The Role of Hybrid FDG-PET/MRI on Decision-Making in Presurgical Evaluation of Drug-Resistant Epilepsy.

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Abstract

Background: When MRI fails to detect a potentially epileptogenic lesion, the chance of a favorable outcome after epilepsy surgery becomes significantly lower (from 60-90 % to 20-65 %). Hybrid FDG-PET/MRI may provide additional information for identifying the epileptogenic zone. We aimed to investigate the possible effect of the introduction of hybrid FDG-PET/MRI into the algorithm of the decision-making in both lesional and non-lesional drug-resistant epileptic patients.

Methods: In a prospective study of patients suffering from drug-resistant focal epilepsy, 30 MRI-negative and 30 MRI-positive cases with discordant presurgical results were evaluated using hybrid FDG-PET/MRI.

Results: The hybrid imaging revealed morphological lesion in 18 patients and glucose hypometabolism in 29 patients within the MRI-negative group. In the MRI positive group, 4 patients were found to be MRI-negative, and in 9 patients at least one more epileptogenic lesion was discovered, while in another 17 cases the original lesion was confirmed by means of hybrid FDG-PET/MRI. As to the therapeutic decision-making, these results helped to indicate resective surgery instead of intracranial EEG (iEEG) monitoring in 2 cases, to avoid any further invasive diagnostic procedures in 7 patients, and to refer 21 patients for iEEG in the MRI-negative group. Hybrid FDG-PET/MRI has also significantly changed the original therapeutic plans in the MRI-positive group. Prior to the hybrid imaging, a resective surgery was considered in 3 patients, and iEEG was planned in 27 patients. However, 3 patients became eligible for resective surgery, 6 patients proved to be inoperable instead of iEEG, and 18 cases remained candidates for iEEG due to the hybrid FDG-PET/MRI. Two patients remained candidates for resective surgery and one patient became not eligible for any further invasive intervention.

Conclusions: The results of hybrid FDG-PET/MRI significantly altered the original plans in 19 of 60 cases. The introduction of hybrid FDG-PET/MRI into the presurgical evaluation process had a potential modifying effect on clinical decision-making.

Trial registration: Trial registry: Scientific Research Ethics Committee of the Medical Research Council of Hungary. Trial registration number: 008899/2016/OTIG. Date of registration: 08 February 2016.

1. Background

Epilepsy is one of the most prevalent neurological diseases with an incidence of 0.4-1‰ and a prevalence of 0.4-1% [1,2]. Approximately 23–30% of the patients are drug-resistant [3–6]. In these cases surgical resection constitutes the best therapeutic option towards achieving seizure freedom [7–11]. In 60–70% of the patients, noninvasive video-EEG monitor and cranial MRI can be conclusive regarding resective surgery without additional investigation(s). In the remaining proportion of the patients, invasive EEG (iEEG) exploration with intracranial electrodes (subdural or depth electrodes) plays a pivotal role in non-lesional drug-resistant epilepsy, or temporal or extratemporal lesional epilepsy with discordant electro-clinical results [12–16]. Epileptologists might have 4 reasonable options for patients with focal onset medically intractable epilepsy: (1) resective surgery without iEEG investigation, (2) iEEG exploration, (3) neuromodulation therapies such as vagus nerve stimulation (VNS) or deep brain stimulation (DBS), (4) giving new antiepileptic drug(s). Among these possibilities, resective surgery can achieve a decidedly higher seizure-freedom rate than the others [9–11]. When MRI fails to detect a potentially epileptogenic lesion, the chances of a favourable outcome after epilepsy

surgery become significantly lower (from 60–90% to 20–65%) [10,11]. Also in this workflow, FDG-PET/MRI coregistration can be utilized to guide a second look at MRI studies previously reported as nonlesional, thus underpinning decision-making [17]. Some epilepsy centers reported the role of PET/MRI coregistration was finding lesion(s) in MRI-negative drug-resistant epilepsy patients [18; 19; 20; 21]. Another option is the hybrid FDG-PET/MRI in preparation for epilepsy surgery in both lesional and non-lesional cases, providing additional sensitivity for detecting possible epileptic foci [22–24].

The aim of the present study was to investigate the possible effect of the results of hybrid FDG-PET/MRI on the decision-making by the epileptologist in both lesional and non-lesional drug-resistant epileptic patients. For this purpose, we selected two drug-resistant epileptic patient groups of the same size (either lesional or non-lesional cases), where the noninvasive video-EEG monitor and brain MRI were not conclusive regarding the resective surgery. We hypothesized that the results of hybrid FDG-PET/MRI may affect the initial judgement of the presurgical team: (1) the patient is eligible for iEEG exploration; or (2) eligible for resective surgery; or (3) the patient is not eligible for any further invasive procedure. Thus, in the present study, findings related to the alterations of decision-making were analyzed in detail with respect to imagery results (FDG-PET and MRI).

2. Methods

2.1. Subjects

We prospectively selected 60 adult patients (35 males, 25 females, mean age: 33.02, range:18–55 years) undergoing pre-surgical evaluation for drug-resistant, focal-onset epilepsy at two tertiary academic medical centers: (1) Department of Neurology, University of Pécs and (2) National Institute of Clinical Neurosciences, Budapest. Of the patients, all suffering from focal-onset epilepsy, 52 were right-handed and 8 were left-handed. Patients were divided into groups based on whether they were lesional (30 patients) with discordant investigational results or non-lesional (30 patients). The MRI protocol applied at this stage of presurgical evaluation is summarized in Table 1. All patients signed a written consent approved by Scientific Research Ethics Committee of the Medical Research Council of Hungary (008899/2016/OTIG).

2.2. Procedure and material

All of the patients underwent presurgical examinations: routine epilepsy clinic visits, noninvasive video-EEG monitoring, cranial MRI following the standard epilepsy protocol [25–28] and clinical semiology was evaluated by two presurgical teams. Before FDG-PET/MRI became available, some patients underwent PET/CT when MRI was negative or clinical and EEG findings suggested multiple seizure foci. A total of 60 patients underwent pre-surgical evaluations with hybrid FDG-PET/MR from June 2016 until January 2018.

A hybrid FDG-PET/MRI system (Siemens Biograph mMR, Siemens Heathineers, Erlangen, Germany) consisting of 3T Verio magnet and MR compatible LSO crystal based APD PET detector system allowing simultaneous PET/MRI acquisition was used. The device was settled in Baka József Diagnostic Center, Kaposi Mór Hospital, Kaposvár, Hungary.

The fluorine-18 fluoro-2-deoxyglucose ([18F] FDG) PET imaging was performed according to the guideline of European Association of Nuclear Medicine Neuroimaging Committee [29]. All patients fasted for at least 6 h

before the scan and blood glucose levels were checked prior to FDG administration. Before the scanning procedure the patients were asked to empty their bladder and were positioned comfortably in a quiet, dark room equipped with a video camera. Then a cannula for intravenous administration was placed. A 2 h-long supervision of the patient and 30 min of video EEG recording was performed before the administration of FDG (bolus of 200 MBq i.v.). We maintained the video-EEG monitoring for the whole uptake phase of FDG to ensure interictal state. If any seizure activities were recorded during video-EEG monitoring, the FDG-PET/MRI investigation was postponed to the following day. The PET/MRI scan was started 60 min after the FDG administration. For the prevention of movement artifacts, we informed the patients that they should avoid voluntary movements in the scanner. After the scanning procedure the patients were further supervised for two half–lives of the radioisotope decay (ca. 240 min). To ensure complete simultaneous PET coverage, a 20 min and a 35 min list mode PET acquisition were applied. For PET attenuation correction purposes vendor-provided T2 UTE sequence was used, μMaps were generated automatically. From the PET RAW DATA a 20 min and a 35 min static image dataset were produced. Attenuation-corrected and uncorrected transaxial slices were generated. For PET image reconstruction OP-OSEM method was applied containing PSF correction (3 iterations, 21 subsets, 4 mm post-recon Gaussian filtering, 344 × 344 imaging matrix).

The MRI sequences were the same as the standard epilepsy protocol [25–28]. The standard MRI epilepsy protocol used at our institutions is described in Table 2., below.

MRI (both the prior studies and those with the accompanying PET) and PET studies were downloaded and blindly and separately re-interpreted, by two neuroradiologists (for MRI: PB and ZV) and nuclear medicine physicians (for PET: KB and ZT). The two MR studies were interpreted separately from each other by each of the neuroradiologists (PB, ZV). Finally, simultaneously acquired MRI and PET images were evaluated on fused images, and clinical decisions were done with these data.

2.3. New variables: MR status change and Clinical decision according to PET/MRI results

2.3.1. MR status change

We created five new categories to describe the changes:

nn: The patient was MRI-negative prior to the study and he/she also remained MRI-negative in this study.

np: The patient was MRI-negative prior to the study and changed to MRI-positive in this study.

nc: The patient was suspect for MRI-positive prior to the study but the lesion was not confirmed in this study.

pp: The patient was MRI-positive prior to the study and the study confirmed the original lesion.

pp+: The patient was MRI-positive prior to the study and the study both confirmed the original lesion and found new epileptogenic lesion(s).

2.3.2. Clinical decisions according to PET/MRI results

The clinical decisions made by a consensus of the two multidisciplinary epilepsy surgery teams at two tertiary academic medical centers were classified into six categories:

1.: Remained as iEEG candidate.

2.: Resective surgery is available instead of iEEG.

3.: Considered as not eligible for any further invasive procedures instead of iEEG.

4.: Became iEEG candidate instead of resective surgery.

5.: Considered as not eligible for any further invasive procedures instead of resective surgery

6.: Remained as candidate for resective surgery.

3. Results

3.1. MRI-negative group

Hybrid PET/MRI examination revealed that 18 of 30 patients were found to have new specific epileptogenic MRI-lesion(s), while 29 of 30 patients had an abnormal FDG uptake. Two lesions were found in five patients. Hybrid PET/MRI helped to indicate resective surgery instead of iEEG monitoring in 2 patients due to congruent MRI, PET, semiological and EEG data. In seven patients, hybrid PET/MRI enabled us to decide to avoid any further invasive diagnostic procedures due to multiple electroclinical and/or hypometabolic epileptic foci with MRI-negativity (6 patients) or negative imagery (both PET and MRI) results (1 patient) (for details, see Table 3.). Of the remaining 21 patients referred to iEEG due to discordant electroclinical and PET/MRI results, in 11 cases one MRI-target was revealed; in 5 patients two potential epileptogenic lesions were found; while 5 cases remained MRI-negative.

3.2. MRI-positive group

Two patients became eligible for resective surgery, because of concordant electroclinical and hybrid FDG-PET/MRI results, which confirmed the MRI-lesion visualized prior to this study. In one patient any further invasive investigation was found to be contraindicated due to discordant electroclinical and PET data; but more importantly, because of altered MRI-status (MRI-negative).

iEEG was planned in 27 patients, of whom three patients became eligible for resective surgery because of concordant hybrid FDG-PET/MRI results and electroclinical data (for details, please see Table 4.).

Six of the remaining 27 patients proved to be inoperable instead of iEEG, 4 of these patients were found not to be confirmed MRI-positive. In 3 patients, any further invasive procedure was contraindicated. Eighteen patients remained candidates for iEEG due to discordant electroclinical and FDG-PET/MRI results.

4. Discussion

In the case of drug-resistant focal-onset epilepsy, the most important issue in the algorithm of the decision-making is to judge whether a drug-resistant epilepsy patient is eligible for (1) resective surgery, (2) iEEG

monitoring, or, (3) not eligible for any further invasive procedures [7,8].

PET/MRI coregistration has long been utilized in epilepsy centers and has been useful to guide a second look at MRI previously reported as nonlesional, thus guiding decision-making [17]. In an earlier publication, PET/MRI coregistration helped to find obvious lesion in 6 of 10 MRI-negative drug-resistant epilepsy patients [18]. In a pediatric study, 31 consecutive pediatric MRI-negative epilepsy patients were reported, of whom nine showed subtle pathologic abnormalities after second MRI-reading guided by PET/MRI coregistration [19]. In another study, 35 consecutive epilepsy patients with refractory focal epilepsy were investigated: structural MRI showed no lesion in 15 patients, of whom PET/MRI coregistration detected hypometabolism in 7 cases that was undetected on PET alone [20]. In a recent paper, 103 consecutive epileptic patients with FCD type 2 were reported, of whom 61 patients were MRI-positive, while 42 cases were dubious or negative. The additional value of PET/MRI coregistration in these 42 patients was predominant, because MRI localized FCD type 2 in 35 of 42 patients [21].

Here we report the role of hybrid FDG-PET/MRI on the decision-making workflow. Thus, in the present study, findings related to the changes in possible decisions of the presurgical team were analyzed in detail with respect to separate imaging results (FDG-PET and MRI) in both lesional and non-lesional epilepsy patients.

Our main finding is that hybrid FDG-PET/MRI decidedly influenced the decision-making of the presurgical team significantly. Its cardinal effect was the increased sensitivity of brain MRI in 60% of MRI-negative patients, which is a principal component in judging the chance for seizure-freedom (MRI-negative cases: 20–65% vs. MRI-positive cases: 60–90%) [10,11].

In an earlier pilot study using hybrid PET/MRI, 11 epileptic patients were investigated by FDG-PET/MRI without gross structural abnormalities that could interfere with image processing. Unfortunately, it is not clear from this publication, whether or not new structural lesions were found [23].

In another pilot hybrid FDG-PET/MRI study, of the twenty-nine patients assessed who underwent epilepsy surgery evaluation, in four cases new structural MR lesions were detected with the aid of FDG-PET findings, and one patient showed a new abnormal hypometabolism without any MRI abnormality. All new FDG-PET/MR lesions were clinically significant with concordant EEG and/or SPECT results as potential epileptic foci [24]. Recently, the same research group reported that hybrid FDG-PET/MR identified new structural or functional lesions in 10 of 74 patients [22].

Our study aimed to clarify the possible role of hybrid FDG-PET/MRI on decision-making in drug-resistant partial-onset epilepsy patients as well as to compare this effect with earlier PET/MRI coregistration studies.

4.1. MRI-negative group

In our study, the hybrid FDG-PET/MRI revealed a new morphological lesion in 18 patients and PET hypometabolism in 29 patients within the MRI-negative group.

Due to hybrid FDG-PET/MRI results, resective surgery was indicated instead of iEEG monitoring in 2 cases; hybrid FDG-PET/MRI results helped to avoid any further invasive diagnostic procedures in 7 patients. The

remaining 21 patients were referred to iEEG. In 16 of the remaining 21 patients, novel specific epileptogenic MRI-lesion(s) were revealed, proposing potential target(s) for iEEG monitoring, hopefully increasing the chance of successful identification of the epileptogenic zone.

As we showed in Table 1. and Table 2., (beyond better image quality/resolution) a major difference was the application of 3D FLAIR sequence which was lacking in the earlier imaging protocol. This might in part explain the newly identified specific epileptogenic lesions in a significant proportion of the MRI-negative group. 9 of these 18 patients showed the newly detected lesions exclusively on the 3D FLAIR images. Another possible explanation is the growing body of experience of our neuroradiologists together with the PET-readings (and these data were new information for them) and thus their increased sensitivity. Finally, the quality of MRI images deriving from the new hybrid PET/MRI systems was much better. These factors combined might explain the 60 percent difference (18 patients/30 MRI-negative patients).

Moreover, in nine of the 30 cases, findings of hybrid FDG-PET/MRI resulted in a significant change in decision-making (iEEG monitoring, resective surgery or not eligible for any further invasive procedures).

4.2. MRI-positive group

Hybrid FDG-PET/MRI disclosed at least one new morphological lesion in 9 patients and glucose hypometabolism in 30 patients within the MRI-positive group.

Four patients found to be MRI-negative in this study. In 17 cases the original lesion was confirmed.

Hybrid FDG-PET/MRI has also significantly changed the original therapeutic plans in the MRI-positive group. 3 patients became eligible for resective surgery, 6 patients were considered as not eligible for any further invasive procedure, and 18 cases still remained as candidates for iEEG. Two patients remained as candidates for resective surgery. In both groups the new anatomical or functional lesions were found to be clinically significant.

In the MRI-positive group, hybrid FDG-PET/MRI investigation altered the the epileptologist’s original decision in 10 of 30 cases: resective surgery, iEEG, or not eligible for any further invasive procedures.

Conclusions

Our study was undertaken to evaluate the potential improvement on decision-making using a hybrid FDG-PET/MRI scanner in epilepsy surgery algorithm, compared to separate 3 T MRI and electroclinical data. The results of hybrid FDG-PET/MRI significantly altered the original plans in 19 of 60 cases. In the MRI-negative group, in 18 cases, novel specific epileptogenic MRI-lesions were revealed, proposing potential targets for iEEG monitoring, thus hopefully increasing the chance of successfully identifying the epileptogenic zone in the most difficult epilepsy patients cohort.

Declarations

Ethics approval and consent to participate

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. This study was approved by Scientific Research Ethics

Committee of the Medical Research Council of Hungary (No. 008899/2016/OTIG).

Name of the registry: Hungarian Health Science Council Research Ethics Committee

Trial registration number: 008899/2016/OTIG

Date of registration: 08 Febr. 2016.

URL of trial registry record: https://ett.aeek.hu/tukeb/eng2016/

Consent for publication

Consent for publication was obtained from each person involved in this study.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Neither of the authors has any conflict of interest concerning the materials or methods used in this study or the findings specified in this paper to disclose.

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Janos Luckl: patients preparation for PET-MRI examination; and follow-up

Imre Repa: ensuring the PET/MRI facility, organization of the imaging examinations; ethical permission

Katalin Borbely: PET planning and analysis, manuscript correction.

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Tables

Due to technical limitations, tables xlsx are only available as a download in the Supplemental Files section.

Figures

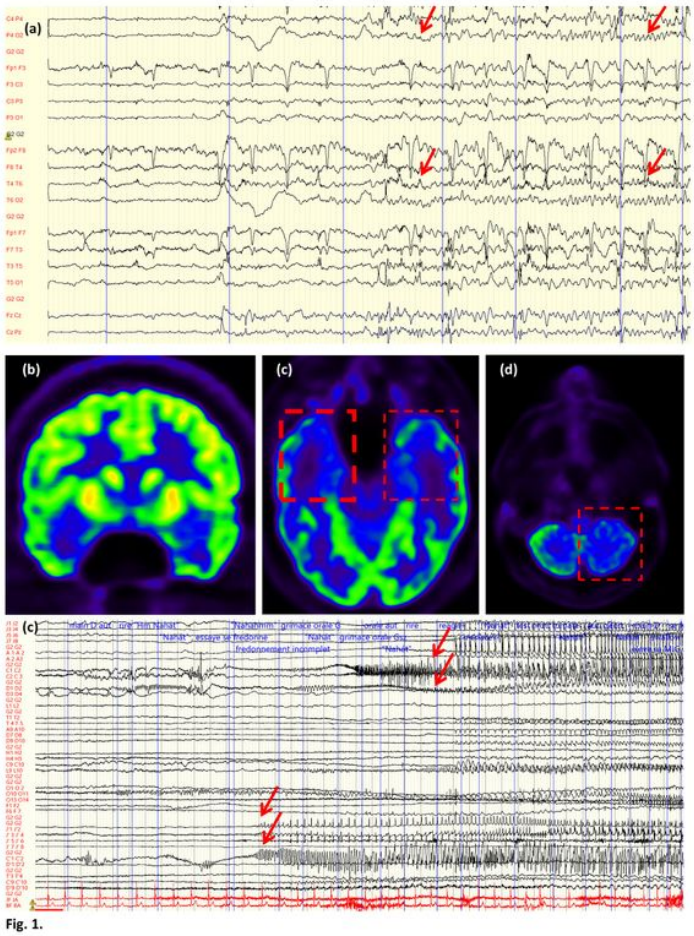

Fig. 1.

Figure 1

(Case 28, Table 3., group nn, decision type 1.): A drug-resistant epileptic patient with the electroclinical features of humming epilepsy. a) Video-EEG monitoring: during one of his habitual seizure, a right frontotemporal seizure activity was registered (red arrows). Originally, he was MRI-negative and this MRI-status did not change yet after this study. b) and c) 18F-FDG PET and PET/MRI presented a bitemporal hypometabolism with a right predominance (red boxes) and d) a left cerebellar hypometabolism (red box). c) This patient remained as an iEEG candidate. iEEG monitor has been performed and showed a bitemporal seizure activity with a left side onset (red arrows, left side of the figure), a left-right propagation in between a 10-second interval (red arrows,

right side of the figure), which was remote-controlled by a possible left orbitofrontal seizure onset zone. The patient did not allow neither a second iEEG intervention, nor VNS or DBS implantation.

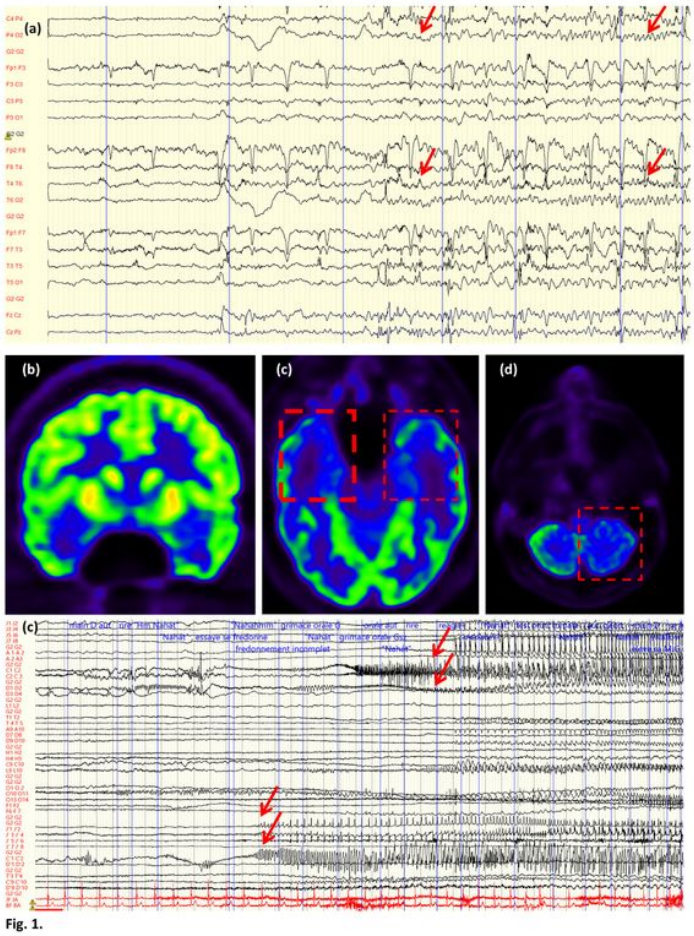

Fig. 1.

Figure 1

(Case 28, Table 3., group nn, decision type 1.): A drug-resistant epileptic patient with the electroclinical features of humming epilepsy. a) Video-EEG monitoring: during one of his habitual seizure, a right frontotemporal seizure activity was registered (red arrows). Originally, he was MRI-negative and this MRI-status did not change yet after this study. b) and c) 18F-FDG PET and PET/MRI presented a bitemporal hypometabolism with a right predominance (red boxes) and d) a left cerebellar hypometabolism (red box). c) This patient remained as an

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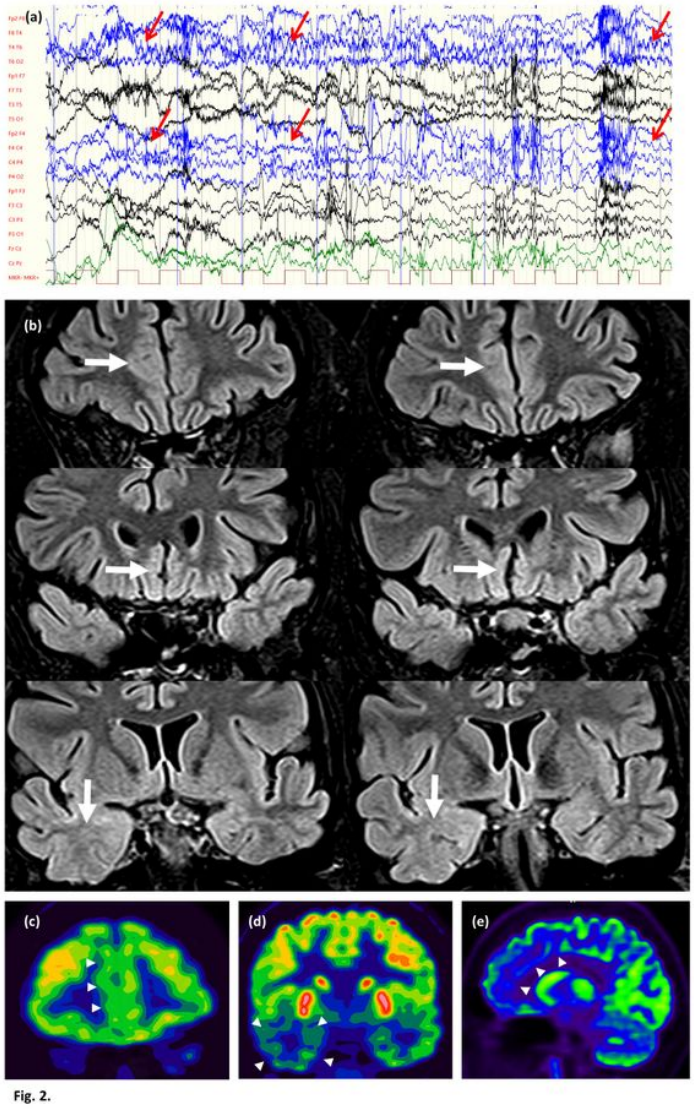
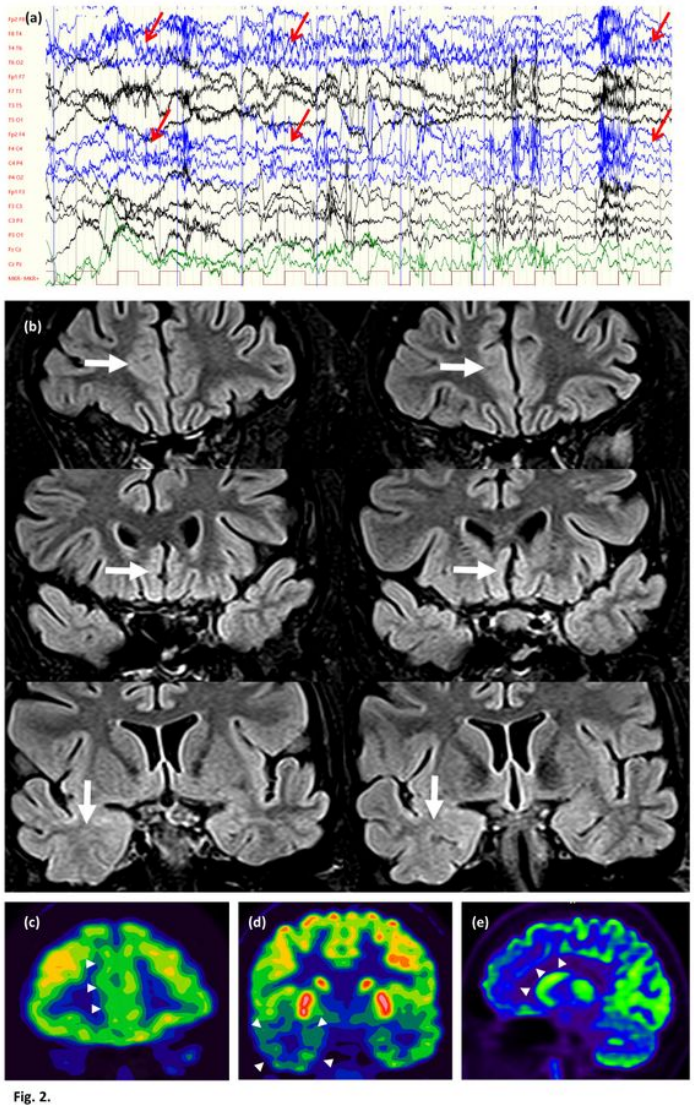


Fig. 2.

Figure 2

(Case 24, Table 3., group np, decision type 1.) A drug-resistant epileptic patient with the electroclinical features of a right frontotemporal epilepsy. a) During video-EEG monitoring, her habitual hypermotor seizure with a right frontotemporal seizure activity was registered (red arrows). Originally, she was MRI-negative and became MRI-

positive in this study. b) Coronal FLAIR images: white arrows show possible focal cortical dysplasia in the right anterior cingulate cortex (upper row), in the medial cortex of the right straight gyrus (middle row), and the mildly increased signal intensity and blurred cortex-white matter interface in the right temporal lobe (lower row) can be seen. 18F-FDG PET and PET/MRI presented c) and e) a hypometabolism in the right mesiofrontal region (white arrowheads), d) as well as in the right temporal lobe (white arroewheads). This patient remained as iEEG candidate; iEEG monitoring has not yet been realised.



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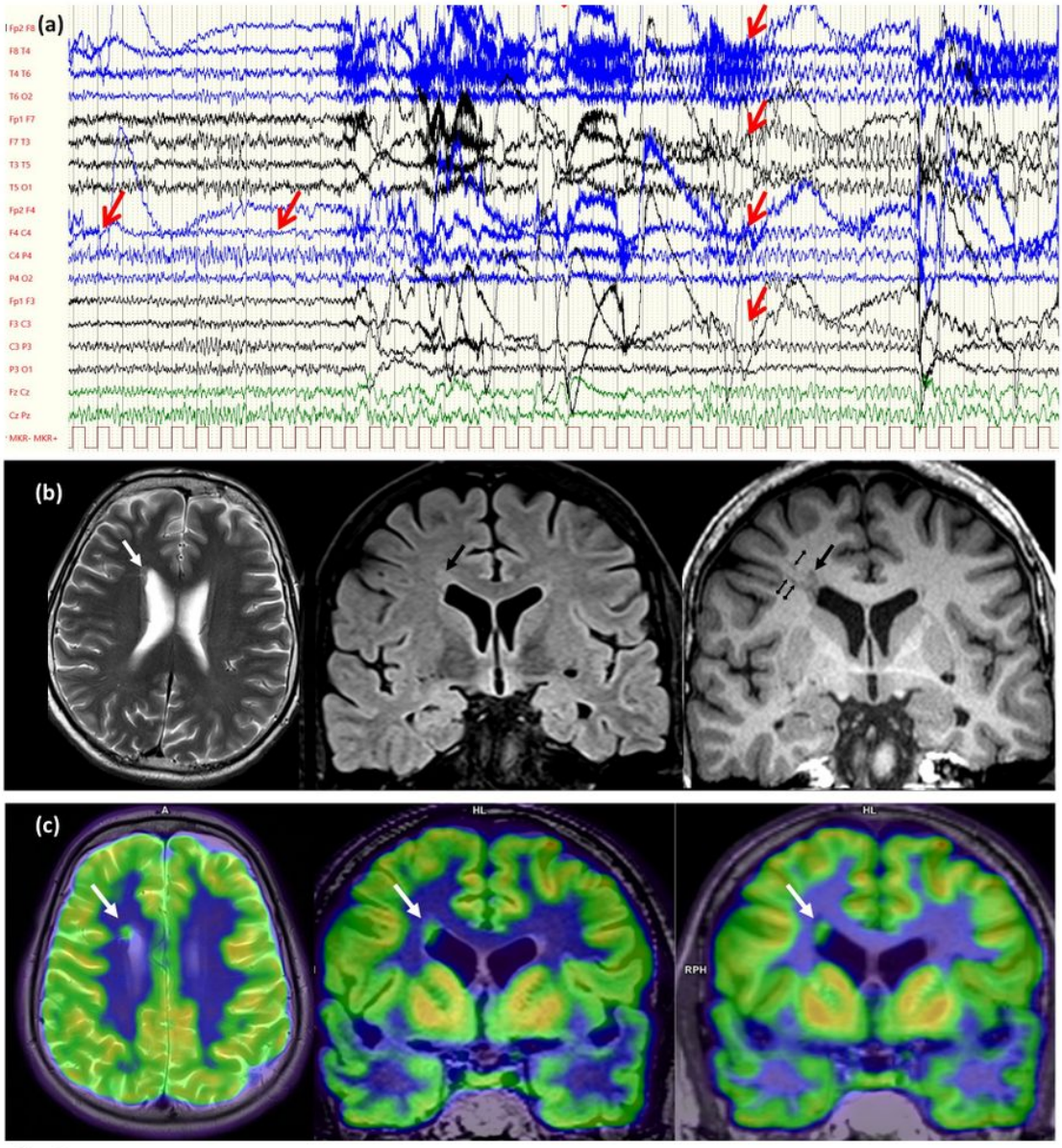
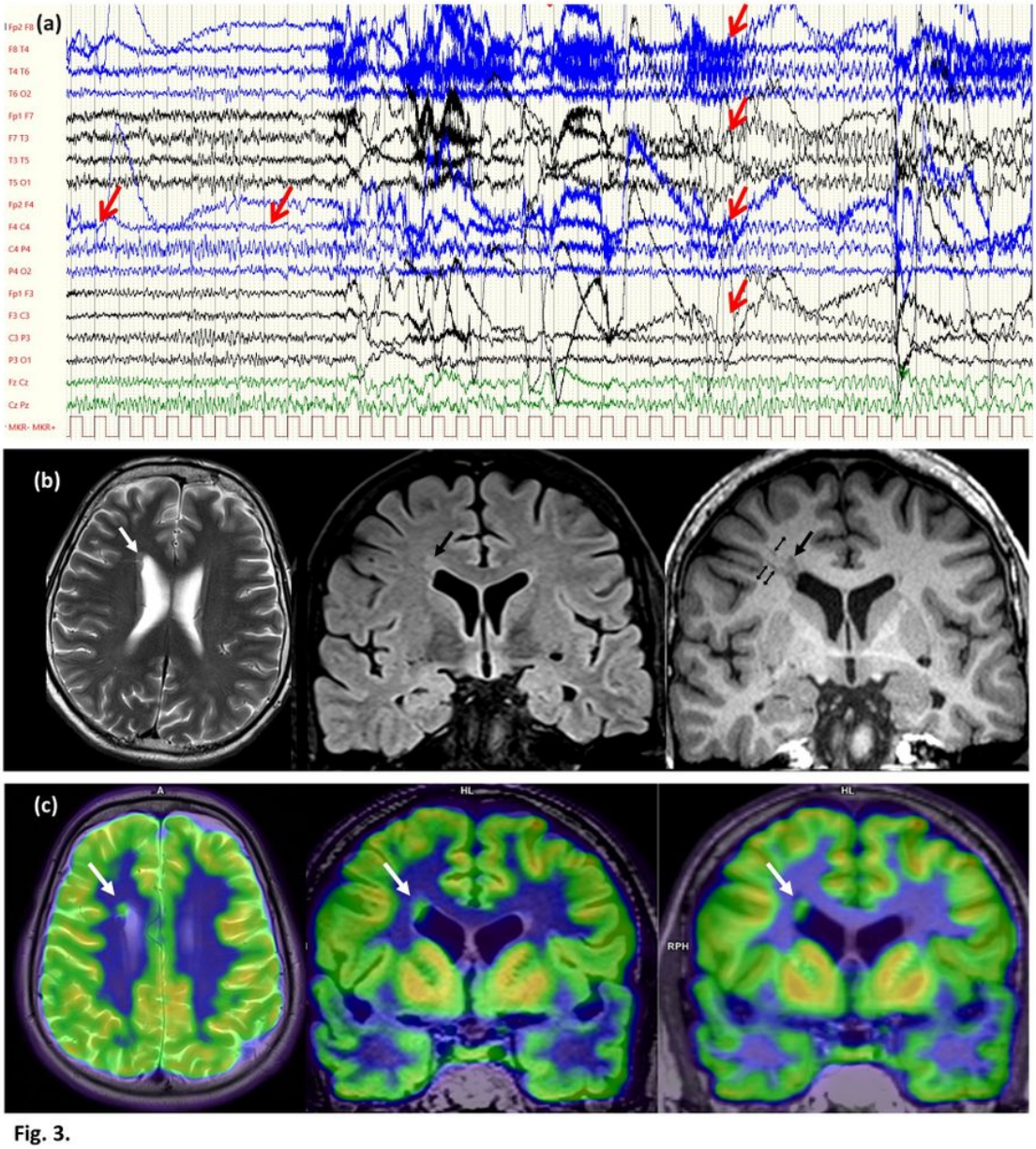


Fig. 3.

Figure 3

(Case 59, Table 4., group pp, decision type 2.): A drug-resistant epileptic patient with the electroclinical features of a right frontal epilepsy. a) Video-EEG monitoring revealed his habitual seizure, a right frontocentral seizure activity was seen, which rapidly became bilateral (marked with red arrows). Concordantly, cranial MRI showed a nodular heterotopia in the right inferior frontal gyrus. b) Axial T2 (left), coronal FLAIR (middle) and coronal T1 MPR (right) images. The white arrow on the T2 image and the large black arrows on the FLAIR and T1 images show focal nodular subependymal grey matter heterotopia. The small black arrows on the coronal T1 MPR image (right) show probable migrational bands. c) Exceptionally compared to the other cases, during 18F-FDG PET and PET/MRI, a circumscribed FDG accumulation reaching the intensity of cortical tracer uptake (and highly exceeding white matter uptake) can be observed, identically to the right periventricular heterotopia. In this case, resective surgery became available instead of iEEG. Because the patient was left-handed, fMRI and also Wada-test were performed and they proved that in this case, active Broca region is localized in the right hemisphere. Thus, resective surgery was performed in awake state and finally, only a partial resection was possible. After the resective surgery, patient had much shorter (1-3 second long) seizures.



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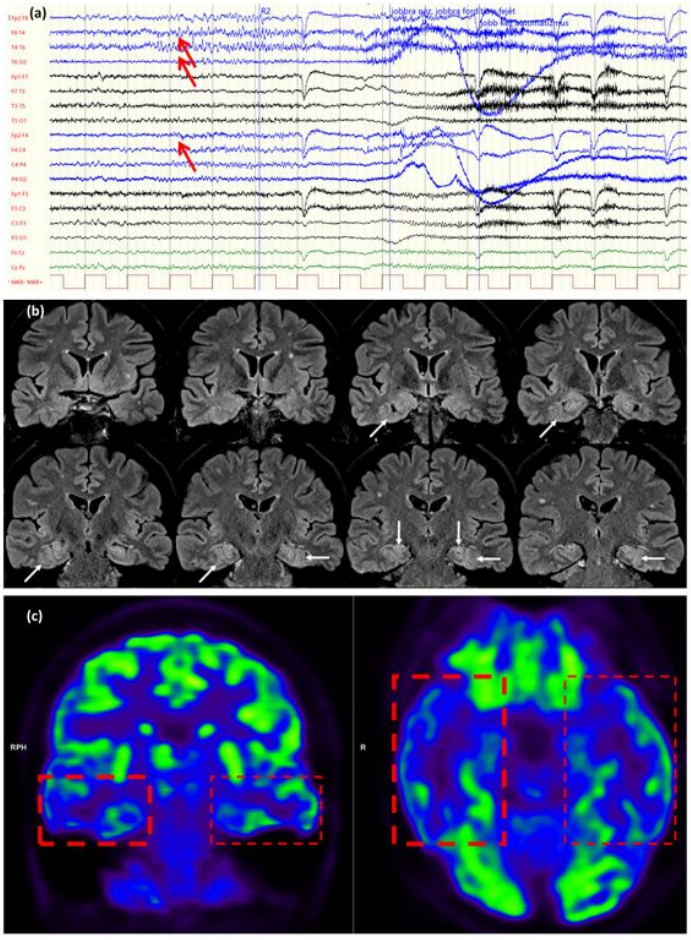

Fig. 4.

Figure 4

(Case 43, Table 4., group pp+, decision type 3.) A drug-resistant epileptic patient with the electroclinical features of a bitemporal lobe epilepsy. a) Video-EEG monitoring. During her habitual seizure, a right frontotemporal seizure rapid activity was seen (marked with red arrows). Meanwhile, original cranial MRI (made before this study) showed an FCD along the left collateral sulcus. b) Cranial MRI made in this study (coronal FLAIR images): horizontal arrows show the originally detected FCD along the left collateral sulcus while the oblique arrows show the newly observed FCD along the right collateral sulcus. The vertical arrows show the typical configuration of bilateral hippocampal malrotation, while c) and d) 18F-FDG PET and PET/MRI presented a hypometabolism in the right and left frontotemporal lobe, with a right predominance (red boxes). In summary, this patient was considered as not eligible for any further invasive procedures instead of iEEG.

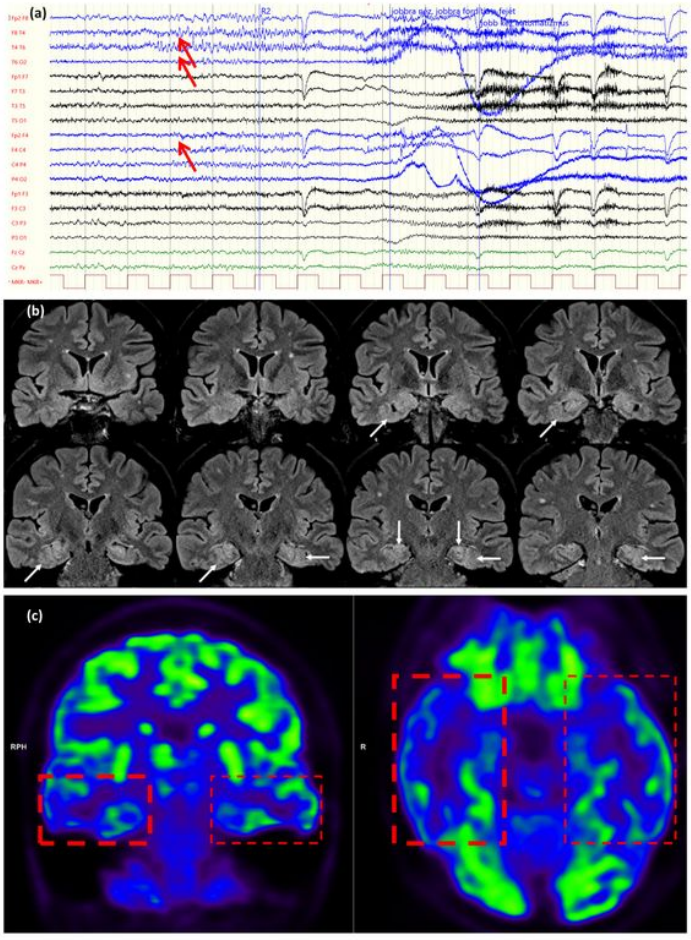

Fig. 4.

Figure 4

(Case 43, Table 4., group pp+, decision type 3.) A drug-resistant epileptic patient with the electroclinical features of a bitemporal lobe epilepsy. a) Video-EEG monitoring. During her habitual seizure, a right frontotemporal seizure rapid activity was seen (marked with red arrows). Meanwhile, original cranial MRI (made before this study) showed an FCD along the left collateral sulcus. b) Cranial MRI made in this study (coronal FLAIR images): horizontal arrows show the originally detected FCD along the left collateral sulcus while the oblique arrows show the newly observed FCD along the right collateral sulcus. The vertical arrows show the typical configuration of bilateral hippocampal malrotation, while c) and d) 18F-FDG PET and PET/MRI presented a hypometabolism in the right and left frontotemporal lobe, with a right predominance (red boxes). In summary, this patient was considered as not eligible for any further invasive procedures instead of iEEG.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.xlsx
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- Table2.xlsx
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- Table3.xlsx
- Table3.xlsx
- Table4.xlsx
- Table4.xlsx