[Frontiers in Bioscience, Elite, 7, 48-65, January 1, 2015]

Multimodal imaging in nonlesional medically intractable focal epilepsy

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1. ABSTRACT

Identification and localization of epileptogenic zone (EZ) is vital in patients with medically-intractable focal epilepsy, who may be candidates for potentially curative resective epilepsy surgery. Presence of a lesion on magnetic resonance imaging (MRI) influences both diagnostic classification and selection for surgery. However, the implications for MRI-negative cases are not well-defined for such patients. Most of these patients undergo invasive long-term Electroencephalography recordings before a final decision regarding resection is possible. Recent developments in structural and functional neuroimaging which include quali-quantitative MRI, Positron Emission Tomography, Single Photon Emission Computed Tomography, and functional MRI have significantly changed presurgical epilepsy evaluation. Source analysis based on electrophysiological information, using either EEG or magnetoencephalography are also promising in order to noninvasively localize the EZ and to guide surgery in medically-intractable focal epilepsy patients that exhibit nonlesional MRI. This chapter aims to review the value of the combined use of structural and functional imaging techniques, and how this multimodal approach improves both selection of surgical candidates and post-operative outcomes in medically-intractable nonlesional focal epilepsy.

2. INTRODUCTION

At least 30% of patients with epilepsy will fail to respond to antiepileptic drug (AED) treatment (1). For those, the best approach is surgical treatment with resection of the epileptogenic zone (EZ) (2, 3). Identification and accurate localization of EZ is vital in patients with medically-intractable focal epilepsy, who may be candidates for potentially curative resective epilepsy surgery. Precise localization of this region should be ideally done using several methods based on different pathophysiological principles. Localization accuracy is a pre-requisite for seizure-free outcome and for minimizing the side effects of the operation, though it remains a challenge, especially for nonlesional epilepsy (4, 5).

Magnetic Resonance Imaging (MRI) is one of the most important diagnostic tools in presurgical evaluation of epileptic patients. However, the proportion of MRI-negative patients in reported epilepsy surgery cohorts ranges from 16 to 47%. Most of these patients undergo invasive long-term EEG recordings before a final decision regarding the possibility of resection. In addition, post-operative seizure freedom rates, with few exceptions, range from 40 to 50% (6-11). There is also evidence that the connotations of normal MRI may be applied more to extratemporal epilepsy than to temporal lobe epilepsy (TLE) surgery (12-19).

Moreover, a satisfactory postsurgical outcome is commonly correlated with positive (MRI) findings, in which focal lesions or cortical abnormalities may be disclosed (7, 20-22).

The ability to localize seizure origin is even more challenging in children with nonlesional epilepsy in whom widespread and extratemporal epileptogenicity related to malformations of cortical development (MCDs) is common. In the pediatric population there is a higher frequency of cortical dysplasia (23), a type of lesion that often shows negative on MRI scans (8, 24, 25). Thus the absence of a MRI lesion weighs heavily against surgical candidacy. That is why, pediatric epilepsy centers typically defer surgical consideration in this population (26).

Structural neuroimaging such as quali-quantitative MRI and functional neuroimaging like Perfusion single photon emission computed tomography (SPECT), using both 99mTc-HMPAO or 99mTc-ECD, and 18F-FDG positron emission tomography (18F-FDG PET) and functional MRI (fMRI) have significantly changed presurgical epilepsy evaluation. Source analysis based on electrophysiological information, using either EEG or magnetoencephalography (MEG) have significantly changed presurgical epilepsy evaluation, particularly in nonlesional cases (5, 27-40). Furthermore, multimodal post-processing and coregistration increase the diagnostic value of all imaging data, and help overcome the intrinsic limitations of individual modalities.

The idea of a poor prognostic implication of normal MRI has been exhaustively stressed. However, relatively little work has focused on identifying the factors that do characterize ‘‘favorable’’ epilepsy surgery candidates within this group (41-43). On the other hand, few studies have proposed that MRI-negative cases, which present challenges in terms of presurgical evaluation and surgery, are indeed surgically treatable with satisfactory outcomes (17, 41-44). Moreover, there is a lack of studies showing the utility of a multimodal approach use in the same patients on individual basis and the value of multimodal imaging in the nonlesional epilepsy population (33, 45-47).

In this chapter we aim to review the value of the combined use of multiple anatomical and functional brain imaging modalities in presurgical evaluation for precise localization of the EZ in epileptic patients with normal MRI. It also reviews the prediction of epilepsy surgery outcome regarding this multimodal imaging approach.

3. MULTIMODAL IMAGING IN PRESURGICAL EVALUATION OF NONLESIONAL MEDICALLY INTRACTABLE FOCAL EPILEPSY

Conventional noninvasive presurgical epilepsy evaluations include ictal and interictal scalp EEG and MRI in practically all patients. Functional imaging is also commonly used, and it plays an important role in localization of seizure onset in patients with nonlesional MRI or multiple potentially epileptogenic lesions. On the other hand, MEG and fMRI are increasingly utilized to localize the EZ and to delineate proximity to eloquent cortex. Each modality has weaknesses and strengths with respect to temporal or spatial resolution, and to functional or anatomical relevance. On the basis of recent research in the field of neuroimaging, several novel imaging modalities have been improved and developed to provide information about the localization of EZ during presurgical evaluation of patients with medically intractable epilepsy (48). Additionally, the concordance of coregistered data from multiple imaging modalities serves as a predictor of seizure-free outcome (49-51).

Several studies, mainly focused on TLE, have described the utility of these techniques including the diagnostic sensitivity and specificity when used separately in various epilepsy groups (47, 52-61). There is also a growing agreement that the combined use of these imaging techniques increases the accuracy of EZ localization (62-64). In other words, a multimodal imaging approach could use concordant imaging findings to achieve better EZ localization.

3.1. SPECT and PET as multimodal neuroimaging

Multimodal post-processing is defined as the simultaneous presentation of two or more modalities which have been spatially coregistered. Although most investigations have focused on the use of single modalities (i.e. SPECT or PET) coregistered to MRI or Computerized Tomography (CT), in practice, combinations of additional postprocessing techniques and imaging modalities are used to improve EZ localization, grid placement, and ultimately outcome (65).

The indications for Subtraction of the interictal SPECT from the ictal SPECT coregistered to MRI (SISCOM) in patients undergoing a presurgical evaluation include nonlesional focal epilepsy, multilobar pathology and conflicting results in the noninvasive evaluation (9). SISCOM may result in better delineation of epileptogenic zone, which may sometimes be missed even on ictal SPECT (66). In patients with normal MRI and refractory epilepsy, SISCOM may also help to detect subtle focal cortical dysplasia, and has been described as particularly useful in identifying the seizure-onset zone in these lesions (56, 67, 68).

The presence of a SISCOM alteration may obviate the need for intracranial EEG (icEEG) recordings in selected patients (69, 70). A prospective study in patients with nonlesional MRI, discordant data in standard presurgical assessment, or widespread MRI lesion showed that SISCOM results altered the electrode implantation scheme in the majority of patients. The concordance of these results with other tests such as EEG, MRI and semiology, were predictive for good seizure outcome (71). In summary, SISCOM significantly improves the results in sensitivity and specificity, particularly in extratemporal lobe epilepsies (54, 55, 72, 73).

Another study that reported the influence of various techniques showed that SISCOM was localizing in 66.7.% of temporal and 84.6.% of extratemporal cases in a selected group of pediatric epileptic patients with excellent surgical outcome (74). Similar results were found by Barba *et al*, showing that SISCOM had a high localizing value and good surgical outcome in this difficult patient group (75). Figure 1 presents SISCOM analysis in one of our patients with nonlesional TLE and postoperative seizure-free outcome.

The use of multimodal coregistration using SPECT and MR spectroscopy in patients with TLE were examined by Doelken, *et al*. This study demonstrated that the combination of modalities increased sensitivity of focus lateralization to 100% and was especially valuable in MRI-negative cases. They also found that combining modalities allowed recognition of bilateral pathology which generally predicts unfavorable postoperative outcome, though it was not examined in their cohort (49).

On the other hand, 18F-FDG PET has higher spatial resolution and lower background activity than perfusion SPECT (29). However, one of the limitations of 18F-FDG PET for the evaluation of epilepsy during the ictal phase is its low temporal resolution. This is due to the fact that 18F-FDG uptake period (30–45 minutes) is significantly longer than the average seizure duration (1-2 minutes) which leads to a mixture of interictal, ictal and postictal phases (76). So, interictal 18F-FDG PET has an established role in the noninvasive localization of EZ (29). Consequently, interictal 18F-FDG PET/MRI coregistration where PET images are fused onto the structural MRI of the same patient provided more sensitivity than PEt alone in the detection of cortical lesions (77).

It has been shown that 18F-FDG PET/MRI has a high sensitivity (up to 98%) to detect focal cortical dysplasia (FCD), especially in patients with mild FCD type I and normal MRI (78). FCDs are highly epileptogenic brain lesions and are one of the most important causes of intractable epilepsy (79, 80). Although the precise mechanisms of epileptogenesis in these lesions are not known, some studies suggest that the over-expression of the multidrug efflux transporter proteins such as P-glyprotein (Pgp) in both malformative and neoplastic glioneuronal tissue from patients with refractory epilepsy may explain one possible mechanism for drug resistance in these pathologies (81-84). A recent result has supported the notion that brain Pgp overexpression contributes to a progressive seizure-related membranes depolarization in hippocampus and neocortex (85). In this context functional neuroimaging techniques such as MR spectroscopy, FDG-PET, or new PET tracers, may infer the presence of abnormality and could help to better localization of pharmacoresistant brain areas (86). (11C)-verapamil (VPM) is the best validated PET tracer to image Pgp function *in vivo* to date. A reduced VPM uptake in refractory compared to seizure-free patients with TLE was reported using (11C)-verapamil. This result supports the hypothesis of Pgp overexpression in refractory epilepsy (87). It is important to highlight that 18F-FDG may be an *in vivo* and *in vitro* marker for multidrug resistant (88, 89).

18F-FDG PET/MRI in nonlesional childhood epilepsy (90, 91) has been also validated. Rubi S *et al*. prospectively evaluated PET and PET/MRI results of 31 nonlesional pediatric patients (92). They demonstrated the ability of this tool to guide a second look at MRI studies previously reported as nonlesional, turning a meaningful percentage of these into subtle-lesional. As a result, 18F-FDG

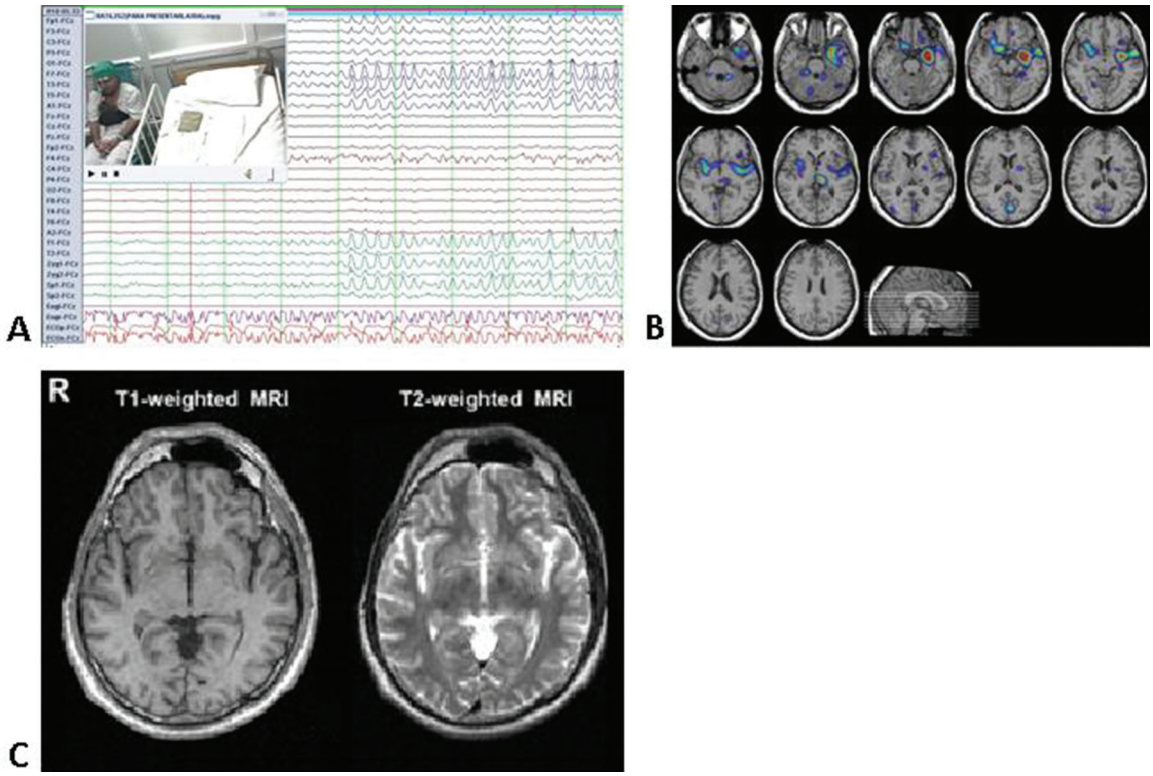

Figure 1. A. Ictal scalp Video- EEG pattern during a habitual complex partial seizure of a 52-year-old patient with nonlesional temporal lobe epilepsy and postoperative seizure-free outcome. Note rhythmic activity at seizure onset in channels containing the temporal leads, F7, T3, Cg3, T1. B. SISCOM study (threshold, + 2 SD) of the patient. SISCOM showed a focal cerebral hyperperfusion in the left temporal lobe, concordant with ictal EEG and clinical data in a region apparently normal by MRI. C. Magnetic resonance imaging of the patient. T1 and T2-weighted sequences did not clearly reveal structural abnormalities.

PET/MRI has become a useful tool for preoperative EZ detection in patients with drug resistant epilepsy and normal or less specific findings on MRI.

Interictal FDG-PET and ictal SPECT have similar sensitivity to localize the EZ, but complementary when the other modality is not localizing in a given patient (93). Both ictal SPECT and interictal PET are sensitive methods for the lateralization of TLE. However, ictal subtraction SPECT is more sensitive when MRI is normal and it is especially useful in frontal epilepsy (31).

In a group of eighteen TLE patients with normal appearing MRI, we found that ictal video-EEG (V-EEG) has the highest percentage of correct lateralization (100%), followed by ictal SPECT/SISCOM and choline/creatine and N acetyl aspartate/creatine metabolic ratios measured by magnetic resonance spectroscopy (94). This study confirmed that localizing data provided by V-EEG and complemented by functional neuroimaging studies can be used to perform successful temporal lobectomies on patients with drug-resistant nonlesional TLE or bilateral structural abnormalities.

Despite the demonstrated utility of nuclear medicine neuroimaging in nonlesional medically intractable focal epilepsy, recent studies combing SPECT and/or PET with electromagnetic source localization data have shown incremental validity to determine EZ for surgical purpose without invasive electrodes or for planning intracranial electrode placement in patients with nonlesional medically intractable epilepsy.

3.2. Electromagnetic source localization and functional neuroimaging

Source analysis based on electrophysiological information, using either EEG or MEG, and neuroanatomical data (e.g. MRI)

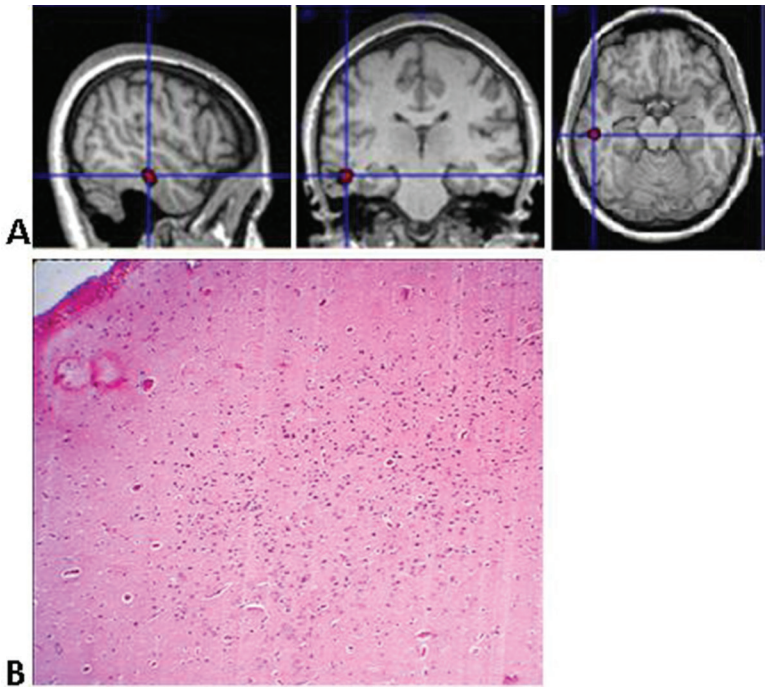

Figure 2. A. LORETA calculated on the average brain space (ab-LORETA) and BMA and LORETA calculated on the individual brain space (ib-LORETA and ib-BMA respectively) in a patient with non lesional right temporal lobe epilepsy. LORETA and BMA solution (time-domain analysis of ictal activity) demonstrated a right temporal source. LORETA solution showed bilateral temporal sources. Note that ib approach introduces a much higher accuracy and precision levels. B. Ictal scalp EEG onset pattern of the patient presented in A. Note rhythmic activity at seizure onset in channels containing the temporal leads, F8, T4, and Cg2.

allow revealing the source localization of interictal/ictal epileptic discharges (IEDs) in patients with focal epilepsy (36-39). These methods include low resolution electromagnetic tomography analysis (LORETA), dipole brain electric source analysis (BESA) and brain distributed variable resolution electromagnetic tomography (VARETA) (5, 34, 95). Recently a bayesian spatio-temporal model for source reconstruction of MEG/EEG data has been also proposed (96). The complementary strengths and weaknesses of established functional brain imaging methods and EEG/MEG-based techniques make their combined use a promising avenue for studying brain processes at a more fine-grained level (97).

Anatomical MRI/CT can also be fused in 3D arrangement with data obtained with other functional neuroimaging such as PET, SPECT, fMRI, near-infrared spectroscopy (NIRS) and optical imaging of intrinsic signals (98). These techniques highlight information on the functional correlates of anatomical or space-occupying lesions and their role in focal epilepsy (98, 99).

During the last decade several studies that compare diagnostic modalities with different underlying mechanisms were published (100-102). A study carried out by Santiago-Rodríguez *et al*. (2006) evaluated the concordance of hypoperfusion zones measured by interictal SPECT with BESA and VARETA in patients with complex partial seizures. They concluded that the concordance of hypoperfusion zones was better with BESA than with VARETA (103). Previous studies had found lower concordance rates of magnetic source imaging (MSI), SISCOM and icEEG in neocortical epilepsies compared to mesial TLE cases (33, 47).

In our study we compared LORETA vs Bayesian Methods Analysis (BMA), average brain vs individual brain in patients with nonlesional focal epilepsy. We found that the methods based on time-frequency decompositions of EEG are useful tools to determine ictal EEG onset and the subsequent estimation of their generators. Besides, BMA solutions estimated on individual brains are less distributed than LORETA (Figure 2).

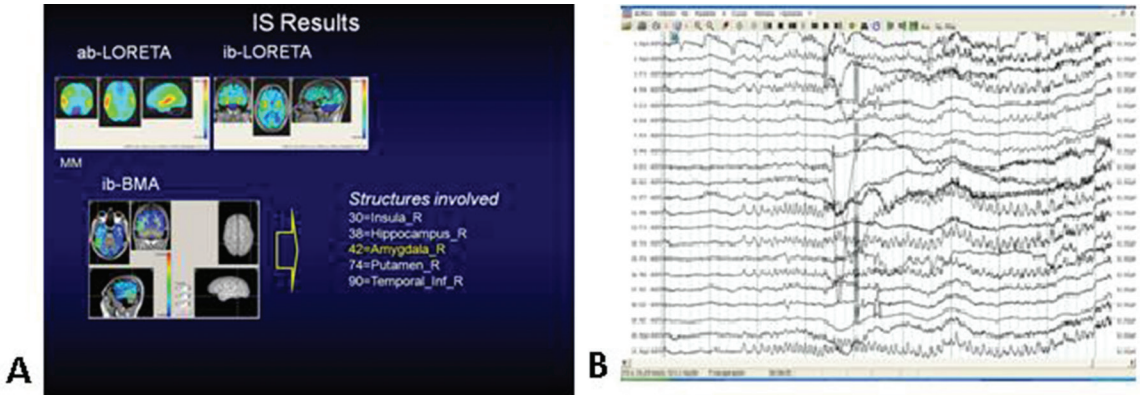

Figure 3. A. Morphometric measurements (volumetric and voxel based morfometry using MRI) in a patient with non lesional qualitative MRI showed in Figure 2. Quantitative RMN localized small signs of structural alteration in the brain medial and inferior temporal girus, consistent with fuctional estimation by inverse solution (BMA and LORETA). B. Focal cortical dysplasia observed in the inferior temporal gyrus resected during epilepsy surgery in the patient with non lesional right temporal lobe epilepsy showed in Figures 2 and 3A. Histopathological features of focal cortical dysplasia type- 1B, (dyslamination associated with giant and immature neurons). Hematoxylin-eosin; bar: 100 µm). Histopathological findings confirmed a diagnosis of neocortical temporal mild Palmini type-IB FCD.

We also found that morphometric measurements (volumetry and voxel based morphometry) are able to localize small signs of structural alteration in the brain when quantitative MRI information is combined with inverse solution estimation. In many cases they can be consistent with functional estimation by inverse solution of the EZ (unpublished data) (Figure 3).

Jayakar P *et al*. (2008) reported that a multimodal integrative approach can minimize the size of resection and alleviate the need for invasive EEG monitoring in a cohort predominantly of children with nonlesional drug-resistant focal epilepsy undergoing successful resective surgery (104).

Various reports on MSI, SPECT, and icEEG in patients with focal epilepsy have been written focused on nonlesional neocortical and mesiotemporal lobe epilepsies (37, 39, 100, 105). One of them, which did not specifically focus on nonlesional neocortical epilepsies, showed that MSI had the highest concordance rate with icEEG compared to SPECT and PET (105).

Not long ago, Schneider F *et al*. conducted the largest retrospective study to examine and compare icEEG with MSI and SISCOM in patients with nonlesional neocortical epilepsy. The most important finding from this study was that sublobar concordance of ictal icEEG with either MSI or SISCOM was superior to ictal icEEG alone in localizing the EZ. Another result was that specificity and positive predictive value of ictal icEEG were higher combined with MSI and SISCOM (102). With regard to the diagnostic values of each modality alone, they did not observe significant differences between icEEG, MSI, and SISCOM. Like previous studies, their findings showed that icEEG had the highest sensitivity for localizing the EZ based on epilepsy surgery outcome (71, 101).

Certainly, few studies have directly compared SISCOM, MEG, and FDG-PET with iEEG in the same patient. One of these studies focused on children with nonlesional epilepsy demonstrated that both SISCOM and MEG had better lobar concordance with icEEG than statistical parametric mapping (SPM) analysis of 18F-FDG-PET (106). These findings suggest that nonlesional neocortical epilepsy with both positive MSI and SISCOM may indicate a higher chance of a localized icEEG result. Therefore, both diagnostic modalities provide additional and not redundant localizing information over the one provided by icEEG alone, even if icEEG is localizing. In a previous study these authors had already suggested that multimodality approach may improve surgical outcome (43).

In recent years, studies have shown that localization accuracy of MEG might be closer to that of the “gold standard” icEEG (100, 101, 107, 108). Knowlton *et al*. observed that MSI had the highest concordance rate with icEEG compared to ictal SPECT and 18F-FDG PET (101). However, MEG is less available and requires more IEDs (38, 64, 109).

Since MEG covers the whole head (e.g., cortices) while icEEG is sample-limited, MEG might be more advantageous in detecting the seizure focus than icEEG in patients with normal MRI. Some reports indicate that MEG may also allow differentiating focal cortical dysplasia (FCD) type I and II (110, 111).

When Leijten, F.S *et al* compared MEG and simultaneous EEG using high-resolution source imaging in mesiotemporal lobe epilepsy, it was found that MEG localized sources were more superficial, whereas EEG localized sources were deeper. They demonstrated that the yield of spikes was too low, and EEG/MEG equivalent current dipoles modeling showed partial correlation with ECoG findings (112).

Further, Kaiboriboon *et al*. (2010) demonstrated that when MRI, and/or ictal scalp EEG is not localizing, MEG/MSI can detect medial temporal spikes and it may provide important localizing information in patients with mesial TLE (113).

High-density EEG and EEG-fMRI are also noninvasive imaging techniques which separately considered are widely used to investigate electrical activity and abnormal neural activity in relation to blood oxygen dependent level (BOLD) activity respectively (114). These imaging techniques can be combined to map noninvasively abnormal brain activation elicited by epileptic processes. Zhang *et al* observed in EEG-fMRI exams that hemodynamic changes related to IEDs in patients with MRI-negative TLE are often localized in extratemporal regions. This might be noninvasive evidence that the ictal onset zone of these patients are not localized in the temporal region (115). Thornton R *et al*. also suggested that EEG-fMRI may provide useful additional information about the seizure onset zone in epileptic patients with FCD. Widely distributed discordant regions of IED-related hemodynamic change appear to be associated with a widespread seizure onset zone and poor postsurgical outcome (114).

In practice, a multimodal imaging approach for presurgical evaluation has been taken by various epilepsy centers in which concordant neuroimaging findings often reduce the need for icEEG in presurgical planning. For example, in the protocol of drug-resistant epilepsy presurgical evaluation in our center, if the findings of noninvasive techniques such as long-term video-EEG, ESI (EEG Source Imaging), MRI, ictal SPECT/SISCOM are convergent, then presurgical icEEG monitoring is unnecessary and surgical treatment with ECoG (electro-corticography) is performed; otherwise, presurgical icEEG monitoring is suggested (5, 94).

It is important to point out that promising noninvasive neuroimaging such as MEG/MSI, PET and ictal SPECT alone or in combination; so far still cannot replace invasive icEEG in localizing EZ especially in nonlesional extratemporal epilepsies. However, these neuroimaging techniques could minimize the need for invasive presurgical monitoring in certain cases. On the other hand fMRI, MEG/MSI and EEG/ESI have reduced the need for ECoG in mapping the eloquent cortex, and also fMRI might replace invasive Wada test in language lateralization.

Lastly, accurate anatomic models using noninvasive presurgical imaging data combined with post-implantation electrode maps can be of immense value after a failed epilepsy surgery, providing important data regarding localization of functional cortex in relation to ictal abnormalities and potentially avoiding duplication of previous invasive studies.

4. MULTIMODAL NEUROIMAGING AND EPILEPSY SURGERY OUTCOME

Multimodal neuroimaging is needed not only in presurgical evaluation, but also during functional navigation in epilepsy surgery (116). Assessment of clinical validity of multimodal imaging in epilepsy surgery requires post-surgical outcome. Up to the present, most studies, have been limited to case reports of correlation with icEEG. However, test concordance in presurgical evaluation is also essential for predicting the epilepsy surgery outcome (77).

Previous studies have found lower concordance rates of MSI, SISCOM and icEEG in neocortical epilepsies compared to mesial TLE cases (32; 33). On the other hand, another investigation had demonstrated that positivity of all tests including MSI, 18F-FDG PET and ictal SPECT predicted increased odds for seizure free outcome after surgery (117).

Correlations to surgical outcome suggest that SISCOM also provides complementary information to MRI or neurophysiological findings (70, 71, 118-122). O'Brien *et al*. reported an excellent outcome when SISCOM localization was concordant with surgical-resection site in patients with medically intractable focal epilepsy and normal

MRI (55). That is to say, resection of the area of increased perfusion is associated with better surgical outcome.

In a multicenter study, Matsuda *et al*. (2009) compared SISCOM with regular ictal SPECT and found that SISCOM provides higher predictive value of good surgical outcome and more reliability on the diagnosis of the epileptogenic focus than side-by-side comparison in medically intractable partial epilepsy (123).

SISCOM has also shown to have high localizing and predictive value for seizure-free outcome in extratemporal lobe epilepsy (74, 101). In 2013, Kurd *et al*. showed that complete resection of the dysplastic cortex localized by SISCOM, FDG-PET or icEEG was a reliable predictor of favorable postoperative seizure outcome in patients with nonlesional extratemporal epilepsy (124).

Lee *et al*. showed that seizure-free outcome could be achieved in 47% and that up to 90% seizure reduction could be achieved in 80% of the patients with refractory epilepsy and normal MRI evaluated with ictal SPECT and 18F-FDG PET (125).

In an interesting study, Knowlton *et al*. (2008b) investigated the prediction of epilepsy surgery outcome regarding ictal SPECT, MSI, and 18F-FDG PET (105). Most of the 34 SISCOM patients in this study had extratemporal lobe epilepsy with no localizing MRI or EEG. SISCOM had the highest predictive value (odds ratio= 9.9.) for excellent surgical outcome. Further, it was found that MEG/MSI, PET and ictal SPECT had clinical value in predicting good surgical outcome for patients with nonlocalized MRI or video-EEG, and MEG/MSI was close to ictal icEEG in predicting a good surgical outcome (105).

Schneider´s investigation also clearly shows that a multimodal approach can significantly contribute to predict surgical outcome (102). They found that specificity and positive predictive value of ictal icEEG were higher combined with MSI and SISCOM. Interestingly, they observed that MSI was more advantageous compared to SISCOM in predicting seizure-free epilepsy surgery outcome, when sublobar concordance of MSI with ictal icEEG was present whereas a positive SISCOM concordant with ictal icEEG and complete resection may have prognostic implications, forecasting a more advantageous epilepsy surgery outcome.

Two recent studies reported that concordance of icEEG with MEG results increased the predictive value for a seizure-free surgical outcome in patients with nonlesional neocortical epilepsy (102, 126). Seo´s *et al*. investigation also compared SISCOM, MEG, and FDG-PET with icEEG and surgical outcome in children with nonlesional epilepsy, and concluded that multimodality approach may improve surgical outcome (106).

The role of fMRI in the prediction of surgical outcome in epilepsy has also been investigated in some studies. For example, the use fMRI triggered by IEDs (EEG-fMRI) can identify not only hemodynamic abnormalities in the seizure onset zone of patients with epilepsy but also detect abnormal networks that may have implications in surgical outcome. In addition, EEG-fMRI has the advantage of single subject analysis that can add patient-specific information for clinical decisions. These studies have demonstrated that the concordance of IED-triggered hemodynamic abnormalities with the localization of surgical resection is associated with better surgical outcome (114, 127).

In spite of the increasing number of multimodal studies showing the utility of this approach in patients with medically intractable nonlesional focal epilepsy, it would be useful to randomize patients to neuroimaging or invasive techniques in order to assess the clinical utility of neuroimaging more accurately. Besides, there is no meta-analysis clarifying the importance of this approach neither cost-effectiveness studies to identify the most cost-effective method. Accordingly, carefully designed multi-center prospective trials can clarify the usefulness of the combined use of these imaging techniques in epilepsy surgery process.

Notwithstanding that appropriate clinical trials are still needed to provide more evidence, the multimodal approach may play a greater role in presurgical evaluation of nonlesional medically intractable neocortical focal epilepsy patients, or those with multiple potentially epileptogenic abnormalities on MRI. This approach could reduce the costs and risks of epilepsy surgery and provide surgical options for more patients with medically intractable epilepsy.

5. CONCLUSION

Selection of surgical candidates and post-operative outcomes may be improved by recent developments in multimodal analysis that combines

structural and functional neuroimaging techniques. In our view, a multimodality approach is needed to identify subtle abnormalities in presurgical evaluation which may reduce invasive EEG monitoring and surgical failure.

Future prospective multicenter studies and ramdomized randomized placebo-controlled trials are required in order to clarify how the multimodal imaging analysis may contribute both to presurgical evaluation and prediction of surgical outcome in nonlesional epilepsy patients. These studies are also needed to determine how each technique can be optimized, not only economically, but also for individual benefit.

6. ACKNOWLEDGMENTS

We thank Odalys Morales Chacón for her English assistance. We would also like to thank Maria Luisa Rodriguez and Abel Sanchez for their useful cooperation.

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Abbreviations: EZ, epileptogenic zone; MRI, Magnetic resonance imaging; EEG, Electroencephalography; icEEG, intracranial EEG; PET, Positron Emission Tomography; SPECT, Single Photon Emission Computed Tomography; SISCOM, Subtraction of the interictal SPECT from the ictal SPECT coregistered to MRI; fMRI, functional MRI; MEG, magnetoencephalography; TLE, temporal lobe epilepsy; MSI, Magnetic Source imaging; ESI, EEG Source Imaging

Key Words: EEG, epilepsy surgery, MEG, MRI, multimodal imaging, nonlesional medically intractable epilepsy, SPECT, PET, Review

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