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

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## Final Exam (and answer key)

HST.583

December 15, 2008

### Instructions:

There are 7 problems. Points for each problem are indicated. Please immediately confirm you have all X pages! This is a closed book/ closed notes exam. You have two hours.

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:

- a) List the major brain regions that comprise the "Default mode network" as originally described by Marcus Raichle and colleagues in 2001 (3 points)
- b) describe the hypothesized role of decreased activation in this network during attention demanding tasks from a cognitive neuroscience perspective (3 points)
- c) give an example of how, assuming that this hypothesis is true, this information could be used to improve the sensitivity or specificity of an fMRI experimental paradigm (3 points).

### [Answer:

a) Extrastriate visual areas, posterior cingulate, precuneus, medial prefrontal cortex, (+/- orbital frontal cortex)

b) decrease in activation when shifting from rest to attention demanding tasks (stimulus-independent, task-independent)

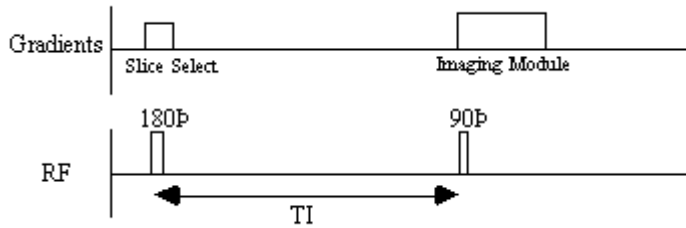
c) Many answers will be accepted. Here are examples of good ones.

-Since the differences between rest with eyes open and closed is still controversial, a paradigm that ensures that during the baseline condition all subjects maintain the same state (eyes open and fixated on center of screen or closed) will decrease between subject variance and perhaps even improve within subject significance of results.

-Any method to ensure that during "baseline" subjects are indeed resting quietly with eyes closed or open and not doing another "off paradigm" task (recalling list of errands to run after experiment is over)- physiological monitoring, low level task- fixate cross hair, etc. will give more consistent results within and across subject.]

### Problem 2:

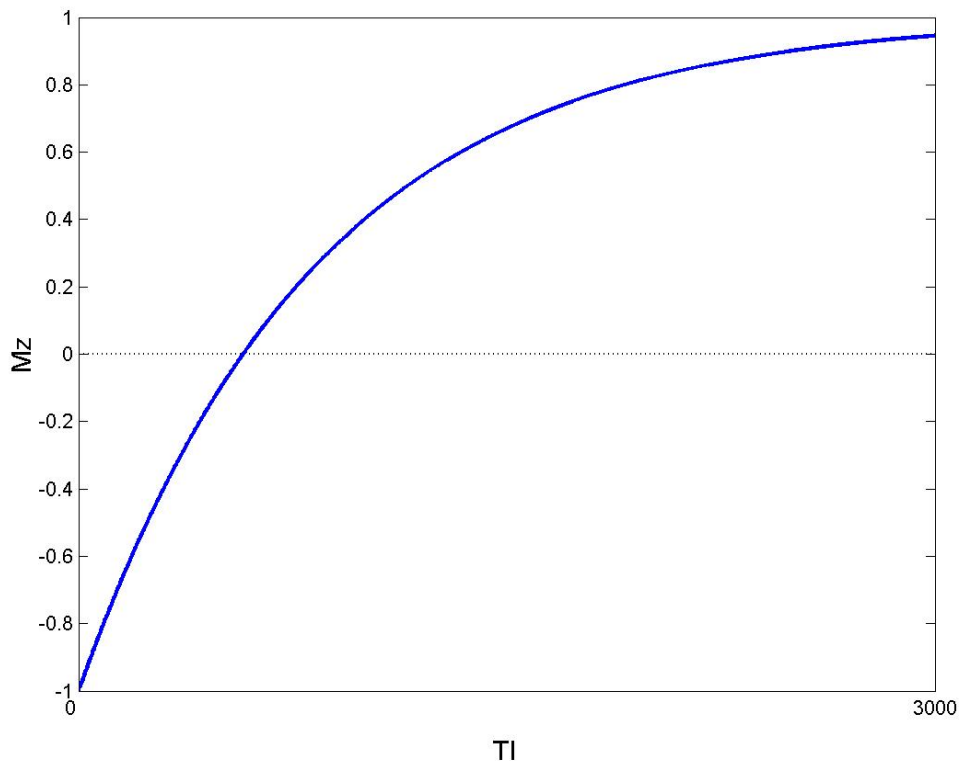
A physics post-doctoral fellow in Dr. Adelsteinsson's lab shows you a generalized pulse sequence for a common imaging technique used boost T1 contrast. The pulse sequence begins with a 180 degree inversion pulse, and is followed by a delay (TI). After the delay imaging commences:



**Figure 1.**

a) This technique is known as inversion recovery, and was used in Dr. Triantafyllou's lab to measure T1 from different tissues. (2 points)

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 2.**

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

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

Draw at zero crossing.  $M_z$  will be zero here, so when you excite with your 90 for imaging, no signal will be knocked down into the transverse plane ( $M_{xy}$ ) and no signal will be detected by the receiver coils.

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

For example if you want to segment out gray matter exclusively - this gives you excellent white matter/gray matter contrast (the best possible actually, since white matter is now dark!).

d) The  $T_1$  of white matter is 832 ms. Compute the TI needed to null white matter signal. (Hint: Modify the longitudinal ( $T_1$ ) magnetization equation to accommodate double the dynamic range). Points for original equation, modified equation, and solution. (3 pts)

Longitudinal relaxation

$$M_z = M_0(1 - e^{-t/T_1})$$

IR equation

$$M_z = M_0(1 - 2e^{-TI/T_1}), \text{ for double dynamic range.}$$

Now set  $M_z$  to zero and solve for  $T_1$ ; should be around 576.7 ms.

### Problem 3:

Given a stimulus schedule where Condition 1 is presented at  $t=2$  and  $t=14$  sec and Condition 2 is presented once at  $t=6$ sec

a. Write out the FIR design matrix assuming  $TR=2$ s, Number of time points =10, and the FIR is window=8s. Include regressors for offset and linear drift (5 points).

Answer:

0	0	0	0	0	0	0	0	1	1
1	0	0	0	0	0	0	0	1	2
0	1	0	0	0	0	0	0	1	3
0	0	1	0	1	0	0	0	1	4
0	0	0	1	0	1	0	0	1	5
0	0	0	0	0	0	1	0	1	6
0	0	0	0	0	0	0	1	1	7
1	0	0	0	0	0	0	0	1	8
0	1	0	0	0	0	0	0	1	9
0	0	1	0	0	0	0	0	1	10

Note: the offset and trend could be the 1<sup>st</sup> two columns (this affects the contrast matrix below).

b. Write out a contrast matrix that tests for the difference between condition 1 and condition 2 at 2s post-stimulus (5 points).

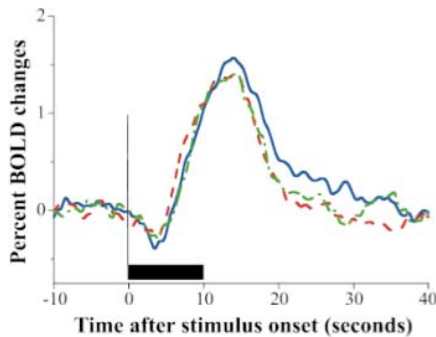
$$[0 \ 1 \ 0 \ 0 \ 0 \ -1 \ 0 \ 0 \ 0 \ 0]$$

What are the trade-offs between using an FIR model and assuming a shape to the HRF? (5 points)

[ Advantages of the FIR: guaranteed to fit the data the best and can handle in HRF shape. Advantages of assuming a shape: increased statistical efficiency and a higher number of DOFs.]

#### Problem 4:

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":



Source: Duong et al. *MRM* 44 (2000): 231-242.

Courtesy of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Used with permission.

- Suggest a possible physiological mechanism for the initial dip. (5 points)
- If the initial dip does exist, why could it be useful for functional imaging? (5 points)
- Why do you think it has been difficult to observe with fMRI? (5 points)

[Answer:

a) The initial dip may represent the initial increase in  $CMRO_2$  before blood flow increases to deliver more oxygen (see Malonek and Grinvald, Menon). As a result, the BOLD signal will initially go down, since there is transiently more deoxyhemoglobin in the local blood, since oxygen is being removed and metabolized by the neuron. As CBF starts to increase, delivery of oxygenated blood will flush out the dHb, leading to the main positive response.

Also acceptable: the Buxton et. al. balloon model can also explain the initial dip, based on a non-linear flow out/ volume relationship. That is, if the curve initially has a shallow slope, so that with a sharp increase of  $F_{in}$  the first effect is a rapid filling of the balloon (because  $F_{out}$  is slow to increase), then the dHb content initially would increase due to the increased venous volume. This would also result in an initial dip.

b) 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. Some believe that CBF may not be regulated with as fine a spatial control as  $CMRO_2$  (recall "watering garden for sake of thirsty flower").

c) Much smaller signal, thus harder to resolve given the limits imposed by the poor contrast to noise of fMRI BOLD signals.]

### Problem 5:

List three possible ways CBF may be regulated in the brain; give a brief description of each. (5 points)

[Answer:

It is increased by an increase in capillary flow, not capillary recruitment. Capillary flow in the brain is regulated by

1- modulation of arteriolar diameter by vasoactive substances (NO, CO<sub>2</sub>, K<sup>+</sup>, adenosine) that bind to vascular smooth muscle receptors (glia, neurons, ?)

2- secretion of vasoactive substances (Adenosine, NO, Prostaglandins, H<sup>+</sup>, K<sup>+</sup>) by neurons that are the byproducts of energy metabolism into surrounding neuropil

3- direct neural innervation of arterioles (NO, VIP, DA, Substance P, NA, GABA, 5-HT, ACh)

4- indirect control by substances (K<sup>+</sup>, Adenosine, CO<sub>2</sub>) released via astrocyte endfeet

5- Pericyte constriction at capillary level

### Problem 6:

a) When registering the fMRI data from one of your subjects to his/her own structural MRI data collected in the same scan session, what are the sources of noise (variance)? For each source of variance listed, indicate what you could do to minimize the variance (5 points).

b) Describe one method for inter-subject registration of the fMRI data from the subjects in one of your experiments so that you can perform a group analysis. What are the sources of noise (variance, error) inherent in this method? (5 points)

[Answer:

a) (at least 2 of these)

--- scanner orientation- ensure subjects are placed in scanner in the same "sweet spot" of scanner and that acquisition parameters are matched for the anatomical and functional scans- e.g. slice orientation

--- image resolution- can't eliminate, optimize to obtain best possible resolution of both scans

--- EPI distortions/imaging physics- low bandwidth of scan acquisition, shim before acquisition, good scanner maintenance, collect field maps and perform a post-processing distortion correction, make sure brain is centered in "sweet spot of scanner"

--- normal range of anatomical variation in subjects- nothing can change this but improved registration algorithms can decrease the negative impact on the results of the analyses

--- pathological abnormality in anatomy- screen subjects, have exclusion criteria to drop subjects if abnormalities are identified on their scans.

b) All the data must be registered to a common "space" the registration can be either landmark based (e.g. average of the cohort or single subject of the cohort, Talairach, MNI305) or image features (e.g. intensity based). Either of these methods can use

many different warping algorithms (e.g. affine, spline, cortical surface). Sources of noise include inter-subject variability in anatomy, inconsistency in image acquisition parameters (e.g. cross site or after upgrade), poor head positioning in scanner with large differences in distortions]

### **Problem 7:**

One of your best friends aspires to do an fMRI experiment to test their hypothesis about how the brain shifts attention from doing a single task to doing two simultaneous tasks. The hypothesis is that there is only a “fixed” amount of attentional ability in the brain and that when shifting from one to two tasks the ability will be “divided” and hence less will be available for either one of the two tasks. The trouble is that they know nothing about fMRI. Since you have just completed HST.583, your friend assumes you are an expert on this topic and has come to you for advice. Most importantly, there is a rich donor who has given unrestricted funds to pay for the scans, subject remuneration and generous consulting fees to you, the expert, for providing the following information. So you accept the job (just in time to pay for your Holiday fun!) and get to work.

(Hint: No knowledge of the cognitive neuroscience in this domain beyond what you learned in the course is required; just apply your own best logical effort and common sense to that base. If you happen to know specific, pertinent references please cite and use them in your response. Take your time thinking all the way through this so that you do the best job you can. Five bonus points are awarded for a fully integrated response.)

### **Answer:**

*Each answer to this problem is unique and is graded by the Course Director for clarity, accuracy, validity and feasibility.*

Design an fMRI experiment to test the hypothesis. Provide:

i. A description of the putative functional neuroanatomic attentional network you will be investigating. (5 points)

*i. Might include (top- down) parieto-frontal (eye fields), cingulate and ascending reticular activating system (bottom-up) network for spatial attention, occipitotemporal network for object/face recognition, prefrontal network for attention & comporment,*

ii. A simple statement of the hypothesis you are testing. Include an explicit statement of what and where you will be measuring to determine if  $H_0$  is true or false. If you are able to give an estimate of an appropriate Power analysis please do so, and/or specify the number of subjects that will be required to test the hypothesis. (5 points)

*All answers must include the following: fMRI data is noisy, signals are small and subjects highly variable. With too small of a sample size, you may miss a real finding completely if the activations in regions are near threshold for detection or if have much inter-subject variability in localization. This is especially important for the smaller brain regions. A minimal sample size to draw meaningful conclusions is typically 12-16 (anecdotally, for many fMRI studies). The actual required sample size, however, required depends on several factors; specifically the expected effect size and the desired power.*

iii. A description of the fMRI paradigm that includes exactly what the subjects will be doing and when and how. (5 points)

*An example of a correct response is:*

*First experiments typically begin with a block design to maximize power to detect regional activation. She is proposing to spend 6 10 minute long scans doing an event related paradigm. A less risky proposal would be to invest in a few block design trials to identify the voxels of interest and then use the event related paradigm to look at the hemodynamic response times of the components of the network. Also, she made no mention of parametrically varying the motor task to allow a more robust detection of movement correlated activation. Such variations could include the dimension of time (duration of movement), complexity, numbers of fingers used.*

*A minimum of two event types must be specified; complex finger movement and imagined finger movement and the duration of each event specified. Adequate time must be given for rest (control condition). Each trial should be 1-5 sec long. We need plenty of trials to have statistical power, so given 10 minutes scan could do about 100 trials per scan. Either spaced events spaced about 16 sec or rapid presentation with 5-10sec with jitter. The number of trials needs to be provided along with information about whether the events are being timed for a block, spaced single trial or rapid event related analysis.*

*To be able to average data across all scans, need to have stable performance of the task during real movement so must practice prior to scans until achieve plateau performance. This also indicates need to collect behavioral data to verify performance accuracy, speed etc. Otherwise, learning/memory effects may confound results. This training will also help to equilibrate the attention level of subjects and will help equilibrate the imagery component across subjects.*

*Keeping still for 10 minutes is difficult for some subjects; a larger number of shorter scans (~5minutes) may yield better quality data with less motion artifact.*

iv. A description of the experimental set-up as needed to perform the experiment. (5 points)

*As noted above, each answer is unique and is graded by the Course Director for clarity, accuracy, validity and feasibility as well as how well it will enable the proposed design.*

v. A list of the image acquisition sequences you will collect including key parameters and a justification for each (why you need it, what you will use it for). (5 points)

#### **anatomical image**

*What matters is good contrast between gray and white matter. Use a sequence that has high spatial resolution and T1 contrast. PD does not. They should recommend an MPAGE or FLASH or SPGR type scan with the highest spatial resolution (smallest voxels) available.*

#### **fMRI scans**



*The strongest BOLD contrast is obtained with T2\* weighted images, like gradient-echo EPI. Spin-echo EPI offers less susceptibility distortions but 5 times less BOLD sensitivity. So, should start using the imaging method that is most sensitive. Unless of course the regions of interest for activation are in or close to an area where there are strong susceptibilities, then should try spin-echo EPI. But I would start with gradient-echo EPI. Spiral is okay too if that is what is available.*

vi. A detailed description of your proposed data analysis methods, including any pre-processing steps, for the single subject and group analyses. (10 points)

*All answers must include not only a correctly described sequence of processing steps but also a justification for each and reasonable parameters/settings where indicated. Minimal processing includes registration to atlas space, skull stripping, motion correction, (+/- artifact detection), spatial smoothing, model fitting with statistical threshold parameters.*

vii. Your prediction of what you will find when the study is completed. (5 points)

*Each answer is unique and is graded by the Course Director for clarity, validity with respect to the proposed design and analysis methods and feasibility.*