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Stereo-EEG: the Sainte-Anne experience in focal cortical dysplasias

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ABSTRACT – Focal cortical dysplasias represent a cause of intractable epilepsy that can be cured by surgery if complete lesional resection can be performed. However, the lesional limits are difficult to assess by imaging, and some focal cortical dysplasias can be missed by magnetic resonance imaging. The combination of high-resolution magnetic resonance imaging and neurophysiological findings provided by direct intra-lesional recordings has greatly improved diagnosis and surgical outcome in focal cortical dysplasias. Stereo-EEG has demonstrated that dysplastic areas show continuous spiking activity persisting after diazepam injection and are the site of ictal discharge onset. Surgery guided by stereo-EEG made seizure-free outcome possible for all patients recently investigated and who had undergone surgery in our centre for extra-temporal partial epilepsy associated with focal cortical dysplasias (10 patients, mean follow-up: 15 months). Moreover, we demonstrated that limited resections can be performed safely in eloquent cortex without permanent disability. These results demonstrate the usefulness of stereo-EEG in surgical treatment for focal cortical dysplasias, despite the invasive nature of this procedure.

KEY WORDS: focal cortical dysplasia, intracranial recordings, epilepsy surgery, positron emission tomography

Focal cortical dysplasias (FCDs) are now recognised as a main cause of intractable epilepsy of early onset [1-4]. Although the classification of cortical dysplasias is still debated, FCDs usually refer to the lesion described by Taylor *et al.* [5], which consists of loss of cortical lamination, and congregations of giant, dysmorphic neurons associated in most instances with voluminous glial cells (balloon cells). Surgical prognosis has been reported as poor when compared to that of patients undergoing resective surgery for other types of lesion [2, 4, 6-8]. Outcome has been related to the extent of dysplastic cortex removed; it has been demonstrated that all the dysplastic tissue needs to be resected because of intrinsic epileptogenicity [9, 10]. However, small lesions may be difficult to detect, even with high-resolution magnetic resonance imaging (MRI) [11], and MRI has been reported as normal in 20% of cases [12, 13]. Moreover, lesional boundaries are often difficult to delineate by neuroimaging or on the basis of the macroscopic appearance of the cortex during the surgical procedure [3, 14].

Sainte-Anne school's experience led to emphasising the role of stereo-EEG (SEEG) in the pre-surgical evaluation of patients with intractable epilepsy associated with FCDs. Before the era of modern imaging, a high rate of successful cortical resections was obtained in patients in whom FCD was retrospectively identified in cortical

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specimen. The methodology was based on electroclinical correlation, with careful analysis of electrical and clinical data during surface and intracranial EEG recordings [15, 16]. Information obtained from a retrospective study based on patients undergoing surgery for FCDs during the last four decades is now integrated into pre-surgical procedures for such lesions at our centre [17].

Retrospective study

In the reported series [17], FCDs were identified in 28 of the 500 patients (5.6%) undergoing corticectomy at the Sainte-Anne Hospital, between 1964 and 1995 (17 females, 11 males, aged from 5 to 41 years, median 16.5). Age at onset of epilepsy ranged from the first days of life to 11.5 years (median 2.75), and preoperative duration of epilepsy ranged from 3.5 to 38 years (median 12). All patients underwent pre-surgical evaluation, including SEEG, but only 10 patients had CT-scan and 7 MRI. Localisation and assessment of the exent of the FCD were based on histological findings in the cortical samples that were compared with imaging data when available, and on intra-operative findings.

The main findings of this study consisted of noting peculiar interictal activity on intra-lesional recordings, co-localisation of the epileptogenic zone and dysplastic areas, and favourable outcome correlating with complete resection of FCDs. Moreover, we reported some characteristic data concerning the location of FCDs and their electro-clinical presentation.

FCD location

We observed a preferential location in extra-temporal areas and mesial aspect of the brain. Crucial areas (posterior frontal lobe, central and post-central areas) were involved in 11 cases (39%). Most small sized FCDs were located in the mesial frontal, central and parietal areas, however multilobar FCDs were found preferentially in posterior areas.

Clinical data

Early onset of epilepsy was noted in this population. Earliest onset correlated with posterior localisation ($P < 0.01$) and multilobar FCDs ($P < 0.01$). High seizure frequency with clusters, epilepsia partialis continua and status epilepticus were frequent in these patients. All had partial seizures, either simple or complex, but secondary generalised seizures were rare (4/28: 14%). Seizure semiology was stereotyped and clearly related to the location of FCDs. Neurological deficit was noted in 19 cases (68%), and was also related to the location of FCDs. Mental impairment was observed in 11 of the 14 children studied (78.5%) and in five of 14 adults (35%). Ten patients had major psychiatric disturbances (35%). Severe cognitive disorders were correlated with early onset of epilepsy ($P < 0.01$). Normal functioning or mild impairment was correlated with limited FCDs ($P = 0.01$). Psychiatric disturbances were correlated with early onset of epilepsy ($P = 0.03$) and posterior localisation of FCDs ($P = 0.02$). No patient had dermatological or neuroimaging features typical of tuberous sclerosis.

EEG and SEEG data

The EEG background was abnormal in 19 cases (68%). Interictal spikes were focalised in only nine cases (32%), and maximum spike activity was concordant with the location of FCDs in 17 cases (60%). The most characteristic interictal pattern consisted of rhythmic or pseudo-rhythmic spikes that were observed in 16 patients (57%). Onset of ictal discharges was characterised by low voltage fast activity (22 cases) or rhythmic spikes (five cases). Ictal discharges recorded on surface EEG had localising value in half the cases; failure to localise usually implied a mesial FCD location.

The SEEG investigation was performed with electrodes located in multiple lobes in the majority of the cases. Correlation with histological findings retrospectively demonstrated that one to six electrodes were clearly placed within the FCD in 25 patients. Electrodes were located at the periphery of FCD in only 3 patients.

Intra-lesional interictal activity consisted of a striking electrical pattern with continuous, rhythmic or pseudo-rhythmic spikes or polyspikes, with frequencies ranging from 0.5 to 10 Hz, but usually from 1 to 3 Hz. In some patients, the activity consisted of pseudo-periodic spikes or burst of spikes interrupted by depression or suppression of activity, resembling suppression bursts. These rhythmic spike discharges (RSDs) were simultaneously recorded on surface EEG in half the cases. Intravenous (IV) diazepam injection (15 cases) did not suppress the RSDs, but decreased both the amplitude and frequency of spikes for 20 to 30 s after injection. Cortical specimens were analysed according to the anatomical location of intracranial electrodes, which allowed precise correlation between neurophysiological data and the histological abnormalities in each cortical sample examined. The site of maximal RSDs correlated with the location of the dysplastic cortex in all cases, with a gradual change from intra-lesional to peri-lesional activity. The areas displaying RSDs could change according to recording conditions. These areas could be enlarged after the occurrence seizure or during sleep, especially in children. We found that the dysplastic cortex corresponded to the rhythmic activity observed during waking and the interictal state. We observed that i.v. diazepam had no effect on RSD activity, and demonstrated that only areas showing RSDs that persisted after injection, corresponded to the dysplastic cortex.

The epileptogenic zone, defined by ictal discharge onset, was concordant with the area of maximal RSD activity,

low voltage fast discharges being preceded by a brief speeding up of RSDs. In half the cases, the postictal pattern was characterised by early reappearance of RSDs. Only intra-lesional stimulation, either high frequency (monophasic rectangular pulses of 1 to 2.5 mA and 1 ms duration at 50 Hz for 5 ss) or low frequency (1 Hz, 1.5 to 3 mA), elicited seizures similar to the spontaneous seizures. The functional organisation of the central area was studied by low frequency stimulation in nine patients who had FCDs in central, pre- or post-central areas. Normal motor and/or sensory responses were obtained in all cases, suggesting no displacement of the motor strip. Comparison of SEEG findings with the extent of the FCD led us to conclude that the lesional zone (site of slow waves or depression of activity) and irritative zone (site of spiking activity) have limited value in estimating the extent of the FCD because they only coincided with the dysplastic cortex in 18% and 41% of the cases respectively. Conversely, RSDs and EZ co-localised with the FCDs in 86% and 82% of the cases respectively, and therefore were highly useful for the delineation of dysplastic cortex.

Outcome

Surgical outcome, analysed according to Engel's classification, showed that 64% of the patients were seizure-free, and only 4 patients were in class IV. Seizure-free outcome correlated with both the histologically-confirmed, complete removal of the dysplastic lesion ($P < 0.01$) and the complete removal of the EZ ($P < 0.01$). Moreover, surgical failure in this series was mainly explained by limited resections related to functional risks in eloquent cortex. This high favourable outcome rate figures among the best reported, despite the lack of adequate brain imaging and limited cortical resections in extra-temporal areas. These results demonstrate the usefulness of SEEG methodology in delineating the dysplastic cortex for surgical resection and has led to a better understanding of the epileptogenicity of FCDs and organisation of the epileptogenic zone.

To summarise, SEEG criteria for identifying the dysplastic cortex and assessing its extent consist of: 1) the maximal site of rhythmic spikes discharges (RSDs), 2) persisting after diazepam injection, 3) the site of onset of ictal discharges, 4) the brief speeding up of RSDs before rapid discharges, 5) the early reappearance of RSDs after ictal discharges, 6) the site of elicited seizure after electrical stimulation, either by high or low frequency stimulation.

Recent series

After this study, these criteria were used prospectively for patients in whom FCDs were demonstrated or suspected on MRI. We recently investigated ten patients (seven males and three females, aged from 12 to 40 years) with a clinical history of FCDs (severe partial epilepsy of early onset, stereotyped seizure related to a focal part of the cerebral cortex, mental and/or neurological impairment). Epilepsy was frontal in seven, central in two and parietal in one. The EEG showed focal rhythmic spiking in half the cases. The MRI demonstrated typical features of FCDs in four patients, and was considered normal in the others. However, careful analysis of imaging, guided by electroclinical data, showed mild gyral abnormalities without signal changes in three cases, and localised poor demarcation between grey and white matter in one other case. Examination findings were normal in two patients, even with high-resolution MRI and FLAIR sequences. Positron emission tomography (PET) with fluorodeoxyglucose (FDG) was performed in nine patients. We found hypometabolic areas concordant with MRI abnormalities in the four cases with typical images, and which were larger than the MRI lesion in two cases. Hypometabolic areas, located in areas supposed to be dysplastic, were also found in three other cases. The two patients with normal MRI also had focal hypometabolism concordant with the epileptogenic zone. The SEEG was performed in all patients, and recorded the typical interictal pattern of RSDs in all cases. Cortical resections were guided by SEEG data, using the criteria identified previously. Histological confirmation of FCDs was obtained, with good concordance between SEEG data and the pathological findings. Interestingly, we observed that very limited resections were possible in eloquent cortex (ie central and post-central areas in three cases) without permanent disability. Eight patients with follow-up ranging from six month to two years (mean 15 months) achieved seizure-free outcome (class IA).

Some cases of this series will be presented for illustration.

Case No 1

DS, an 18-year-old girl, was investigated for severe partial epilepsy that began at the age of three years. She presented with several seizures per day, mainly during sleep. She had a normal neurological examination and mild mental retardation. Clinical semiology implicated the anterior part of the right frontal lobe, and EEG demonstrated a right frontal focus. Magnetic resonance imaging was considered to be normal, but careful analysis of to the right orbito-frontal cortex demonstrated localised blurring of grey and white matter demarcation. The FDG-PET showed a focal hypometabolism involving this area. During interictal SEEG, we recorded very impressive, continuous spiking activity, located in the orbito-frontal gyrus. Ictal discharge onset was located in the same area *(figures 1A, B)*. After 22 months of follow-up, the patient is currently seizure-free (class IA) and has shown significant psychosocial improvement.

Case No 2

YL, a 20-year-old man had presented with drug-resistant, partial epilepsy from the age of 14 years. This patient had very frequent, stereotyped, pre-motor seizures (15 per

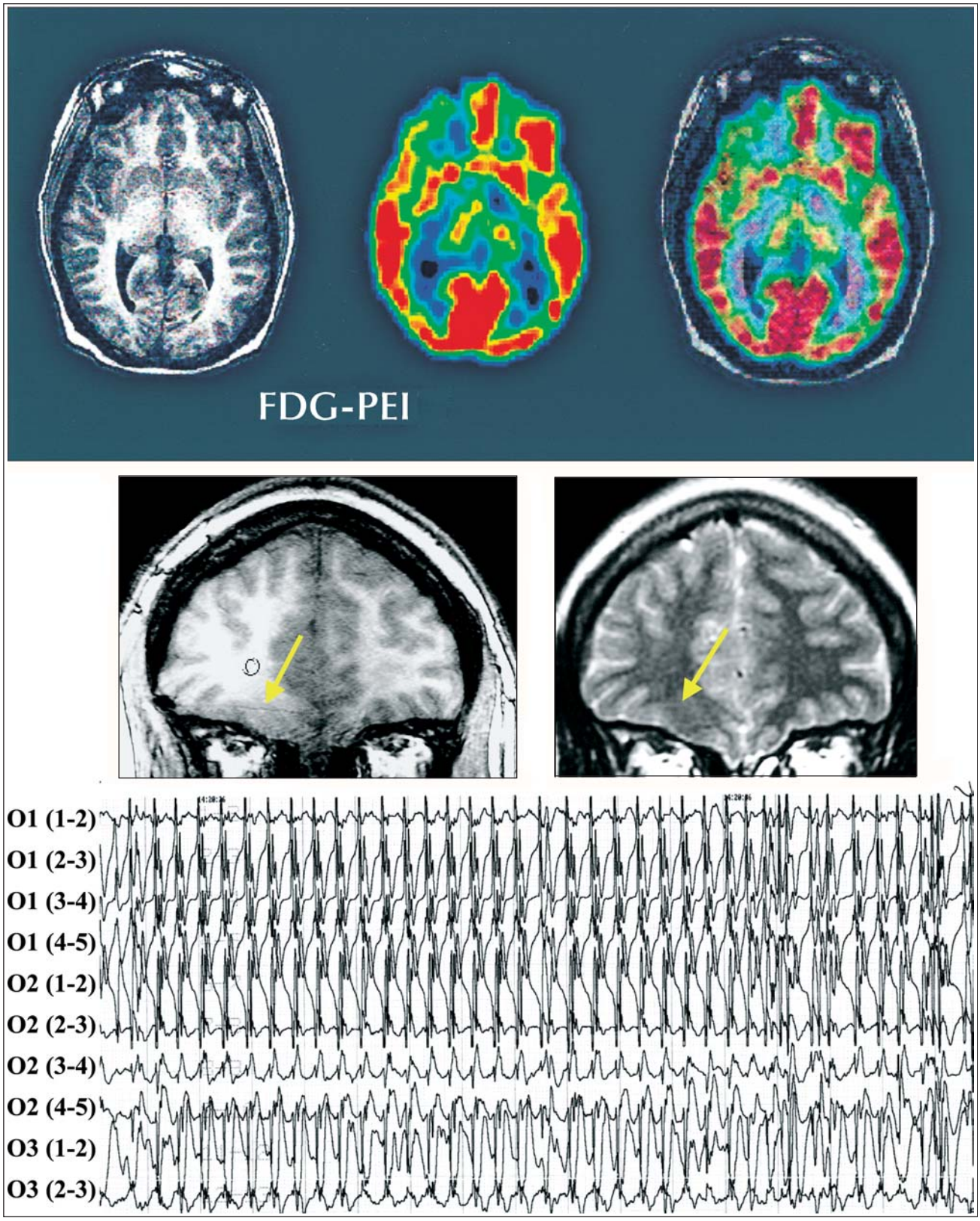

Figure 1. *Case n°1;* **A.** *FDG-PET, axial slices: right orbito-frontal hypometabolism concordant with an area of poor demarcation between grey and white matter on MRI (SHFJ, CEA,Orsay).*
B. *SEEG: interictal activity recorded by the intracerebral electrode located in the right orbito-frontal cortex (electrode 0, arrow). Note the high frequency spiking activity that was continuous during the recordings.*

day) and a left fronto-central focus on EEG, with pseudo-rhythmic spiking activity. The MRI showed a minor gyral abnormality in the left mesial pre-motor area that could have corresponded to FCD. The FDG-PET demonstrated mild hypometabolism concordant with the MRI abnormality *(figures 2 A, B)*. During SEEG, we observed the previously described peculiar interictal activity located in the abnormal gyrus. Ictal discharges arose from the same area *(figures 2 C, D)*. Cortical resection was limited to this gyrus; the histological diagnosis was FCD. After surgery, the patient was seizure-free (class IA) without any deficit (follow-up: 2 years). He is currently working and driving a car.

Case No 3

ME, an 18-year-old girl who had intractable partial epilepsy from the age of three years with high seizure frequency (several per day). Seizure semiology indicated the right lateral parietal lobe, more accurately the shoulder area. She had a mild, permanent disability of the left arm with chronic pain and motor neglect. A continuous spiking activity, located on the right parietal area, was recorded on EEG. Magnetic resonance imaging showed an unusual morphology of the right post-central sulcus with no other abnormality. Motor activation on functional MRI showed normal organisation of the central area that correlated with the functional mapping performed during SEEG. The FDG-PET demonstrated hypometabolism involving the lateral post-central and central areas *(figures 3 A, B)*. During SEEG, we found a very focal spiking activity located deep in the post-central sulcus (electrodes U and X). This activity was continuous, and persisted after diazepam injection. Very low intensity, high frequency stimulation (0.5 mA, 50 Hz) performed in this area elicited seizures similar to spontaneous seizures. Ictal discharge onset was localised in the depth of the post-central sulcus with early propagation to the central area *(figures 3 C, D, E, F)*. A very focal resection performed deep in the post-central sulcus led to the discovery of a small FCD. The patient is currently seizure-free (class IA, follow-up: 1 year) with improvement in quality of life and normal neurological examination.

Discussion

Despite the progress in imaging, epilepsy surgery for FCDs remains challenging. It is now well established that all the dysplastic area needs to be resected to obtain complete seizure relief [9, 10, 17]. However, imaging criteria are not always sufficient to perform adequate resections. Moreover, MRI can be normal in one out of five cases [12, 13]. We have demonstrated the usefulness of the methodology developed at the Sainte-Anne Hospital by Bancaud, Talairach and coworkers [15-16] for delineating the dysplastic cortex [17]. Peculiar patterns of ictal or continuous epileptogenic discharges (I/CEDs) recorded by electrocorticography (ECoG) in FCDs have already been described by Palmini *et al*. [10]. The authors concluded that this pattern permitted the identification of dysplastic cortex, and emphasised the intrinsic epileptogenicity of FCDs that they found to be more epileptogenic than other structural lesions. However, other authors found that although this pattern was correlated with high seizure frequency and with the balloon cell cortical dysplasia subtype, it could also be observed in other types of lesions [18]. We have reported that the striking pattern of RSDs recorded by SEEG was very useful for identifying and delineating FCDs [17]. However, we recognised that this pattern cannot be considered specific for dysplastic tissue, and appears to be more a marker of high lesional epileptogenicity than a histological marker.

While both ECoG and SEEG permit detection of dysplastic cortex, some differences related to methodology should be pointed out. We observed RSDs on intracerebral recordings in all but two patients (93%) in our retrospective study, and in all our recent cases, whereas a similar pattern was found in 67% of the cases on ECoG [10]. The direct intra-lesional recordings made possible by SEEG may be more sensitive than ECoG because of the deep location of FCD within the sulci or on the mesial aspect of the brain. Furthermore, SEEG provides a three-dimensional approach for delineating FCDs, despite the fact that depth electrode recording implies limited sampling of lesional and peri-lesional areas.

The combination of modern imaging and SEEG data have obviously improved surgical strategy and outcome in FCDs. Despite the small number of patients undergoing surgery in our recent series, we have demonstrated that seizure-free outcome (class IA) can be achieved in all patients after resections that were more limited than in the first series. Moreover, we have shown that in some cases of small FCD not detected by conventional MRI, safe and successful procedures can be performed with limited resections, even in eloquent cortex. The usefulness of surgery guided by SEEG in FCD has also been demonstrated by another group [13, 19, 20], with a high success rate. The FDG-PET can be useful for detecting small FCDs that were not identified on MRI or were associated with subtle gyral abnormalities. However, this type of FCDs can be easily missed by visual analysis. While new imaging techniques will probably soon provide more information [21] and replace invasive procedures, neurophysiological investigation is currently necessary in most cases, especially when dealing with eloquent cortex. □

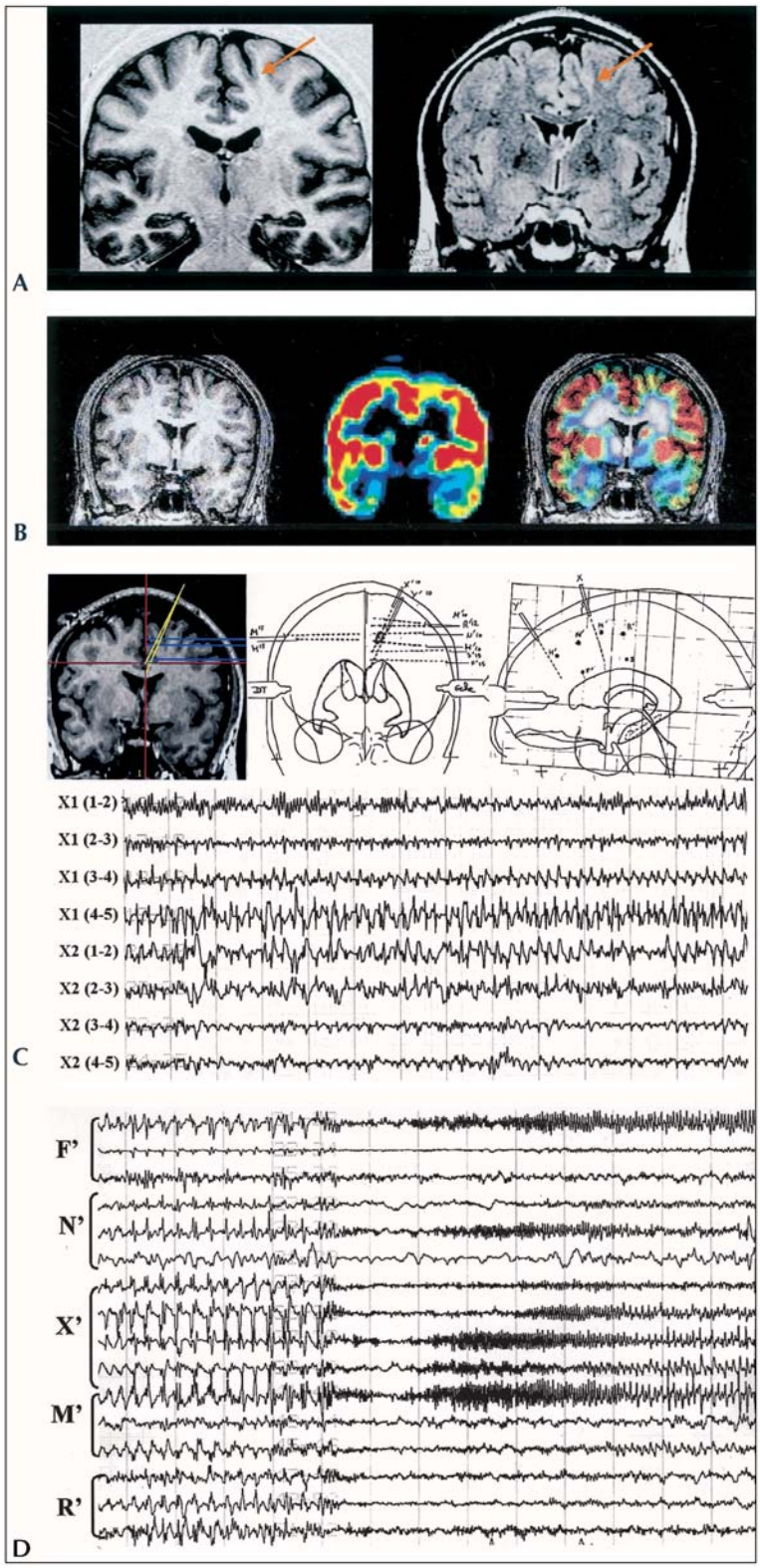

Figure 2. *Case n°2;* **A.** *MRI, coronal slices, T1 and FLAIR sequences: mild gyral abnormality on the left mesial pre-motor area (arrow).*
B. *FDG-PET, axial slices: mild hypometabolism concordant with the gyral abnormality (SHFJ, CEA, Orsay).*
C. *SEEG: interictal continuous rhythmic activity located in the abnormal gyrus: electrode X, contacts X1(4-5) and X2(1-2).*
D. *Spontaneous seizure: ictal discharge onset in the same area after a brief spreading of RSDs, early propagation to the adjacent areas (M'1).*

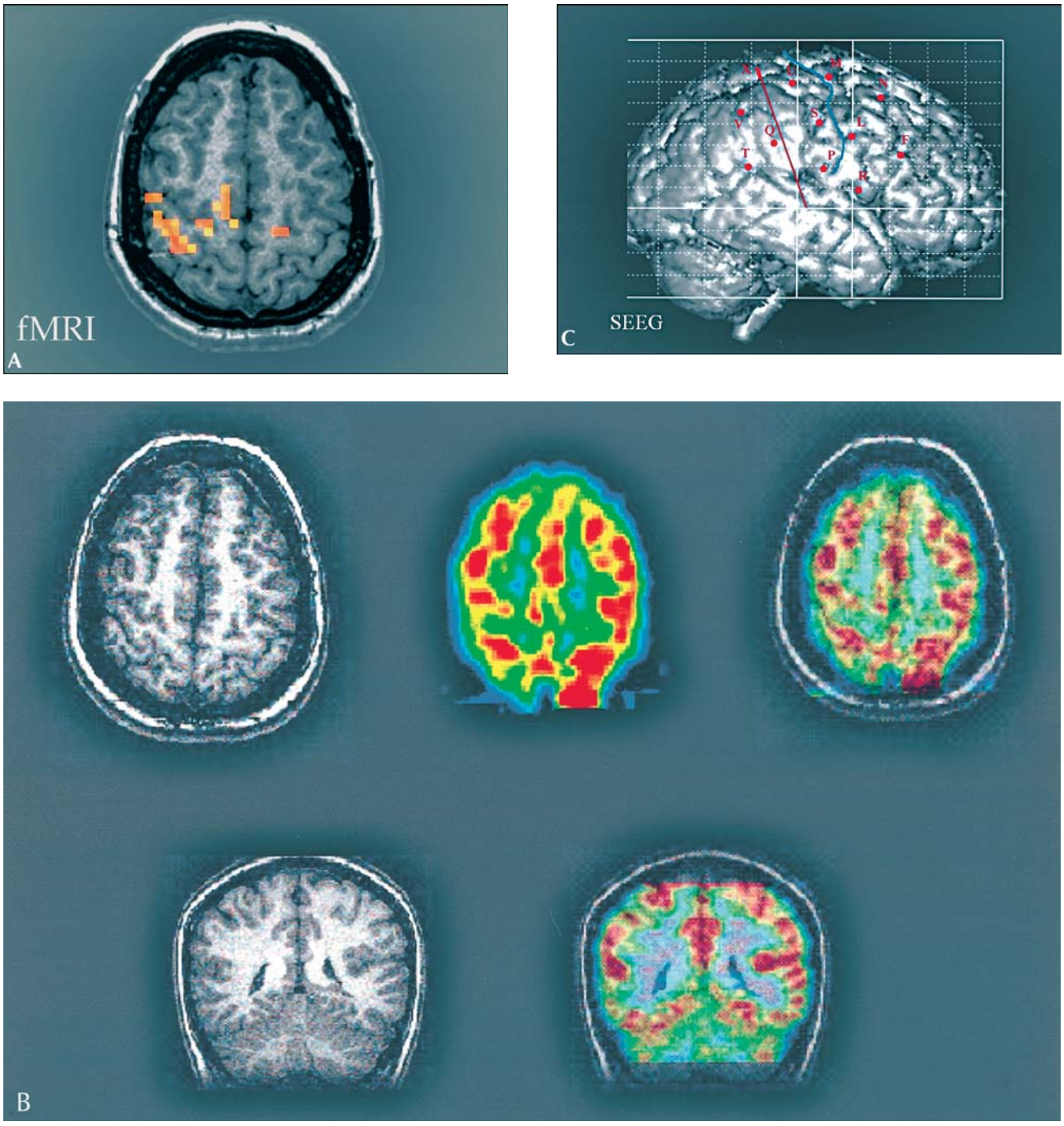

Figure 3. ***Case n°3;***
A. *functional MRI (motor activation): normal activation of the central and post-central areas. Note the unusual morphology of the post-central sulcus.*
B. *FDG-PET, axial and coronal slices: mild hypometabolism located on the right lateral post-central and central areas (SHFJ, CEA, Orsay).*
C. *Case n°3; location of depth electrodes.*

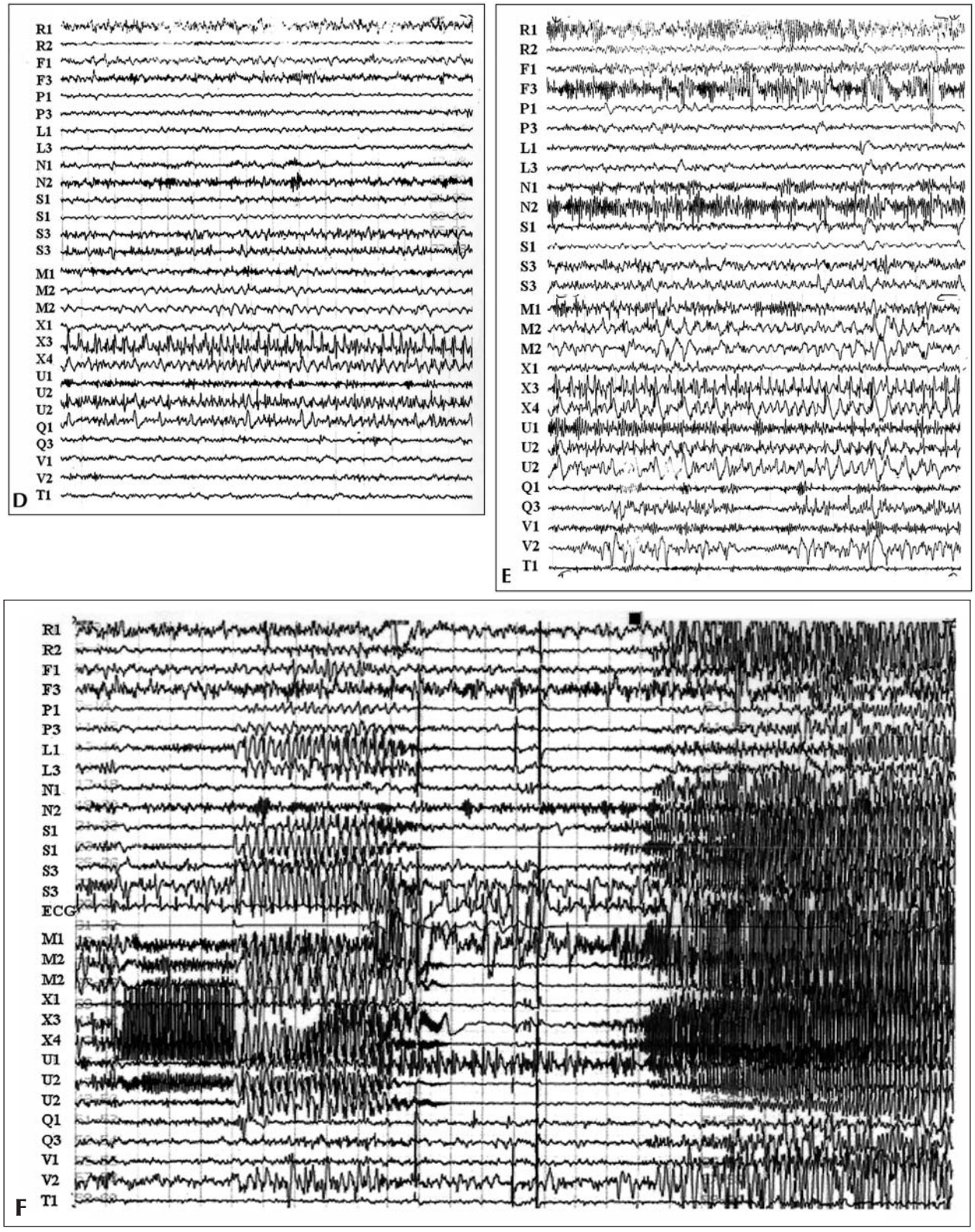

Figure 3. ***Case nº 3.***
D. *SEEG, interical activity: focalised rhythmic activity located deep in the post-central sulcus (contacts X3 and U2).*
E. *Persisting rhythmic activity after diazepam injection. Note the occurrence of fast activity related to diazepam on other areas.*
F. *Elicited seizure after high frequency stimulation (0.5 mA, 50 Hz) applied to contact X3. Low voltage fast discharge immediately propagated to the central area (electrodes M and S).*

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