Clinical Applications of fMRI and DTI.

Andrei I. Holodny, MD

Director of the Functional MRI Laboratory, Associate Attending Neuroradiologist, Department of Radiology, Memorial Sloan-Kettering Cancer Center,
Associate Professor of Radiology, Weill Medical College of Cornell University
1275 York Avenue, New York, NY 10021 USA

Introduction:

Functional MRI (fMRI) and diffusion tensor imaging (DTI) including diffusion tractography have allowed scientists to make great strides in understanding how the brain functions. However, these techniques have also have made possible advances in the clinical arena, which will be the focus of this presentation. We will address current and emerging applications of fMRI and DTI in the diagnosis and treatment of diseases, while focusing on brain tumors. We will also address some of the peculiarities in fMRI and DTI, including paradigm optimization, methods of data analysis and image interpretation of patients with brain pathology including those with cognitive and neurological deficits.

Brain tumors:

Pre-operative localization of eloquent cortices adjacent to brain tumors is probably the most common clinical application of fMRI and DTI. The goal of brain tumor surgery is to maximize tumor resection while preserving important brain function. Traditionally, the eloquent cortices, such as the motor cortex, have been identified intraoperatively by physiological methods such as direct cortical stimulation or somatosensory evoked potentials. This method remains the gold standard for defining the location of eloquent cortices. Performing pre-operative fMRI, however, presents a number of distinct advantages.

First, pre-operative fMRI allows the neurosurgeon to make the decision of whether to attempt a resection, a stereotactic biopsy or not to operate at all. Second, a pre-operative fMRI may influence the trajectory that a surgeon will take in approaching the tumor. Third, fMRI can identify the localization of sulcal activity otherwise not accessible using direct cortical stimulation. Fourth, pre-operative fMRI can also shorten the operation and the time under anesthesia. Fifth, pre-operative localization by fMRI of eloquent cortices can guide the intra-operative cortical stimulation instead of trying to map the eloquent cortices de novo [1].

Patient selection and preparation:

Most fMRI studies in the literature are performed on young, healthy, motivated volunteers. fMRI in the clinical setting is markedly different. Performing fMRI studies on patients with neurological or neurosurgical disorders, which could impede their performance, deserves special attention. The basic outline for performing an fMRI study to guide a neurosurgical resection is as follows: 1) acquisition of the functional MRI data; including paradigm selection and patient preparation 2) acquisition of high resolution anatomical data; 3) analysis of the fMRI data; 4) co-registration of the functional MRI data to the high-resolution anatomical data; 5) downloading of the co-registered data onto the neurosurgical navigational computer.

Optimizing the fMRI study begins well in advance of the fMRI scan itself. First, it is imperative to review the patient's scan to determine the location of the tumor, and the parts of the brain involved. This will dictate the type of paradigms that will be performed during the fMRI study. Most pre-operative fMRI paradigms involve motor, language and occasionally memory and other cortical functions. Generally, neurosurgeons will sacrifice other areas (including auditory, gustatory, olfactory and even those leading to visual field defects) to maximize tumor resection. As a result, these are not commonly mapped pre-surgically.

One must assess the clinical status of the patient and determine if there is a reasonable chance that the patient will be able to perform the planned paradigms, and also make sure that there are no prohibitive factors like claustrophobia. The paradigm to be administered must be practiced by the patient prior to being placed in the magnet. The timing of the administration of the paradigm must also be explained and practiced with the patient. In addition, the tester must make certain that the patient can actually perform the paradigm and if this is not the case, the paradigm must be modified.

An important job for the administrator of the paradigms is to make sure that the patient is actually performing the required activity. For example, if the patient is asked to perform finger tapping, s/he must be watched to make sure that the fingers are actually tapping. Also, the tester must make sure that the patient is not moving excessively. This occasionally becomes an issue, especially with neurologically impaired patients. The patient may have difficulty understanding the instructions (even if they are simple), following these instructions, or the patient may simply forget or become tired. If the patient does not follow the instructions (for example, taps his/her finger and rests at the wrong time) the fMRI results will be meaningless.

In basic science studies, the majority of fMRI language paradigms are covert (where the patient is responding silently). Not having to actually verbalize spoken speech decreases motion artefacts. The problem with silent speech paradigms is that they may not accurately represent the whole of the patient's speech network. In addition, it is difficult to assess if the patient is actually performing the paradigm. This is especially true in patients with neurological or cognitive deficits. Overt responses allow the experimenter to monitor the patient's responses. Hence, both overt and covert paradigms have their respective advantages and disadvantages and it is often up to the person administering the paradigms to decide which is best for the situation at hand.

Neurosurgical navigation systems:

An advance in the treatment of patients with brain tumors was the ability to co-register functional images onto the anatomical images in the neurosurgical navigational system. This was first introduced by Maldjian [2]. The neurosurgeon can visualize the relationship of the tumor to the adjacent eloquent cortices, which aids both in the planning of the operation and in the actual resection [3].

In practice, many neurosurgeons still revert to the traditional method of identifying the location of eloquent cortices by direct cortical stimulation. However, with the introduction of fMRI into the neurosurgical navigational system, the neurosurgeon only has to confirm the location of an eloquent cortex that is defined by the fMRI. Also, when one test serves to confirm the findings of another, one can feel that much more confident that the results are accurate and that the patient will not suffer neurological consequences following the resection.

Interpretation of the fMRI scan:

As with any imaging technique, one must learn how to interpret the fMRI images correctly, while understanding the strong points of the technique as well as the limitations. There are a number of vagaries and pitfalls that make interpretation of patients with neurological disorders different from research fMRI in healthy normal adults.

Susceptibility Effects including Prior Surgery:

Susceptibility artifacts become a more pressing issue in patients who have undergone prior neurosurgery. The presence of metallic plates to secure skull flaps, metallic staples to close surgical incisions, hemorrhage from surgery or from the tumor, and residual metal from the skull drill (32) can lead to an increase in the susceptibility artifact, which, in turn, can lead to a decrease in the accuracy of BOLD fMRI. The presence of these artifacts can affect BOLD signal acquisition and thus the accuracy of fMRI. Therefore, it is imperative to at least perform a visual inspection of the T2*-weighted images to exclude prominent signal dropout from the susceptibility artifact [4].

Effect of the tumor vasculature on the BOLD signal:

It is known that there is a loss of neurovascular coupling in malignant gliomas due to the presence of abnormal tumor neovascualture. In angiographic and MR studies, the vasculature of gliomas revealed an abnormal response to various physiological and pharmacological challenges (34-36). BOLD fMRI is based on the premise that increased neural activity is inherently linked both temporally and spatially to an increase in blood flow and resultant changes in deoxyhemoglobin concentration (37). If, however, the brain's ability to autoregulate the flow of blood is lost in brain tissue that is still functioning, then this area may not respond to increased neural activity by a corresponding increase in blood flow. Consequently, the area in question may not show a statistically significant change on BOLD fMRI. This may preclude an increase in blood flow in the expected area of activation that normally occurs secondary to motor activity. A lack of increased blood flow to the expected area of activation could limit the ability of BOLD fMRI to detect activation [5,6].

However, notwithstanding this effect, we would like to stress that in the study where we reported this finding, the motor cortex was correctly identified in all 64 patients. In this study, the fMRI data was confirmed in all cases by intra-operative cortical mapping. Therefore, even though there may be some loss of sensitivity in fMRI due to the presence of abnormal vasculature, which may lead to a loss of accuracy on a capillary level, fMRI was successful in its main objective – identification of the motor strip.

Cortical reorganization:

Cortical reorganization can be defined as follows: as a disease process destroys part of the brain, rendering it incapable of performing its function, another part of the brain takes over that function. There are a number of important questions currently being asked regarding fMRI of cortical reorganization: Is there reorganization of the cortical function due to the growth of a brain tumor or other brain lesions in adults? When and under what conditions does it occur? Can this be detected by fMRI? This concept is clearly important in neurosurgical planning.

Neuroimaging studies demonstrate altered cortical activation patterns that suggest cortical reorganization in areas that deal with motor function in patients suffering from stroke [7], arteriovenous malformations (AVM) [8], and other lesions. Cortical reorganization of motor function could be shown by a decrease in activity in the lesioned hemisphere, and increase in activity in the non-lesioned hemisphere or some combination of these effects. Reorganization has been shown to occur across hemispheres, where the ipsilateral primary motor area for example, as well as non-primary motor areas, is recruited; as well as intra-hemispheric reorganization, where increased functional activity is observed in the contralateral primary motor area or adjacent cortices. The magnitude and anatomical location of activation depends on many factors, such as lesion size and location, as well as extent of therapy after the incident. It is imperative that these factors are considered with more detail when analyzing the fMRI results on an individual patient basis as the details of cortical plasticity in adults with brain lesions are yet unknown.

Language function has traditionally been mapped to two discrete loci: Broca's area, which controls the expressive aspects of language, and Wernicke's area, which is largely responsible for comprehension. The former is located in the left inferior frontal lobe anterior to the Rolandic fissure, and the latter is located in the left posterior temporal lobe, although the exact location of these functional areas is somewhat variable. Our group described two cases where one of the dominant language areas was translocated to the contralateral side of the tumor. In this setting, translocation is defined as the reorganization of most cortical function to the homologous or near-homologous regions in the contralateral hemisphere.

In the first case [9] the growth of the brain tumor in the left inferior frontal lobe led the transfer of the functional Broca's area to the contralateral side. The other case [10] showed the translocation of Wernicke's area in an adult due to the presence of an anaplastic astrocytoma. Both cases were documented by fMRI, and in the latter, direct cortical stimulation and pre- and postoperative neuropsychological testing were also conducted. The mechanism by which such transfer occurs is unknown. Because disease can alter the map of language function in an unexpected fashion, fMRI has the potential to reveal cortical reorganization that could affect the neurosurgeon's decision to offer surgery.

These cases can serve to emphasize another important issue regarding the preoperative assessment of eloquent cortices adjacent to brain tumors. Surgical resection is the mainstay of treatment of primary brain tumors. Assumptions regarding language dominance that are based solely on handedness may be misleading, at least in part. This may result in an unnecessarily conservative treatment approach for certain patients with brain tumors in whom surgery is, in fact, safe and clinically desirable. These occurrences show that fMRI should routinely be done preoperatively in patients with lesions in the language cortex, particularly when brain tumors are deemed inoperable because of their proximity to essential language centers. Preoperative fMRI can identify unexpected language organization as a result of tumor growth, affording surgery to patients who may otherwise be deemed inoperable.

Diffusion tractography

It would not be an exaggeration to aver that diffusion tractography has revolutionized the study of white matter tracts in the living human brain. Tractography has made it possible to study basic human anatomy on a new fundamental level. This technique has had great impact on more practical issues such as intraoperative guidance of the resection of brain tumors adjacent to crucial white matter tracts [11]. A number of recent publications have demonstrated remarkable images of specific white matter tracts in normal subjects using diffusion tractography.

It can be argued that correct pre-operative identification of white matter tracts is perhaps even more important than the identification of eloquent cortices, such as the motor cortex. First, direct intra-operative white matter stimulation is much less reliable than cortical stimulation. Second, the precentral gyrus (the location of the motor cortex) can usually be identified by the operating neurosurgeon by visual inspection. On the other hand, it is essentially impossible to identify separate white matter tracts, such as the cortico-spinal tract (CST - the main motor tract) or the thalomo-cortical tract (the main sensory tract) by visual inspection as they traverse the corona radiata.

Inadvertent transection of important white matter tracts can lead to devastating neurological consequences. For example, transsection of the CST leads to paralysis. Therefore, in order to improve the surgical treatment of patients with neurological malignancies, it is imperative to develop a method which could accurately depict the relationship of the CST to a tumor both pre-operatively and intra-operatively. Such a method would improve neurosurgical planning as well as the actual resection.

Nevertheless, important questions remain including validation of diffusion tractography by other methods. This question becomes most acute when the diffusion tractography results are unexpected or contradict previously held beliefs.

A number of technical challenges exist in DTI such as “crossing” and “kissing” fibers. Tracking of essential white matter tracts through pathology, including brain tumors raises a number of specific issues. Fractional anisotropy (FA) maps do demonstrate that there is a decrease in the diffusion anisotropy as one enters the tumor from normal white matter tracts. This is an expected finding when one considers the microscopic structure of the changes in white matter tracts with the infiltration of a tumor. The decrease in diffusion anisotropy is due to a number of factors that contribute to a loss in the orderliness and directionality of the axons. First, free water (edema) and tumor cells infiltrate the space between the axons. This leads to less axons per voxel and consequently less myelin sheaths and cell membranes that restrict water diffusion in a particular direction. Second, focal areas of necrosis are present in tumors. In these areas, there is destruction of the cytoarchitecture and drop in the FA to the point where it approaches zero. On the thresholded FA images the areas involved by the tumor demonstrate a drop off in signal indicating that the FA has dropped below the threshold. This factor makes it difficult to trace specific white matter tracts, which still may be functioning, through tumors [12,13].

Conclusion:

In conclusion, it is clear that fMRI is an untapped resource for our patients and their physicians. It is non-invasive and can be implemented on most existing MRI scanners. With training in anatomical, technical, and statistical considerations, fMRI can be mastered by most clinicians. It can define eloquent language, motor and memory areas in some cases negating the need for invasive intraoperative testing and is a great asset to the operating neurosurgeon in terms of planning and guiding operations. We believe that as more and more professionals are trained in functional brain mapping, fMRI has the potential to contribute to great strides in the understanding of the human brain and the treatment of our patients.

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