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REVIEWS

History of MRI

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Abstract | A brief account of the basic principle and methodologies of MRI technique, right from its beginning, are outlined. The final pulse sequence used for MRI using Fourier Imaging (phase encoding), Echo-Planar Imaging (EPI) for detection of a whole plane in a single excitation and T_1 and T_2 contrast enhancement is explained. The various associated methods such as, MR-spectroscopy, flow measurement (MRI-angiography), Lung-imaging using hyperpolarized Xe-129 and He-3 and functional imaging (f-MRI) are described.

1 Introduction and MRI Protocols

The history of MRI, whether one likes it or not, started with Dr. Damadian. He demonstrated that relaxation times (T_1 & T_2) of tissues with and without cancer are different, and hence NMR can be used for cancer detection.[1] Relaxation time was measured by moving the tissue into the most homogenous part of the magnetic field of an NMR spectrometer, in which the static magnetic field was shaped in such a way that good homogeneity was obtained only in a single area, near a saddle point of the field. The signals from inhomogeneous parts were broadened by the inhomogeneity and detectable signal came only from the saddle point. The T_1 & T_2 of various parts of the tissue were measured by moving the tissue in and out of the saddle point.

The first protocol of NMR–Imaging (known as MRI) was given by Lauterbur in 1972, using a very homogeneous field of an NMR spectrometer and dispersing the frequencies by applying a 'linear Gradient'.[2,3] The NMR spectrum obtained was then a 'Projection' of the distribution of water (two capillaries) perpendicular to the direction of the gradient. Several projections were obtained by changing the direction of the gradient and a two dimensional image (Fig. 1) was reconstructed by using a 'projection reconstruction algorithm'. The same algorithm is used in CT-Scan, where a three dimensional image is reconstructed from several two dimensional digital X-ray projections. In the first paper itself, Lauterbur also demonstrated that image intensity can be made sensitive to T_1, of the water in two capillaries (Fig. 1).[2]

This discovery of Lauterbur prompted intense activity in NMR community and several methods of imaging were explored. Waldo Hinshaw (1974) came up with the 'sensitive point method'. Hinshaw sinusoidally-modulated time-dependent orthogonal-gradients and came up with signal detected from a single null point (for 3 orthogonal gradients). The null was electronically controlled along with a chart recorder, which was also swept along with a null point. The method utilized the signal from a single point at a time and was a very low sensitive method.[4] The method was further improved to 'sensitive line' method using two orthogonal time dependent gradients and a static gradient applied along third dimension, yielding the image of a whole line, yielding early images of human wrist.[5,6] Still the method was of low sensitivity, since signal from all other parts of body were saturated, except those along the sensitive line. This was overcome by Mansfield by first selectively exciting a single (Y) plane orthogonal to a gradient, say along X axis, with all other planes being saturated by a selective saturation pulse. A line is this plane was then excited using an orthogonal gradient, say along Z axis and signal from Y line, detected by using a selective excitation pulse in presence of a linear Z gradient. By moving the detected line a whole plane could be imaged. Since a selective excitation pulse was used to detect a line, the experiment could be repeated without delay. All these techniques directly yielded the images without further processing.[7,8]

The next development was the Fourier Imaging method using the Lauterbur's 'projection

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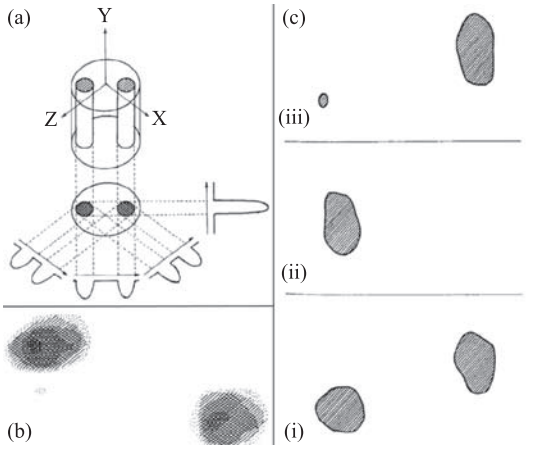


Figure 1: (a) Two-dimensional projections of two tubes of water for gradients perpendicular to the two tubes. (b) The first MRI images of two tubes of water obtained by Lauterbur by the method shown in (a). (c) The T_1 of the water of one of the tubes was reduced by adding paramagnetic substance and T_1 weighted image shows saturation of the signal for the tube with longer T_1 (ii). The difference between unsaturated (i) and saturated (ii) shows only the saturated tube (iii). [Reproduced from Lauterbur, Nature 242, 190 (1973); Bull Am Phys. Soc. 18, 86 (1972).]

reconstruction' technique. The projection from one plane could be recorded by a CW method (as was done by Lauterbur) or by using a Fourier Transform (FT) method. This would lead to enhancement of S/N ratio inherent in the FT method over CW. However, the major breakthrough came with the use of two orthogonal time switched gradients and using two-dimensional Fourier Transform.[9,10]

Ernst had earlier (in 1966) revolutionized NMR spectroscopy by demonstrating that NMR spectrum can be recorded in much shorter time by exciting all resonances within the bandwidth of an rf impulse, recording the response [known as Free Induction Decay (FID)] in a digital computer and Fourier transforming the time dependent signal, to yield simultaneously all the frequencies contained in the FID. He demonstrated that this could enhance the S/N ratio of NMR spectra by a factor of 100.[11] As a result, by end of 1960s, all manufacturers of NMR instruments shifted from CW to FT NMR spectrometers.

For the imaging protocol, the application of FT technique to record each projection was an obvious extension. However, Ernst came up with the brilliant idea of two-dimensional Fourier Transform in the imaging protocol (following a suggestion by Jean Jeener of Belgium for two-dimensional NMR spectroscopy).[12] He suggested that if we use a 90° pulse to excite all resources in a body and use two orthogonal gradients as a function of two time variables t_1 and t_2, recording the data $[s(t_1, t_2)]$, as a function of t_2 for a complete set of values of t_1, and subjecting this to a two dimensional Fourier Transform, it would yield a two dimensional image.[9,10] My colleague Dieter Welti (student of Prof. Ernst), wrote a few subroutines, Ernst and myself wrote the remaining subroutines and I did the experiment. We basically reproduced the images of the two tubes of water, but in a much more efficient manner than any other technique (Fig. 2). This 'Fourier Imaging Method' is sometimes referred to as the 'KWE' method using the initials of the three authors.

Extension of the above method to three dimensions is obvious; by using three time periods, three orthogonal gradients and a three dimensional Fourier Transform, yielding a 3D image. However, it was suggested that a better method is to selectively excite a thin plane (slice) perpendicular to a (say Z) gradient and use the 2D FT method to image its whole XY plane. The experiment can then be repeated for other planes (slices) without waiting.

Two modifications were added to this method, (i) The first gradient as a function of t_1, known as the 'phase encoding gradient', uses either (a) a fixed gradient value and increment t_1, as was done by KWE method or (b) keep t_1 fixed to some value 'τ' and increment the value of the gradient in a step wise manner (spin warp imaging) Hutchison et al.[13,14] The latter method is preferred in MRI protocols, since a fixed τ has fixed relaxation, in all projections and achieves relaxation independent images. (ii) The other major improvement to this protocol was the Echo-Planar-Imaging (EPI) by Peter Mansfield (for which he shared the Physiology/Medicine Nobel prize with Paul Lauterbur in 2003). In this protocol, during the detection period (t_2), the FID was recorded in the presence of two orthogonal gradients (a constant gradient, g_x and a orthogonal gradient g_y), which is switched between a positive value (during which an FID is recorded as a function of t_2) and a negative value which refocuses the FID forming a spin echo.[15] This procedure is repeated N times allowing the recording of a whole plane (Fig. 3). The whole pulse sequence is repeated after waiting for a time TR, which again can be used to change the T_1 contrast of the image. Echo-Planner-Imaging made it possible to record a whole plane in a single shot and tremendously reduced the total imaging time (Fig. 3). The spin echo time TE and recycle delay TR provide the much needed T_1 and T_2 contrasts

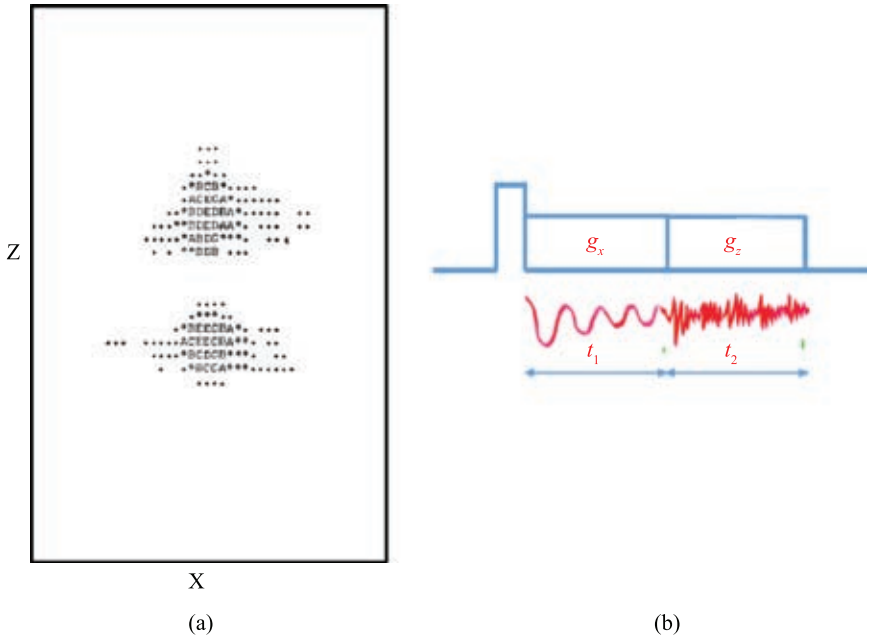


Figure 2: (a) The two-dimensional Fourier Image of two capillaries filled with H_2O, placed in a 5 mm NMR sample tube containing D_2O. The image was obtained by the method outlined in Fig. (b) [Reproduced from Kumar, Welti and Ernst, J. Magn. Reson. **18**, 69 (1975)].

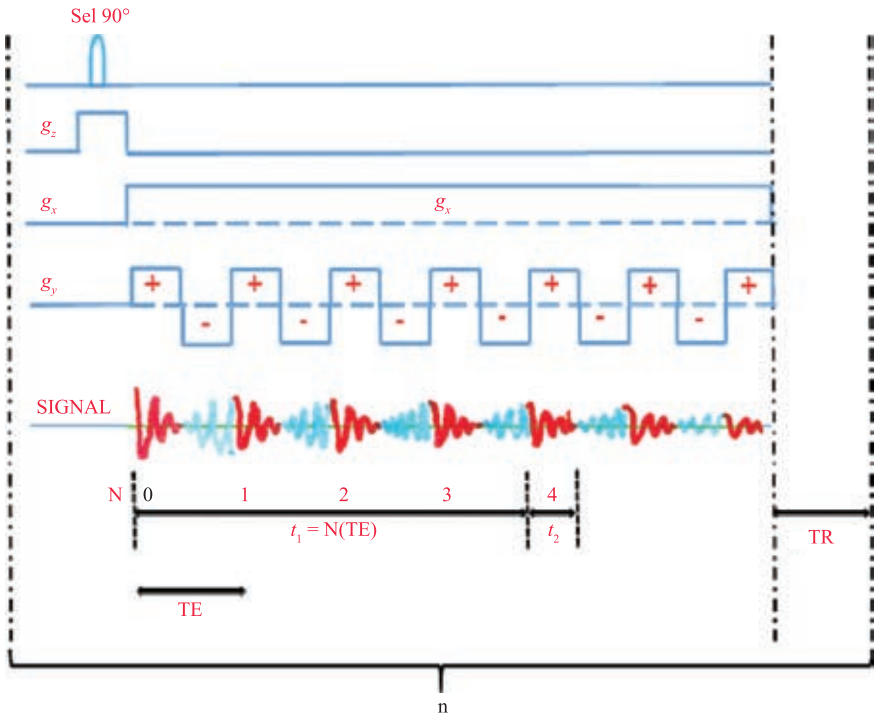


Figure 3: Echo Planar Imaging (EPI) method: The magnetization of a plane is excited selectively in the presence of a ***z***-gradient, which in turn is observed in the presence of a weak static ***x*** gradient with switched (+ and –) ***y***-gradient to form an echo. This way the whole plane is imaged in one excitation. TE is the time of echo and TR is the repetition time. These can be varied respectively for T_2 and T_1 contrast. Signal averaging can be performed by repetition of the experiment '*n*' times. Signal (FID) is recorded during the observation period t_2. t_1 is the phase encoding period. The next ***z***-plane can be imaged without waiting since selective excitation of a whole plane is performed. This is thus, the final imaging protocol and can also be used for T_1, T_2 contrast. Adopted from Fig. 10.4.10 of Ref. 16.

to MRI protocol. This method is now the basic method used in all MRI methodologies.

Another improvement was added in 1986 by Haase et al., known as "Flash (**F**ast **L**ow **A**ngle **Sh**ot) Imaging".[17] Here they used the well-known Ernst Angle approach for optimum flip angle and recycle delay. Ernst has earlier demonstrated that the most efficient Fourier Transform spectroscopy method, for highest S/N ratio, one should use a smaller excitation angle (rather than 90°) and short recycle delay. The optimum Ernst angle for spectroscopy was TR = T_1 and $\theta = 67°$.[11] However, Haase et al. suggested the use of $\theta = 15°$ and much shorted delay.[17] The flash method can be used only for simple pulse sequences, where there are no additional pulses except the excitation pulse.

All these developments have made MRI a versatile tool in the hands of radiologists all over the world (Fig. 4), and MRI has become a household name.

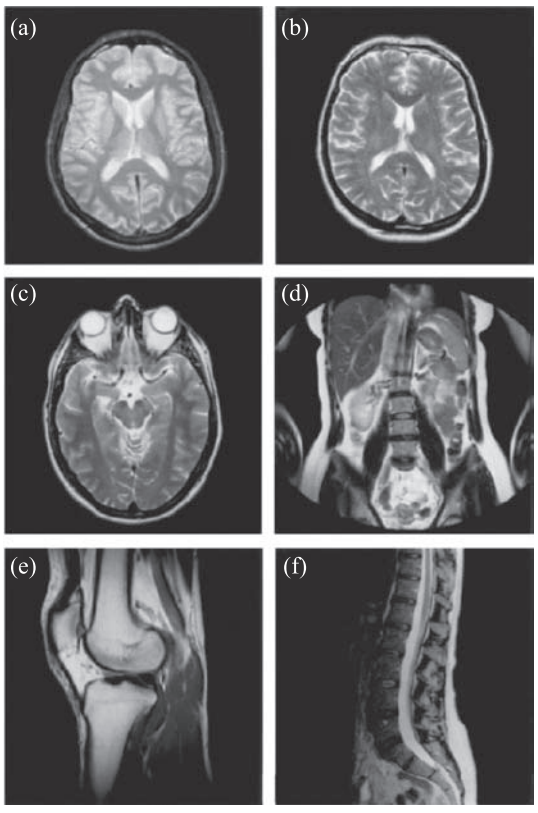


Figure 4: MR images using Echo Planar Imaging. These include three brain images (a, b, c), liver (d), knee (e), and a lumbar (f) image. These images demonstrate the high quality of MR images as obtained in mid 90s. [Reproduced from Marseille, Beer, Fuderer, Mehlkopf, and Ormondt, J. Magn. Reson., Series B 111, 70–75 (1996).]

2 Other MR Methods

Besides the above methods that very efficiently provide the anatomical images with T_1, T_2 contrast (TR and TE contrast) and have become very useful, there are other significant developments that have taken place during last two decades which make MRI even more useful. These are (i) Magnetic Resonance Spectroscopy (MRS), (ii) MR-angiography for flow measurement, (iii) Lung imaging using hyper polarized ^{3}He/^{129}Xe, and finally (iv) Functional Imaging. Each one of the above will be described briefly in the following.

2.1 *Magnetic Resonance Spectroscopy (MRS)*

In this method, signal from a chosen pixel (smallest unit of MR resolution) is picked-up and its spectrum (^{1}H or ^{31}P) is recorded and compared with the spectrum of a symmetrically placed pixel (say in the brain) Fig. (5). Phosphorous-31 NMR spectrum can yield information about the energetic of the brain. If the signal from phosphocretin (PCr at 0.0 ppm) is greater than Inorganic phosphate (Pi at +5.0 ppm), then that part of the brain is 'active'. If, on the other hand, the reverse is true, then the cells in that part of the brain are dead (not active). This crucial information cannot be obtained by a simple anatomical MRI of the brain.

2.2 *MR-Angiography*[18]

The flow of blood in a human body can also be measured using MR-Angiography. There are two methods known for doing MR angiography (a) Time of flight method (b) phase contrast method. In time of flight method, a series of $\alpha°$ pulses are applied for the MR Imaging protocol with a given TR. If the velocity of blood flow (v) is greater than TR, then each pulse sees fresh polarized blood and the signal intensity in the MR image is high. If on the other hand, the flow velocity is less or comparable to TR, then saturation sets in and the MR intensity is less. Fig. (6) shows one such case where there is decrease flow in the left interior branches of the middle cerebral artery (arrow). This is an important information, not available in a pure anatomical MR image. In the phase contrast method, one applied two gradients of opposite sign with a time interval between them. The non-flowing blood does not experience any phase change while the flowing blood does.[17] This way one can monitor the flow of blood.

2.3 *Lung imaging*[19]

MR imaging of lung provided novel challenges, since there are hardly any protons (H_2O) in the

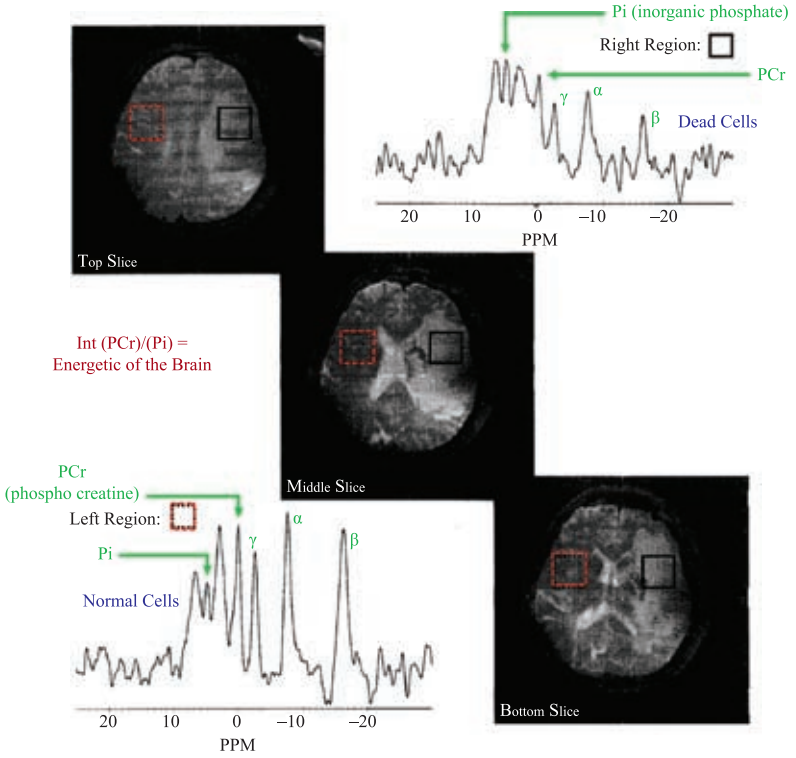


Figure 5: MR images and ^{31}P spectra obtained from a stroke patient. The two regions studied using ^{31}P MRS investigated simultaneously (TR = 1.5 s, number of acquisitions = 768, MRS study completed in 20 min), and incorporate tissue extending the regions shown in the top slice through to those in the bottom slice (volume of each cube = 3 × 3 × 3 cm^3). The spectrum from stroke-affected tissue (right) should be compared with that from the unaffected contralateral region (left). [Reproduced from Ordidge, Helpeen, Hugg, and Matson, Single noxel whole body phosphorus MRS, Encyclopedia of NMR, Volume 7, 4427 (2002).]

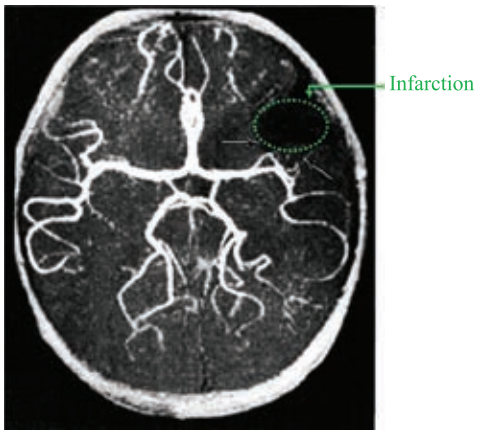
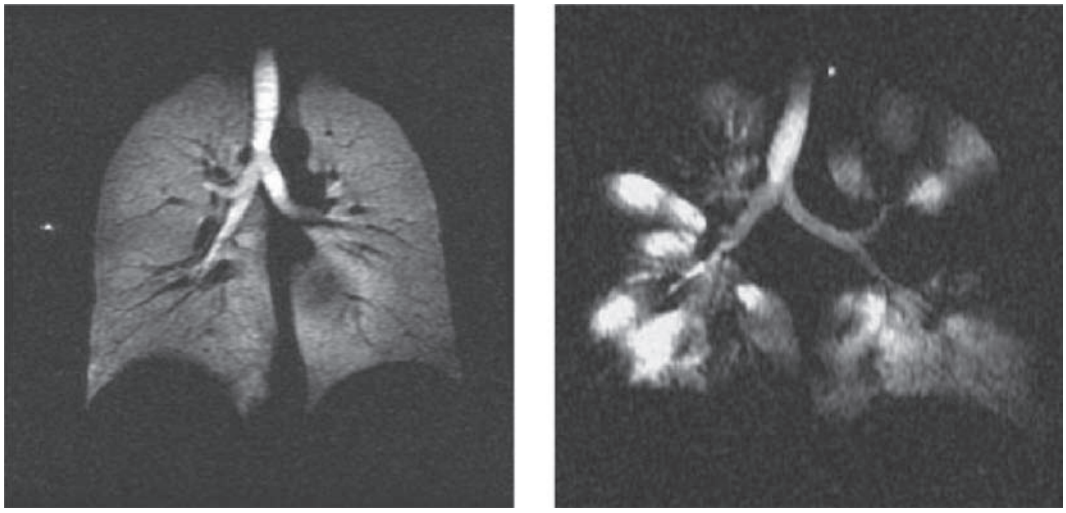


Figure 6: Three dimensional time of flight (TR = 44, TE = 8) angiogram; an 18 month old male infant with known infarction of the left middle cerebral artery. The anterior, posterior and middle cerebral arteries are seen, but there is a paucity of vessels on the left in the anterior branches from the middle cerebral artery (arrow). [Reproduced from Pennock, Pediatric Brain MRI; Applications in Neonates and Infants, Encyclopedia of NMR, Volume 6, 3488 (2002).]

lung. Lung basically contains air that we inhale, thus posing a challenge of 'how to image empty spaces'. This was achieved by the use of hyperpolarized ^{3}He or ^{129}Xe gases. Both these gases have a nuclear spin of ½, can be polarized by collusion with Rubidium atoms which in turn can be hyperpolarized by laser irradiation. A. Kastler obtained the 1966 Nobel Prize in Physics for achieving these hyper polarizations using optical pumping. The polarization stays for quite a long time (minutes to hours) in spherical glass containers. These gases are then inhaled by a person, and MRI of the lung is obtained by tuning the radio frequency to the Larmor frequency of these gases. Both these gases are inert and exhaled out without any harmful effect on the lung and the person. Beautiful lung images have thus been obtained both of healthy lung, and lung devastated by cancer (Fig. 7).

2.4 *Functional MRI*[20]

Perhaps the most fascinating development in MRI is the so called functional MRI. The idea, first proposed by Seji Ogawa of Japan, and named as BOLD (**B**lood **O**xygenation **L**evel **D**ependent)



(a) (b)

Figure 7: (a) Healthy lung visualized with hyperpolarized ^{3}He, appears different from that ravaged by cystic fibrosis (b). [News and Analysis, Scientific American 280, 36 (1999).]

technique, works in the following way: Whenever the human body performs any physical or mental action, it is controlled by certain portions of the brain. The activated brain has increased blood flow and changes in the oxygenation of blood leads to MRI-Signal changes due to changes in the T_1 and T_2 of the nearby protons. Two MR-images are taken (i) with and (ii) without the activity. A difference between the two images cancels out everywhere except where the actions are taking place, thus identifying the part (or parts) of the brain involved in that particular activity.

The success of such a protocol is critically dependent on the speed with which MR images of the brain can be taken. With the use of EPI, the measurement of single slice is activated in a fraction of a second or thousands of images in a minute, allowing signal averaging with and without activation. This has now produced consistent f-MRI results. Anatomical mapping of human brain for various physical and visual activities have confirmed some well-known facts such as when a person learns two languages at the same time, the same part of the brain is used, but if he/she learns them after a significant interval, two different parts of the brain are used.

f-MRI is now being exploited to study higher function of the brain such as love, hate, fear as well as lie detection. Studies are going on to study how brain reacts to yoga, meditation, listening to music, classical and modern etc. This is an infinite field and we are just observing the tip of an iceberg. The ultimate hope is that it will throw some light on 'how the human brain works'.

I like to conclude by making two observations. A friend of mine, Prof. Jozef Gruska of Czech Republic, has a quote: ***"While most advances in science are made by pessimists, most advances in technology are made by optimists"***. This statement is very true for the development of MRI. Most of us, the scientists, were very pessimistic about its future. In 1974 we made a statement after initial experiments—"*this will be never be used*". As late as mid 80's (1984) in an International Conference, when a doctor was describing detection of cancer by MRI, one of the well-known NMR chemist 'a scientist' in the audience asked if the patient was still alive, implying that in 1984 one could detect cancer by MRI only at very late stages. The medical companies were much more optimistic and invested heavily in research and development of this field to bring it to the level that it is now available to common man all over the world, in every major hospital and diagnostic Centre. Indeed MRI has now become an integral part of diagnostic tools with radiologists, who often prefer it over CT-scan. This brings me to my second quote—**"*The development of MRI is a glowing example of non-directed research and is now hailed as one of the 'major contributions of 20th Century Science to Humanity'".***

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