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fMRI of Epilepsy

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Introduction

Since the demonstration a decade ago that functional magnetic resonance imaging (fMRI) is able to provide high spatial resolution maps of brain function, considerable effort has been directed at applying this technique to the study of patients with epilepsy, in particular, patients with intractable epilepsy considered for epilepsy surgery. Successful epilepsy surgery is vitally dependent on the accurate determination of the epileptogenic zone and of the risks of postoperative neurological deficits. Functional MRI can be used to address these issues in different ways. First, through determination of eloquent cortical areas, fMRI may predict deficits in cognitive (e.g. language and memory) or sensorimotor functions that might arise from surgical intervention. Second, functional asymmetries in activation may facilitate the lateralization and localization of an epileptogenic focus. Lastly, fMRI may provide evidence for the localization of focal epileptogenic regions through ictal or interictal blood oxygenation level-dependent (BOLD) signal changes.

Special Issue in Patients with Epilepsy

Only in the last few years has fMRI been increasingly applied to larger numbers of neurological patients. Working with clinical populations in general and patients with epilepsy in particular requires special considerations. The issue of task compliance and difficulty has to be addressed carefully in neurological patients. Patients may be less motivated than normal volunteers to perform well on tasks. If the epilepsy is associated with intellectual impairment, patients may be less able to perform cognitive tasks that were developed for neurologically normal subjects. Emotional distress from MRI scanning is reported to interfere with completion of the procedure in as many as 20% of patients.[1,2] Although these situations often are managed with tranquilizing agents

in standard MRI studies, use of such drugs in fMRI complicates interpretation of cognitive activation pattern. The effects of medication on the BOLD signal response have not yet been systematically studied. In a recent study by Jokeit and colleagues,[3] the extent of fMRI activation of the mesial temporal lobes (MTLs) induced by a task based on the retrieval of individually visuo-spatial knowledge[4] was correlated with the carbamazepine serum level in 21 patients with refractory temporal lobe epilepsy (TLE). Compared to normal controls, the activation over the supposedly normal MTL (i.e., contralateral to the seizure onset) was smaller in patients. In the patient group, the extent of the BOLD activation over the MTLs was correlated inversely to the carbamazepine drug level. The reduction of fMRI cluster size was most marked when the drug levels were close to toxic levels. There was no behavioral data concerning memory function described for the patient group, and a possible bias of the study was the possibility that a high carbamazepine level is associated with more severe epilepsy. However, these preliminary data provide some evidence that antiepileptic drug (AED) treatment may significantly influence fMRI activation of cognitive tasks.

Another consideration with epilepsy patients relates to the effects of epileptic activity to fMRI activation. A recent case report described a patient in whom fMRI falsely lateralized language cortex to the right hemisphere when performed after a cluster of left temporal lobe seizures.[5] The interaction between ictal and interictal activity with fMRI activation tasks is unclear and requires further investigation. In patients with frequent seizures or epileptiform discharges, results of fMRI activation studies should be interpreted carefully, and in some patients, electroencephalogram (EEG) monitoring before or during the fMRI study might be necessary.

fMRI Applications in the Definition of Eloquent Cortical Areas in Epilepsy

No technique used in the identification of eloquent cortical areas is without a limiting sensitivity and specificity, including the gold standard direct cortical stimulation. Whereas cortical stimulation is essentially a lesion study, fMRI measures endogenous function. Thus, these modalities may be expected to differ somewhat in functional localization. Functional MRI has the advantage of being able to acquire functional and anatomic maps concurrently and preoperatively; it is equally sensitive to superficial and deep regions, non-invasive, cost effective, and easy to employ, even using routine clinical scanners.[6]

Lateralization and Localization of Language

Just three years after the first reports on fMRI, a preliminary study showed that the BOLD signal contrast obtained in simple tests of language and motor function was very similar between subjects with

epilepsy and normal controls, demonstrating the feasibility of the technique in studies of patients with epilepsy.[7] Since then, fMRI of language processing has become one of the most clinically relevant applications in the field of epilepsy. The main aim of localizing language functions is to predict and minimize postoperative language deficits in patients considered for epilepsy surgery, who are mainly patients with TLE.[8] In these patients, fMRI is predominantly used for language lateralization (i.e., determination of hemispheric dominance), and only to a lesser extent for intrahemispheric distribution of eloquent cortex. Numerous studies have demonstrated fMRI to identify language hemispheric dominance reliably.[9–22] However, the areas identified in different studies of language processing have varied markedly, likely relating to use of different linguistic activation or control tasks and imaging and postprocessing techniques, among other factors. There is no single fMRI paradigm that identifies language cortex. Language is a complex process that involves specialized sensory systems for speech, text, and object recognition, access to whole-word information, access to word meaning, and processing of syntax and multiple mechanisms for written and spoken language production.[23] Hence, the activation pattern is crucially dependent on the chosen fMRI task design. Hearing words—whether the task involves passive listening, repeating, or categorizing—activates the superior temporal gyrus bilaterally when compared with a resting state.[19,24,25] The symmetry of this activation can be explained by the task contrast (complex sounds compared with no sounds). The rest condition contains no control for prelinguistic auditory processing that engage auditory cortex in both superior temporal gyri. These activation patterns bear almost no relation to language dominance measured by Wada testing.[26] A further problem of such word-listening tasks is that brain areas associated with semantic processing also might be activated during the rest state, and hence reduce sensitivity for the activation task.[27]

Similar problems occur in designs that contrast reading or naming tasks with a resting or visual-fixation baseline. In a study consisting mostly of patients with lateralized lesions but not epilepsy, Benson and colleagues[28] found that such procedures did not reliably produce lateralized activation and did not correlate with language dominance measured by Wada testing.

The most common types of tasks successfully used for lateralization purpose are word-generation tasks (also called verbal-fluency tasks) and semantic decision-making, the former tending to show relatively consistent activation of anterior language areas and the latter demonstrating a more widely distributed network, including anterior and posterior hemispheric regions.[20]

In word-generation tasks, subjects are given a beginning letter, a semantic category (e.g., animal, food), and must retrieve a phonologically or semantically associated word. In verb-generation tasks, the subject generates a verb in response to seeing or hearing a noun. These tasks reliably activate the dominant inferior and dorsolateral frontal lobe, including prefrontal and premotor areas,[25,29–31] and lateralization

measures obtained from this frontal activation agree well with Wada language lateralization.[9,26,28,32] There is evidence that semantic language tasks such as verb generation in response to nouns, noun categorization, or noun generation within specific categories may be more effective in lateralizing than phonologically based generation tasks such as covert repetition.[26]

Word-generation tasks usually are performed silently in fMRI studies to avoid movement artifacts. The resulting absence of task-performance data usually is not a problem when clear activation is observed, but bars the investigator from assessing the contribution of poor task performance in cases with poor activation.

A semantic decision task was used by Springer and colleagues to address the issue of language dominance in patients with epilepsy.[33] Fifty right-handed patients with epilepsy were compared with 100 right-handed normal controls. Language activation was accomplished by contrasting a semantic decision task with a tone discrimination test. For the semantic task, subjects listened to animal names and responded to those animals that met the semantic criteria of being "native to the United States" and "commonly used by humans." The contrast task required patients to listen to sequences of 500 and 750 hertz pure tones and identify those sequences that contained two high tones. The tone-discrimination task was developed to control for nonlinguistic components of the task (e.g., attention, sound processing, manual response). Using a categorical dominance classification, 94% of the normal control subjects were considered left hemisphere dominant, six percent had bilateral language representation, and none of the subjects had rightward dominance. In the epilepsy group, there was greater variability of language dominance, with 78% showing left hemisphere dominance, 16% showing a roughly symmetric pattern, and six percent showing right hemisphere dominance. Atypical language dominance in the epilepsy patients was associated with an earlier age of brain injury and with weaker right-hand dominance. The relatively high prevalence of atypical language representation in epilepsy patients stresses the importance of assessment of hemispheric dominance before interventional procedures are performed in areas potentially relevant for language in either cerebral hemisphere.[34] Further studies with the paradigm described above were performed by Binder and colleagues.[20–22] The activation pattern was, in general, strongly left lateralized and involved both prefrontal and posterior association areas. In patients with epilepsy, the activation was correlated strongly with Wada language lateralization.[22] Another study using a semantic decision task by Desmond and colleagues came to the same result. Seven postoperative patients with TLE were examined and the BOLD signal correlates were compared with a preoperative Wada test. In all cases, using a region of interest (ROI) based analysis looking only at inferior frontal regions, the lateralization by fMRI was the same as by the Wada test.[35] An attractive feature of semantic decision tasks is that measured behavioral responses consisting of simple button presses for stimuli that meet response criteria permit task performance to be precisely quantified.

As mentioned above, both word-generation and semantic decision tasks identify mainly frontal lobe language areas, but are less consistent activators of temporal language regions. An fMRI paradigm with a consistent temporal lobe activation was recently reported by Gaillard and colleagues.[36] The paradigm consisted of silent naming of items in response to silent reading of item description. The authors found language lateralization in 27 of 30 patients with TLE. The fMRI dominance was in agreement with the Wada test in 15 of 20 patients.

There are several fMRI studies reported in children with epilepsy.[11,14,37,38] Successful fMRI lateralization paradigms have been reported on children with epilepsy as young as six years.[37] The hemodynamic response appears to be similar in children and adults.[14,39] Word-generation tasks are the most commonly used tasks for evaluation of pediatric epilepsy surgery candidates, and, as in adults, show general agreement with Wada testing and electrocortical stimulation.[11,14,38] There is some evidence that young children activate more widely than adults, at least in verbal-fluency tasks.[40] Other fMRI studies in children were performed with reading tasks or naming to description.[41] Special considerations in children, like choice of suitable experimental and control conditions, have been reviewed recently.[42,43]

In addition to information on lateralization, fMRI has the potential to provide detailed maps of the intrahemispheric localization of critical language areas. There are a number of studies suggesting a close spatial relation between fMRI activation and intraoperative electrocortical stimulation.[10,44–50] A recent study by Rutten and colleagues compared the results of fMRI quantitatively with intraoperative electrocortical stimulation mapping (ESM) in thirteen patients with temporal lobe epilepsy.[51] In eight patients, critical language areas were detected by electrocortical stimulation, and in seven of eight patients, sensitivity of fMRI was 100% (i.e., fMRI correctly detected all critical language with high spatial accuracy). This indicates that such areas could be resected safely without the need for intraoperative electrocortical resection. A combination of three different fMRI language tasks (verb generation, picture naming, and sentence processing) was needed to ensure this high sensitivity, as no single task was sufficient for this purpose. On the other hand, on average, only 51% of fMRI activations were confirmed by electrocortical stimulation, resulting in a low specificity of fMRI. Both sensitivity and specificity are strongly dependent on the statistical threshold. This study illustrates the current problems of basing clinical decisions (e.g., surgical strategies) on fMRI activation maps. Different language-related paradigms activate a different set of brain regions, and a combination of different tasks is necessary to achieve high sensitivity in identifying critical areas.[52] However, a generally accepted standard protocol has not yet been established. Furthermore, the extent of the activation is critically dependent on the applied statistical threshold. An observer-independent statistical methodology (i.e., a fixed statistical threshold) would be necessary to standardize fMRI for clinical use. Finally, the presence of fMRI

activation at noncritical language sites limits the predictive value of fMRI for the presence of critical language areas. Some regions activated during language tasks obviously play a minor, supportive role for language function, and resection of these areas may not necessarily produce clinically relevant deficits. Still, because of these problems, the clinical role of fMRI in identifying eloquent cortical areas of cognitive function needs to be investigated further. Currently, it can be useful to compliment intraoperative electrocortical stimulation rather than replace this method.[53]

Language fMRI Compared with Wada Testing

One primary goal of fMRI is to displace Wada testing as the standard of care for determining language and memory dominance in candidates for epilepsy surgery. If established as a valid and reliable technique, fMRI will either render the Wada test obsolete, or at least reduce its role to a secondary procedure to be used only when fMRI is not practical because of either technical considerations or patient variables. In the Wada test [intracarotid amobarbital test (IAT)], the portions of one hemisphere supplied by the anterior circulation are transiently anesthetized using a bolus of short-acting amobarbital, allowing the contralateral hemisphere to be assessed independently.[54] The Wada test is invasive, carries significant risks, and the validity of individual Wada test results can be compromised by acute drug effects, which may produce behavioral confounds of sedation and agitation. Although the Wada test is commonly designated as the gold standard in language lateralization tests,[55] it is not a single standardized procedure. Differences in almost every aspect of methodology and design can be found in the Wada test protocols described in the literature and make between-center comparisons of the results difficult.

In a recent review by Baxendale[56], 70 patients were found in the literature who have undergone both fMRI language studies and Wada testing.[9,14,16,22,26,28,32,35,45,57,58] With the exception of one study[16] that showed a comparatively low concordance of only 75% with a verbal fluency task used as fMRI paradigm, all other studies report impressive concordance rates between the two techniques despite the use of different language tasks and Wada test protocols. A study by Binder and colleagues correlated the Wada test and fMRI assessment of language laterality using a laterality index for the Wada test (a continuous variable) and a laterality index from fMRI calculated as an asymmetry in the voxels activated in each hemisphere by a semantic decision task.[22] The correlation was extremely strong ($r = 0.96$, $p < 0.0001$), and all 22 subjects were classified to the same laterality by the two tests. Concordance at or near 100% also was found in the other studies that have employed categorial analyses to classify language representation.[32,58] While these findings are promising, there are reasons to be cautious about replacing the Wada test with fMRI procedures at this time. In all of the Wada–fMRI comparison studies

reviewed above, there were less than thirty cases collectively with crossed or atypical cerebral dominance patterns as defined by Wada, an extremely limited sample on which to base clinical decisions. As mentioned above, there is evidence for a greater variability of language dominance in epilepsy subjects compared to normal controls.[33,45] Atypical language representation is the very condition that is, perhaps, the most important to detect, and the small numbers currently available do not allow any firm conclusions to be drawn about sensitivity or specificity of the various fMRI tests. Moreover, the incidence of significant discrepancy between fMRI and Wada lateralization measures is not known, nor have the reasons for the occasional discrepancies been investigated. For example, Hammeke and colleagues reported a significant discrepancy between fMRI and Wada lateralization indices in approximately one in ten patients.[59] In particular, temporal tumors of the dominant hemisphere have been reported to lead to false-negative activation of the dominant hemisphere.[60,61]

Finally, it has to be emphasized that the Wada test is not only undertaken to determine language dominance only, but also, and perhaps more importantly, to reveal the ability of each hemisphere to sustain verbal memory. Before fMRI can fully displace the Wada test, further large scale studies are necessary to establish its equivalence to the Wada test, which has been validated repeatedly with respect to memory function, language representation, and prediction of both cognitive and seizure outcome.[23] Moreover, acceptance of fMRI will depend largely on the perceived clinical need for the lesion test aspect of the Wada test, which provides more direct information about how well language and memory functions can be supported after functional removal of the contralateral hemisphere Presently, the diagnostic value of fMRI and the Wada test seems to be rather complementary. Killgore and colleagues found that, when combined, fMRI and the Wada test provided complementary data that resulted in improved prediction of postoperative seizure control compared with either procedure alone.[62]

Memory

In addition to the investigation of language functions, the study of long-term memory systems is central to the presurgical evaluation of patients with TLE. There is long-standing evidence from animal and clinical lesional studies that memory function depends on the functional integrity of the hippocampus and parahippocampal regions in the MTL.[63–65] Whereas the hippocampus proper is the brain region most commonly associated with episodic memory function,[66] fMRI studies have often demonstrated activation more posteriorly in the parahippocampal formation. The explanation for this is poorly understood.

Functional imaging studies of these structures are potentially useful in two ways. First, identification of functionally hypoactive temporal lobe structures may have predictive value for lateralization of seizure

foci in TLE. Second, maps of fMRI activation associated with memory tasks may help in predicting the risk of postoperative memory deficits from temporal lobe surgery and could assist in planning surgical strategies that spare functional tissue.

Tasks that reliably activate the mesial temporal structures in normal subjects using fMRI have been developed only relatively recently,[67–69] and have rarely been used in patients with epilepsy.[4,70–74] These studies suggest that (1) complex visual and especially spatial memory tasks are generally superior to verbal memory tasks in activating mesial temporal lobe structures, (2) nonverbal materials activate bilateral mesial temporal lobe structures, (3) encoding, as well as retrieval, recruit overlapping mesial temporal lobe structures, and (4) retrieval rather than encoding tends to activate bilateral mesial temporal lobe structures.[4]

Two studies have compared the fMRI activation of memory tasks with the memory assessment procedures in the Wada test. Detre and colleagues were the first to demonstrate that fMRI could be used to detect clinically relevant asymmetries in memory activation in patients with TLE.[71] They used an environmental scene-encoding task[69] in which subjects were asked to memorize each stimulus. In the baseline condition, subjects passively viewed a repeating nonsense stimulus (a spatially scrambled picture). Region-of-interest analysis of the resulting bilateral activation of posterior mesial temporal lobe structures was then used to calculate a memory lateralization score. Functional MRI lateralization scores were compared with lateralization indices derived from Wada memory scores. Whereas temporal lobe activation was symmetrical in a normal control group, significant asymmetries were observed in the epilepsy group. In all nine patients, the asymmetry of the activation concurred with the assessment of memory skills from the Wada test, including two patients in which memory was located paradoxically ipsilateral to the seizure focus.

In a recent study by Golby and colleagues, fMRI was used to study the lateralization of memory-encoding processes (patterns, faces, scenes, and words) within the mesial temporal lobe in nine patients with TLE.[74] In eight of nine subjects, lateralization of memory encoding was concordant with that obtained from the Wada test. Group level analysis demonstrated greater activation in the mesial temporal lobe contralateral to the presumed seizure focus. Furthermore, results suggested that there is reorganization of memory encoding to the contralateral mesial temporal lobe.

Jokeit and colleagues[4] used a task employing mental navigation and recall of landmarks based on the retrieval of individually familiar visuospatial knowledge (Roland's Hometown Walking[75]), which is known to be associated with symmetrical mesial temporal lobe activation. In 14 of 16 patients with left-sided TLE and 13 of 14 patients with right-sided TLE, interhemispheric differences in mesial temporal lobe activation lateralized the side of seizure onset correctly, resulting in a correct classification rate of 90%.

A study using a verbal memory encoding and retrieval paradigm compared seven patients with left TLE with a normal control group.[73]

During retrieval, normal controls activated bilateral parahippocampal regions, right more than left. In the patient group, this pattern was less marked, but an additional left frontal region also was activated. The authors interpret this different activation pattern as a dysfunctional response due to the epilepsy and left hippocampal sclerosis. However, there was a vast difference in performance between patients and normal control groups, which makes a comparison between groups difficult.

The tasks in the studies mentioned above were chosen partly because they produced bilateral and broadly symmetrical temporal lobe activations in normal controls. Other investigators have utilized memory tasks that produce rather unilateral activations. Bellgowan and colleagues reported that mesial temporal lobe activation during a verbal encoding task could differentiate between patients with left and right TLE.[70] The group with right TLE showed much stronger activation of the left mesial temporal lobe than did the left TLE group. Neither group showed activation in the corresponding regions of the right hemisphere. However, these findings were on the group level only and do not allow inferences to be made on an individual subject basis.

In respect to memory function, fMRI still has to be considered a research tool. Large-scale validating trials of fMRI against Wada test and longitudinal studies before and after surgery need to be performed. If prospective studies clearly demonstrate that resection in a region of fMRI activation results in a decrement in memory performance, fMRI data might be used further in planning specific resections in the mesial temporal lobe.

Sensorimotor Systems

Among the earliest clinical applications of fMRI was the localization of motor cortices, particularly in patients with mass lesions around the central sulcus.[11,44,49,76–92] Lesions in the vicinity of the central sulcus often are associated with epilepsy. However, the treatment strategies often are dependent on the nature of the underlying lesion rather than the epilepsy. In any case, it is important to avoid new, unacceptable deficits, or at least to predict a possible loss of function as a consequence of a surgical treatment. Because activation of the primary sensory and motor areas yield robust BOLD signals (near 5% signal change on a 1.5 T scanner), it is relatively easy to determine precise boundaries of functional tissue in these regions with fMRI.[50,77,93] Motor cortex representing tongue, hand, finger, arm, and foot areas are readily identified with tongue movement, finger tapping, and toe wiggling; analogous sensory areas are identified with brushing or an air puff. With more complex motor paradigms, the supplementary motor area and cerebellar areas also are activated.[94] Somatotopic activation has been demonstrated by many studies.[95–97] Most of the clinical studies used fMRI for identifying eloquent cortical areas in preparation for tumor or vascular malformation surgery. Several studies have compared the fMRI localization of the sensorimotor cortex with

invasive electrocortical stimulation.[50,76,77,79,86,89,98,99] The differences in fMRI versus cortical stimulation localization varied from zero to 20 millimeters and are typically below 10 millimeters. The greatest differences were found in tumors surrounded by significant perilesional edema.

The most frequent causes for fMRI failure in sensorimotor mapping are stimulus-correlated head movement, inability to move adequately because of existing neurological deficit, and altered hemodynamic response, therefore due to arteriovenous malformations or vascular tumors.[84]

Malformations of Cortical Development

Malformations of cortical development are an important cause for refractory epilepsy in adults and children.[100] Results of surgical treatment are less favorable compared with mesial temporal lobe epilepsy (MTLE), with about 40% of patients rendered seizure-free over a minimum two-year follow-up period. Space-occupying lesions of the brain primarily displace functional cortex. For this reason, resection within the boundaries of a lesion should not directly damage eloquent cortex and result in a significant deficit. In contrast, cortical stimulation studies showed functional reorganization within dysplastic cortex, as well as functional overlap between dysplastic cortex and normal brain tissue. Over the last years, fMRI has shown its ability to demonstrate coactivation of malformations of cortical development during physiological activation tasks.[101] Two studies on patients with subcortical laminar heterotopia[102,103] showed fMRI activation both in the outer cortex and the subcortical band heterotopia during performance of a motor task. In another patient with epilepsy and a microgyric visual cortex, the dysplastic cortex was activated by visual stimulation.[104]

In contrast, another case report found a common cortical representation of both hands on the unaffected hemisphere and no activation in the hemisphere with a complex malformation.[105] Cortical reorganization and participation of ectopic neuronal tissue in physiologic cerebral functions are of clinical importance in patients who are considered for epilepsy surgery with resection of cortical dysplasia. In addition to localized physiological activation, fMRI has the potential to identify epileptogenicity of dysplastic cortex by imaging ictal or interictal events.[106–108]

Localization of the Epileptic Focus

Beside the identification of eloquent cortices and the prediction of functional deficits caused by epilepsy surgery, fMRI is also capable of providing evidence for the localization of the epileptic focus by identifying ictal or interictal epileptic activity, as described in the next section.

Ictal fMRI

Ictal fMRI activation has the advantage that it can be expected to reflect changes within the epileptogenic region itself (and propagation sites). Currently, only a few anecdotal reports on ictal fMRI have been published. The section provides a brief review of the literature.

The first attempt to use fMRI for localization of epileptic activity was reported in 1994 by Jackson and colleagues.[109] This case report dealt with a 4-year old patient with the diagnosis of Rasmussen's encephalitis. A standard MRI of the patient's brain showed widespread right hemispheric atrophy primarily over the more dorsal lateral frontal region and inferior Rolandic Area. The patient was prone to frequent and prolonged focal motor seizures that involved the left arm, hand, and face. These bouts of epilepsia partialis continua were then targeted for investigation using a FLASH sequence to obtain susceptibility-weighted images every eight seconds from a single slice only. This study demonstrated a seizure-related perfusion change over the right inferior motor cortex, corresponding to the area of maximum atrophy seen on the conventional MRI and to the region of maximum abnormality as identified with an ictal single photon emission tomography (SPECT) study.[109] Another case was reported by Warach and colleagues.[110] The patient in this study had prolonged focal status epilepticus and demonstrated a perfusion MRI abnormality over the left parieto-frontal region using a susceptibility-weighted sequence and dynamic enhancement with gadolinium. This abnormal region was in keeping with the localization of the spike focus of scalp EEG and the hyperperfusion defect detected with ictal SPECT. The EEG, perfusion-based MRI abnormality, and SPECT findings normalized after more aggressive medical management.[110] Further case reports with equal findings were subsequently published.[106,111,112] In not one of these report was EEG recording available during MR image acquisition; seizure detection was only possible by clinical observation of the patient in the MR scanner. The first ictal fMRI with simultaneous EEG recording was reported by Salek-Haddadi and colleagues.[113] A patient with partial and generalized tonic–clonic seizures showed ictal EEG changes (rhythmic delta and theta activity maximum over F7/T3 lasting for about 40 seconds) in the EEG recorded inside the MR scanner. A continuous BOLD-fMRI series was simultaneously acquired and revealed an two and a half percent signal increase mainly over the left temporal lobe peaking at around six seconds into the seizure, followed later by a prolonged undershoot.[113]

In summary, ictal fMRI studies have demonstrated that fMRI, analogous to ictal SPECT, is capable of imaging reversible perfusion or BOLD abnormalities associated with epileptic seizures, with the abnormality localized closely to the site of maximum electric abnormality. However, in contrast to ictal SPECT, which is costly but feasible in specialized epilepsy units, ictal fMRI is not routinely practicable for a number of reasons: Most ictal events are associated with head and body movement and impairment of consciousness usually to a degree that the required level of cooperation for an MRI scan cannot be achieved.

Furthermore, BOLD-fMRI is not sensitive to detecting low-frequency state-related changes due to large intersessional effects and scanner noise characteristics. Together with the slow hemodynamic response function (HRF), this limits detection power to a narrow frequency band and will tend to necessitate capturing both seizure onset and termination. Seizures, however, are usually of short duration and unpredictable. It is impracticable for a patient, even with frequent seizures, to lie for hours in a MR scanner awaiting the onset of one or several seizures. Functional MRI studies with concurrent EEG recording are complicated further by the extra time involved in attaching electrodes and equipment set up. For these practical reasons, the investigation of ictal activity will be limited to selected patients who have very frequent seizures without gross head movement, in particular, seizure series, status epilepticus, or epilepsia partialis continua, or have epilepsy syndromes with seizures occurring predictably, therefore, reflex epilepsy.[114]

Interictal fMRI

Like physiological brain activity (and epileptic seizures), interictal epileptiform discharges (IED) are associated with alterations of cerebral blood flow (CBF) and deoxyglobin concentration in the venous bed. Hence, fMRI should be able to identify the sources of IED in the same way that it can identify sources of functional activation from movement or cognitive processing. This is in contrast to methods such as dipole modeling, which can find only possible intracerebral sources of surface potentials and rely on assumptions that are not always easy to justify.

Compared with ictal fMRI, mapping of interictal activity has several advantages: (1) IED are a common phenomenon in patients with epilepsy; (2) IED are not associated with stimulus-correlated motion; and (3) fMRI activation associated with single discharges are less likely to be confounded with propagation effects compared with ongoing ictal activity. On the other hand, fMRI correlated with IED localizes brain areas involved in generating these particular EEG events. The area of cortex that generates IED is labelled as the irritative zone, which is not necessarily indicatory for the epileptogenic zone, the area of cortex that is indispensable for the generation of epileptic seizures.[115]

As IED are by definition a sub-clinical phenomenon, a second modality is necessary to identify these events. Hence, this approach was only made possible by recording EEG inside the MR scanner (EEG-correlated fMRI).

Methodological Aspects of EEG Correlated fMRI

The MRI scanner is a hostile environment for EEG recordings. Magnetic resonance-compatible EEG recording equipment must ensure patient safety, sufficient quality of the EEG signals and avoid compromising MR image quality. Since the first report on EEG recording during MRI 10 years ago,[116] these issues have been addressed by several studies and technical solutions have been proposed.[117–119] Several com-

mercial systems for intra-MR EEG recordings are now available. The main additional features implemented in these systems are a battery-powered nonmagnetic amplifier with a fiberoptic link, a high dynamic range of the amplifier, and careful choice of materials for the electrode assembly. The most crucial practical difficulty that must be overcome before useful functional data can be acquired is EEG quality. The two most relevant artifact obscuring the EEG recorded inside the MR scanner are (1) pulse artifact (or cardioballistogram) and (2) image-acquisition artifact (Figure 12.1).[120]

Cardioballistic and other movment-related artifacts are caused by movements of the body and EEG leads relative to the magnetic field of the MR scanner. It can be reduced by minimizing the area of the EEG wire loops, lead fixation, and bipolar montage of the EEG with small inter-electrode distances. Remaining pulse artifact can be removed by averaging and subtraction of the artifacts synchronized to the ECG.[120–122] These methods provide a degree of EEG quality sufficient for the accurate identification on IED,[123] sleep stages,[124] or physiological EEG rhythms.[125] During MR image acquisition, the EEG is obscured completely by large artifacts, mainly due to induced voltages in the EEG leads subjected to the rapidly changing gradient fields.

Two solutions to the problem of EEG-imaging artifact removal have been proposed.[122,126] Both rely on amplification with sufficient dynamic range to avoid saturation of the EEG amplifier due to the artifact. The method developed by Allen and colleagues[126] uses a scanner-generated slice-timing pulse. For each channel, online subtraction of a running time-averaged waveform, followed by adaptive noise cancellation, reduced any residual artifact. Hoffmann and colleagues[122] proposed a postprocessing filtering method based on the Fast Fourier transform (FFT); segments of EEG without MR activity are compared with the FFT of the EEG recorded during imaging. Frequencies with amplitudes over a threshold determined based on the FFT of the normal EEG are then discarded. The inverted FFT gives the corrected EEG.

The ability to remove image artifacts determines the data acquisition of EEG-correlated fMRI experiments. Without image artifact removal, the EEG is obscured during imaging and interleaved data acquisition has to be applied. In epilepsy studies, this approach was introduced as spike-triggered fMRI (Figure 12.2). This method takes advantage of the delayed BOLD response after a neuronal event. This makes it possible to observe the EEG recording on-line (which requires the presence of an experienced electroencephalographer during data acquisition), and to start image acquisitions manually at a fixed interval after the event of interest (usually three seconds, as the BOLD response peaks at two to seven seconds after an event) or during control periods. However, spike-triggered fMRI suffers from two main limitations, both linked to the obliteration of the EEG during the image acquisition. First, there are constraints on the scanning rate and the duration of each scan. The minimum time gap between successive image acquisitions must be of the order of 15 seconds to avoid signal variations due to the T1 signal decay, and the maximum duration of each image acquisition must be less than the expected duration of the BOLD response in order to

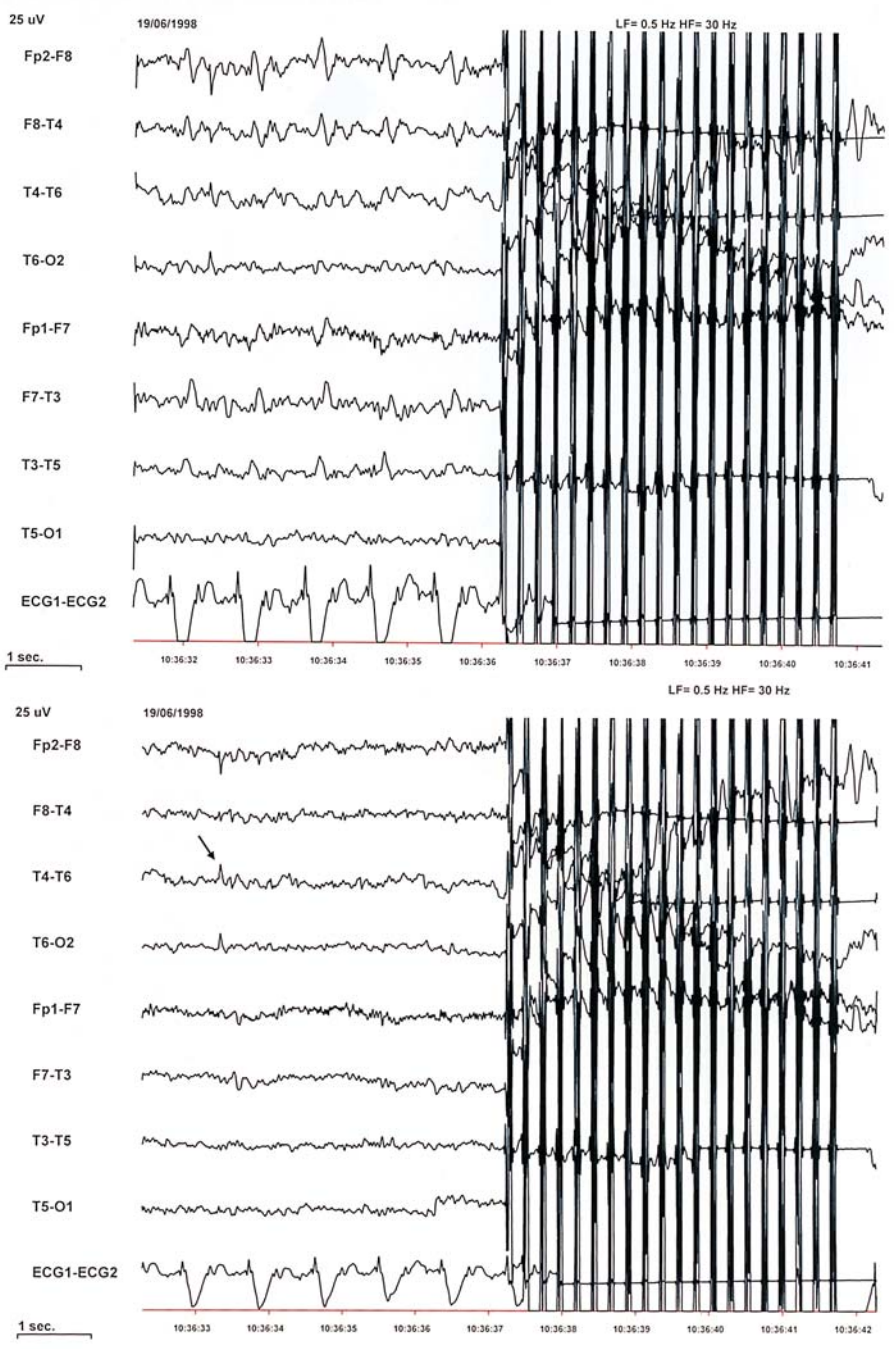


Figure 12.1. Electroencephalogram recorded inside a 1.5T scanner. In (a), an ECG-related artifact is obscuring the EEG activity (pulse artifact, cardioballistogram), making the identification of IED difficult; (b) shows the identical EEG sequence after on-line pulse artifact subtraction. A small amplitude spike is clearly detectable over the right hemisphere. Three and a half seconds after the spike, a 20 slice EPI sequence is triggered, leading to a large EEG artifact (image acquisition artifact). The result of the spike-triggered fMRI experiment is demonstrated in Figure 12.2.

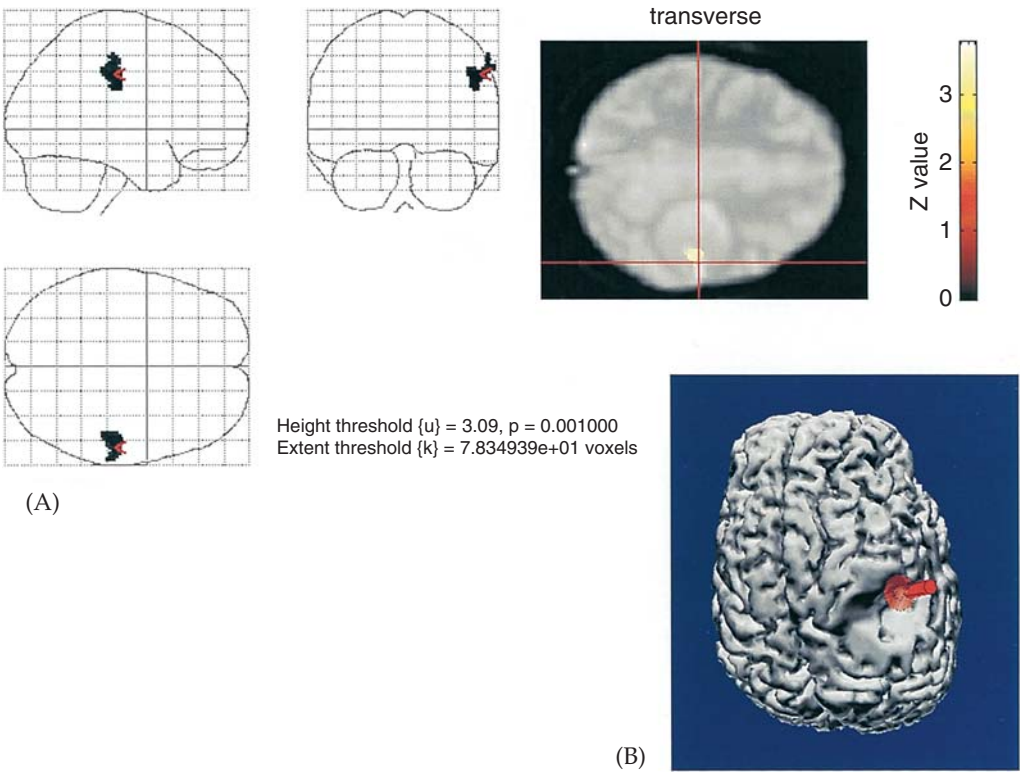


Figure 12.2. (A) The statistical parametric mapping BOLD activation map of a spike-triggered fMRI experiment, which was performed on an 22-year-old patient with refractory partial and secondarily generalized seizures. Standard MRI showed subcortical nodular heterotopia of the right hemisphere with a large mass in the central region. Interictal EEG demonstrated frequent focal IED over the temporal and parasagittal region of the right hemisphere. Functional MRI result shows an axial image with crosshair through the center of the activation (overlaid in yellow) in the center of the nodular heterotopia of the right hemisphere. (B) Result of a 64-channel EEG source analysis (multiple unconstrained moving dipole model, CURRY 3.0), superimposed on a T1-weighted anatomical scan, showing co-localization with the result of the spike-triggered fMRI. (Neurologic coordinates).

ensure proper separation of the responses from events that may occur during image acquisition, and therefore be undetected. Second, as mentioned above, the spike-triggered approach relies on assumptions about the BOLD response peak time and duration. However, spike-triggered fMRI is not able to reveal the hemodynamic response function due to a delayed image acquisition and the lack of preactivity baseline images.

With the possibility of image artifact subtraction, these limitations can be overcome by continuous and simultaneous EEG and fMRI. In principle, continuous EEG/fMRI should be more sensitive than the spike-triggered approach for the following reasons: a larger amount of data can be acquired per time unit, and the time course of the response in individual subjects can be measured. Furthermore, it should allow more flexibility in patient selection concerning the frequency of IED (Figure 12.3).

EEG Correlated fMRI in Patients with Epilepsy

Most of the studies used spike-triggered fMRI,[108,123,127–132] only since 2001 have several cases and small scale studies with continuous EEG/fMRI been reported.[133–135]

In summary, the studies showed that EEG-correlated fMRI is a practicable method to be applied to patients with epilepsy showing frequent IED on scalp EEG. The EEG quality was sufficient to detect spontaneous IED off- or on-line. Discomfort or injuries of the patients due to the EEG recording were not reported and the MR image quality was not significantly compromised by the EEG recording. In the studies listed, a total number of 75 patients was reported. Most of the patients had intractable focal epilepsy, some of the patients were considered for epilepsy surgery, and in a few, surgery was carried out after the EEG/fMRI experiment.[130] Patients for EEG/FMRI experiments were, in general, highly selected, particularly with regard to the frequency of their IED. Nevertheless, in many patients, the EEG/fMRI experiments failed, mainly because of absence of IED or due to motion artifacts. In the lager studies, fMRI activation was reported in about 50% of patients.[108,129–131] In general, the activations were anatomically related to the proposed epileptic focus (as defined by interictal EEG, EEG source analysis, structural MRI, ictal video-EEG, or, in less than 10 patients, intracranial EEG).

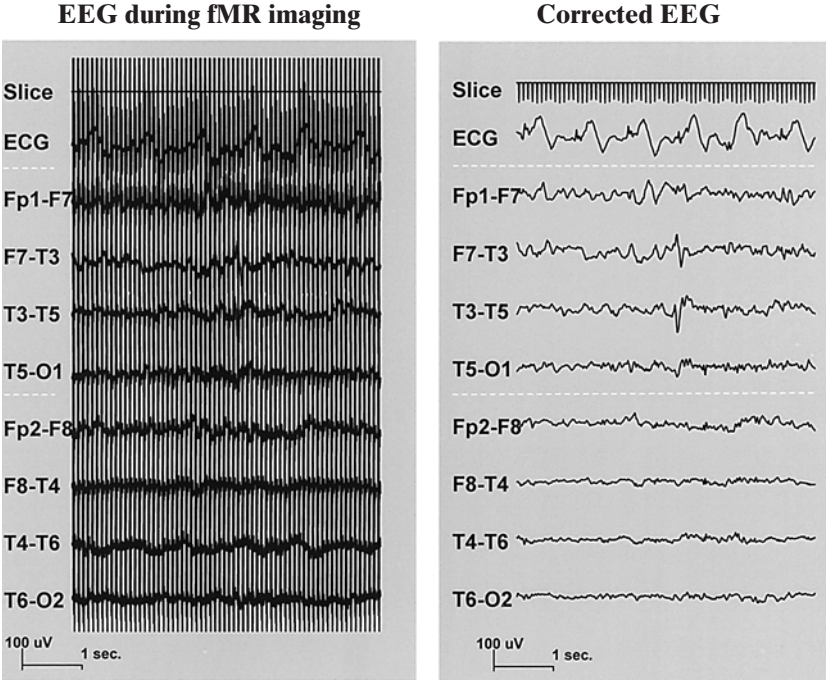


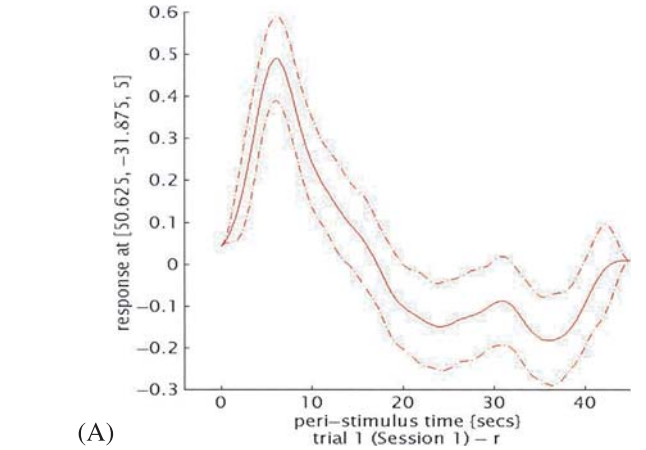
Figure 12.3. Two segments of an EEG recording made during a continuous EEG/fMRI experiment before and after image artifact subtraction. The possibility of removing image acquisition artifact enables continuous and simultaneous EEG/fMRI in contrast to spike-triggered fMRI. (Neurologic coordinates).

While the studies mentioned above dealt predominantly with patents with focal epilepsy, there exists only one study applying EEG-correlated fMRI to a patient with idiopathic generalized epilepsy and absence seizures. A 36-year old patient with intractable juvenile absence epilepsy had four prolonged runs (from 31 to 60 seconds) of three hertz generalized spike-wave discharges during continuous and simultaneous EEG/fMRI. There were two highly significant patterns of seizure-related BOLD changes. Positives changes of around three percent relative to baseline were seen exclusively within the thalamus bilaterally (three percent signal change relative to the baseline). Negative signal changes were present symmetrically over large areas of cortical grey matter with a frontal emphasis and a maximum of around minus eight percent relative to baseline. This result suggests the reciprocal participation of focal thalamic and widespread cortical networks during human absence seizures. The negative cortical BOLD response may be interpreted as an inactive cortical state with low mean synaptic activity during absence seizures.[136]

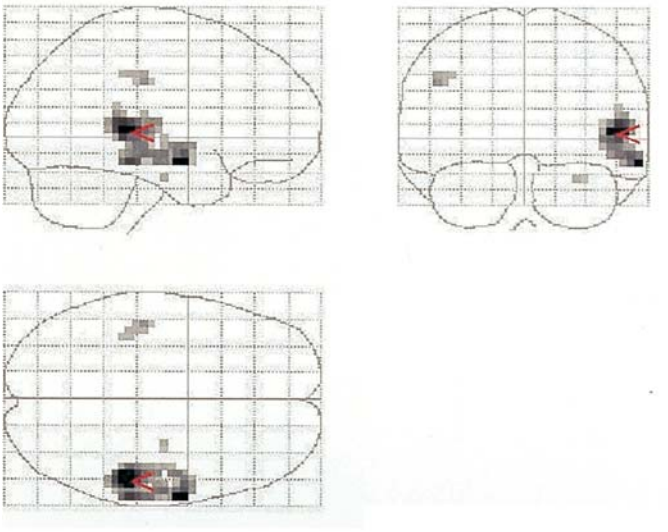
The possible clinical application of EEG-correlated fMRI would be contributing to the accurate localization of the epileptogenic zone, which is the basis for successful epilepsy surgery in patients with medically refractory focal seizures. Information on the epileptogenic zone is derived from the convergence of diverse investigations. In some patients, particularly with neocortical cryptogenic epilepsy, additional intracranial EEG recordings often have to be applied to reliably identify the epileptic focus. It remains unclear whether EEG-correlated fMRI has the potential to replace invasive techniques, or at least provide additional information to guide the placement of invasive intracranial electrodes where necessary. The clinical interpretation of the fMRI activation maps is difficult for various reasons:

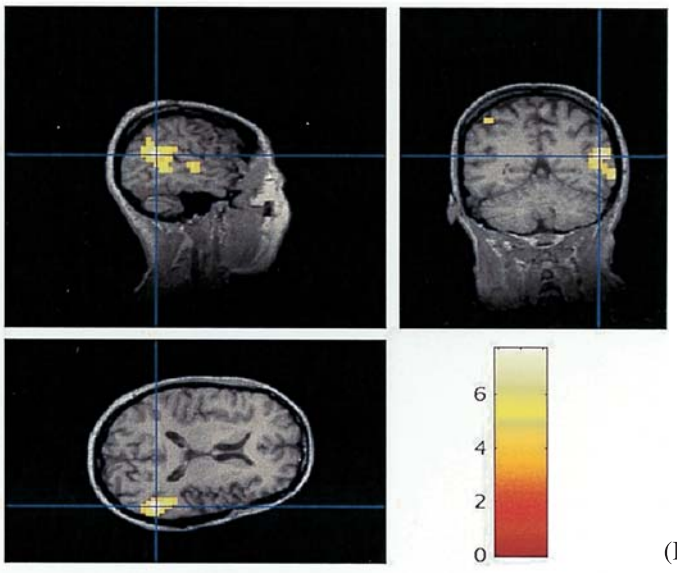
1. The size of the fMRI activation cluster is greatly variable between studies and between subjects in individual studies. Some patients have a widespread, multifocal activation, others show a circumscribed activation (Figure 12.4). The extent of the activation is critically dependent on the applied statistical threshold, which partly explains differences between studies. However, the reason for the variability between patients who were studied with identical methodology and thresholds remains unclear. No significant correlations were found between clinical characteristics (e.g., epilepsy syndrome, spike amplitude) and the size of the fMRI activation. The same applies for the number of IED that have been analyzed. In some patients, even individual IED are associated with large activations;[137] in other patients, as many as 50 IED are not associated with significant activations. Hence, EEG-correlated fMRI may contribute to localize the source of IED, but currently it cannot provide information about its extent.

In patients with widespread fMRI activation, another problem is to distinguish the primary sources from activation, which may represent areas of propagation. In such cases with equivocal information on localization, a combination of fMRI data with EEG source analysis may provide complementary information.[128]



(A)





(B)

Figure 12.4. (A) Result of a continuous and simultaneous EEG/FMRI experiment in a patient with partial seizures due to a right tempro-parietal malformation of cortical development and frequent right temporal spikes. The time course of the event-related response at location of the cross-hair. (B) The fMRI activation is located within the subtle cortical dysplasia. (Neurologic coordinates).

2. Until now, the results of EEG-correlated fMRI have not been validated systematically with a gold standard, which are intracranial recordings and outcomes after epilepsy surgery. Before EEG-triggered fMRI can be used as a decisive method in the presurgical assessment of epilepsy patients, the relation between fMRI results, invasive EEG recordings, and surgical outcome in relation to resection of the activated area has to be established.

3. The high percentage of negative results (up to fifty percent in studies using spike-triggered fMRI,) currently hinders the wider clinical application of EEG-correlated fMRI. In spike-triggered fMRI, the physiological explanation of a negative fMRI result is most likely that a non-significant difference in the blood oxygenation exists between activation and control states. This might be due to there being only a modest cerebral hyperperfusion following an IED, or due to an absence of a true control state, therefore, such as ongoing epileptic activity not detected on scalp EEG. In both cases, the relative signal change within the spike generator may not achieve significance.

As mentioned above, it is conceivable that continuous and simultaneous EEG/fMRI will increase the sensitivity of the method; however, this has to be proven by larger scale studies using this technique and comparative studies between spike-triggered and simultaneous EEG/fMRI. Furthermore, the use of higher-strength magnets will increase the signal-to-noise ratio, and hence, fMRI sensitivity. Multichannel EEG has already been recorded in a four Tesla MR scanner on humans and in a seven Tesla MR scanner in animals.[138] An improved signal-to-noise ratio may not only increase the proportion of fMRI-positive experiments, but also may reduce the number of analyzed IED necessary for a significant fMRI activation, thus rendering this method applicable to patients with less-frequent IED. In summary, EEG-correlated fMRI has to be considered a research tool providing insights to the pathophysiological processes underlying epileptic disorders and in the future may be used in the clinical work-up of epilepsy patients.

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