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The role of functional neuroimaging in pre-surgical epilepsy evaluation

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The prevalence of epilepsy is about 1% and one-third of cases do not respond to medical treatment. In an eligible subset of patients with drug-resistant epilepsy, surgical resection of the epileptogenic zone is the only treatment that can possibly cure the disease. Non-invasive techniques provide information for the localization of the epileptic focus in the majority of cases, whereas in others invasive procedures are required. In the last years, non-invasive neuroimaging techniques, such as simultaneous recording of functional magnetic resonance imaging and electroencephalogram (EEG-fMRI), positron emission tomography (PET), single photon emission computed tomography (SPECT), electric and magnetic source imaging (MSI, ESI), spectroscopy (MRS), have proved their usefulness in defining the epileptic focus. The combination of these functional techniques can yield complementary information and their concordance is crucial for guiding clinical decision, namely the planning of invasive EEG recordings or respective surgery. The aim of this review is to present these non-invasive neuroimaging techniques, their potential combination, and their role in the pre-surgical evaluation of patients with pharmaco-resistant epilepsy.

Keywords: focal epilepsy, EEG-fMRI, ESI, PET, SPECT, MRS, functional neuroimaging

INTRODUCTION

Epilepsy is one of the most frequent chronic neurological disorders, with an incidence of 50/100,000/year and a prevalence of 0.5–1% (1, 2) in the Western society. One-third of patients with epilepsy are resistant to anti-epileptic drug treatment (3, 4) and this outcome is already evident after the first 12 months (5). The majority of patients with epilepsy suffer from focal seizures caused by an abnormal neuro-electrical activity of a focal epileptogenic zone that can subsequently spread to other brain regions. This concept is intimately linked to the correlation between early ictal signs and symptoms, electro-physiological activity, and structural lesion [anatomo-electro-clinical correlation, (6)]. Epilepsy surgery is the only treatment that can possibly cure epilepsy in patients with pharmaco-resistant epilepsy; this option should therefore be considered as soon as pharmacoresistance is manifest or even before in clear cases. In well-selected patients, epilepsy surgery is highly effective: the best outcome is obtained for temporal lobe surgery (up to 84% seizure freedom), followed by lesional extra-temporal epilepsy (up to 74%). The persistence of good outcome (over 50% seizure freedom) has been reported at a longer follow-up (5 or 10 years) (7, 8). Nevertheless, postponing surgery is a major problem and mostly reflects concerns of the medical community that diverge from the available evidence and expert guidelines (9, 10). Misconception of eligibility criteria, variable perception of pharmacoresistance and potential outcome of drug treatment, fear of complications, and/or presumably witnessed complications are the most common causes (11–13).

The risk and benefit assessment prior to epilepsy surgery needs to consider the morbidity and mortality associated with chronic pharmaco-resistant epilepsy. A systematic review on studies between 1990 and 2008 reported a mortality of 0.4% in patients with temporal and 1.2% with extra-temporal lobe resection and major neurological complications due to epilepsy surgery in 4.7% of patients (mostly as major visual field defect) (14). On the other hand, several studies have shown that patients with active epilepsy have mortality three times higher than the general population (expected age- and sex-adjusted mortality) (15, 16). Pre-surgical assessment should therefore be offered to any patient with persistence of seizures despite two treatment trials in sufficiently high dosages (17). The aim of epilepsy surgery is to remove the epileptogenic zone with the preservation of the eloquent areas (18). If the focus cannot be indentified or if it is impossible to remove it because it is located in eloquent cortex, then pre-surgical work-up will not lead to resective surgery; nevertheless in most cases, pre-surgical work-up allows a diagnosis with an inherent prognosis, and the evaluation of other treatment options. In the last 10–20 years, non-invasive functional neuroimaging techniques have proved their usefulness in the pre-surgical assessment of epilepsy, especially thanks to their continuous development. Non-invasive techniques provide information for the identification of the epileptic focus in the majority of cases; nevertheless the use of intracranial EEG is additionally required in 25–50% of patients (19–21). The core of pre-surgical evaluation consists of accurate clinical evaluation, interictal and ictal EEG, dedicated structural MRI with an epilepsy protocol, and neuropsychological assessment.

The aim of this review is to present different functional imaging techniques, currently used to localize the epileptic focus in

the pre-surgical evaluation of patients with drug-resistant focal epilepsy. This review will focus on the functional imaging techniques and will not consider advanced structural techniques such as post-processing of structural MRI, quantitative analysis, and diffusion imaging.

METHODS

An electronic literature search was conducted for articles on this topic regarding human subjects (in all age groups). Sources searched included PubMed and relevant books. To summarize the literature search strategy: (1) words used in the searches included the text words and subject headings of "seizure*, epilep*, localizing value, spectroscopy (or MRS), positron emission tomography (or PET), single photon emission computed tomography (or SPECT), simultaneous functional MRI (or fMRI), and EEG (or EEG-fMRI), electric and magnetic source imaging (or MSI, ESI)." The words were searched independently and in combination. (2) PubMed was also checked for articles already retrieved through other searches. For each citation considered, the abstract was read (when available), and articles were excluded if they were outside the scope of the review. Studies published only in abstract form, letters, and technical reports were excluded. Also excluded were any articles reporting the use of the explored techniques for other indications. The bibliography of each of the retrieved papers was examined to identify relevant references that could have been missed by electronic search. The findings were described taking into account the limit of words and the critical insight of the authors.

ELECTRIC SOURCE IMAGING

PRINCIPLE

Electroencephalography (EEG) has long been the key diagnostic tool for epileptologists and remains at the heart of the pre-surgical evaluation. In the past decades, EEG analysis has been revolutionized by digital and computer technology. Beyond multichannel temporal oscillations EEG data can be represented as time-series of scalp potential maps that vary across time with the temporal resolution in the order of milliseconds (22). Electric source imaging (ESI) allows the estimation of the electric sources underlying these maps (23–25). Several studies have now confirmed its role as an accurate tool for estimating the source of focal epilepsy (26–29).

Electric source imaging is obtained by (i) building a head-model to describe the propagation of electro-magnetic fields through the head and (ii) solving the inverse problem of source localization, which consists of inferring the location of the generators of brain activity from signals detected outside the head. The methodological details and a review of head models and inverse solutions are beyond the scope of this clinically oriented paper. Most important with respect to the head-model in the context of epilepsy is to use the patient's own brain anatomy in order to account for cerebral abnormalities (30–32). Concerning the inverse solution, equivalent dipole or distributed solutions have been applied to epilepsy. While equivalent dipole models assume that the momentary brain electrical activity is confined to a few focal regions, distributed inverse solutions estimate the current density distribution in the whole brain, usually restricted to the gray matter of the individual brain (33, 34). Multiple algorithms for distributed inverse solutions have been developed, each integrating specific *a priori* mathematical and biophysical assumptions (35). These have been the subject of several recent reviews (24, 28, 36).

An important factor to consider is how precisely the electric field is sampled at the head surface. The localization of interictal spikes is significantly improved by increasing the number of electrodes from a standard 31-electrode montage to 128 electrodes (37). Sampling the electric field below the top of the ears is also fundamental to localize generators in the inferior and medial parts of temporal lobes (38). The recent introduction of EEG caps with more than 200 electrodes (up to 256) and easy ways of application has made high-density EEG available in the clinical neurophysiology laboratory (39). A recent reappraisal of the skull conductivity toward higher values reduces the skull "blurring" effect and suggests that even a higher density of electrodes could be beneficial to sampling the brain activity on the scalp. There is evidently a stronger case in children where the conductivity is higher than in adults.

INTERICTAL LOCALIZATION

The majority of studies of ESI (and MSI, see next section) in epilepsy have focused on localizing interictal spikes rather than seizures. Indeed interictal spikes are usually more frequent than seizures, can be averaged together in order to improve the signal-to-noise ratio, and their spatio-temporal dynamics are simpler (40). The temporal resolution of EEG allows differentiating the generation of a spike from its propagation: concerning ESI, the EEG map at its 50% rising phase is selected for source localization, as the IED peak is contaminated by propagation (34). ESI of interictal spikes attempts to localize the irritative zone. The clinical usefulness of these techniques depends both on its absolute accuracy and on the value of the irritative zone as a surrogate for the seizure-onset zone and the epileptogenic zone (which needs to be removed for obtaining seizure freedom (18)). When other clinical informations are integrated in the analysis, the localization of spikes appears to be a valid index of the seizure-onset zone and the epileptogenic zone (41).

Several clinical studies have shown the reliability of ESI in a wide patient spectrum, adults, and children with non-lesional epilepsy or large lesions (32, 36, 38, 42, 43). In a recent ESI study of non-lesional extra-temporal epilepsy (44) only focal interictal, but not ictal discharges, were highly associated with excellent surgical outcome, indicating that the careful analysis and localization of interictal spikes lead to important information for the surgical result. Another recent study validated by intracranial recordings in 33 patients has shown that ESI of interictal spikes is an excellent surrogate for localizing the seizure-onset zone, which is a key to the surgical planning (45), thereby confirming previous intracranial EEG studies of spikes and seizure-onset localization (41). Like the results of each diagnostic tool, the results of ESI must always be integrated within the patient's overall clinical, neurophysiological, and radiological picture, in order to assess its reliability in estimating the epileptogenic zone and identify electroclinical discrepancies that might explain discordant ESI localizations.

The accuracy of ESI has been assessed in large groups of patients with different epilepsy types using intracranial EEG as a gold

standard. Concordance between dipolar sources and intracranial EEG has been found in a high percentage of cases with either temporal or frontal lobe epilepsy (46, 47). ESI is able to localize correctly mesial temporal discharges (i.e., 4–5 cm deep sources) in most of the patients. This has been shown by recording interictal discharges simultaneously from scalp and foramen ovale electrode recordings of the mesial temporal structures (48, 49) as well as in cognitive tasks involving the hippocampus studied with scalp and invasive EEG (50, 51). Recently, simultaneous high-density scalp EEG and intracranial EEG reports have supported these findings (52).

The accuracy of ESI can be also assessed by comparing the results with the resected brain volume as a function of post-operative outcome: the validation is proven if the localization of the studied technique falls within the resection and if the patient is subsequently seizure-free. This approach makes sense in the clinical context of epilepsy surgery, although other factors can play a role in this evaluation (extension of the resection, neuro-surgeons choice). Regarding ESI, in the largest study investigating 152 subsequently operated patients (39), a sensitivity of 84% and specificity of 88% were found, superior to those of more classical localization techniques, such as the presence of a lesion on structural MRI (76% sensitivity, 53% specificity) or focal abnormalities on nuclear functional imaging (interictal PET 69% sensitivity, 44% specificity, ictal SPECT 58% sensitivity, 47% specificity). False positive cases on MRI or PET could be caused by multifocal abnormalities and non-lesional MRI offers obvious false negative cases. Of note, only patients with interictal spikes detected on high resolution EEG were included in the high resolution ESI group, while low resolution ESI was obtained for the others. Importantly, ESI performed as well for patients with temporal lobe epilepsy as it did for patients with extra-temporal lobe epilepsy. The inferior and mesial temporal brain foci were correctly localized when individual head models are used and by providing a sufficient electrode number. Regarding this last point, the accuracy of ESI decreased when ESI was performed based on the standard, 32-channel EEG recordings instead of the 128- or 256-channel high-density EEG systems (sensitivity and specificity around 60%). Other studies with smaller patient numbers support these findings (27, 53). Low density ESI is a valuable additional imaging tool, which only requires a good quality EEG with a well-thought electrode distribution, a standard 3D anatomical MRI from clinical epilepsy imaging protocol, and processing with freeware tools. Therefore, ESI could be performed with little additional cost in any epilepsy surgery center.

ICTAL LOCALIZATION

Also ictal activity can be localized by ESI (54–56). This type of analysis showed good results when computed in the time domain (26, 57) or by using the dominant frequency at the seizure-onset (58). The best concordance between ESI and Stereo-EEG (SEEG) has been obtained for ictal spike patterns and for paroxysmal fast activities on the scalp (55). Different findings, even with lower spatial sampling, have been validated with intracranial EEG recordings (59–61). It is important to apply ESI at the very beginning of the seizure because of fast propagation of the activity and the increasing contamination by muscular artifacts. High-density EEG caps that allow recording for at least 24 h, including period of sleep, will likely increase the number of seizures to be analyzed with ESI. Currently, ictal ESI remains difficult to perform given the low signal-to-noise ratio fueled by artifacts, non-stationary patterns, and the paucity of the recorded events. Post-processing methods, attempting at extracting ictal patterns from the EEG have shown some promises but require further validation (62).

MAGNETO-ENCEPHALOGRAPHY AND MAGNETIC SOURCE IMAGING

PRINCIPLE

Magneto-encephalography (MEG) differs from EEG by the fact that it detects magnetic instead of electric fields produced by neuronal currents, using sensors homogeneously placed around the head (63, 64). The amplitude of magnetic fields for physiological brain activity is very low (from femto-teslas to pico-teslas, eight orders of magnitude smaller than the magnetic field of the earth). For this reason very sensitive magnetometers (superconducting quantum interference devices) and strict shielding from outside interferences are required.

Both MEG and EEG measure cerebral activity in real time, but they measure different physical properties of this activity. This leads to differences in their sensitivity to different configurations of neural generators, but they do not provide independent information about the neuronal generators in the brain as initially postulated [for in-depth discussions, see Ref. (65, 66)]. Magnetic fields diffuse across skull and scalp with no appreciable distortion, whereas electrical potentials are distorted due to the different electrical conductivities due to variations of skull thickness, cranial foramina, previous craniotomies, etc. (63). This allows recording MEG in patients with traumatic or post-operative skull breeches without the major limitations encountered with EEG/ESI, which would require very accurate modeling of the skull anatomy. However, MEG is only sensitive to the activity of neurons located tangentially to the skull. Therefore, MEG reflects the activity in cortical sulci or in the major brain fissures (sylvian, interhemispheric) that is unbalanced by the contralateral surface. On the contrary, EEG is able to record the activity of neurons regardless of their orientation (67), although it can substantially affect the spatial distribution of the observed EEG. An additional difference between the two techniques is that MEG sensors are attached to the machine and not to the patient's head, making MEG very sensitive to patient motion. For this reason, MEG recordings cannot last more than a couple of hours, and it is difficult to perform studies of seizures or in sleep, and in young children or non-cooperative patients.

INTERICTAL STUDIES

Magnetic source imaging can influence the strategy for implanting intracranial electrodes (68, 69). In these two studies, the implantation strategy was decided twice for each patient: first after reviewing the results of all investigations except MSI, and then again after showing the results of MSI. MSI brought to change the implantation strategy in 23–33% of cases, showing that this technique supplies non-redundant information to a significant proportion of patients who have already undergone multiple non-invasive testing modalities. A recent study on 21 MRI-negative patients has demonstrated, by using a recently described method that allows

a delineation of the brain spiking volume [volumetric imaging of epileptic spikes, VIES, (70)], that patients having focal VIES-MEG results are good surgical candidates and the implantation strategy should include VIES results. In contrast, patients with non-focal MEG results have less probably a localized seizure-onset zone; in these cases SEEG is not advised unless clear localizing information is provided by other pre-surgical investigation methods (71). The concept that MSI should be taken into account when defining the strategy for resective surgery is supported by other previous findings of a positive association between inclusion of MSI results in the resection and further seizure freedom (72, 73).

Agirre-Arrizubieta et al. (74) reported concordant localization findings with MSI in 90% of lateral temporal spikes, 80% of interhemispheric and peri-central spikes, and 60% of superior frontal spikes. However, concordant localization was only 40% for orbitofrontal spikes, and 0% for medial temporal spikes. Similar results were obtained by another study by Knowlton et al. (75) who found the concordance between MSI and the seizure-onset zone to be about 80% in patients with lateral temporal lobe epilepsy and 45% in those with medial temporal lobe or extra-temporal lobe epilepsy. The poor performance with mesial temporal and basal frontal discharges can be explained by the difficulty of MEG to visualize deep-seated electrical sources (28). Also studies from the groups of Oishi (76) and Huiskamp (77) have shown, by comparing MEG spikes with Electro-CorticoGraphy spikes that MEG sensitivity varies for different regions in the brain. Knowlton et al. (75) have reported that the performance of MSI was on average similar to that of PET and ictal SPECT. When comparing MSI with depth electrode recordings (69, 78), MEG source localization did show excellent spatial accuracy, especially for neocortical sources.

ICTAL SOURCES

Few cases of seizures occasionally captured during an MEG recording (79) have been also described. The impossibility to record for more than a few hours, limits the ability to record ictal events with MEG.

ESI/MSI COMPARISON

The comparative clinical value of ESI and MSI remains unsettled and controversial. To date, no study has investigated simultaneously recorded interictal spike, with similar numbers of sensors and head coverage with an undisputed gold standard. Studies published until now comparing high-density MEG systems against (at most) moderate resolution EEG recordings artificially tip the balance in favor of MEG (80–82). MEG and EEG are sensitive to different physical features of neural activity, and the two techniques can therefore bring complementary information with different strengths and weaknesses (66). Given their complementary nature, there are many reasons to believe that EEG/MEG combination with high spatial sampling of both modalities could be valuable in specific difficult clinical situations.

SIMULTANEOUS EEG-fMRI

PRINCIPLE

The first fMRI signal modifications related to ictal activity were obtained without concurrent EEG recording (83). By comparing images acquired during seizure and during interictal period, BOLD (Blood Oxygen Level Dependant) signal changes measured by fMRI were observed in regions nearby the epileptic focus. Other fMRI-only studies have confirmed that we can observe BOLD signal variation in concordance with the epileptic focus during simple partial seizures (84) and even in subclinical seizures (85). These results demonstrated the possibility to locate epileptic results in fMRI during ictal or interictal state. To improve the usefulness of this technique, simultaneous temporal detection of epileptic events was needed.

The combination of the temporal resolution of EEG and of the spatial resolution of fMRI offers the opportunity to locate non-invasively the epileptic focus and to better understand the epileptic networks (86, 87). Simultaneous EEG and fMRI recordings (EEG-fMRI) can detect cerebral hemodynamic changes related to interictal epileptiform discharges (IEDs) identified on scalp EEG [(88); for methods: (89)].

While the first EEG-fMRI recordings were spike-triggered acquisitions (90–92), the development of effective removal of MRI-gradient artifacts and pulse-related artifacts allows to record continuously and simultaneously EEG during fMRI (93), offering much improved modelization of the BOLD signal.

INTERICTAL IMAGING

Multiple studies have demonstrated BOLD signal changes mostly in areas tightly coupled with the region generating focal IEDs (94) and concordant with intracerebral findings (95). EEG-fMRI results have proved to be reproducible between scans and more sensitive at higher field scanners (96). The reliability of IEDs-related BOLD responses has been assessed (97) and the importance of an accurate marking and classification of IEDs has been demonstrated (98, 99).

Deep generators have been successfully identified in patients with gray matter heterotopias, illustrating the whole-brain coverage of the technique (100). In malformations of cortical development, EEG-fMRI may help to establish the role of the lesion in the epileptogenesis and to determine the potential surgical target (101). In nine patients with non-lesional frontal epilepsy, focus localization with EEG-fMRI has been subsequently confirmed by other imaging modalities or pathology (102).

A good post-surgical outcome has been linked to surgical removal including the BOLD changes (103). A recent study on 35 operated patients has shown that if the cortex concordant with the maximal BOLD changes was completely removed during surgery, the positive predictive value of seizure freedom (follow-up at 12 months minimum) was 70%, whereas if all the BOLD changes were outside the resection, the negative predictive value was 90.9% (104). In 11/23 patients with focal cortical dysplasia and BOLD responses to spikes, EEG-fMRI was able to provide help in predicting post-operative outcome: focal BOLD changes concordant with the intracranial EEG suggested a good prognosis (4/5 cases), in contrary to diffuse or multifocal BOLD changes (5/6 cases) (105). It has been shown that EEG-fMRI allows a more specific localization of the epileptic focus when compared with scalp EEG alone, in half of patients with epilepsy from heterogeneous etiology (106). In another study, 4/8 patients previously discounted from epilepsy surgery, EEG-fMRI was able to provide complementary information that changed the clinical management (107). All these

studies, invasively validated in some patients, support EEG-fMRI as a clinically useful non-invasive tool in drug-resistant epilepsy to define the epileptic focus. However, the usefulness of the technique remains limited, mostly due to a lack of spikes during fMRI, calling for a continuing effort in methodological improvements. Clear-cut BOLD changes in the resection area appear rather specific for a good outcome while diffuse changes suggest extensive epileptic activity and a worse prognosis.

Other studies demonstrated that EEG-fMRI is an interesting tool to characterize the spatio-temporal dynamics of reflex epilepsies (108–110). Several studies on patients with different types of epilepsy using non-invasive or invasive techniques have shown that focal epilepsies are actually related to an abnormal function of a network of cortical and subcortical brain structures rather than to a single epileptogenic region (87, 111–115). The concept of epileptic network could be explained by the hypothesis that the areas activated or deactivated together with the irritative zone represent privileged areas of discharge propagation. An area that is currently considered as a common node in human IEDs is the anterior frontal part of the piriform cortex (110, 116, 117), called "area tempestas." In animal kindling models of temporal lobe epilepsy, this is an epileptogenically sensitive area (118–120). These and many other findings open the way to the transition from the "focus era" to the "network era" and EEG-fMRI coupled with other non-invasive and invasive techniques offers interesting possibilities in this field. Indeed, epileptic activity can propagate very fast toward neighboring areas, but also toward more distant and even controlateral regions (117, 121, 122). The combination of EEG-fMRI with ESI could help to distinguish activation cluster related to initiation of IED from propagated areas (123–126). The estimated EEG source activity can be used to improve the model of IEDs-related BOLD response and may enhance the localization of the irritative zone (127).

To improve the temporal resolution of fMRI, a newly established fast fMRI sequence called magnetic-resonance-encephalography (MREG) has been recently published and provides a temporal resolution of around 100 ms (128), increasing the yield of EEG-fMRI in epilepsy. This study on 13 patients showed that the patients' number in whom BOLD responses correlated with the spike topography was higher with MREG, compared to conventional echo planar imaging and that the t-values of the BOLD response in the spike field were also significantly higher with MREG. This tool might prove useful in the study of temporal relationships between the different regions of the network, although the temporal resolution will remain two orders of magnitude lower than EEG and MEG.

Studies with large cohorts revealed that no significant spike-related BOLD changes are observed in 40–70% of the EEG-fMRI recordings in patients with focal epilepsy (129, 130). The reasons are twofold: in many patients, the absence of spikes during fMRI acquisition precludes statistical analysis; while in other patients there may be no significant spike-related BOLD changes. One cause of absence of BOLD response could be an imperfect modeling. Concerning this issue, the inclusion of additional confounding variables can improve the modeling of MRI and is variably used across centers: large motion (131), cardiac activity (132), fluctuating physiological rhythms (133), sleep-specific activity (134), eye blinks, and swallowing (135).

Given the high proportion of patients without spikes or the absence of BOLD changes, alternative methods have been proposed. BOLD changes related to focal EEG slowing have been demonstrated (136). The detection of pathological EEG patterns using Independent Component Analysis of the EEG (137) increased the finding of concordant BOLD correlate of epileptic activity from 10 to 16/20 patients. In patients with concordant ICA components, BOLD and IEDs amplitude appear to be correlated (138). To overcome the problem of absence of IEDs in around 40% of the EEG-fMRI recordings, the use of patient-specific voltage map of epileptic spikes obtained from a long-term clinical EEG recording outside the MR scanner was proposed (**Figure 1**). The correlation of this epileptic topographic map with the EEG recorded inside the scanner was used to quantify the presence of ongoing epileptic activity and allow finding BOLD changes concordant with the presumed epileptic focus in 78% of the patients without IEDs during the simultaneous recordings, all with invasive validation (139). This method has subsequently been applied successfully in a pediatric group (140) offering the possibility to drastically improve the sensitivity of EEG-fMRI and to reduce the recording duration.

Different ways to analyze fMRI data, using various signal processing strategies such as independent component analysis or temporal clustering analysis, have been proposed to identify BOLD signatures of interictal activity independently from EEG (141–144). While such strategies represent promising efforts to address the problem of "non-spiking" EEG-fMRI, these methods still need to be validated in larger population of patients.

NEURO-VASCULAR COUPLING

Spike-related BOLD changes occur most often in the form of an increase, but a decrease can sometimes be observed, mostly (but not always) in regions remote to the epileptic focus (145). This phenomenon is still not fully understood (130, 146, 147). When located in the spike field, negative BOLD changes appear to have the same localization value as the positive BOLD (148). Localizing negative BOLD responses are rare, around 10% of all localizing BOLD responses. They are probably linked to a perturbation of the excitation/inhibition metabolic balance (149) and could be related to electro-physiological characteristics of the IEDs, like the presence of slow wave after the spike (150, 151). This could reflect a reduced neuronal activity following the spike, possibly the result of local inhibitory mechanism (152–154), or an impaired neuro-vascular coupling (151).

A modification in shape and/or in time of the canonical hemodynamic response function (HRF) has been reported in some patients especially in children (155–158). In some cases, hemodynamic changes even precede the IEDs (146, 147, 159–161). A study on a homogeneous cohort of children with benign epilepsy with centro-temporal spikes showed that the average BOLD response to centro-temporal spikes had significant differences to the canonical HRF, including an earlier onset and time-to-peak for the positive BOLD signal change, suggesting a possible role of the increase in synaptic activity preceding the spikes (154). Different other hypotheses have been proposed to explain this finding: (i) cerebral

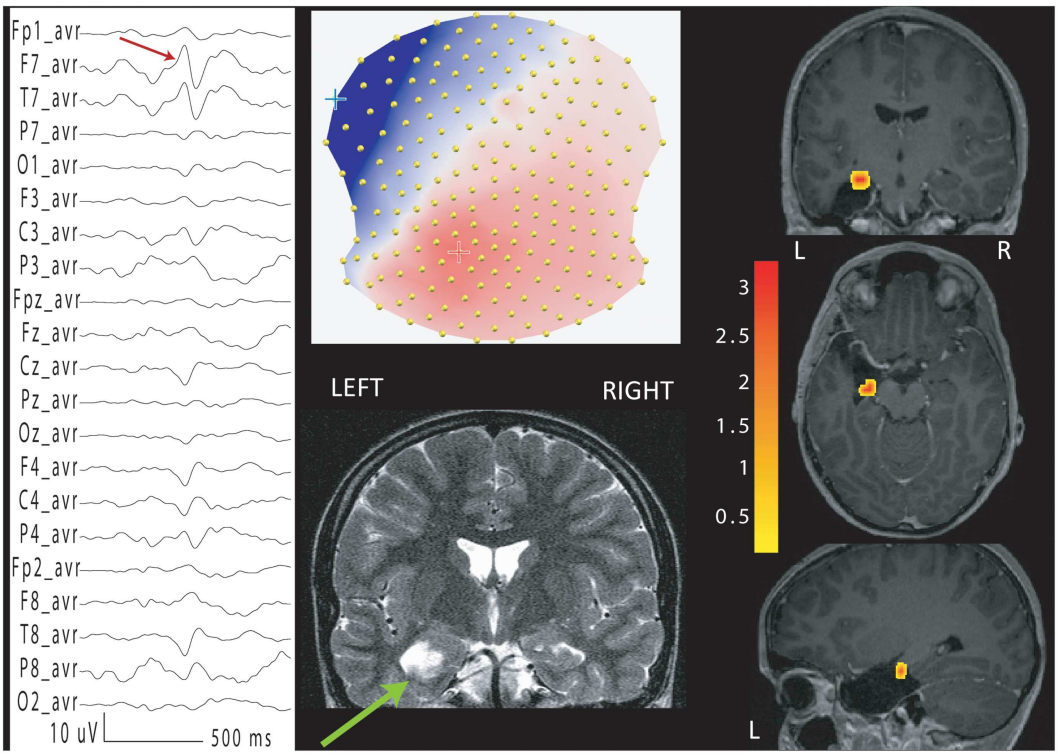

FIGURE 1 | EEG-fMRI in a patient with left temporal lobe epilepsy and left hippocampal cystic lesion (green arrow, bottom center). No IEDs were recorded during EEG-fMRI acquisition. IEDs acquired outside the scanner were averaged (the average spike is indicated by an arrow in average montage, on the left) and the corresponding voltage map was fitted (top center) to the EEG recorded inside the scanner [for method, see Ref. (139)]. The correlation coefficient was taken as a marker of epileptic activity and used as regressor for fMRI analysis. BOLD response showed a maximal activation in the left mesial temporal structures, that were subsequently surgically removed (co-registered EPI image with post-surgical MRI is shown on the right). The patient is seizure-free at 36 months follow-up.

blood flow variations observed could be a source instead of a consequence of epileptic activity (162, 163); (ii) a neuronal discharge from deep structures not visible on scalp EEG occurs before the detected epileptic event (161); (iii) pre-spike metabolic responses could result from non-neuronal mechanisms including glia, and particularly astrocytes, which could be involved in epilepsy and in the regulation of cerebral blood flow (164–166). Different studies have demonstrated an inverted relationship between the resting state GABA measured by MR spectroscopy concentration, and amplitude of BOLD responses (167). New methods without assumptions on HRF based on the mutual information between EEG and fMRI (168) or on the decomposition of fMRI into independent components have been applied to focal epilepsy (169–171).

ICTAL IMAGING

Ictal EEG-fMRI is challenging due to the possible movements of the patients and to the low probability to record a seizure during the acquisition. Nevertheless, some studies demonstrated its usefulness for better understanding the hemodynamic correlates involved in the generation and the propagation of the seizures (162, 172–175). The simultaneous recording of video-EEG during ictal fMRI may help to detect BOLD changes associated to the different phases of the seizure (176). While ictal recordings remain serendipitous, longer scanner time and recruitment efforts have managed to build interesting case series with valuable insights into the seizure dynamics. The clinical value of such investigation remains difficult to assess except in patients with extremely frequent seizures.

SIMULTANEOUS INTRACRANIAL EEG AND fMRI

Several studies also demonstrated the possibility to record simultaneously intracranial EEG and fMRI offering the opportunity to study epileptic networks with unprecedented sensitivity and specificity (177–180). Local and remote BOLD changes to very focal epileptic activity were demonstrated. Given the partial spatial sampling inherent to intracranial EEG, EEG-fMRI could offer a whole-brain investigation of epileptic networks in selected patients with intracranial electrodes. It is also a unique window to investigate neuro-vascular coupling of healthy and pathological implanted brain structures.

POSITRON EMISSION TOMOGRAPHY

In the late seventies, PET has been the first functional technique applied for the localization of epileptic focus in patients with drug-resistant epilepsy (181). It typically uses radio-labeled fluoro-deoxy-glucose (FDG-PET) to show images of interictal brain glucose metabolism. Areas of functional deficit related to

epileptic activity are characterized by reduced interictal metabolism. One of the first PET studies on patients with various epilepsy syndromes suggested that it may obviate the need for intracranial evaluation (182). This too optimistic view of the technique already revealed its potential usefulness especially in unclear clinical situations. FDG has a half-life of ca. 2 h and patients are observed before and after injection, ideally for 30–45 min. Then data is acquired for ca. 40 min, so the image represents the average glucose consumption over that time, with the earlier phase weighing more into the image. Ideally, EEG should be monitored during the "consumption period" (and even longer before) to avoid false "isometabolic" pattern (for instance, the result of a hypometabolic interictal pattern plus hypermetabolic pattern due to subclinical seizures). The spatial resolution of the technique is in the order of 4–8 mm, but the images should be viewed side-by-side with the subject MRI, or best, co-registered with MRI. In some centers, newer systems allowing single-session or even simultaneous acquisition of PET and MRI (183). Visual inspection is usually performed to interpret results in the clinical context, while statistical analyses are mostly used for group analysis. Statistical analysis seemed to improve the yield of FDG-PET in patients with extra-temporal lobe epilepsy compared to patients with temporal lobe epilepsy, increasing the sensitivity from 19–38 to 67% (184).

In surgical candidates with unilateral temporal lobe epilepsy, PET showed clearly visible unilateral hypometabolism, independently of the presence of a MRI abnormality (185). The same study showed that patients with PET hypometabolism concordant with EEG findings benefit from surgery as much as patients with hippocampal sclerosis identified on MRI: around 80% of them were seizure-free after 38 months of follow-up.

Focal interictal hypometabolism of FDG-PET is usually larger than the epileptogenic cortex, reflecting probably the altered function not only of the ictal focus, but also of the areas involved by the first ictal spread (186). It has been shown that the extent of resection of the hypometabolism correlates to outcome of temporal lobectomy (187). The assumption "more resection = better outcome" may well be true when considering only post-operative seizure outcomes in epileptic patients, but it is questionable in terms of cognitive and neurological outcome.

The mechanisms underlying the hypometabolism in epilepogenic cortex are still mostly unresolved: it is known that FDG-PET distribution reflects mainly synaptic activity, rather than cellular loss (188). It has been hypothesized that repeated seizures or dysfunctional cortex (like dysplasia or tubers) induce a protective inhibitory effect through synaptic plasticity (189). This hypothesis is corroborated by the fact that reduction in glucose metabolism is related to epilepsy duration (190). Also, metabolism is affected by anti-epileptic drugs: patients on GABAergic drugs (e.g., benzodiazepines, barbiturates) often exhibit a diffuse hypometabolism which may hinder the identification of discrete areas of the true epileptogenic hypometabolism (191).

Several studies in patients with antero-mesial TLE have shown that hypometabolism can be found not only in the affected area, but also, to a lesser extent, ipsilaterally in the frontal, parietal, insular cortex, thalamus, and basal ganglia (186), corroborating the concept of epileptic network. In unilateral mesial temporal lobe epilepsy bilateral temporal lobe hypometabolism can often be detected, causing ambiguity in lateralizing the epileptogenic zone. It has been shown that having had a recent seizure is the major factor related to this situation: bilateral temporal lobe hypometabolism can be avoided by performing PET scan more than 2 days after the last seizure (192).

Concerning extra-temporal lobe epilepsy, the role of PET is promising, but less well established. A retrospective study on 23 patients with MRI-negative focal cortical dysplasia, who then underwent to surgery, has shown focal or regional concordant PET abnormalities in 22/23 cases, detected either by visual analysis alone or PET/MRI co-registration (193). Twenty of 23 patients were seizure-free at 4 years after a limited areas resection that showed a Taylor-type focal cortical dysplasia in all cases. Another study on 14 patients with similar clinical characteristics has shown that the complete resection of the dysplastic cortex localized by FDG-PET, SISCOM, or intracranial EEG is a reliable predictor of favorable post-operative outcome (194). Therefore, in extra-temporal lobe epilepsies, PET is best used as a guide for focusing the review of MRI in the search for subtle overlooked cortical dysplasia or to inform the placement of intracranial electrodes.

Various other tracers potentially useful in the setting of pre-surgical evaluation are currently limited to few centers and mostly for research purposes, as most of them are based on radiolabeled carbon whose production and use is more difficult than FDG. These are either ligands of specific receptors or neurotransmitters precursor, or transporters, like GABA, glutamate, serotonin, adenosine, acetylcholine, and opioid system. Among these, alpha-methyl-tryptophan has been shown to be superior to FDG for identifying the epileptogenic tuber (195) in a population of seventeen operated children with tuberous sclerosis. The GABA antagonist flumazenil (FMZ) seems to be more sensitive than FDG for lateralizing the focus in temporal lobe epilepsy (196). Increased periventricular [11C] FMZ binding, reflecting heterotopic neuron concentration, has been described as one predictor of bad outcome in patients operated for hippocampal sclerosis (197).

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY

Sir Victor Horsley was the first to notice directly during brain surgery that cortical blood flow increases during a seizure more than 100 years ago (198). SPECT imaging uses tracers, like 99mTc-labeled compounds [hexamethylpropylenamine oxime (HMPAO) or ethyl cysteinate dimer (ECD)] (mainly used in our work-up) that freely cross the blood brain barrier, providing, in this way, information about cerebral blood flow (199). The tracer distributes rapidly and then their distribution is stable for some hours. So, even if acquired a few hours from the injection (time sometimes necessary to move the patient in the SPECT scanner), the images reflect the focal increase of perfusion at the moment of the seizure. If given during the interictal period, reduced or normal uptake can be observed, thus results are ambiguous regarding focus localization. It is important to perform interictal SPECT so that a baseline is available to compare the ictal results.

The SPECT procedure requires expert and vigilant video-EEG monitoring to determine the presence of a seizure. Within a few seconds, the staff needs to read the EEG and/or identifies the patient's habitual seizures, and inject the tracer. Analysis should be done by comparing the ictal with the interictal exam, either

by visual analysis or by computer-aided algorithms, like SISCOM (Subtraction of ictal SPECT co-registered to MRI) (200). The area of maximal perfusion change during the seizure is then co-registered to the patient's MRI.

It has been shown that in temporal lobe epilepsy the initial hyperperfusion of the seizure-onset zone and the propagating areas is followed by a hypoperfusion of the same areas, probably because of an auto-regulatory mechanism (201). Indeed there is a gradual change from the hyper- to the hypoperfused state of the focus with adjacent hypoperfusion, which evolves toward an isoperfused state and gradual recovery in the adjacent regions (202). Depending on the time of injection, SPECT images can reflect the seizure-onset zone, or the propagation areas (203). If the tracer is injected more than 20 s after the onset of the seizure, the precise localization can no more reliably be determined (204, 205). Careful review of the seizure video during which the SPECT was carried out is important to verify ictal injection. Another important concept is that, the accuracy of SPECT in the evaluation of short seizures (i.e., $<$20 s) is much less precise, as 10–20 s are necessary to transport the tracer to the brain.

Different studies have addressed the yield of (ictal SPECT), or have compared it with other pre-surgical techniques.

An extensive review of 39 SPECT studies found that ictal SPECT was correct in 70–100% of patients with temporal lobe epilepsy, suggesting that the technique has a better localization yield in this type of epilepsy (206). Nevertheless, a later study has shown an equivalent or even better yield for extra-temporal epilepsy [86% in extra-temporal compared to 67% in temporal lobe epilepsy (207)]. Some studies that included specifically patients with non-lesional extra-temporal epilepsy have shown that the resection of the SISCOM area is related to good post-operative outcome (194, 208). Similar findings have been corroborated by a prospective study (209), which has shown that if SISCOM is concordant with the future resection site, there are higher chances of having good to excellent post-operative outcome. A study on 71 patients with non-lesional temporal epilepsy with a follow-up of $>$2 years has shown that SPECT is less performant than PET (210): the sensitivity of ictal SPECT was 76% (vs. 37% for the interictal SPECT) and specificity was only 25%. Nevertheless, in patients with intracranial EEG validation of the seizure-onset zone, SPECT/SISCOM appeared to be more sensitive than PET, providing new, and complementary information (211). Our experience (39), using post-operative outcome as gold standard, suggests grossly comparable sensitivity between PET and SPECT (PET: 68%, ictal SPECT/SISCOM: 57%) as well as for sensitivity (PET: 44%, ictal SPECT/SISCOM: 47%).

MAGNETIC RESONANCE SPECTROSCOPY

Magnetic resonance spectroscopy is a non-invasive technique that maps brain metabolism by measuring concentrations of metabolites and neurotransmitters in the brain tissue. Reduced neuronal markers (*N*-acetyl-aspartate) and increased glial markers (choline) are compatible with focal epileptogenic lesion; lactate increase suggests the presence of epileptic activity, which can have local and remote effects, even on contralateral structures (212).

Whereas studies in temporal and extra-temporal epilepsies (some of them with post-operative validation) have showed multifocal metabolic changes without reliable lateralization or localization value (213–215), a recent study suggests that spectroscopy might have a higher predictive value at 7T (216).

MULTIMODAL IMAGING, CO-REGISTRATION AND PERSPECTIVES

The combination of functional techniques can yield complementary information. For instance, EEG-fMRI and ESI measure different signals with different time scale: electrical signal is in the milliseconds order, whereas metabolic response is in the seconds order. In most patients with focal epilepsy, part of the BOLD response to IEDs is highly concordant with ESI (**Figure 2**) even when the two techniques were applied subsequently (217). ESI performed during fMRI recordings allows distinguishing between hemodynamic changes related to spike onset vs. propagation, giving important complementary information to the limited fMRI temporal resolution (125). A study investigating the possibility of using electric source time course for guiding fMRI analysis found that this solution could improve EEG-fMRI analysis. This strategy represents some spatial and temporal filter of EEG-fMRI based on ESI (127). A similar approach improves the interpretation of IED-associated networks of BOLD changes in pediatric focal epilepsies and in epileptic encephalopathy with continuous spikes and waves during slow sleep (123, 126, 218). Such validation of topographic analysis of EEG during fMRI supports the use of advanced EEG features for guiding fMRI analysis. Likewise, BOLD-correlates of pathological EEG topographies markedly improved the sensitivity and specificity of EEG-fMRI, even in the absence of IED (**Figure 1**) (137, 139, 219). It could be wondered how reliable is ESI when performed on pre-processed in-scanner EEG data. ESI outside and inside the scanner is reportedly unchanged but no formal comparison is available. A current problem is that ESI and EEG-fMRI acquisitions and analysis change a lot across centers (220), so comparison among centers could be difficult. Guidelines or recommendations on state of the art of these techniques would be useful in the future.

Integrating these studies with simultaneous scalp and intracranial EEG (52) as well as simultaneous intracranial EEG and fMRI (179, 180) will help address some important issues in the field, such as the ability of ESI to detect mesial temporal activity and important aspects of the neuro-vascular coupling. This is a crucial topic in order to understand mechanisms of EEG-fMRI as it has been reported that electro-physiological and fMRI maps have intrinsic spatial differences (221).

The combination between functional connectivity and structural connectivity, revealed by MRI tractography, could inform on direct and indirect connections within these networks (222, 223).

The understanding of the etiopathogenesis of epileptic syndromes, particularly those with unknown causes, can be provided by PET and SPECT, by revealing various underlying abnormalities that may not be fully appreciated from MR imaging studies (224). The yield of the different combinations of techniques might depend on the localization and etiology. For instance, in tuberous sclerosis, the combination of ESI and PET had a higher yield for localizing the epileptic tuber than the combination of SPECT with either technique (225).

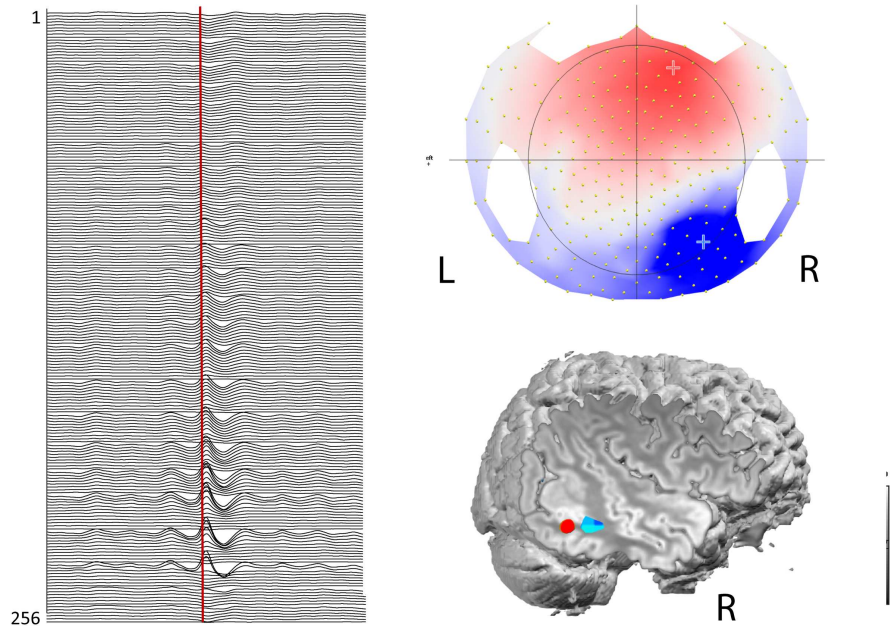

FIGURE 2 | EEG-fMRI and ESI in a patient with right posterior quadrant epilepsy and temporo-parieto-occipital heterotopia. On the left: averaged spikes with equipotential at T8-P8 in a 256 channels EEG recording (voltage map: on the right superior corner). Right inferior corner: co-registration between the patient's MRI, ESI (in red) and BOLD response (in blue) to the same type of spikes, recorded in a separate EEG-fMRI session. Both ESI and EEG-fMRI show a maximum value in the same part of the lesion. ESI was computed at the 50% of arising phase of the spike.

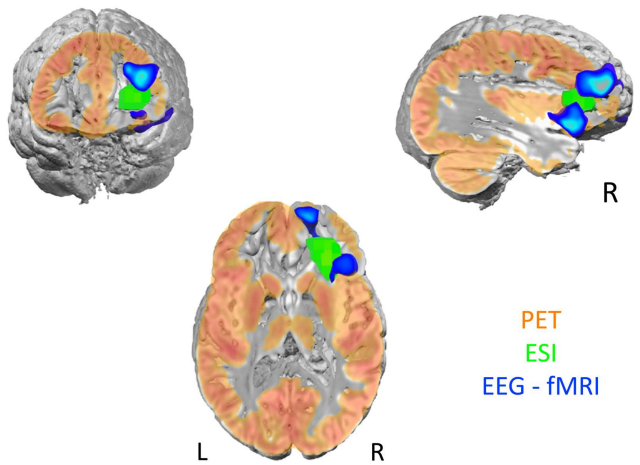

FIGURE 3 | Multimodal functional imaging approach to localize the epileptic focus in a patient with right orbito-frontal focal cortical dysplasia. The hypometabolic region detected by PET (orange) contains both the ESI (green; 256 electrodes, ISMAC, LORETA) and the IED related BOLD response (blue; marked events: FP2-F8 spikes).

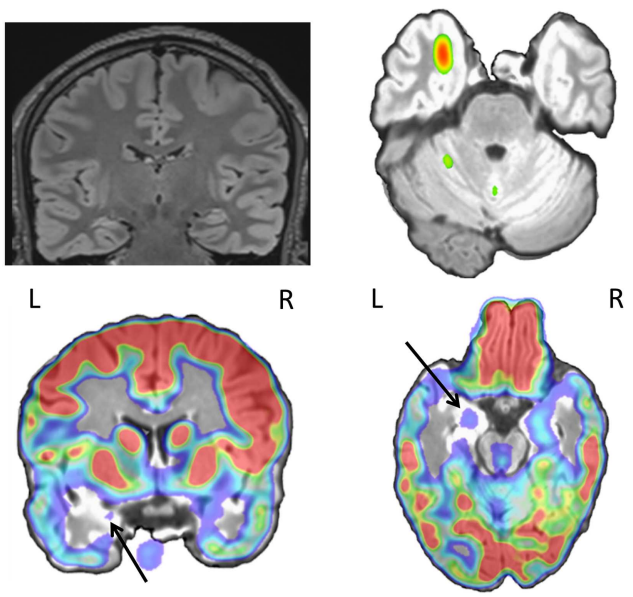

FIGURE 4 | Twenty-seven-year-old patient with left mesial temporal lobe sclerosis (FLAIR sequence, coronal view) and bitemporal interictal spikes. PET showed hypometabolism on the left mesial temporal structures and temporal pole (black arrow). SISCOM showed concordant ictal hyperperfusion (maximum in the temporal pole, shown in the figure).

Beyond clinical MRI and EEG, the pre-surgical work-up shows a high variability across centers depending on the accessible technology and local expertise in structural functional and multimodal imaging. However, a broadly recognized common point is that concordance between the different tests (**Figures 3** and **4**) is crucial for guiding clinical decision. Multimodal functional imaging offers a more detailed picture of the brain networks involved in epileptic activity in individual patients. As a consequence, surgery with or without intracranial recordings can be offered to increasingly difficult cases, while multimodal concordance increases the

chances of favorable outcome (226). A precise co-registration between modalities, with alignment of structural and fMRI, isotopic imaging, electro-physiological sources and high resolution structural MRI for anatomical localization, is obligatory to assess concordance between modalities and guarantee precise intracranial electrode placement and resection margins based on the imaging findings. Co-registration of post-implantation imaging is useful to validate the placement of intracranial electrodes and co-registration with post-operative images. The outline of the performed resection will reveal whether the targeted brain structures and lesions have been entirely removed. In this process, it is important that brain deformation and distortions specific to each image modality are taken into account. Automatization and reduced processing time now allow considering the integration of multimodal preoperative data into the neuronavigation suite for assisting intra-operative decision-making.

CONCLUSION

Multimodal imaging and future developments of neuroimaging techniques improve our understanding of the dynamics of brain with high spatial and temporal resolutions. The detection of subtle structural or functional abnormalities allow considering surgery in a greater number of difficult cases. Imaging findings have a role in guiding the implantation of intracranial electrodes, for improving the success of subsequent surgery. Hopefully, more patients will benefit from surgery without the need for invasive recordings. The concordance between different imaging techniques facilitates better mapping of epileptic zone, epileptic networks, and eloquent cortices. The understanding of functional brain networks will allow us to better understand the neurobiology of epilepsies and develop new diagnostic, prognostic and therapeutic tools.

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