atom found in our body (70% of our body is H_20)
- All protons (in atomic nucleus) spin creating a small magnetic charge
- A magnetic field aligns the spins of hydrogen atoms (usually they are all randomly oriented)
- A radiofrequency pulse (energy) is introduced that disrupts the protons and forces protons to a different alignment with the magnetic field (e.g. 90 degrees; depends on amplitude and duration)
- If pulse is turned off then protons slowly go back to their original alignment releasing electromagnetic energy
- MRI (a radio frequency coil) can detect this energy and can differentiate different tissue based on the time it takes the protons to go back to their original state





The 'decay rate' is different depending on what kind of tissue the H atom is in → this is how we 'build' a MRI picture.



In normal state, the orientation of spinning protons is randomly distributed.

Exposure to the magnetic field of the MRI scanner aligns the orientation of the protons.

When a radio frequency pulse is applied, the axes of the protons are shifted in a predictable manner and put the protons in an elevated energy state.

When the pulse is turned off, the protons release their energy as they spin back to the orientation of the magnetic field.

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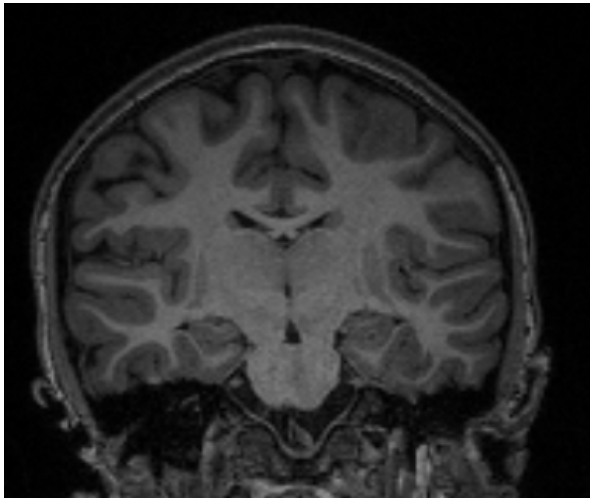
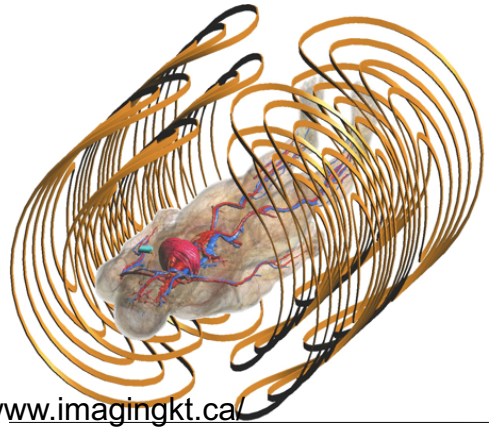
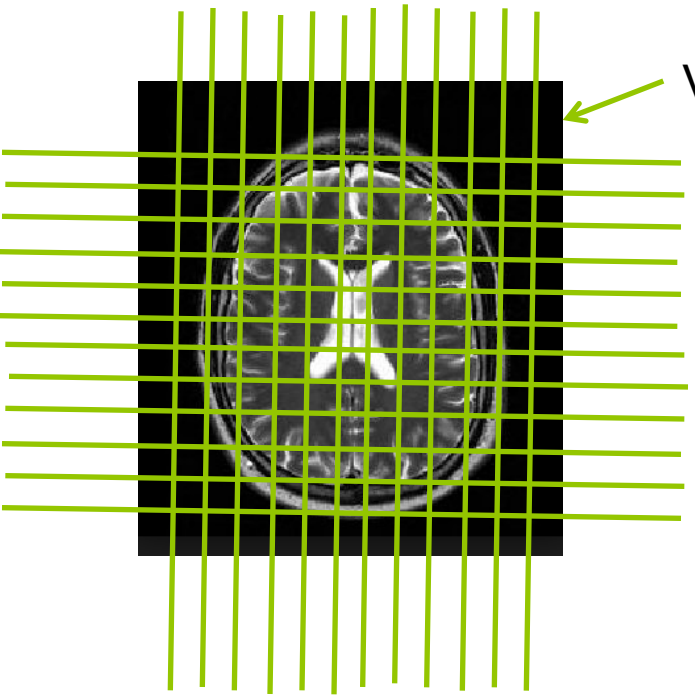
Gazzaniga, Ivry, R., Mangun (2013)



Gradient Coils



http://www.imagingkt.ca/



Gradient coils are other magnetic coils that are next to the main magnetic coil

We "pulse" these coils: turn them rapidly on and off by introducing current into them and then removing it rapidly.

This creates a kind of grid where the magnetic field is slightly different across the brain – allowing better spatial resolution because you know where in space the spins are who are decaying more or less rapidly.

For more details…

- https://www.youtube.com/watch?v=Ok9ILIYzmaY

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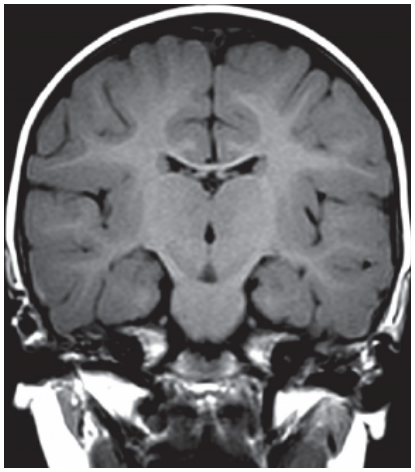
Brain Organization

- The cells of the brain are highly organized with respect to structure and function
- The tissues of the brain include:
  - Grey matter, which is mostly comprised of cell bodies. It's main function is information integration.
  - White matter, which is mostly comprised of axons. It appears 'white' because the axons are covered in a fatty myelin sheath, or 'myelinated'. It's main function is information transfer.
  - Cerebrospinal fluid is the clear liquid that circulates through and surrounds the brain. The brain actually floats like a sponge in the CSF.
  - The meninges are several thin membrane layers that cover and protect the brain.



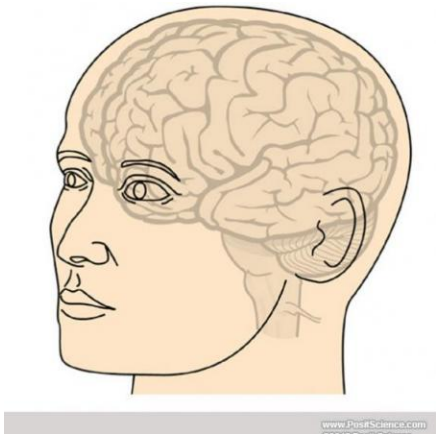
Griffiths et al., 2010

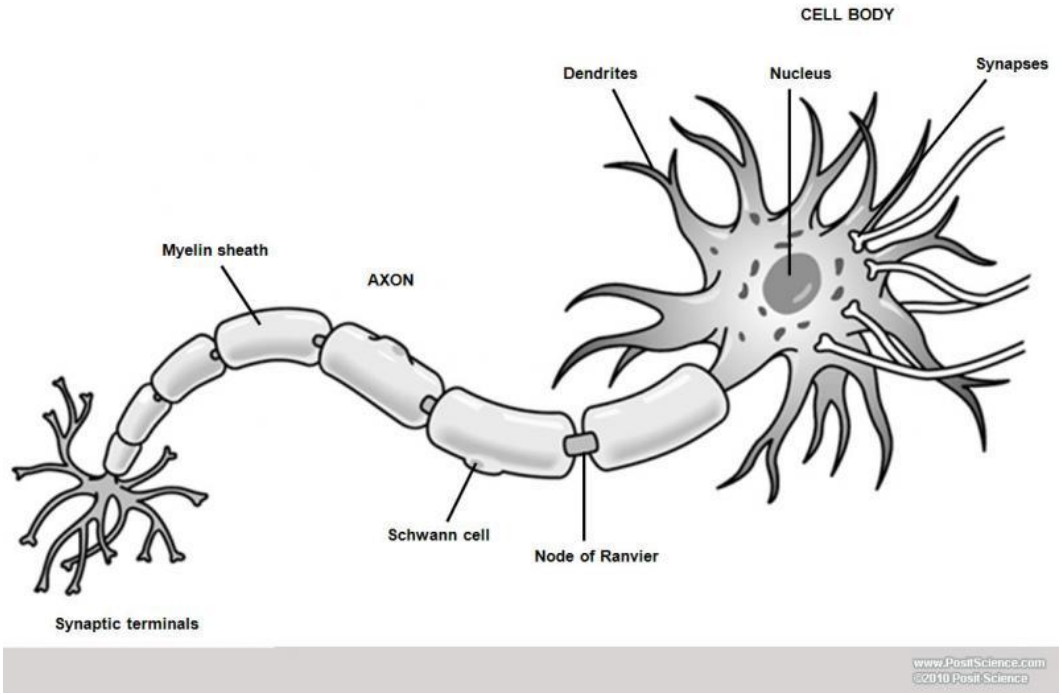
Brain Cells

The brain is made up of a variety of cells that have different functions.

- **Nerve cells**, or **neurons** are the basic working unit of the brain. They process information and send and receive signals

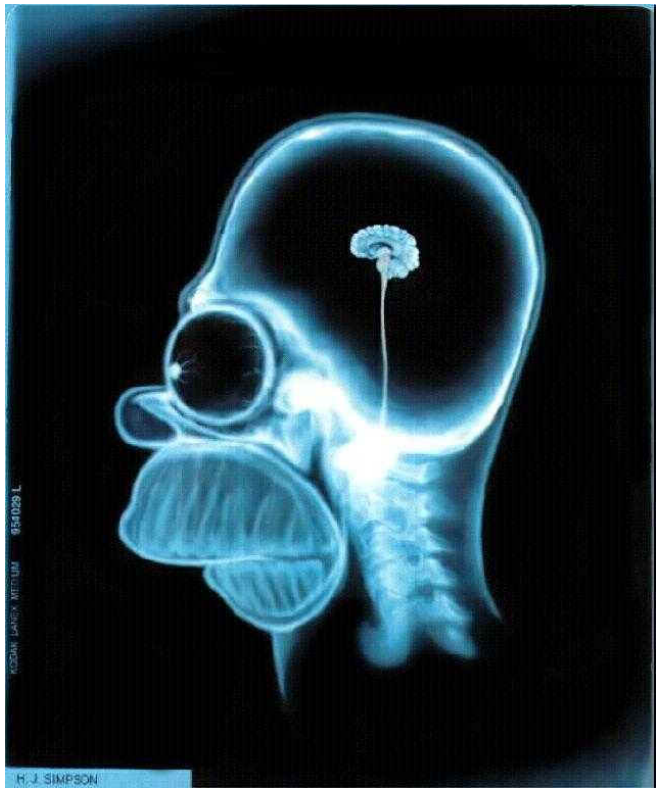
- **Glial cells**, or **glia**, play a variety of supporting roles to the neurons. One of their most important jobs is to make up the myelin sheath that surrounds the axon, insulating them so that the signal doesn't degrade over distance. This is analogous to the plastic coating on wires.





MRI vs. fMRI

MRI studies brain anatomy.



Functional MRI (fMRI) studies brain function.

Source: www.**fmri**4newbies.com/

MRI vs. fMRI

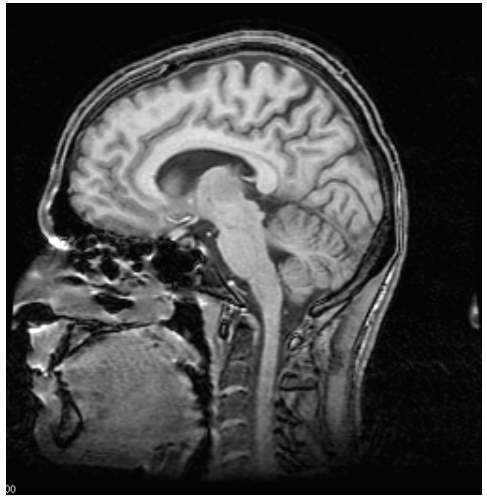
MRI

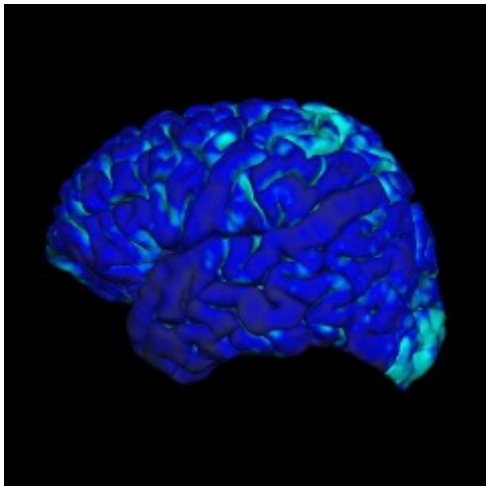
- shows difference between different types of tissues
("difference in space", e.g. white vs. gray matter)

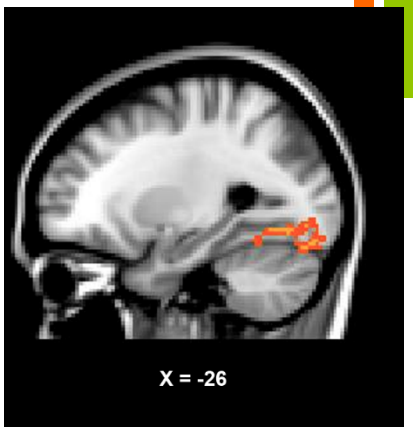
fMRI

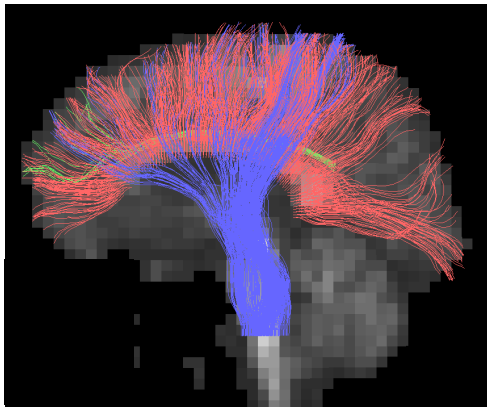
-shows difference between stimulated and non-stimulated tissue
("difference in time course")

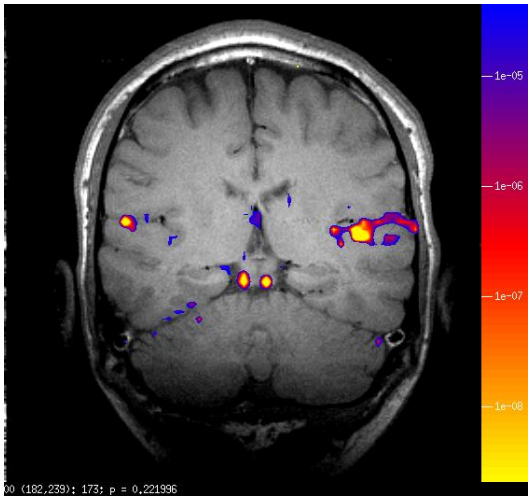
Structural MRI & Functional MRI











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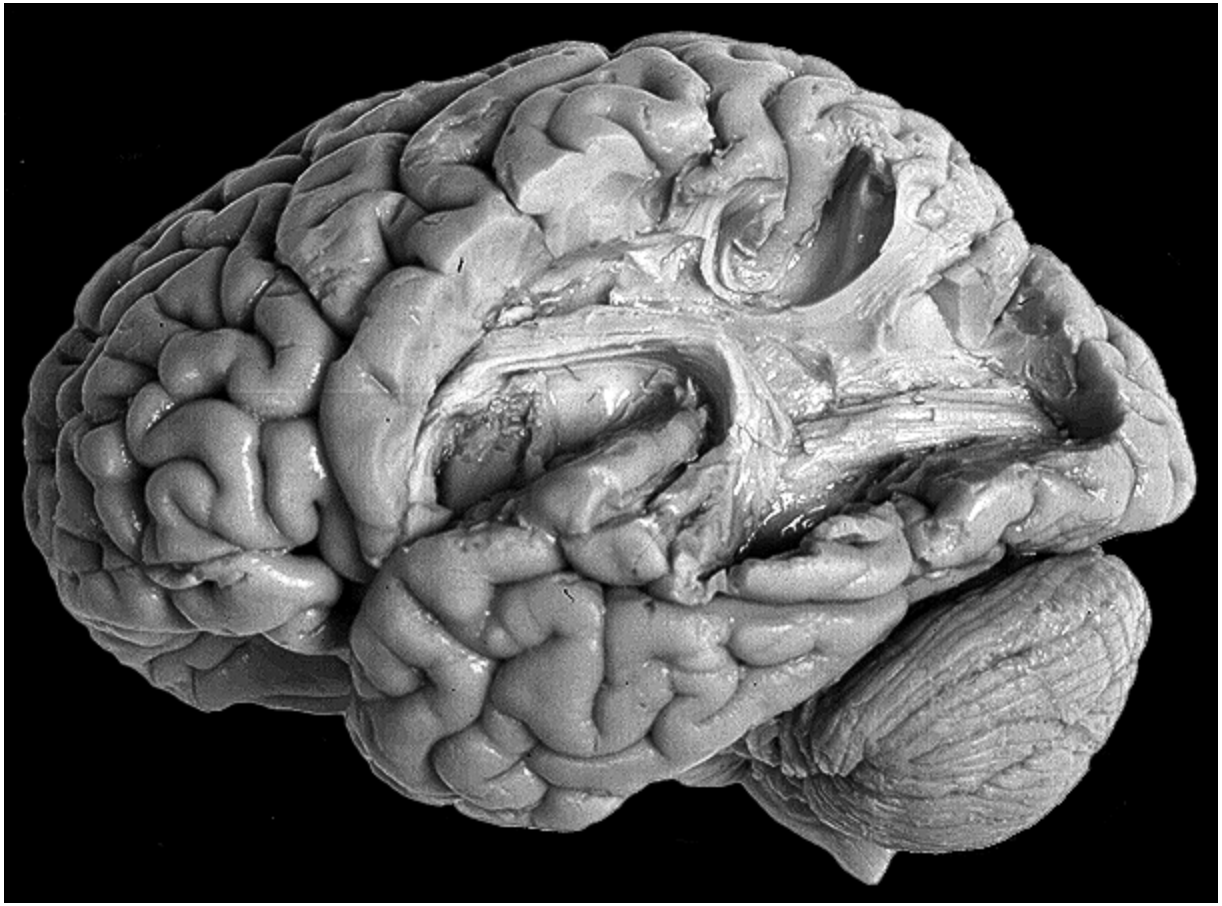
White matter tracts

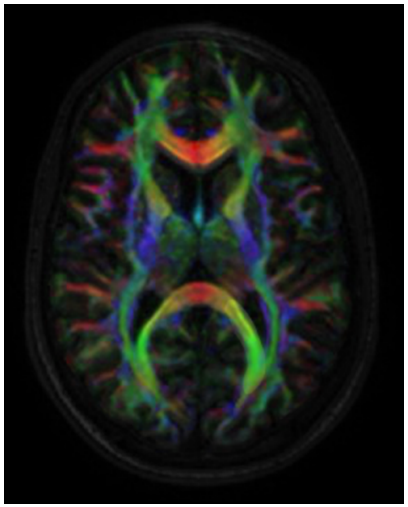


http://www.biocfarm.unibo.it/aunsnc/pictef14.html

Diffusion Weighted Imaging data

- Diffusion weighted imaging (DWI) is a form of MR imaging based upon measuring the random Brownian motion of water molecules within a voxel of tissue.

Color-FA map



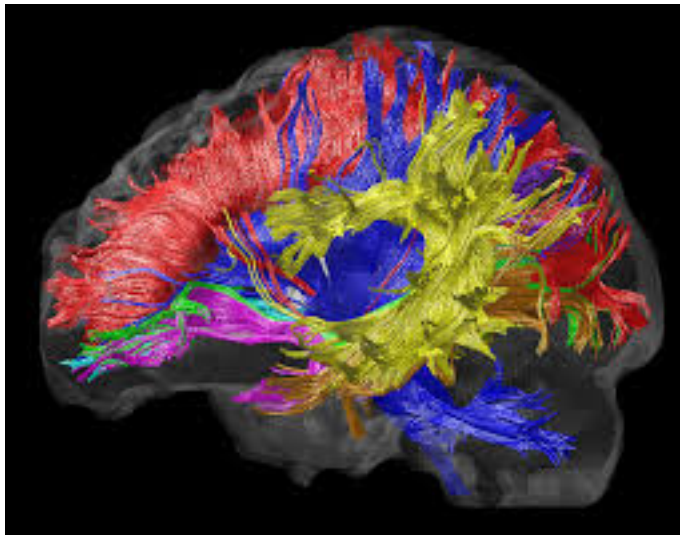
Red
transverse axis (x-axis)

Blue
superior-inferior (z -axis)

Green
anterior-posterior axis (y-axis)

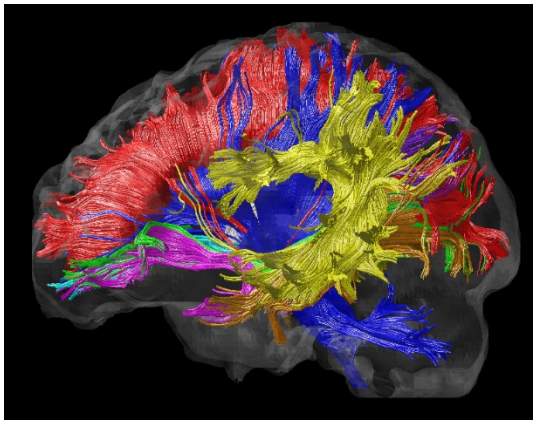
Demonstrates the direction of fibres

Whole-Brain Tractography



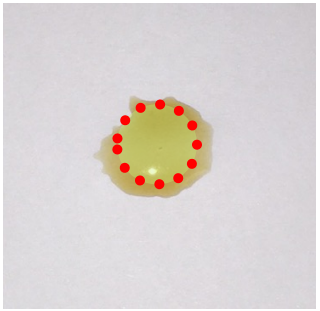
Diffusion tensor imaging

- Measures structural connectivity (white matter fiber bundles)
- Isotropy (uniformity in all orientations) versus anisotropy (directionally dependent)

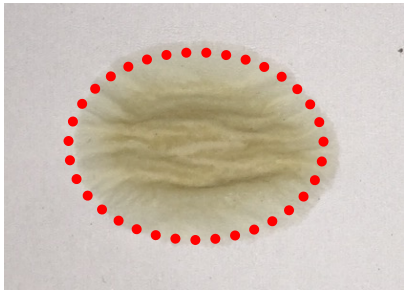


neuroimaging.tau.ac.il

vs.



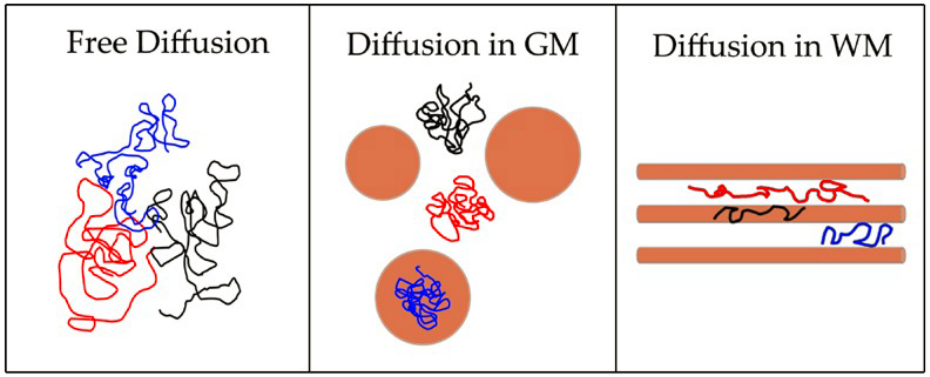
Coffee drop on a sheet of B5 paper



Coffee drop on a tissue paper

Diffusion tensor imaging

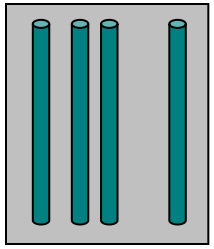
- Water diffuses in a selective direction along bundles of fibers
- Nerve fibers represent cylindrical-shaped physical spaces with membrane acting like a barrier
  - DT shows diffusion preference along axon
- Measuring the diffusing anisotropy, we can estimate the dominant direction of the nerve bundle passing through each voxel



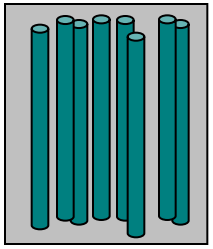
Fractional Anisotropy (FA)

- Helps to determine the number, size and myelination of fibers. But FA only gives information about directionality, can not differentiate microscopic characteristics.

Number of fibers

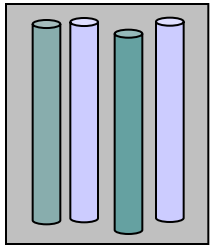


High Diffusivity
Low FA

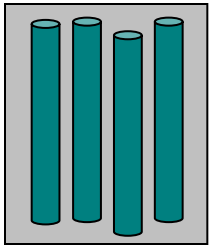


High FA
Low Diffusivity

Myelination of fibers

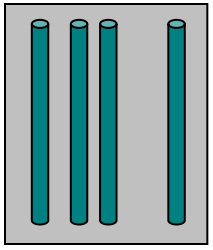


High Diffusivity
Low FA

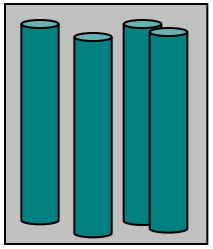


High FA
Low Diffusivity

Size of fibers

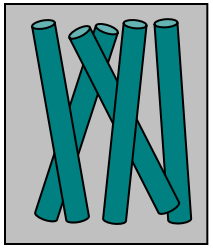


High Diffusivity
Low FA

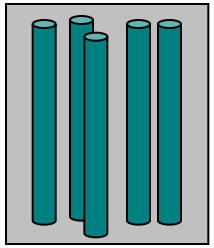


High FA
Low Diffusivity

Directionality of Fibers



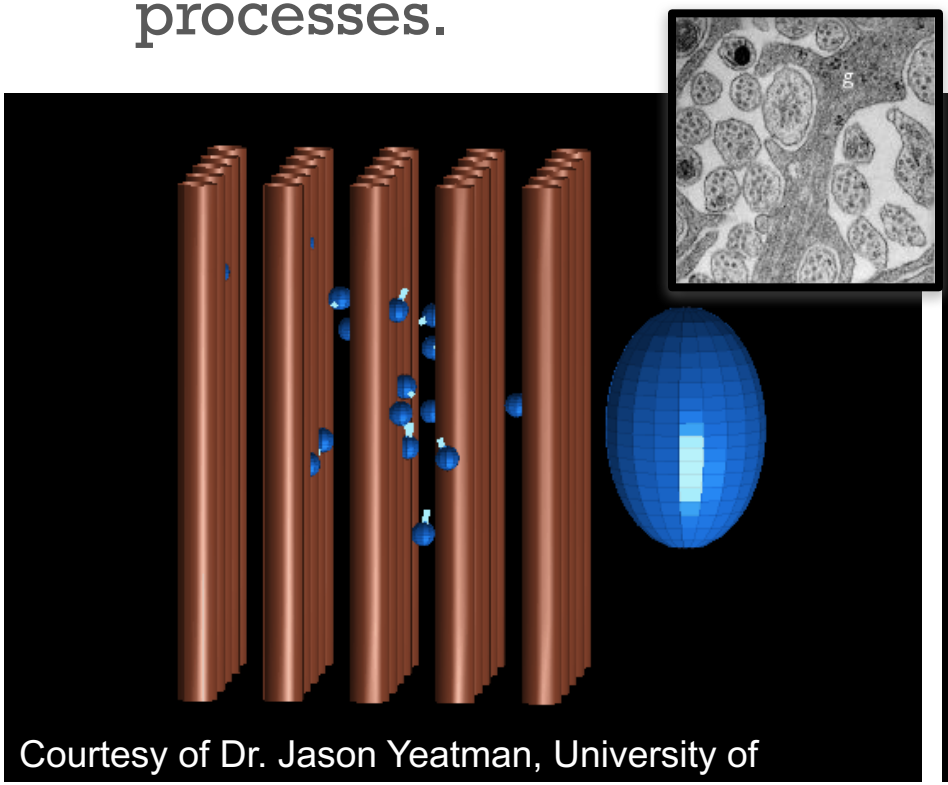
Low FA
Same Diffusivity



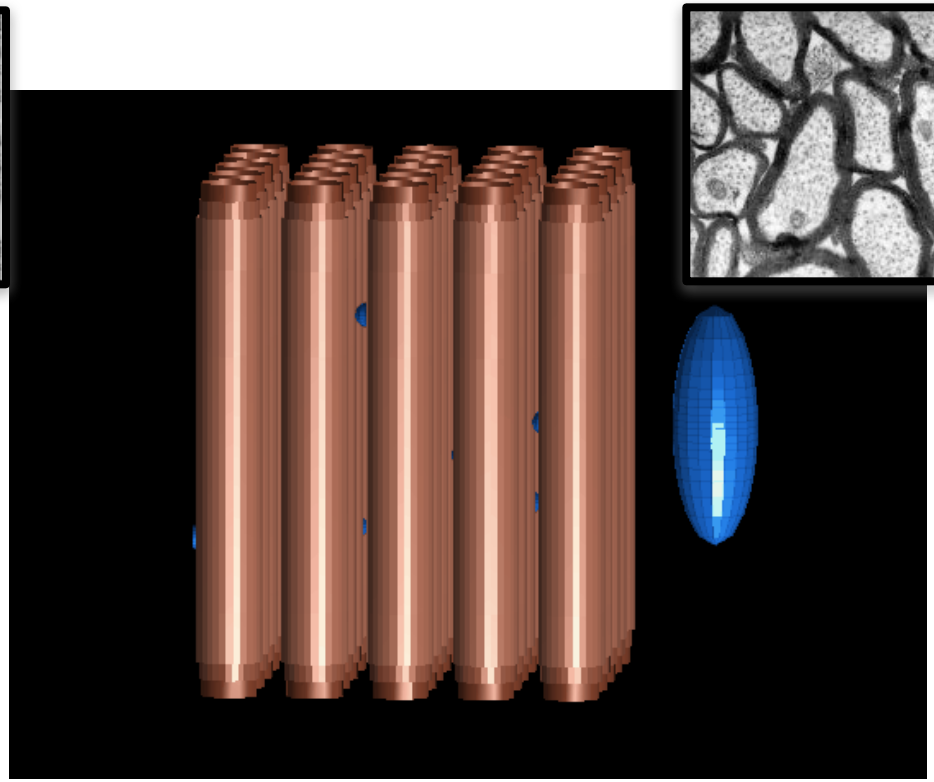
High FA
Same Diffusivity

Inferring tissue biology from diffus

- Diffusion is very sensitive to tissue changes and can help generate hypotheses about potential biological processes.



Low Fraction Anisotropy (FA)
High Mean Diffusivity (MD)

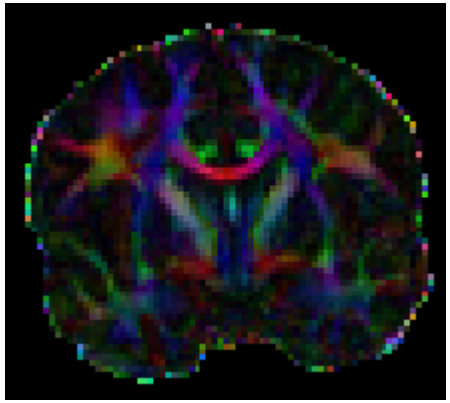


High Fraction Anisotropy (FA)
Low Mean Diffusivity (MD)

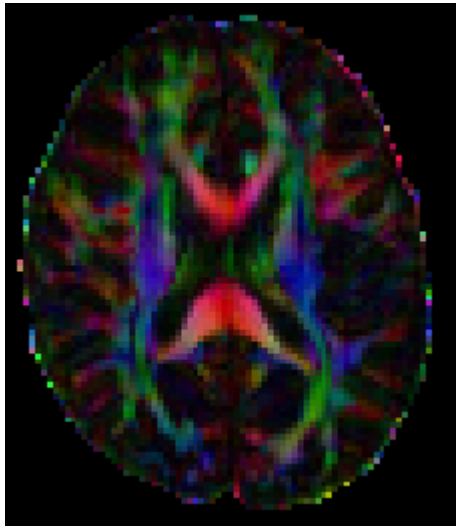
Wandell & Yeatman (2013); Stikov et al., (2011); Assaf & Pasternak (2008); Beaulieu

Visualization: Color FA

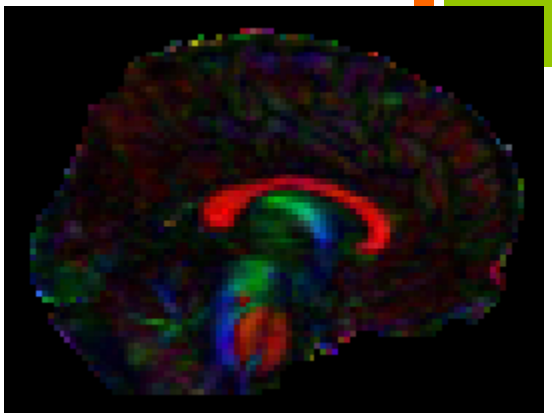
Coronal slice

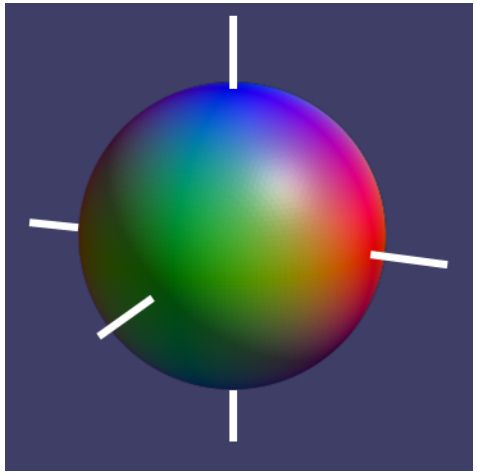


Axial slice



Sagittal slice





R = Red indicates directions in the X axis: right to left or left to right.

G = Green indicates directions in the Y axis: posterior to anterior or from anterior to posterior.

B = Blue indicates directions in the Z axis: foot-to-head direction or vice versa

Overview

- Neuropsychology and behavioral testing
- MRI: The physics behind it
- Structural versus functional MRI
- Diffusion tensor imaging
- What are we measuring in fMRI? The BOLD effect
- The subtraction logic
- fMRI analysis or 'Where do the colored blobs come from'?
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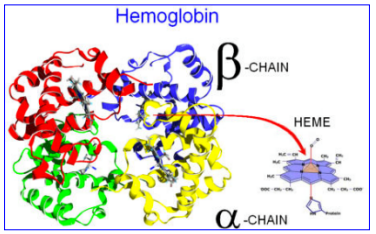
Discovery of the BOLD contrast

- To assess changes in brain function, we must use a measure that indexes neuronal activity.
- Single-unit recordings are too invasive so we need to assess neuronal activity indirectly by measuring its metabolic correlates.

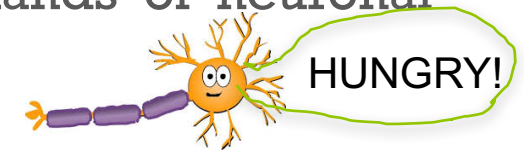


- Linus Pauling and Charles Coryell found that oxygenated hemoglobin (the molecule in red blood cells that carries oxygen) is diamagnetic (it does not affect a surrounding magnetic field since binding of oxygen suppresses magnetic properties of iron)
- However, deoxygenated hemoglobin is paramagnetic, so it distorts a local magnetic field. So, if blood oxygenation varies spatially according to brain function, it should be measurable by MRI.
- Increased neuronal activity = increased oxygen consumption?

[Song *et al.*]

Physiological Basis of BOLD (Blood-Oxygenation-level-dependent)

- The concentration of deoxygenated hemoglobin increases for the first several seconds after stimulation of neurons and then decreases (reflecting the initial demands of neuronal activity)



- More striking are the changes of oxygenated hemoglobin which increases extensively (even beyond regions of stimulation)

- We could call it the 'Oxygen paradox': neural activity evokes a coarse vascular response that OVERCOMPENSATES for metabolic demands.

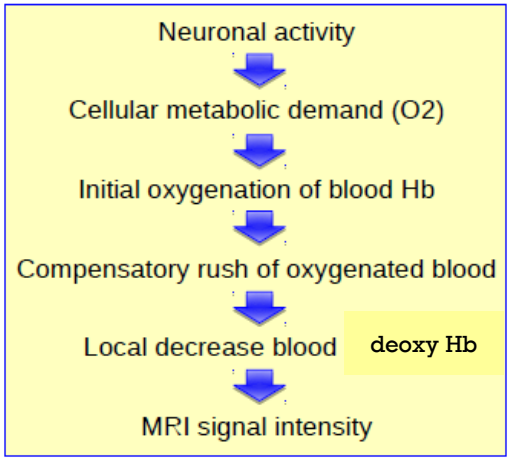
- So, even if only a small region is active for a short period of time, the vascular system supplies oxygen to a larger surrounding region for a longer period of time.

[Song *et al.*]

Physiological Basis of BOLD (con't) or BOLD fMRI hemodynamics

- As, the excess oxygenated blood flows through active regions, it flushes the deoxygenated hemoglobin from the capillaries supporting the active neural tissues.

- The BOLD signal increase following neuronal activity occurs therefore not because the oxygenated hemoglobin increases the MR signal, but because it displaces the deoxygenated hemoglobin that had been suppressing the MR signal.



[Song *et al.*]

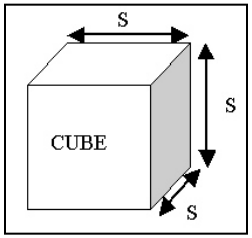
The BOLD (Blood Oxygen Level Dependency) effect:

1. You are "using" a specific area of your brain (e.g. Broca) to perform a task (e.g. listening to a story).

2. Decrease of oxygen in your blood in Brocas's area .

3. Increase in your blood flow to overcompensate for the "use" of oxygen and therefore increase of oxygen in your blood.

4. This oxygen change alters the magnetic-resonance signal in a measurable way (therefore we do not measure deoxygenated hemoglobin but detect the unused blood or oxygenated hemoglobin; delay 4-6 seconds).



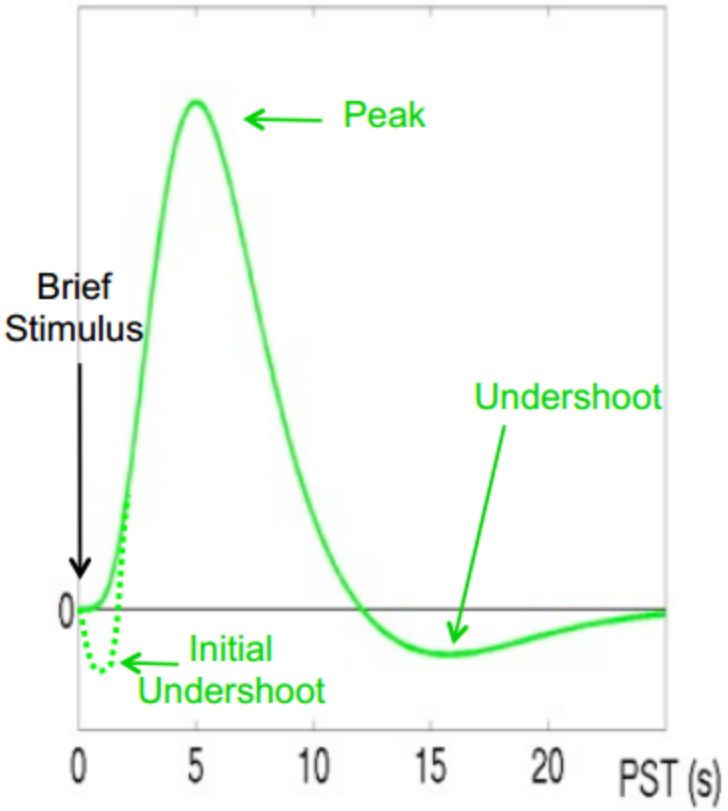
5. Changes can be seen by comparing the oxygen level voxel by voxel (*a voxel is a unit of graphic information that defines a point in three-dimensional space*) to a so called baseline

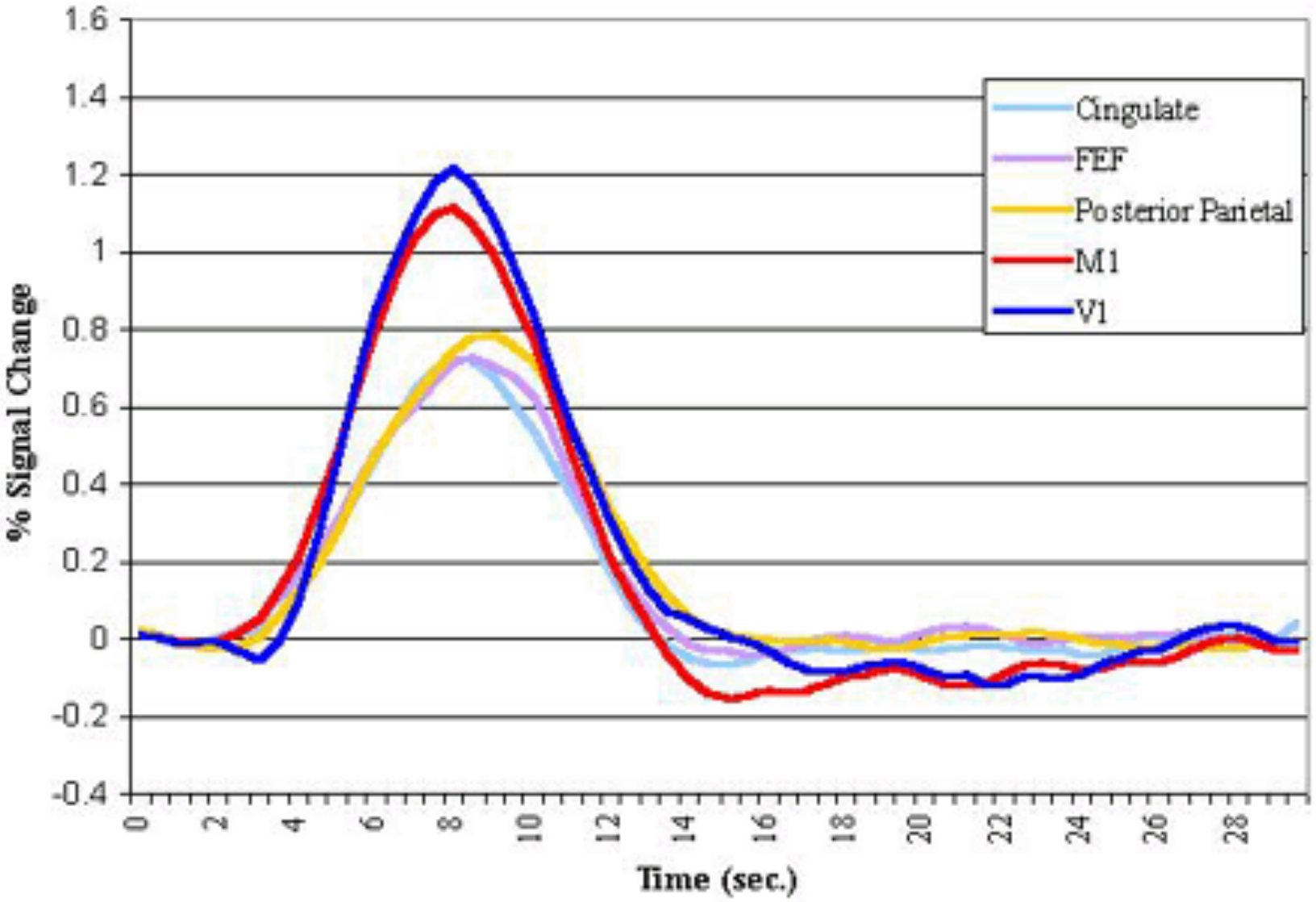
6. A recent study suggests that the hemodynamic response function provides a reliable measure of the firing rate of human cortical neurons and/or the amplitude (and duration) of local field potentials
(Mukamel et al., 2005; Logothesis et al., 2001; Huettel et al., 2004)

BOLD impulse response

Hemodynamic response is the term used to describe the coupling between blood flow and neuronal activation

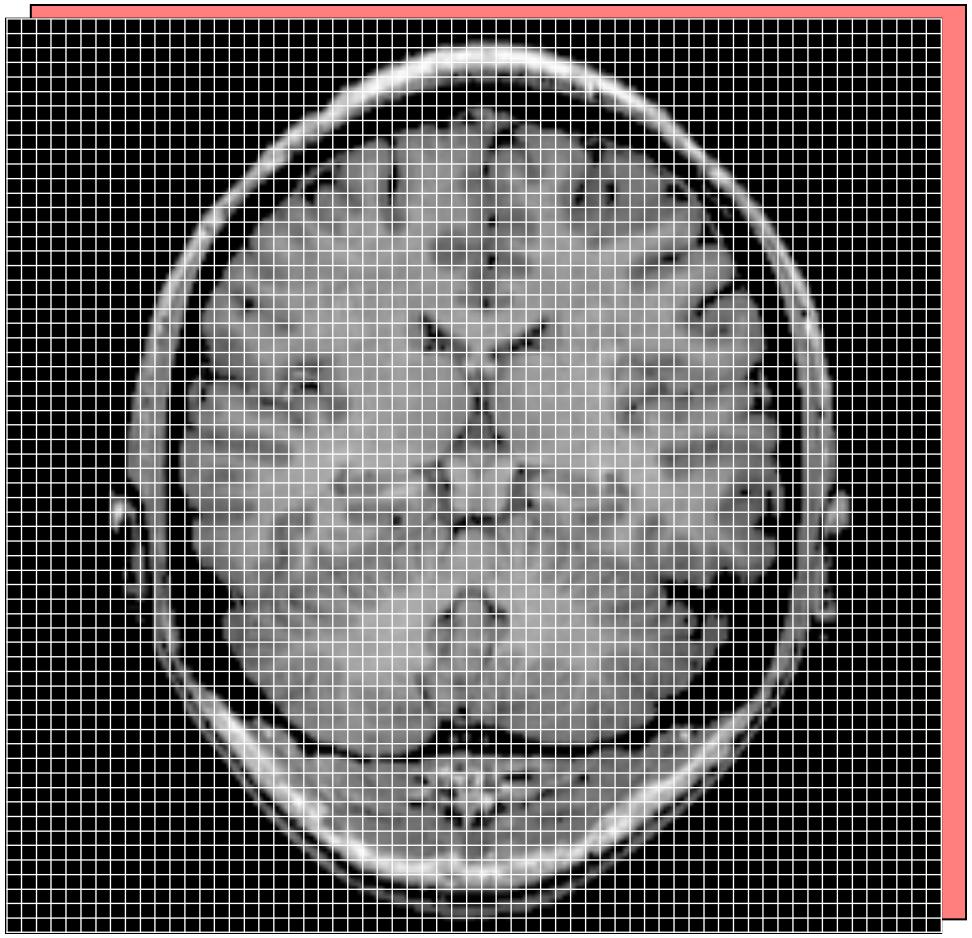
- Function of blood oxygenation, flow, volume
- Peak (max. oxygenation) 4-6s poststimulus; baseline after 20-30s
- Initial undershoot can be observed
- Similar across V1, A1, S1…
- … but possible differences across:
  - other regions
  - individuals





http://www.radiology.northwestern.edu/research/neuroimaging/investigation-of-the-hemodynamic-response-function/

We collect the hrf in each voxel…



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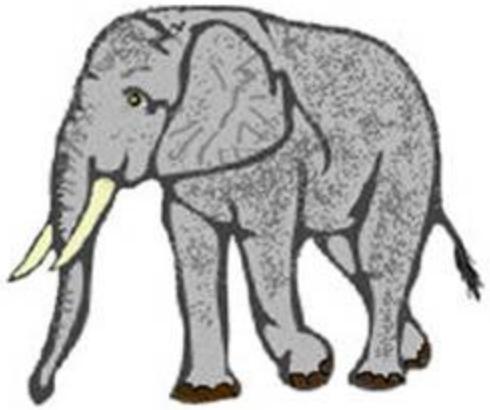
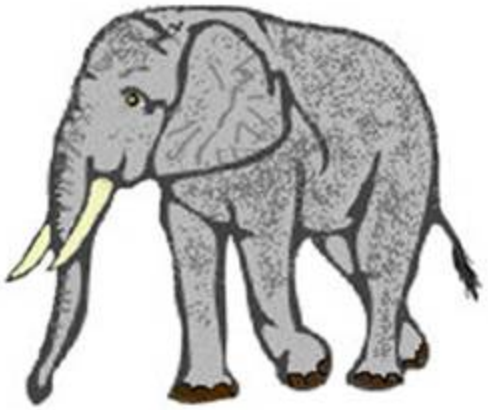
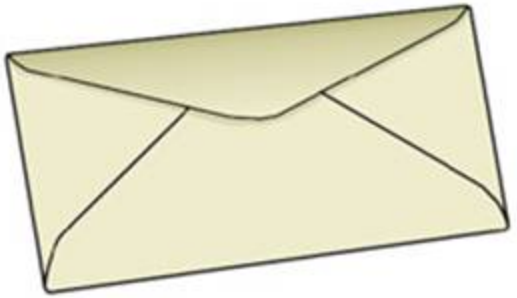
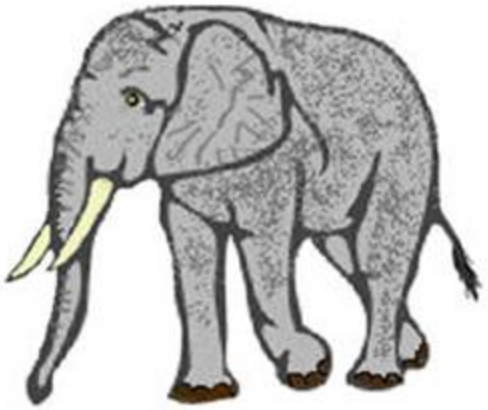
TASK EXAMPLE









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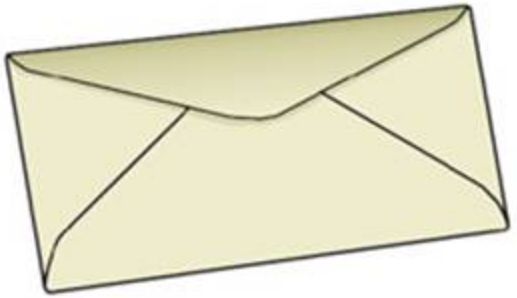

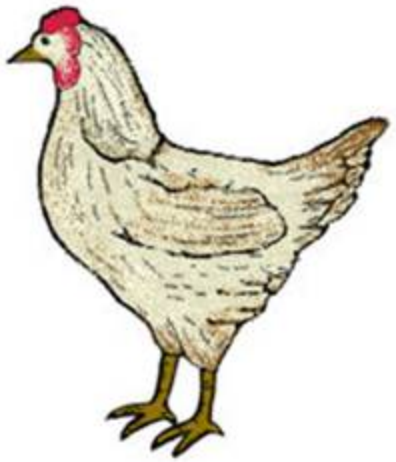

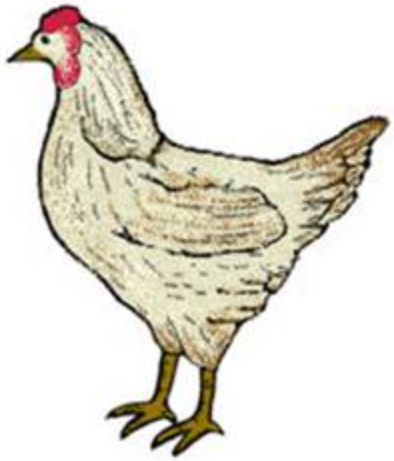

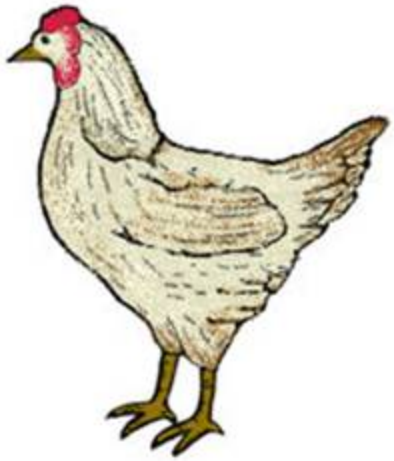

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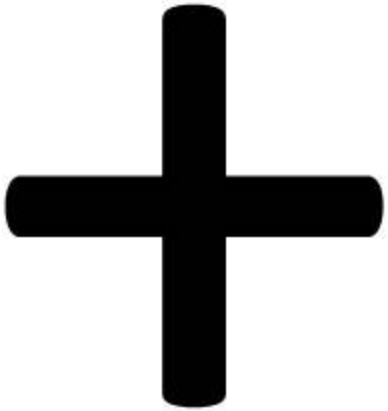

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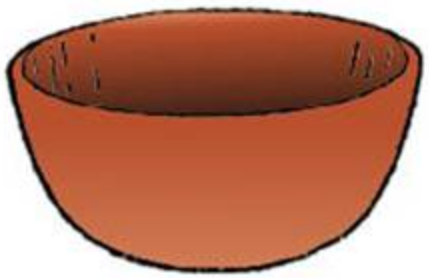

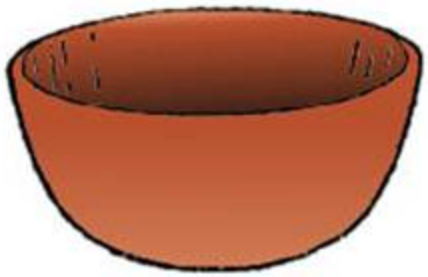

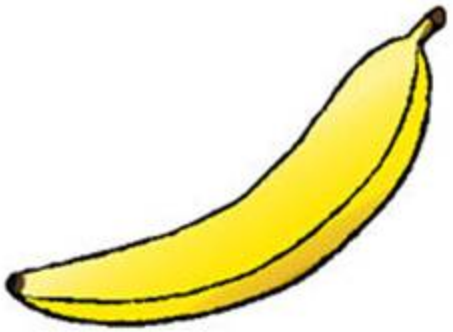

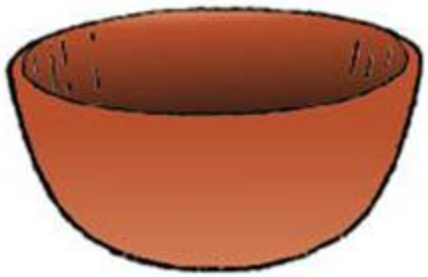

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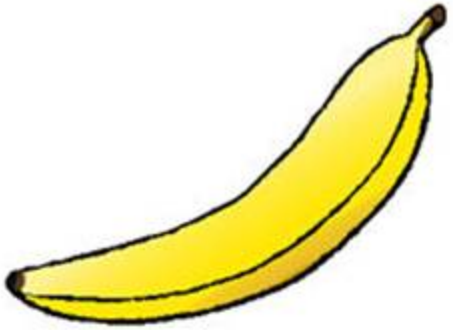



Great Job!

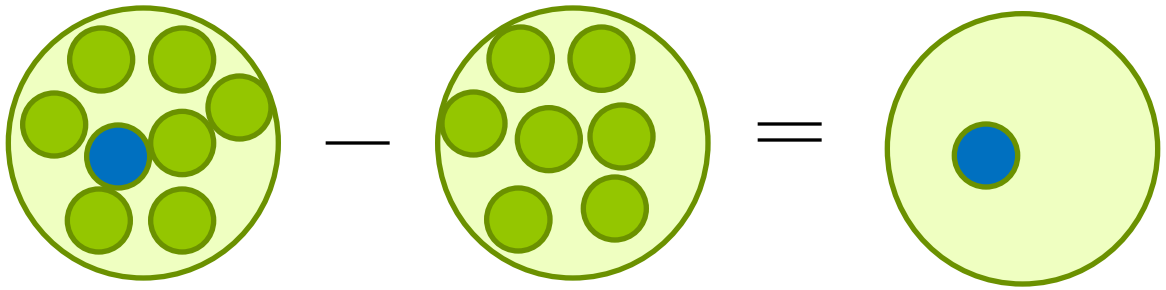
Subtraction Logic

- In order to localize BOLD signal associated with a particular task we use subtraction logic
- Task A = our task of interest (e.g. motor task, perception task, memory task, etc.)
- Task B = a less demanding control task (controlling for all aspects that are not the function your experiment aims to examine)

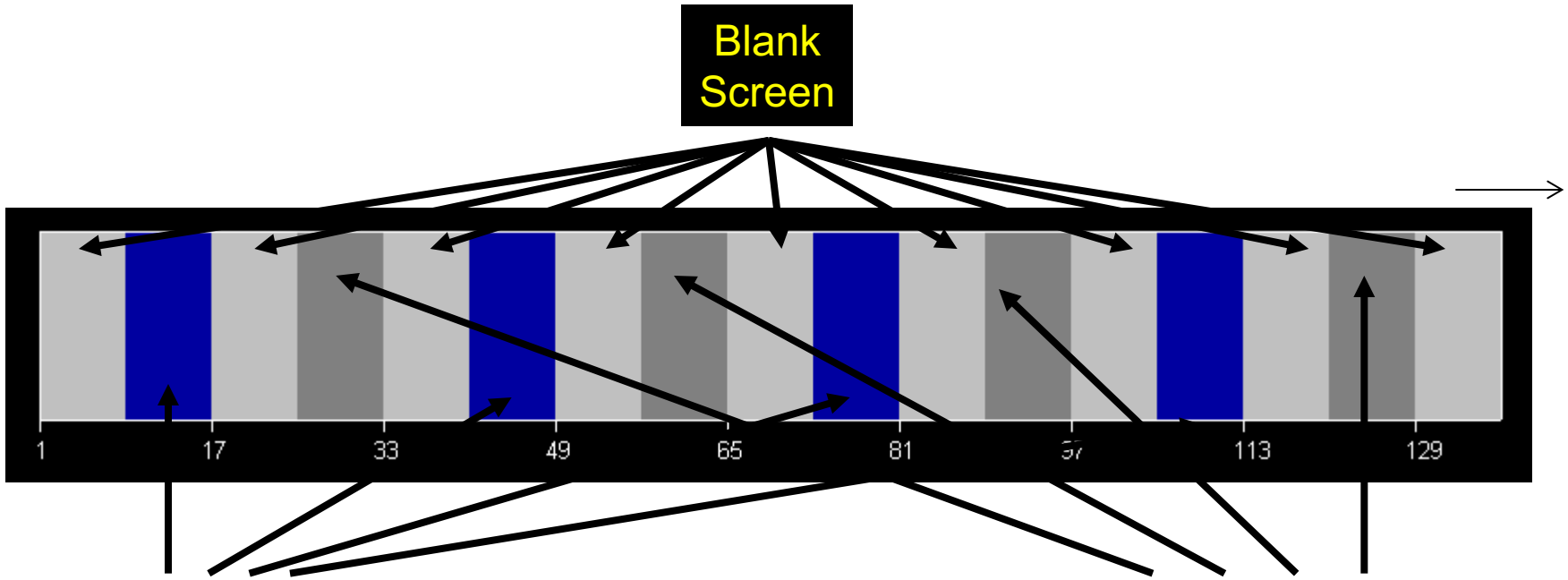
[BOLD signal during task A]

– [BOLD signal during task B]

= [BOLD signal associated with task A]



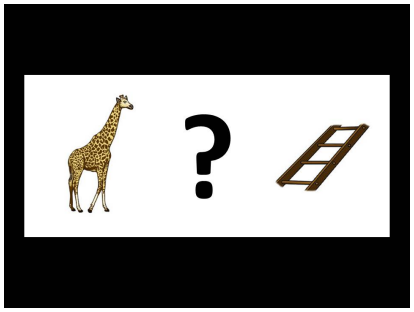
Our Experiment

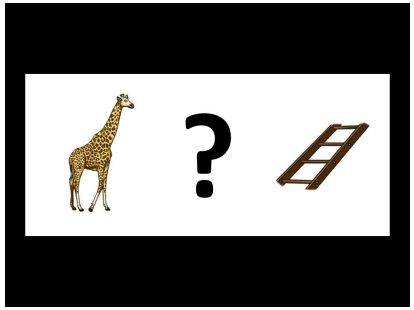


First Sound Matching

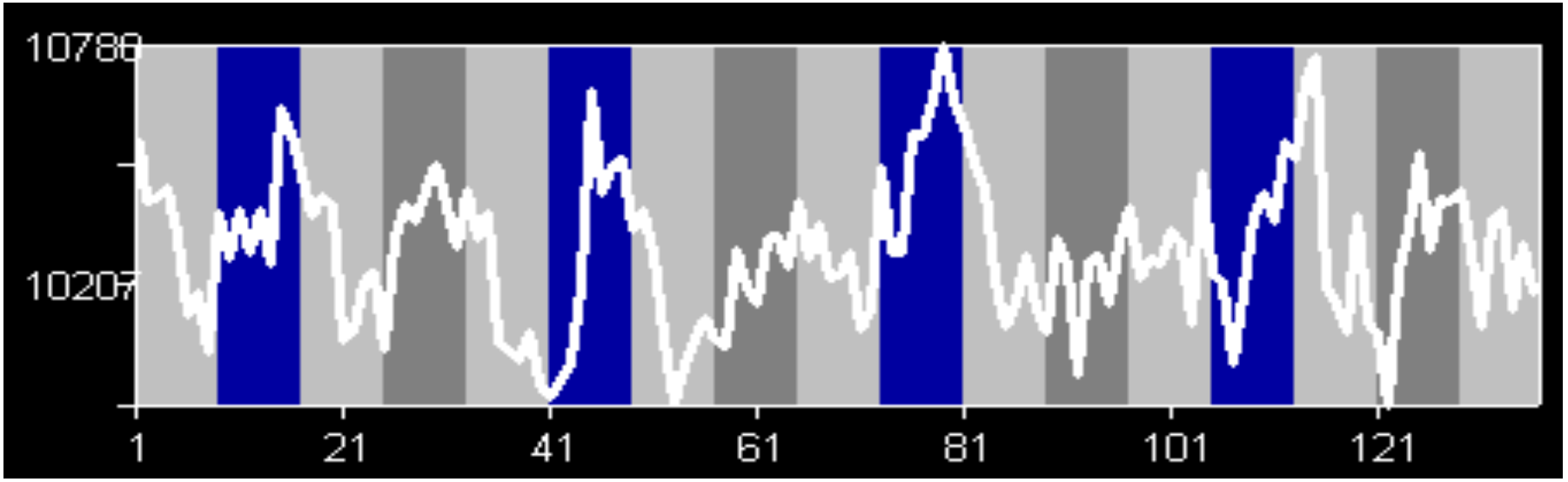
TIME

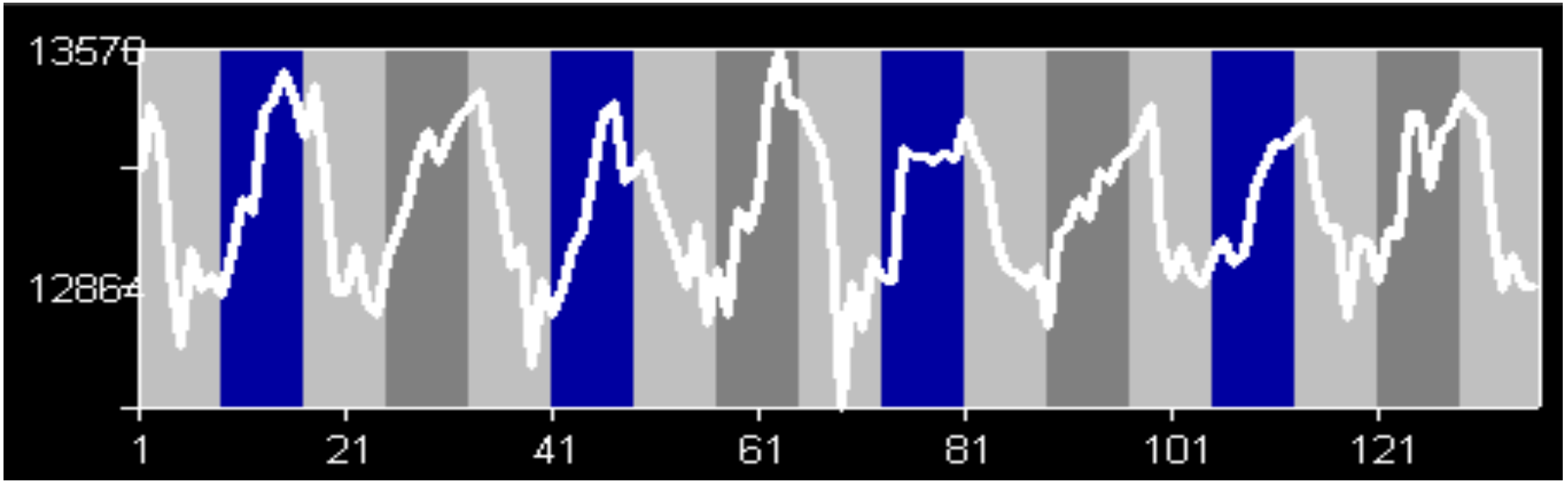
Voice Matching

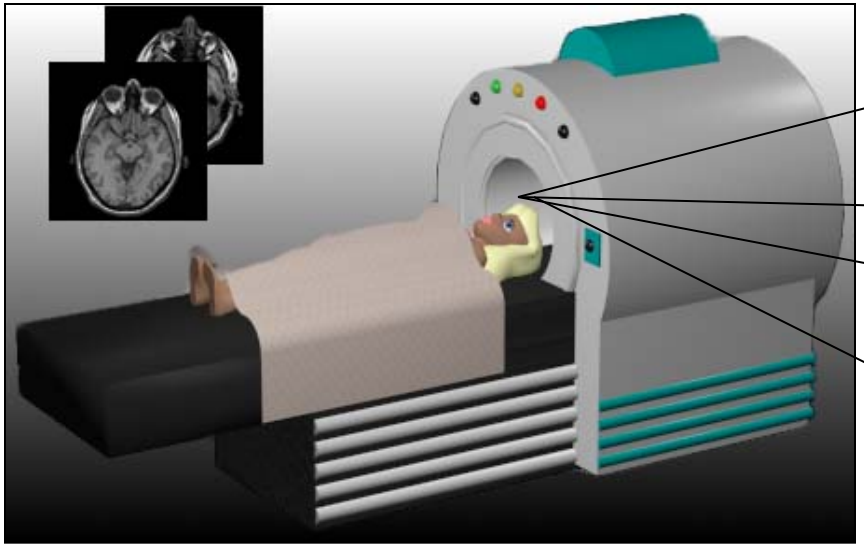




Where are these voxels located?







Experimental condition

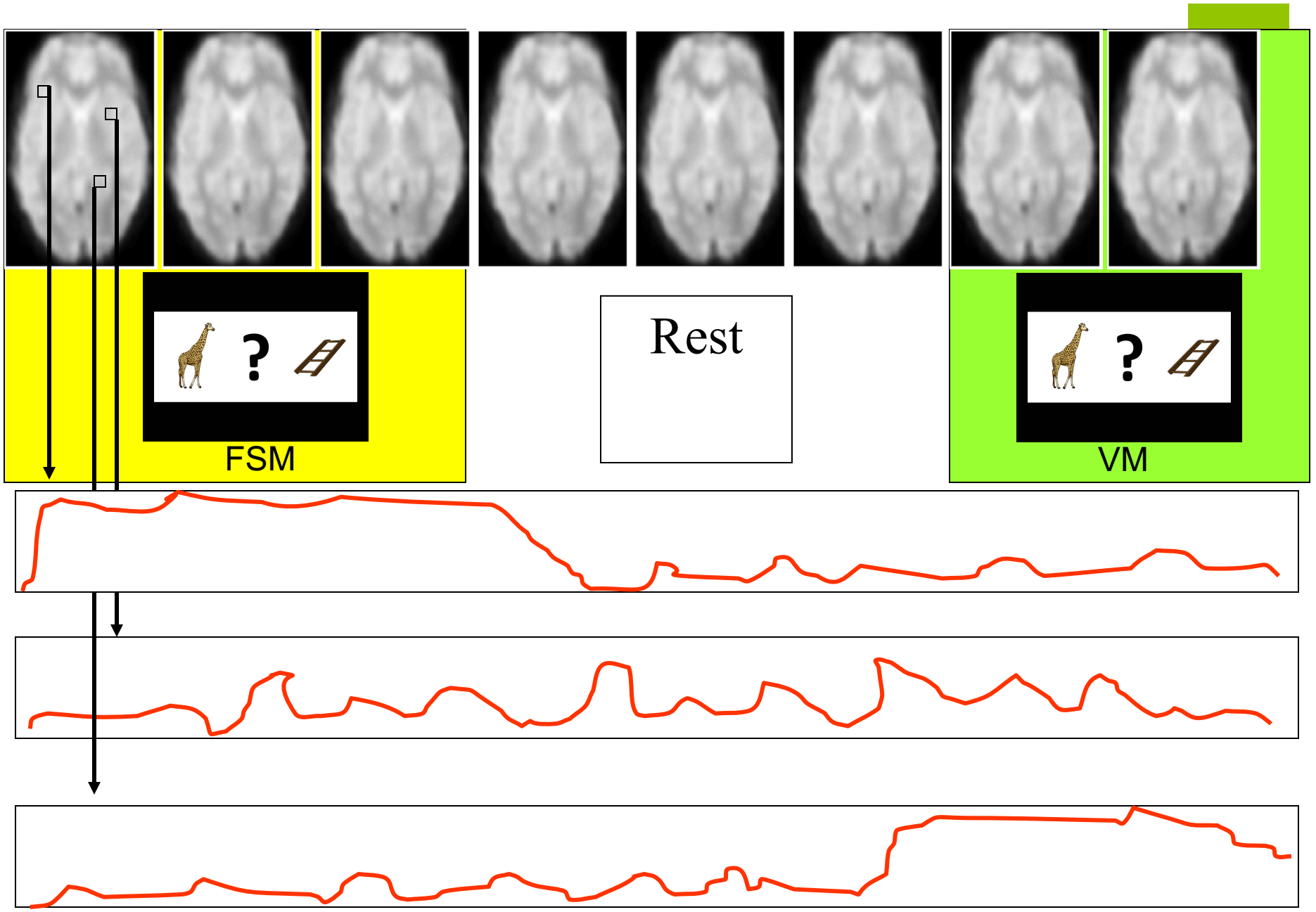
Control condition

FSM

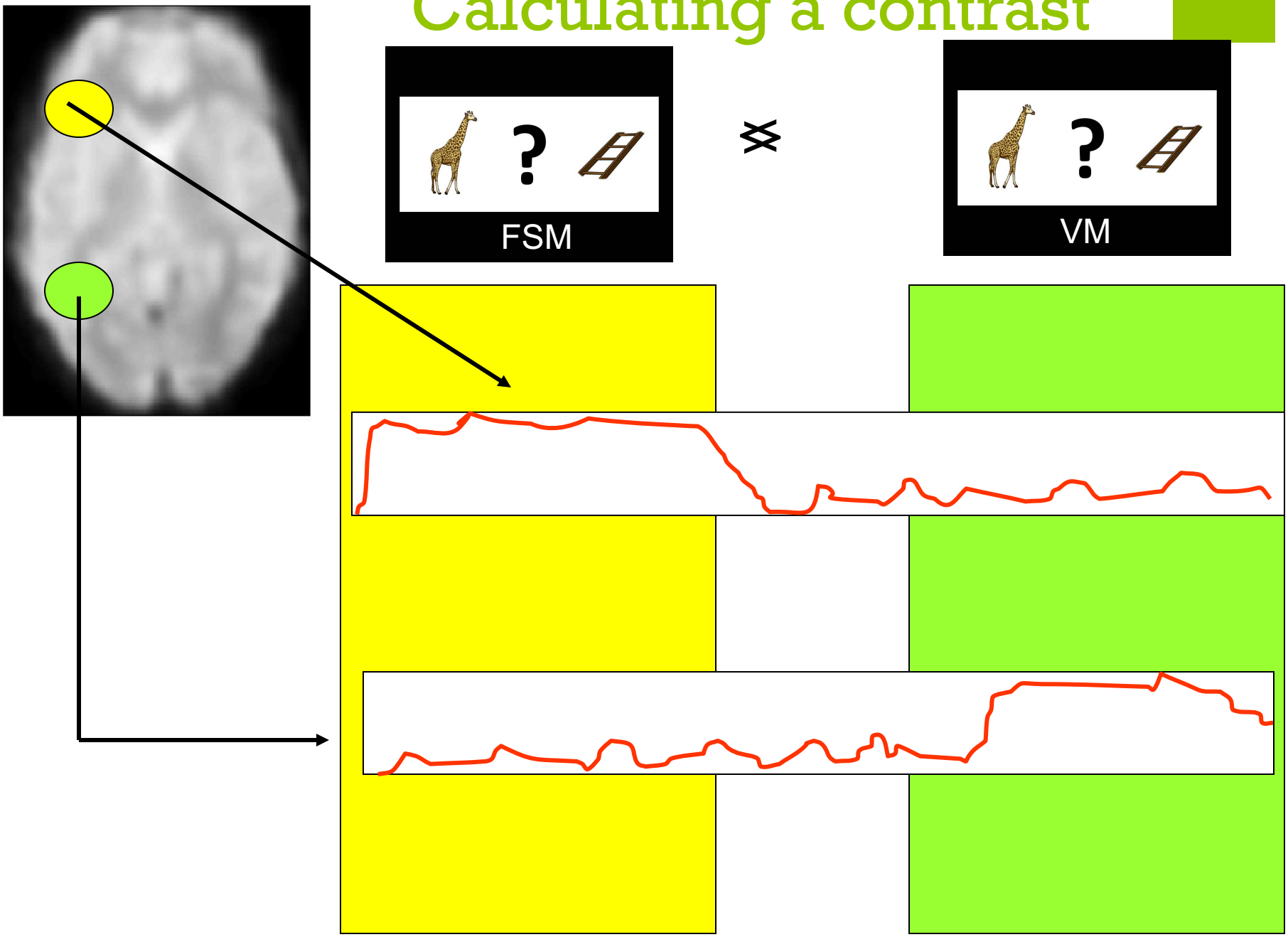
Rest

VM

time


?
FSM
Rest
?
VM

Calculating a contrast

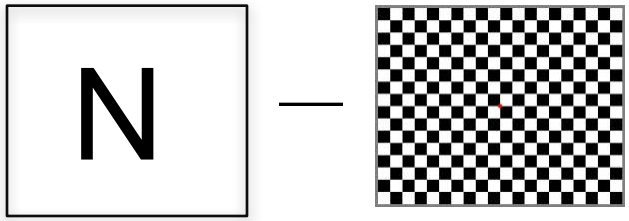


Let's try another example…

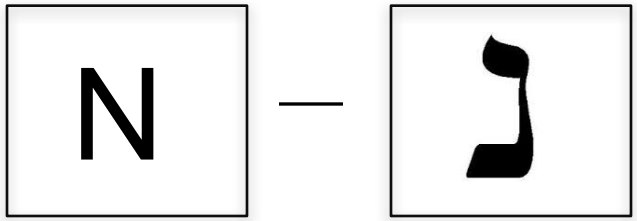
Cognitive subtraction: Baseline problems

- Which neuronal structures support letter recognition?

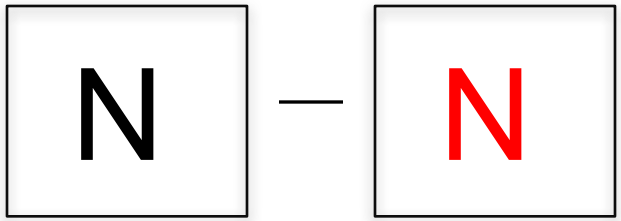
Distant stimuli



Related stimuli



Same stimuli, different task



Name Letter! Name Color!

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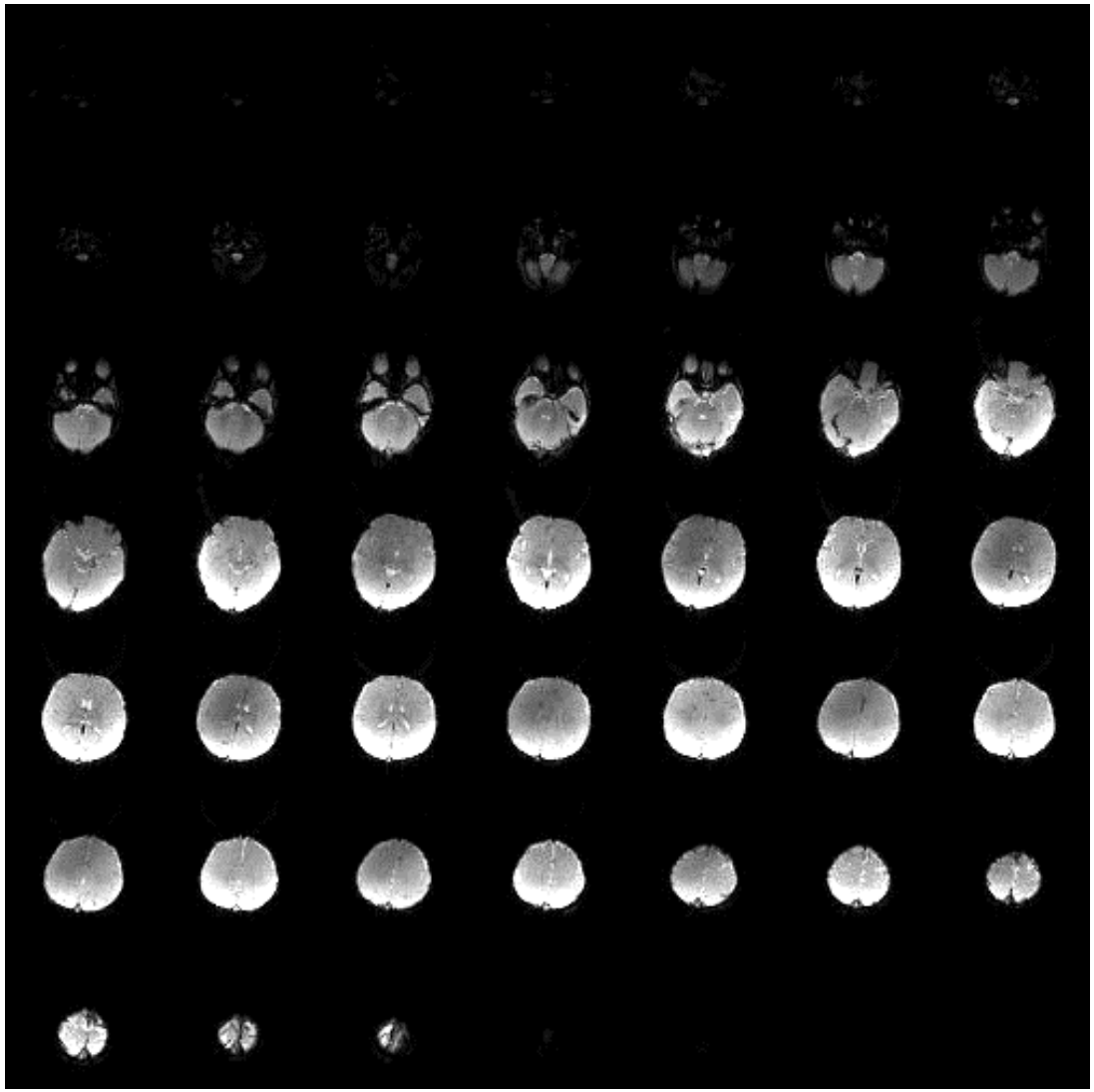
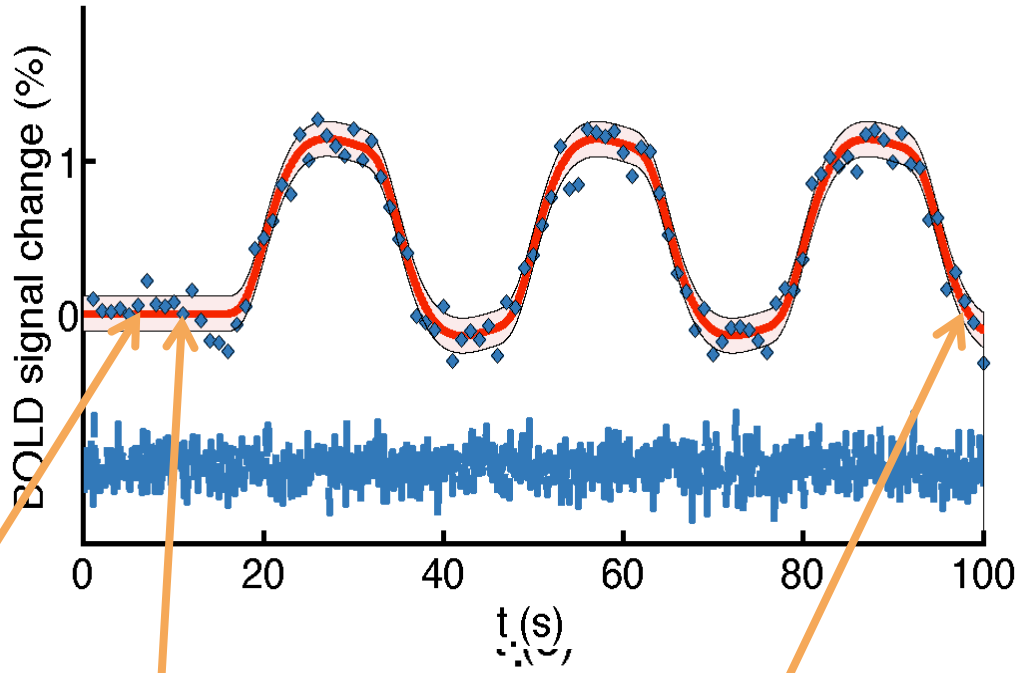
FMRI movie (infant)



fMRI = Acquiring Movies

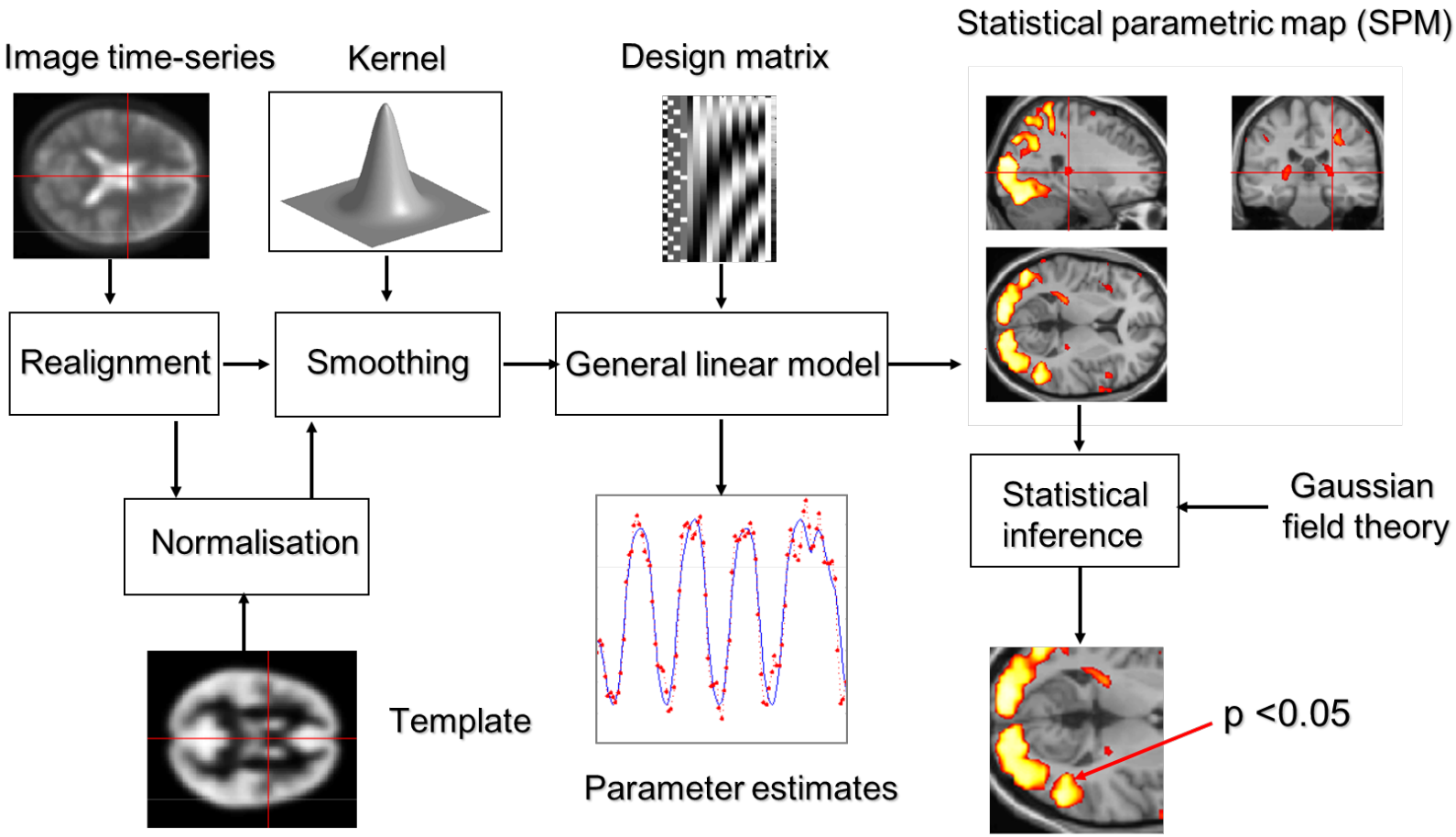
- The Localized Time-series is the Fundamental Information Unit of fMRI

Signal: Fluctuation through Blood oxygen level dependent (BOLD) contrast

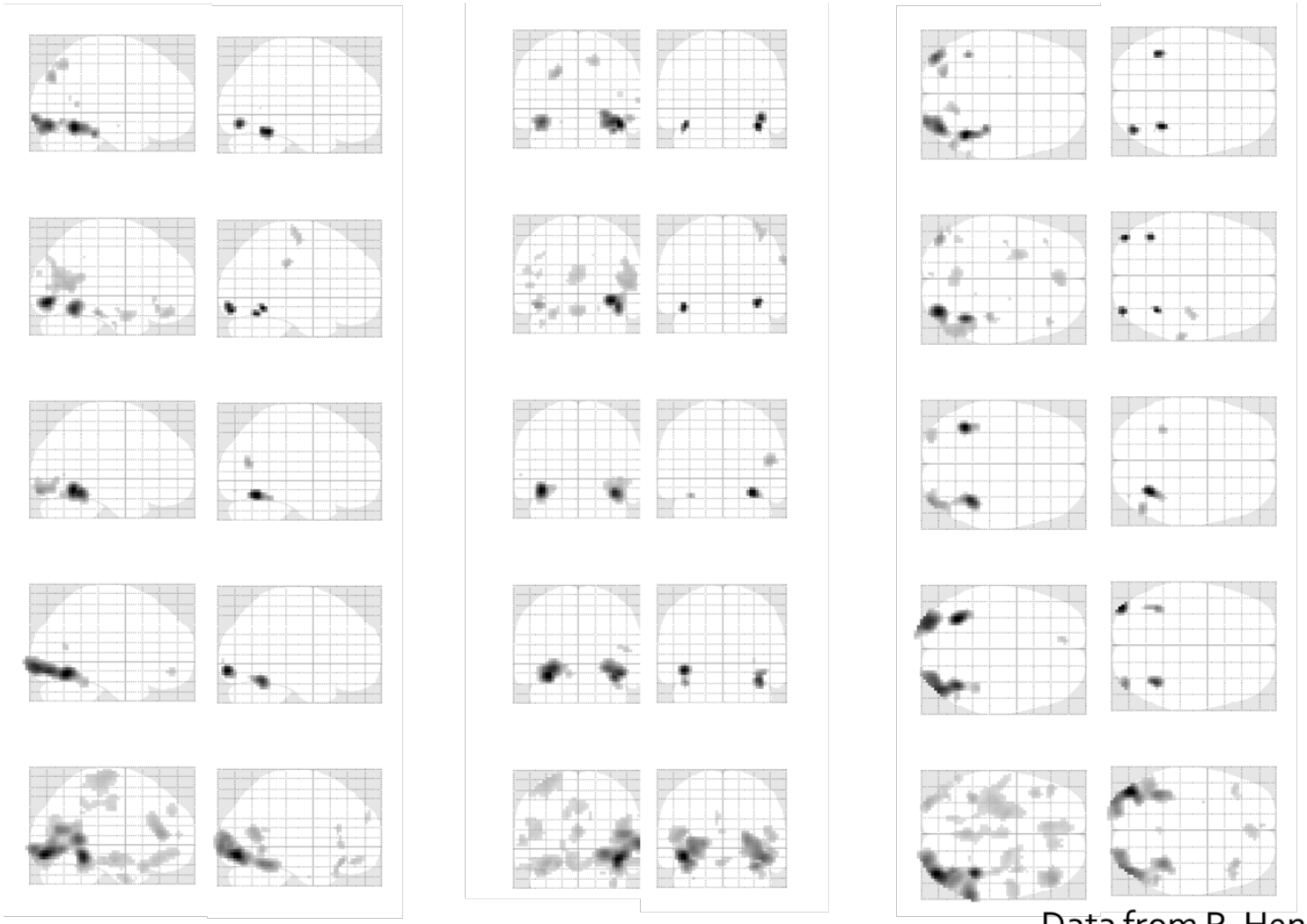


- Run/Session: Time Series of Images

Overview of fMRI analysis…

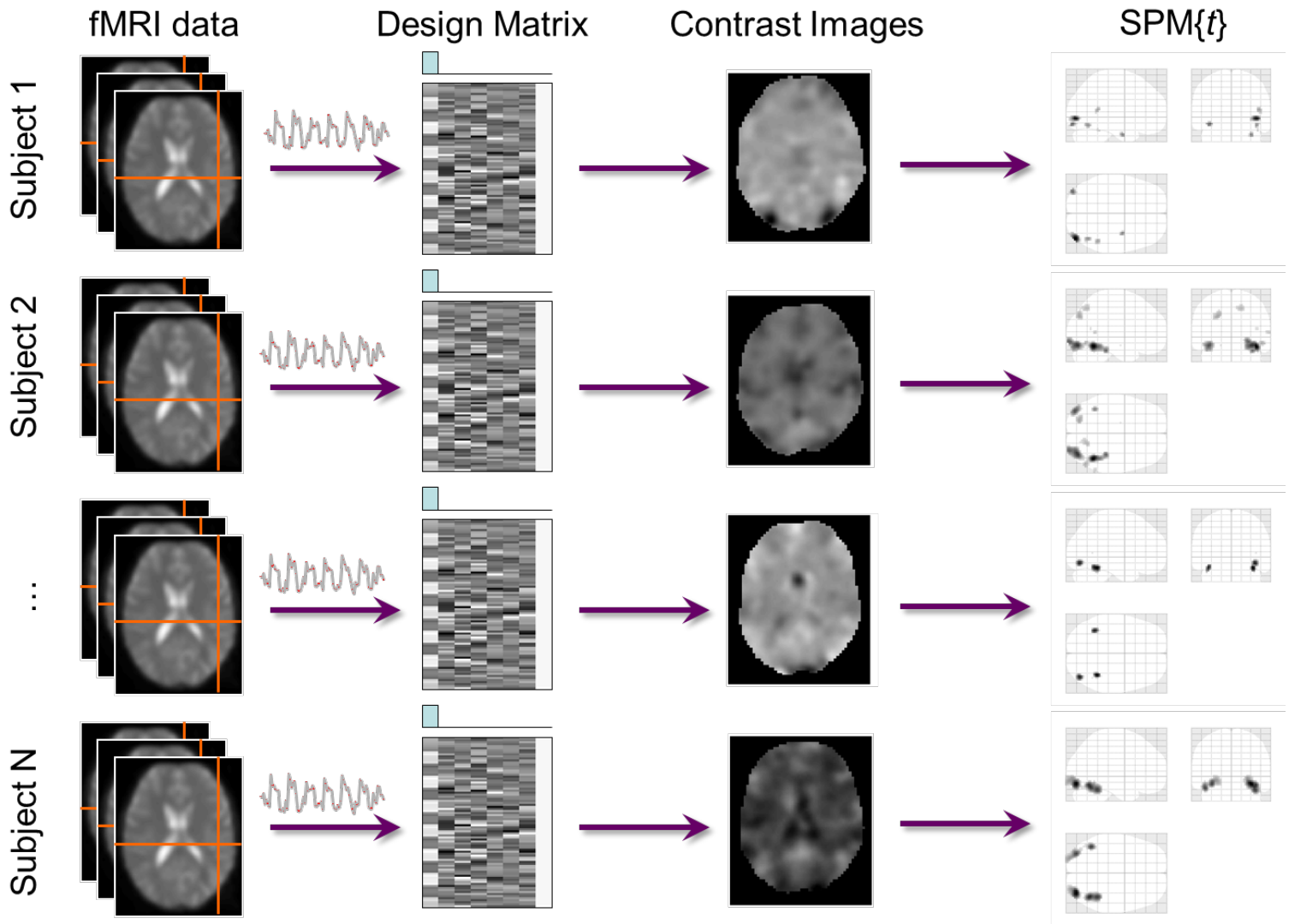


Single-subject analysis



Data from R. Henson

GLM: repeat over subjects

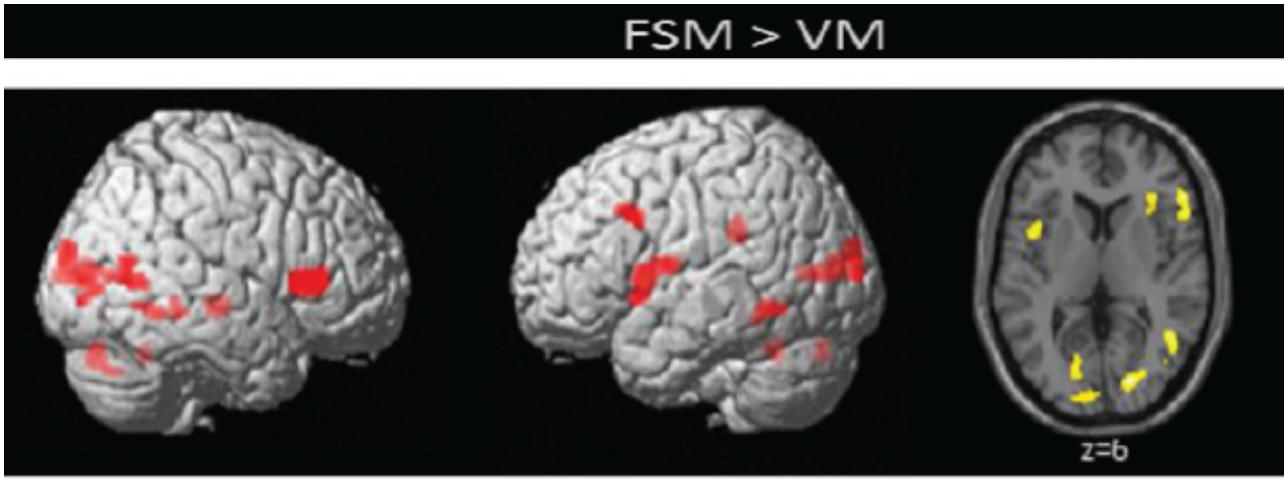


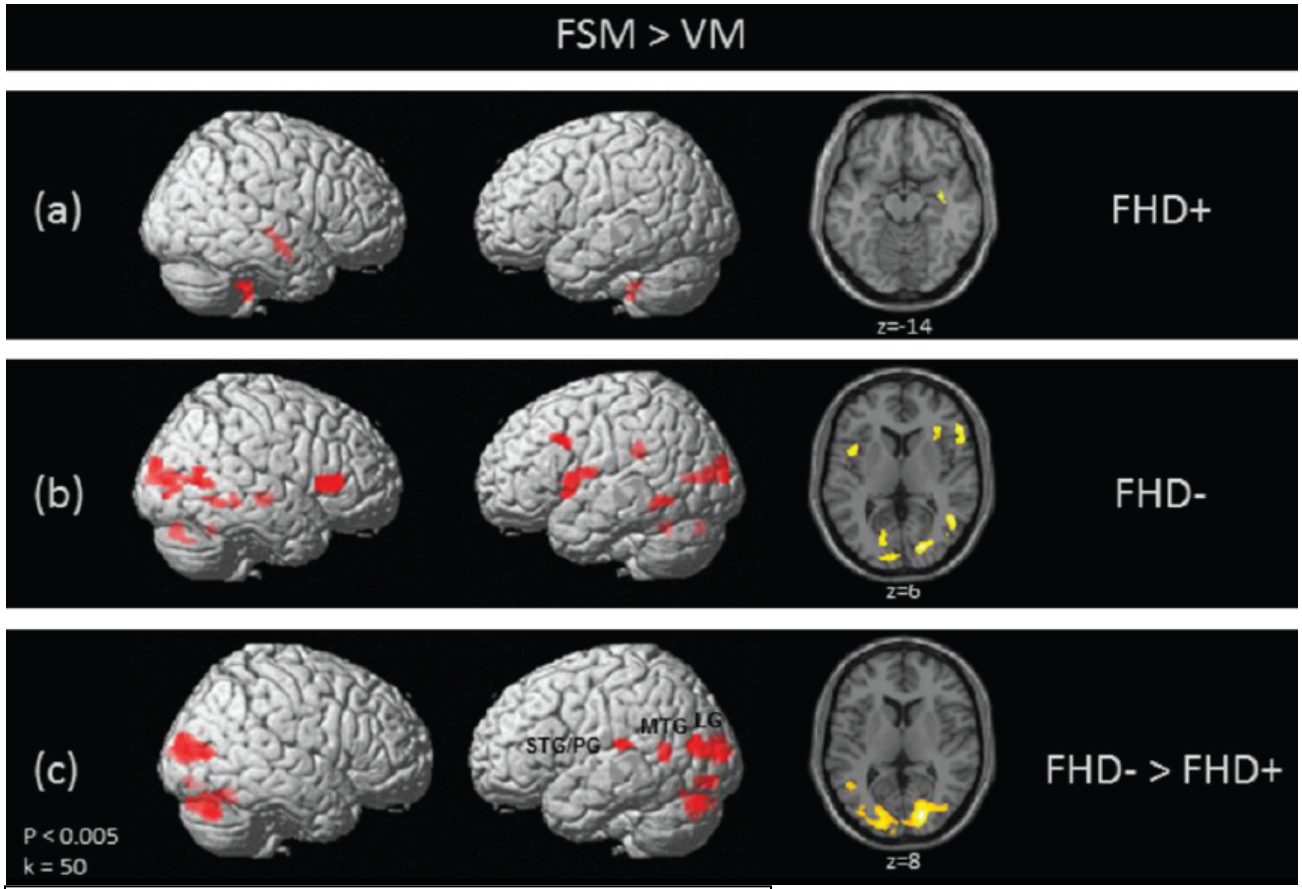
Colorful blobs

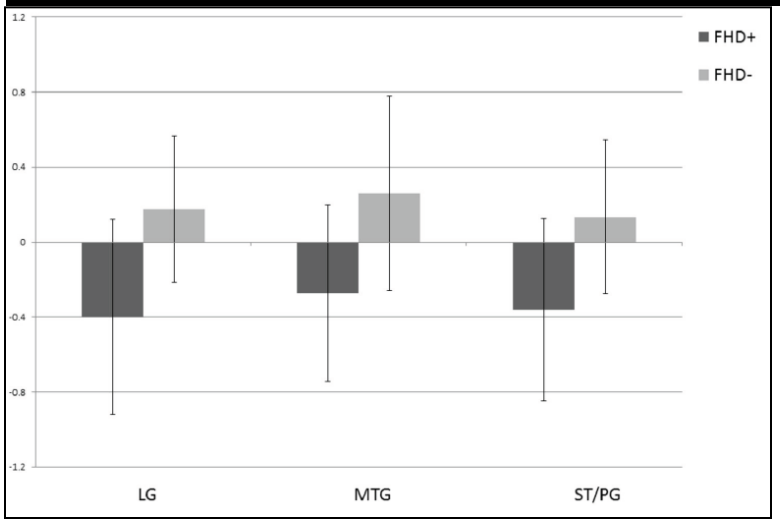
[BOLD signal during task A]

– [BOLD signal during task B]

= [BOLD signal associated with task A]







[Raschle *et al*., PNAS 2012]

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Important questions to ask…

- What do you hope to find? Which brain regions relative to which tasks?
- If we find one brain area that 'light's up for task X ...did we find the holy grail?
- What would that tell you about the cognitive process involved?
- Would it add anything to what is already known from other techniques?
- Could the same question be asked more easily & cheaply with other techniques?
- Would fMRI add enough to justify the immense expense and effort?

- What would be the alternative outcomes (and/or null hypothesis)?
- Or is there not really any plausible alternative (in which case the experiment may not be worth doing)?
- If the alternative outcome occurred, would the study still be interesting?
- If the alternative outcome is not interesting, is the hoped-for outcome likely enough to justify the attempt?
- What would the headline be if it worked?

- What are the possible confounds? What else could it be?
- Can you control for those confounds? Are appropriate baselines and contrasts available?

- Are there behavioral experimental precedents for your study?
- Has the experiment already been done?

Source: www.**fmri**4newbies.com/

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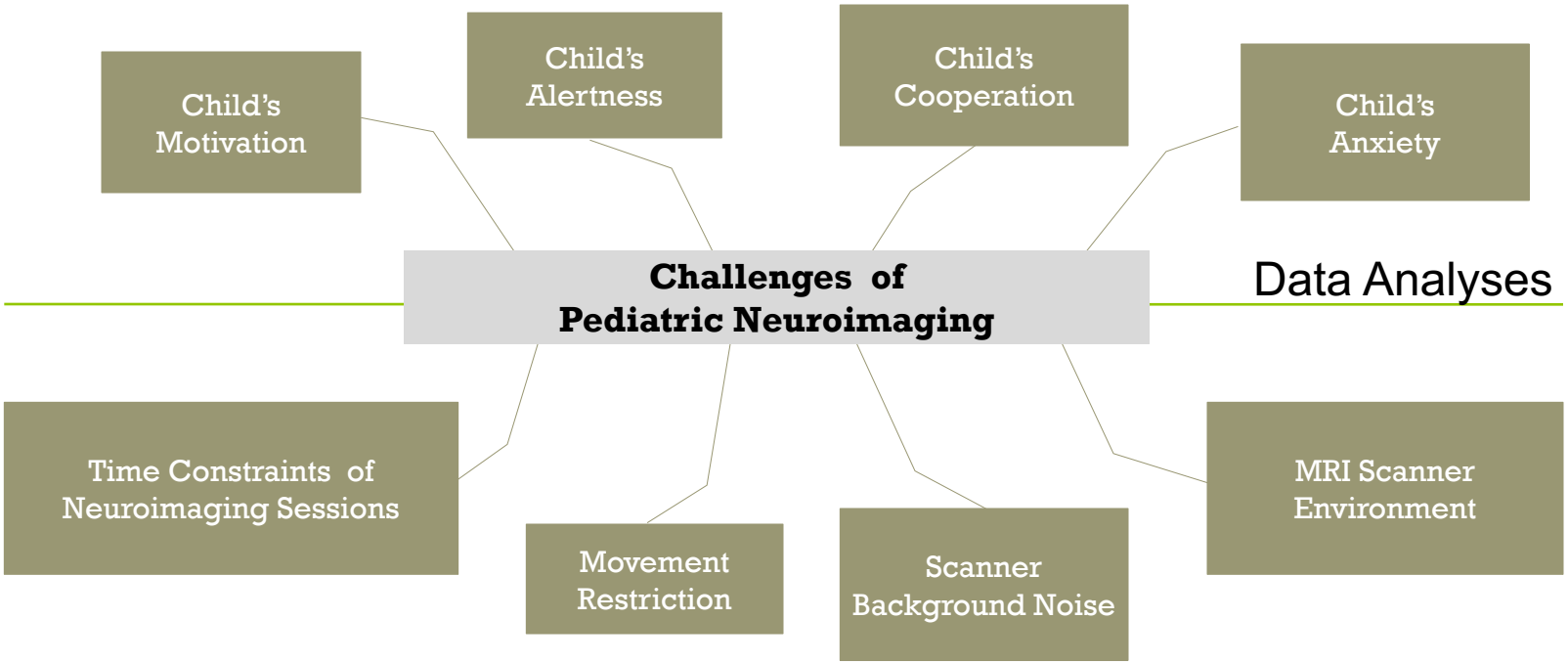
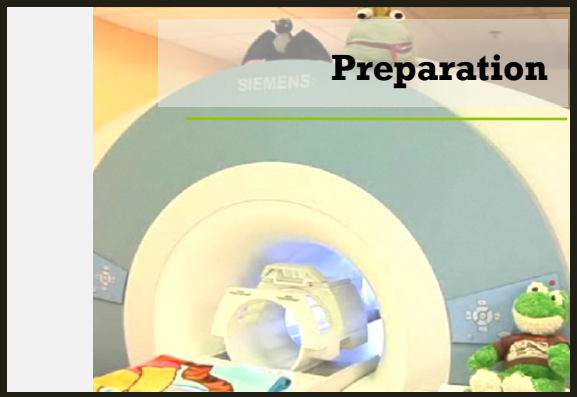
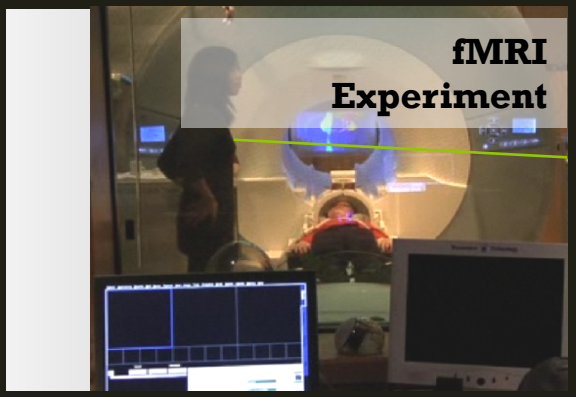
- Pediatric Imaging: Special considerations







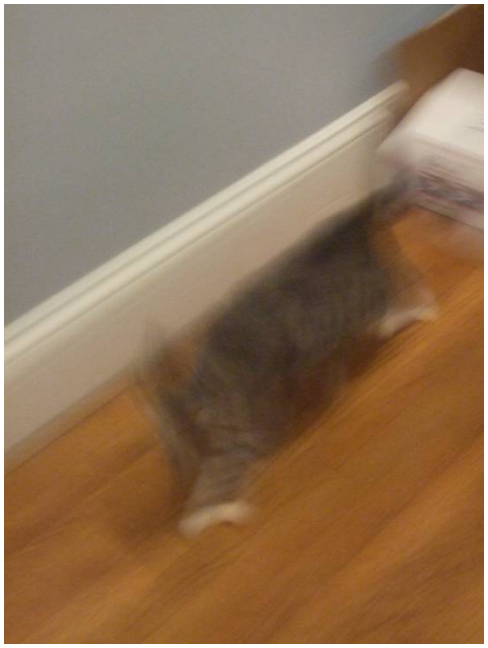
Raschle et al. 2009

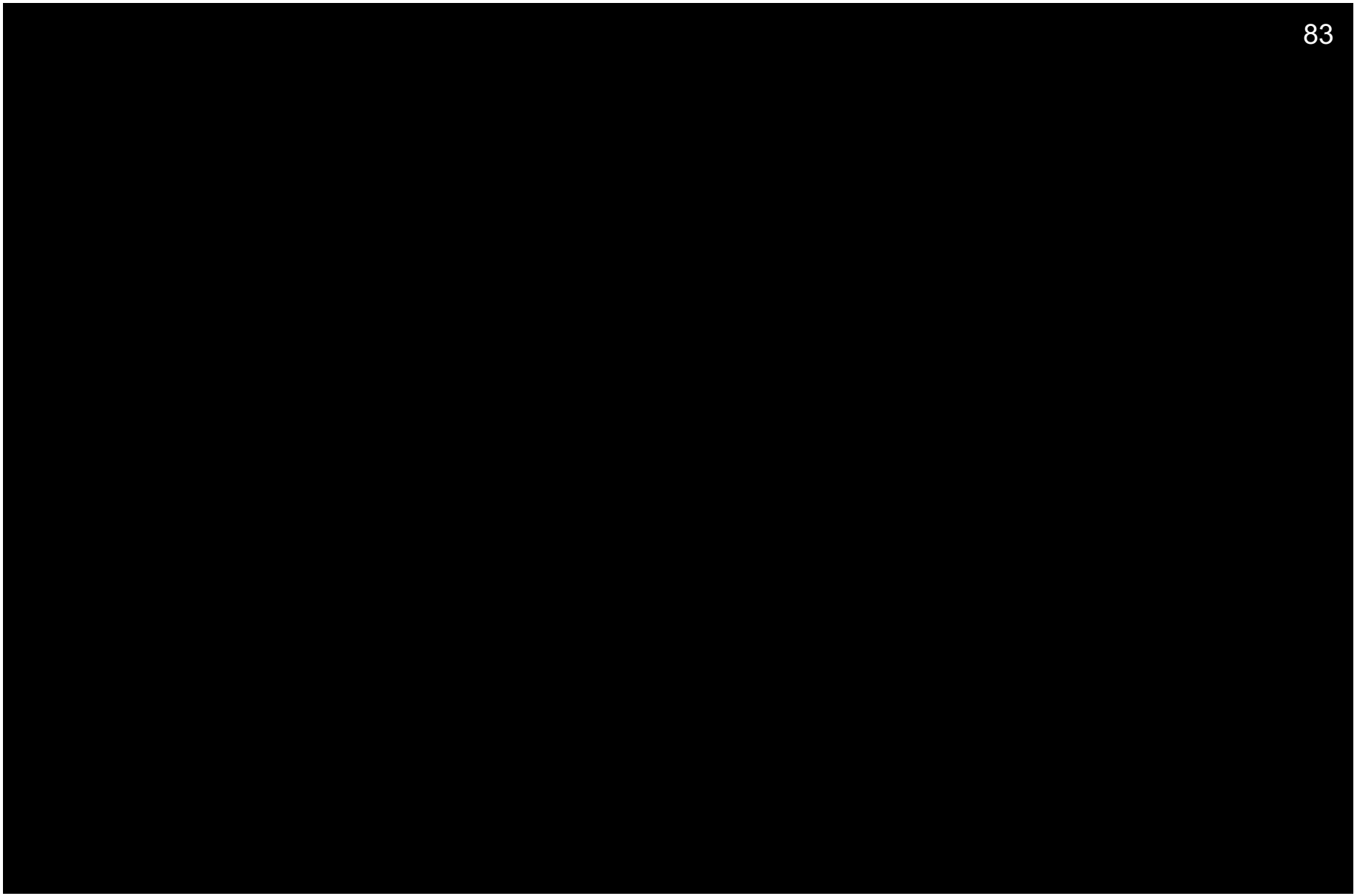
Example Training procedure (with/without Mock)

- Child-appropriate Website
- Introduction to task/task training
- Movement minimization (freezing game, camera game, hand on leg procedure)
- Dice game
- Task repetition
- Ensure understanding of tasks

Movement prevention

- How to introduce movement restriction in a child-friendly way?
- "Freezing-Game" or "Statue Game": Requires child to stay very still (i.e. count how long the child can stay still, child pretends he/she is a statue)
- Practice lying still in the mock scanner while playing the pre-recorded sequence sounds





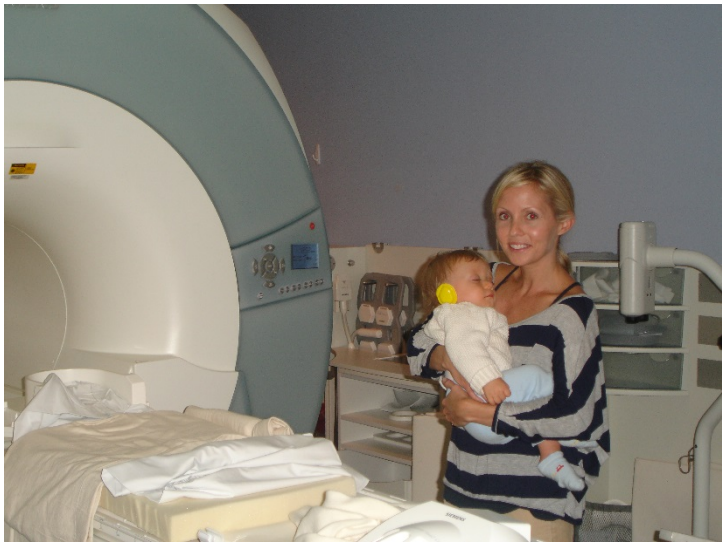
http://www.jove.com/Details.stp?ID=1309

[Raschle *et al.* 2009]

Imaging Naturally Sleeping Infants

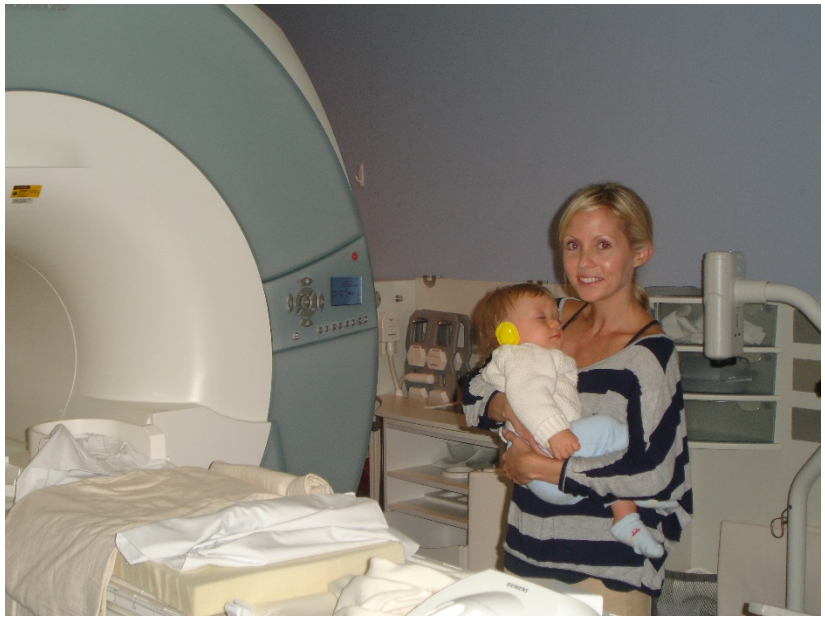

SIEMENS
Trio
A Tim System


My Baby Bra
Thank you!



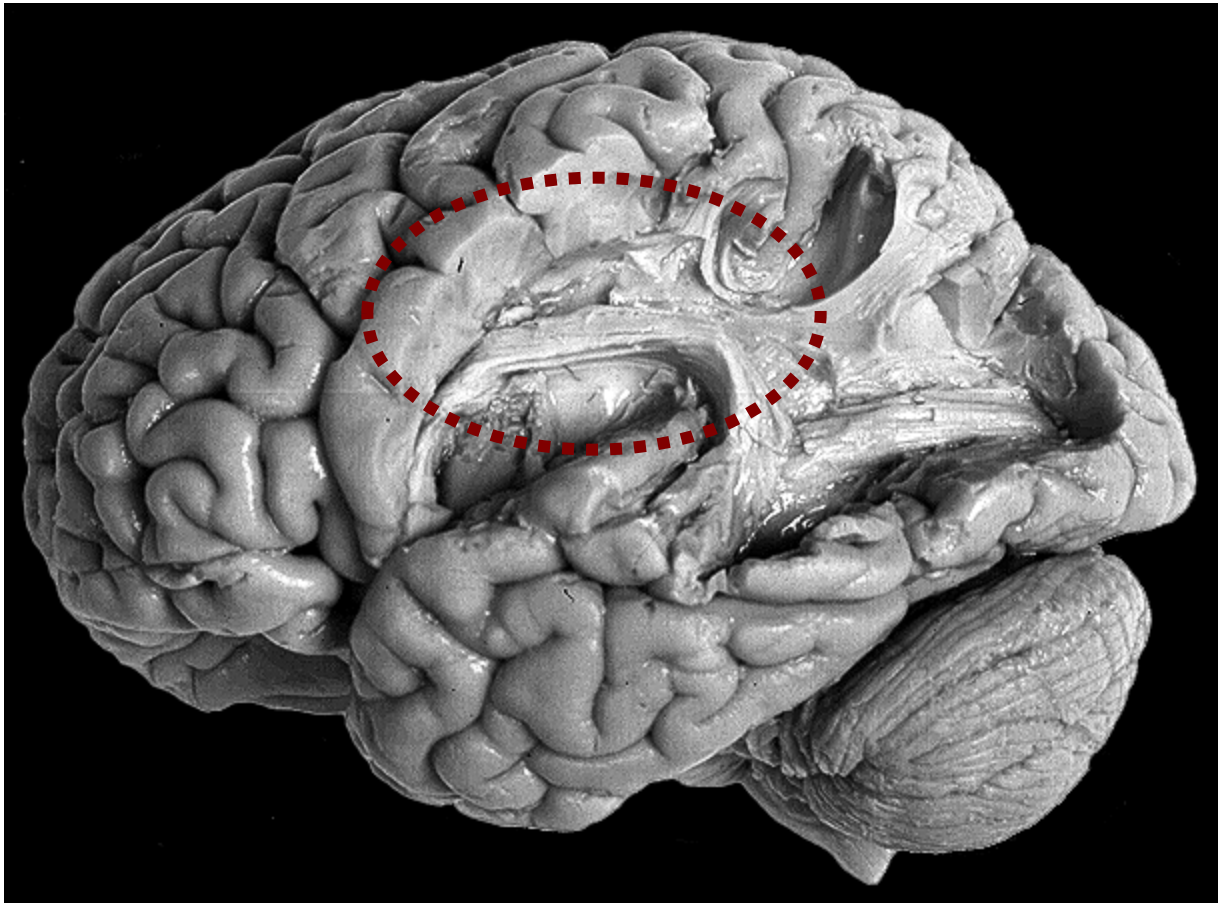
Imaging Sleeping Infants

- Preparing the parent before the visit
- Picking the right 'sleep' window (plus longer scan slot)
- Mirroring sleep habits and sleep environment
- Scanner background noise on CD
- Equipment (ear protection, crib, etc.)
- Affective state



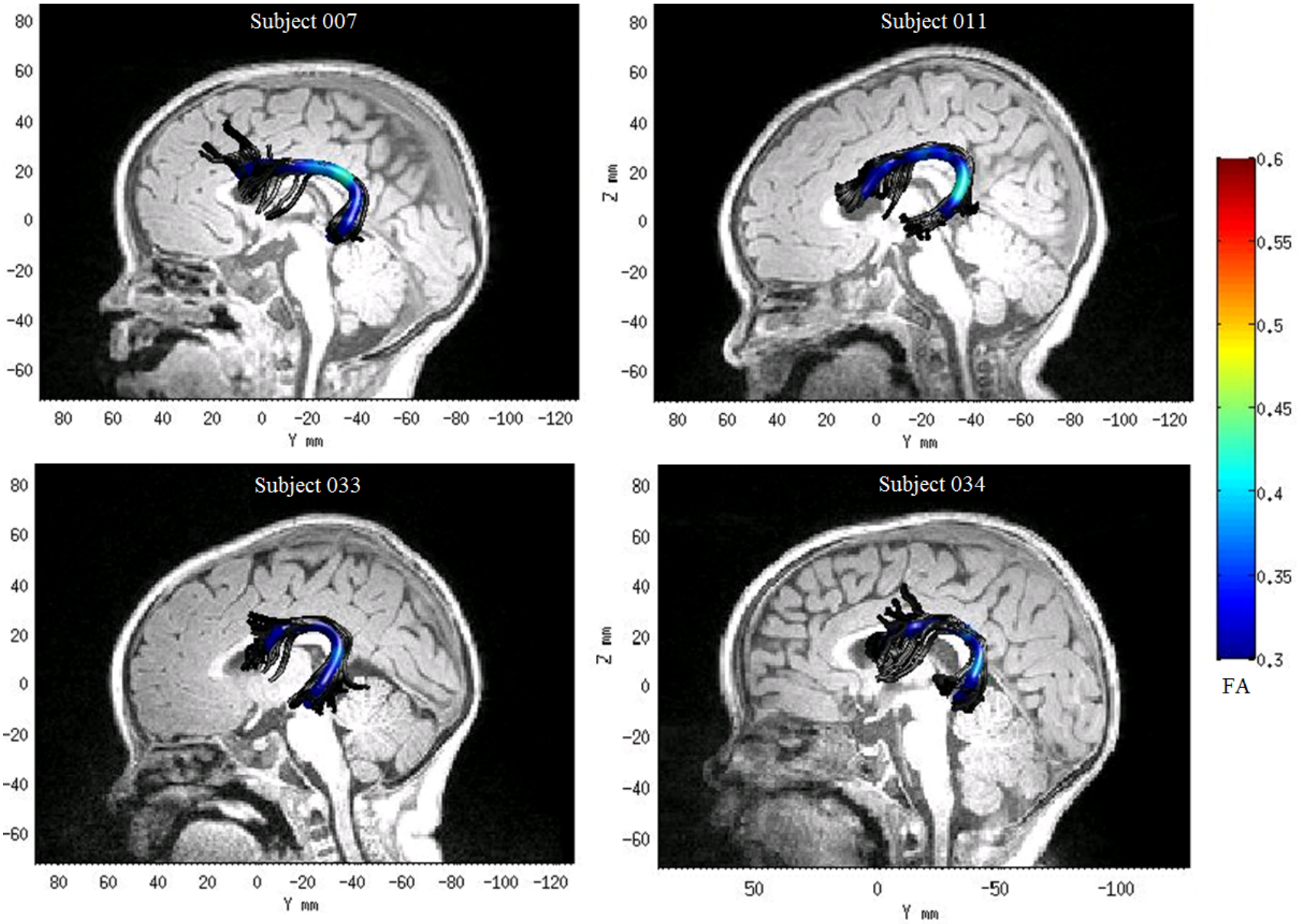
The Arcuate Fasciculus

neural pathway connecting the posterior part of the temporoparietal junction (Wenicke‘s area) with the frontal cortex (Broca‘s area).



http://www.biocfarm.unibo.it/aunsnc/pictef14.html

AFQ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