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Original article

Perioperative functional neuroimaging of gliomas in eloquent brain areas

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ABSTRACT

Surgical resection of gliomas involving eloquent brain areas must be maximal in order to improve patients' survival, and safe to prevent postoperative impairments. Therefore, the precise spatial relationship between the lesion and eloquent brain areas needs to be established. Functional magnetic resonance imaging and diffusion tensor imaging are robust methods with increasing indications in neurosurgery for past decade. The aim of this review article is not only to pinpoint the major limitations of these methods in order to avoid erroneous conclusions, but also to detail practical aspects associated with the main paradigms routinely used in functional magnetic resonance imaging, and to discuss recent validation of functional magnetic resonance imaging and diffusion tensor imaging results with direct electrical stimulation during awake surgery.

1. Introduction

Surgical resection of infiltrative supratentorial gliomas in adults involving eloquent brain areas must be maximal to improve patients' survival, and safe to prevent postoperative impairments [1,2]. An accurate cortical and subcortical functional mapping is therefore needed intraoperatively to guide tumor resection while sparing essential eloquent areas. In neuro-oncology, direct electrical stimulation (DES) during awake surgery remains the gold standard to achieve this goal, with increased indications for surgical resection within eloquent areas, less postoperative morbidity and maximized extent of glioma resection [3]. Meanwhile, magnetic resonance imaging (MRI), which tremendously improved our knowledge of functional networks in healthy subjects, recently established itself as the most popular and accessible neuroimaging technique for preoperative planning of patients with gliomas [4]. This non-invasive technique provides insights for both cortical functional mapping, through blood oxygen level dependent (BOLD) functional MRI (fMRI), and subcortical identification of neural networks, using diffusion tensor imaging (DTI). However, its reliability depends on the function under study: while primary cortical areas and pyramidal tracts characterization is fully consistent with DES, the identification of higher-level functions, such as a precise localization of language or memory areas and networks, seems to be scarcely characterized.

The aim of the present article is to explore clinical applications of fMRI and DTI in infiltrative glioma surgery in adults with a description of available methods in clinical routine practice as well as their main limitations. Based on recent validation studies and on the experience of our own neuroimaging and neurosurgery center, this article aims to highlight practical aspects associated with fMRI and DTI, and the validation of these techniques with DES. Several important limitations that justify cautious interpretation of functional neuroimaging will also be reviewed.

2. Methods for clinical presurgical functional neuroimaging

There are numerous advantages of functional neuroimaging using MRI: non-invasive, no injection of contrast media, high spatial resolution (about 1 mm for whole brain coverage) compared

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to positron emission tomography (PET), ease to set up in a routine MR unit. For these reasons, MRI has become the most popular technique in the past decades and has superseded other methods such as (PET). Advantages also include the ability to explore, during the same procedure, both cortical response to a cognitive stimulus and subcortical neural tracts.

2.1. Functional MRI

The BOLD contrast is the most frequently employed acquisition method to evaluate the hemodynamic response of brain areas to a cognitive task. It is thus an indirect estimation of the neural activity, which may result in an important bias in the interpretation of the images. This contrast is modified by the oxy/desoxy-hemoglobin concentration ratio in a sample of brain tissue a voxel in response to a modification of their activation state. The imaging technique employed to explore the whole brain with highest susceptibility to the different states of oxygenation of the blood is echo planar gradient echo imaging. Its spatial resolution (about 1–2 mm for whole brain coverage) and temporal resolution (less than 3 seconds with most recent MRIs) are relatively low. For clinical application, the most robust technique consists of a task-based fMRI, for which the patient is asked to alternate at least two different cognitive conditions, which allegedly differ only in the target function (i.e. action vs. rest; reading words vs reading random series of letters, etc.). The presentation of the stimuli may correspond to two different designs: block and/or event-related designs. The block-designed paradigms are generally preferable in glioma presurgical mapping because they are easy to process and statistically more robust than event-related paradigms. However, time resolution is restrained as the hemodynamic response function (HRF) is averaged during each block period (about 15 to 30 seconds, depending on the cognitive task).

Recent imaging techniques such as multiband echo planar imaging have increased temporal and spatial resolution by allowing the acquisition of multiple slices simultaneously to shorten acquisition time [5].

2.2. Diffusion tensor imaging

DTI provides a structural analysis of subcortical neural networks and thus does not require the participation of the patient, as opposed to BOLD fMRI. Its principle relies on the measurement of the diffusivity of water molecules in the three dimensions. In cerebrospinal fluid for example, water molecules move randomly without restriction in any direction (isotropy). In white matter however, their diffusion is facilitated along the main orientation of axonal bundles and constrained along the cross-sectional plane (anisotropy). The fractional anisotropy (FA) can thus be calculated in each voxel, which captures the coherence of white matter tracts orientation and thus can be a marker of axonal integrity, beyond signal anomalies visible on conventional sequences. The result can be displayed with two kinds of parametric maps: FA maps that reflect the average directional constraint of molecules in a given voxel; and the color map displaying the principle orientation of bundles in each voxel (red = left-right; blue = dorso-ventral; green = anteroposterior). Beside these parametric maps, DTI can also provide a tridimensional visual representation of the main fiber tracts and connections with tractography. By analyzing the directional diffusion constraint in adjacent pixels, the path of the major white matter tracts can be inferred. There are numerous algorithms for aligning voxels with the same orientation. A representation of the major tracts in three dimensions allows subdividing the white matter into functionally relevant regions. A major limitation of DTI is that it represents only the main direction of diffusion in each voxel and ignores crossing fibers. Newer techniques such as diffusion imaging at high angular resolution (HARDI) and diffusion spectrum imaging (DSI) used to partially overcome this limit. Due to the robustness of the DSI, finer fiber bundles have also been identified [6]. Another limitation is that DTI identifies white matter fiber tracts without knowledge of the functions they carry or of their integrity. In glioma presurgical imaging workup, this sequence has a double aim: to qualify the alteration of connectivity by a local decrease of the underlying anisotropy inside and beyond the limits of the tumor, and to illustrate the relationship between a glioma and the streamlines of an existing fiber tract. These streamlines can be seeded using two or more regions of interest (ROI) positioned on the anatomical path of the streamline (for example, the pyramidal tract can be delineated using a ROI in the posterior limb of the inner capsule and in the medulla oblongata). The risk of false-negative streamlines will decrease with the number of ROI.

In conclusion, fMRI and DTI helps the neurosurgeon to identify the theoretical cortical and subcortical functional organization in the vicinity of the infiltrative gliomas but do not replace the intraoperative functional mapping using DES.

3. What is not possible – main limitations in functional neuroimaging

Functional MRI and DTI are reliable methods. However, before interpreting the results, the main limitations of these techniques have to be known in order to avoid erroneous conclusions, which could lead to inadequate decision or treatment. Some of these limitations are inherent to the physical principle of MRI or to the technique itself and therefore unavoidable. Other limitations can be corrected or adjusted by algorithms. The neuroradiologist and the neurosurgeon must be aware of the inherent limitations to interpret the results.

3.1. Magnetic susceptibility artifacts

DTI and fMRI use echo planar sequences, which are prone to magnetic susceptibility artifacts, associated with signal loss and geometric distortions [7]. They are often found at air/tissue interfaces and around hemosiderin deposit, and this can be problematic for gliomas located in medial and basal parts of the frontal and temporal lobes, and in hemorrhagic lesions [8]. Such artifacts can affect fMRI responses and create a false-negative in the immediate vicinity of any lesion with hemosiderin deposit, even of a small quantity. This issue especially concerns not only cavernous angiomas and other vascular lesions, but also hemorrhagic gliomas, and also postoperative modifications [9]. This is all the more confounding that this artifact is, in most cases, absent from morphological sequences such as FLAIR and T1-weighted sequences. Raw images should thus always be checked before registration on structural imaging.

3.2. Gliomas and neurovascular uncoupling

The loss of neurovascular coupling reduces the fMRI response, which theoretically increases the occurrence of false-negative answers. As mentioned above, the BOLD is an indirect reflect of the electrical neuronal activity and thus might be disturbed in the cortex surrounding highly vascular tumors such as malignant gliomas [10,11]. Indeed, risk factors associated with uncoupling effect include tumor grade of malignancy [12] and modified brain perfusion in the vicinity of the glioma [13]. The neoangiogenesis modifies the autoregulation and vasoactivity, resulting in the absence of activation, which could be falsely interpreted as brain plasticity. Methods that account for HRF variability may improve fMRI reliability [14,15].