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ISSN 2544-1361 (online); ISSN 2544-2406
doi: 10.15584/ejcem.2017.2.4

http://www.ejcem.ur.edu.pl/en/
European Journal of Clinical and Experimental Medicine
Eur J Clin Exp Med 2017; 15 (2): 120–126

REVIEW PAPER

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Functional MRI – how does it work?

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ABSTRACT

Magnetic Nuclear Resonance (MRI) is a non-invasive tissue imaging method. This technique is based on the influence of a strong magnetic field and electromagnetic wave of strictly defined frequency on the nucleus of elements with non-zero spin. The study describes one of the variants of functional MRI, (fMRI), which has become a key technique in brain imaging. This technique has excellent spatial and temporal resolution and involves a changing signal intensity depending on the degree of oxygenation of the blood. Blood oxygenation levels are known to vary in accordance with neural activity and these differences can be used to detect brain activity. This is due to increased demand for energy and oxygen in the area of increased neural activity. The basis of this imaging is the so-called Blood Oxygenation-Level Dependent (BLOD) effect. The aim of this paper is to present the scope of fMRI as a diagnostic method in neurology and in neurosurgery. This paper presents the principles of fMRI, methods of application, research result development, and suggests areas of possible medical applications. The limitations of fMRI as a clinical tool in medical applications will also be addressed. Studies presented in this paper are based on clinical fMRI experience and a literature review.
Keywords. deoxyhemoglobin, oxyhemoglobin, Magnetic Resonance Imaging, functional Magnetic Resonance Imaging

FMRI as a method of brain research and more

Introduction

Imaging the human brain, the main component of the central nervous system, is critical for disease diagnosis. Although brain mass is estimated to be 2% of total body weight, it consumes 20% of the oxygen that passes through the body. The brain has an enormous number of neurons connected to each other by dendrites and axons that connect this supercomputer with its "outer world," which is the body. The number of neurons is in the order of 100,000,000,000, and each of them can create up to several thousand connections with other neurons. Each

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Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

Received: 08.03.2017 | Accepted: 17.06.2017
Publication date: June 2017

Truszkiewicz A, Aebisher D, Przypek A, Guz W, Bartusik-Aebisher D. *Functional MRI – how does it work?* Eur J Clin Exp Med. 2017;15(2):120–126. doi: 10.15584/ejcem.2017.2.4

neuron has several thousand synapses which act as axon communication points. Synapses are of two main types, electrical and chemical, and they are distinguishable.

The brain has two hemispheres separated by a longitudinal slot and connected by the corpus callosum. Externally, the brain is covered by a gray matter or the cerebral cortex. Brain tasks include memory, speech, interpretation of stimuli, movement, association, and control of skeletal muscle movements. It is strongly folded and accounts for more than half of the total number of brain cells. The inner layer of the hemisphere is a white matter consisting essentially of axons connecting different areas of the brain. Anatomical and physiological studies have revealed that the individual patches on which each hemisphere divides perform different functions. The frontal lobe is responsible for, inter alia, action and interaction with the sensory area. Other important tasks are mating, as well as analysis and control of emotional states. The temporal lobe is the center of the, inter alia, hearing and smell centers. In the parietal lobe sensory cells, cells responsible for pain, spatial orientation, coordination of movement as well as spatial-motor coordination are located. The occipital lobe contains visual centers, color analysis, depth, and visual associations.

The brain has a complex connection structure and a central question is: how does it work? Historically, the only way to find out what role a particular part of the brain plays is observation of damaged or surgically removed parts of the brain and subsequent behavior. This indirect way of inference was to answer the question: what are the effects of the damage on a given part of the brain?

Today we have methods to observe the workings of the brain in a living person including electroencephalography[1], positron emission tomography (PET), functional cerebral resonance (fMRI) and magnetoencephalography (MEG).[2-6] Each of the above methods has both advantages and disadvantages. Below is a tabular summary of some non-invasive imaging methods (Table 1).

Magnetic resonance imaging

Magnetic Resonance, or Magnetic Resonance (MRI), is a phenomenon discovered by Isidor Isaac Rabi (1898-1988), an American physicist of Polish origin. This discovery was honored with the Nobel Prize in Physics in 1944 for the resonant method of observing the magnetic properties of nuclear nuclei. I.I. Rabi was born in Rymanów, Poland after which he and his parents emigrated to the United States. He studied chemistry at Cornell University, and physics at Columbia University where he obtained his doctorate in 1929. In 1937 he became a professor of physics. In 1952, Edward Mills Purcell (born August 30, 1912 in Taylorville, Illinois, March 7, 1997 in Cambridge, Massachusetts) and Felix Bloch (born October 23, 1905 in Zurich, September 10, 1983), also received the Nobel Prize in Physics for developing new methods of precision measurement of nuclear magnetism and for the development of new methods for precise measurements of the atomic nucleus.

The phenomenon of MRI is based on the interaction of nuclei of non-zero spin elements placed in a strong magnetic field with a strictly defined frequency electromagnetic wave. To approximate the phenomenon, let us assume that we put in a certain space a number of atoms with non-zero spin and that these atoms are hydrogen atoms because it is the most common element in our body and its' relative sensitivity is greatest. These two characteristics determine the choice of this element as the one by which the image of anatomical structures is created. Generally speaking, magnetic resonance is present in many nuclei, but only some have practical applications in medical imaging. In clinical practice, ^{1}H MRI is most often used, but is increasingly implemented with ^{13}C, ^{15}N, ^{19}F, and ^{31}P.

Positively charged protons in the nuclei of the atoms rotate around their own axis. They have their own momentum or spin. Spin is the basic property of particles like mass or charge. The movement of charge is accompanied by the formation of a magnetic field. So for the purpose of this discussion, we consider each of the protons as a small bar magnet. In cases where the protons are not subjected to a magnetic field, their magnetic momentum will be extinguished. A different situation occurs when the same atoms are placed in a strong magnetic field; protons having their own small magnetic field will be par-

Table 1. A summary of some non-invasive imaging methods

Parameter / method	fMRI	EEG	PET	MEG
Time resolution	5 s	0.001 s	60 s	0.001 ms
Spatial resolution	5 mm	10 mm	5 mm	50 mm
Disadvantages and limitations	Limitations of MR examination (claustrophobia, implants, etc), motion, expensive imaging systems	Examination of the cortex of the brain, interpretation difficulties	The need for isotopes, movement, difficulty in accessing the study, very expensive imaging systems	Poor spatial resolution, interpretation difficulties
Advantages	Functional analysis, non-invasive method	Easy patient access to the study, a method of cheap	Functional analysis	Action within deeper structures

allel or antiparallel to the main magnetic field lines. The setting of a given proton decides its energy state. A state that is privileged is a condition that requires less energy. The proton also performs a precession movement. To put it bluntly, it is a movement similar to that of a child's toy - a top. The speed of this movement, and hence the frequency, depends on the intensity of the magnetic field and the magnitude, which is different for different elements.

This frequency is defined by the Larmor formula:

$$\omega_0 = \gamma B_0$$

and

$$f = \frac{1}{2\pi}\gamma B$$

where
Ω - resonance pulsation, γ - γ-intercept, B - magnetic field induction.

To understand this phenomenon, we now place the entire sample in a three-dimensional coordinate system so that the Z axis coincides with the direction of the magnetic field force lines. The vector of the magnetic force of a single proton will have a certain value on the Z axis and a direction parallel to the field force lines. The component along the Y axis will be 0. Now looking globally across the whole sample, we will notice that these single vectors of parallel and antiparallel forces sum up to form a resultant vector of longitudinal magnetization. Its value will depend only on the very small number of protons aligned parallel to the force lines of the magnetic field, and thus on the lower energy level. The vast majority of parallel and antiparallel vectors will be abolished and will not participate in the experiment. This is where all the hardships in nuclear magnetic resonance research are hidden - a very poor signal is received from the sample. If the sample is now exposed to a strictly defined frequency called the resonant frequency, the energy will be absorbed by the protons and converted to higher energy levels. This affects the magnetization of the object. After switching off the RF signal, we will be dealing with the opposite phenomenon, namely the energy transfer by the protons going from the higher to the lower energy level. This will again be a resonant frequency electromagnetic wave. If now, for a permanent magnetic field, we add an additional three magnetic fields of the X, Y, Z axes. We are able to change the additional fields accordingly to establish magnetic resonance. It should be added that this frequency will depend on the magnetic field in a given voxel, which in turn will be the sum of the fixed field and the operation of the three fields of the gradient. Similarly, if you receive a frequency, you will receive a signal that is a sum of multiple frequencies. By analyzing Fourier's received signal, we divide it into individual components, which, combined with the knowledge of the magnetic field distribution inside the magnet, will allow us to show where the given frequency originates.

By manipulating the gradient of the magnetic field in the respective X, Y, Z axes, you can scan the volume of layer to be tested.

Principles of fMRI action

At the base of the method lies the assumption that the rate of metabolism of a given area of the brain depends on its activity. Seiji Ogawa was the first to observe this phenomenon in 1990.[7] Ogawa *et al.* Based on in vivo studies, blood oxygenated level dependent (BOLD) contrast can be used to map blood oxygenation in the brain.[8]

This method utilizes the physiologically occurring phenomenon of local increase in blood flow through the stimulated brain area and the magnetic properties of hemoglobin, which, as a result of metabolic changes, becomes a natural contrast agent. Hemoglobin is an oxygen carrier and when it passes through the capillaries of oxygenated lungs it takes the form of oxyhemoglobin. After release of oxygen to tissues it takes the form of deoxyhemoglobin. Both hemoglobin forms have different magnetic properties. Unlike structural imaging, where the source of the MR signal is the hydrogen nucleus, functional differences in signaling from the oxygenated or oxygenated hemoglobin content are used in functional imaging.[9] Performing specific activities (movement, memorization, speaking) is accompanied by stimulation of the areas of the brain responsible as active neurons have increased oxygen requirements. Local blood flow increases and hence the amount of oxyhemoglobin in a particular area allowing for a stronger MR signal from that region. The intensity of the signal from the degree of hemoglobin oxidation is determined BOLD.

The BOLD signal is therefore a reflection of the current activity of the neurons. With Echo Planar Imaging (EPI), in the stimulated areas of the brain, there is a discrete but measurable signal change in the range of 2-5% for scanners of 1.5 T and about 15% for very high 4 T field scanners.[10] This signal change is recorded and is the basis for further analysis. The fMRI study is characterized by high spatial resolution.[11] The invaluable advantage of this method is its non-invasiveness, reproducibility, and the possibility of widespread clinical use. The disadvantage is its relatively low temporal resolution despite EPI.

The fMRI study requires that the experimenter take into account the state and ability of the patient. This is crucial for success and can determine the outcome of the measurement scheme. It is based on the use of alternating control and activation blocks at regular intervals.[12] Figure 1a presents a fMRI block design paradigm. The received response signals contain activation regions, as shown in Figure 1b, and areas in which brain stimulation

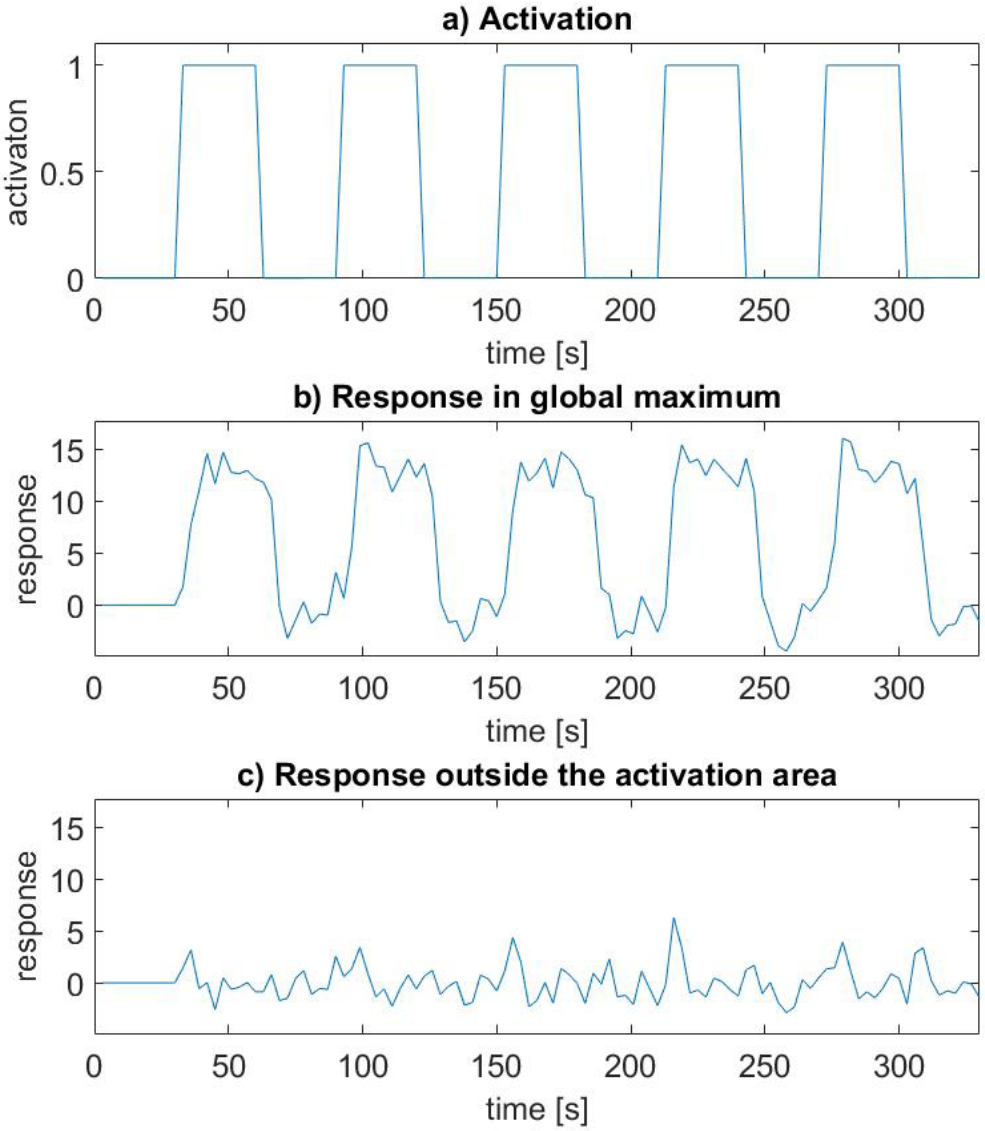

Figure 1. a) temporary activation, b) response at the global maximum, c) response from the place where activation did not take place

did not occur, as illustrated in Figure 1c. On this basis, the correlation can be clearly seen as well as the increase in the signal from the activated part of the brain with the activation signal.

Hardware and software

Performing functional tests with the fMRI method carries much higher technical and methodological requirements than MR imaging.[13] This study requires the use of additional equipment and specialized signal analysis software, which are not required in morphological studies.

The basic equipment of MR imaging equipment that performs fMRI studies is, inter alia, an auditory pacemaker device, a visual stimulation device, a stimulus response recording device, and a device for synchronizing a scanner with stimulation devices. Devices working in the scanner room should meet the very strict requirements of the PN-EN 60601-2-33 standard on the safety of magnetic resonance devices for medical diagnostics.[14]

The necessity to meet the standard can force the elimination of devices that may interfere with the tomographic signal. Hearing stimulation is performed by means of headphones, to which the sound wave is delivered with a sounder or by means of piezoelectric transducers. Visual stimuli are triggered by special goggles or, as a result of observation, in the mirror placed on the head coil of an image displayed on the screen with an image projector or special built-in monitors. Magnetic compatibility is achieved by the use of fiber optics, which can transmit patient response signals by pressing a button. In general, the specificity of equipment used in MR systems should be emphasized. These devices must be resistant to strong

magnetic fields and cannot themselves interfere with magnetic resonance.

Although manufacturers of magnetic resonance systems offer their own software, other signal analysis tools are also available. Because of the nature of the data and the way they are collected in time, the software should provide traffic correction, temporal and spatial data matching, and statistical analysis. One of the most popular software tools is the SPM (Statistical Parametric) using the MATLAB software package.[15,16] It allows you to perform a complete processing of the signal coming from DICOM scanners and their graphical representation.

Experiments

The fMRI study requires the preparation of both patient and staff. The paradigm and method of stimulation must be selected both for the purpose of the experiment and for the state of the patient. It may turn out that the person being tested due to his or her medical condition is not able to perform the instructions. Before the test the instructor should be carefully prepared in both the purpose and the test method. It is advisable to practice with the person taking part in the study and, in particular, with the patient before the experiment. This will allow you to avoid jittery or incorrectly executed commands, which can ultimately undermine the test itself. For example, in a simple experiment involving words that start with a particular letter, it is important that the patient does not try to speak because he activates the centers of the facial muscles movement and also causes head movement. This will lead to additional changes in other areas of the brain. In some cases, especially when the researcher is looking for answers to the question "which brain regions are responsible for the task", such additional changes may cause interpretation errors.

The study itself involves placing the patient in a magnet, performing a location scan, and then selecting layers in the area of interest to make an EPI sequence during which an experimental condition is generated to stimulate the investigated center. In addition, a sequence is created to obtain an accurate picture of the structural brain.

The first sequence with EPI, due to its speed and sensitivity, allows the BOLD signal to be recorded, while the other is used to obtain very good quality anatomical images. The results of the analysis of statistical images of EPI sequences are, in a sense, overlapping.

Signal Analysis

A separate discussion requires analysis of the signal from the experiment. A series of hundreds or even thousands of digital images are produced. The series is a time series showing the changes taking place in the brain. Owing to its nature and amplitude, very specific and sophisticated measures are needed to catch interesting changes. Pre-treatment of the signal is intended to minimize the effects of interference that affect the image. The most important sources of interference are involuntary movements of the head or whole body. It is important to note that the patient is required to remain completely immobilized during the study period, which is difficult or impossible for people suffering from various diseases although currently produced MR systems have motion compensation but are unable to completely remove this artifact. Flow artifacts occurring near large blood vessels, noise generated by the non-patient system itself related to receiving systems, amplifiers, ADC converters, mathematical processing, disturbances caused by the presence of metal elements in the patient's body, of which dental implants are a good example. Sometimes this artifact can completely distort the image and make it impossible to perform the test. Interference with MR findings and its effects on the patient, such as the impact of noise generated by the EPI sequence on the BOLD signal in the auditory cortex.

The most important methods for detecting functional activity include: correlation analysis, frequency analysis, multivariate analysis, analysis of the main components, and analysis of independent components. It should be emphasized that a poorly-selected mathematical apparatus that allows data to be developed can lead to serious errors and even to quite the opposite conclusion. It is not enough to get a large amount of data from a high-end measuring system, but it is important to properly develop research results. A leading example of data misconception is the experiment with dead salmon.[17] Conducted with all the rigors of scientific work, the experiment showed that the dead brain tissue of Atlantic salmon responds to a series of images presented. When analyzing the data, the researchers were astounded as they noticed the activity of two groups of nerve cells, which should not have been the case. The error was in the statistical methods used by neuroscientists. EPI is the fastest method of fMRI data acquisition that gives one image in 100 ms. However, it causes random noise that may be mistakenly identified as nerve cell activity. In the second step, the researchers used additional mathematical tools to help control the data from accidental noise and recalculate everything and the result turned out to be in line with the actual situation. Signal analysis of on-screen results may be misinterpreted. For example, let's use a fMRI experiment, which allegedly argued that rejection by others causes "psychological pain." The test participant participated in the virtual game of throwing a ball to other players mapped on the screen. At a time specified by the investigator, other "players" stopped throwing the ball to the test subject resulting in activation of a specific area of the brain. This result was interpreted as evidence of "internal pain". Unfortunately, this part of the brain activates, among others cognitive conflict, misunderstanding, and fatigue.[18] The more likely interpretation of the results was: "wondering what to do in the unexpected," as confirmed later.

Areas of application

The fMRI study is a constantly evolving research method. It finds its application to a large number of medical specialties associated with the brain. The use of functional cerebrovascular resonance in areas where it may not seem to apply, namely rehabilitation, forensics, or marketing research, is also being observed. Here are some examples to illustrate the enormous potential of functional cerebral resonance.

The pre-operative fMRI study of patients with brain tumors allows identification of important centers (mostly motor-sensory and speech) adjacent to tumors, as well as the possibility of complete resection, postoperative risk assessment and presumptive neurological deficits.[19] Analysis of these factors makes it possible for a neurosurgeon to make a rational decisions to optimize the planning of the surgery and to save important cortical centers. In neuroscience, this method is used to study emotions, decision making, speech and addictions.[20-26]

In psychology this method is also used, among others. For detecting lies.[27,28] The image of cortical activation in the course of speaking lies is well illustrated in fMRI. Lying requires more engagement of cognitive resources than telling the truth, and thus more intense brain work. This explains the fact that activation of the brain is greater in the course of lying than in telling the truth, and in particular the activation of the prefrontal cortex, which is the neuroanatomical substrate of memory. There was no significant difference in patients with schizophrenia compared to healthy subjects with pre-cortical activation. The presence or absence of delusions did not alter these results.[29]

A. Bryńska in his work entitled "In Search of the Causes of Autism Spectrum Disorders - Functional Neuroimaging (Part II)" describes the use of FMRI in the study of disorders in the spectrum of autism.[30] With fMRI you can also diagnose the occurrence of certain diseases. Studies have been performed on the risk of Alzheimer's disease.[31,32] Some apolipoprotein carriers of ApoE4 have seen increased levels and intensity of activation of relevant regions compared with ApoE3 carriers, which was associated with progressive memory loss, observed two years later.

A very interesting application is the study of the effectiveness of rehabilitation and plasticity of the brain. Having more knowledge about brain plasticity mechanisms is conducive to the development of new therapies for people with various brain injuries. In the case of patients experiencing a stroke, it is now possible to accurately plan rehabilitation taking into account which brain region has been damaged by cutting off the blood supply and selecting a set of specific exercises for recruiting new synapses.[33]

Another interesting area of fMRI applications is marketing research. It analyzes the impact of product advertising on the activity of each brain region and on the decisions a customer makes.

Summary

The paper describes a method of study called functional magnetic resonance. In such a short discussion it is impossible to include the full spectrum of possibilities offered by this imaging method. The method allows you to peek into not only the brain but also the awareness of human reactions to the surrounding world. Certainly in the coming years we will see the development of this method and its new applications.

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