Original article

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Combining advanced neuroimaging techniques in presurgical workup of non-lesional intractable epilepsy

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ABSTRACT – *Purpose.* The rationale for this case report is to assess the degree of congruency between the results of several advanced functional, metabolic, and structural neuroimaging techniques used in patients with MRI-negative focal epilepsy. *Methods.* We investigated the presurgical evaluation and postoperative outcome of a patient with intractable, extratemporal epilepsy. Because the habitual seizures in this patient could be easily induced, six, advanced, neurodiagnostic techniques were successively applied (SISCOM, ictal FDG-PET, ictal fMRI, postictal diffusion-weighted imaging, voxel-based morphometry, and MRS imaging). *Results.* The findings for the neuroimaging methods investigated, within the left central region, were fairly congruent. Subsequent, invasive EEG recordings revealed a seizure-onset zone at the site where most of the neuroimaging had shown abnormal findings. The surgical removal of the epileptogenic zone, as defined by concordant neuroimaging and SEEG data, resulted in seizure-free postoperative outcome. Histopathological findings revealed mild focal cortical dysplasia. *Conclusion.* Great efforts should be made to combine most of the advanced neuroimaging methods in the preoperative assessment of non-lesional epilepsy surgery candidates.

Key words: non-lesional extratemporal epilepsy, SISCOM, ictal FDG-PET, ictal fMRI, voxel-based morphometry, MRS, postictal DWI, SEEG, focal cortical dysplasia

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Patients with an intractable, localization-related seizure disorder and normal MRI, *i.e.* with non-lesional focal epilepsy, may be considered for surgical treatment. However, it is difficult to localize the epileptogenic zone in these patients, and epilepsy surgery results are less favorable (Cascino *et al.* 1992; Smith *et al.* 1997, Mosewich *et al.* 2000). This is the main reason for the increasing use of supplementary neuroimaging methods in epilepsy surgery candidates. Multimodal preoperative evaluation with advanced structural, functional, and metabolic neuroimaging techniques may help significantly in the delineation of the epileptogenic zone, and can improve the post-operative outcome. In the last decade, the focus has been on single photon emission computed tomography (SPECT), which is the most appropriate ictal imaging method for identifying the seizure-onset zone in epilepsy surgery candidates. Advanced subtraction ictal SPECT co-registered to MRI (SISCOM) is obviously superior to traditional visual analysis of the interictal and ictal images, and it has thus become a standard part of the presurgical protocol in many epilepsy surgery centres (O'Brien *et al.* 1999, Cascino *et al.* 2004). However, although ictal PET studies and ictal fMRI are difficult to perform, they still may complement ictal SPECT studies because of the different temporal resolutions of these techniques (Engel *et al.* 1983; Detre, 2004). Proton MR spectroscopic imaging (^{1}H-MRSI) providing specific biochemical information in selected brain regions, and voxel-based morphometry (VBM) investigating the local concentration of grey matter, represent other modern screening tools for subtle brain lesions that are invisible on conventional MRI scans (Woermann *et al.* 2001; Kassubek *et* al. 2002; Colliot *et al.* 2006). Another neuroimaging method which may be applicable in the presurgical assessment of non-lesional patients seems to be diffusion-weighted MRI imaging (DWI). Postictal local increase of the DWI signal was repeatedly observed in humans after partial status epilepticus and rarely after single seizures (Hufnagel *et al.* 2003). Recently, many research papers have evaluated the use of these neuroimaging techniques in the investigation of epilepsy patients. Questions remain as to whether data obtained from different advanced neuroimaging techniques point to the same abnormal areas in non-lesional epilepsy. The degree of concordance among the results from various imaging methods is unknown. Many of the techniques above mentioned are difficult to perform, and therefore using all of them in a particular subject is very rare. We report on a patient, investigated in a parallel fashion with six, advanced, neuroimaging methods (SISCOM, ictal FDG-PET, ictal fMRI, VBM, ^{1}H-MRSI, and postictal DWI), the results of which were confirmed by subsequent invasive EEG and successful surgery.

Case report

This study concerns a 25-year-old, right-handed male university student, who presented with an intractable seizure disorder. The age at seizure onset was 13 years. His gestation, birth, and early development were normal. No history of remote symptomatic neurological disease was reported. He suffered from frequent simple partial seizures (SPS) with an initial unpleasant, strangling, throat sensation. In some seizures, somesthetic sensations, localized to the right mouth corner, clearly preceded laryngeal symptoms. In both cases, clonic jerks of the right mouth corner subsequently developed and spread to the right side of the face. In most seizures, tonic posture of the right arm followed these symptoms. The seizures lasted around 15 to 30 seconds, and their frequency gradually increased to 25 per day. Secondarily generalized tonic-clonic seizures were less frequent (≈ 1-2/month). The seizures were consistently associated with awakening, but they also occurred during the day. Repetitive tactile stimuli applied on the right mouth corner and cigarette smoking frequently provoked habitual seizures. Because the seizures remained refractory to different antiepileptic drugs at the maximal tolerated doses (CBZ, VPA, PRM, PHT, LTG, TPM, LEV), the patient underwent a presurgical evaluation.

The neurological examination was normal. Interictal EEG showed focal theta activity in the left frontal temporal region; the ictal scalp EEG displayed a left frontal-central-temporal, low voltage fast activity followed by a rhythmic theta activity lateralized to the left side. Repeated high-resolution MRI examinations, cerebrospinal fluid study and carotid angiography were normal.

Because of the ease of induction of the habitual seizures, six, advanced, neurodiagnostic techniques were successively applied on different days *(figure 1)*. Interictal and ictal ^{99}Tc hexamethylpropylene-amine oxime SPECT scans were obtained (ictal injection was performed 3 seconds after seizure onset; seizure duration was 25 seconds; scans were acquired within 2 hours of the injection). The SISCOM study showed a region of focal hyperperfusion in the left central region. An ictal FDG-PET scan was experimentally acquired during a series of provoked, habitual partial seizures. Subtraction of interictal and ictal PET images co-registered to MRI (SIPCOM) depicted a focal increase in glucose metabolism in practically the same area where the SISCOM revealed ictal hyperperfusion. Functional MRI was performed during two, provoked, habitual partial seizures (seizure duration was 20 and 10 seconds = two active periods, block-design experiment; 1.5 T scanner, EPI sequences: TR = 4520 ms, TE = 40 ms; SPM99). Ictal fMRI data analysis showed significant activation in the left-sided subcortical perirolandic and periventricular occipital regions. Voxel-based morphometry – comparing the grey matter (GM) map of our patient with the average GM maps of 25 age-matched, healthy male controls (Colliot *et al.* 2006) revealed a significant, circumscribed increase in GM within the anterior rim of the left central sulcus, corresponding well with the region of focal hyperperfusion in SISCOM images. By analogy, ^{1}H-MRSI focused on the left pericentral region

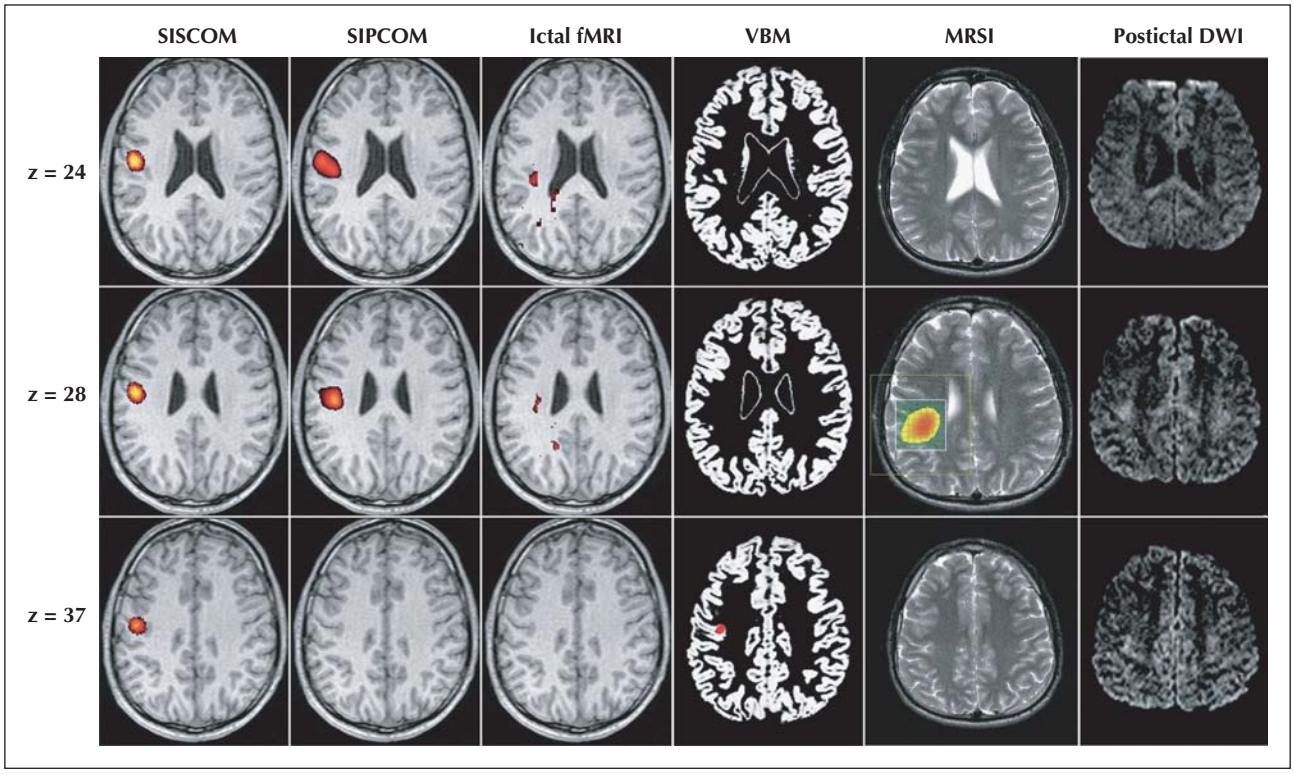

Figure 1. SISCOM and subtractive ictal PET (SIPCOM) [normalized images; depicted pixels with > 70 % of the maximal pixel value (for details see Koo *et al.* 2003)]; ictal fMRI (normalized images; activated voxels meet a significance threshold of $p < 0.007$ uncorrected at a voxel level); voxel-based morphometry (normalized GM concentration Z-score map) – area with GM increase greater than the mean of the controls + 4.5 SD is given in red (Colliot *et al.* 2006); ^{1}H-MRSI (spectroscopic map of NAA levels overlaid to the most corresponding anatomical brain slice; pixels with > 75 % of the maximal pixel value) – increased NAA level is depicted in red; Postictal DWI – focal hyperintensity in the left central region (z = 28 and 37).

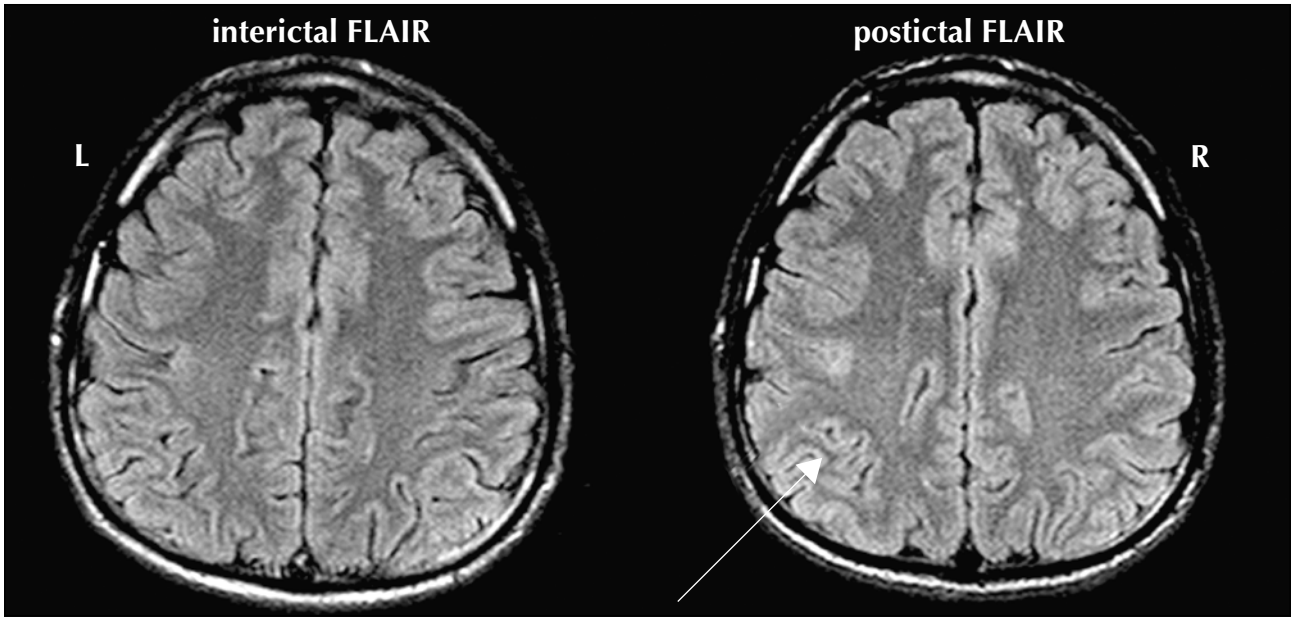

Figure 2. Focal increase in FLAIR signal intensity after the series of simple partial seizures (indicated with arrow).

consistently revealed an obvious focal metabolic abnormality – increase in N-acetyl aspartate levels – which was well matched with the previously described, functional lesions (1.5 T scanner, TE = 80 ms, TR = 1500 ms, voxel size = 5 x 5 x 10 mm). Finally, diffusion-weighted imaging was performed 5 minutes after a short series of four habitual SPS (seizure duration was 20-35 seconds; 1.5 T scanner, TR = 4400 ms, TE = 137 ms, slice thickness = 5 mm). An unequivocal increase in the DWI signal was seen postictally in the left central region. In the corresponding brain area, we also observed a slight increase in the signal intensity in postictal FLAIR sequences *(figure 2)*.

Based on the results of previous investigations, six depth electrodes were implanted in the left pericentral and insular regions. Ictal SEEG then revealed a seizure-onset zone at the site where most of the advanced neuroimaging techniques showed abnormal findings *(figure 3)*. Preoperative mapping of the motor functions (fMRI and cortical electrical stimulation) disclosed a clear-cut shift of cortical representation for the right hand movements to the left postcentral gyrus. The surgical removal of the epileptogenic zone, as defined by SEEG data, included the left precentral region. There was no functional deficit observed postoperatively. With the exception of several, acute, postoperative seizures in the days immediately after surgery, as of the follow-up examination nine months later, the patient was seizure-free. The pathology findings confirmed the presence of mild focal cortical dysplasia (type IA) (Palmini *et al.* 2004).

Discussion

Results of resective surgery in patients with intractable, MRI-negative epilepsy are greatly dependent on a thorough, preoperative invasive EEG investigation. The appropriate choice of intracranial EEG and the correct placement of subdural or depth electrodes are crucial for the post-operative clinical outcome. If a conventional MRI

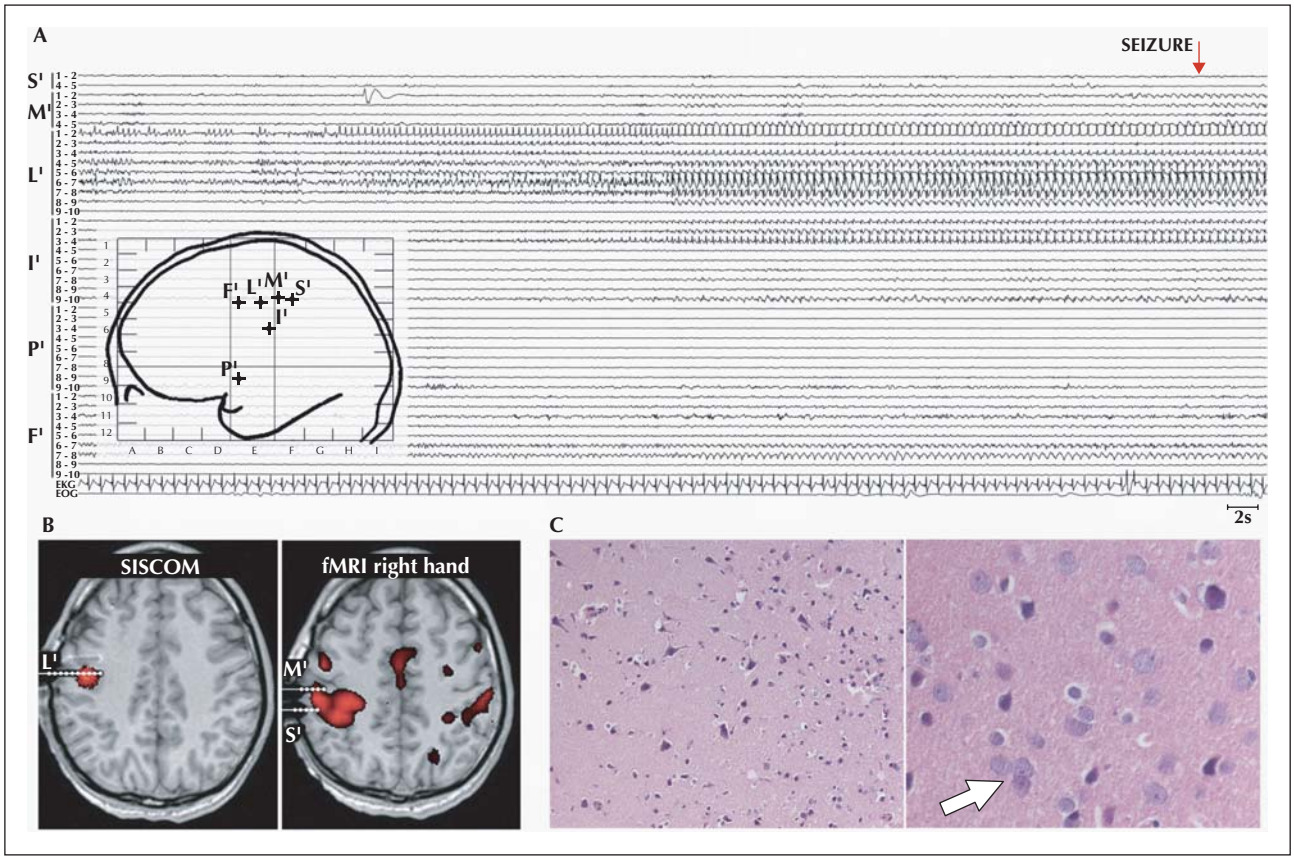

Figure 3. A/ SEEG recording from six multicontact depth electrodes in the left hemisphere: S' – inferior parietal lobule, M' – postcentral gyrus, L' – precentral gyrus (targeted to the region of converging results from neuroimaging studies), I' – upper part of the posterior insula, P' – lower part of the anterior insula, F' – premotor cortex. The ictal discharge arises from the inner contacts of the electrode L'; B/ Subtracted ictal SPECT co-registered to normalized MRI with depth electrode L' *in situ* (left) and functional representation of the right hand motor area (fMRI, red) co-registered to MRI with depth electrodes M' and S' *in situ* (right); C. Histopathological findings underlying the epileptogenic zone revealed focal cortical dysplasia: slightly abnormal cortical stratification, molecular layer neurons, misalignment of neurons (left), and focal neuronal clustering (right).

fails to reveal an obvious epileptogenic lesion, advanced neuroimaging methods may provide important data for a more accurate identification of intracranial electrodes targets. These targets can be more precise when different neuroimaging techniques are combined in the same patient and especially if consistent findings are obtained. However, a complete concordance of different structural, functional, and metabolic neuroimaging findings is strictly theoretical. In practice, many factors prevent definitely concordant results. Miscellaneous pathological conditions, demonstrated by different neuroimaging methods, different temporal resolutions of the functional techniques, distinct seizure durations, and the timing of data collection are just a few of these factors. Despite this, fairly congruent findings were obtained in our patient with MRI-negative focal cortical dysplasia. In addition, invasive EEG recordings revealed a seizure-onset zone precisely at the site where most of the neuroimaging showed abnormal findings. SISCOM and ictal FDG-PET provided the most useful functional data, which matched the results of structural VBM and metabolic MRSI. Yet very little can be said, from this single subject study, about the real sensitivity of the functional neuroimaging techniques used. There is no doubt that the results of our ictal fMRI were greatly limited by the small number of the "active" seizure periods and possibly also by some ictal movement artefacts to which the method is extremely prone. In such a case, a statistical analysis of the data obtained will very likely provide underestimated results. Interestingly, undisputed contributions were also made by postictal diffusion-weighted MRI, even though DWI changes after single seizures has not been previously reported in extratemporal epilepsies. Based on our observation, postictal DWI seems to be another promising diagnostic tool for the *in vivo* depiction of functional focal changes in patients with frequent partial seizures of extratemporal origin. Congruent changes were also observed in postictal FLAIR imaging, the role of which in the presurgical workup has not yet been evaluated.

Even if our study clearly demonstrates a significant contribution of the multimodal approach to the identification of epileptogenic zone, there are clearly potential limits to this strategy for patients with nonlesional extratemporal epilepsies with less localizing ictal semiology. An obvious favourable aspect in this patient was the very suggestive semiological features, pointing to the inferior third of the rolandic cortex. It is very likely that less positive results would be obtained in patients suffering from hypermotor seizures or in patients presenting substantially shorter-lasting ictal signs.

The usefulness of many neuroimaging techniques for the delineation of the epileptogenic zone in patients with single, short seizures is currently under investigation, and their separate use might thus be risky. However, efforts should obviously be made to combine as many techniques as possible in the preoperative assessment of non-lesional epilepsy surgery candidates. □

References

Cascino GD, Jack Jr. CR, Parisi JE, *et al.* MRI in the presurgical evaluation of patients with frontal lobe epilepsy and children with temporal lobe epilepsy: pathological correlation and prognostic importance. *Epilepsy Res* 1992; 11: 51-9.

Cascino GD, Buchhalter JR, Mullan BP, *et al.* Ictal SPECT in the definition of the seizure onset zone. In: Rosenow F, Lüders HO, eds. *Presurgical Assessment of the Epilepsies with Clinical Neurophysiology and Functional Imaging. Handbook of Clinical Neurophysiology*. Amsterdam: Elsevier BV, 2004: 147-54; (Vol. 3).

Colliot O, Bernasconi N, Khalili N, *et al.* Individual voxel-based analysis of gray matter in focal cortical dysplasia. *Neuroimage* 2006; 29: 162-71.

Detre JA. fMRI: Application in epilepsy. *Epilepsia* 2004; 45 (Suppl.4): 26-31.

Engel J, Kuhl DE, Phelps ME, *et al.* Local cerebral metabolism during partial seizures. *Neurology* 1983; 33: 400-13.

Hufnagel A, Weber J, Marks S, *et al.* Brain diffusion after single seizures. *Epilepsia* 2003; 44: 54-63.

Kassubek J, Huppertz HJ, Spreer J, *et al.* Detection and localization of focal cortical dysplasia by voxel-based 3-D MRI analysis. *Epilepsia* 2002; 43: 596-602.

Koo CW, Devinski O, Hari K, *et al.* Stratifying differences on ictal/interictal subtraction SPECT images. *Epilepsia* 2003; 44: 379-86.

Mosewich RK, So EL, O'Brien TJ, *et al.* Factors predictive of the outcome of frontal lobe epilepsy surgery. *Epilepsia* 2000; 41: 843-9.

O'Brien TJ, So EL, Mullan BP, *et al.* Subtraction SPECT co-registrated to MRI improves postictal localization of seizure foci. *Neurology* 1999; 52: 137-46.

Palmini A, Najm I, Avanzini G, *et al.* Terminology and classification of the cortical dysplasias. *Neurology* 2004; 62: S2-S8.

Smith JR, Lee MR, King DW, *et al.* Results of lesional vs nonlesional frontal lobe epilepsy surgery. *Stereotact Funct Neurosurg* 1997; 69: 202-9.

Woermann FG, McLean MA, Bartlett PA, *et al.* Quantitative short echo time proton magnetic resonance spectroscopic imaging study of malformations of cortical development causing epilepsy. *Brain* 2001; 124: 427-36.