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The role of functional imaging in the tumor patient

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Summary

Functional imaging studies complement structural magnetic resonance imaging (MRI) in the assessment of patients with brain tumor–associated focal epilepsy. ^{11}C-Methionine (MET) and ^{18}F-fluoro-ethyl-L-tyrosine (FET) are amino acid analogues that highlight metabolically active areas in positron emission tomography (PET). Ictal single photon emission computed tomography (SPECT) can provide information about perilesional areas of seizure onset and early propagation. Functional MRI (fMRI) and diffusion tensor imaging (DTI) allow noninvasive identification of potentially eloquent motor, sensory, and language cortical areas and pathways with an accuracy of 10–15 mm compared to electrocortical stimulation (ECS). Repetitive navigated transcranial magnetic stimulation (TMS) allows even more precise noninvasive delineation of primary motor cortex. Information from functional imaging studies helps in the planning of brain tumor biopsies, resections, and the planning of intracranial video–electroencephalography (EEG) studies.

KEY WORDS: Tumoral epilepsy, Positron emission tomography, Ictal SPECT, Functional MRI, Navigated transcranial magnetic stimulation.

Patients with pharmacoresistant focal epilepsy in the setting of brain tumors are unique in that the morphology of the tumor, its expected behavior over time, and epilepsy-related morbidity need to be taken into account in the decision-making process. In this setting, functional imaging studies may fulfill several purposes, and these can be categorized according to different questions that can arise in the management of such patients (Table 1).

Functional Imaging to Evaluate the Morphology of Brain Tumor Tissue

Although structural magnetic resonance imaging (MRI) with and without gadolinium allows precise identification of the brain tumor, its limitations need to be recognized. Dysembryoplastic neuroepithelial tumors (DNTs) and gangliogliomas are the most common forms of low grade brain neoplasms encountered in patients with refractory focal epilepsy. Structural MRI currently does not distinguish these in all cases from focal cortical dysplasia (FCD). Gadolinium enhancement reflects breakdown of the blood–brain barrier. However, changes in gadolinium enhancement may not provide adequate information with regard to changes in tumor morphology over time. In particular, it does not help to differentiate between radiation-induced necrosis and tumor progression. In this context, "pseudoregression" refers to a situation where gadolinium enhancement diminishes over time, although the tumor does not shrink significantly. Conversely, "pseudoprogression" reflects an increase in gadolinium enhancement that is not mirrored by disease progression. Functional imaging techniques can complement structural MRI to address these questions.

Positron emission tomography (PET) utilizes radioactively labeled analogues of glucose, amino acid, or nucleotide metabolism to visualize metabolic aspects of a brain lesion. Compared to ^{18}F-fluorodeoxyglucose (FDG), the most commonly used agent in epilepsy, ^{11}C-methionine (MET) and ^{18}F-fluoro-ethyl-L-tyrosine (FET) may be more specific for brain tumor tissue. Although they provide comparable diagnostic information, the short half-life of MET (20 min) requires a cyclotron on site (Grosu et al.,

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Table 1. Functional imaging studies utilized in the evaluation of patients with focal epilepsy in the setting of brain tumors

	Functional imaging modality
Tumor morphology	MRI, MRS, PET
Tumor recurrence vs. treatment response vs. iatrogenic changes	MRI, PET
Relationship of tumor to ictal onset zone	Ictal SPECT
Relationship of tumor to eloquent cortical areas or pathways	fMRI, DTI, TMS

MRS, magnetic resonance spectroscopy.

2011). FET (half-life 120 min) does not have this limitation, which makes it more practical in the clinical setting (Rapp et al., 2013).

A recent large series (Hutterer et al., 2013) characterized the uptake of FET in 393 patients with a variety of central nervous system (CNS) pathologies (neoplastic, inflammatory, and others). Structural MRI with gadolinium was available in all patients, and 80% of patients underwent resection or biopsy, resulting in histopathology data available for comparison. In this largest series to date, 79% of low grade glioma (World Health Organization [WHO] grade I or II) and 96% of high grade glioma (WHO grade III and IV) had increased FET uptake. Seventy-two percent of tumors without gadolinium enhancement expressed an increase in FET, compared to 97% of those with gadolinium enhancement. However, FET uptake was also increased in a variety of nonneoplastic lesions, including hippocampal sclerosis (33%), FCD (32%), cavernous angioma (63%), as well as inflammatory lesions and nonglial brain tumors (Hutterer et al., 2013). Therefore, results of FET PET need to be interpreted in conjunction with standard MRI. One useful clinical application of FET is the identification of metabolically active tumor regions when planning a biopsy (Rapp et al., 2013). Of interest, MET uptake is lower in DNTs compared to other low grade and high grade brain neoplasms (Maehara et al., 2004; Rosenberg et al., 2005). In seven patients with pharmacoresistant temporal lobe epilepsy in the setting of low grade brain tumors, MET uptake was low in the four patients with histopathologically confirmed DNT, and high in the three patients with ganglioglioma, low grade astrocytoma, and pleomorphic astrocytoma (Maehara et al., 2004). These results were confirmed in a larger sample of temporal and extratemporal low grade brain tumors associated with pharmacoresistant epilepsy. MET uptake was moderate or high in all 16 gangliogliomas and low grade gliomas, and low (n = 7, including all six mesial temporal DNTs) or moderate (n = 4) in all DNTs (Rosenberg et al., 2005). An increase in MET uptake thus makes a diagnosis of DNT unlikely.

Functional Imaging in Visualization of Perilesional Epileptogenic Areas

Ictal single photon emission computed tomography (SPECT) provides a functional imaging correlate of the zone of seizure onset and early ictal propagation. Most centers utilize it in MRI-negative patients or in those where structural imaging and video-EEG provide discordant information. In this setting, ictal SPECT may allow the bypassing of intracranial recordings. For example, if it can provide further support for localizing perilesional seizure onset in patient with unusual ictal semiology and/or nonlocalizing EEG findings (Fig. 1). Four series have examined the contribution of ictal SPECT in the presurgical evaluation of patients with focal epilepsy to date (Ahnlide et al., 2007; Rathore et al., 2011; Lee et al., 2011; Von Oertzen et al., 2012). Only 14 (5.5%) of 253 patients in these series had brain neoplasms, and it is unknown whether the yield of ictal SPECT in this setting is different from that of patients with other MRI-detectable pathology or nonlesional cases.

One potential indication for nuclear medicine studies in the presurgical evaluation of patients with refractory focal epilepsy and low grade brain tumors is the identification of tumor-associated MRI-negative FCD. In a study of nine patients with temporal lobe DNTs, hyperperfusion on ictal SPECT was restricted to the mass lesion in three patients without associated FCD. In six patients with DNT-associated FCD, the area of hyperperfusion was more extensive and included perilesional areas that appeared normal on MRI (Valenti et al., 2002). The epileptogenic zone may extend beyond the MR-visible lesion in the nodular-like and dysplastic/diffuse subtypes of DNTs (Chassoux et al., 2012), and DNT-associated areas of FCD are frequently implicated in seizure generation. Advances in structural and functional imaging might allow identification of tumor-associated areas of FCD noninvasively, which in turn could help to delineate the resection margins or even eliminate the need for intracranial EEG recordings in some patients.

Functional Imaging in the Identification of Eloquent Areas

Functional MRI (fMRI) is widely used in preoperative planning, both for resection of tumors and prior to intracranial EEG. Motor fMRI utilizing finger tapping, toe wiggling, or tongue movements allows identifica-

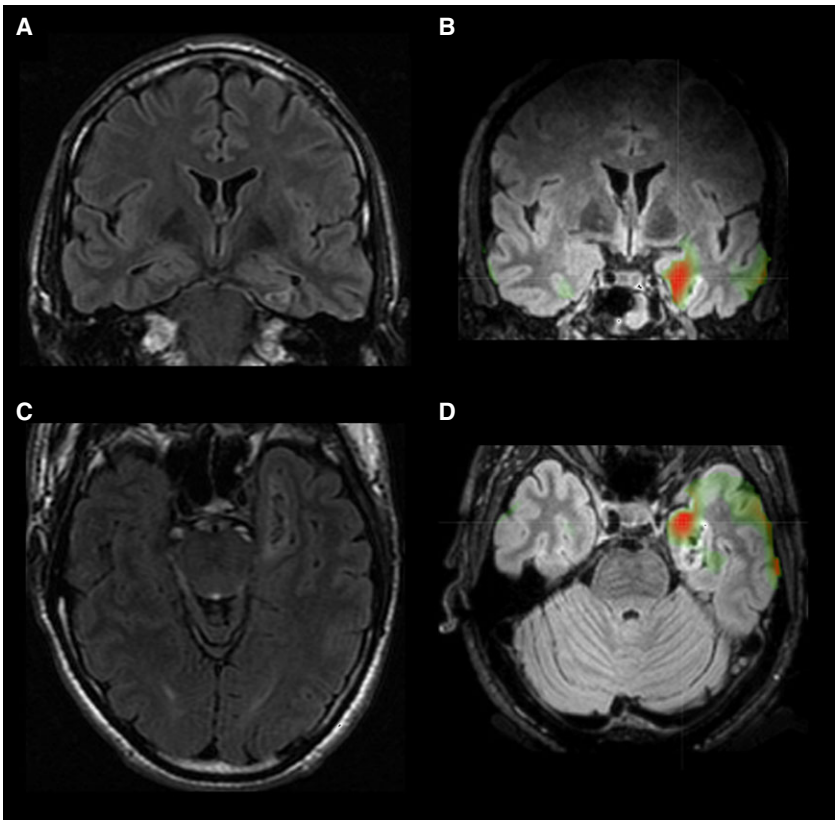

Figure 1.
Ictal SPECT in a 38-year-old man with disconcordant imaging and video-EEG findings. Seizures were characterized by gross hyperkinetic proximal movements of all extremities, facial grimacing, and loss of awareness, followed by late right-sided manual and oral automatisms. The ictal EEG was nonlocalizing, and there were no interictal epileptiform discharges. Brain MRI (coronal FLAIR, **A**, **B**; axial FLAIR, **C**, **D**) shows a mass lesion in the left parahippocampal gyrus that abuts the hippocampus and extends anteriorly. Ictal SPECT was performed, since neither seizure semiology nor ictal EEG was suggestive of left mesial temporal onset. Subtraction ictal SPECT coregistered to MRI (SISCOM, **B**, **D**) demonstrates peak hyperperfusion (red) in the left mesial lesion and left hippocampus. Based on this information, the patient was offered a left temporal resection including the mass lesion and the mesial structures. Pathology revealed a DNT and mild hippocampal end-folium sclerosis. He has been seizure free postoperatively for 15 months. SISCOM pictures courtesy of Prof Wim van Paesschen, Department of Neurosciences, University of Leuven, Belgium.

tion of plausible regions of interest in up to 99% of patients, and it may thus be superior to reliance on anatomic landmarks ("hand knob" sign and foot sign on MRI), especially in patients with a neoplastic lesion in the pericentral area, where distortions may be present from mass effect (Lehéricy et al., 2000; Wengenroth et al., 2011). Compared to electrocortical stimulation (ECS), hand motor fMRI had a sensitivity of 88% and specificity of 87% (Bizzi et al., 2008). The sensitivity was lower and the specificity higher in patients with grade IV gliomas compared to those with grade I–III gliomas.

For language lateralization, fMRI has largely replaced the intracarotid amobarbital procedure (Wada test, Janecek et al., 2013). However, fMRI does not allow precise localization of essential anterior and posterior language areas. In a study of 14 right-handed patients with neoplasms originating from the middle or inferior frontal gyrus on the left (i.e., in the vicinity of the anterior language area by anatomical criteria), fMRI had a sensitivity of 59% and a specificity of 97% compared to intraoperative ECS. One has to keep in mind that the essential eloquent anterior language area is often confined to a cortical region measuring a few square centimeters; the high specificity in this study was therefore driven by the large number of areas that were "language silent" both by fMRI and ECS criteria (Roux et al., 2003). The results of fMRI depend on statistical analysis ("thresholding"). Changes in metabolism and neovascularization in the vicinity of a brain neoplasm reduce the blood oxygen level dependent (BOLD) effect, which is the fundamental mechanism of fMRI (Hou et al., 2006; Jiang et al., 2010), and areas of

maximal activation may be displaced by one gyrus in the setting of high grade gliomas and meningiomas. Some patient cooperation is needed, although successful fMRI studies have been reported in children as young as 4 years of age with extensive preparation (Shurtleff et al., 2010). Areas of activation in fMRI highlight functional networks involved in a specific task; however, at present they do not allow precise extraoperative delineation of resection borders.

DTI approximates white matter tracts based on the preferred direction of water diffusivity (fractional anisotropy). It thus visualizes pathways that should be preserved during surgery, such as Meyer's loop of the optic radiation or the corticospinal tract. This information can be integrated into a neuronavigation system and thus made intraoperatively available for the neurosurgeon (Fig. 2). In a study of 28 patients with brain tumors, visualized trajectories modified the resection margins in 82%

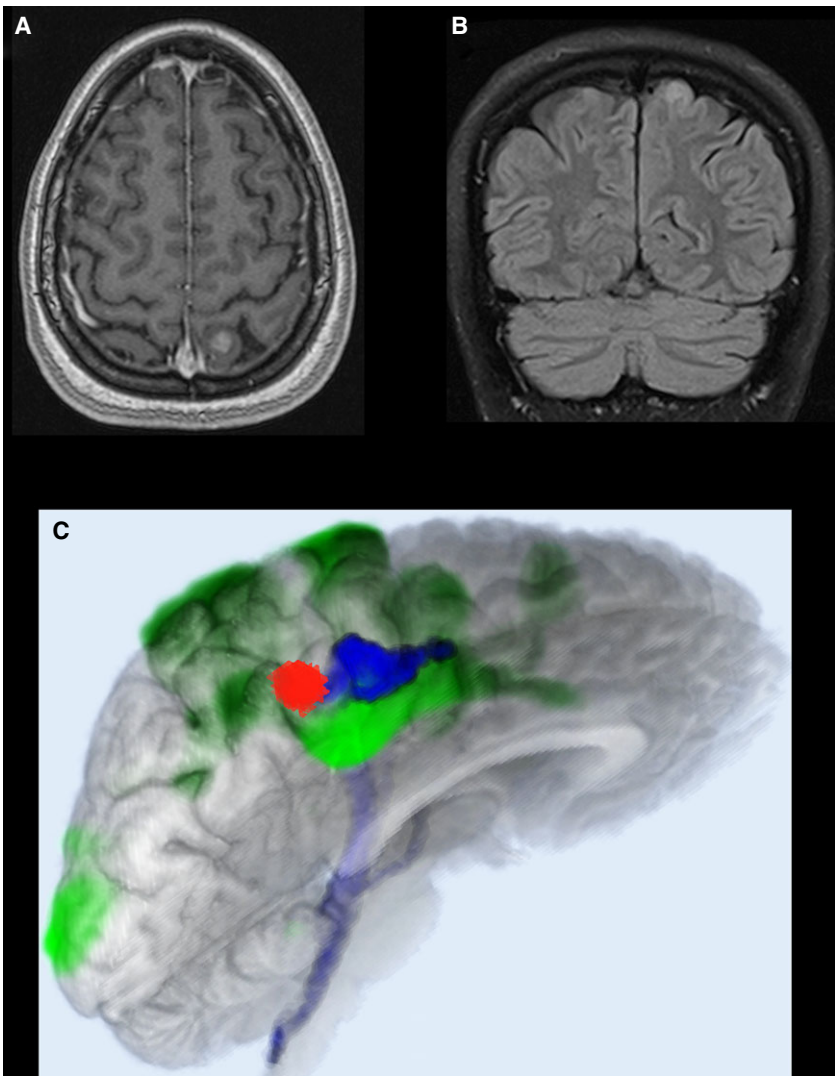

Figure 2.
Multimodal MRI integration for presurgical planning in a 30-year-old right-handed woman. The patient described an electrical sensation in the right arm and leg with subsequent generalized convulsions. Structural MRI (**A**, axial T_1 with Gadolinium; **B**, coronal FLAIR) demonstrated a low grade tumor in the left postcentral gyrus. (**C**) Multimodal integration of structural MRI (lesion manually outlined in red), functional MRI (light green, foot tapping paradigm; dark green, hand and foot sensory paradigm), and DTI (blue, corticospinal tract) illustrates the proximity of the brain tumor to eloquent cortical areas and pathways. The patient underwent an awake lesionectomy with intraoperative electrocorticography. Image courtesy of Dr Roman Rodionov, Department of Clinical and Experimental Epilepsy, Institute of Neurology, University College London, United Kingdom.

(Romano et al., 2009). The processing of DTI information is user dependent, and perilesional distortions of normal white matter architecture via compression, degeneration, and edema can affect the results (Dimou et al., 2013).

Navigated transcranial magnetic stimulation (TMS) is a technique that may overcome some of the limitations of fMRI. It allows extraoperative delivery of magnetic stimulation in precise relation to the patient's individual MRI-based gyral anatomy. Its theoretical error (defined as the discrepancy between maximum stimulus intensity and area of maximum cortical activation) is in the order of 6 mm (Ruohonen & Karhu, 2010). Although intense stimuli may cause some discomfort, most patients reportedly tolerate the procedure well. Navigated TMS allows direct identification of motor cortex/corticospinal tract in 99% of patients. In patients with peri-Rolandic brain tumors, the precision compared to ECS was 6 mm, compared to 10–15 mm for fMRI (Lehéricy et al., 2000; Roessler et al., 2005). It is important to note that there was no gyral discrepancy (i.e., both TMS and ECS localized the primary motor area to the same gyrus; Picht et al., 2012; Takahashi et al., 2013). The technique is better in identifying eloquent areas of the upper extremity than the lower extremity, due to the location of the hand motor cortex on the lateral convexity. In a pilot study (Picht et al., 2013) of navigated TMS for the detection of eloquent language areas in 20 patients with neoplasms (n = 18) or cavernomas (n = 2) in the left frontotemporal areas, navigated TMS produced naming errors in 1–32% (mean 12%) of 166–683 (mean 450) stimulated locations per patient. Compared to intraoperative ECS, the technique identified language areas (i.e., sensitivity) in 90% (100% of anterior language areas), with a specificity of 24% (13% for the anterior language area; Picht et al., 2013). This resulted in a positive predictive value of 57% and a negative predictive value of 100% for identifying the anterior language area. One patient did not tolerate navigated TMS at meaningful intensities. It has to be emphasized that experience of this technique in patients with pharmacoresistant focal epilepsy is limited (Vitikainen et al., 2009), and more data are needed to define its role in this setting.

Conclusion

In patients with refractory focal epilepsy due to brain tumors, functional imaging studies provide noninvasive information about tumor morphology, treatment response, and the relationship of tumor tissue to ictal-onset zone and eloquent areas. This information is helpful in the planning of tumor biopsies, intracranial EEG evaluations, and resections. Technologic advances might further improve identification of FCD and delineation of eloquent cortical areas.

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Disclosure

The author has no conflict of interest to disclose. I confirm that I have read the Journal's position on issues involved in ethical publication and affirm that this review is consistent with those guidelines.

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