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1.1 MRI physics

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Magnetic resonance imaging (MRI) is founded on the principle of nuclear magnetic resonance (NMR), which exploits the magnetic properties of the hydrogen nucleus that contains a single proton. The proton is not static, but rotates around its own axis, and as the proton is positively charged it creates a magnetic moment in the direction described by the thumb rule, and can interact with an external magnetic field. The human body consists of approximately 10% hydrogen atoms, but as the hydrogen nuclei spins are randomly orientated, the net magnetic moment equals zero, as the nuclei cancel each other out. Placing the body in a strong magnetic field will align the nuclei. A property of the hydrogen nucleus is its quantum spin rate, which can either be $\frac{1}{2}$ or $-\frac{1}{2}$ - either in the direction or the opposite direction of the main magnetic field. Most will align in the direction of the magnetic field, while some align in the opposite direction, possibly as a result of heat radiation. The direction of the nucleus is determined by its energy level, leaving the former in a low energy state and the latter in a high energy state. The nuclei do not simply point in the in the direction or opposite the direction of the magnetic field, but precess. Insert illustration The rate of precession can be calculated by the Lamour frequency:

$$f = y * B_0 \tag{1.1}$$

, where f is precession frequency, y is gyroscopic ratio and B_0 is magnetic field strength. The equation states that the precession frequency is proportional to the strength of the magnetic field. After canceling out all opposing precessing nuclei, the net magnetization, or longitudinal magnetization, will point in the direction of the external magnetic field. However, the longitudinal magnetization can not be detected directly as it points in the direction of the strong external magnetic field. Additional techniques are therefore used in MRI, to facilitate a detectable signal.[1]

A radio frequency pulse (RF pulse) tuned to the precession of the nuclei is transmitted in the vicinity of the nuclei. The RF pulse is absorbed by the nuclei and more, favorably half of the targeted nuclei population, will enter the high energy state, leaving the longitudinal magnetization to equal zero. The number of nuclei that flip is determined by the amount of energy the RF pulse injects, and the nuclei only exchange energy efficiently if the frequency of the energy from the RF pulse matches the precession rate. The RF pulse furthermore shifts the precession of the nuclei into same phase angle, which creates resonance, and a net magnetization pointing 90° to the longitudinal magnetization. This magnetization is called the transverse magnetization. The coherent nuclei produce a radio signal, or free induction decay signal (FID signal), that can be detected by a radio antenna. After the RF pulse is removed, the nuclei will relax into baseline state. Firstly, the spins of the nuclei will repel each other, as they are positively charged, and thus shift phase. The net magnetization will return to zero. This relaxation is called T_2 or "spin-spin" relaxation, as the energy exchange between the nucleus spins is causing the relaxation.

The second relaxation happens as the high energy nuclei returns to the low energy state. The energy that was previously absorbed by the nuclei is dissipated in to the surrounding lattice in the form of heat. During this relaxation the longitudinal magnetization is regrown. This relaxation is called T_1 or "spin-lattice" relaxation, as the spins transfer energy to the surrounding lattice.[1] (Insert illustration)
The hydrogen nuclei are located in different local environments in the body. Some are for instance associated with free-floating water molecules, while others are associated with structural and storage molecules such as proteins and lipids, and thus more fixed in position. The nuclei have different T_1 and T_2 relaxation characteristics, depending on the local environment or tissue they are associated with. This can be accentuated and measured in NMR.[1]
The chosen pulse sequence is key to how the tissue will be portrayed on an image, and is described by the T_{echo}, time before the FID signal is measured, and T_{rep}, time before a new RF pulse is applied. In a case of nuclei in lipid and water molecules, the nuclei in lipids are fixed and will have a fast T_1 relaxation. Meanwhile the nuclei in the water molecules will maintain being in a synchronized phase. At T_{echo}, the nuclei associated with the lipids will have a low FID signal, as the transverse magnetization is weak, and the nuclei associated with the water molecules will have a high FID signal, as the transverse magnetization is strong. The water molecules will be assigned a white color on a greyscale image and the lipids as dark grey/black. In this case there is a long T_{echo} and a long T_{rep}, and is referred to as T_2-weighted MRI.[1]
In case of T_1-weighted MRI, the T_{echo} and T_{rep} are short. As in T_2-weighted MRI a RF pulse is applied and the nuclei associated with lipids will quickly return to baseline state and the water molecule nuclei will remain a strong transverse magnetization. At this point a second RF pulse will be induced, referring to the short T_{rep}. Now the lipid nuclei will return to a strong transverse magnetization state and excite a high FID signal. More low energy state nuclei of the water molecules will absorb the RF pulse and shift to a high energy state, leaving a majority of nuclei in a high energy state. The water molecule nuclei now has a weak transverse magnetization and 180 degrees longitudinal magnetization, thus producing a low-amplitude FID signal. A short T_{echo} after the second RF pulse then shows lipids as white and the water molecules as dark grey/black in a greyscale image.[1]

1.2 MR image reconstruction

Following the Lamour frequency equation (1.1) the main magnetic field causes all hydrogen nuclei to precess with the same frequency. Without any specification of spatial localization a MRI of a human body would consist of a single number. To prevent this, separate coils in the x, y and z directions are introduced. These coils can be adjusted in position, and thus produce gradient magnetic fields with a varying strength depending on position. According to the Lamour frequency the nuclei will precess with different frequencies when in a magnetic field with varying strength. The gradients can be turned on in combination to create any direction in space. These varying frequencies can be exploited to separate parts of the anatomy and ultimately illustrate a desired area.[1]
Insert Illustration As mentioned, the nuclei only exchange energy efficiently if the frequency of energy, or RF pulse, matches the precession rate. Thus, by altering the magnetic field along the body in one direction, z-direction for the sake of the example, the nuclei will have

slightly different precession rates, and the RF pulse will only efficiently affect a desired slice of the nuclei. The nuclei of that slice now precess at the same rate. To get an image with a spatial resolution, the voxels that make out the image needs to be discriminated between. By turning on the gradient of the x direction the lines in the y-direction are now encoded with a particular frequency. This gradient functions as a frequency encoding gradient.[1]
Turning the y-gradient on and quickly off, will de-phase the nuclei while still remaining the same frequency as before. This gradient functions as a phase encoding gradient. When comparing two locations approximately one voxel apart in the x-direction, then based on the amount of gradient strength difference, there will be a certain amount of change in phase between the spins spread across that distance. The farther away from isocenter, where the magnetic field strength is B_0, the higher the change in phase will be. This notion is used to assign the correct spatial location of each voxel, when translating the FID signals into an image. This phase encoding procedure is done in different gradient strengths in iterations to assign unique phases to the nuclei in the both directions. One iteration of a certain strength of the phase encoding gradient followed by a digital measurement is performed at a time. The only change per iteration is the phase encoding gradient strength. These iterations are then series of measurements acquired at different points in time, where each entry of the slice then represent a certain signal intensity. This time domain measurement is referred to at the raw data.[1]
The next step is to Fourier Transform (FT) the raw data, which will yield frequency information to the acquired signal intensities. This step gives a summation of the signal intensities at the different frequencies produced by the frequency encoding gradient. This is called the k-space, as the k-numbers of a signal describes its relative orientation and frequency. The k-space image contains the contrast in the center and the resolution in the periphery, as there is low or no phase encoding at the center and increasing towards the periphery, giving more brightness in the center and dimmer in the periphery. To allocate the voxels in correct spatial localization an inverse 2D discrete FT is performed on the k-space image. This provides the desired image of the anatomy slice.[1] (insert image of k-space => MRI)

1.3 Functional MRI

Many different techniques exist to accentuate different tissues, physiological phenomena etc. using MRI, of which a few will be described further in the following section.

1.3.1 Introduction to BOLD fMRI

Functional magnetic resonance imaging measure the metabolic changes associated with different neurological tasks in different brain areas. fMRI offers advantages predominantly, high temporal and spatial resolution, low cost, and most importantly being non-invasive, which has made it a exceedingly popular method for imaging brain activity. The versatility of fMRI has made it very important tool in being a biomarker for diseases and to study the efficacy of pharmaceuticals. The method offers high resolution of anatomical structures and localization and visualization of vessels. [2]

Multiple steps in forming and transmitting a neurological signal requires energy Adenosine tripolyphosphate (ATP) consumption e.g. reception and reformation of an action potential. When activating a brain area as done in the most often used example, finger tapping, the ATP starts to be processed, leading to a decrease in oxygen concentration and increase in waste. Thereby the metabolic need for oxygen increases. As the movement is planned and executed, factors, which are present in the local tissue of the corresponding brain area, activate a vasodilation, increasing the blood flow to that area and reestablishing the local homeostasis. Though one special and not fully understood phenomenon occurs during this process. More oxygenated blood than needed to compensate for the offset is delivered. Thereby an overshoot occurs. The increase in neural activity in that specific area thereby permits two conditions which can be assessed through fMRI, being the cerebral blood flow and blood oxygen level dependent contrast. An example illustrating the measurable hemodynamic response can se found in figure 1.1[2, 3]

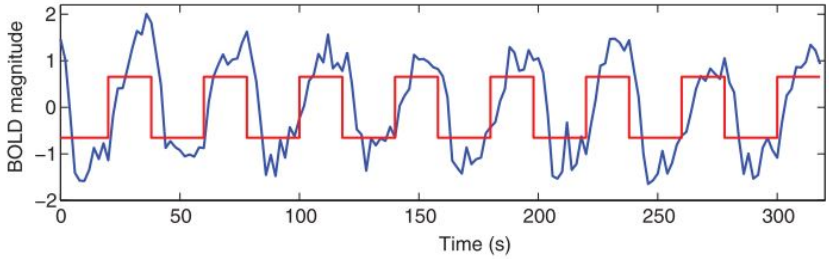


Figure 1.1: Figure showing an induced series of stimuli (red) and the hemodynamic response to the neural activity measured using BOLD (blue). It is shown that the measurable hemodynamic response is delayed compared to the stimuli. [3]

As established in the above section the BOLD signal is effected by the neural activity producing changes in the local blood flow, blood volume and blood oxygenation. The crucial part to why MRI can detect this natural contrast, is that fully oxygenated blood, is diamagnetic and fully deoxygenated blood has four unpaired electrons thereby making it highly paramagnetic. Thereby more oxygenated blood in the area the larger the contrast, compared to other brain regions, is seen as illustrated in figure 1.2. [2, 4, 3]

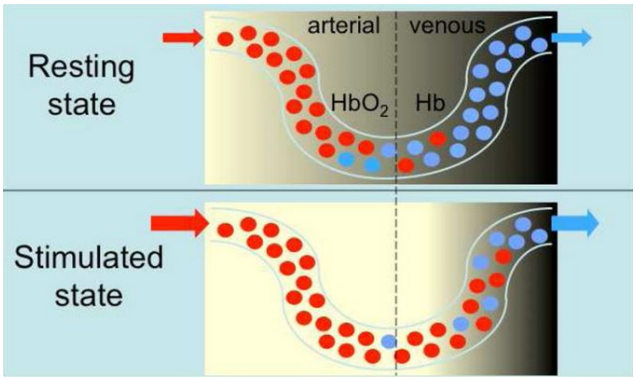


Figure 1.2: Illustration of how the difference in oxygen concentration in the hemoglobin change the magnetic properties, resulting in a higher measurable contrast [2].

This change in local magnetic properties increases the magnetic susceptibility leading to a greater MRI signal when acquiring an T_2^*- weighted sequence.

1.4 General MRI pre-processing

Maybe do a top saying something about the program we choose to use. Derved lave en afgrænsning der

There are multiple steps to preprocess fMR images depending on the apparent application and outcome intended. However, there is a standard set of methods that is usually used across all applications. The following section seek to elucidate some of the most commonly used correction methods, including those considered for the standard preprocessing method used in this project. An example of some of the general processing steps for MR imaging can be seen on figure 1.3.[3]

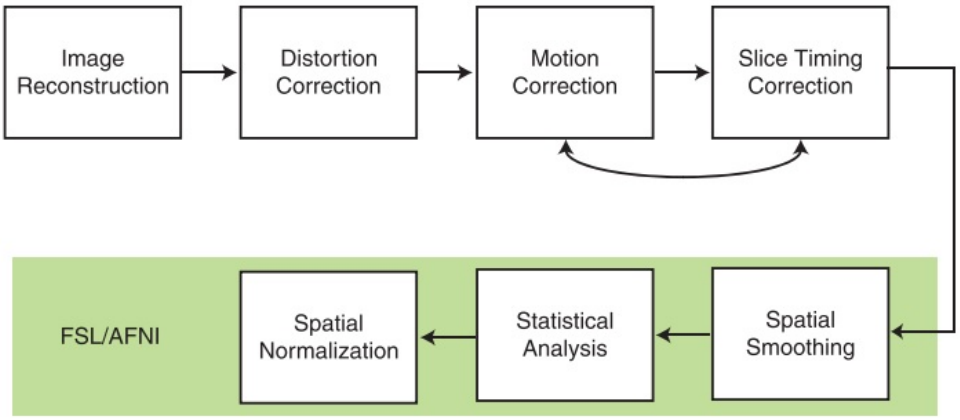


Figure 1.3: The general pipeline for MRI processing done in either FSL or AFNI, showing the different processing steps considered before final statistical analysis. Modified from [3].

1.4.1 Quality control

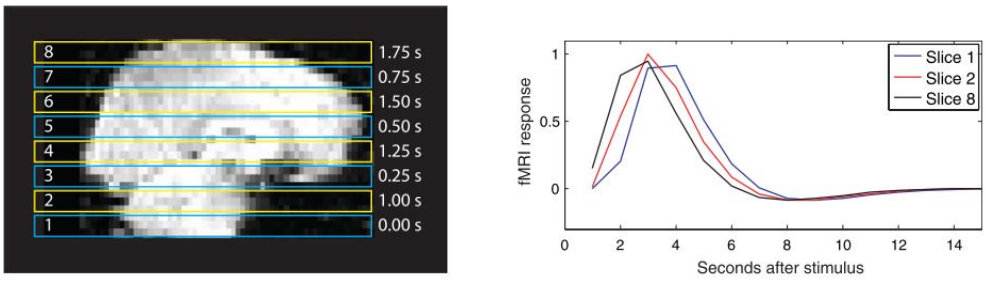
Conducting a continues quality control is highly recommended after each performed correction step. Various scanner artifacts can occur while acquiring an MRI series. Before performing any common correction steps, one should consider to look for spike or ghosting artifacts. Spike artifacts are seen as a regular pattern of change in brightness across the entire image. This problem can occur due to instability inside the scanner deriving from e.g. electrical discharges. The artifact called ghosting occur mainly due to two reasons. One being an offset in phase between different lines in K-space and the other due to periodic motion as in heartbeat and respiration. Ghosting can be seen as light copies of the object appearing to either side of the object. Both types of artifacts can corrupt the information contained in the images. However, artifacts of this kind rarely present themselves in newer scanners, nevertheless it is still recommended to perform a quality control of the scan.[3]

1.4.2 Distortion correction

Some fMRI acquisition methods, including the most widely used method of gradient-echo echo planar imaging, suffers from artifacts at regions air and tissue meet. The ear canal and sinuses are areas especially vulnerable. Inhomogeneity in the magnetic field in these areas can cause two types of artifacts, dropout and geometric distortion. A dropout will result in a reduced signal intensity in regions close to the air to tissue transition. When a dropout during an acquisition occurs, the lost signal cannot be restored and the damage is permanent. Therefore it is wise to consider the appropriate acquisition method taking the area of interest into addition. Air to tissue passages can also be subject to spatial distortion due to inhomogeneity created in the magnetic field. This will lead to structures not being located correctly in the captured image. This distortion makes is difficult to align two different scans, as done when aligning fMRI images with structural images. The spatial distortion can partially be corrected by employing field maps. In order to do a field map, the pulse sequence from the scan needs to be known. The process involves acquiring images at two different echo times. This results in images with two different phases which can be used to compute the field inhomogeneity. Thereby it becomes possible to calculate the relative distance each voxel has shifted. This makes up a map for the distance shift for each voxel, and by inverting the map the original image can be restored.[3]

1.4.3 Slice timing correction

Acquiring fMRI scans is nearly always done in two-dimensions, where the slices are taken one by one. This can either be in an ascending, descending or interleaved order. Interleaved order [1] is sequentially skipping every either odd or even slice and then afterwards do to skipped slices. Regardless of which order the slices are acquired, a difference in effect in each slice to the same hemodynamic response will be present due to the time difference in the slices. The method and result of interleaved MRI acquisition order can be seen figure 1.4 The difference in time between slices can range up to a couple of seconds depending on the acquisition protocol.



(a) (b)

Figure 1.4: Figure a illustrates an example of an MRI acquisition using interleaved order, where initially every odd slice is acquired followed by every even. The information about the hemodynamic response in each slice, and thereby also the difference at each time-point is shown in figure b. Figure modified from [3].

[1] FiXme Note: think it is done to avoid crosstalk

The difference in slice timing constitutes a problem when analyzing the data. The data is formed into statistical model, but since this model assumes that all slices are acquired at the same time point, the actual signal and the statistical model creates a mismatch. To counter this problem slice timing correction was introduced. The common approach of this method is to choose a reference slice, usually the slice acquired at T/2, and use this slice to interpolate the others. Linear interpolation can be used for simplicity, but most often sinc interpolation is used as it imposes less smoothing to the signal.[3]

1.4.4 Motion correction

Correcting for motion artifacts when doing MRI is inevitable, since even the best subjects will not be able to hold still. Even subtle movements as swallowing will be visible in the raw acquired image.[3]

Multiple internal and external factors can cause a subject to move. Internal factors are none avoidable physiologic motion. The heartbeat causes a pulsating movement which makes the brain move. Additionally motion created during respiration can cause small changes in the magnetic field around the head. External factors like imposed stimulus might also cause the subject to make sudden movements. Often when doing fMRI the brain activation is measured while the subject is subjected to some kind stimulus. The stimulus would make the patient move, while some brain center might also show activation associated with stimulus, and therefore it is easy to mistake brain activation with stimulus correlated movement when analyzing the data, resulting in a weaker or even false statistical analysis.[3]

Motion during image acquisition can result in two primary artifact effects, being bulk motion and spin history. Bulk motion refers to the movement of the head as a whole and requires standard correction methods, e.g. the images throughout the series to be realigned to a reference image. The effect of bulk motion can be visual in the entire image of the brain, but the effect will be most predominant at the edges of the brain. Here the artifact will be noticeable as either a drop or increase in intensity as a voxel would switch from containing brain tissue to suddenly not during head motion. Spin history is head movement interfering with MRI signal itself. The interference occur during acquisition when a voxel of excited protons is moved in to a neighboring slice. The scanner will thereby receive a different signal than expected which do not correctly represent the actual local properties. This results in an image where the intensities change in a striped pattern, visible when acquiring slices in interleaved order. The standard motion correction methods cannot cope with this type of artifact, but Independent Component Analysis (ICA) might be able to correct for this artifact.[3]

As mentioned earlier motion correction is to realign the series of images to a reference image trying to minimize cost in an introduced cost function. The reference image is usually the one taken midway into the series, justified by it being the closets to the average as well as the scanner at that time would have achieved stable contrast, as the magnetization would have reached steady state. The images are thereafter realigned utilizing an image registration method as it register the brain in each image. The general methods for motion correction treats the

brain rigid objects, thus only performing rigid body transformations. Subsequently, the brain can either translate or rotate along the three axis, but the shape of the head cannot change. This method is therefore only applicable for bulk motion.[3]

1.4.5 Spatial smoothing

In some cases, introducing spatial smoothing in the preprocessing pipeline proves to be beneficial. Spatial smoothing allows the possibility of gaining a higher signal to noise ratio within the image, though with the consequence of a decrease in spatial resolution as the image gets blurred and smaller areas of activation gets smeared together. The operation can be justified by the closely neighboring pixel being correlated in effect to the hemodynamic response. Spatial smoothing removes the higher-frequency information. This might wash out some of the smaller features in the image, but this is favorable if the signal is increased for the higher features. Especially when acquiring small voxels spatial smoothing as it reduces the overall noise. Smoothing can also be applied to lessen the anatomical variability in images when doing studies with multiple subjects.[3]

Smoothing is done by applying a kernel, also called filter, to the image. The three dimensional image is convoluted with a three dimensional filter. The most commonly used is a Gaussian filter, where the extent of smoothing is controlled by the width of the distribution. The filter works by for each pixel calculating a new value based on a weighted average of the neighboring pixels, where the ones closest contributes the most and those further away less. The amount of smoothing to implement highly depend on the application and purpose. When smoothing fMRI signals for noise, the width of the filter distribution should not be bigger than the area of activation signals of interest. The effect of smoothing is shown on figure 1.5, where it is seen that as width increases smaller activation area get removed and bigger area of activation gets smeared together. Using smoothing to reduce the effect of anatomical variability, the optimal distribution width depends on the amount of variability in the subject population.[3]

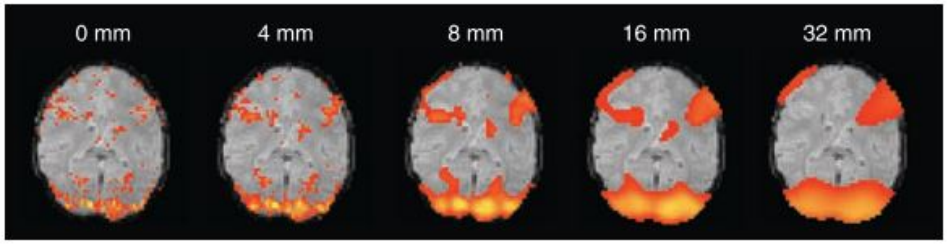


Figure 1.5: Illustration showing the impact of using different distribution width on the activated areas. An increase in width results in greater areas of activation smearing together and the removal of smaller.[3]

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