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Brain Mapping 1 Midterm Exam

Student ID: 2020711608
Name: Lee Dong Hee

1. **To measure MRI signals, spins need to be excited to a transverse plane (xy). At 7T, how can you excite spins for maximal sensitivity?**

When the strength of the main magnetic field (B_0) increases up to 7 Tesla, the proportion of spins aligned with the main magnetic field is greater. And proton spins of hydrogens precess much faster up to approximately 298 MHz (i.e., faster Larmor frequency ω). So, more magnetic moments line up in the parallel direction (i.e., larger net magnetization M_0). Spins only respond to Radiofrequency (RF) at frequency matched to the Larmor frequency. In order to receive maximum MR signal through RF coils, RF pulses (B_1) are induced by the RF coil aligned orthogonal to B_0 and the flip angle has to be 90 degree. One of components to determine flip angle is pulse duration. The duration of RF pulse should be sufficient to allow the flip angle to be 90 degree. This duration at 7T is shorter than at 3T. After spins are excited by RF pulse, the entire M_0 gets tipped in the x-y plane. The measurable MR signal is greatest when the net magnetization precesses within the x-y plane.

2. **In MRI, multi-slice 2-D images are obtained for covering the entire brain. Please describe principles of how to select slice position, thickness, and orientation. What are the limiting factors to obtain extremely thin slices?**

Image formation of MRI scanners consists of three steps for three dimensional images, which are slice selection, frequency encoding, and phase encoding. Each step needs additional gradient coil to generate different spatial magnetic field. Additional magnetic fields ($B_{z,}B_x, B_y$) by three different gradient coils are added to the main magnetic field (B_0) in the scanner.

The first step of image formation is slice selection. I will explain this step in the perspective of transaxial slice orientation. In order to select any particular slice, it is required to excite spins within that slice, but none of other spins. For this, additional gradient along the z direction is needed and it makes possible to differentiate spatial location along z direction based on different resonance frequency due to the spatially different magnetic fields.

$$\omega_i = \omega_0 + \omega \pm \Delta\omega/2 = \gamma(B_0 + B_z) = \gamma\big(B_0 + G_z \cdot (z \pm \Delta z/2)\big)$$

- ω_i: Larmor frequency at any particular slice i
- ω_0: Larmor frequency at iso-center (=$\gamma \cdot B_0$)

- ω_0: center of frequency
- $\Delta\omega$: the frequency bandwidth of the exciation field (i.e., the range of frequencies)
- γ: Gyromagnetic ratio of hydrogen, 42.58 MHz/T
- B_0: the strength of the main magnetic field (e.g., 3 Tesla, 7 Tesla)
- G_z: the strength of the gradient field along z direction (gauss/cm)
- z: the distance from iso-center (cm)
- Δz: slice thickness

The slice position is determined by two factors, the gradient field (G_z) and the center frequency (ω). The position of slice can be changed or moved along the gradient by using a slightly different RF pulse frequency (ω_i). The slice selection gradient is present whenever the RF excitation pulses are applied at frequency tuned to specifically to the frequencies in a particular slice. The unit of the gradient strength is gauss/cm and the center at the range of gradient strength is called iso-center, which means z is zero. For example, if someone wants to select a slice located 2 cm away from the iso-center at 7T MRI, he or she can get it by turning on the slice selection gradient and applying 42.58 MHz×(298 MHz + 4258 Hz×2cm) frequency of RF pulse. And 298 MHz + 4258 Hz×2cm frequency is called the center of frequency.

The slice thickness is determined by two factors, the strength of the gradient (G_z) and the range of frequencies in the RF pulse ($\Delta\omega$). If G_z is fixed, slice thickness could be changed by applying different bandwidth of RF pulse. After deciding the center of frequency in a slice, it is necessary to choose specific thickness of that slice. For example, if you want to select 5 mm slice thickness and the center of frequency is 298 MHz + 4258 Hz×2cm, then 4258 Hz×0.5 cm frequency is added to the RF pulse and it is called the width of frequency. This happens because resonance happens not only at the exact same Larmor frequency but also near the frequency.

Furthermore, the shape of RF pulse muse be time amplitude given by a sinc function. This pulse gives a rectangular frequency profile and allows excitation of spins within a rectangular slice.

So far, the slice orientation that I dealt with was a conventional transaxial slice orientation. Other orientations, such as sagittal, coronal, and angled combinations, are created by interchanging and combining gradient directions.

Thin slices require the great gradient field and the narrow frequency bandwidth of the excitation field. The bandwidth is determined by the duration of the RF pulse. When the duration of RF pulse is long, the slice thickness is small, and it results in increased resolution. In the case of extremely thin slices, it requires very long duration of RF pulse. It makes the time of data acquisition increase for both structural and functional MR images. Also, when a given TR is limited, thinner slices are associated with more noise, and so the signal-to-noise ratio decreases with the slice thickness.

3. Although MRI measures water protons, it can be used to measure brain structure, functional activity, diffusion, etc. In conventional brain mapping studies, anatomical images and BOLD fMRI are obtained. What are the underlying MR biophysical bases of a) anatomical contrast, and b) BOLD images?

MR images are sensitive to a wide range of tissue properties. There are three important tissues in the brain, gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Each tissue has intrinsic properties about the net magnetization (M). Before I explain about anatomical contrast and BOLD images, relaxation mechanisms of a spin system are needed to describe.

RF pulses (B_1) aligned orthogonal to the main magnetic field (B_0) are applied to measure MR signal. Each proton possesses a magnetic moment and angular momentum. It potentially contributes to the MR signal. After turning off RF pulses, the MR signal generally decays over time. This phenomenon is called spin relaxation and the sum of all magnetic moments from spins is referred to the net magnetization (M). Spin relaxation phenomenon could be divided into two primary components, longitudinal relaxation and transverse relaxation. In a particular tissue in a magnetic field, these relaxation mechanisms are determined by time constants such as T_1 and T_2.

$$M_z(t) = M_O\left(1 - e^{-t/T1}\right)$$

Longitudinal relaxation (also known as T1 relaxation) occurs when the net magnetization recovers along the z direction after turning off the RF pulse. It keeps recover until the equilibrium state, which means that longitudinal magnetization ($M_z(t)$) is essentially equal to its final value original magnetization (M_O). And the recovery time of longitudinal relaxation depends on the size of molecules where the proton exists in each tissue. For example, the recovery time duration of CSF is longer than the duration of GM because the molecules within CST are smaller than the ones within GM, so the efficiency of relaxation is low when the energy leaves the spin system and is transferred to external environment of spins (i.e., lattice). The total net magnetization (M_O) and the recovery time of each tissue are constant in a magnetic field of a given strength. So, T_1 is defined by the time constant value of about 63% ($1 - e^{-1}$) of M_O. Different tissues have different T_1. For example, at 3 Tesla, T_1 of CSF is 3000 ms, one of GM is 1500 ms, and one of WM is 850 ms. Normally, the signal intensity of a tissue that recovers faster is high.

$$M_{xy}(t) = M_O e^{-t/T2}$$

Transverse relaxation (also known as T2 relaxation) is the phenomenon that the net magnetization within the x-y plane decays after excitation of a spin system because of the loss of phase coherence of the spins. This loss intrinsically occurs due to spin-spin interactions. The decay time of transverse relaxation is determined by the distance between protons in each tissue. For example, the proton density of CSF is lower than the one of GM,

so the effect of spin-spin interactions is smaller, and it makes dephasing slower. The original net magnetization (M_O) and the decay time of each tissue are intrinsic to type of tissues in a magnetic field of a given strength. So, T_2 indicates the time constant value of about 37% (e^{-1}) of M_O. T_2 is the almost same regardless of type of tissues. For example, T_2 of CSF is 2500 ms, one of GM is 100 ms, and one of WM is 90 ms. Generally, the signal intensity of a tissue that decays slower is high.

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_2'} = \frac{1}{T_2} + \gamma \cdot \Delta B$$

In addition, the decay of the net magnetization practically results from not only intrinsic spin-spin interactions but also extrinsic local magnetic field inhomogeneities. This phenomenon is called T2* relaxation. Because of additional cause for dephasing, the decay speed is faster than T2 relaxation. That's why T_2^* is always shorter than T_2. BOLD-contrast image in fMRI is based on T_2^* contrast.

In pulse sequence, two parameters are important to obtain MRI contrast images, the repetition time (TR) and echo time (TE).

$$M_{xy}(t) = M_O\left(1 - e^{-t/T_1}\right)\left(e^{-t/T_2}\right) = M_O\left(1 - e^{-TR/T_1}\right)e^{-TE/T2}$$

The MR signal, $M_{xy}(t)$, could be illustrated by replacing t with TR and TE. This provides the foundation for manipulating the signal from an articular tissue type by controlling TR and TE. Contrast images are based on the comparison MR signals from different tissue types by measuring a difference in signal between tissues.

Now, anatomical contrast and BOLD contrast are going to be described with the concepts that have been explained so far. First of all, anatomical contrasts are influenced by several factors such as spin density (e.g., proton density) and relaxation time (e.g., T_1, T_2, T_2^*). Most of anatomical contrast images are T_1-weighted images. T_1-weighted images show impressive contrast between GM and WM. This image type maximizes T_1 contrast and minimizes T_2 contrast and proton density contrast. Intermediate TR shows the greatest difference of T_1 values between tissues. On the other hand, TE must be short in order to minimize T_2 contrast because the MR signals decrease as long as TE becomes long.

Second, BOLD contrasts are based on physiological process in the brain. BOLD contrast images are acquired by T_2^* weighted images. Neuronal activity leads to increases in blood flow and in the supply of oxygen that exceed oxygen demand through red blood cells in blood vessels. This results in a decrease in the amount of deoxygenated hemoglobin.

$$\Delta\chi = \Delta\chi_O \cdot Hct \cdot (1 - Y)$$

$$R_2^* = \frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_2'} \approx \frac{1}{T_2} + \alpha \cdot \Delta\chi_O \cdot Hct \cdot \omega_O(1 - Y) \cdot CBV$$

Oxygenated hemoglobin (Hb) is diamagnetic due to no unpaired electrons and this is similar to tissue, so Hb doesn't affect dephasing of environmental tissues. On the other hand, Deoxygenated hemoglobin (dHb) is paramagnetic because of 4 unpaired electrons. Magnetic susceptibility (χ) of dHb is about 20% grater than Hb. The difference of magnetic susceptibility results in different precessing frequencies, which affects different rate of dephasing (R_2^*). So, the decrease in the amount of deoxygenated hemoglobin causes local field disturbances. The relative decrease in the signal loss due to T_2^* effects, which indicates high signal intensity. In both inside and outside the blood vessels such as venous vessels and capillary, the frequency shift by deoxyhemoglobin occurs when neurons are activated. Extravascular protons are greatly sensitive to the frequency shift and the rate of dephasing is faster in near vessels than far ones.

$$M_{xy}(t) = M_O e^{-TE/T_2^*}$$

T_2^* contrast is provided by pulse sequences with long TR and intermediate TE because these parameters maximize T_2^* effect and minimize T_1 and proton density effects. An intermediate TE can capture information about indirect neural activity due to extrinsic local magnetic field inhomogeneities by the presence of dHB.

4. Please 1) list all of the typical preprocessing steps, then describe what they do and why they are necessary. 2) What factors should you take into account when making decisions at each step? Under what conditions can you skip each step?

1) Data Quality

- This step is necessary because sometimes raw image data have unexpected problems. Without check for data quality, unnoticed problems might spoil up the final results of studies. Many artifacts are easily visible in the raw images. In that cases, a time-series movie is a good way to examine them. In addition to visual inspection, statistical tests could be applied to evaluate the data quality such as the calculation of raw SNR. To check whether there is physical noise in the MR scanner, it is good to test a phantom. During this step, you might find ghosts in images, hardware errors, unexpected spikes and etc.

2) Distortion Correction

- Inhomogeneities in the B0 magnetic field cause distortions for fMRI because of EPI sequence and gradient-echo pulse sequence. MR signals decrease in the presence of B0 field inhomogeneities. When the MR scanners show great performance, you can skip this step because inhomogeneities are not so much in the static magnetic field

3) Skull removal and T1 segmentation (for anatomical images)

- Brains are extracted from nonbrain structures such as the skull and dura matter for further analysis. And the extracted image is segmented into CSF, GM, and WM. The segmentation is necessary to use average activity in CSF and WM as covariates for the nuisance regressors in the statistical analyses. Also, these segmentations can be used for brain masks for further analyses.

4) Field Map correction

- Functional EPI images often show crushed regions because the main magnetic field B0 is not entirely homogeneous. After obtaining field map in both phase encoding direction, AP and PA, you can correct the part of distortions by interpolating with the field map. Like distortion correction, this step could be skipped if the main magnetic field is quite homogeneous.

5) Slice Timing Correction

- EPI methods acquire images a slice at a time (or several slice at a time using multiband). The order in which slices are obtained is an acquisition option for most sequences on the scanner. There are many types of ordering such as sequential, interleaved, or group orders and the two types of acquisition direction such as descending or ascending is important to match the timing of any comparison data with the timing of the data in the voxel. Slice timing correction is a method of shifting the data to make them as if they were all collected at a fixed set of times, which are the same across the whole image. You can skip this step if you use multiband slices acquisition or TR less than 2 seconds because it might distort signals while interpolating signal across cans to attempt to align timing in that cases.

6) Motion correction

- Head movement in the scanner and the associated motion-induced changes in the images are a big problem in fMRI. This is largely because the changes in the signal due to the BOLD effect are quite weak, whereas the changes in signal intensity that can be induced by motion are much larger, even for very small motions. Also, it is more likely that the timing of the motion could match the timing of key features of the acquisition with task-related movement and this may lead to spurious activations. To correct head motion, there are two types of spatial transformations, linear (rotation, translation, scaling, skew/shear) and non-linear transformations. Given images are linearly or nonlinearly transformed to minimize mean squared error between individual image and reference image). Goodness of alignment can be measured using one of cost functions such as least squares, normalized correlation, correlation ratio, and mutual information. As well as cost function, interpolation function is required to fill up missing data points, which leads the loss of spatial resolution. It is important to remember that a few problems might still remain after motion correction. Motion correction and slice timing correction are interchangeable

7) Coregistration

- Within participant, it is necessary to align the functional images to the structural image of that participant. This step allows functional activation to display on anatomical

images with greater spatial resolution. Note that brighter voxel indicates higher signal intensity in T_1-weighted images and the voxels within CSF are brighter. Whereas the voxels within CSF are darker in T_2^*-weighted images. The most commonly method for coregistration is mutual information.

8) Spatial Normalization

- For group analyses, it makes sure that the information at a voxel location corresponds to the same point in the anatomy for every participant. After coregistration, the individual brain image is warped into standard brain template. The most commonly templates are Talairach space and Montreal Neurolgical Institute space. You can select one of them. There are several normalization methods. One is Landmark based normalization, but this method is not common. Volume based normalization and surface based normalization are frequently used these days. Lastly, nonlinear normalization is an option.

9) Spatial Smoothing

- This step involves blurring the functional images by calculating a locally weighted average of the intensities around each voxel, done separately at each point in time. The main reason for this step to improve SNR. Smoothing is able to improve the SNR because averaging the noise will reduce its amplitude, whereas averaging the signal maintains the same value. This is helpful as long as the neighboring voxels contain signal of interest. The amount of smoothing is a parameter you have to choose, specified by the full width at half maximum (FWHM) in millimeters of Gaussian kernel. Small values of FWHM (e.g., 2.2 mm) are often preferred in order to get some SNR benefit without losing the ability to find small regions of activity. Using too large FWHM might eliminate meaningful information in data.

10) Temporal filtering/Temporal Drift Correction

- MR signals are mixed intensities with both signals of interest and noises. Temporal filtering is a method that removes or suppresses signals on the basis of their frequencies. Typically, low frequency noise and high frequency noise stem from hardware noise or physiological noise. Since the neuronal signals usually have frequencies in a relatively well-defined range, it is possible to separate and remove some of the artifactual signals that are outside of this range by using either high pass filter or low pass filter or both. You have to choose filter frequency parameter, that is cut-off frequency. Be aware that you might lose signals of interest by filtering too much.

5. **Won Mok is trying to design an experiment where subjects make gender judgments on common names. Specifically, she wants to know whether there are brain regions that will predict whether subjects will categorize ambiguous names like her as either male or female in comparison to when people judge names that are canonically male (e.g., Seong-Gi) or female (e.g., Minah). Help**

Won Mok design the study. What kind of design should she use? Why? How many different conditions should she use? What scan parameters (e.g., TR, voxel size, # of runs, run length, etc.) and task do you recommend? Provide a rationale for each of your choices.

I think she should use 2 x 2 factorial designs. Simple event-related design might be boring too much because the stimulus is just a name and block design is not appropriate in that it is necessary to have sufficient time to predict when the name stimulus is presented. I assumed she runs this experiment in Korea and every participant is Korean. Under the assumption, I'm concerned the number of characters. The number of characters in Korean name is mostly one or two. One of main effects is difference between one vs. two in the number of characters. The other is, of course, difference between male name vs. female name. Following these two factors, four conditions turn out and I added additional two conditions: 1) male name with one character, 2) female name with one character, 3) male name with two characters, 4) female name with two characters, 5) ambiguous name (e.g., Won Mok), and 6) baseline condition (fixation). She is able to examine whether there are interactions between main effects.
Below are my recommendations for scan parameters.
- Telsa: 3 Tesla (the most commonly used)
- TR: 1000 ms (considered by hemodynamic response, slice timing correction)
- voxel size: 3 x 3 x 3 (
- number of slices: 34 (multiband)
- slice orientation: 9 degree (avoid empty space in frontal area)
- number of runs: 10 (sufficient sample size for a participant)
- run length: 5 min (should not be boring)