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Functional magnetic resonance imaging for neurosurgical planning in neurooncology

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Abstract Functional magnetic resonance imaging (fMRI) is a non-invasive technique that is widely available and can be used to determine the spatial relationships between tumor tissue and eloquent brain areas. Within certain limits, this functional information can be applied in the field of neurosurgery as a pre-operative mapping tool to minimize damage to eloquent brain areas. In this article, we review the literature on the use of fMRI for neurosurgical planning. The issues addressed are: (1) stimulation paradigms, (2) the influence of tumors on the blood oxygenation level-dependent (BOLD) signal, (3) post-processing the fMRI time course, (4) integration of fMRI results into neuronavigation systems, (5) the accuracy of fMRI and (6) fMRI compared to intra-operative mapping (IOM).

Keywords Functional magnetic resonance imaging · Computer-assisted image processing · Neurosurgery · Neuronavigation · Brain neoplasm

Introduction

In neurooncology, one of the principal surgical goals is to minimize neurological deficits and to maximize resection of the lesion. In order to achieve this goal, eloquent brain areas must be identified. This can be difficult for a number of reasons. First, it has been shown that even in the normal brain there is a considerable variability between function and anatomy [1]. Secondly, in case of undistorted anatomy, eloquent areas may be identified using specific sulcal landmarks. For instance, the hand-function can be located at the O-shaped structure of the pre-central gyrus, and language areas can also be located using such landmarks [2]. Mass effects associated with brain tumors can distort these common relations, making anatomy-based localization of functional areas impossible [3]. In the third place, in response to pathology, functional areas may be relocated to other areas in the brain, thereby altering the normal relationships between function and anatomy [4, 5].

The golden standard for identifying eloquent areas is intra-operative mapping (IOM), for which cortical stimulation or sensory-evoked potential monitoring can be used. However, these techniques are difficult and invasive, awake procedures place great demands on the patient, IOM does not assist in pre-operative planning, and IOM often requires a craniotomy larger than necessary with respect to the tumor to be removed.

Functional magnetic resonance imaging (fMRI) is a non-invasive and widely available technique for mapping brain functions. It is based upon the blood oxygenation level-dependent (BOLD) effect [6–8]. The current understanding of this effect is that functional increases of oxygen consumption by neuronal cells induce concomitant relative increases of the local perfusion that exceed the relative oxygen consumption changes [9]. The decreased concentration of deoxygenated hemoglobin induces a higher signal on T2*-weighted images [10].

Within certain limits, functional information derived from fMRI can be applied in the field of neurosurgery for preoperative planning and for intraoperative navigation. An extensive number of papers have been published on this subject. Several studies demonstrated that fMRI data can be used for patient management at three levels: (1) assessment of the feasibility of surgical resection, (2) surgical planning and (3) selection of patients for invasive IOM [11–14]. In this article, we review the literature on the use of fMRI for neurosurgical planning.

Literature review

Stimulation paradigms

Many stimulation paradigms have been used for preoperative mapping, the most commonly mapped functions being sensorimotor functions, language generation (located in Broca's area), language reception (located in Wernicke's area) and vision.

Sensorimotor functions have been mapped by having the patient perform motor tasks such as finger tapping [4, 11, 15–30], hand clenching [3, 5, 12, 14, 31–37], elbow and shoulder movement [30], tongue movement [30, 38, 39], lip movement [3, 30, 38, 40], foot movement [3, 13, 26, 41] and toe movement [3, 27, 39–41]. These tasks may be self paced or cue paced. Pure sensory functions have been mapped by rubbing, stroking or brushing the body part under investigation [12–14, 21, 25, 33, 37, 42].

Speech production has been mapped by word generation tasks. Word generation tasks can be guided by different visual or auditory cues, and these cues may include letters, pictures or words. Most of the time, the patients are instructed to perform covert word generation, as words spoken out loud induce too much head-motion. These word generation tasks include picture-naming tasks [21, 43, 44], verbal fluency tasks [18, 26, 38, 45, 46] and verb generation tasks [13, 43, 44, 47]. Other word generation tasks are recital tasks, for example, naming the days of the week or counting [12, 38, 43].

Wernicke's area has been activated by tasks that require language comprehension. Semantic or grammatical judgment tasks are tasks in which the patient has to decide to which category a word belongs [4, 16]. The words may be presented visually or auditorily. Another approach is having the patient listen to spoken language or read written language [13, 21, 27, 45, 48].

Vision has been mapped by paradigms showing visual stimuli, such as light-emitting diodes [11, 27, 49], flashing light [12], photostimulators [50] or flickering checkerboards [21, 51]. It has even been demonstrated that it is possible to identify the borders of the visual areas V1, V2, V3/VP, V3A, V4 and V5/MT [52, 53].

Activation paradigms are usually selected on the basis of lesion location, and both the neurosurgeon and neuroradiologist can be involved in this decision. Another approach is to map a standard set of functions, for example, Hirsch et al. developed and tested a comprehensive task battery, including motor, visual and language tasks, and this task battery was applied for all patients [21].

The supplementary motor area (SMA) is considered eloquent by some authors and not eloquent by others. Although damage to the SMA can lead to severe motor deficits and language deficits, these deficits resolve completely in the majority of patients [26, 36, 46, 55, 56]. Mapping the SMA can be performed both with motor tasks and language generation tasks.

Besides high specificity, fMRI paradigms should have high sensitivity. For healthy volunteers, sensitivity does not seem to be a problem, but for patients it can be. For example, Hirsch et al. found that the mapping of functions in healthy volunteers was more successful than in patients. According to the authors, this could be attributed to tumor-related neurological deficits and to motion [21]. In general, the presence of brain lesions can severely reduce the sensitivity of fMRI, see "The influence of tumors on the BOLD signal." As a partial solution, Hirsch et al. suggested that the combination of multiple language tasks and multiple repetitions of tasks increases sensitivity [21]. Rutten et al. arrived at similar conclusions regarding fMRI for language mapping: after combination multiple language tasks to increase specificity, sensitivity remained sufficiently high. Because of this high sensitivity, fMRI can be used to speed up IOM by reducing the number of locations that need to be investigated [45]. Roux et al., however, came to opposite conclusions: sensitivity of language mapping was too low to be useful, but the specificity was very high [44]. These inverse findings can have two possible reasons. First, it might be an issue of statistical thresholds, and second, it might be due to different patient populations: Roux et al. investigated tumor patients, while Rutten et al. investigated patients with temporal lobe epilepsy. As is discussed in the next section, tumors can have the effect of reducing the sensitivity of fMRI.

The influence of tumors on the BOLD signal

A first problematic feature of certain tumors is the inclusion of active brain tissue. Activation has been demonstrated within tumors or at the radiological tumor boundary [16, 57, 58]. Another problem is the possibility of increased susceptibility artifacts in arteriovenous malformations, in cystic tumors or with intra-cranial bleeding. Susceptibility artifacts can be problematic with echo planar imaging (EPI) sequences, which are used to acquire the fMRI time series. Furthermore, if patients previously underwent brain surgery, there is the possibility of resid-

ual metal from a skull drill, which may induce severe image artifacts.

The BOLD signal stems from a local change in cerebral blood volume, cerebral blood perfusion and blood oxygenation. Changes in physiological conditions can influence the coupling between neuronal activation and the hemodynamic response; alterations in the BOLD response have been described with hypercapnia, hypoxia, hypertension and anemia [59, 60]. The BOLD signal can also be influenced by various pharmacological agents. There are indications that antihistaminics reduce the BOLD response, caffeine is a known booster of the BOLD response [61], and cocaine and levodopa have also been described as modifiers of the BOLD response [62, 63]. It is not unlikely that many more pharmacological agents influence the BOLD response, and patients harboring brain tumors may receive such medication.

Schreiber et al. found that fMRI activation is reduced near glial tumors, but usually is not affected by non-glial tumors [64]. They suggested that this phenomenon might be explained by the fact that glial tumors grow more infiltratively, altering the cellular architecture, and that non-glial tumors show more delineation from normal tissue, leaving the cellular architecture intact. Holodny et al. found that the amount of activated voxels was 35% less at the tumor site compared to the contralateral site. Two possible reasons given by the authors are a loss of autoregulation and a changed venous response because of compression of the tumor on neighboring vasculature [22]. In paretic patients, Krings et al. found a smaller BOLD response in the primary motor area and a larger BOLD response in secondary motor areas. The authors hypothesized that this could be due to loss of active neurons and/or tumor-mediated changes in local hemodynamics [65]. Pujol et al. described that the main clinical factor associated with poor functional results was the presence of moderate to severe paresis in the involved hand [32]. Roux et al. described the possibility that inactivated tissue becomes active postoperatively when a mass effect associated with the tumor is removed and normal perfusion is restored [35]. Normal cortical function may have been altered, the normal hemodynamic response may have been altered, or both. It is important to realize that a lack of functional perfusion changes is not necessarily due to a lack of neuronal activity [66]. Ulmer et al. described this phenomenon as tumor-induced neurovascular uncoupling [30]. Carpentier et al. classified these various patterns of activation changes in response to pathology: (1) shifts due to mass effects, (2) reduced activation due to interfacing of the tumors with the activation site, (3) flipsilateral plasticity and (4) contralateral plasticity [5].

In summary, accumulating evidence seems to indicate that the BOLD response in the vicinity of certain tumors does not reflect the neuronal signal as accurately as it does in healthy brain tissue [22, 30, 50, 64, 67].

Post-processing the functional MRI time course

The BOLD signal change is relatively small, and therefore reliable detection is challenging. A number of post-processing steps are required to find significantly activated voxels. These steps often include motion correction, smoothing and the application of a statistical model to find voxels of which the signal behavior matches the task executed by the patient.

Motion correction is required to remove artifactual signal change due to motion, especially as motion can be correlated with the stimulation paradigm. In a publication concerning the quality of motion correction, it was shown that a tool called mcflirt offers the best possible motion correction compared to two other tools [68].

Smoothing (blurring the image) may serve a number of purposes: it can be used to increase the contrast-to-noise ratio, smoothing must be used when certain statistical models are applied, and smoothing is required when the fMRI results of multiple subjects are to be averaged (spatial normalization). In preoperative mapping, however, most authors do not apply smoothing, for an obvious reason: it decreases spatial accuracy. From the articles listed in Table 1, 10 out of 44 applied smoothing.

Functional maps are generated through a voxel-by-voxel statistical analysis of the functional MR time series. However, statistical procedures for preoperative mapping have not been standardized. First, there is no consensus on what statistical model would be best in the field of preoperative mapping. Table 1 shows the statistical models used in various articles and demonstrates that no single model is universally accepted. Secondly, there is also no consensus on how to estimate significance levels. Some authors apply a Bonferroni correction [16, 28, 34, 35, 41, 45], and some put minimal thresholds on cluster sizes [19, 32, 40, 44, 69]. Others perform permutation testing to estimate significance levels [14, 23], and two authors applied the methods developed by Friston et al. [70, 71] implemented in SPM [13, 46], but the majority of the authors did not perform a correction on the individual voxel statistics. In the third place, the choice of significance thresholds remains arbitrary. Roux et al. showed that high thresholds give the best match with other mapping modalities [41], but high thresholds levels may result in reduced sensitivity. Although most authors apply fixed thresholds, finding good threshold levels has proven to be difficult [41, 45]. Because so many different statistical models have been used, it is not possible to compare the threshold levels between the different papers.

Integration of functional MRI results in neuronavigation systems

Frameless stereotactic surgery, also known as neuronavigation, is widely applied in brain surgery and has be-

Table 1 Summary of the methods as described by several papers regarding functional MRI for neurosurgery. *N*, number of patients; *S*, amount of smoothing (in mm); +, smoothing was applied, amount was not reported. GLM, general linear modal. The column "Correction" denotes which modifications were made to the raw pixel-wise statistical tests to correct for multiple comparisons; "Cluster size" means that a minimal threshold on the cluster size was used; "Spatial" means that a spatial correction as implemented in SPM was used, FPR means that permutation testing was used to estimate the false-positive detection rate. The "Threshold" column denotes whether the applied statistical thresholds were fixed or variable. The column "Functional neuronavigation" reports whether the authors fused the fMRI results with the neuronavigation image set and how this fusion was achieved; a "+" means that the method for fusion was not reported in detail, mostly because proprietary software was used

First author	Year	*N*	*S* (mm)	Statistical model	Correction	Threshold	Functional neuronavigation
Jack CR [89]	1994	2	–	Substraction	–	Not applicable	–
Latchaw RE [11]	1995	3	–	Student's *t*-test	–	Fixed	–
Yousry TA [31]	1995	6	–	Mann-Whitney *U*-test	–	Unknown	–
Atlas SW [16]	1996	7	9	Cross-correlation	Bonferroni fixed	–	
Debus J [17]	1996	10	–	Student's *t*-test	–	Fixed	–
Maldjian JM [4]	1996	6	11	Cross-correlation	–	Fixed	–
Mueller WM [18]	1996	12	–	Cross-correlation	–	Fixed	–
Pujol J [19]	1996	4	–	Student's *t*-test	Clustersize	Fixed	–
Righini A [15]	1996	17	–	Student's *t*-test	–	Variable	–
Madjian JA [72]	1997	1	–	Cross-correlation	–	Fixed	Slice geometry
Stapleton SR [12]	1997	16	–	Student's *t*-test	–	Fixed	–
Yetkin FZ [38]	1997	28	–	Cross-correlation	–	Fixed	–
Dymarkowski S [13]	1998	40	8	GLM	Spatial	Fixed	–
Pujol J [32]	1998	50	–	Student's *t*-test	Cluster size	Fixed	–
Achten E [20]	1999	6	–	Student's *t*-test	–	Fixed	–
Fandino [42]	1999	11	15	Student's *t*-test	–	Fixed	–
Lee CC [14]	1999	46	–	Cross-correlation	FPR	Fixed	–
McDonald JD [73]	1999	2	–	*t*-test or correlation	–	Unknown	Landmarks
Nimsky C [33]	1999	7	–	Cross-correlation	–	Fixed	Contour fit
Roux FE [34]	1999	8	–	GLM	Bonferroni	Fixed	–
Hill DL [23]	2000	8	–	BAMM	FPR	Unknown	–
Hirsch J [21]	2000	125	4	Other	–	Fixed	–
Holodny AI [22]	2000	10	–	Cross-correlation	–	Fixed	Slice geometry
Lehericy S [40]	2000	60	–	Cross-correlation	Cluster size	Fixed	–
Lurito JT [48]	2000	3	+	Student's *t*-test	–	Fixed	–
Roux FE [35]	2000	5	–	GLM	Bonferroni	Variable	–
Schreiber A [64]	2000	21	6	Student's *t*-test	–	Fixed	–
Carpentier AC [5]	2001	44	–	Student's *t*-test	–	Fixed	–
Kober H [37]	2001	34	–	Cross-correlation	–	Fixed	–
Krainik A [36]	2001	12	–	Cross-correlation	Cluster size	Fixed	–
Krings T [3]	2001	103	–	Kolmogorov-Smirnov	–	Fixed	–
Krings T [74]	2001	50	–	Kolmogorov-Smirnov	–	Fixed	+
Lee YJ [50]	2001	7	–	Cross-correlation	–	Fixed	–
Roux FE [41]	2001	32	–	GLM	Bonferroni	Variable	+
Gumprecht H [47]	2002	27	–	Cross-correlation	–	Variable	Landmarks
Hoeller M [25]	2002	94	–	Kolmogorov-Smirnov	–	Fixed	–
Krings T [65]	2002	110	–	Kolmogorov-Smirnov	–	Fixed	–
Nelson L [26]	2002	12	+	Cross-correlation	–	Fixed	–
Rutten GJ [45]	2002	13	–	Z_t-map analysis	Bonferroni	Fixed	Intermediate scan + mutual information
Sabbah P [27]	2002	8	?	Student's *t*-test	?	Fixed	Contour fit (Chamfer matching)
Krainik A [46]	2003	12	5	GLM	Spatial	Fixed	–
Liu H [69]	2003	16	–	Cross-correlation	Cluster size	Unknown	–
Roux FE [44]	2003	14	–	GLM	Cluster size	Fixed	–
Wilkinson ID [28]	2003	19	4	Cross-correlation	Bonferroni	Fixed	Landmarks

come a standard procedure in most neurosurgical centers nowadays. It is based upon registration of the physical space of the operating room to the virtual space of an MR or CT image set. These image sets have typical resolutions of 1×1×1 mm^3. Printed fMRI activation maps are of limited use in frameless stereotactic neurosurgery. Therefore, the fMRI activation maps need to be matched and fused with high-resolution MR or CT images. The

integration of fMRI activation maps into neuronavigation is often referred to as "functional neuronavigation."

The matching can be achieved in a number of ways: (1) with the MR data sets for neuronavigation and fMRI acquired in the same MR session, the geometric relationship between these data sets can be used [22, 72], (2) landmark-based solutions can be applied [47, 73], (3) surface-based solutions are possible [27, 33], (4) mutual information can be used [45], and (5) unknown proprietary methods within neurosurgical equipment are available [41, 69, 74] (see Table 1).

In an article about the matching of medical images, Viergever et al. compared different matching techniques. Their conclusions were that landmark-based methods are subjective, inaccurate and time consuming; surface-based methods are not robust, and only mutual information, also known as voxel-based matching, should be used [75]. They did not investigate the method that exploits the geometric relationship between data sets from the same MR session. One author applied mutual information [45].

For DICOM conversion, Maldjian et al. have presented a solution based upon the free software of the Mallinckrodt Institute of Radiology DICOM Central Test Node (CTN, http://wuerlim.wustl.edu/DICOM/ctn.html) [76].

Factors influencing the accuracy of fMRI results

In order to achieve high accuracy, fMRI has to be reproducible. The issue of reproducibility has been extensively addressed, mainly in healthy volunteers [49, 51, 77–80]. The most important findings were that the amount of activated voxels could be reproduced to about 75%. Individual voxels reproduced to 35–60% depending on the MR scanner used [51].

Another factor influencing the accuracy is the rather large voxel size of the EPI images compared to the voxel sized used in neuronavigation. Scanning the EPI images with a larger matrix (smaller voxels) may seem to increase accuracy, but generally this is not the case. In the first place, smaller voxels lead to a lower signal-to-noise ratio (SNR), while the SNR is already quite low in BOLD imaging. Secondly, a larger matrix needs a longer EPI echo train, which increases image blurring, and thus reverses the effect of larger matrices [81].

A third factor reducing accuracy is geometric distortion of gradient echo EPI [41]. Several solutions have been proposed that require only a short extra scan to be performed, with the small disadvantage that they also require additional post-processing [82–84]. The extra scan maps the inhomogeneity of the magnetic field, and the post-processing reverses some of the geometric distortions arising from this field inhomogeneity.

Motion can reduce the accuracy of fMRI, and, more important, it can render it completely useless. Indeed, motion is the most important reason for unsuccessful fMRI runs [3, 25]. Unfortunately, patients tend to move their heads more than healthy subjects [23]. Lee et al. and Righini et al. had 30% of the fMRI examinations rendered useless because of motion [14, 15]. An important step in reducing motion is immobilizing the head by using appropriate devices, for instance bite bars, chin cups, bitemporal pushing cushions or vacuum pillows. Modern MR scanners may reduce the effects of motion by applying prospective motion correction during acquisition. Matching and fusing statistical parametric maps with an anatomical 3D-scan also influences accuracy, see "Integration of functional MRI results into neuronavigation systems."

Another important factor reducing the accuracy of fMRI is the fMRI contrast mechanism, i.e., the BOLD signal, which originates from hemodynamic changes, and only indirectly from changes in the activity of individual neurons [9]. The hemodynamic response includes a venous component, inducing uncertainty about the location of the activated neurons [85]. The spatial uncertainty arising from this draining-vein effect was estimated to be no larger than 4.2 mm for an activated region of 100 mm^2 [86].

After craniotomy, a certain amount of brainshift occurs, up to 20 mm according to Hartkens et al. [87]. This very important factor can severely reduce the registration of the brain tissue to the MR image set. Unfortunately, reliable prediction of brain shift remains impossible [88].

Comparing fMRI with the gold standard for mapping of eloquent brain areas

The gold standard for mapping eloquent areas is IOM. This can be performed in a number of ways, of which direct electrocortical stimulation, the use of subdural grids, and strips and sensory-evoked potential monitoring are the most common.

Several authors investigated the concordance between IOM and fMRI. Jack et al. qualitatively compared fMRI to IOM and found that the two procedures matched well, a finding that was reproduced in other studies [18, 19, 31, 32, 42, 48, 89].

Performing quantitative comparisons is, however, hindered by a number of problems. In the first place, craniotomy and debulking may induce deformation, which reduces image registration [23, 74]. Secondly, electrocortical stimulation is not very precise; although the extent of the stimulation is roughly 1.5 cm around the tip of the electrode, it has a substantial margin of error [48, 90]. In the third place, the extent of areas activated by fMRI depends on the statistical thresholds that were chosen. This extent directly influenced the distance between locations found with fMRI and those found with mapping procedures [24]. In the fourth place, the extent of

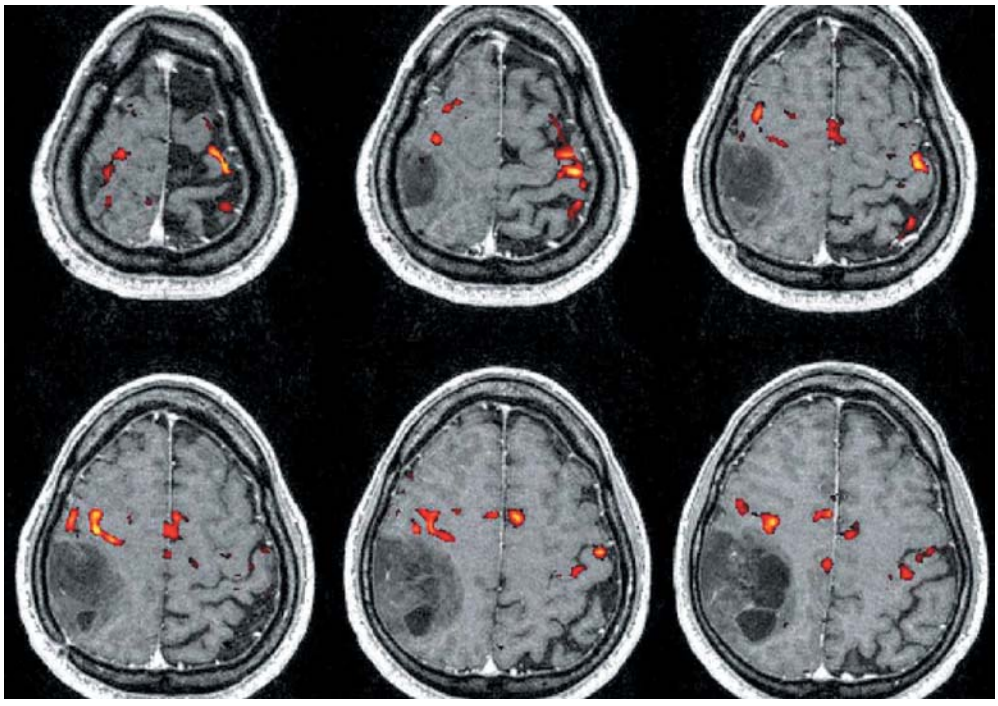

Fig. 1 fMRI maps of the bilateral hand function of a 47-year-old man with biopsy-proven right parietal protoplasmatic astrocytoma. Note anterior displacement of the left-hand functional activation compared to the normal right-hand functional activation in the left hemisphere. The supplementary motor area is also activated. Note also the close relationship between the area of activation and the tumor boundary, limiting the surgical resection

critical areas found with IOM may be influenced by the depth of the anesthesia [41]. And fifth, the paradigms applied for IOM and fMRI cannot be exactly the same because of different setups [48]. Finally, mapping principles for IOM and fMRI can be radically different. Functional MRI shows all brain areas involved in a task, while direct electro-cortical stimulation only points at brain tissue essential to the task.

Despite these problems, quantitative comparisons have been performed. Yetkin et al. found a distance between locations found with IOM and locations found with fMRI of less than 10 mm in 87% of the patients [38]. Lehericy et al. found 95% of the locations indicated by IOM to be within the area indicated by fMRI, the remaining 5% being within 15 mm [40]. Krings et al. found distances between IOM and fMRI of less than 1 cm in 69%, and less than 2 cm in the remaining 31% [74]. Roux et al. found the locations indicated by IOM to be within the area indicated by fMRI in 87% of the cases [41]. Nimsky found a distance of maximal 1.5 cm between fMRI and IOM [33].

Examples

Figures 1, 2, 3 show some examples of preoperative fMRI mapping performed at our institution. For images 1 and 2, image acquisition was performed on a 1.5-T MR scanner (Siemens Vision VB33, Siemens, Erlangen, Germany). The fMRI time series were acquired using gradient echo EPI with a voxel size of 2×2×6 mm^3. For image 3, image acquisition was performed on a 3.0-T MR scanner (Intera R10, Philips, Best, The Netherlands) using gradient echo EPI with a voxel size of 2.5×2.5×2.5 mm^3. For neuronavigation, a 3D T1-weighted image set with a voxel size of 1×1×1 mm^3 was acquired. From the fMRI time series, a statistical map was created using "FMRI Expert Analysis Tool" (feat, http://www.fmrib.ox.ac.uk/fsl/feat4/index.html). For matching and fusion of fMRI results and 3D-T1, the following steps were used. From both the EPI and the 3D-T1 image sets, "brain only" image sets were created with "Brain Extraction Tool" (BET) [91]. The matrix matching these "brain only" image sets was calculated with "FMRIB's Linear Image Registration Tool" (flirt, http://www.fmrib.ox.ac.uk/fsl/flirt/index.html [68]). The statistical map was resliced to the 3D-T1 image set by applying the matrix calculated in the previous step, and the resliced statistical map was fused with the 3D-T1 image set. The fused data set was sent to the surgiscope computer (LEKSELL ScopePlan version 2.15 with SurgiScope version 1.7.5, ISIS Robotics, Saint Martin d'Heres, France).

Summary and future developments

In summary, successful fMRI mapping can be obtained routinely in most patients with cerebral tumors. Knowledge of the limitations of fMRI, and in particular of fMRI in patients harboring a brain tumor, is essential both for the neuroradiologist and the neurosurgeon. It is possible to use the fMRI results intraoperatively if they

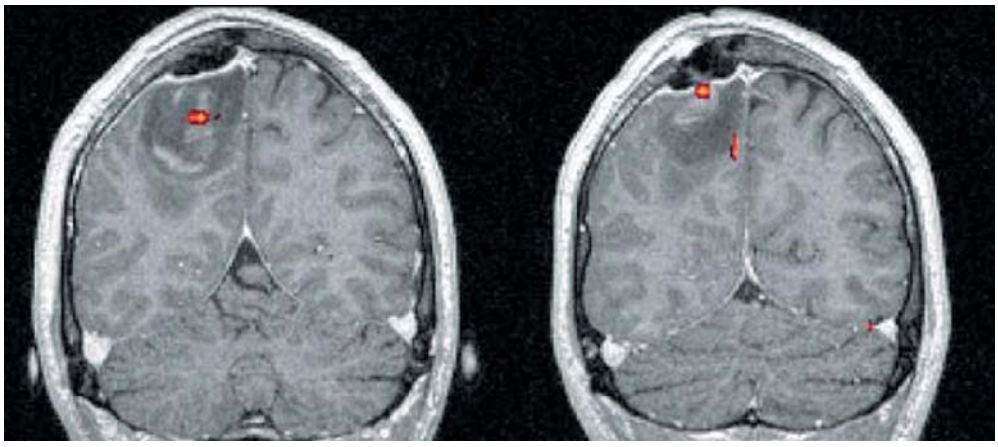

Fig. 2 fMRI maps of the left-foot motor function of a 30-year-old man with biopsy-proven right fronto-parietal anaplastic astrocytoma. One area of functional activation is located in the tumor, one area just outside the tumor. It is most likely that the medial region outside the tumor is the primary sensorimotor cortex, and the region in the tumor is in the vicinity of the intra-parietal sulcus. The distorted anatomy makes interpretation of this case difficult, which makes good knowledge of neuroanatomy even more essential for interpretation

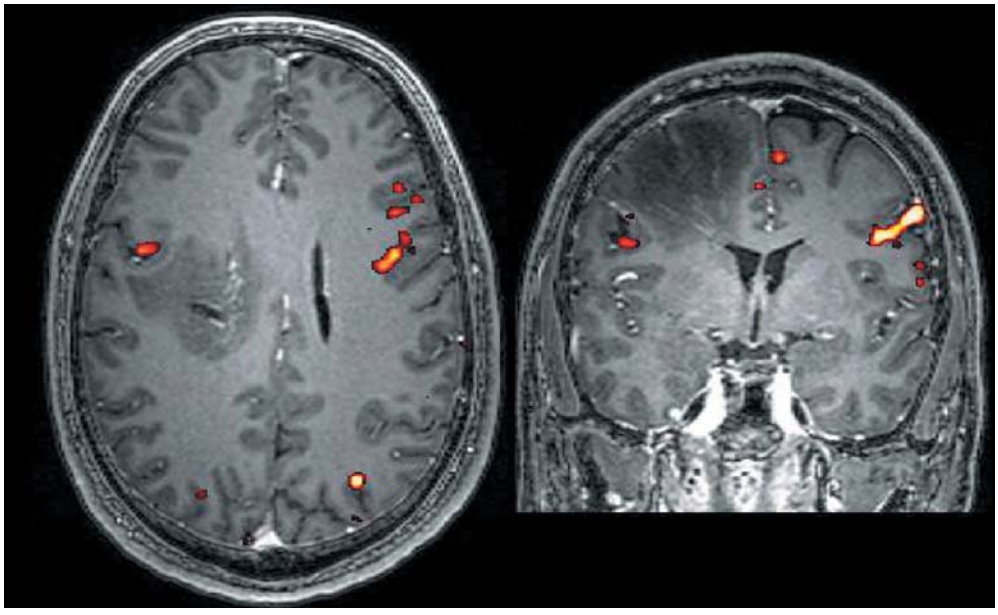

Fig. 3 fMRI maps of a 28-year-old man presenting with epileptic seizures. Conventional MR images (not shown) were consistent with a right-sided low-grade astrocytoma. Since the patient was left-handed, the location of Broca's area was assessed. The *axial* (left) and *coronal* (right) fMRI-maps show the combined results of a picture-naming task and a verb-generation task. Note a left hemisphere dominance for these motor language tasks

are integrated into a neuronavigation system, for which several approaches have been presented in the literature. Unfortunately, no randomized trials or outcome studies have been performed that definitively showed benefits to the patient of applying fMRI preoperatively.

Over the last few years, various manufacturers have started to offer 3.0-T MR scanners for clinical practice. The BOLD signal change is considerably larger on such MR scanners, which implies that the sensitivity of fMRI is increased; however, improved sensitivity, improved reproducibility and reduced uncertainty remain to be proven. One potential problem is the decreased magnetic field homogeneity on such systems, possibly resulting in larger geometric distortions.

The application of sensitivity encoding (SENSE), a technique that can speed up acquisition by applying the redundancy of information coming from multiple coil elements, has been shown to be very beneficial to fMRI. It decreases geometric inhomogeneity and blurring and can be used to increase either the spatial or temporal resolution [39, 92].

The effects of brain shift can be reduced considerably by using intraoperative imaging during the process of tumor resection using MR scanners positioned in the operating room [87, 88]. Such scanners would allow for intraoperative, post-craniotomy fMRI. However, to date only examples of pre-craniotomy fMRI performed on these scanners have been published [69]. Intraoperative imaging does allow for re-matching the functional neuronavigation data to the (updated) anatomical data [93, 94].

fMRI is sensitive to cortical changes, but provides limited information concerning the integrity of the white matter structures [95]. Since postoperative interruption

of these tracts can lead to major disruptions in neurological functions, the combination of fMRI and tractography based on diffusion tensor imaging may be beneficial for reducing postoperative deficits [95–98].

Finally, it is important to realize that fMRI-BOLD imaging is not the only preoperative mapping modality. There are other MRI techniques to measure brain activity, of which perfusion fMRI using arterial spin labeling seems to be the most promising [99]. Furthermore, there are other techniques to map brain activity, such as magnetoencephalography (MEG), positron emission tomographic imaging (PET), single photon emission computed tomographic imaging (SPECT) and transcranial magnetic stimulation (TMS). It has been shown that the addition of MEG to functional neuronavigation is beneficial to the patient [29], something that remains to be proven for functional MRI.

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