FUNCTIONAL MAGNETIC RESONANCE IMAGING

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Since the discovery of x-rays by Professor Roentgen in 1895, radiologists together with physicists and electrical engineers have been obsessively refining the techniques for detection of morphologic alterations in organ systems in health and disease. Recent advances in computed tomography (CT), and magnetic resonance imaging (MRI) have allowed for exquisite visualization of in vivo anatomy essentially in real time.

Modern medicine is however, increasingly moving beyond gross anatomy and histopathology into the domain of molecular medicine. Radiology has tried to keep pace with this "molecular biological revolution". In recent years "Functional Imaging" has evolved as a new subspecialty of radiology. A variety of novel MRI sequences and nuclear medicine probes are now routinely used in clinical medicine, not to image diseased anatomy, rather to study in vivo tissue perfusion, metabolism and chemistry.

WHAT IS FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI)?

Functional MRI is a specialized MRI sequence for mapping the functioning of human brain non-invasively and without the need to administer any exogenous contrast agent or a radio-tracer. The technique measures the local hemodynamic response which accompanies the neural activity resulting in changes in local blood oxygenation level. The sequence most commonly used for fMRI is therefore also called Blood Oxygenation Level Dependent or BOLD imaging sequence. The first experiments on fMRI were performed at Massachusetts General Hospital in Boston in 1991[1] when activation of visual cortex was demonstrated in humans. The ability of fMRI to safely and repeatedly provide high resolution imaging of brain function together with anatomic detail, using standard MRI equipment with certain hardware with software upgrades, is making it the imaging modality of choice for detection of brain dysfunction in a variety of neurological and psychiatric disorders, for assessing clinical efficacy of drug treatment, and also as an alternative to invasive procedures, e.g., Wada test, for localization of eloquent cortex prior to neurosurgical intervention.

Although there are other relatively non-invasive clinical modalities for mapping human brain function including electro-encephalography (EEG) or magneto-encephalography (MEG), which directly assess the electrical or electromagnetic activation of brain with excellent temporal resolution, these modalities lack sufficient spatial resolution (one to several cm). Another category involves in vivo assessment of cerebral metabolism as a consequence of altered electrical activity, e.g., positron emission tomography (PET) or single photon emission computed tomography (SPECT). Both of these techniques require administration of radio-nuclides, and demonstrate somewhat suboptimal spatial and temporal resolution as compared to fMRI, which has spatial resolution of few millimeters and temporal resolution of few milliseconds.[2] Moreover, the scan time is also very short, on the order of 1.5 to 2.0 minutes per scan, depending on the paradigm being studied. The ability of fMRI to image the entire 3-D volume of the brain together with inputs from visual and auditory stimuli, and cerebellar functions as well as high level cognitive tasks and executive functions, makes it as ideal tool to study a host of clinical and research paradigms by a variety of sub-specialists.

PHYSIOLOGY AND PHYSICS OF BOLD FMRI

Conventional MRI primarily maps the distribution of water in the brain. The source of useful contrast in MR images however comes from both the spatial variations in the density of water as well as from differences in fundamental nuclear magnetic processes known as "Relaxation times." There are three relaxation times that are of interest-T1, T2, and T2*. T1 is a measure of how quickly a tissue can get magnetized, while T2 conveys how quickly a given tissue loses its magnetization. T2* is the magnetization decay time with gradient recalled echo imaging and is most relevant relaxation time for understanding contrast in fMRI images.[3]

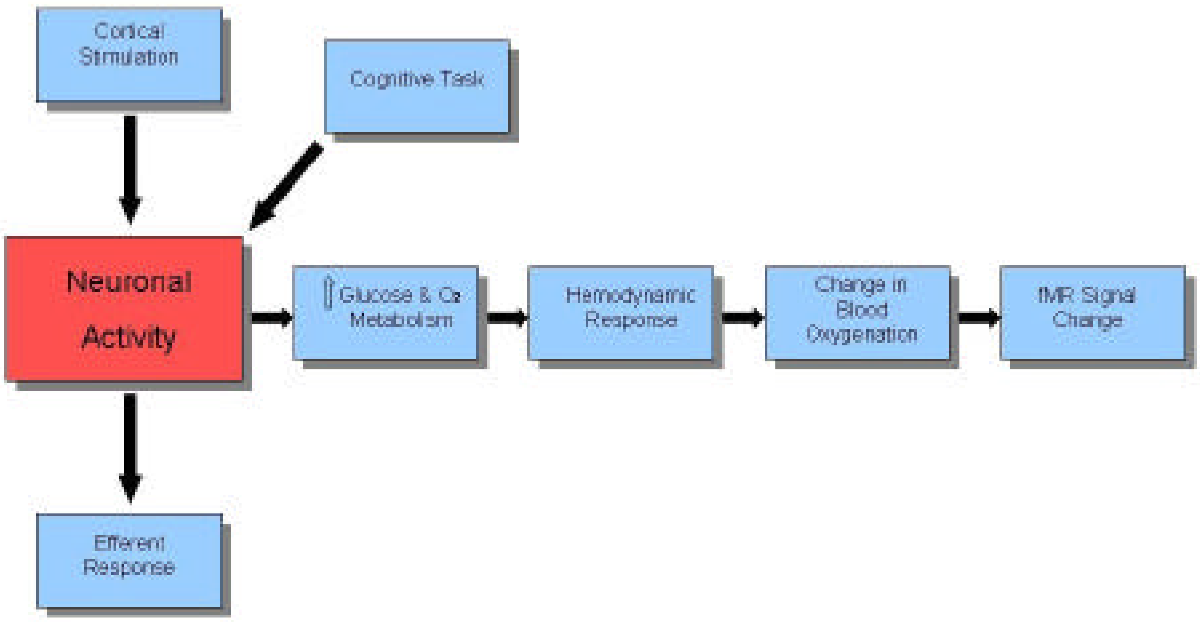

Figure 1: Schematic representation of mechanisms responsible for the generation of BOLD signal in the region of neuronal activity.

When there is increased neuronal activity in response to an afferent stimulus, energy metabolism is increased with increased local blood flow, which appears to be a direct consequence of neurotransmitter action reflecting local signaling. This increased perfusion is a function of local auto-regulation determined by the feeding arterioles and results in increased supply of oxygenated blood to the locally active neurons. Due to this increased supply of oxygen there is a temporary increase in the ratio of oxy- to deoxy-hemoglobin (deoxy Hb) in a region of neuronal activation. This local change in relative amounts of hemoglobin-carrying oxygen (oxyHb) and deoxyHb is responsible for the BOLD signal on fMRI. Since deoxyHb is paramagnetic relative to brain tissue, whereas oxyHb is diamagnetic, capillaries and veins containing partially deoxygenated blood distort the magnetic field thus shortening the T2* relaxation time. As the oxygen extraction falls with compensatory increased local blood flow in a region of greater neuronal activity, the T2* becomes longer thus resulting in the BOLD MRI signal (Figure 1).

During fMRI the subject lies in the bore of the magnet, while the BOLD response to the presented stimulus is monitored. A variety of stimuli, including motor, sensory, visual, auditory, gustatory, verbal as well as covert phenomena such as thinking, planning, emotions, and memory can therefore be studied. Since fMRI studies are non-invasive, multiple sequential studies on the same subject can be performed. The fMRI BOLD signal is then presented as an overlay on the traditional high resolution anatomic images obtained concurrently (Figure 2).

CLINICAL AND RESEARCH APPLICATIONS OF FMRI

One of the most common indications of fMRI in clinical practice is lateralization of language function[4] and localization of the eloquent cortex in relation to the pathology[5], as part of the neurosurgical planning. While traditional clinical methods for language lateralization (for example, the Wada test) are highly invasive, fMRI offers a promising alternative and provides more specific anatomical information.

A general issue in pre-surgical planning for excisions near regions of eloquent cortex is the precise localization of essential functions. fMRI is an attractive strategy for this mapping since it provides precise delineation of both structure and function in a single image. Individualized mapping of brain function can reliably be performed even when the presence of a lesion, for example a tumor, alters the expected location of functional cortex, or when a tumor is located near a region of association cortex or language related processes.

Simultaneous EEG and fMRI can also be performed to identify ictal foci in patients with sub-clinical seizures,

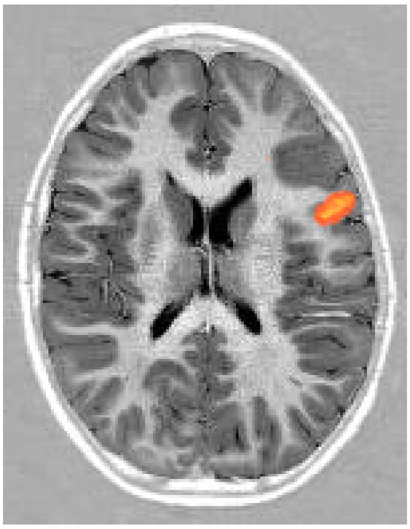

Figure 2: fMRI broca

hence aiding the operative planning for epilepsy surgery.[6] Functional MRI has been extensively used in recent years to study brain plasticity with injury or disease[7], which may result in functional re-organization in the brain, or recruitment of intact brain regions to compensate for functional deficits arising from the pathological process.

Adult brain shows considerable potential for adaptive plasticity. Several studies of patients after strokes have suggested that new regions of intact brain are recruited in the motor cortex. An exciting clinical extension of this concept is the application of fMRI in defining functional changes in the brain with neuro-rehabilitation.[8] Functional MRI promises to enhance our understanding of the mechanisms underlying the beneficial effects of a particular intervention. fMRI studies of learning in healthy subjects show that changes in functional brain organization may even be induced. Specific regions of the brain change activity with clinical improvements after treatment. With definition of the functional anatomy it may be possible to better identify patients who will benefit from a particular treatment thus opening doors to the possibility of individually tailored neuro-rehabilitation programs.

Functional MRI may be able to identify the preclinical expression of disease. In a study of a group of apparently healthy subjects at risk of developing earlier onset Alzheimer's disease, one year after fMRI scanning, those who were beginning to develop memory problems in early clinical expression of presumed Alzheimer's disease were identified.[9] Functional MRI also has a great research potential for studying the memory dysfunction[10], in the study of learning disorders in children[11], autism[12], and attention deficit and hyperactivity disorder.[13]

A related application is the use of fMRI to study a variety of psychiatric illnesses including mood disorders. Functional MRI may be able to identify patients who are at a higher risk for recurrence of depression after successful therapy.[14]

Functional MRI has rapidly developed as a powerful tool in cognitive neurosciences. Studies have shown activation of Heschl's gyrus during auditory hallucinations in patients with schizophrenia, increased activation of amygdala in post traumatic stress disorder, and diminished activation of orbito-frontal cortex in patients with substance abuse.[15]

Studies using brain stem changes associated with pain suggest that the peri-aquiductal grey matter is an important locus for such action.[16] Similar mechanisms may contribute to the placebo effect. The BOLD signal of fMRI has also been detected in the spinal cord in both animals and humans, in response to motor, sensory, and thermal stimuli, providing avenues for more research in this area.[17] The BOLD signal in the brain can also be elicited in mildly sedated children.[18]

The use of fMRI has spread beyond the realms of clinical neurosciences. Sports psychologists are using fMRI to study how an athlete deals with his or her dashed Olympic dreams, consumer industry is adapting fMRI to develop effective advertisements for products, politicians are using fMRI to generate exciting campaign slogans, and fMRI is replacing the lie detector in the interrogation process of the suspected criminal.[19,20]

LIMITATIONS OF FMRI

Like any imaging modality fMRI has its own limitations. The technique is very sensitive to motion artifact, hence the subject has to be cooperative and generally be able to follow commands. There may be artifactually diminished BOLD signal in inferior frontal or medial temporal lobes due to geometric distortion, thus resulting in false negative studies in these regions. Moreover the hemodynamic response to neuronal activation may be altered adjacent to a tumor or an arterio-venous malformation due to abnormal vasculature. Finally, the technique offers a rather awkward environment for studying emotional paradigms. An experienced neuroradiologist is therefore necessary to optimize the imaging protocols, and extract useful information after careful analysis of the imaging data.

CONCLUSION

Functional MRI is an extremely useful tool and has revolutionized the study of human brain. fMRI is providing images of brain in action with pictures of human mind unraveling the neuro-circuitry and metabolic pathways superimposed on detailed neuro-anatomical images of the brain. The field of fMRI is rapidly finding clinical applications and exciting scientists from a wide range of disciplines including neurologists, neurosurgeons, psychiatrists, and behavioral scientists. Functional MRI offers avenues for basic research and clinical applications, which could not have been imagined only a few years ago, and the next decade or so promises to be just as exciting.

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