Advanced Imaging and Contrast Concepts

An Offprint from

Peter A. Rinck

Magnetic Resonance in Medicine
A Critical Introduction

The Basic Textbook
of the European Magnetic Resonance Forum

13th edition • 2023
335 figures, 36 tables

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Medicine and the sciences are ever-changing disciplines. Research and clinical experience are continually broadening our knowledge, in particular the knowledge of proper treatment and use of pharmaceuticals. Insofar as this book mentions any dosage or application, or proposes certain imaging, pharmaceutical applications, spectroscopy or other procedures, readers may rest assured that the author and Foundation have made every effort to ensure that such references are strictly in accordance with the state of knowledge at the time of production.

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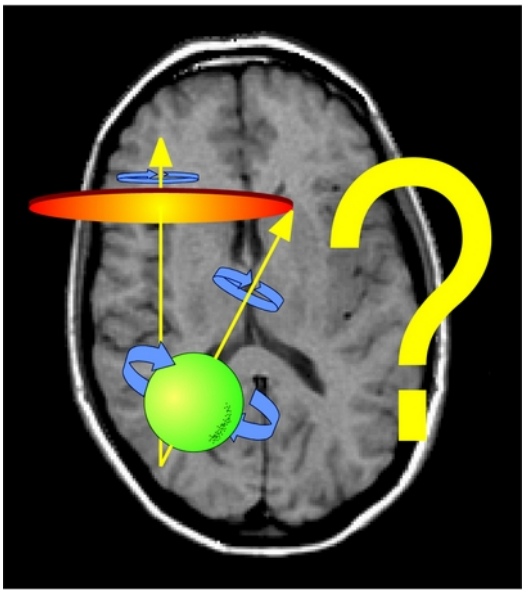
Foreword



"Why, sometimes I've believed as many as six impossible things before breakfast."
The White Queen in Lewis Caroll's
'Alice Through the Looking Glass'.

We like books – printed on paper, if possible with a beautiful hard-cover binding. Thus, putting this standard textbook on the internet some years ago was a challenge. Now we return with a printed version of the magnetic resonance textbook. The reasons I have described elsewhere.[1]

Celebrating the 50th anniversary of MR imaging in 2021 was a good occasion to publish a new edition. The textbook-child has grown up, become an adult or, in our case – a rather successful standard textbook. The reviews and public reaction to the book were extremely positive.

The first version of this primer – a little booklet – was written at Paul C. Lauterbur's laboratories in the early 1980s. Lauterbur was the father of MR imaging and received the Nobel Prize twenty years later. The text was intended to be used as the Basic Textbook for EMRF, the European Magnetic Resonance Forum. After Lauterbur saw the first edition, he commented: "It looks like a fine book, especially for residents, nurses, and technicians."

Initially we thought this statement was not very encouraging, but in hindsight this was exactly what we had intended to write. We worked on it for another twenty years – and finally Lauterbur found the last edition he read before his death "gratifying". How-

1 Rinck PA. An expensive dilemma: Tablets versus textbooks. Rinckside 2015; 26,7: 17-19.

ever, the target audience today includes scientists and university professors. They should be able to acquire a basic knowledge which enables them to pursue studies of their own and to cope with some of the most common problems, among them tissue relaxation, image contrast and artifacts or questions concerning possible hazards to patients – and to become aware of how to perform reliable research, and to ask and be critical.

The main author and the contributors have not attempted to cover the field completely nor to be exhaustive in the topics discussed, as the field of magnetic resonance still is in a permanent stage of development and therefore changing year by year. Clinical MR machines and even equipment sold for scientific purposes have been increasingly altered into push-button black boxes with pre-fab, given and unchangeable protocols. We are not interested in certain gadgets or "apps" of commercial machines, and won't mention or describe them. We try to explain the fundamentals any user should know and understand.

As with everything in life, MR imaging does not only require knowledge of facts but also of background information and of the historical development of the field for critical decision making. Therefore we have interspersed some subjective, critical, and opinion-oriented sections – interludes – intended to offset the technical nature of the teaching sections and provide some insights into more practical questions faced by MR users.

Most of them were taken from *Rinckside* (www.rinckside.org), a collection of columns published since 1990.

Many of the recent developments concerning MR equipment and its medical and biological applications have turned away from magnetic resonance itself to novel engineering and software approaches in image processing including artificial intelligence. Techniques, ideas and algorithms were imported from fields outside medicine and adopted by software engineers with little or no background in MR and medicine nor insight into medical needs. We mention some of the prime approaches without going into details of signal or image processing – they are of no importance for the understanding of fundamental facts of magnetic resonance imaging.

There has been a long list of contributors to this and earlier versions (see page 418). Their support, ideas, dedication, and feedback have added much to the quality of this work. This book was peer-reviewed by a number of competent reviewers in different fields whom I thank for their efforts.

If you want to learn something about magnetic resonance imaging or its applications choose your topic of interest. If you want to learn it from scratch start with Chapter 1; and if you want to air your brain, read the interludes that are scattered in between.

If you find any mistakes in this book, rest assured that they were left intentionally so as not to provoke the gods with something which is perfect. Still, we would be happy about your feedback. We hope that this textbook will be useful for you and that you will enjoy it. If you have comments or suggestions, please write to us.

Peter A. Rinck, January 2023

Contents

Chapter Eleven

Advanced Imaging and Contrast Concepts

Figure 11-01:
What are the bright spots in the sky on these images: sun or moon? Think about it. Sometimes one cannot determine exactly what is seen on a picture — even when the details are clearly visible. Then, additional information or specific approaches are helpful.
Top: Moonrise in southern Switzerland.
Bottom: Sunset in Manhattan.

Introduction

Over the years, several ideas and concepts were developed on how to influence and enhance contrast by either suppressing or highlighting certain tissue structures.

To a certain extent, these concepts have added to the diagnostic options of MR imaging and are commonly used to solve specific questions or particular research tasks (more or less similar to those in Figure 11-01).

We will introduce some of these techniques on the following pages:

- suppression techniques,
- diffusion imaging,
- functional imaging,

as well as *MR Elastography* which is less an independent concept but rather a mechanical application.

There are a number of other "advanced imaging" gadgets and "apps" introduced by several manufacturers; they fulfill mostly consumerist marketing strategems or remain in the realm of constant research; they will not be discussed here.

Suppression Techniques

Fat and, in a similar way, water can create contrast problems for a number of clinical issues. It possesses high signal on T1-weighted SE images, which can obscure other tissues or pathologies with high signal adjacent to the fatty tissue.

Thus, it would be of great advantage to eliminate its signal in certain cases. This includes lesions in fatty tissues such as the orbit or in examinations of fatty livers, in heart examinations, and in the differentiation of bone and marrow diseases.

We have already described two of the suppression techniques in Chapter 10: fat and fluid suppression with STIR and FLAIR. We will discuss three different approaches below.

Phase-Sensitive Methods

In Chapter 5, we have introduced *chemical shift*: the molecular difference between fat and water makes them precess at slightly different frequencies. If MR imaging is performed at high fields, chemical shift can lead to two different images of the same anatomical structure, which is known as chemical-shift artifact. Figure 11-02 explains the origin of this artifact.

There is a positive side to this feature: it can be used to eliminate the unwanted fat signal. In gradient-echo sequences chemical-shift effects are not refocused and will depend on the echo time, as the following description exemplifies.

Water and fat have a chemical shift of 145 Hz at 1.0 T or of 225 Hz at 1.5 T. At the latter frequency, the off-resonance fat signal rotates through 360° every 4.4 ms.

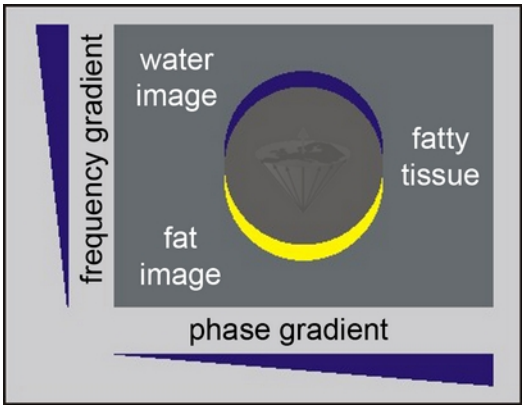


Figure 11-02:
Because of the chemical shift between water and fat signals, the image representation of fat (yellow) is shifted in the frequency encoding direction with respect to the neighboring water image (blue); in other words, there are two images from the same tissue: a chemical-shift artifact.

Thus, at echo times which are even multiples of 4.4 ms, the fat and water signals are in phase, while for echo times which are odd multiples of 2.2 ms, the signals are out of phase (Figure 11-03).

ΔB_0 effects cause local variations in the exact phase of each component, but their phase difference is preserved.

By choosing an appropriate echo time, we can emphasize or minimize the contribution of the fat signal and by adding two averages which use in-phase and out-of-phase echo times respectively, the fat signal can be removed. This kind of fat suppression sequence is also known as the Dixon method. It is similar *to chemical shift imaging* or *phase contrast*.[164, 165]

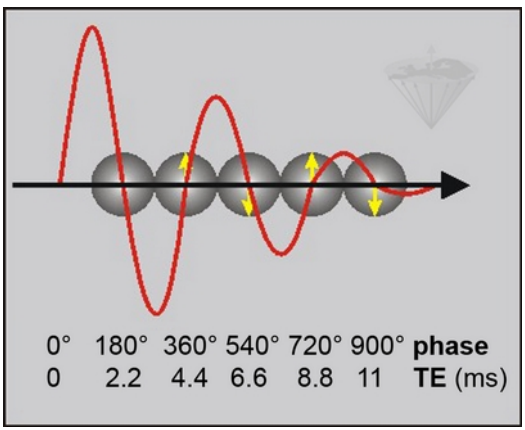


Figure 11-03:
Phase-contrast behavior at 1.5 T where the frequency difference between water and fat is 225 Hz. By choosing an appropriate TE in a GRE sequence, the fat signal is either in phase with the phase of water or out of phase. The fat signal rotates through 360° every 4.4 ms (1/225 s). This means that water and fat signal are in phase at 0.0, 4.4, 8.8, etc. ms (↑) and 180° out of phase at 2.2, 6.6, 11.0, ... ms (↓).

164 Dixon WT. Simple proton spectroscopic imaging. Radiology 1984; 153: 189-194.
– Dixon WT, Lee JKT. Separate water and fat MR images (letter). Radiology 1985; 157: 552-553.
165 Szumowski J, Plewes DB. Fat suppression in the time domain in fast MR imaging. Magn Reson Med 1988; 13: 534-535.

Presaturation

By applying an RF pulse of the appropriate frequency before the regular imaging pulse sequence, one can eliminate the signal of a specific tissue. Again, this method is field strength-dependent and best used at high fields where water/fat shifts are high.

A presaturation pulse is applied at the precession frequency of fat (or the compound to be saturated); this pulse does not influence the water component of the tissue (Figure 11-04).

Usually a chemical-shift selective pulse sequence (CHESS) or a variation of this sequence are used. With a frequency-selective 90º pulse, the magnetization of fat is rotated into the transverse plane where its dephasing is accelerated by a *spoiler* (or *crusher*) gradient. Then the regular pulse sequence follows, but it only excites the water in the sample.

Figure 11-05 shows an example of the application of fat suppression.

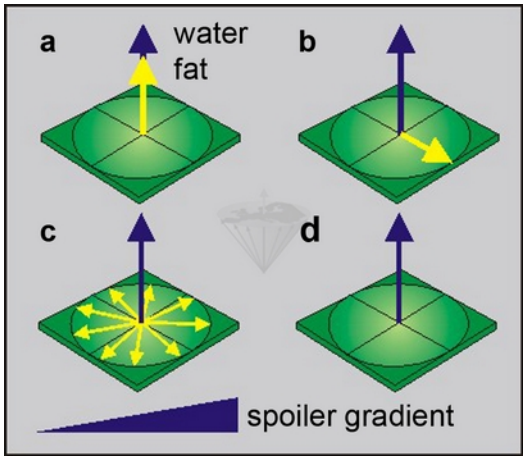


Figure 11-04:
Selectively saturating the fat component:
(a) a fat-saturating RF pulse is transmitted, and
(b) rotates the yellow fat magnetization into the transverse plane.
(c) The fat spins start dephasing in the *x-y* plane, accelerated by a dephasing gradient.
(d) Only the blue water magnetization remains.

A different kind of presaturation is used for artifact suppression in flow imaging (see Chapter 17).

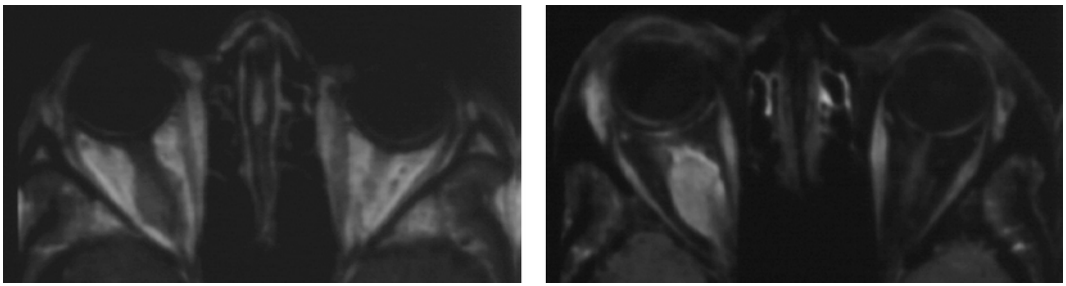


Figure 11-05:
Example of fat suppression – tumor in the right orbit. T1-weighted SE images.
Left: Plain image.
Right: Contrast enhancement of the tumor after gadolinium contrast agent. The tumor has become bright. The fat signal has been eliminated; both orbits now are dark and the enhancing parts of the tumor are easily delineated.
Simulation software: MR Image Expert®

Magnetization Transfer

The idea of altering contrast by *off-resonance irradiation* of the sample was first described by Muller and collaborators in 1983.[166] Wolff and Balaban coined the term *magnetization transfer* (magnetization transfer contrast = MTC) for this kind of alteration of image contrast.[167] Lipton, Sepponen and collaborators improved contrast enhancement of the method.[168]

MTC is a suppression of protein-bound water and related to spin-lock imaging. It is based on the fact that in most biological tissues there is a cross relaxation between the free proton pool H_f representing mobile water protons and the restricted proton pool (H_r) representing the protons associated with macromolecules or immobile water.[169]

The restricted H_r pool has a much shorter T2 than the mobile H_f pool, and consequently is not directly observed with standard MR techniques.

Thus, its influence upon image contrast cannot be exploited with standard pulse sequences. The cross relaxation and/or chemical exchange between these two pools means that saturating the resonance corresponding to one of them also affects the second pool (Figure 11-06).

Saturating the H_r pool leads to a loss of signal from the H_f pool.

The cross relaxation is a short range process and, therefore, the direct effect is limited to interfaces between the two pools, although diffusion relays the effect to the bulk of free water.

The H_r pool is known to have a very short T2 value; thus, the behavior of the magnetization during the RF pulse is dominated by relaxation.

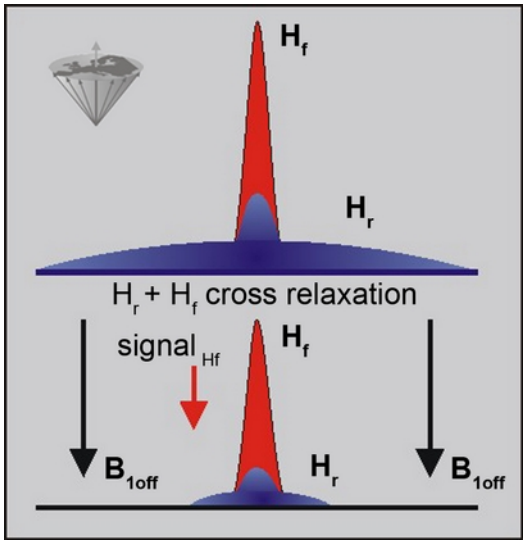


Figure 11-06:
The signal in a conventional MR examination consists of the part created by the narrow peak of the mobile protons (free protons: $Hf_)$ and the broad peak of the immobile protons (restricted protons: $Hr_)$. Both pools interact and exchange information. The restricted pool can be saturated by off-resonance irradiation, which reduces its magnetization to 0 (in the best case). The exchange between the two pools then leads to a reduction in the free water signal.

166 Muller RN, Marsh MJ, Bernardo ML, Lauterbur PC. True 3-D imaging of limbs by NMR zeugmatography with off-resonance irradiation. Eur J Radiol 1983; 3, Sl: 286-290.

167 Wolff SD, Balaban RS. Magnetization transfer contrast (MTC) and tissue water relaxation *in vivo.* Magn Reson Med 1989; 10: 135-144.

168 Lipton MJ, Sepponen RE, Tanttu JI, Kuusela T. Magnetization transfer technique for improved magnetic resonance imaging contrast enhancement in whole body imaging. Invest Radiol 1991; 26 S1: S255-256; and S263-265.

169 Edzes HT, Samulski ET. The measurements of cross-relaxation effects in the proton NMR spin-lattice relaxation of water in biological systems: hydrated collagen and muscle. J Magn Reson 1978; 31: 207-208.

The majority of sequences developed to date for MTC imaging use a relatively long, low-power, off-resonance saturation pulse to selectively saturate H_r.[170, 171]

However, new pulse sequences have been proposed to optimize MTC.[172]

The clinical applications of MTC are limited; it can be used in time-of-flight MR angiography to suppress background tissue. In T2-weighted images, MTC may help to detect early demyelination.

A combination of MTC and contrast agent application enhances contrast at times where one of the techniques alone does not create sufficient enhancement, for instance in some cases of multiple sclerosis and other brain lesions, of brain infarctions, and in the detection of recent myocardial infarctions (Figure 11-07).[173, 174]

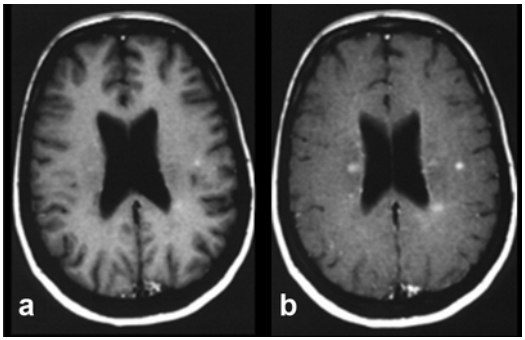


Figure 11-07:
Example of magnetization transfer contrast. Patient with multiple sclerosis.
(a) T1-weighted brain images after enhancement with a gadolinium-based contrast agent.
(b) Image with additional magnetization transfer contrast. The combination of contrast agent and MTC clearly enhances contrast and shows more lesions, although it remains unclear whether all of these lesions are active.

170 Jones RA, Southon TE. A magnetization transfer preparation scheme for snapshot FLASH imaging. Magn Reson Med 1991; 19: 483-488.

171 Wolff SD, Balaban RS. Magnetization transfer contrast (MTC) and tissue water relaxation *in vivo*. Magn Reson Med 1989; 10: 135-144.

172 Jones RA, Southon TE. Improving the contrast in rapid imaging sequences with pulsed magnetization transfer contrast. J Magn Reson 1992; 97: 171-176.

173 Jones RA, Haraldseth O, Schjøtt J, Brurok H, Jynge P, Øksendal AN, Rinck PA. Effect of Gd-DTPA-BMA on magnetization transfer: application to rapid imaging of cardiac ischemia. J Magn Reson Imaging 1993; 3: 31-39.

174 Tanttu JI, Sepponen RE, Lipton MJ, Kuusela T. Synergistic enhancement of MRI with Gd-DTPA and magnetization transfer. J Comput Assist Tomogr 1992; 16: 19-24.

Diffusion Imaging

Diffusion is but one mechanism of the transport phenomena on the molecular level: fluid transfer, heat transfer, and mass transfer. It is very closely related to thermal conductivity and viscosity – and a vast and open scientific area.[175]

The fundamentals of thermodynamics were explained by Fourier's law of heat conduction, those of viscosity by Newton's law of viscosity, and those of diffusivity by Fick's law of diffusion.

Fluids in the human body move in different ways, as bulk flow and perfusion in blood and lymph vessels, from the great vessels down to the capillary level, or as diffusion on the cellular level (Table 11-01). Tissue cells are surrounded by extracellular water through which small molecules shuttle between cells and the grand circulation. In the blood vessels the transport is active, mostly pumped by the heart, rather than passive, as in tissue, where it is controlled by diffusion in response to ever-changing chemical potentials.

Diffusion is defined as the process resulting from random motion of molecules by which there is a net flow of matter from a region of high concentration to a region of low concentration (Figure 11-08). However, diffusion exists even in thermodynamic equilibrium.

Displacement distribution is the fraction of particles that will move over a certain distance during a given time. The *rate of diffusion* is governed by the *diffusivity*, D;

Description of Motion Types
Flow
... usually bulk flow of blood or CSF, is defined as (blood) volume per time unit, i.e., the macroscopic physiological motion of blood. *See also:* ***Flow and angiography*** in Chapter 14.
Perfusion
... relates to blood delivery to tissues, which usually is motion at the capillary level. *See also:* ***Functional MRI*** in this chapter, and ***Dynamic MRI*** in Chapter 16.
Diffusion
... is the random (Brownian) motion of tissue water molecules within cells. They collide with each other and also pass through cell membranes.

Table 11-01:
Forms of fluid motion in the human body.

Figure 11-08:
Distribution in water of blue ink from the top and potassium permanganate from the bottom of the glass. This kind of molecular movement is easily visible. Diffusion inside the body is far more difficult to explain, to conceptualize – and to unveil.

175 Bird RB, Stewart WE, Lightfoot EN. Transport phenomena. New York: Wiley. 2nd ed, 2007 [textbook].

its dimension is cm²/s. This coefficient depends on several factors such as size of particles and temperature; the most important factor is viscosity. Changes of intra- or extracellular viscosity induce alterations of diffusion, and thus can change image contrast in *diffusion-weighted MR imaging* (*DWI*).

Diffusion had been a topic of research in NMR since the early 1950s.

Erwin L. Hahn showed that by forming a spin echo one could recreate the seemingly irreversible NMR signal.[176] He used three subsequent 90° pulses and tried to calculate T2 values with this method. However, these values were not reliable: they were distorted by molecular diffusion. Herman Carr found a way around this problem and to overcome diffusion with a train of 180° pulses after the first 90° pulse: The *Carr-Purcell spin echo sequence,*[177] later modified as the *Carr-Purcell-Meiboom-Gill (CPMG) sequence* by changing the phase of the 180° pulses relative to the initial 90° pulse.[178]

In 1968, Edward O. Stejskal and John Tanner proposed to apply pulsed gradients for easier and more precise measurement of spin echoes to study restricted diffusion. They called this method *Pulsed Field Gradient, Spin-Echo NMR*.[179]

The feasibility to visualize diffusion was discussed for a long time because it would allow differentiation between tissues according to their cellular structure. In 1986, Denis Le Bihan took this up and applied it to MR imaging by using appropriate gradient pulses to depict *intravoxel incoherent motion (IVIM)*.[180]

Diffusion is independent of the relaxation times and thus adds another factor to contrast.

Techniques

Tissue water diffuses randomly, but barriers such as cell membranes can influence its diffusion and alter its random motion to a partly directed motion.

For instance, diffusion in white matter shows a clear directional dependence because, most likely, the myelin envelope covering the nerve fibers is virtually impenetrable for diffusing water molecules. This leads to an *anisotropically restricted motion*.[181]

In more or less free diffusion, the *displacment distribution* is a bell-shaped (Gaussian) function; the more complex manner of diffusion in tissue cells is non-Gaussian. *Diffusion-weighted imaging*

176 Hahn EL. Spin echoes. Phys Rev 1950; 80: 580-594.

177 Carr HY, Purcell EM. Effects of diffusion on free precession in nuclear magnetic resonance experiments. Phys Rev 1954; 94: 630-638.

178 Meiboom S, Gill L. Proton relaxation in water. Rev Sci Instrum 1958; 29: 688

179 Stejskal EO, Tanner JE. Spin diffusion measurements: spin echoes in the presence of a time-dependent field gradient. J Chem Phys 1965; 42: 288-291

180 Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M. MR imaging of intravoxel incoherent motions: applications to diffusion and perfusion in neurologic disorders. Radiology 1986; 161: 401-407.

181 Moseley ME, Cohen Y, Kucharczyk J, et al. Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system. Radiology 1990; 176: 439-445.

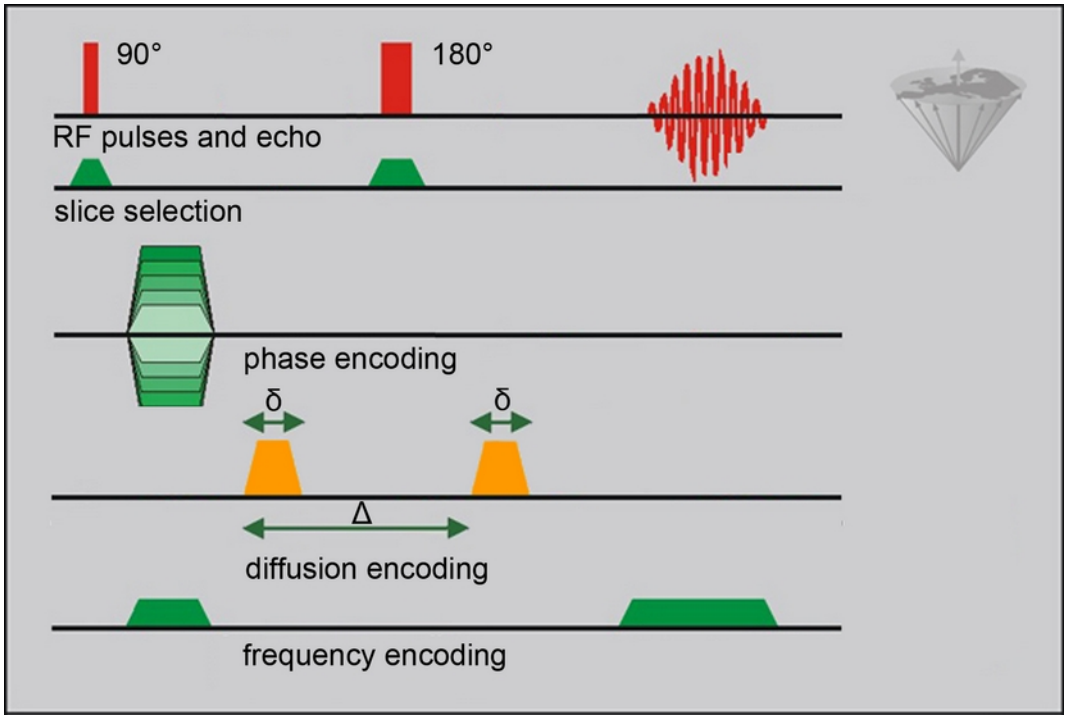


Figure 11-09:
Complete 2DFT spin-echo imaging experiment with pulsed diffusion encoding. δ is the duration of the diffusion-encoding gradient, Δ is the diffusion time interval (be aware that δ and Δ have different meanings in other applications of MR imaging).

(DWI) is the elementary imaging method; the next step is a pictorial depiction of the calculated *Apparent Diffusion Coefficient, ADC*. More complex methods include *Diffusion Tensor Imaging (DTI)* and related techniques such as *Diffusion Tensor Tractography (DTT)*.

Diffusion-Weighted Imaging. DWI is commonly performed in the three orthogonal directions x, y, and z created by the existing gradient coils of the MRI machine. A Carr-Purcell spin echo sequence is adapted to diffusion imaging by the addition of two gradient pulses at a duration δ and a time difference Δ, the *diffusion time* (Figure 11-09).

A phase shift dependent on the strength of the gradient pulse is induced by the first of the diffusion pulses. The second diffusion pulse is applied after the 180° pulse of the CP sequence (this 180° pulse reverses the phase change that was induced by the earlier pulse; cf. the explanation of the spin-echo creation in Chapter 6). After the first diffusion pulse, all proton spins in the excited area are dephased; now, diffusing spins move away randomly and, partly, out of the area of interest. Thus, they are not rephased by the second diffusion pulse, re-

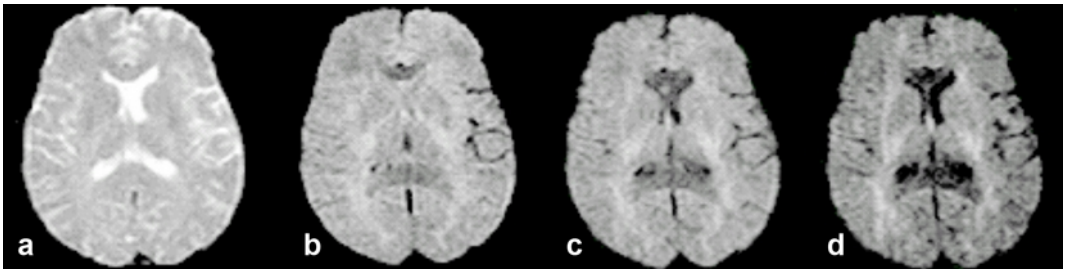


Figure 11-10:
Transverse, increasingly diffusion-weighted images.
(a) b = 0 s/mm² (no diffusion weighting); **(b)** b = 600 s/mm²; **(c)** b = 900 s/mm²; **(d)** b = 1200 s/mm².

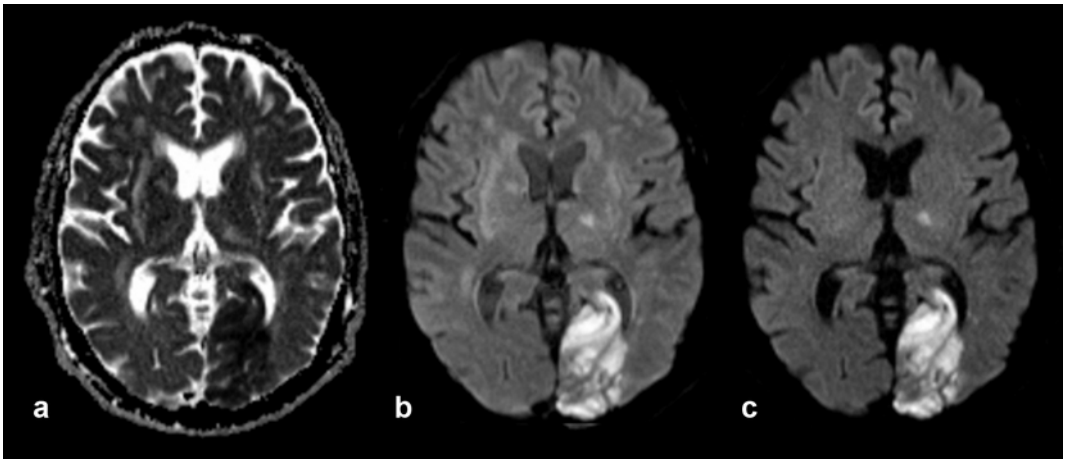


Figure 11-11:
Elderly patient with old and recent brain infarctions. New large infarction in left occipital lobe, also affecting other parts of the brain. **(a)** ADC image, the area of the infarction is dark; **(b)** diffusion-weighted image, b = 500 s/mm²; **(c)** diffusion-weighted image, b = 1000 s/mm². The area of the infarction is bright.

sulting in a decrease (attenuation) of the signal.

The *b value* is a term describing the diffusion sensitivity or the degree of the diffusion weighting of the final image: $b \sim q^2 \times \Delta$ (dimension: s/mm²). The *b value* is estimated on the basis of q, a vector in the direction of the diffusion. The length of this vector is proportional to the gradient strength.

Figure 11-10 gives an example of how diffusion influences contrast and its dependence upon gradient direction.

Regions with a high diffusion gradient show low signal intensity, regions with low or obstructed diffusion are brighter. This is the reason for contrast enhancement in diffusion weighted imaging (DWI), allowing for instance the early depiction of brain infarction.

Appreciation of the contrast enhancement always requires the comparison of at least two images with different b-values.

Pathologically increased diffusion patterns in the brain have been observed in infarction, tumors, edema, multiple sclerosis, and cysts.

Diffusion changes indicate ischemia at a very early stage. This finding helped MR imaging become the modality of choice in patients with suspected brain infarction.[182, 183]

Apparent Diffusion Coefficient Imaging. The imaging method based on the apparent diffusion coefficient ADC serves as graphical illustration of the ability of protons to diffuse through tissue where they are restricted in their movement by, e.g., cell membranes or increased cellularity – which might be the case in tumors. ADC imaging requires at least two data acquisitions; its contrast behavior is reversed: areas of restricted diffusion are dark, those of free diffusion bright (Figure 11-11).

182 Buxton R, Kwong K, Brady T, Rosen B. Diffusion imaging of the human brain. J Comput Assist Tomogr 1990; 14: 514-520.

183 Doran M, Hajnal JV, Van Bruggen N, King MD, Young IR, Bydder GM. Normal and abnormal white matter tracts shown by MR imaging using directional diffusion weighted sequences. J Comput Assist Tomogr 1990; 14: 865-873.

Diffusion Tensor Imaging is also called *DTI* or *tractography*. It is a mathematical processing technique of diffusion-weighted measurements and potentially valuable for brain diagnostics in areas of anisotropic diffusion, allowing the depiction of the direction and, possibly, interruption of tissue tracts. It is mainly applied to white matter axonal fiber bundles and, at the time being, remains a research technique.[184, 185]

DTI relies on algorithms that assemble two- or three-dimensional visualizations of main white matter axonal fiber bundles. It allows to delineate fiber bundles from each other, as well as from gray matter and CSF (Figure 11-12).

For MR tractography fiber bundles must be aligned in one direction only and must not intersect. The tracts (fiber bundles) depicted on such an image are not the fibers *per se*, but local diffusion maxima.

There are a number of even more complex methods related to MR tractography, such as *diffusion spectrum imaging*, *q-ball imaging*, and *angular resolution imaging* which are beyond this introduction to MR imaging.

It remains to be seen whether such images will have true research or clinical relevance.

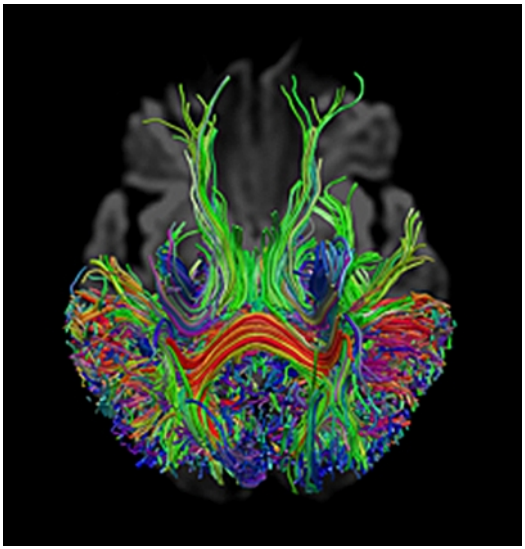


Figure 11-12:
Tractography calculated from DW imaging data. The signal of the neural tract is strongest when the diffusion gradient is directed orthogonally to white matter bundles, such as in the corpus callosum.
The different diffusion directions (gradient directions) *x, y,* and *z* are color-coded in these images: x = red, y = blue, and z = green.

Critical remarks. Pitfalls and problems of DTI are manifold and stretch from imperfect algorithms to motion artifacts.

Crossing, converging or diverging white matter tracts might not be adequately depicted as only diffusion maxima are shown. In particular the hypothetical, complex algorithm-based variants of DWI should applied with caution. In research, DTI is an excellent complementary examination to functional brain imaging (BOLD imaging).

For details on the use of color in medical imaging confer Chapter 15, page 290.

The technique should only be used by qualified and critical scientific specialists.

184 Hagmann P, Jonasson L, Maeder P, Thiran J-P, Wedeen VJ, Meuli R. Understaind diffusion MR imaging techniques: from scalar diffusion-weighted imaging to diffusion tensor imaging and beyond. Radiographics 2006; 26: S205-S223 [review].

185 Nucifora PGP, Verma R, Lee S-K, Melhem ER. Diffusion-tensor MR imaging and tractography: exploring brain microstructure and connectivity, Radiology 2007; 245: 367-384 [review].

Functional Imaging

Functional imaging is a misleading term because it is mainly used for the depiction of changes of local blood supply in the brain activated by specific stimuli. Commonly, *dynamic or cine imaging* of other organs or, e.g., joints are not described as *functional MR imaging* (*fMRI*). However, the term is not sharply defined, and sometimes diffusion, perfusion as well as brain activation studies are subsumed under fMRI. In contrast to EEG and MEG, functional MR imaging of the brain does not provide a direct measure of neural activity.

In 1990, Belliveau and colleagues published the first observation of the stimulation of the human visual cortex by magnetic resonance imaging.[186] They watched the first pass effect of a contrast agent after bolus injection to demonstrate changes in cortical perfusion upon activation with a photic stimulus. The use of bolus tracking to study changes in perfusion was an exact analog to previous experiments using the observation of radioactive tracers with PET or SPECT. It required the injection of a contrast agent in two consecutive scans, one with and one without stimulus.

The performance of such an experiment with MR has the advantage of vastly superior spatial and temporal resolution and the lack of radioactive tracers (cf. cerebral and regional cerebral blood-volume described in Chapter 16). However, the need for dual contrast agent injection poses a problem, especially for studies of brain activation in normal individuals.

This disadvantage was resolved by the demonstration of brain activation using the BOLD (blood-oxygen-level dependent) contrast mechanism first described by Ogawa.[187] This technique has led to a fast proliferation of fMRI in hundreds of centers over the last 25 years.

BOLD-Contrast

The basis for BOLD-contrast was described by Pauling and Coryell in 1936.[188] It relies on the fact that paramagnetic deoxyhemoglobin – by comparison to diamagnetic oxyhemoglobin – has a strong magnetic moment. Thus, by interaction of the bulk magnetization of deoxygenated blood with the external field, local field variations in and around blood vessels are created. These susceptibility effects can be measured using appropriate MR imaging sequences.

The only source of energy of normal brain cells is the oxidation of glucose. Since the glucose storage capacity of brain cells is negligible, the brain very heavily depends on a constant supply of glucose and oxygen via the capillary bed. This increased demand appears to lead to an increased amount of blood flowing to the activated area. This in turn decreases the local

186 Belliveau JW, Rosen BR, Kantor HL, et al. Functional cerebral imaging by susceptibility-contrast NMR. Magn Res Med 1990; 14: 538-546.

187 Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on Blood oxygenation. Proc Natl Acad Sci USA 1990; 87: 9868-9872.

188 Pauling L, Coryell CD. The magnetic properties and structure of hemoglobin, oxyhemoglobin and carbonmonoxyhemoglobin. Proc Natl Acad Sci USA 1936; 22: 210–216.

susceptibility effect, which can be visualized using appropriate susceptibility-sensitive imaging techniques (Figure 11-13).

Susceptibility differences are greater at higher fields, and thus higher fields are desirable for this kind of studies.

For the first human brain activation studies Kwong applied gradient-echo-planar imaging (GRE-EPI).[189] The EPI sequence uses multiple gradient refocusing to acquire all data necessary for image reconstruction after a single excitation pulse. In spite of its not very well defined signal behavior, EPI has turned out to be a very efficient technique for brain activation studies due to its short acquisition time.

Conventional gradient-echo imaging with long echo times (40-60 ms, depending on field strength) has also turned out to be a useful technique for fMRI.[190] Its advantage over EPI lies in the fact that it allows the acquisition of high-resolution images, whereas the resolution in EPI is determined roughly by the number of echoes which can be acquired within the T2 of brain parenchyma.

Conventional gradient-echo imaging does, however, suffer from a number of severe drawbacks. The long acquisition time per image restricts the application to a single slice and thus requires prior knowledge about the area of activation. Partial volume effects can lead to difficulties in data interpretation.

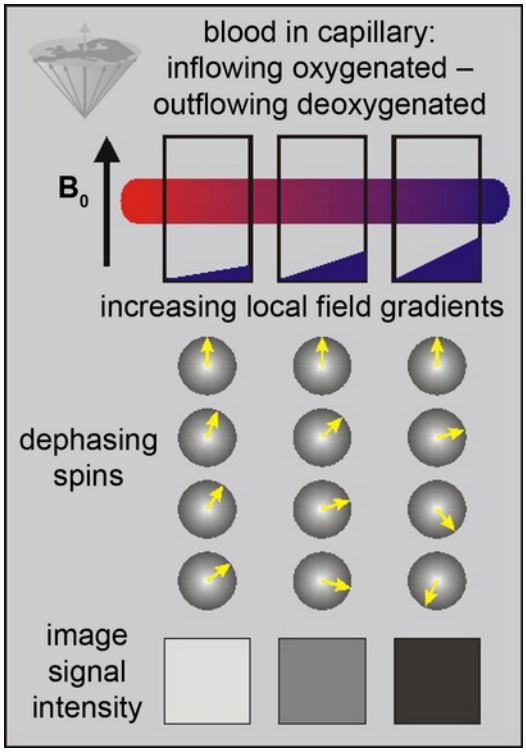


Figure 11-13:
BOLD-contrast. The presence of deoxyhemoglobin in a capillary causes a susceptibility difference between the blood vessel and the neighboring tissue. It induces a dephasing of the spins, thus a decrease in T2* and signal loss on T2-/T2*-weighted images.

Gradient-echo techniques also are very sensitive to inflow. Since vascular flow – especially in large veins – also changes upon stimulation, this can lead to the measurement of activation effects many centimeters from the area of activation.[191] These vascular signal changes can be much

189 Kwong KK, Belliveau JW, Chesler DA, et al. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc Natl Acad Sci USA 1992; 89: 5675-5679.

190 Frahm J, Bruhn H, Merboldt KD, Hänicke W. Dynamic MR imaging of the human brain oxygenation during rest and photic stimulation. J Magn Reson Imag 1992; 2: 501-505.

191 Segebarth C, Belle V, Delon C, et al. Functional MRI of the human brain. NeuroReport 1994; 5: 813-816.

Features of BOLD Imaging
• not a direct measure of brain acitivity, but measurement of hemodynamic changes; • motion artifacts due to cardiac and respiratory motion; • physiological noise by arterial and cerebrospinal fluid pulsations; • spatial resolution limited to ~3 mm; • partial volume effects; • temporal resolution limited by hemodynamic response; the MR equipment is able to acquire images every 100 ms but the hemodynamic response is slower.

Table 11-02:
Features and limitations of monitoring of brain activity with BOLD imaging.

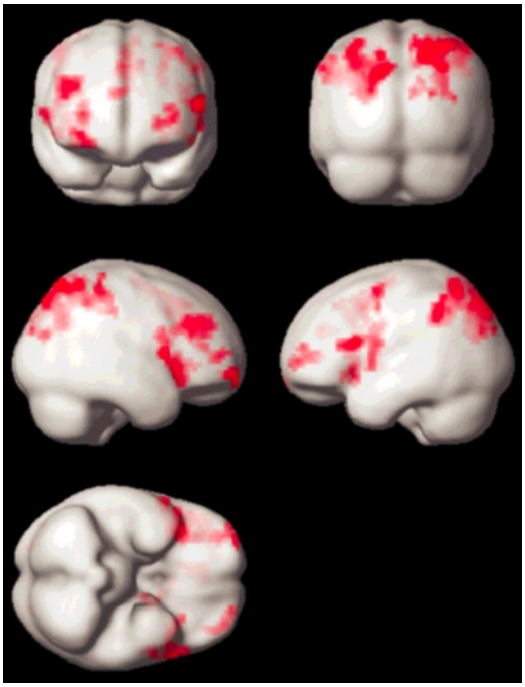


Figure 11-14:
Working memory test: typical activation pattern in the parietal cortex; cognitive / speech processing dorsolaterally.

larger than the actual parenchymal effects, which seldom exceed 2-3%.

The image quality of all susceptibility-sensitive techniques is strongly dependent on macroscopic susceptibility problems occurring especially at soft tissue – bone – air interfaces, leading to magnetic field inhomogeneities over several centimeters.

These long-range effects will cause image distortions when occurring in the direction of the readout gradient which is normally of no practical consequence. Field inhomogeneities across the selected slice, however, will lead to signal attenuation and thus severely affect the image quality.

The use of thin slices (or 3D data acquisition) is, therefore, to be preferred for fMRI.

The strength of the stimulation effect will not be dependent on the slice thickness due to the small range of the BOLD effect (Table 11-02).

Applications. The first experiments performed with fMRI used the well known paradigm of photic stimulation with an alternating checkerboard pattern or a flicker display. This is known to lead to significant changes in perfusion and thus serves as a test tool for sequence development.

Meanwhile, quite a number of experiments have been performed, which led to new insights in neurocognitive research. Apart from activation in the primary visual cortex, activation of associated areas was demonstrated using a number of paradigms to test cognitive processing of motion, texture, color, object recognition, sound, memory, and others (Figure 11-14). Various paradigms using motor activation have been

successfully examined. Numerous groups have investigated language processing using a number of well established paradigms. In addition to activation of the cerebral cortex, the involvement of the cerebellum in learning tasks has been demonstrated. Subcortical activation has been found, for example, in the nucleus geniculatus (upon visual stimulation).

Nomenclature. In some articles on fMRI, NMR/MRI terms are used wrongly or confusingly, for instance T2* for apparent T2 ($T2_{app}$), and T1* (a term which is not appropriate because T1 is not affected by susceptibility effects) for an apparent T1 (T_{app} or $T1_{influx}$).

Critical remarks. Unfortunately, BOLD imaging at common (high and ultrahigh) fields strengths for investigative fMRI, such as 1.5 or 3.0 T, has a very low sensitivity and signal-to-noise ratio. The signal changes related to cerebral activation are close to the noise level and therefore numerous signal processing techniques are used to overcome it.

Besides, T2* to estimate blood oxygen saturation is only one singled-out factor; oxygen supply and saturation are dependent on several additional and independent parameters, among them lung and heart function, vessel size, and hematocrit. At the present stage this means that some groups look again – after the first description in 1990 by Belliveau et coll.[192] – into exogenous agents, e.g., manganese, to highlight hemodynamic changes in the brain[193, 194, 195, 196] (see also page 307).

Some BOLD or, perhaps, bold comments ...

… about functional imaging and applications of fMRI: BOLD, bolder, the boldest ... and akward statistics

To be read on page 223.

fMRI tickles the imagination of researchers, as well as the laity of all medical and paramedical disciplines including neuroeconomics and neuromarketing, and the population at large because it shows the brain at work and reacting to the environment in beautiful color images. Such applications are often doubtful. fMRI has been used and abused.

Obstacles such as high expenses, low resolution, complexity beyond the education of many users, pitfalls and snags of the technique and of the interpretation of the outcome are copious.

192 Belliveau JW, Rosen BR, Kantor HL, et al. Functional cerebral imaging by susceptibility-contrast NMR. Magn Res Med 1990; 14: 538-546.

193 Chen YC, Mandeville JB, Nguyen TV, Talele A, Cavagna F, Jenkins BG. Improved mapping of pharmacologically induced neuronal activation using the IRON technique with superparamagnetic blood pool agents. J Magn Reson Imaging 2001; 14: 517-524.

194 Christen T, Lemasson B, Pannetier N, et al. Is T2* enough to assess oxygenation? Radiology 2012; 262: 495-502.

195 Kim SG, Ogawa S. Biophysical and physiological origins of blood oxygenation level-dependent fMRI signals. J Cereb Blood Flow Metab 2012; 32: 1188-1206.

196 Leite FP, Tsao D, Vanduffel W, Fize D, Sasaki Y, Wald LL, Dale AM, Kwong KK, Orban GA, Rosen BR, Tootell RB, Mandeville JB. Repeated fMRI using iron oxide contrast agent in awake, behaving macaques at 3 Tesla. Neuroimage 2002; 16: 283-294.

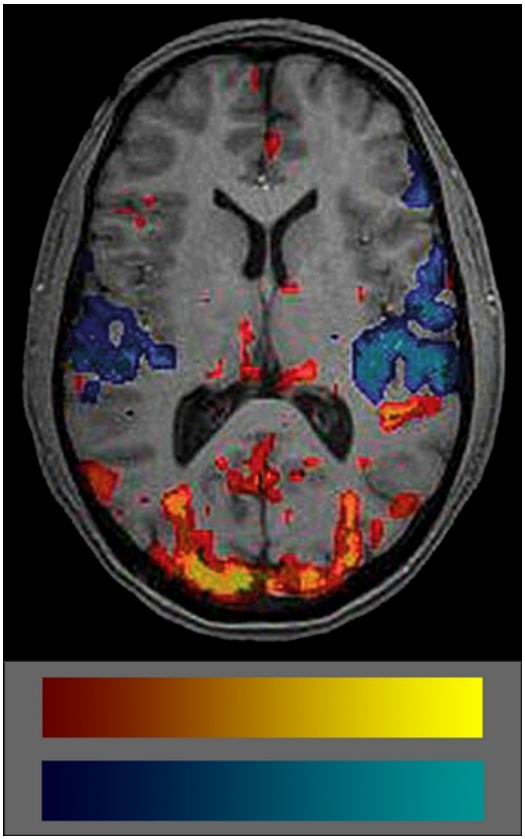


Figure 11-15:
fMRI image and color coding scale: red to yellow to indicate increased blood volume and dark blue to cyan to indicate decreases. The frequent absence of any color scale explication is a major set-back of most publication on BOLD imaging.

Commonly, BOLD data are shown coded in colors. Many users don't really understand what the colors mean because they are not intuitive (Figure 11-15). The semiotics of the commonly used BOLD color code is red-yellow colors for increased blood volume – which attract attention – and blue-cyan for decreased blood volume which are easily put aside and overlooked. Thus, attention is commonly paid to blood flow increases but not to decreases which biases interpretation. Another problem is the lack of any standard in color schemes of BOLD studies (for details on the use of color in medical imaging cf. Chapter 15, page 290).

It is important to always keep in mind that the colored blots in BOLD images show statistical significances of blood supply, not of brain activity.

More than 25 years after the pioneering work of Belliveau, Kwong and Ogawa fMRI remains an imperfect and unfinished method – that might be replaced by other, more accurate techniques in the future. It is helpful for surgical planning and has given some new insights into the physiology of cognition; however, it will not further scientific research in the understanding of the dynamics of cognition.[197]

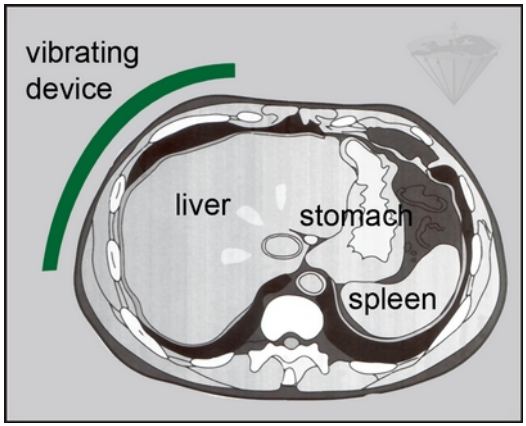
197 Cohen MS, Schmitt F. Echo planar imaging before and after fMRI: a personal history. Neuroimage 2012; 62: 652-659.

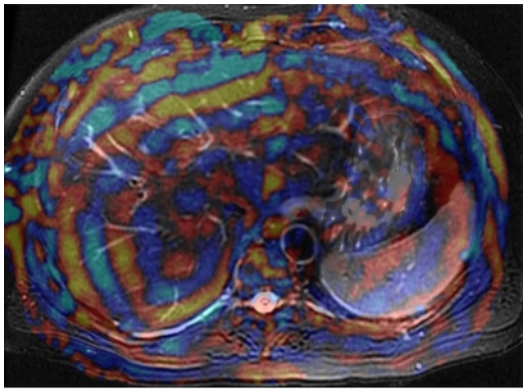
MR Elastography

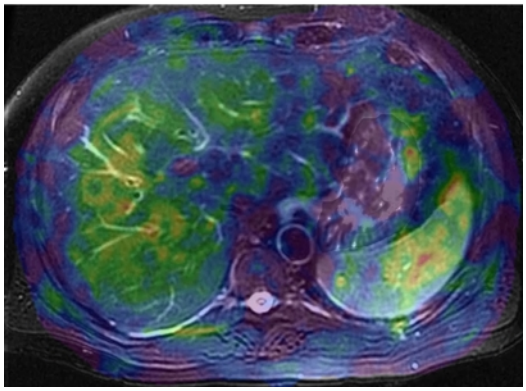
Magnetic resonance elasticity imaging (MR elastography, MRE) is a conversion of palpation of tissues and organs by a physician into a two- or three-dimensional color-coded depiction of tissue stiffness. It was first described in 1995.[198]

The technique is non-invasive and permits the evaluation of the shear elasticity of tissues by using a mechanical excitation with a vibration source and special MR pulse sequences with synchronized motion encoding (Figure 11-16). Stiffer tissues possess longer wave lengths, softer shorter ones. The wave images are processed to create scaled, quantitative images representing the relative stiffness (elastograms), commonly depicting shear stiffness on a scale from 0 to 8 kPa. The spatial resolution is one-third to one-fifth of the MRI resolution (Figure 11-17).

At present, the main focus of MRE are hepatic diseases such as fibrosis and cirrhosis. The stiffness of the diseased liver tissue is significantly higher than that of normal tissue.[199] Nearly everybody in MRE research is aiming for the liver; applications beyond the liver include possible indications in the brain, breast, and the musculoskeletal system.







198 Muthupillai R, Lomas D, Rossman P, Greenleaf J, Manduca A, Ehman R. Magnetic resonance elastography by direct visualization of propagating acoustic strain waves. Science. 1995; 269: 1854–1857.

199 Venkatesh SK, Yin M, Ehman RL. Magnetic resonance elastography of liver: technique, analysis and clinical applications. J Magn Reson Imaging. 2013; 37: 544–555 [review].

Figure 11-16 (left top):
A vibration source (green) is attached to the body of a patient to mechanically generate waves through the organ of interest, in this case the liver. Then, a 2D or 3D gradient echo-based MR elastography sequence is applied.

Figure 11-17 (left bottom):
(Top) wave image; **(bottom)** processed elastogram. Both are overlay images (cf. Chapter 15); they are superimposed on the respective high-resolution MR image in the liver/stomach,/spleen level.

Critical remarks. MR elastography images are colorful and nice to look at. However, there are no comparison and outcome studies. In many instances elastograms seem not to add any information of use to the clinical case.

Ascites, iron deposition, and obesity can cause failure of MRE studies. The technical failure rate increases substantially at ultra-high fields.[200]

200 Wagner M, Corcuera-Solano I, Lo, G, Esses S, Liao J, Besa C, Chen N, Abraham G, Fung M, Babb JS, Ehman RL, Taouli B. Technical failure of MR elastography examinations of the liver: experience from a large single-center study. Radiology 2017; 284: 401-412.

BOLD, bolder, boldest

This interlude on functional MR of the brain condenses three columns published between 2005 and 2016.

Functional MRI has replaced MR spectroscopy as the favorite MR research modality. MRS fascinated researchers, but this early enthusiasm has faded. Results from fMRI, on the other hand, continue to tickle the imagination of researchers and the population at large because it shows the brain at work and reacting to the environment. MR imaging can detect changes in brain hemodynamics that correspond to mental operations.

fMRI fascinated me from its very beginning. Suddenly, we had access to a non-invasive safe technique that could be repeated in the same person. One could see almost real-time cerebral responses to a range of activities, including viewing a picture (activation of the occipital lobe), listening to music (activation of the area around the Sylvian fissure in the temporal lobe), and physical interaction (activation mostly in the contralateral temporal lobe).

fMRI maps could show brain regions responsible for speech, thus help presurgical planning. They enabled estimation of the risk of postoperative deficits and appropriate selection of treatment: surgery versus radiation or chemotherapy.

The technique also started playing a role in the assessment of psychiatric disorders. Cognitive scientists were at the forefront of research applying fMRI to better understand brain function. One such study cast doubt on the belief that a group of severely

brain-damaged people were unaware of their surroundings. The researchers discovered that these individuals could, in fact, register what was going on around them, but they could not respond.[201]

Consumer industries were also harnessing fMRI. Automobile manufacturer Daimler, in collaboration with the University Hospital in Ulm, Germany, discovered that male test subjects tended to use a different thought process than females when navigating a maze. Comparison of fMRI maps revealed that most men try to configure a map of the maze in their mind, while women are more likely to use landmarks for orientation.

Other studies of *in vivo* brain activity have looked at gamblers and the process of deciding between options. Researchers at Baylor College of Medicine in Houston, Texas, used fMRI to examine the mental activity of people drinking soft drinks. Images indicated that Pepsi activated parts of the brain linked to pleasure, while Coca-Cola activated areas dealing with trust and memory.[202] In another study, Daimler concluded that the reward centers in men's brains are activated when they look at racy sports cars.[203]

These and similar studies form part of neuroeconomics and neuromarketing, a fascinating offshoot of economic science. Neuroeconomics combines psychology, economics, and the medical neurosciences. James Montier has written an entertaining review of state-of-the-art neuroeconomics.[204] I decided to read some of the original articles that Montier cited. The authors of one paper describe their results:

> "This study examines the bold response one TR (1.5 s) before the results screen, because decision making for cooperation is likely to be salient at this TR independent of the subject's position in the game."[205]

This sentence does not actually describe the results of a study. Basically, it does not make sense at all.

Research in fMRI had slipped into the hands of amateurs playing with MR imaging and functional MR, lacking the background in physics, chemistry, and medicine – and the scientific rigor necessary to work in a new field.

The combination of medical sciences (particularly imaging) and economics has created a hybrid discipline that lacks any solid scientific basis. Economic theories are based on observations, and, in this respect,

201 Schiff ND, Rodriguez-Moreno D, Kamal A, et al. fMRI reveals large-scale network activation in minimally conscious patients. Neurology 2005; 64(3): 514-523.

202 Jakobson L. Tech watch: mental marketing. Neuromarketers believe medical technology can help them understand what consumers really think about products. Incentive Magazine, Sept. 20, 2004.

203 Blakeslee S. If your brain has a 'buy button,' what pushes it? The New York Times, 19 Oct 2004.

204 Montier J. Emotion, neuroscience and investing: investors as dopamine addicts. Global Equity Strategy. Dresdner Kleinwort Wasserstein Securities, 20 Jan 2005.

205 McCabe K, Houser D, Ryan L, et al. A functional imaging study of cooperation in two-person reciprocal exchange. PNAS 2001; 98(20): 11832-11835.

they are close to history and philosophy. Economic science uses mathematics to create models of social processes or speculative predictions of the stock markets. Such models are prone to failure. If you take "scientifically created" pictures, however, people believe that the pictures show something relevant. The higher the color signal on the fMRI image, the better the product must be. Yet, unlike electroencephalography and magnetoencephalography, it does not provide a direct measure of neural or synaptic activity.

Some people even believe that fMRI can be used to read thoughts, allowing market researchers to pry a little. But fMRI does not show what people think.

Unfortunately, BOLD studies have a very low sensitivity and signal-to-noise ratio. The signal changes related to cerebral activation are close to the noise level and therefore numerous signal processing and, beyond this, statistical techniques are used to overcome this handicap. Many blood flow alterations described in functional brain imaging rely on signal-intensity changes of less than 5%. More so, T2* to estimate blood oxygen saturation is only one singled-out factor; oxygen supply and saturation are dependent on several additional and independent parameters, among them lung and heart function, vessel size, and hematocrit.

More and more researchers admit that acquisition and processing techniques of BOLD data lack the required meticulousness and thus the biased results and conclusions are scientifically irrelevant. Even the inventor of BOLD fMRI, Seiji Ogawa was among the harshest critics. Twenty-two years after his first description in 1990[206] he published a 19-page review paper where he, in a roundabout way, discusses and disputes his technique.[207]

Several thousand papers on fMRI appear every year, Kim and Ogawa mention 3,000, PubMed's numbers stretch between 42,000 and nearly 170,000 since 1990, depending on the search terms one uses. Meanwhile it has become clear that many of these papers, apparently a majority, rest on shaky foundations. Some scientists read Seong-Gi Kim's and Seiji Ogawa's review as a farewell to BOLD imaging, but this conclusion seems too drastic and far-reaching.

However, the publication alludes to the intricacy of the scientific background:

> "The BOLD effect in fMRI is very complex, and this is still an area of intense research."

The authors also observe in their concluding remarks:

> "Dynamic properties and magnitudes of BOLD functional responses are dependent on many physiological parameters as well as baseline conditions. In patients with neurovascular disorders, the BOLD response could be sluggish, or even decreased relative to baseline. This

206 Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci USA 1990; 87: 9868-9872.

207 Kim S-G, Ogawa S. Biophysical and physiological origins of blood oxygenation level-dependent fMRI signals. Journal of Cerebral Blood Flow & Metabolism 2012; 32: 1188-1206.

> should not be interpreted simply as a decrease in neural activity, because neurovascular coupling may be hampered … Resting-state fMRI studies are widely performed, but its physiological source needs to be systematically investigated."

As Gustav von Schulthess pointed out in the early days of fMRI:

> "... a caveat for fMRI: it is a very interesting technique but signal changes are but a few percent. Hence, the method is technically demanding and 'the threshold of nonsense production is low'".[208]

An outstanding proof of his claim can be found reading one of the most famous publications in this field published in the last years: the fMRI story (at 1.5 Tesla) of a dead Atlantic Salmon (Salmo salar).[209] Here are some excerpts.

> **From the Methods Section:** "The task administered to the salmon involved completing an open-ended mentalizing task. The salmon was shown a series of photographs depicting human individuals in social situations with a specified emotional valence, either socially inclusive or socially exclusive. The salmon was asked to determine which emotion the individual in the photo must have been experiencing. The photo stimuli were presented in a block design, ..."
>
> **The beginning of the Results Section:** "A t-contrast was used to test for regions with significant BOLD signal change during the presentation of photos as compared to rest. The parameters for this comparison were $t(131) > 3.15$, $p(\text{uncorrected}) < 0.001$, 3 voxel extent threshold. The relatively low extent threshold value was chosen due to the small size of the salmon's brain relative to voxel size. Several active voxels were observed in a cluster located within the salmon's brain cavity. The size of this cluster was 81 mm^3 with a cluster-level significance of $p = 0.001$."

This article presents in a really imaginative way the often overlooked main problem of fMRI. If the fMRI study of the little brain of a dead fish appears to give cognitive social scientists indications of brain functions and answers to some of their puzzles, how much confidence can we have in studies that follow the same or similar paradigms in far bigger live human brains? With their very catching experiment and a later paper, Bennett and collaborators stressed how pivotal it is in fMRI to apply statistics properly and scrupulously because random noise may yield spurious results in the acquired images.[210]

208 von Schulthess G. Clinical MR in the year 2010. Mag Res Med 1999; 8: 133-145.

209 Bennett CM, Baird AA, Miller MB, and Wolford GL. Neural correlates of interspecies perspective taking in the post-mortem Atlantic Salmon: An argument for proper multiple comparisons correction. Journal of Serendipitous and Unexpected Results 2010; 1(1): 1–5.

210 Bennett CM, Miller MB. fMRI reliability: influences of task and experimental design. Cogn Affect Behav Neurosci. 2013; 13: 690-702.

Sadly, a few papers are bad and ugly. The problem is not the bad research performed; this is common; it's the ugly and deeply disturbing conclusion, where the authors turn dilettantism into a weapon, as in this case of fMRI of supposedly pedophile subjects:

> "Functional brain response patterns to sexual stimuli contain sufficient information to identify pedophiles with high accuracy. The automatic classification of these patterns is a promising objective tool to clinically diagnose pedophilia." [211]

This conclusion is, politely phrased, highly problematic. Using fMRI as a biomarker (i.e., a detector) for pedophilia is unethical – because the technique does not allow to identify pedophiles. The employment of fMRI to diagnose pedophilia may have unforeseen consequences. It is a misuse and abuse of medical imaging. None of these articles has the rock-solid foundation which would be necessary for the conclusions the authors draw at the end.

The impact of such papers might be hurtful and detrimental, even deadly for some members of our societies. Readers of the articles might draw conclusion and take actions that are not appropriate, taking for granted that "scientific" publications even in obscure journals can be taken as the last truth.

The history of MRI is a story of successes but also a story of empty promises. Certain events have implications and consequences that only slowly unfold over the years.

At the end, the critical reader's conclusion is: BOLD and fMRI should stay in the hands of genuine scientists. Clinical and psychological or commercial applications should be limited to trained and principled researchers. Today, the concepts of fMRI rely on a great many hypotheses, calculations, and simulations; however, practical proof to establish the validity of these models lags behind.

Functional MRI seemed one of the most promising research techniques for and beyond neuroimaging: the true study of brain organization.

Now one fears the waste of hundred of millions euros of research grants and the shattered remains of thousands of scientific papers. Since nobody really feels responsible or in charge it will be difficult to minimize the repercussions of this debacle.

This interlude contains parts from:
Rinck PA. Functional imaging leads hunt for 'buy' trigger. Rinckside 2005; 16,2: 5-8.
Rinck PA. Functional charlatans. Rinckside 2015; 26,4: 9-11.
Rinck PA. Debacles mar "Big Science" and fMRI research. Rinckside 2016; 27,7: 17-18.

211 Ponseti J, Granert O, van Eimeren T, Jansen O, Wolff S, Beier K, Deuschl G, Bosinski H, Siebner H. Human face processing is tuned to sexual age preferences. Biology Letters 2014; 10(5), 20140200 DOI: 10.1098/rsbl.2014.0200

The Author

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After a classical school education he attended medical school in Berlin (Free University of Berlin) and served his internship and residency in radiology, nuclear medicine and radiation therapy at Charlottenburg University Hospital in Berlin.

Afterwards, until 1983, he was involved in the very early development of magnetic resonance imaging as Senior Research Associate at the State University of New York at Stony Brook where he worked in Paul C. Lauterbur's research group (Nobel Prize in Medicine 2003). The first version of this textbook was written at this time.

Subsequently Rinck worked as physician-in-charge of one of the first two German government sponsored MR machines in Wiesbaden, Germany.

Between 1987 and 1994 he was head of Europe's biggest clinical and research MR facility – at that time – at the University of Trondheim, Norway. Between 1986 and 2012 he was also Adjunct Professor at the School of Medicine and Pharmacy of the University of Mons-Hainaut in Belgium.

Since 1982 Rinck is Chairman of the European Magnetic Resonance Forum, EMRF, and since 2008 President of the Council of The Round Table Foundation, TRTF.

He is also Chairman of the Selection Committees of the the Pro Academia Prize and of the European Magnetic Resonance Award.

Visiting Professorships: The Neurological Institute of Colombia. Bogotá, Colombia (1986); Charité University Hospital, Medical Faculty of Humboldt University, Berlin, Germany (1991-1992); et al.

President of the European Society for Magnetic Resonance in Medicine and Biology, 1985-1987; president of the annual meetings 1989, 2002. Scientific consultant and expert adviser to international organizations and foundations (among them WHO, European Commission, UNIDO, the Nobel Committee). Honorary, founding, or ordinary member of numerous professional and learned societies.

Among others, awards and prizes from the Alexander von Humboldt Foundation, Max Kade Foundation, NATO, European Commission, Fonds National de la Recherche Scientifique de Belgique, the Research Council of Norway, and German Research Society (DFG).

Author and/or editor of several books – not only scientific or medical – an e-learning website, numerous papers in refereed journals and communications to international scientific meetings; and since 1990 *Rinckside* (learned columns).

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