IMAGE CONTRAST IN MRI

In order for a pathology (or any process for that matter) to be visible in MRI, there must be contrast or a difference in signal intensity between it and the adjacent tissue.

Signal contrasts can arise in MRI from differences in four basic physical parameters:

- ***ρ: The spin density of the various tissues/fluids being analyzed***
- ***T_1: The time constant with which the spin magnetization of a given tissue will build up after being saturated/inverted/pulsed-away***
- ***T_2^*: The time constant with which the spins' signals arising from a given tissue will diphase due to inhomogeneous broadening –this is the kind of signal decay that can be echoed away by π pulses; for instance the one arising from field inhomogeneities or susceptibility differences***
- ***T_2: The (longer) time constant with which the spins' signals arising from a given tissue will decay away due to homogeneous broadening – this is the kind of irreversible decay that can't be echoed away, arising from microscopic random fluctuations in the magnetic field.***

Contrast in most MR images is actually a mixture of all these effects; but careful design of the imaging pulse sequence allows one contrast mechanism to be emphasized while the others are minimized. **The ability to choose different contrast mechanisms by tailoring the appropriate pulse sequence and choosing the right pulse sequence parameters, is what gives MRI its tremendous flexibility.**

For instance: **Achieving contrast via T_1, T_2 relaxation parameters**

Malignant and healthy tissues have minor differences in their overall water content.

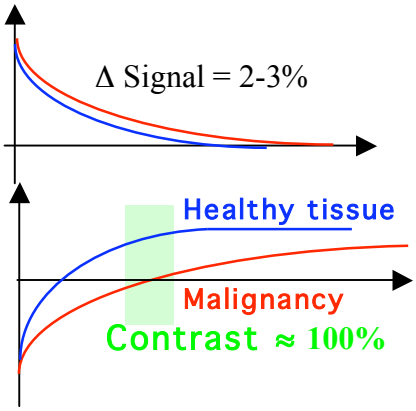
But they exhibit substantial differences in their T_1's & T_2's

Tissue	T_1 (s)	T_2 (ms)	ρ*
CSF	0.8 - 20	110 - 2000	70-230
White	0.76 - 1.08	61-100	70-90
Gray	1.09 - 2.15	61 - 109	85 - 125
Meninges	0.5 - 2.2	50 - 165	5 - 44
Muscle	0.95 - 1.82	20 - 67	45 - 90
Adipose	0.2 - 0.75	53 - 94	50 - 100

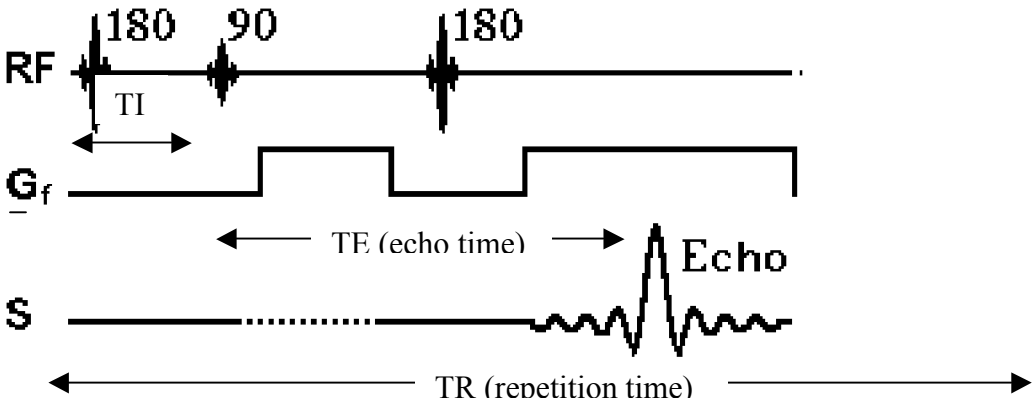
Therefore

little diagnostic contrast can be based on fully relaxed magnetizations, but…

excellent contrast can be achieved on partly saturated signals (e.g., using sat-rec or inv-rec sequences)

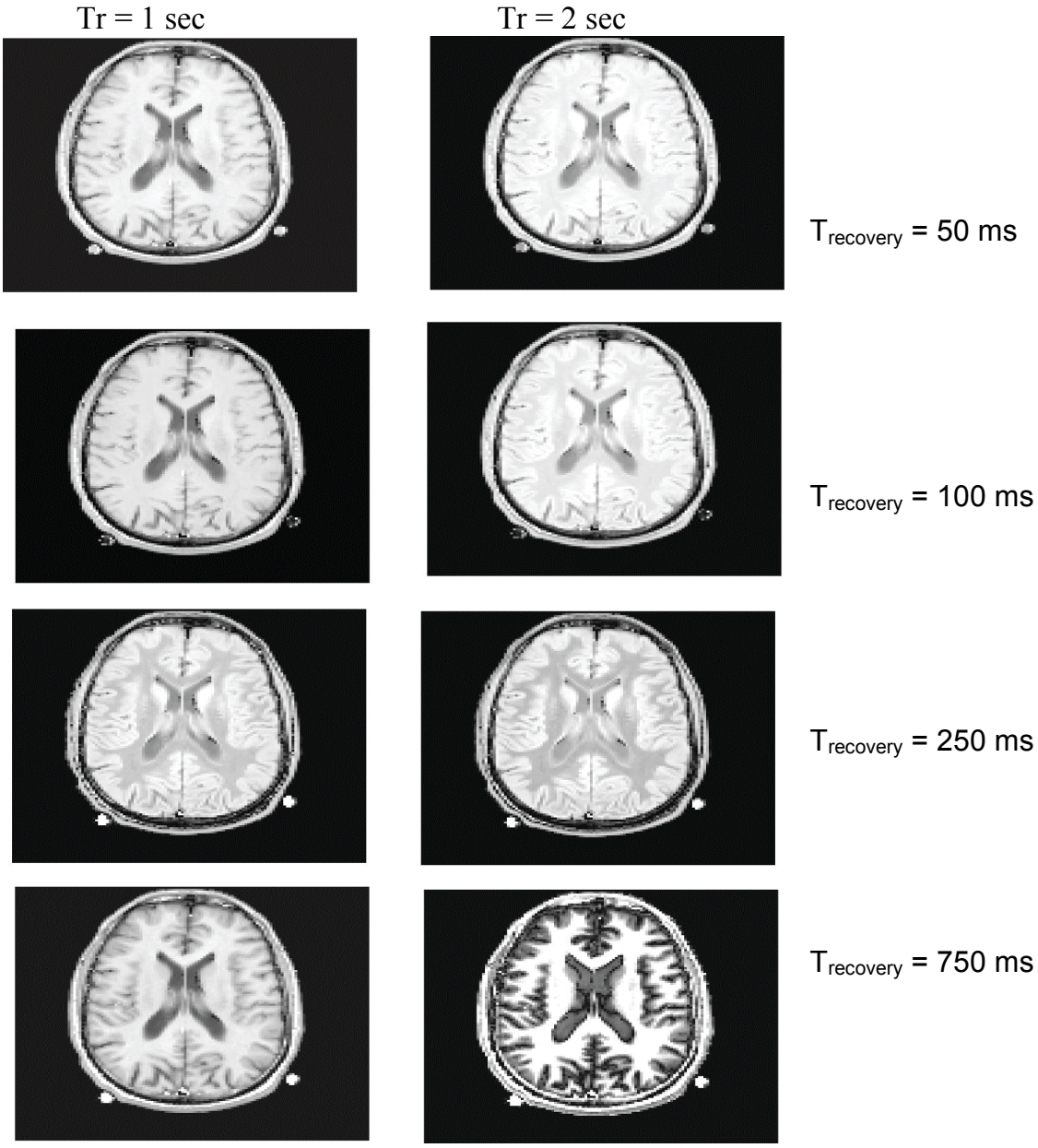


Consider for further clairty, a MRI sequence including suitably-timed inversion-recovery module:

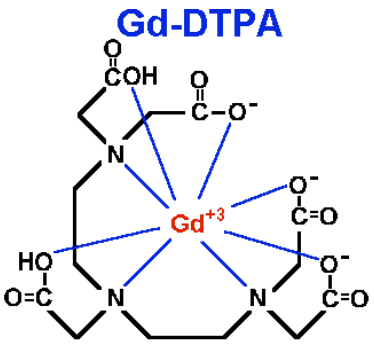


This can achieve almost 100% contrast of the tissues.

For example:



Even when this natural contrast is not available MRI distinctions can still be exacerbated via **relaxation agents**: paramagnetic chemicals that via their isotropic shifts and enhanced relaxation, change the T1, T2 or T2* properties of nearby tissues.



0 ms

There are other, more subtle ways by which MRI allows one to introduce contrast into its images. These include exploiting water/fat ratios, mobility differences through flow- or diffusion-weighting modules, and even intrinsic increases in paramagnetic compounds due to differing degrees of blood supply/consumption.

1. BASIC MRI SEQUENCES AND THE CONTRAST THEY WILL HIGHLIGHT

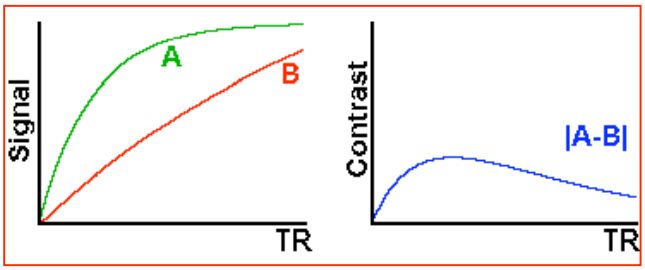
Basic experimental parameters at the disposal of an MRI exam include

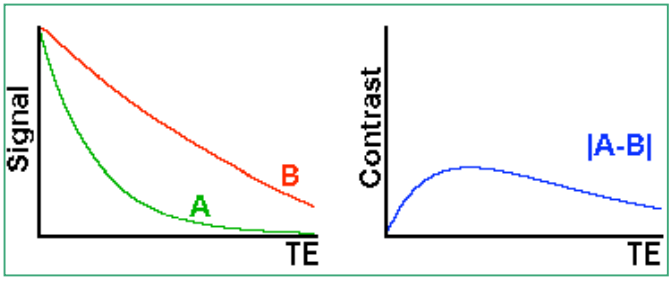
The Repetition Time, TR
The Echo Time, TE
The Inversion Time, TI if using an inversion-recovery sequence
The Excitation Angle, θ (related to TR/T1 effects)

For instance given a standard spin-echo (T2*-refocused) MRI sequence, one can

increase the $\{T1, T2, \rho\}$ weighting by using TR values $\{<= T1, >> T1, >> T1\}$ and TE values $\{<< T2, >= T2, << T2\}$

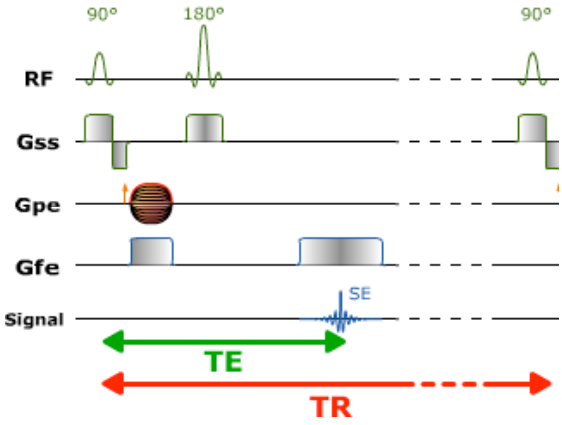
The actual contrast $C = |S_A - S_B|$ achieved between signals S_A & S_B, will depend on the intrinsic T1 & T2 of the two tissues, and on the TR & TE parameters used:





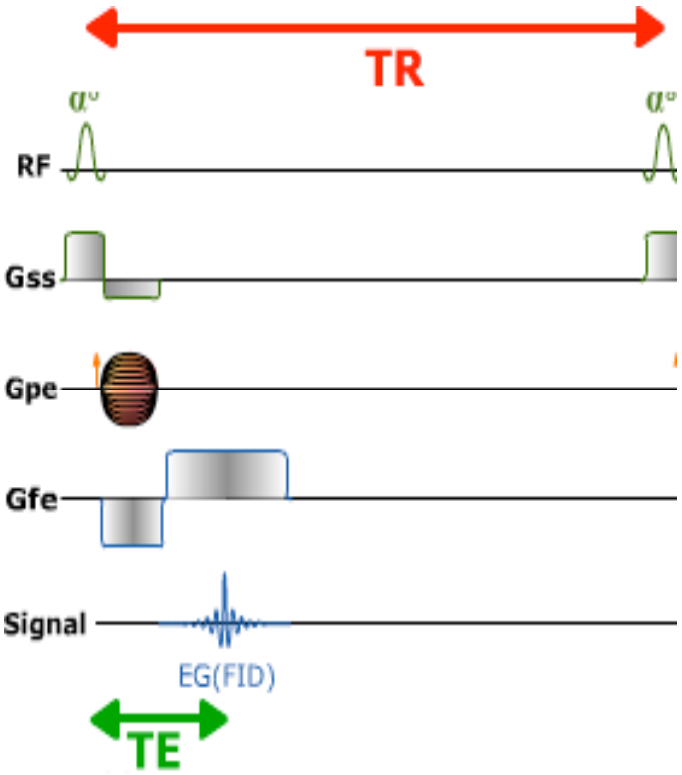
Key approaches to achieve a given kind of contrast include

- ***T2-weighting:*** **Use a spin echo (SE) sequence with "longish" TE (to magnify T2 decay differences) and long TR (to minimize T1 recovery differences).** The SE sequence is a routine clinical echo sequence as it is less susceptible to inhomogeneities in the magnetic field (which contribute to T2* but not T2). SE MRI is particularly well suited to edema as

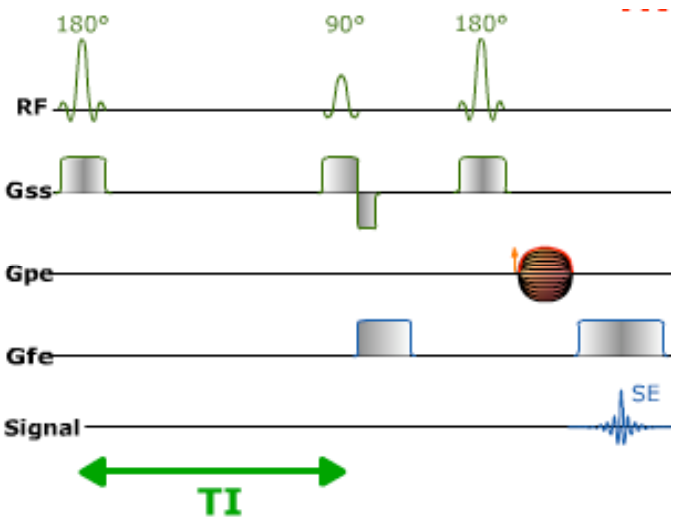


they are sensitive to water content (edema is characterized by increased water content). If TE is very short, the fat signal can be magnified.

- ***T2*-weighting:*** **Use a gradient echo (GRE) sequence, with not-so-long TE (to highlight T2* effects) and long TR (to minimize T1 differences).** The gradient echo sequence used does not have the extra refocusing pulse used in spin echo, and so it will be subject to the additional inhomogeneous broadening losses that will overtake the slower T2 decay. In particular field inhomogeneities will dominate this sort of MRI, leading to T2* contrast based on factors such as tissue heterogeneity or susceptibility differences. This also makes GRE sequences more prone to susceptibility losses at air/tissue boundaries, but can increase contrast for certain types of tissue, such as venous (ie, paramagnetic) blood. Together with SE, GRE constitutes the "workhorse" of clinical MRI.



- ***T1-weighting:*** **Also use a GRE or a SE sequence, but this time with short TE (to make differences in T2* irrelevant) and short TR (to make T1 recovery differences important).** This is also one of the basic types of MR contrasts and is commonly used in clinical scans. Due to the short repetition time (TR) this scan can be run very fast allowing the collection of high resolution 3D datasets. **The T1 weighting can be increased (improving contrast) with the use of an inversion pulse.** The critical parameter in this case becomes TI, the pre-acquisition inversion time. This inversion can then be followed up with either a gradient or a spin-echo sequence. For instance:



- ***ρ-weighting*: Last but not least one may also be looking for simple density weighting, with no contrast from T2*, T2 or T1**. To do so one may use a spin echo (naturally T2*-free) or even a gradient echo sequence, with short TE and long TR. The only signal change coming from differences in the amount of available spins.

The signal dependencies for the various sequences discussed, are

Spin-Echo: $S = \rho\,(1-\exp(-TR/T1))\,\exp(-TE/T2)$

Inversion Recovery : $S = \rho\,(1-2\exp(-TI/T1)+\exp(-TR/T1))$

Inversion Recovery with SE (180-90-180):

$$S = \rho\,(1-2\exp(-TI/T1)+\exp(-TR/T1))\,\exp(-TE/T2)$$

Gradient Echo

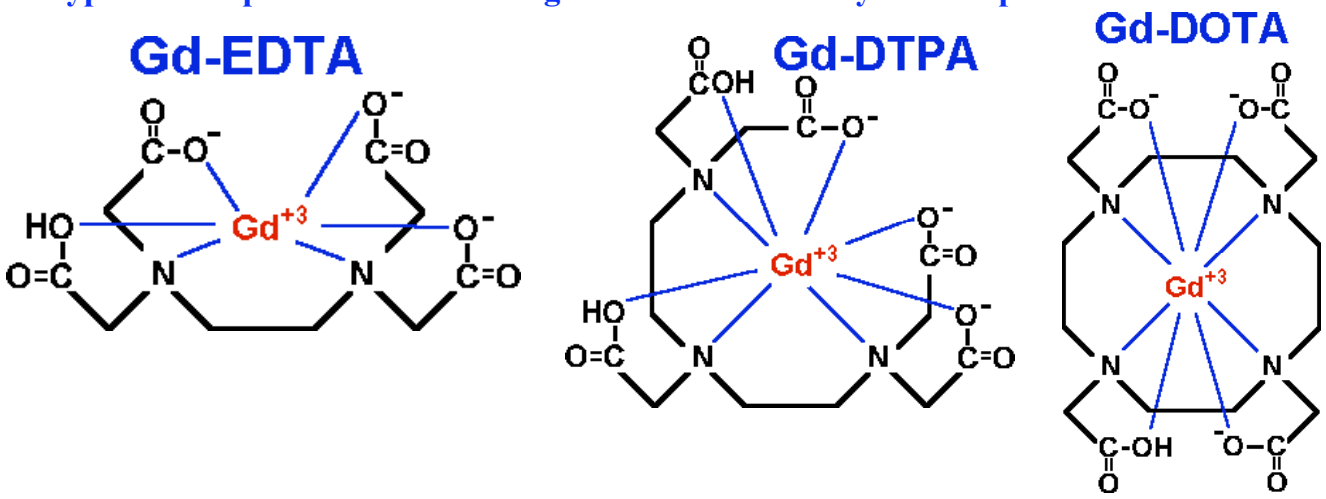
$$S = \rho\,(1-\exp(-TR/T1))\,\sin\theta\,\exp(-TE/T2^*) / (1-\cos\theta\,\exp(-TR/T1))$$

2. CONTRAST AGENTS

In certain cases, the intrinsic differences in T1, T2, T2*, etc, may not be sufficient to achieve the desired degree or kind of contrast. In those cases additional differences can be introduced by adding **contrast agents**: paramagnetic chemicals that localize in certain tissues/fluids, and artificially change their spin relaxation properties.

Contrast agents are paramagnetic chemicals: chemicals with at least one free, unpaired electron. Unpaired electrons can be found in organic radicals (usually unstable) or in metals (stable). Unfortunately most metals with unpaired electrons are heavy metals: **also toxic**. To reduce/eliminate the toxicity, metals can be *complexated with ligands.* This prevents them of interacting biochemically with organs, and make them wash away quickly. When this does not happen (e.g., when treating renally-compromised patients) there is a risk of a rare but serious illness: nephrogenic systemic fibrosis (NSF). Although a causal link between quelates & NSF has not been definitively established, current guidelines in the United States are that dialysis patients should only receive contrast agents where essential, and that dialysis should be performed as soon as possible after the scan is complete in order to remove the agent from the body promptly.

Typical examples of T1 contrast agents are furnished by Gd complexes:



Gd works as T1-shortening agent thanks to the numerous (up to seven) unpaired electrons it may have, whose extremely strong (inter-electronic) spin-spin couplings lead to a very fast electronic T1e. This T1e is in fact so short that in solutions the Gd's electrons never make a "DC field" => they do not distort the external Bo field and therefore do not contribute to T2*. The very short T1e does, however, provide a source of nuclear T1 relaxation (coming from fluctuations happen at ≈ the nuclear Larmor frequency). Moreover, Gd can bind numerous ligands –including water molecules, which exchange in-and-out of ligation at a very high rate. Each time a water binds to the metal it undergoes T1 relaxation. ***As a result of all of this Gd complexes lead to hypersignals: wherever they are incorporated they shorten the T1, and highlight their presence upon using short TR sequences.*** (There is also a T2 shortening, but this effect is negligible at the usual contrast agent concentrations).

Typical clinical applications of Gd contrast agents: Vascularity characterization, measure of the healthiness of the blood-brain barrier, tissue angiogenesis & permeability (tumor grow)

Examples of a different, T2*-based contrast agents, are furnished by superparamagnetic iron oxide (SPIO, USPIO) nanoparticles. Superparamagnetism is a form of magnetism, which appears in small ferromagnetic particles. If small enough, the nanoparticles' magnetization will randomly flip direction under the influence of temperature. The typical time between two flips is called the Néel relaxation time. In the absence of external magnetic field, the magnetization of the nanoparticles, their magnetization appears to be in average zero (short Néel relaxation time): they are said to be in the superparamagnetic state. In this state, an external magnetic field is able to magnetize the nanoparticles, similarly to a paramagnet. However, their magnetic susceptibility is much larger than that of paramagnets**.** This

can be used to make MRI contrast agents, which consist of suspended colloids of iron oxide nanoparticles. When injected during an imaging exam they reduce the T2* signals of absorbing tissues: they yield a *hyposignal* of the regions where they localize, upon being examined by gradient-echo MRI sequences. SPIO and USPIO contrast agents have been used successfully in some instances for liver tumor enhancement.

In a related development, there is now an emerging field of "smart" or "molecular" contrast agents, capable to release paramagnetic metal complexes upon changes in pH, release of hormones, of neurotransmitters, of Ca^{2+}, etc.

3. AN INTRINSIC CONTRAST AGENT: FUNCTIONAL MRI

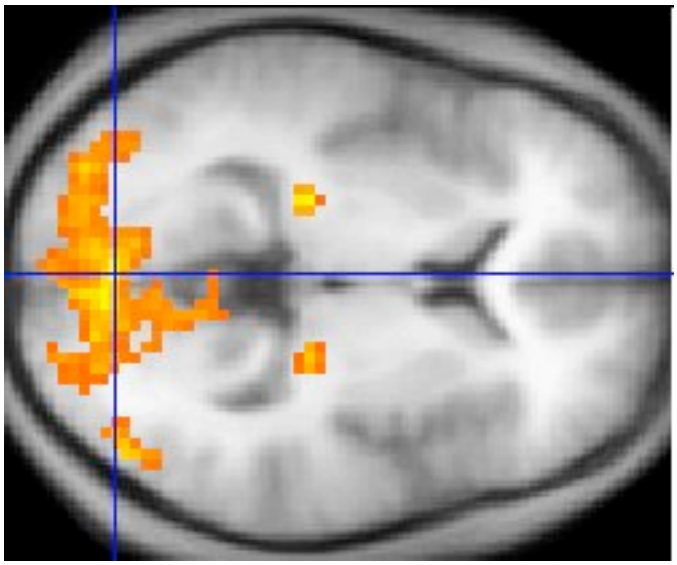
FUNCTIONAL MRI (FMRI) is an indirect method of imaging brain activity at high spatial / medium-temporal resolution, based on the changes that happen in the concentration of a paramagnetic contrast agent intrinsically present in all of us: BLOOD. fMRI relies on detecting the transient hemodynamic response provoked by neuronal activity (i.e., the coupling between neuronal cell function and the concentration of oxygenated blood), via the differences that changes in the blood flow and oxygen consumption will cause on the T2 and T2* of the neighboring tissues.

PRESUMED PRINCIPLES OF FMRI: When nerve cells are active they increase their oxygen consumption, switching to the energetically less effective but more rapid anaerobic glycolysis. The local response to this oxygen utilization is an enhanced blood flow to regions of increased neural activity, occurring after a delay of approximately 1–5 seconds. This hemodynamic response peaks over 4–5 seconds, and leads to increases in the relative concentration of oxyhemoglobin vis-à-vis that of deoxyhemoglobin in local cerebral areas. As hemoglobin is diamagnetic when oxygenated but paramagnetic when deoxygenated, the MRI signal of blood and of surrounding tissues will change – particularly the T2*, which will normally lengthen. This weak, transient rise in T2*-weighted signals is known as the Blood Oxygenation Level Dependent (BOLD) mechanism. By collecting the BOLD increase (and sometimes subsequent decrease) in the MRI with sequence parameters sensitive to changes in magnetic susceptibility, one can assess changes in BOLD contrast and from there brain activation.

FMRI SEQUENCES AND MODELING:
To cope with the constraints of temporal resolution and to magnify T2* sensitivity, functional MRI sequences are generally of the ultrafast echo planar type, with small matrixes. GE-EPI will magnify all susceptibility changes, but particularly those involving larger veins and arteries. Whereas SE-EPI wll compensate the main

inhomogeneities but still highlight the capillary BOLD effect.

In either case, the BOLD contrast obtained is very small – amounting at best to a low percentage (2-4%) of the standard signal intensity. Acquisitions therefore need to be repeated in time for different activation tasks, and statistically correlated in comparative studies of signal variations measured in each pixel and variations in task. Differences in activation will thus relate to the difference between tasks. This mode of repetition constitutes a so-called activation paradigm: it consists of at least one reference task, and another task whose only difference is in the activity we wish to study. Typical paradigms for motor activities involve rest (the reference) and repeated finger movements (the activity). For cognitive activities (vision, language, memory...) the paradigms may involve flashing images in right- and left-hand goggles. In any case, there is lots statistical analyses and modeling integrated into the data processing.



Advantages of fMRI:

* *It can noninvasively record brain signals without risks of radiation inherent in other scanning methods, such as CT or PET scans.*

* It has high spatial resolution. 2–3 mm is typical but resolution can be as good as 1mm.

* It can record signal from all regions of the brain, unlike EEG/MEG which are biased towards the cortical surface.

* fMRI is widely used and standard data-analysis approaches have been developed which allow researchers to compare results across labs.

Disadvantages of fMRI

* The images produced must be interpreted carefully, since correlation does not imply causation, and brain processes are complex and often non-localized.

* Statistical methods must be used carefully because they can produce false positives. (One team of researchers studying reactions to pictures of human emotional expressions reported seeing activating in the brains of dead salmon.)

* The BOLD signal is only an indirect measure of neural activity, and is therefore susceptible to influence by non-neural changes in the body.

* BOLD signals are most strongly associated with the input to a given area rather than with the output.

* fMRI has poor temporal resolution. The BOLD response peaks approximately 5 seconds after neuronal firing begins in an area. This means that it is hard to distinguish BOLD responses to different events which occur within a short time window. To deal

with this some research groups are attempting to combine fMRI signals having high spatial but poor temporal resolution, with signals recorded with other techniques (electroencephalography, EEG or magnetoencephalography MEG), which have higher temporal resolution but worse spatial resolution.