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Title: Visual and semi-automated evaluation of epileptogenicity in focal cortical dysplasias - an intracranial EEG study

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Abstract: Introduction: Aim of the study was the evaluation of the added value of depth to subdural electrodes in delineating epileptogenicity of focal cortical dysplasias (FCD) and to test the Epileptogenicity Index (EI) in this setting.

Material and Methods: 15 FCD patients underwent iEEG with subdural and depth electrodes. Visual/EI analysis was performed in up to three habitual seizures per patient.

Results: Visual analysis: grid onset seizures (n=10) started in electrodes overlying the lesion in 7 and remote from it in 3 cases. Depth onset seizures (n=7) affected only intra-lesional contacts in 4, intra- and extra-lesional in 2 and exclusively extra-lesional in 1 patient. Seizures started in depth and grid contacts simultaneously in 2 cases.

EI-analysis: EI completely confirmed visual localisation of seizure onset in 8 cases and depicted ictal onset-time accurately in 13. Beta / gamma ictal patterns were most reliably captured. Impact on surgical decision: Resection outline differed from MRI lesion in 7 patients based on grid and in three based on depth electrode information.

Discussion: In FCD, seizures can be generated within gyral/deep tissue appearing normal on imaging.

Conclusion: Investigating FCD with subdural and depth electrodes is efficient to outline seizure onset zone. EI is a helpful additional tool to quantify epileptogenicity. Specific ictal patterns are prerequisite for reliable results.

HIGHLIGHTS:

1. Depth and subdural electrodes combined enable better understanding of the EZ in FCD.
2. The EI is a useful tool if applied complementary to visual analysis.
3. The clear numerical labelling of epileptogenic electrodes can simplify communication.

Visual and semi-automated evaluation of epileptogenicity in focal cortical dysplasias – an intracranial EEG study

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INTRODUCTION

Focal cortical dysplasia (FCD) is increasingly recognized as one of the most common causes of early onset intractable focal epilepsy both in adults and children.[1, 2] Although favorable outcomes after focal resections with up to 60% of patients being rendered seizure free have been reported [3-5], pre-surgical evaluation of the epileptogenic zone (EZ) is still challenging. This is in part due to the fact that even high resolution MRI does not always detect the pathology and especially mild type I FCD is missed on imaging in 35 to 63% of patients.[6, 7] Moreover, boundaries of the lesion are often difficult to delineate as dysplastic areas can be more extensive than apparent on MRI.[3, 8] In addition, scalp EEG can correctly localize the ictal onset zone in only 40-70% of cases.[6, 9] As complete resection of the epileptic lesion, incorporating both MRI pathology and EEG ictal onset zone, is the best predictor of good postoperative seizure outcome, intracranial EEG recordings (iEEG) are often necessary in order to develop a surgical strategy.[4, 10-13]

No consensus on the design of an intracranial EEG study optimal for both definition of the ictal onset zone and differentiation from eloquent cortex has been reached. While subdural grid and strip electrodes provide excellent spatial resolution on the gyral surface and allow for detailed mapping of cortical function, sampling is restricted to cortex immediately beneath the convexity and cerebral tissue radial to the plane of the grid or strip.[14] Multiple depth electrodes (Stereo-EEG; SEEG), in contrast, enable sampling from deep cortical tissue and regions non-accessible by subdural electrodes, e.g. depth of sulci or opercular areas. They can also provide direct intra-lesional recording. Information gained from depth electrodes, however, can be fragmentary as sampling is limited to tissue in the immediate vicinity of electrode contacts, and traditionally SEEG implantation schemes are designed to sample from a wider network rather than a lesional and perilesional volume. In order to

develop a comprehensive understanding of the three dimensional ictal onset zone and eloquent cortex a combined approach appears reasonable.

We retrospectively audited our experience on 15 patients who underwent invasive EEG with both subdural and additional depth electrodes and evaluated the impact of the different modalities on the imagined shape of the epileptogenic zone and the proposed resection margins.

In addition to visual analysis we calculated the Epileptogenicity Index (EI), a quantitative measure designed for the automated analysis of depth EEG recordings and evaluated in mesial temporal lobe epilepsies and focal epilepsies in the context of focal cortical dysplasias and neuro-developmental tumors.[13, 15] Although shown to be reliable in different subtypes of focal epilepsies studied with multiple depth electrodes, the EI has not been systematically tested in a subdural or combined intracranial EEG approach before.

MATERIAL AND METHODS

Patients

15 consecutive patients (8 male, 7 female, mean age 35.2 years, age at epilepsy onset 8.3 years) with intractable focal epilepsy due to suspected focal cortical dysplasia most likely IIB according to MRI criteria [16, 17] who underwent iEEG recordings with subdural grid and / or strip electrodes and additional depth electrodes inserted through the grid at the National Hospital for Neurology and Neurosurgery, London, between 2009 and 2013 were included and retrospectively reviewed. The FCD was located in the frontal lobe in ten, in the parietal lobe in four and in the occipital lobe in one patient. In all cases a scalp EEG video telemetry, 3Tesla MRI and functional MRI for localization of language, motor or sensory areas were performed prior to iEEG. Additionally, some patients underwent ictal SPECT, FDG PET or

MEG (table1). The study was approved as retrospective audit into efficacy and safety of intracranial EEG implantations by the hospital.

Intracranial EEG

The implantation scheme was based on the hypothesis of the epileptogenic zone derived from semiology and pre-surgical assessment. Prior to implantation each case was discussed in a multidisciplinary team meeting. Individual targets for depth electrode insertion were defined on a case-by-case basis, aiming to target the center of the migration disorder based on MRI appearance, and ideally also informing anterior/posterior and rostro-caudal extent of epileptogenicity intracortically and in the depth. Electrodes were inserted into the center of the cortical thickening based on T1 weighted MRI; the T2 hyperintensity and if present a transmantle sign was also targeted. In case of bottom of sulcus dysplasias, sampling of the lesion was attempted, respecting pial boundaries. The exact target within the MRI abnormality was also guided by semiology, non-invasive diagnostics and anatomical considerations. If, for example, the seizure onset zone was expected in the anterior portion of the visible lesion, an electrode was inserted anteriorly to the center of the lesion. Thus, a tailored implantation scheme was designed for each patient.

An average number of 75 subdural and 15 depth electrode contacts were inserted in each patient. After implantation, CT scans were performed and images co-registered with pre-implantation MRI. Thus, electrode maps were generated on 3D brain surface rendering allowing for localization of electrodes with respect to anatomical structures and lesional boundaries as outlined on MRI. This approach leads to a specific co-registration error caused by brainshift and dependent on the size of the craniotomy. In order to minimize this effect, each co-registered scan was visually reviewed and manually corrected.

EEG monitoring was maintained for 6 days on average.

EEG Data was recorded with the standard clinical video EEG system (Nicolet One) sampled at 500 Hz per channel, with bandpass filtering between 0.5 Hz and 1/4 sampling rate. Cortical stimulation for functional mapping was performed in all patients, using bipolar stimulation of adjacent electrodes[18].

Visual analysis

In 12 patients three consecutive habitual seizures were reviewed by a certified electroencephalographer (SG); in three patients (patient 6, 10 and 12) only one seizure occurred during the recording and was analyzed. We defined the ictal onset for each seizure as the time of first appearance of the ictal pattern, characterized by rapid discharges, an amplitude decrement or repetitive spike wave or sharp wave discharges. We then identified the electrodes bearing the ictal onset and assigned the ictal onset zone to an anatomical region, which was either on the cortical surface, represented by the grid or the two most lateral depth electrode contacts, or in the cortical depth represented by the mesial depth electrode contacts. For each patient we analyzed the overlap between the three dimensional EEG ictal onset zone and the lesion visible on MRI. We also reviewed the resection margins proposed on the basis of the visual analysis of iEEG as documented by the physician reporting the study, as is routine practice for clinical care. Surgical outcome was evaluated according to the ILAE classification [19].

EI

The EI was calculated according to the methods previously described [15] to obtain a quantification of epileptogenicity. In brief, it is an algorithm that takes two factors into account: first, the propensity of brain tissue to generate rapid discharges, mirrored by a shift of the spectral energy ratio (ER) between high (beta and gamma) and low (delta, alpha and theta) frequencies, and second the delay of involvement of every regarded structure in

relation to the first structure involved. The seizure onset is characterized by a dramatic increase in the ER derived from a Fast Fourier Transform using a sliding window technique. In order to increase sensitivity and specificity for the detection of onset time two parameters can be adjusted manually: bias ν refers to the amount of power fluctuations regarded as “normal”, threshold λ marks a significant ER change. When the seizure onset time has been noted for electrodes involved, the energy ratio averaged over time after detection is divided by the time delay of involvement with respect to the first electrode involved. Thus, after normalization, a numerical value between 0 and 1 is generated for each electrode contact. Electrodes with EI values exceeding a specific cut-off are regarded as epileptogenic. A detailed description of the method is given in the original publication introducing the algorithm [15] and in supplementary files.

The EI was computed in each of the visually analyzed seizures for a preselected number of electrodes involved in the seizure as judged by visual analysis, and values were averaged across seizures in each individual patient. A preselection of electrodes is necessary for an interference-free operation of the computational system. We selected electrodes that were involved in the ictal onset and those that became involved in the seizure in the course of its propagation. The latter were not regarded as epileptogenic per se and served as negative controls for the EI. We chose parameters ν and λ for optimal onset detection in the first seizure of each patient and generally maintained the settings for all consecutive intra-individual seizures.

In order to evaluate the validity of the EI in this setting, we compared the results of EI analysis with electrodes visually involved in seizure onset. For the definition of the EI cut-off differentiating best between epileptogenic and non-epileptogenic electrode contacts and leading to the highest agreement between visual and automated assessment we applied receiver operator characteristics. We then assigned the EI-defined ictal onset zone to an

anatomical region being either in the depth or on the cortical surface and congruent or incongruent with the MRI lesion analogously to visual assessment. For this purpose we took into account all electrodes generating EI values above the EI cut-off.

RESULTS

Visual analysis

Three seizures were available in 12 patients while three patients only had one seizure during the recording. In 12 patients imaging co-registration revealed depth electrode contacts localized within the visible lesion, in three patients, all depth electrodes were placed outside of the MRI-defined lesion but several contacts were localized in close proximity to it. Seizures originated from the cortical surface in ten patients. Of these, only in seven cases the ictal onset zone was overlying the MRI-visible lesion while in three patients the onset appeared remote from it. Seven patients exhibited seizures starting in deep cortical tissue, four of them only involving contacts within the lesion, two showing the ictal pattern both within and outside visible abnormalities and one displaying the ictal onset in depth electrodes outside the lesion exclusively. In two patients seizures started simultaneously in the depth electrode contacts and on the surface.

Cortical stimulation of the grid showed an overlap between eloquent cortex and the ictal onset zone in four patients who accordingly did not proceed to surgery. EEG and imaging outlined an identical assumed epileptogenic zone in two cases, leading to a complete but exclusive resection of the visible lesion.

In five patients the information gained from subdural grid electrodes led to definition of the epileptogenic zone exceeding the MRI abnormality, thus, a larger resection was proposed and carried out (table 2; example figure 1).

Likewise, a resection exceeding the MRI lesion was planned in four patients based on depth electrode sampling from visually normal but electrographically epileptogenic cortex.

In four cases, cortical stimulation allowed for discrimination between eloquent and epileptic cortex, thus enabling a tailored resection that spared functional tissue overlying the lesion on the surface.

Histological examination of the specimen was consistent with FCD IIb in 10 out of 11 (90.9%) surgical cases. In one patient the specimen did not give clear evidence of dysplasia. According to ILAE outcome classification, 9 patients (81.8%) were rated class 1 one year postoperatively, 1 patient class 3, and one patient class 5. The unfavorable outcome coincided with the equivocal histology result, despite clear evidence on MRI. Two year follow-up was available for 8 patients, seven achieved class 1 and one class 5 (table 2).

EI analysis

We found full agreement between electrodes rated as part of the seizure onset zone by EI and by visual analysis in eight out of 15 cases (53.3%, example figure 2). Completely contradictory results between automated and visual analysis did not occur. Anatomic areas regarded as part of the seizure onset zone according to visual assessment were also defined as epileptogenic by the EI in all cases but one. In this patient two depth electrode contacts considered epileptogenic by visual analysis did not generate high EI values. In six cases EI analysis suggested a larger ictal onset zone than visual judgement.

In one patient EI values deep within the lesion and on the cortical surface overlying it exceeded the threshold, while visually seizures originated from the cortical surface only and involved the depth later. In five cases the EI defined grid electrodes remote from the cortical lesion as epileptogenic that had not been regarded as such by visual judgement. One of these patients did not proceed to surgery, as eloquent and epileptogenic cortex overlapped. In the remaining four cases a resection was carried out based on visual EEG evaluation only. Of

these, three patients became seizure free postoperatively while one suffered seizure recurrence within the first year after operation (table 2).

Validation of the method

The optimal EI cut-off according to Receiver operator characteristics was 0.3. This value is similar to the cut-off value chosen in previous studies.[13, 15]

The EI depicted the seizure onset time correctly after adjustment of parameters ν and λ in 13 out of 15 patients. The number of electrodes classified as epileptogenic by the EI was higher than the number of visually involved electrodes (104 visually involved electrodes vs. 158 EI positive electrodes in total) but still closely correlated (Spearman's correlation $r=0.76$, $p=0.01$). A similar number of cases was assigned to a focal onset, affecting six or less electrodes by the EI ($n_{EI}=5$) and visually ($n=7$), and also to a widespread onset, involving ten or more electrodes ($n_{EI}=6$, $n_{vis}=3$).

We found excellent concordance (sensitivity and specificity $\geq 60\%$) between visual rating and EI epileptogenic electrodes in six and good consistency (sensitivity $\geq 70\%$, specificity $\geq 40\%$) in two patients (53.3%), while in one case two depth electrode contacts were not identified by the EI (6.67%), although they appeared clearly involved by visual analysis. In two cases the ictal onset time was missed (13.3%) and ictal onset seen several seconds later by the EI than by visual analysis. In one of these the localization of the seizure onset zone was still consistent with visual assessment (sensitivity 63%, specificity 99%), while in the other visually involved electrodes were missed by the EI (sensitivity 20%, specificity 99%). Adjusting the size of the sliding window lead to a better identification of the ictal onset time in this case, but did not improve sensitivity (figure S1). In four patients a large number of false positive electrodes was calculated (26.67%). Regarding correctly depicted epileptogenic

and non-epileptogenic electrodes with respect to visual labelling the EI reached an average sensitivity of 73% and specificity of 69%.

We then examined which features of the seizures determined the utility of the EI. Good EI results were seen both in seizures with depth (n=3) and grid (n=5) electrode onset (figure 3) and also poor EI performance was found in both conditions likewise (depth onset n=3, grid onset n=4). Circumscribed ictal onset zones defined as involving six or less electrodes at onset, or more widespread ictal onset zones could be both captured (widespread n=3, circumscribed n=5) and missed (widespread n=5, circumscribed n=2) by the EI. A common characteristic of all seizures with good EI results was an ictal pattern in the beta and gamma range, leading to a massive increase in spectral power, reaching values of up to $5000 \mu V^2/Hz$ in this frequency band (figure 2). Divergent patterns, for example rhythmic spikes, attenuation or high frequency oscillations (HFO) above 70 Hz were far less reliably depicted (table 3). Spectral analysis in these cases showed a massive increase in the theta range for spikes, while HFO were generally low in amplitude, causing a relatively small increase in high frequency power in the range of $50-100 \mu V^2/Hz$ that was outweighed by underlying slow activity in the theta and delta band.

DISCUSSION

Impact of subdural and depth electrodes on determination of the EZ and surgical decision making

The aim of iEEG is the definition of the epileptogenic zone (EZ), the area of cortex sufficient and necessary to resect in order to achieve seizure freedom, taking into account all test results gathered during the pre-surgical investigation.[20] In FCD it is especially challenging to form a good pre-surgical hypothesis on the EZ, as boundaries between normal and dysplastic tissue

are often blurred on imaging, and in fact seizure onset may involve areas adjacent to the main imaging abnormalities. For assessment of a three-dimensional shape it appears reasonable to choose an approach that provides information from more than one plane and combines the advantages of different modalities. However, there are very few systematic analyses that examined the contribution of grid and depth electrodes in a combined invasive EEG study, none of them, to our knowledge, focusing on FCD in adults. A retrospective review of 12 pediatric patients stressed the safety and feasibility of a combination of grid and depth electrodes in children and found considerable added value of depth electrodes. [14] In another approach, a combination of subdural electrode bundles and depth electrodes, both inserted through burr-holes, has been shown to be safe and useful for comprehension of the ictal onset zone in different underlying pathologies.[21]

In our cohort of FCD patients grid coverage was essential to map eloquent cortex and spare indispensable tissue accordingly. It also led to a delineation of the epileptogenic zone on the surface that differed remarkably from the MRI lesion. Depending on the number and exact localization of electrodes, an SEEG approach might have missed involved areas on the gyral crown in five patients leading to a smaller resection. Depth recording, on the other hand, gave evidence of epileptogenicity in the depth remote from visibly altered tissue in three cases. The resection was therefore expanded to include these areas that would not have been identified as epileptogenic by subdural recording only.

Confirmatory value of the EI for EZ determination and applicability of the method in a combined iEEG approach

The EI is a semi-automated computational method that has been shown to differentiate reliably between highly epileptogenic mesial structures and less epileptogenic lateral structures in mesial temporal lobe epilepsy.[15] Likewise, significantly higher EI values have

been reported for intra-lesional than extra-lesional electrode contacts in FCD patients. [13]

The algorithm allows for a numeric classification of the degree of involvement in seizure generation in anatomical regions of interest represented by single electrode contacts. It can further outline the dimension and distribution of the ictal onset zone, elicit patterns of propagation and reveal epileptogenic networks.

Prior to our study, however, the EI has not been evaluated in grid electrodes and no direct comparison to visual analysis of ictal iEEG has been made.

In our cohort, EI analysis was in complete agreement with visual delineation of the anatomical location of the ictal onset zone in 53.3% of cases and was contradictory to it in none. The added value of the combination of grid and depth electrodes was clearly emphasized by EI results. Especially the visually defined epileptogenicity of cortical tissue appearing normal on MRI was almost always verified by the EI. In one patient, however, the involvement of two intra-lesional depth electrode contacts generating low amplitude fast activity in the high gamma range at ictal onset was missed by the EI. In six cases the EI ictal onset zone exceeded the visually defined EZ showing high epileptogenicity within the lesion in one and remote from it on the surface in five cases. Of the latter, four proceeded to surgery. Although cortex specified as epileptogenic by automated analysis only was not resected, three patients were rendered seizure free by surgery, the follow-up period being two years in two and one year in one patient. Therefore, in these cases areas generating high EI values were not part of the EZ. In one patient, however, seizure freedom was not achieved. It remains unclear if a larger resection, incorporating EI epileptogenic cortex would have led to a more favorable outcome.

In order to define criteria for good applicability of the EI and develop a greater awareness of its limitations in our setting we also performed a detailed comparison of EI results and visual results being regarded as gold standard. Size and distribution of the ictal onset zone had no

influence on EI performance and our data shows clearly that the method is suitable for depth and grid electrodes alike. Crucial for good EI applicability, however, is the morphology of the ictal pattern. As the algorithm focuses on a sudden increase in the energy ratio between high frequencies in the beta and gamma range and low frequencies in the delta, alpha and theta range, it shows best results if the ictal pattern fulfils exactly these criteria. The ictal onset is indeed characterized in iEEG by rapid discharges in the majority of cases,[22, 23] therefore it appears reasonable to direct the EI to this specific morphology. Although less common, divergent patterns, such as rhythmic spikes or spike waves,[24] rhythmic sharp activity <13 Hz [25] or voltage attenuation can also be the iEEG correlate of seizure onset. In our cohort, rhythmic spiking led to a power increase in the theta band and was therefore undetectable by the EI. Similarly, attenuation and low amplitude very fast activity did not cause a sufficient increase in gamma power for EI analysis. Accordingly, visual pre-selection of suitable seizures is prerequisite for the successful application of the method. In addition, good results are dependent on arbitrary adjustment of parameters λ and v , which leads to decreased objectivity and requires input of a trained electroencephalographer.

As a limitation of our method, we are aware that the adjustment of the aforementioned parameters within the sample and also in patients with one available seizure increases the accordance between visual and semi-automated analysis, and adds to the good performance of the EI. However, the algorithm is clearly not a stand-alone method working in a purely computational setting uncoupled from human expertise. In fact, it is developed as a semi-automated tool, supporting human iEEG evaluation and adjustment of parameters is explicitly demanded. We therefore decided to use the method as originally intended in order to evaluate it objectively.

CONCLUSION

We have shown that depth and subdural grid electrodes reveal important and complementary information about the EZ in adult patients with focal cortical dysplasia. In over half of the patients the seizure onset was best seen in the depth electrodes.

Visual and automated iEEG analysis showed consistently that a combination of subdural and depth electrodes enables better understanding of the epileptogenic zone than any one modality alone. This conclusion is supported by the favorable surgical outcome in our cohort.

We are aware, however, that the beneficial effect of the combined invasive EEG on seizure outcome remains hypothetical, as no direct comparison to control groups of patients who have been operated on the basis of different types of pre-surgical assessments is available.

However, the outcome in our cohort with 82% seizure freedom compares favorably with the average percentage of FCD patients reported to be seizure free postoperatively in recent publications (approximately 60%) [26], supporting a beneficial effect of our method.

The EI is a useful tool if applied complementary to visual analysis and in consideration of the limitations of the method. The clear numerical labelling of epileptogenic electrodes can be helpful to systemize results and to simplify interdisciplinary communication. It should be emphasized, however, that the EI has to be interpreted with care and results have to be critically examined by an experienced electroencephalographer in order to prevent misjudgments. Only specific ictal patterns are reliably detected by the algorithm, therefore preselection of suitable EEG characteristics is necessary in order to achieve reliable results.

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Conflicts of interest: None of the authors have potential conflicts of interest to be disclosed.

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Tables

Table 1: Demographics, non-invasive presurgical diagnostics and implantation scheme

Patient	Age	Sex	Age at onset	Lobe	Side	Diagnostics	Subdural electrode contacts	Depth electrodes contacts
1	39	M	6	F	R	fMRI,MEG	54	10
2	49	F	5	F	L	fMRI	70	22
3	34	F	7	F	L	fMRI,PET	80	24
4	38	M	9	F	L	fMRI,PET	124	12
5	28	M	12	F	L	fMRI,PET,SPECT	80	8
6*	24	F	1	F	L	fMRI,SPECT	60	8
7	27	M	14	F	L	fMRI	80	8
8	33	F	1	P	L	fMRI	56	14
9	25	F	11	P	L	fMRI	66	12
10*	21	M	2	F	R	fMRI	64	18
11	28	M	7	P	R	fMRI	64	16
12*	43	F	11	O	L	fMRI,MEG,PET, SPECT	104	20
13	54	M	8	F	L	fMRI	64	32
14	25	M	6	P	L	fMRI,MEG	80	10
15	60	F	25	F	L	fMRI	86	12

M: male, F: female, affected lobe: P: parietal, F: frontal, O: occipital; affected hemisphere: R: right, L: left; fMRI: functional MRI; MEG: magnetencephalography; PET: positron emission tomography; SPECT: single photon emission computed tomography; * patient with one analyzed seizure only.

Table 2: Ictal onset with respect to anatomical region and MRI lesion according to visual and automated iEEG analysis, impact of grid and depth electrodes on resection design, surgical outcome and pathology results

Ictal onset					Surgical design				Outcome		Pathology
Deep		Superficial			Extended resection		Tailored resection	No resection	Years		
Pat.	Within lesion	Outside lesion	Overlying lesion	Remote from lesion	Due to grid information	Due to depth information	Due to grid information	Due to grid information	1	2	
1	A		VA	VA	X				5	5	no FCD
2			VA					X			no surgery
3				VA	X				1	1	FCD IIb
4			VA		X		X		1	1	FCD IIb
5			VA						1	1	FCD IIb
6	V		VA	VA	X	X	X		1	1	FCD Iib
7	A	VA	A	A		X			1	1	FCD IIb
8			VA	A			X		1	1	FCD IIb
9			VA				X		1	1	FCD IIb
10	VA		A	A				X			no surgery
11	VA	VA		A		X			3		FCD IIb
12				VA				X			no surgery
13	VA	VA			X	X			1		FCD IIb
14	VA		VA					X			no surgery
15	VA			A					1		FCD IIb

Superficial onset: affecting grid and two most lateral depth electrode contacts; deep onset: affecting mesial depth electrode contacts; V: onset according to visual analysis, A: onset according to automated analysis defined by EI values exceeding the threshold (0.3); X: surgical design based on visual EEG interpretation only; tailored surgical design: functional tissue overlying MRI lesion spared. Outcome: seizure outcome after surgery assessed according to ILAE criteria (Wieser *at al.*, 2001)

Table 3: Seizure characteristics and impact on EI performance

Pat.	Onset localisation	Baseline interictal	Onset pattern	Onset distribution	IE performance
1	superficial	alpha/theta	spikes →HFO	widespread	-
2	superficial	theta	fast	circumscribed	+
3	superficial	mixed	HFO → attenuation → spikes	circumscribed	-*
4	superficial	alpha/theta	spikes and theta; on-off	medium	+*
5	superficial	theta	spikes → fast	medium	+
6	deep	theta	HFO and fast	medium	+**
7	deep	theta	HFO	widespread	-
8	superficial	theta	spikes→ fast	circumscribed	-
9	superficial	continuous spikes	spikes → fast	circumscribed	(+)
10	deep	theta	fast	medium	+
11	deep	continuous spikes	HFO	widespread	-
12	superficial	spikes and theta	fast	circumscribed	(+)
13	deep	spikes and theta	fast	circumscribed	+
14	superficial	continuous spikes	fast, HFO	medium	+
15	deep	theta and spikes	fast, HFO	circumscribed	+

*ictal onset time missed, **depth electrode involvement missed; HFO: high frequency oscillations >70Hz; fast: beta and gamma range; onset distribution according to visual analysis: circumscribed: six or less electrodes involved, medium 7-9 electrodes involved, widespread: 10 or more electrodes involved; EI performance: "+": sensitivity and specificity>50%, "(+)": sensitivity ≥ 70% and specificity >40%, "-": sensitivity or specificity <40%

Figure Captions

Fig. 1: Patient 1, iEEG ictal onset remote from MRI lesion in subdural grid electrodes, resection including both imaging pathology and EEG epileptogenic zone; A: 3D brain surface with co-registered electrodes, lateral view showing subdural grid electrodes (left) and mesial aspect showing depth electrodes and a six contact interhemispheric strip electrode (right), contacts 2 and 3 of the posterior depth electrode are localized within the MRI lesion; T2 MRI lesion outline (red), iEEG ictal onset zone (blue) and proposed resection margins (black); B: T2 FLAIR hyperintensity in the right superior frontal gyrus; C: ictal EEG during brief axial myoclonic seizure, onset seen in electrodes G18,20,25-29, 33,34.

Fig. 2: Patient 14: iEEG ictal onset overlying MRI lesion. High concordance between visual and EI analysis (sensitivity 78%, specificity 100%). A: 3D brain surface with co-registered subdural grid electrodes (left) and additional depth electrodes targeting deeper aspects of the lesion (right), contacts 3 and 4 of depth electrode D1 are localized at the border of the MRI lesion; T2 MRI lesion outline (red); iEEG-defined ictal onset zone (blue); electrode contacts of highest EI ictal onset (marked **x**). B: EEG ictal onset pattern consisting of fast activity in grid electrodes G 27, 28, 35 and 36. C: spectral analysis electrode 27 showing massive increase in gamma power ($>5000\mu\text{V}^2/\text{Hz}$, peak 54 Hz) at ictal onset.

Fig. 3: Patient 14: grid and depth electrode contacts involved in seizure onset are equally captured by EI analysis (normalized EI values exceeding threshold 0.3 in grid contacts GA27, GA28, GA35, GA36, GA 44 and depth contacts D1-2,D1-3)

Figure 1
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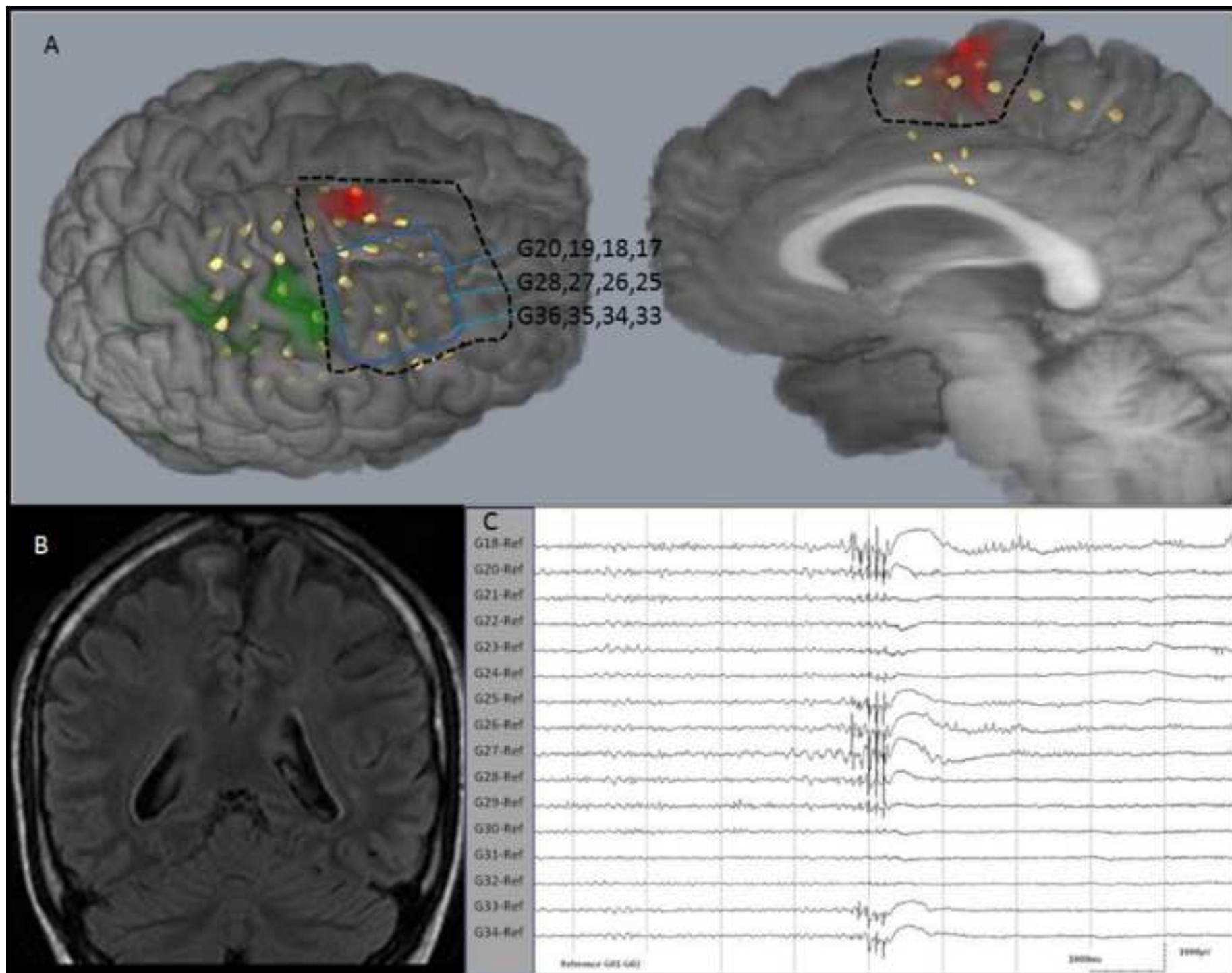


Figure 2
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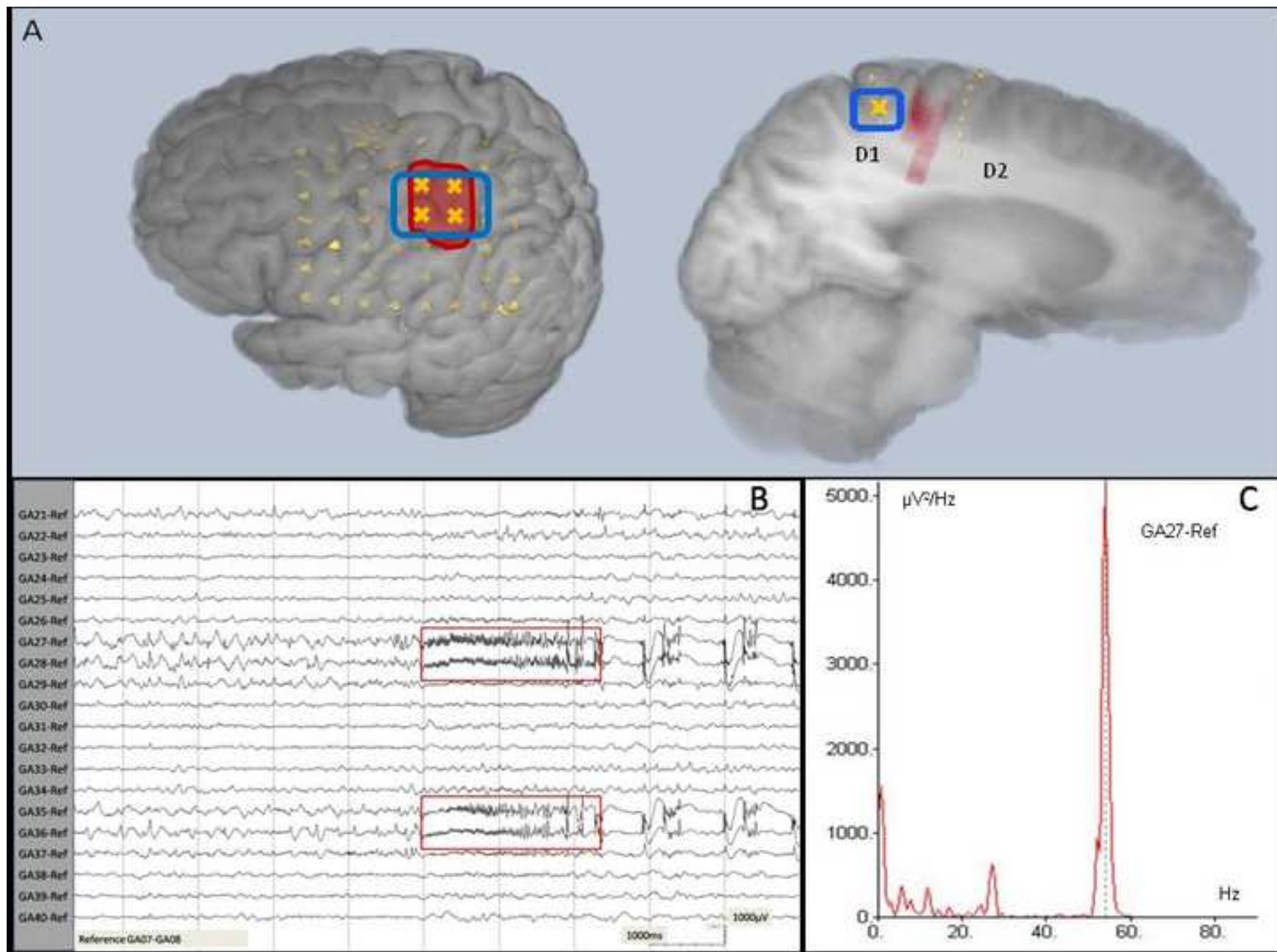
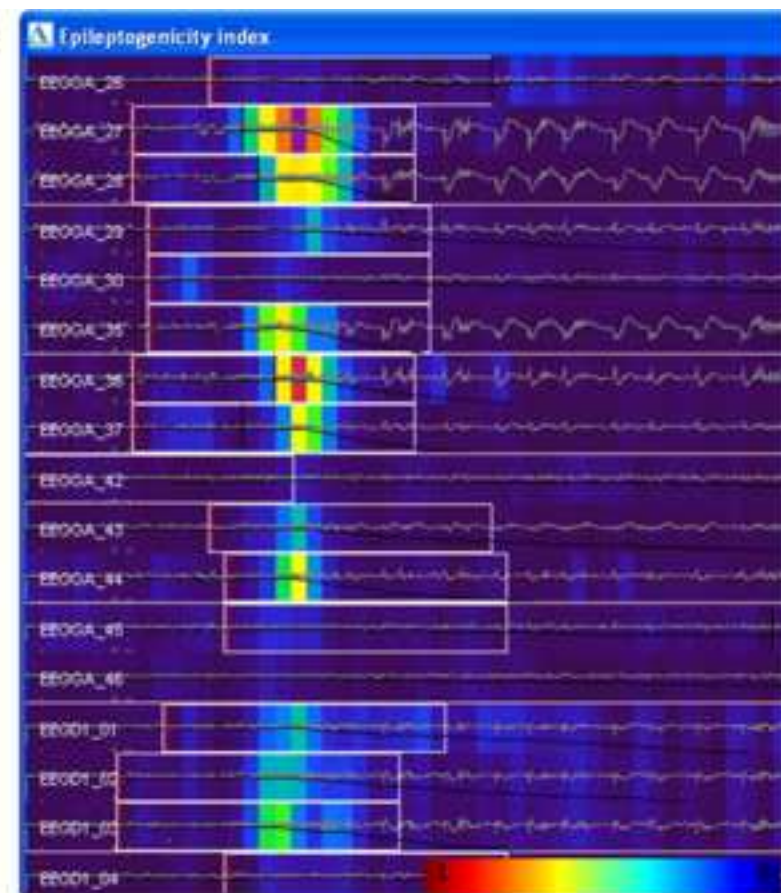


Figure 3
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A



B



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