HST.583 Functional Magnetic Resonance Imaging: Data Acquisition and Analysis
Fall 2006

**Midterm Exam
HST.583
November 8, 2006**

Instructions:
There are 4 problems, 25 pts per problem. Please immediately confirm you have all nine pages! This is a closed book/ closed notes exam. You have one hour.

Read the whole exam first. Write legibly. Describe what you are thinking. Even if the final answer is wrong, you will be given credit for your reasoning and approach to the problem. Be efficient, assess what you can answer right away; divide your time so that you can cover all the problems, allocating less time to the easiest parts. Don't spend too much time on a single question.

Problem 1: Neural Systems
Memory is understood to be composed of a number of unique systems each optimized for specific functions. Choose one of the specific memory systems and

a) describe its function (5pts)

Lots of possible answers; e.g. declarative, non-declarative, working, episodic, etc., (obviously some are broader than others – e.g., episodic and semantic memory are both considered types of declarative memory).

b) list the brain regions associated with this function (5 pts)

Different areas depending on what you listed above. See a functional neuroanatomy book like Nolte. Brad Dickerson went over many examples.

c) design yourself or describe a published experimental paradigm to probe this function (10 pts)

Several described in textbook and in Brad Dickerson's lecture notes; will of course depend on what type of memory you are looking at. E.g., an N-back task will be a good experiment to look at working memory – probably not so hot for long-term memory.

d) choose an appropriate acquisition sequence for collecting this scan noting type of sequence, and relevant parameters (5 pts)

For example:
Gradient echo EPI at 3T, TR = 2000 ms, TE = 30 ms, 20 slices, 5 mm thickness, 1 mm gap, FOV = 220 mm, matrix size = 64x64, BW = 2520 Hz/pixel, etc.

Bonus (come back to this if you have time)
e) comment on any particular concerns you would have in acquiring or analyzing this data (+ 5pts)

Many... depends on your experiment
Some general ones: subject tiredness, boredom, motion, scanner drift for long scans, subject habituation, task too difficult/ easy. Task is culturally biased. Complicated experimental design may required advanced post-processing/ analysis methods… Just looking for some thoughtful answers.

Problem 2: Imaging Physiology & the BOLD effect
We have learned that there is an intimate coupling between neural activity, metabolic activity, blood flow, and the BOLD effect.

"Increased cellular metabolism can lead to increased blood flow."

a) Briefly describe the physiological mechanism behind this statement. (6 pts)

Increased cellular metabolic activity causes vasodilatory factors to be released from the cell (e.g. NO). These factors will act on the smooth muscle of surrounding arterioles and cause relaxation, thereby increasing the radius of the vessels. This causes increased local blood flow (directly related to radius^4).

Arterial spin labeling (ASL) is a technique that allows quantitative measurement of blood flow. In many ways this offers theoretical advantages over standard BOLD imaging for fMRI.

b) Briefly describe one potential advantage that ASL has over BOLD for functional MRI. (6 pts)

Many possible answers; here are a few:
1) *Activation measured with ASL is based on changes in flow in arterioles and capillaries, whereas activation measured with BOLD is based primarily on changes in deoxyhemoglobin concentrations in venules and draining veins. As a result, ASL-measured activation should be better spatially correlated to neural activation; there exists experimental evidence supporting this idea. ASL should also not suffer from the "brain versus vein" problem.*
2) *Several physiological factors contribute to the BOLD effect – blood flow, CBV, and $CMRO_2$. ASL directly measures a single physiological parameter: blood flow.*
3) *ASL offers an absolute measure of blood flow, not a relative change as in BOLD. Longitudinal multi-subject studies may benefit from having absolute measures of blood flow (i.e. a true baseline), as the same percent change can have different meaning depending on baseline state. Additionally, clinical functional neuroscience studies can benefit from absolute measures, which can aid in interpreting different neuroimaging results seen in patient and control groups.*

The BOLD effect depends on the local concentration of deoxyhemoglobin. Hemoglobin is the primary carrier of oxygen in the blood; it is referred to as oxyhemoglobin and deoxyhemoglobin, depending on whether it is in its oxygenated or deoxygenated state, respectively.

Deoxyhemoglobin is a paramagnetic agent and thus decreases the MR signal, as its concentration increases. "But wait!" exclaims a young neuroscientist, "if increased neural activity leads to increased oxygen consumption, shouldn't the local concentration of deoxyhemoglobin *increase* - causing the BOLD signal go *DOWN*?!"

c) Briefly explain to him why this is not the case (i.e. why the BOLD signal *increases* in response to activation). (7 pts)

While the rate of $CMRO_2$ (i.e. consumption of oxygen) increases, this triggers an increase in blood flow that is GREATER than the $CMRO_2$. The increased blood flow brings in freshly oxygenated blood faster than neurons/ glial cells are consuming O_2, resulting in an increase *of oxygenated blood and a* decrease *of deoxyhemoglobin on the venous side. The dHb is in fact flushed away by incoming fresh blood. Thus the signal goes up.*

Interestingly, this means that the increased blood flow brings in more O_2 than is actually needed by the metabolizing neurons, which may seem "wasteful" at first glance; there are several theories behind why this may happen: e.g., the "watering the garden for the sake of a thirsty flower" analogy...

In modeling of the BOLD signal, the hemodynamic response often displays the so-called "post-stimulus undershoot" (black arrow):
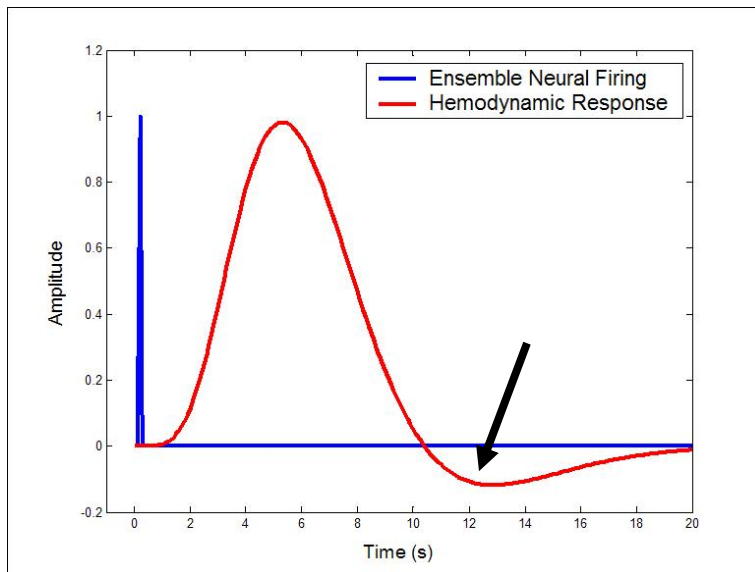

Figure 1. Simulated hemodynamic response

d) Explain why this may occur, from a physiological point of view. (6 pts)

One possible explanation: after neural activity ceases, blood flow returns to baseline faster than the venous vasculature can shrink back to its original size (venous vessels are compliant and increase in volume in response to increased pressure and flow). Since flow returns to baseline more quickly than blood volume, there ends up being a greater amount of deoxyhemoglobin present transiently. Once volume returns to baseline, the BOLD signal does as well (as seen above).

BONUS: One controversial claim for BOLD fMRI is that the positive change in signal amplitude is preceded by a smaller decrease in signal. This postulated decrease has been termed the "initial dip" or "early dip":
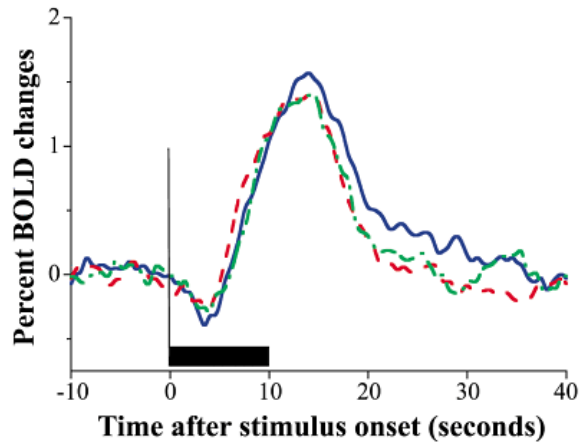
Figure 2. Traces represent averaged hemodynamic responses; black bar between 0 and 10 seconds designates stimulus duration. Clear decrease in signal is notable after stimulus onset.

Supporters of the initial dip believe that it may be even a more spatially accurate marker of activation than the main rise of the hemodynamic response. From what you know of BOLD physiology, hypothesize the origin of this effect, and subsequently explain why it may be more spatially specific to true activation. (+7 pts)

*The initial dip may represent the initial increase in $CMRO_2$ **before** blood flow increases to deliver more oxygen. As suggested in part c), the BOLD signal will actually go DOWN, since there is transiently more deoxyhemoglobin in the local blood, since oxygen is being removed and metabolized by the neuron. Because $CMRO_2$ should be more spatially specific to neural activity (since an increase in $CMRO_2$ is closely associated with firing neurons) the initial dip may be a more spatially accurate measure of activation.*

Problem 3: fMRI Physics

Part a.
Standard functional imaging at the Martinos Center uses an echo planar (EPI) imaging paradigm (30 slices, 4 mm slice thickness, TE = 30 ms, TR = 2000 ms, matrix size = 64x64). A bright young physicist recommends a new spiral imaging sequence with a near-zero echo time (TE), to reduce distortions often found in EPI images.

a) What is the phenomenon that causes EPI distortions called? (1 pt)

Magnetic susceptibility, which leads to B_o-field inhomogeniety

b) Name one region of the brain you think this student wants to functionally image. Explain. (2 pts)

orbitofrontal, medial-temporal, e.g.; any regions where distortions in EPI are serious.
So we'd want a technique to minimize these distortions if we are looking at activations.

c) From a k-space perspective, what does it mean to have a near-zero TE (you can approach this by first defining TE, if you'd like)? (2 pts)

TE is the echo-time and is the time between the middle of the RF excitation and when the center of k-space is traversed during the readout.
A near-zero TE means that the center of k-space is sampled nearly immediately after excitation.

d) Why is it possible to have a near-zero TE with spiral imaging? (2 pts)

Spirals start at the center of k-space and spiral out to the periphery.

e) What relaxation parameter allows the generation of contrast through the BOLD effect? (3 pts)

T2*; the paramagnetic nature of deoxyhemoglobin will slightly alter the local magnetic field, leading to spin dephasing. This is a concentration-dependent phenomenon; as the amount of dHb changes, so will the local T2*. **T2 is also acceptable**; *SE-BOLD also produces functional contrast that is more sensitive to changes around smaller vessels (why?).*

d) Would you agree to let him implement this new sequence for BOLD functional imaging? Why or why not? (5 pts)

NO! You need a finite TE to let BOLD contrast develop. If your TE is too low, you will not have any BOLD contrast for functional imaging. While it is true that a near-zero TE will buy you additional SNR, the CNR lost by having such a short TE will severely diminish the BOLD signal.

BONUS: After some technical difficulty with his spirals, our star student grumbles that he "wishes the phenomenon causing EPI distortions never existed!" You hold your tongue, but secretly realize that without this phenomenon, the entire field of fMRI may have never existed. EXPLAIN. (+ 5 pts)

Inhomogenieties in the magnetic field lead to both EPI distortion and T2* relaxation. Inhomogenieties are largely caused by differences in magnetic susceptibility of different tissues/ regions of the brain. Deoxyhemoglobin is paramagnetic and has a large observed susceptibility effect; the degree of this effect is related to the local concentration of deoxyhemoglobin. Brain activation modulates this local concentration by mechanisms discussed in class, and thus produces the BOLD effect. If magnetic susceptibility did not exist, there would be no means to generate contrast based on the concentration of deoxyhemoglobin.

Part b.

The same student shows you a generalized pulse sequence for a common imaging technique used to boost T1 contrast. The pulse sequence begins with a 180 degree inversion pulse, and is followed by a delay (TI). After the delay, imaging commences:
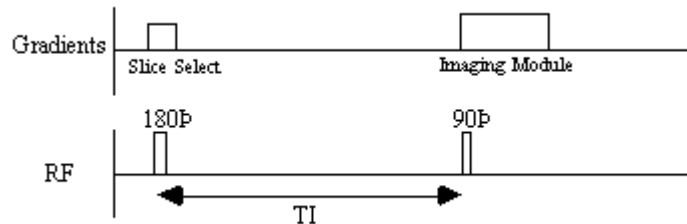

Figure 3.

e) This technique is known as __*inversion*___ __*recovery*___, and was used in Lab 5 to measure T1 from different tissues.   (2 pts)

Because the 180 degree pulse flips the net magnetization to the negative state, it effectively doubles the dynamic range of the signal. The Mz magnetization profile for white matter at 3.0 T looks like this:
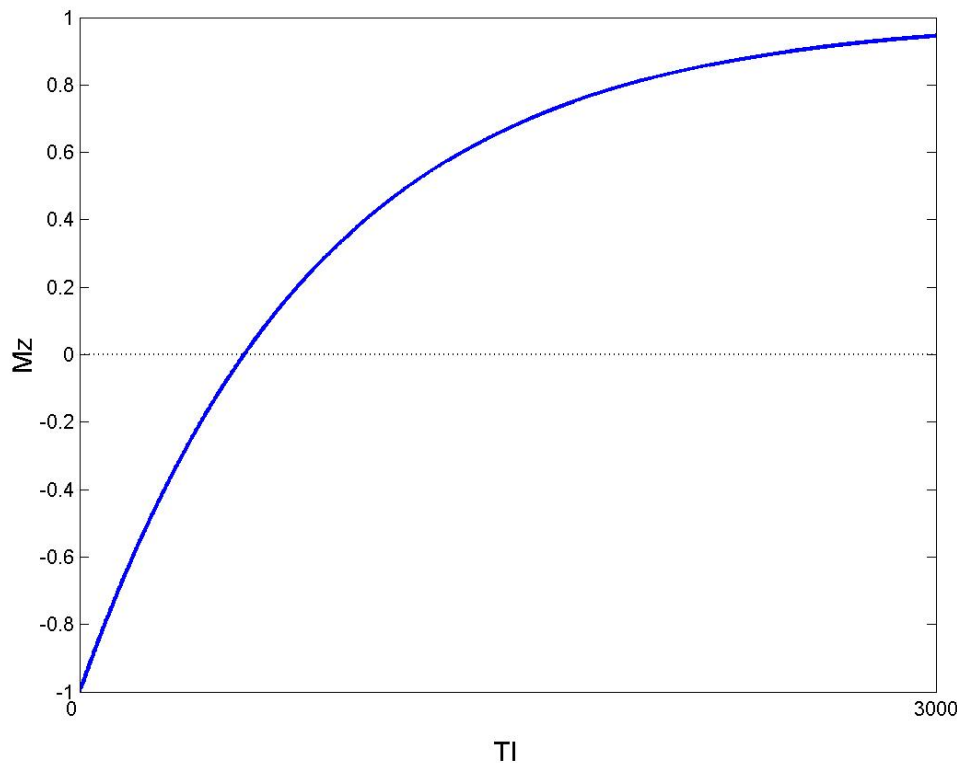
Figure 4.

The physicist points out to you that it is possible to eliminate MR signal from a particular tissue type by properly choosing TI.

f) Qualitatively show on the above figure the TI that would eliminate white matter signal. Explain your choice. (3 pts)

Draw at zero crossing. Mz will be zero here, so when you excite with your 90 for imaging, there is no magnetization available for rotation into the transverse plane (M_{xy}) and our receiver coil will not detect any signal.

g) Why would it be useful to eliminate white matter signal when performing functional imaging analyses? (1 pt)

For example if you want to segment out gray matter exclusively - this approach gives you excellent WM/GM contrast (the best possible actually, since WM is now dark!). Since gray matter is where most our neural activity is occurring, this is where we'd like to probe for activation/ changes in blood flow, etc.

h) The T1 of white matter is 832 ms. Compute the TI needed to null white matter signal. (Hint: Modify the longitudinal (T1) magnetization equation to accommodate double the dynamic range).   *Points for original equation, modified equation, and solution. (4 pts)*

Longitudinal relaxation
Mz = Mo(1-e$^{-t/T1}$)

IR equation
Mz = Mo(1-2e$^{-TI/T1}$), for double dynamic range.

Now set Mz to zero and solve for T1; should be around 576.7 ms.

Problem 4: Experimental Paradigms for fMRI
Part a
Timing issues in paradigm design

a) Give two advantages of Block Design over Spaced Event Related or Rapid Event Related design. (5 pts)

1) less sensitive to order effects
2) The massed trials summate to give a much larger "activation signal" or BOLD response thus facilitating detection of what otherwise might be sub-threshold signals (more sensitive, excellent detection power)
3) Block design is easier to design and analyze than rapid event related fMRI
4) Useful for studying state changes.
5) Requires less scan time, thus easier for vulnerable populations, limited budget, or other constraints

b) When would one use Spaced Event Related versus Rapid Event Related designs? (5 pts)

1) When the neurobiological signal of interest must be temporally separated to maintain stability (e.g. sensitization or habituation of sensory neurons)
2) When your scanner can't acquire images sufficiently fast enough to sample the HDR in Rapid Event Related design for your particular stimulus of interest.
3) When elements of your cognitive task must be sequential creating "mini-blocks" (e.g. stimulus followed by rating)
4) When one needs a response for an individual trial (in contrast to an individual trail type... made up of the average of many individual trials)
5) When one wanted to take advantage of the hemodynamic lag, as in an auditory experiment or head movement experiment.

c) Why, in general, is Rapid Event Related superior to Spaced Event Related as a design? (5 pts)

1) *more efficient in terms of scan time (because spaced event related has a low density of events over time).*
2) *it is far less boring to the subject (thus subjects have better attention) and yields more behavioral data.*
3) *You will actually have more detection power for a fixed scan time. Despite having less power than spaced/periodic ER designs PER EVENT, you have so many more events in a given interval, that you end up having more power.*

Part 2
Cognitive processing issues in paradigm design

Describe two different types of experimental manipulation commonly used in fMRI studies that allow an investigator to relate specific mental processes to specific brain regions. Illustrate your answer by writing brief descriptions of exemplar paradigms. (10 pts)

Answer:
1) Hold the stimulus constant and vary the task (component, categorical, psychological processes):
E.G. For the self-reference task, the stimulus (trait adjectives) is held constant and the task varies between self-reference and semantic questions.

2) Hold the task constant and vary the stimulus (demands parametric):
E.G. For the SIRP task, the task (maintain information in WM) is constant and the stimulus varies (parametric modulation of working memory LOAD).

Several of you had (very nice) answers (e.g. parametric versus categorical versus factorial). We definitely accepted these answers, and any other good answers.