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SISCOM and FDG-PET in patients with non-lesional extratemporal epilepsy: correlation with intracranial EEG, histology, and seizure outcome

Martin Kudr [1], Pavel Krsek [1], Petr Marusic [2], Martin Tomasek [2], Jiri Trnka [3], Katerina Michalova [4], Monika Jaruskova [5], Jan Sanda [6], Martin Kyncl [6], Josef Zamecnik [7], Jan Rybar [1], Alena Jahodova [1], Milan Mohapl [8], Vladimir Komarek [1], Michal Tichy [9]

[1] Department of Pediatric Neurology, Charles University, 2nd Faculty of Medicine, University Hospital Motol
[2] Department of Neurology, Charles University, 2nd Faculty of Medicine, University Hospital Motol
[3] Institute of Nuclear Medicine, Charles University, 1st Faculty of Medicine, General University Hospital
[4] Department of Nuclear Medicine and Endocrinology, Charles University, 2nd Faculty of Medicine, University Hospital Motol
[5] Department of Nuclear Medicine - PET Centre, Na Homolce Hospital
[6] Department of Radiology, Charles University, 2nd Faculty of Medicine, University Hospital Motol
[7] Department of Pathology and Molecular Medicine, Charles University, 2nd Faculty of Medicine, University Hospital Motol
[8] Department of Neurosurgery, Charles University, 1st Faculty of Medicine, Military University Hospital
[9] Department of Neurosurgery, Charles University, 2nd Faculty of Medicine, University Hospital Motol, Prague, Czech Republic

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Correspondence:
Pavel Krsek
Department of Pediatric Neurology
Motol University Hospital
Charles University
2nd Faculty of Medicine
V Uvalu 84
CZ 15006 Prague 5, Czech Republic
<pavel.krsek@post.cz>

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ABSTRACT – *Aims.* To assess the practical localising value of subtraction ictal single-photon emission computed tomography (SISCOM) coregistered with MRI and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) in patients with extratemporal epilepsy and normal MRI. *Methods.* We retrospectively studied a group of 14 patients who received surgery due to intractable epilepsy and who were shown to have focal cortical dysplasia, undetected by MRI, based on histological investigation. We coregistered preoperative SISCOM and PET images with postoperative MRI and visually determined whether the SISCOM focus, PET hypometabolic area, and cerebral cortex, exhibiting prominent abnormalities on intracranial EEG, were removed completely, incompletely, or not at all. These results and histopathological findings were compared with postoperative seizure outcome. *Results*. Two patients underwent one-stage multimodal image-guided surgery and the remaining 12 underwent long-term invasive EEG. SISCOM findings were localised for all but 1 patient. FDG-PET was normal in 3 subjects, 2 of whom had favourable postsurgical outcome (Engel class I and II). Complete resection of the SISCOM focus (n=3), the area of PET hypometabolism (n=2), or the cortical regions with intracranial EEG abnormalities (n=7) were predictive of favourable postsurgical outcome. Favourable outcome was also encountered in: 4 of 8 patients with incomplete resection and 1 of 2 with no resection of the SISCOM focus; 4 of 7 patients with incomplete resection and 1 of 2 with no resection of the PET hypometabolic area; and 2 of 7 patients with incomplete resection of the area corresponding to intracranial EEG abnormality. No correlation between histopathological FCD subtype and seizure outcome was observed. *Conclusion*. Complete resection of the dysplastic cortex localised by SISCOM, FDG-PET or intracranial EEG is a reliable predictor of favourable postoperative seizure outcome in patients with non-lesional extratemporal epilepsy.

Key words: ictal SPECT, PET, focal cortical dysplasia, epilepsy surgery, MRI-negative epilepsy

Patients with intractable focal epilepsy and normal MRI represent the most difficult-to-manage group of epilepsy surgery candidates. No exclusive diagnostic test to localise the epileptogenic zone is available and choice of an appropriate therapeutic approach is therefore challenging in these patients. Resective epilepsy surgery is commonly associated with less favourable outcome (Smith *et al*., 1997; Siegel *et al*., 2001; Cukiert *et al*., 2001; Park *et al*., 2002; Chapman *et al*., 2005), although several recent studies have reported no significant difference of surgical outcome between subjects with and without MRI-detected brain lesions (Paolicchi *et al*., 2000; Blume *et al*., 2004; Alarcón *et al*., 2006; Jayakar *et al*., 2008). There is, however, no standard diagnosis or treatment for non-lesional patients.

Functional neuroimaging techniques such as ictal single-photon emission computed tomography (SPECT) and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) are employed when no lesion is seen on MRI. The yield of ictal SPECT can be increased by coregistration of subtracted SPECT images with MRI (SISCOM). Concordance of a SISCOM focus with the site of surgery was shown to predict favourable postsurgical outcome (O'Brien *et al*., 1998a; O'Brien *et al*., 2000; O'Brien *et al*., 2004). Similarly, concordance between focal FDG-PET hypometabolism and the resection site was reported as a significant prognostic factor for surgical success (Salamon *et al*., 2008; Rubí *et al*., 2011; Chassoux *et al*., 2012). It remains, however, unclear whether SISCOM and PET findings represent a reliable guide for planning the extent of surgical resections. The majority of studies still regard intracranial EEG as a "gold standard" for the diagnosis of non-lesional epilepsy patients (Jayakar *et al*., 1994; Paolicchi *et al*., 2000; Chassoux *et al*., 2000; Francione *et al*., 2003; Krsek *et al*., 2009a).

The goal of our study was to assess whether SISCOM and FDG-PET have a practical localising value in extratemporal non-lesional epilepsy, due to FCD, which may help to improve surgical outcome. We carefully correlated functional neuroimaging findings with intracranial EEG, postsurgical MRI, histopathology, and seizure outcome.

Methods

Patient selection

A cohort of patients, who were presurgically evaluated and subsequently underwent an excisional epilepsy surgery from 2003 to 2010, was retrospectively studied. We selected subjects who had: (1) a diagnosis of intractable extratemporal or multilobar epilepsy (based on seizure semiology and EEG findings); (2) at least two good-quality negative preoperative MRI scans; (3) available preoperative SISCOM and FDG-PET examination data; (4) a definitive histological diagnosis of FCD; and (5) known seizure outcome at two years after (last) surgery. Of a total of 270 patients who received surgery during this time period, 85 patients with extratemporal or multilobar epilepsy were identified. Of these, 14 subjects met the above-mentioned criteria and were included in the study. All patients were examined according to the diagnostic presurgical protocol for patients with intractable MRI-negative focal epilepsy, including video-EEG monitoring with scalp electrodes, ictal and interictal SPECT, and interictal FDG-PET. FDG-PET/MRI coregistration and SISCOM in the neuronavigation system were used only for the 2 patients who most recently underwent surgery (Patients 4 and 14). FDG-PET, not coregistered, and subtracted ictal and interictal SPECT studies were used for planning the intracranial electrode placement for the remaining 12 patients.

Magnetic resonance imaging

MRI examinations were performed on a 1.5-T whole-body MR imager (Gyroscan Intera, Philips) with a standard head coil. The MRI protocol used in patients with focal, intractable epilepsy included 1.5-mm thick T2-weighted turbo spin echo (TSE) and T1-weighted inversion recovery slices, as well as 5-mm thick fluid attenuated inversion recovery (FLAIR) in all planes. All images were re-evaluated by an experienced neuroradiologist (M Kyncl) and two neurologists (PK and PM). For this assessment, the reviewers had knowledge of clinical history, other diagnostic tests, and the resection site. No obvious MRI lesion was found in any subject. We retrospectively identified a mild widespread right-hemispheric loss of volume, not associated with apparent signal change or abnormal gyration, in Patient 11, and subtle or questionable gyral morphological asymmetry on the same side as surgery in Patients 12 and 14, but without a clear increase of cortical thickness, altered cortical signal, or grey-white matter blurring.

SISCOM

Both ictal and interictal injections of radiotracer were performed by epileptologists or trained technicians during video-EEG monitoring. The radioisotope agent 99mTc-ECD (NEUROLITE®) was used; the injected dose was calculated according to the patient's weight (*i.e.* 10 MBq/kg). The SPECT images were acquired within three hours of the radiotracer injection on a hybrid SPECT/CT camera, Siemens Symbia T. The acquisition parameters were: matrix size=128 × 128; number of projections=120; time per projection=20 seconds; and zoom=2. Tomographic reconstruction was provided by filtered backprojection with Chang's attenuation correction with its parameter equal to 0.11 (including absorption and scatter effects). No sedation during the acquisition was necessary in patients included in the study.

Video-EEG recordings of all seizures with injection were re-evaluated from original files and injection times (intervals between seizure onset and injection) and lengths of seizures with injection were determined as described previously (O'Brien *et al.*, 1998a; O'Brien *et al.*, 1998b; O'Brien *et al.*, 1999). Seizure onset was considered to be the time of the earliest indication of a warning (either verbal or by pushing the call button) or abnormal movements, behaviour, or impaired awareness. The end of a seizure was defined as the time at which point ictal movements or behaviour ceased. When the start and end of the seizure could not be established with confidence, based on clinical features, the ictal EEG of the seizure with injection was reviewed in order to establish the beginning and end of the rhythmic seizure discharge. The time of injection was defined as the time at which point the plunger of the syringe containing the radiotracer was fully depressed. Injection times ranged from 15 to 46 seconds (mean: 22.6 seconds). Length of seizures with injection ranged from 24 to 302 seconds (mean: 76.9 seconds). By comparing injection times and lengths of seizures, we regarded the administration of all radiotracers to be ictal.

The coregistration of ictal and interictal scans was performed using the SPM5 package. Normalisation was performed in order to account for different total activity within the brain. The normalisation volume was defined semi-quantitatively, using an activity threshold which separates brain tissue from the surrounding background. After normalisation, the two images were subtracted; ictal minus interictal. The differences were expressed in terms of statistical deviations from the mean difference within the whole brain. "Hot spots" were sought where the difference between ictal and interictal images was significantly higher ($Z>2$) than the mean difference within the brain, *i.e.*, all SPECT images were thresholded to 2 SDs. The difference of image was coregistered with a postoperative MRI scan of the patient, also using SPM5, and the hot spots were highlighted in order to compare the results (SISCOM focus) with the resection cavity. Since the administration of all radiotracers was ictal, only images of hyperperfusion (and not hypoperfusion) were reviewed.

FDG-PET

Patients included in the study underwent FDG-PET examination on a Siemens ECAT EXACT PET scanner. The patients fasted from midnight and the following morning their blood glucose level was checked prior to the injection of radiopharmaceutical. Depending on body weight, the patients were given 133-403 MBq (median: 209 MBq) of ^{18}FDG, intravenously. The doses were calculated as described before (Jacobs *et al.*, 2005). After the injection of radiopharmaceutical, the patients rested on a bed in a dark room with eyes closed for 29-62 minutes (median: 38 minutes). The scanning was performed in 3D mode with transmission attenuation correction and the images were reconstructed iteratively. All examinations were performed as an interictal study (video-EEG monitoring was not routinely used, however, patients were continuously monitored by parents or trained technicians in order to exclude clinical seizures) and local glucose hypometabolism was therefore regarded as an abnormality.

The semi-quantitative image evaluation was performed by trained nuclear medicine physicians, as described before (Rubí *et al.*, 2011). Evaluation of images was based on a search for significant asymmetry of intensity of glucose metabolism; the images were therefore reoriented to be orthogonal to the sagittal, coronal, and transverse planes. For a more precise evaluation of metabolic activity in temporal lobes, alignment in the long axis of temporal lobes was also performed. The evaluation was comprised of assessment of relative glucose metabolism in deep brain structures (thalami and basal ganglia), cerebellar hemispheres, temporal lobes, and other neocortical structures. Coregistration of FDG-PET and postoperative MRI was performed in order to compare functional information from PET images with the resection cavity.

Blinded review of the overlap between SISCOM/PET abnormalities and the resection cavity

Both SISCOM and FDG-PET images, coregistered to postoperative MRI scans, were reviewed independently by two reviewers (SISCOM: M Kudr and J Sanda; FDG-PET: M Kudr and M Jaruskova). The reviewers were blinded to the clinical data, results of other diagnostic tests, and surgical outcome. They were required to correlate functional imaging findings (the SISCOM focus and FDG-PET hypometabolic area) with the resection site and classify the correlation as "completely resected", "incompletely resected" or "non-resected" (*figures 1 and 2*). We included minimal overlap between borders of functional imaging abnormality and the resection cavity in "complete" resections (no more than two millimetres) since minimal postsurgical retraction of the brain tissue in surgical margins was anticipated (see *figure 1A*). If the assessments made by the two primary reviewers were inconsistent, a third blinded reviewer (PK) analysed the images and a final assessment was based upon agreement between the third reviewer and one of the primary reviewers.

Intracranial EEG

Twelve subjects underwent long-term invasive monitoring using implanted, subdural electrodes (the number of contacts used in individual patients ranged from 50 to 120); intraoperative electrocorticography was performed in the remaining 2 subjects (Patients 5 and 14). Intracranial EEG data were independently re-evaluated by two reviewers (PK and PM) in order to assess the extent of cortical areas which exhibited significant abnormalities. The reviewers were provided with original EEG files, cortical maps with positions of individual contacts, and the extent of resections documented by both intraoperative photos and postsurgical MRI scans. The reviewers were required to evaluate whether the under-defined cortical regions were removed completely or incompletely. Resections were considered complete if the region of significant EEG abnormality was entirely removed.

We used previously published criteria to evaluate intracranial EEG data (Jayakar *et al.*, 1994; Turkdogan *et al.*, 2005; Krsek *et al.*, 2009a). The most critical factor to determine the epileptogenic region was the seizure onset zone, defined as a region exhibiting focal rhythmic activity, bursts of high-frequency discharges, repetitive spiking, or electrodecremental patterns. If secondary foci (*i.e.* cortical regions demonstrating evidence of early spread of ictal activity and active independent spiking) occurred during seizures in tissue adjacent or in regional proximity to the primary ictal focus, they were also included in the resection.

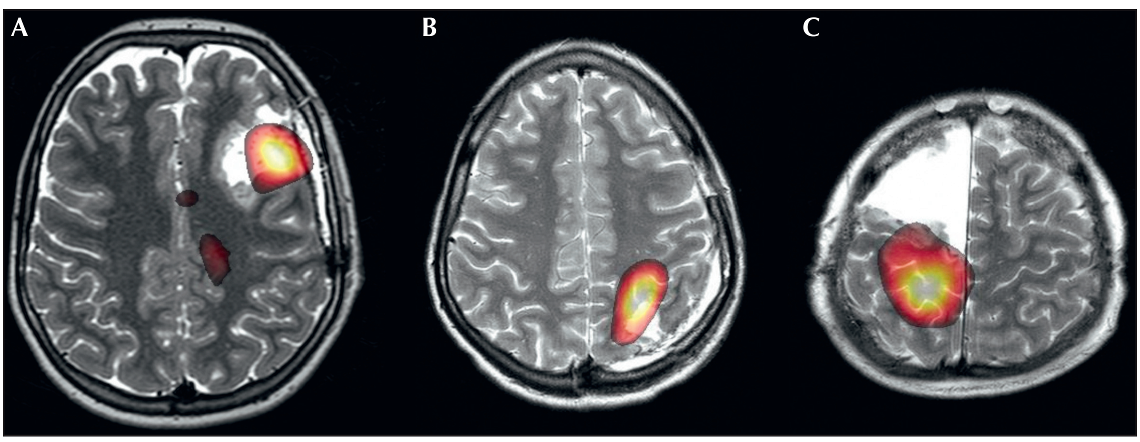

Figure 1. Examples of SISCOM findings and their relation to the site of resection.
SISCOM focus (A) completely resected (Patient 5), (B) incompletely resected (Patient 1), and (C) non-resected (Patient 2).

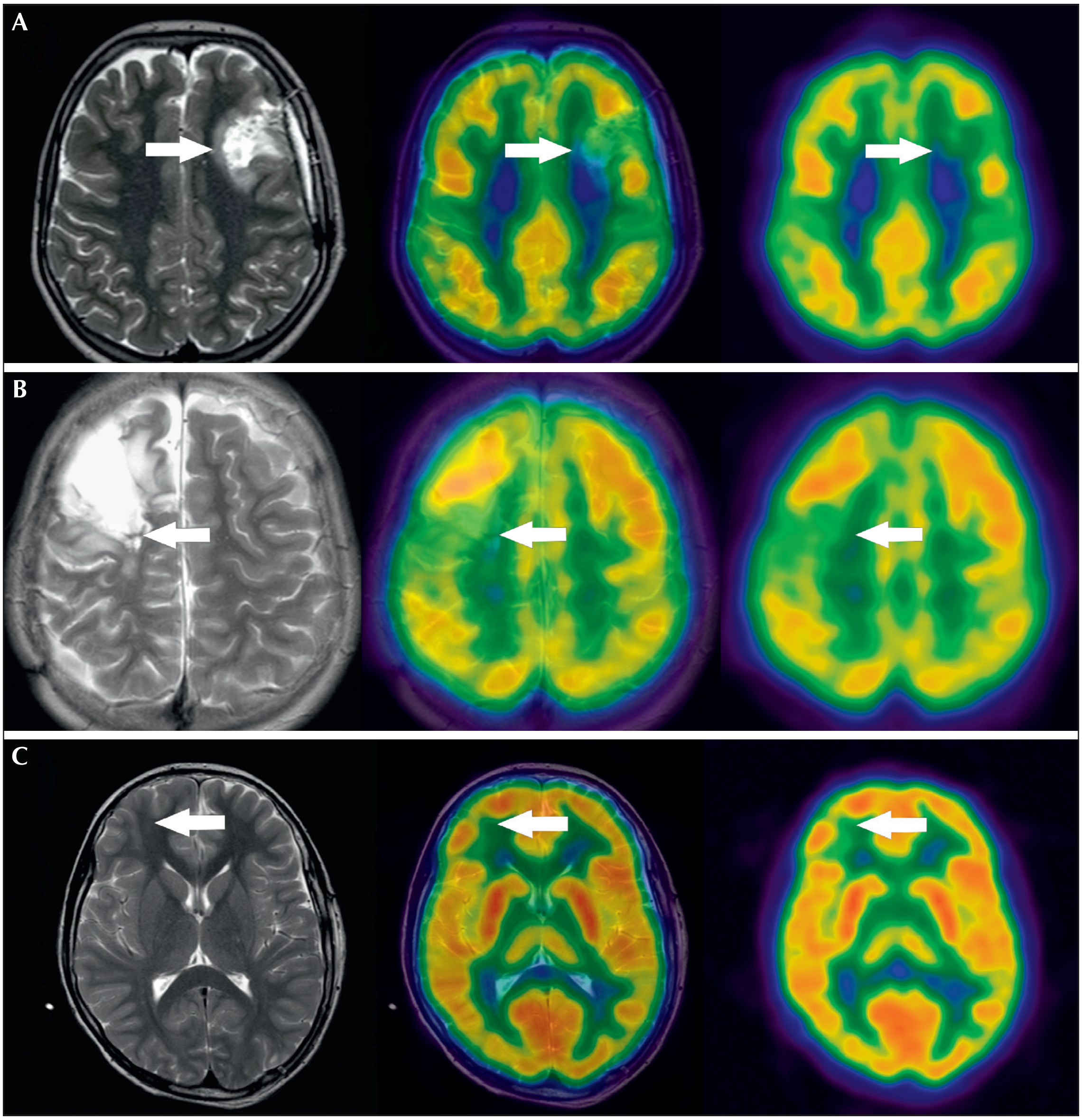

Figure 2. Examples of PET findings and their relation to the site of resection.
PET hypometabolic area (A) completely resected (Patient 5), (B) incompletely resected (Patient 12), and (C) non-resected (Patient 8).

Cortical regions of frequent focal interictal spiking and background abnormalities with consistent focality were also considered to be significant in patients with long-term invasive monitoring and used as primary markers of the epileptogenic region in patients with only intraoperative electrocorticography. Slow waves occurring over widespread regions shortly after seizure onset were not considered to be significant with regards to completeness of resection.

Neuropathological analysis and classification

All neuropathological findings were reclassified according to the current classification scheme of FCD (Blümcke *et al.*, 2011) by an experienced neuropathologist (JZ). Patients with FCD type Ia and Ib were not recognised in our series. FCD type Ic was defined as abnormal radial and tangential cortical lamination together with minor cellular abnormalities (giant and immature neurons). Findings with more pronounced architectural and cytoarchitectural disturbances, especially dysmorphic neurons, but without balloon cells, were classified as FCD type IIa. FCD type IIb was recognised by the same features as type IIa, but demonstrated balloon cells that are pathognomonic for this neuropathological subtype.

Follow-up and outcome

Postoperative seizure outcome two years after final surgery was analysed. Surgical outcome was classified according to Engel's classification scheme: Engel class I (completely seizure-free, auras only or atypical early postoperative seizures only), Engel class II (≥90% seizure reduction or nocturnal seizures only), Engel class III (≥50% seizure reduction), and Engel class IV (<50% seizure reduction). For the purpose of this study, patients were divided into two subgroups: patients with favourable outcome (Engel class I and II) and non-favourable outcome (Engel class III and IV).

Correlation of results

Completeness of resection of SISCOM focus, FDG-PET hypometabolic area, cerebral cortex exhibiting significant abnormalities on inracranial EEG, as well as histopathological findings were related to postsurgical seizure outcome. Statistical evaluation was not possible because of the small size of the data set.

Results

Subjects

Our series was composed of 11 children or adolescents (4 boys and 7 girls) and 3 adults (one man and two women). Mean age at seizure onset was 6.5 years (ranging from 1-14.5 years), mean duration of epilepsy was 9.5 years (ranging from 2.6-33.8 years), and the mean age at surgery was 16 years (ranging from 7.6-41.8 years). Twelve patients had daily seizures. Epilepsy was considered to be frontal or fronto-central in nine, parietal in one, and multilobar in 4 subjects. All subjects, except 3 with mild hemiparesis, had normal neurological examinations. One patient had mild mental retardation; the others had normal intelligence.

Surgery and postsurgical seizure outcome

The following resections were performed: 8 frontal, 1 fronto-central, 2 parietal, 1 temporal neocortical (in a patient who was later shown to have a larger extratemporal epileptogenic zone), o1 temporo-parietal, and 1 temporo-parieto-occipital. Surgery was repeated for 4 subjects and the results presented refer to the last surgical procedure. At two years after the (last) surgery, 9 patients had favourable seizure outcome (Engel class I in 6 and Engel class II in 3 patients) and 5 patients had unfavourable outcome (Engel class III in 1 patient and Engel class IV in 4 patients).

SISCOM

Details of SISCOM findings and the relationship between completeness of the resection of SISCOM focus and seizure outcome are described in *tables 1 and 2*. SISCOM findings were localised for 13 patients; only one finding was not localised (bilateral cerebral hyperperfusions, predominantly on the right, in Patient 4). Favourable seizure outcome was identified for all 3 patients with completely resected SISCOM focus, 4 of 8 patients with incompletely resected SISCOM focus, and 1 of 2 patients with non-resected SISCOM focus.

FDG-PET

Details of PET findings are described in *table 1* and the relationship between completeness of resection of PET hypometabolic area and seizure outcome is shown in *table 2*. We identified normal PET findings in 3 subjects, 2 of whom had favourable seizure outcome. Favourable outcome was identified for 2 patients with completely resected PET hypometabolic area, 4 of 7 subjects with incompletely resected FDG-PET hypometabolic area, and 1 of 2 patients with non-resected FDG-PET hypometabolic area.

Intracranial EEG

Localisation of the epileptogenic zone according to intracranial EEG is shown in *table 1* and the relationship between completeness of resection of intracranial EEG abnormality and seizure outcome in *table 2*. All 7 patients with complete surgical removal of the cortical region, which exhibited prominent abnormalities on intracranial EEG, had favourable outcome, compared with only 2 subjects with favourable outcome in the group of 7 patients with incomplete resections.

Neuropathology

Details of histopathological classification of FCD in individual patients are shown in *table 1* and the relationship with seizure outcome is shown in *table 2*. No correlation between seizure outcome and FCD subtype was found. Favourable postsurgical outcome was determined for 3 of 5 patients with FCD type Ic, 2 patients with FCD type IIa, and 4 of seven subjects with FCD type IIb.

Analysis of surgical failure

The explanation for unfavourable outcome in the 5 patients with unsuccessful surgery was investigated in detail. In all 5 patients, incomplete resection of the epileptogenic zone was caused by overlapping

Table 1. Details of the resection site, functional imaging findings, intracranial EEG, and histopathological findings.

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Sex	F	M	F	M	F	F	F	M	F	M	F	F	M	F
Age at onset of epilepsy	7	3.5	1	13	3.5	14.5	5	4.5	8	6.5	5.5	4.8	9	4.8
Age at surgery	14.3	7.6	13.6	17.7	10.1	17.1	23	11.5	41.8	10	13.3	8.1	24.7	11.1
Resection site	Left P	Right F	Left TPO	Right F	Left F	Left T	Right F	Left F	Left FC	Left P	Right TP	Right F	Left F	Right F
Localisation of SISCOM focus	Left P	Right C	Left PO	Non-localising	Left F	Left CT	Right F	Left FC	Left C	Left TP	Right T	Right F	Left FC	Right F
Resection of SISCOM focus	In-complete	Non-resected	In-complete	Non-localising	Complete	In-complete	In-complete	In-complete	Non-resected	In-complete	In-complete	Complete	In-complete	Complete
Injection time	16	15	20	16	18	27	16	30	39	46	18	17	19	20
Duration of seizure with injection	302	60	79	24	26	102	43	56	113	42	103	38	43	45
Localisation of PET hypometabolism	Normal	Right FCP	Left TPO	Right F	Left F	Left T	Normal	Right F	Normal	Left FTP	Right FTPO	Right FCP	Left FCTP	Right F
Resection of PET hypometabolism	Normal PET	Non-resected	In-complete	In-complete	Complete	In-complete	Normal PET	Non-resected	Normal PET	In-complete	In-complete	In-complete	In-complete	Complete
Localisation of epileptogenic zone according to intracranial EEG	Left P	Right F	Right CTPO	Right F	Left F*	Left CT	Right F	Left FC	Left C	Left CTP	Right TP	Right F	Left F	Right F*
Resection of intracranial EEG abnormality	In-complete	Complete	In-complete	Complete	Complete	In-complete	Complete	In-complete	In-complete	In-complete	Complete	Complete	In-complete	Complete
Histological type of FCD	IIb	IIa	IIb	Ic	IIb	IIb	Ic	Ic	Ic	IIa	Ic	IIb	IIb	IIb
Seizure outcome at two years (Engel scale)	II	I	IV	I	I	IV	I	III	IV	II	II	I	IV	I

F: frontal; C: central; T: temporal; P: parietal; O: occipital. *intracranial EEG findings according to intraoperative electrocorticography.

Table 2. Relationship between seizure outcome and completeness of resection of SISCOM focus, FDG-PET hypometabolic area, cerebral cortex exhibiting prominent abnormalities on intracranial EEG, and histopathological findings.

	Favourable outcome (*n*=9)	Unfavourable outcome (*n*=5)
Resection of SISCOM focus		
Completely resected (*n*=3)	3	0
Incompletely resected (*n*=8)	4	4
Non-resected (*n*=2)	1	1
Non-localising (*n*=1)	1	0
Resection of PET hypometabolism		
Completely resected (*n*=2)	2	0
Incompletely resected (*n*=7)	4	3
Non-resected (*n*=2)	1	1
Normal PET finding (*n*=3)	2	1
Resection of intracranial EEG abnormality		
Complete resection (*n*=7)	7	0
Incomplete resection (*n*=7)	2	5
Histopathological type of focal cortical dysplasia		
Ic (*n*=5)	3	2
IIa (*n*=2)	2	0
IIb (*n*=7)	4	3

dysplastic and eloquent cortical regions (motor cortex in Patients 8, 9, and 13), language cortex (Patient 6), and both motor and language cortices (Patient 3).

Discussion

Planning of epilepsy surgery is challenging in patients with normal MRI, especially in children, because of frequent large epileptogenic zones due to widespread type I cortical dysplasia (Krsek *et al*., 2008; Krsek *et al*., 2009b). The ability to define and fully remove the dysplastic cortex is the most powerful variable that influences outcome in FCD patients; accurate delineation and also, commonly, complete removal, due to a risk of damage to eloquent cortical areas, is however difficult in subjects with normal MRI (Paolicchi *et al*., 2000; Siegel *et al*., 2001; Cascino *et al*., 2004; Jayakar *et al*., 2008; Seo *et al*., 2011). In this study, we were able to critically assess different diagnostic tests used for the localisation of the epileptogenic zone in a series, albeit small, which we believe is representative of patients referred to epilepsy surgery centres with non-lesional extratemporal epilepsy.

The most powerful predictive factor for favourable postsurgical outcome in our series was the complete resection of the cortical region exhibiting prominent abnormalities on intracranial EEG (all 7 patients with complete resection had favourable outcome; of whom 6 were seizure-free). This observation is in accord with previous studies which report intracranial EEG as a "gold standard" for MRI-negative patients (Jayakar *et al*., 1994; Paolicchi *et al*., 2000; Chassoux *et al*., 2000; Francione *et al*., 2003; Krsek *et al*., 2009a). It is, however, important to remind ourselves that some patients with incomplete resection of electrophysiologically-defined epileptogenic regions have favourable outcome (2 of 7 in our series). On the other hand, previous studies have repeatedly reported surgical failure in patients with "complete" resection of the epileptogenic zone, defined by different techniques of intracranial EEG (Chassoux *et al*., 2000; Paolicchi *et al*., 2000; Francione *et al*., 2003; Krsek *et al*., 2009a).

Most previous reports of non-lesional FCD patients included, almost exclusively, subjects undergoing long-term invasive EEG (O'Brien *et al*., 2000; Siegel *et al*., 2001; O'Brien *et al*., 2004; Alarcón *et al*., 2006). However, case reports and small series of patients managed with one-stage surgical procedures have recently emerged (Chapman *et al*., 2005; Jayakar *et al*., 2008; Chassoux *et al*., 2012). The considerable disadvantages of long-term invasive EEG include: discomfort, morbidity and rarely mortality (Pilcher and Rusyniak, 1993), as well as added costs of the procedure (Spencer *et al*., 1993). Similar to intraoperative electrocorticography, a limited area, that may not cover the epileptogenic zone, is sampled (Kaminska *et al*., 2003). Thus, a combined multimodal imaging approach has been proposed to alleviate the need for long-term invasive EEG monitoring in selected subjects with non-lesional epilepsy (Jayakar *et al*., 2008; Seo *et al*., 2011). It remains, nevertheless, unclear with which neuroimaging tests and, in particular, in which patient groups, is it possible to obviate intracranial electrode implantation.

We studied FDG-PET and SISCOM since these neuroimaging tests are currently most widely used for non-lesional epilepsy surgery candidates (Jayakar *et al.*, 2008; Seo *et al.*, 2011). Spatial relationships between SISCOM and FDG-PET findings and the resection cavity were evaluated visually, implying an element of subjectivity and thus a limitation of our study. However, we believe that our method was sufficient to differentiate between patient groups (completely resected, incompletely resected, or non-resected). A quantitative measurement of overlap would have been useful, particularly for the "incompletely resected" group.

We showed that complete removal of either the SISCOM focus or PET hypometabolic area was associated with favourable surgical outcome, although complete resection was achieved only in a minority of our patients (3 patients with complete resection of SISCOM focus and 2 with complete resection of PET hypometabolic area). However, whereas a SISCOM finding was localised (confined to one lobe in 10 subjects) in 13 of 14 patients and at least lateralised for the remaining case, 3 patients had normal PET and 6 of 11 subjects with positive PET had extensive (multilobar) hypometabolic areas which were not useful for precise localisation of the epileptogenic zone. Thus, our results suggest a superior localising value of SISCOM, relative to FDG-PET, in non-lesional extratemporal epilepsy.

FDG-PET did not provide a reliable guide for planning the extent of surgical resections in our series. Four of the 6 patients with extensive PET abnormalities achieved favourable surgical outcome; all of whom underwent incomplete resections of the hypometabolic areas. A few studies have reported a considerably higher number of correctly localising focal or regional PET hypometabolic areas in FCD patients with normal MRI: 68% (Rubí *et al.*, 2011) and 84 % (Chassoux *et al.*, 2012). It was also suggested that incorporation of FDG-PET coregistration in presurgical evaluation enhances non-invasive detection and successful surgical treatment of patients with FCD (Salamon *et al.*, 2008). Other studies, nevertheless, found that hypometabolic areas in non-lesional neocortical epilepsy are often larger than the epileptogenic zone which is, moreover, often observed in the periphery of hypometabolism rather than in the centre (Juhász *et al.*, 2000). Our results are consistent with a recent study that demonstrated better concordance with SISCOM and intracranial EEG than with FDG-PET in children with non-lesional epilepsy (Seo *et al.*, 2011).

The number of SISCOM localisation studies in our cohort (13 of 14) was superior to that of previous series of adults with aetiologically diverse extratemporal epilepsy (67% in all reported patients and 77% in a subgroup of non-lesional subjects [O'Brien *et al.*, 2000]), as well as adult (86%; O'Brien *et al.*, 2004) and paediatric (53%; Gupta *et al.*, 2004) series of FCD patients. All 3 patients with complete removal of SISCOM focus reported here achieved favourable surgical outcome. However, favourable outcome was also encountered for 4 of 8 subjects with incompletely resected and in 1 of 2 with non-resected hyperperfusion zone. These results are in accord with previous studies which report similar methods to compare SISCOM focus and resection site (O'Brien *et al.*, 1998a; O'Brien *et al.*, 2000; O'Brien *et al.*, 2004), and have practical implications for surgical planning: Complete removal of a SISCOM focus is not always required for seizure freedom. This is an important observation since complete resection of a SISCOM focus is not always possible, for example, because of overlap with eloquent cortical areas (see *figure 1C*). Favourable outcome in subjects with incomplete removal of SISCOM focus might be explained by the fact that hyperperfusion areas represent different modes of seizure propagation (Dupont *et al.*, 2006).

The high proportion of patients with incomplete removal of SISCOM focus reflects the fact that our study was retrospectively based on SISCOM data used to confirm the location of the epileptogenic zone and guide intracranial electrode implantation, rather than delineate surgical resections. We have only used the SISCOM method intraoperatively (*i.e.* coregistered to other neuroimaging data in our neuronavigation system) in the 2 most recent cases, managed by one-stage surgery without long-term invasive monitoring. Both these patients (Patients 5 and 14) were rendered seizure-free following complete resection of the hyperperfusion areas. We are, nevertheless, fully aware that these preliminary, yet promising, results of the multimodal imaging approach do not guarantee surgical success in other patients without MRI lesions, since the value of different diagnostic methods may vary in this diverse population.

Because of the size of our cohort, it is difficult to discuss the relationship between histopathological findings and surgical outcome. Three of 5 patients with FCD type I and 6 of 9 subjects with FCD type II achieved favourable postsurgical outcome. Less favourable outcome in patients with FCD type I, relative to type II, was previously reported (Krsek *et al.*, 2008; Krsek *et al.*, 2009b). In order to interpret the results fully, we investigated the reasons for surgical failure in individual subjects. The leading cause of incomplete resections in our series was overlap of dysplastic and eloquent cortical areas. In accord with previous observations (Marusic *et al.*, 2002; Krsek *et al.*, 2009a), we suggest that overlapping dysplastic and eloquent cortex might fundamentally influence postoperative outcome in non-lesional patients, regardless of histopathological FCD subtype. ☐

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