Advanced imaging in epilepsy: literature review and our experience

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ABSTRACT

Background. The diagnosis of epilepsy is mostly based on clinical features of seizures and the results of electrophysiological and neuroimaging methods. Unluckily, there is no single imaging technique that can provide all the needed information: to confirm the etiology of seizures, to prognose the outcome of the disease and provide both structural and functional information that is required in pre-surgical evaluation of patients with drug-resistant epilepsy.
Aims and Objectives. 1. Systematic literature review of existing evidence. 2. To share our experience with epilepsy imaging.
Materials and methods. 1. A systemic search for relevant studies was performed from Medline (PubMed), Lippincott Williams & Wilkins, ScienceDirect, SpringerLink and Cochrane Library databases (these databases have been submitted on LSMUNI Library list of subscribed databases). 2. Thirty five patients with clinically proven refractory epilepsy were included into the study. All patients underwent a Fluorodeoxyglucose-18-PET/CT scan, MRI scan with epilepsy protocol used in our center, and an EEG at least 1 hour prior to a PET study and minimum 60 min in duration. The MRI was performed not earlier than 6 months before the PET/CT scan. All diagnostic tests were performed at Lithuanian University of Health Sciences hospital.
Results. We reviewed literature and characterized the complex correlation between imaging studies. Neuroimaging plays an important role in workup of patients with epilepsy. It helps to identify brain pathologies that require specific treatment. Identification of these lesions often helps in managing epilepsies more effectively.
In our experience most common localization of epileptogenic focus on all three imaging methods we chose were right temporal lobe. According to Wilcoxon signed ranks test results there is statistically significant difference in lesion amount between the different diagnostic methods.
Conclusions. This review compares available advanced imaging modalities, their specific role in patients with epilepsy, and practical applications of imaging data in the management of patients with epilepsy.

Keywords: epilepsy, MRI, FDG-PET, SPECT, spectroscopy, diffusion tensor imaging.

BACKGROUND

Epilepsy is a neurological disorder when activity in the brain becomes abnormal, causing seizures or periods of unusual behavior. As the disease itself the diagnosis is also very complex. The diagnosis is mostly based on clinical features of seizures and the results of electrophysiological and neuroimaging methods. Unluckily, there is no single imaging technique that can provide all the needed information: to confirm the etiology of seizures, to prognose the outcome of the disease and provide both structural and functional information that is required in pre-surgical evaluation of patients with drug-resistant epilepsy. While in most of the epilepsy cases magnetic resonance imaging (MRI) and computed tomography (CT) are the imaging tests of choice, the acquired information may not be enough when planning the outcome of surgical treatment [1]. There are other imaging tests and techniques that can be performed in this case like different MRI techniques: magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI), functional MRI (fMRI) and nuclear imaging techniques: positron emission tomography (PET) and single-photon emission computed tomography (SPECT). Although the value of these techniques are still sometimes controversial in everyday practice, the possibilities are almost endless.

MAGNETIC RESONANCE SPECTROSCOPY

MRS is a non-invasive diagnostic tool for

measuring biochemical changes in the brain. N-acetylaspartate (NAA) peak concentration is quantified and usually compared with creatine or choline peaks [1]. Due to the limited voxel coverage and long spectra acquisition time, MRS is mostly used for patients with focal epilepsies. Decreased NNA peaks strongly correlate with EEG and surgical results, thus MRS can be used for epileptogenic area lateralization and localization (changes are found in 70-80%), especially in MTLE patients with drug resistant epilepsy undergoing pre-surgical evaluation [1, 2, 3, 4]. Some studies suggest that NNA concentrations normalize after surgery, also NNA concentration appears to measure neuronal density, and in some cases NNA peak changes are bilateral in MTLE patients, therefore NNA changes should be interpreted with caution [1]. For properly selected patients MRS proves to be a valuable tool for pre-surgical evaluation and planning.

DIFFUSION TENSOR IMAGING

DTI is a subtype of diffusion weighted imaging (DWI) which measures the diffusion of water molecules within the white matter of the brain. This allows a non-invasive three-dimensional mapping of white matter tracts (tractography), including location, orientation and anisotropy [5, 6, 7]. DTI tractrography has shown to be valuable in patients with drug-resistant temporal lobe epilepsy (TLE) undergoing anterior temporal lobe resection (ATLR) [8, 9]. Although, surgically treated patients have a high rate of seizure freedom (50-60% at 10 years) [10], 50-100% suffer postoperative visual field defect [9, 11, 12, 13]. DTI may be employed for presurgical planning and intraoperative navigation in order to avoid injury to the temporal loop of the optic radiation (Meyer‘s loop), alongside conventional MRI imaging, DTI tractography has also proven helpful for evaluating post-operative damage to the Meyer‘s loop [9, 14, 15, 16]. Another possible application of DTI is fractional anisotropy analysis for lateralizing epileptogenic area in temporal lobe epilepsy patients. Ahmadi, et al. Found that DTI correctly localized left vs right TLE in 90% of all cases [17]. It suggests possible DTI application for MRI negative epilepsy patients and might give some insights for further radiological investigation. Although, DTI is not well established in clinical practice, it shows promising results with possible clinical application.

FUNCTIONAL MAGNETIC RESONANCE IMAGING

fMRI is a non-invasive imaging tool that can map functional areas in the brain by measuring changes in the cerebral blood flow. The most widely used fMRI technique employs blood oxygenation level - dependent (BOLD) effect. Due to different magnetic properties, changes in the ratio of oxyhemoglobin and deoxyhemoglobin concentrations can be measured, this allows to evaluate areas of altered neuronal activity. BOLD fMRI proved to be useful for functional area mapping related to specific tasks (i.e. language, memory, motor function) [3, 18, 19, 20, 21, 22]. Studies show evidence that task-based fMRI may be considered as an option to replace the invasive intra-carotid amobarbital procedure (IAP, also known as Wada test) which is the current standard for language and memory lateralization and outcome prediction prior to epilepsy surgery [23-25]. A study by Janecek et al. yielded promising results, showing 14% discordance rate between Wada and fMRI [26]. Another currently published practice guideline supports the idea, stating that fMRI could be used in place of IAP for lateralizing functonal language and memory areas in the presurgical evaluation, and prediction of postoperative deficit [27]. However, there are no standardised protocols for fMRI tasks (a set of questions or commands), results vary between the institutions, technical IAP aspects also differ depending on the institution, this is the possible cause of notable concordance between the two techniques, thus leading to potential drawback of fMRI implementation in day-to-day clinical practice.

Another possible application of fMRI is simultaneous EEG-fMRI recording. While fMRI maps hemodynamic changes, EEG represents electri-

cal activity of the brain allowing to better understand epileptogenic regions, their extent and connection to other areas of the brain [3, 19-22]. In one study EEG-fMRI helped to identify epileptogenic regions in 55% of MRI-negative epilepsy patients, which was helpful for further search of subtle lesions or guidance for intracranial placement of EEG electrodes [28]. A number of studies have found that the change in fMRI BOLD signal correlates with recorded EEG electric discharges (ED) during the seizure. As mentioned, it not only helps to locate the area of the epileptogenic zone but also gives information about more remote structures that contribute to the ED. This could help for further investigation of epileptic networks, moreover to the better understanding of the pathophysiology of epilpesy [28-31]. In summary, although fMRI is still considered to be experimental, recent studies show potential applications for epilepsy diagnostics and surgery, that one day may become routinely used in clinical practice.

NEUROIMAGING IN NUCLEAR MEDICINE

Functional neuroimaging using PET or SPECT are well established techniques that help observe metabolic processes and can localize a focal abnormality in patients with drug-resistant epilepsy while planning surgical treatment (32, 33, 34). Functional neuroimaging is essential in pre-surgical evaluation of the epilepsy patient especially when other previous CT or MRI scans were negative. Physiologic ligand with a connected radioactive tracer is administered intravenously and attach to targeted areas. A scanner detects the emission of gamma rays and then might be transferred to structural images made with CT or MRI to provide both anatomic and metabolic information.

POSITRON EMISSION TOMOGRAPHY

Fluorodeoxyglucose (FDG) is the most common ligand used in PET scan to measure glucose metabolism in epilepsy patients. FDG-PET is usually performed between the seizures (inter-ictal FDG-PET). Epileptogenic zone in interictal FDG-PET appears as hypo metabolic. FDG-PET has the most value in determining the temporal lobe epilepsy with specificity of 80-84 % [32]. The found temporal hypo metabolic zone accurately coincides with EEG abnormalities even when a patient is MRI-negative (32, 35, 36, 37). However, FDG-PET is less valuable in extra temporal epilepsy. PET does not provide much information about the size or structure of lesion because the hypo metabolic region usually extends farther than the epileptogenic zone. Thus other imaging techniques like CT or MRI are performed together with FDG-PET. FDG-PET might also be valuable if there is more than one registered epileptogenic zone in EEG or if the symptoms and the findings in EEG do not correlate [3]. There are other experimental and less known and less widely used ligands that each asses different functions. They are mostly used in clinical trials, for example 11C- or 18F-flumazenil. 11C-FMZ binds to (GABA)-A benzodiazepine receptors. The number of benzodiazepine receptors is significantly decreased in epileptogenic zone. Therefore, the uptake of 11C-FMZ is also decreased in this zone and this change may help to identify the hypo metabolic epileptogenic zone. The found zone is usually smaller and better defined while comparing the epileptogenic zone found with FDG-PET and 11C- FMZ. Even though this could be very useful while planning the surgical treatment and help to perform the smallest resection possible, the use of 11C-FMZ is limited due to technical difficulties like very short half-life. So the role of 11C- FMZ – PET in pre-surgical workup is not very well established, although it suggests many ideas for the future. [3, 32].

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY

SPECT assess the cerebral blood flow using radiotracers like technetium-99m-hexamethylpropylene amine oxime (99mTc-HMPAO). The radiotracer is administered intravenously and the scan is performed after 30 to 60 s after the administration. The half-life of radiotracer is long

so the scan can be performed up to 4 hours after the intravenous administration [2]. Although the inter-ictal SPECT is usually performed to use the images for subtraction, but it can also be used to evaluate the decreased cerebral blood flow between the seizures [2]. Ictal (during the seizure) SPECT scan allows to identify the epileptogenic zone which appears as hyperperfusion. It is especially important when the patient is MRI-negative [3]. The radiotracer must be prepared in advance and administered as soon as the seizure starts. Then the scan is performed and compared with the inter-ictal scan of the same patient. The success of the scan highly depends on the speed of radiotracer administration. The faster the radiotracer administration and the scan is performed, the better the probability to identify the epileptogenic zone is. SPECT is not recommended if the usual seizure is less than 15 s in length [1]. SPECT subtraction is the image sum of both ictal and inter-ictal scans [32]. SPECT is even more valuable when the scan data is compared with the symptoms and EEG data as it might be important in planning the surgical treatment even when the patient is MRI-negative [2, 3, 32, 37]. SPECT shows better results in identifying the temporal epileptogenic zone [1]. SPECT scan can also be combined with MRI scan and it is then called SISCOM (subtraction ictal SPECT co-registered to MRI). With the additional step of data normalization and statistical analysis it is called STATISCOM (Statistical ictal SPECT co-registered with MRI). The importance of those tests is still debatable, although it is possible that they will be widely used in the future.

OUR EXPERIENCE

Patient characteristics (table 1)
Cases comprised 35 patients with clinically proven refractory epilepsy. Gender of the patients was distributed almost equally: there were 18 women and 17 men patients. Twenty seven patient were adults, 8 were children at the time of hospitalization for epilepsy imaging. Mean age of all patients was 28.31. Most of the cases (32) were with structural epilepsy. Other 3 had unknown etiology.
All patients had been admitted for a comprehensive assessment including EEG monitoring, MRI scan with epilepsy protocol and a Fluorodeoxyglucose-18-PET/CT scan.

Descriptive Statistics (table 1)

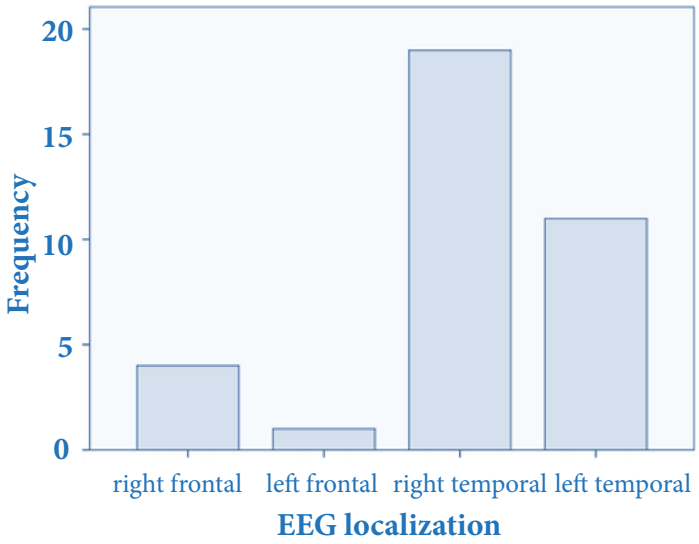
	N	Range	Minimum	Maximum	Mean		Std. Deviation	Variance
	Statistic	Statistic	Statistic	Statistic	Statistic	Std. Error	Statistic	Statistic
patient_age	35	61	2	63	28.31	2.550	15.088	227.634
Valid N (listwise)	35							

RESULTS

1. Most common localization for epileptogenic activity on EEG was right temporal lobe with 54.3% (table 2); most common lobe with structural changes on MRI was right temporal lobe with 42.9% (table 3); most common hypometabolism zone on PET/CT was in right temporal lobe with 45.7% (table 4).

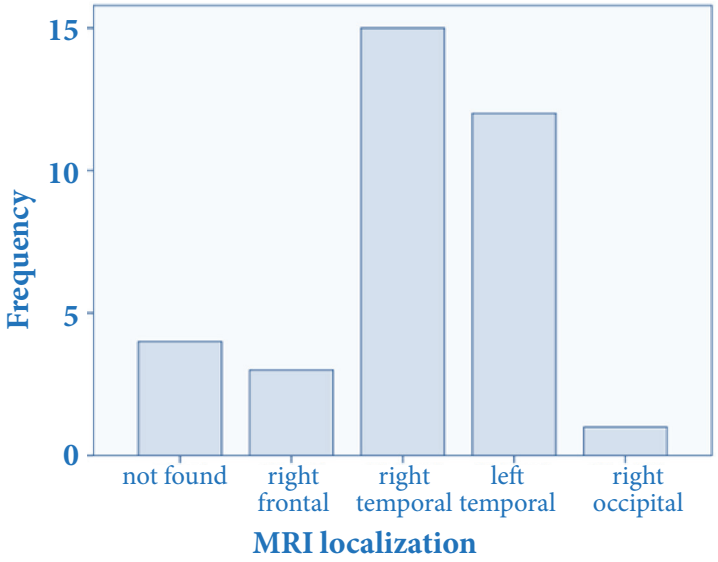
eeg_localization (table 2)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	right_frontal	4	11.4	11.4	11.4
	left_frontal	1	2.9	2.9	14.3
	right_temporal	19	54.3	54.3	68.6
	left_temporal	11	31.4	31.4	100.0
	Total	35	100.0	100.0	



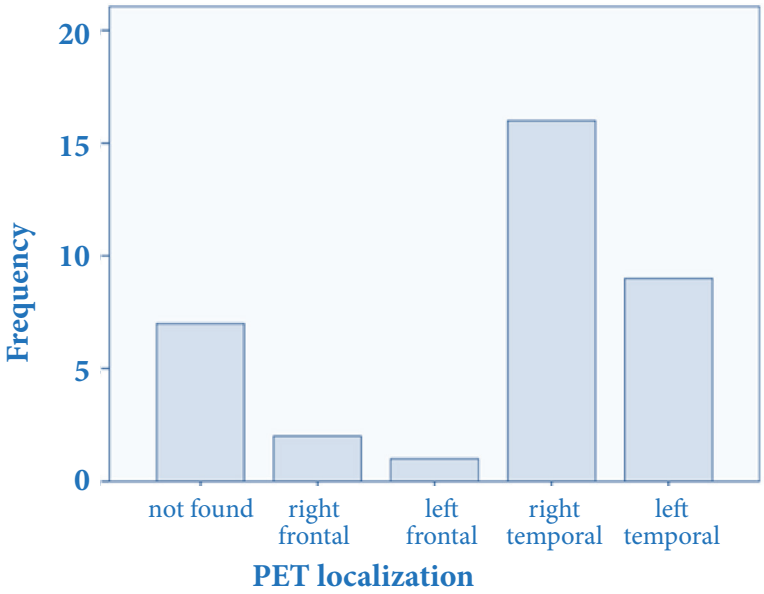
mri_localization (table 3)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	not found	4	11.4	11.4	11.4
	right_frontal	3	8.6	8.6	20.0
	right_temporal	15	42.9	42.9	62.9
	left_temporal	12	34.3	34.3	97.1
	right_occipital	1	2.9	2.9	100.0
	Total	35	100.0	100.0	



pet_localization (table 4)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	not found	7	20.0	20.0	20.0
	right_frontal	2	5.7	5.7	25.7
	left_frontal	1	2.9	2.9	28.6
	right_temporal	16	45.7	45.7	74.3
	left_temporal	9	25.7	25.7	100.0
	Total	35	100.0	100.0	



WILCOXON SIGNED RANKS TEST

Ranks (table 5)

		N	Mean Rank	Sum of Ranks
eeg_lesion_amount - mri_lesion_amount	Negative Ranks	3[a]	13.50	40.50
	Positive Ranks	22[b]	12.93	284.50
	Ties	10[c]		
	Total	35		
mri_lesion_amount - pet_lesion_amount	Negative Ranks	8[d]	8.25	66.00
	Positive Ranks	5[e]	5.00	25.00
	Ties	21[f]		
	Total	34		
pet_lesion_amount - eeg_lesion_amount	Negative Ranks	18[g]	11.33	204.00
	Positive Ranks	4[h]	12.25	49.00
	Ties	12[i]		
	Total	34		

a. eeg_lesion_amount < mri_lesion_amount
b. eeg_lesion_amount > mri_lesion_amount
c. eeg_lesion_amount = mri_lesion_amount
d. mri_lesion_amount < pet_lesion_amount
e. mri_lesion_amount > pet_lesion_amount
f. mri_lesion_amount = pet_lesion_amount
g. pet_lesion_amount < eeg_lesion_amount
h. pet_lesion_amount > eeg_lesion_amount
i. pet_lesion_amount = eeg_lesion_amount

Test Statistics[a] (table 6)

	eeg_lesion_amount - mri_lesion_amount	mri_lesion_amount - pet_lesion_amount	pet_lesion_amount - eeg_lesion_amount
Z	-3.443b	-1.460c	-2.665c
Asymp. Sig. (2-tailed)	.001	.144	.008

a. Wilcoxon Signed Ranks Test
b. Based on negative ranks.
c. Based on positive ranks.

Wilcoxon signed ranks test results (tables 5, 6):

Correlation of EEG violations with MRI abnormalities

First line in the Ranks table indicates number of cases (N=3) when number of epileptogenic foci found on EEG were lower than established on MRI. The sum of the rankings was 40.50; Average rank 13.50. Similar information was provided in 22 cases where number of epileptogenic foci detected by the EEG method was higher than established on MRI. The second table shows the Z-value (-3.443) and the p value (Asymp. Sig. (2-tailed) = 0.001). Since p <0,05 - there was a statistically significant difference between the number of epileptogenic focal points detected on EEG and MRI.

MRI correlation with PET / CT lesions

There were 8 cases where number of epileptogenic foci detected on MRI was lower than those which were found on PET/CT. These tests correspond to rank=66.00; average rank=8.25. In 5 cases epileptogenic foci number detected on MRI was higher than identified on PET/CT. Z-value was
-1.460, p=0.144. Since p>0.05 - there was no statistically significant difference between the number of epileptogenic foci detected on MRI and PET/CT.

PET / CT correlation with EEG lesions

In 18 cases number of epileptogenic foci detected on PET/CT was lower than on EEG. Corresponding ranking=204.00; average rank=11.33). In 4 cases number of epileptogenic foci detected on MRI was higher than established on PET/CT. Z-value was -2.665, p = 0.008). As
p<0.05 - there was a statistically significant difference between epileptogenic foci found on PET/CT and EEG.

CONCLUSIONS

This review compares available advanced imaging modalities, their specific role in patients with epilepsy, and practical applications of imaging data in the management of patients with epilepsy. Conventional MRI is the common choice for imaging for now, mostly because of its ability to detect small lesions like mesial temporal sclerosis, cortical dysplasias and small tumors, that are not detected by CT, which is often needed only for the initial investigation and in acute situations. However, different MRI techniques, functional nuclear imaging methods like PET/CT is extremely useful imaging methods to assist in the localization of epileptogenic zones. Information that these neuroimaging methods provides is complementary to anatomical imaging of MRI and functional information of EEG and is a very important techniques in the process of sorting out patients in whom surgery may be indicated.
According to our experience - there was a statistically significant difference in lesion amount between MRI, PET/CT and EEG diagnostic methods for epilepsy.
Most common localization of epileptogenic focus on all three imaging methods we chose were right temporal lobe, which might be associated with fact that hippocampus is often involved in seizures, even if they are not generated there.

REFERENCES

1. Cendes F. Neuroimaging in investigation of patients with epilepsy. Continuum (Minneap Minn). 2013;19:623-42.

2. Cendes F, Theodore WH, Brinkmann BH, Sulc V, Cascino GD. Neuroimaging of epilepsy. Handb Clin Neurol. 2016;136:985-1014.

3. Pardoe H, Kuzniecky R. Advanced Imaging Techniques in the Diagnosis of Nonlesional Epilepsy: MRI, MRS, PET, and SPECT. Epilepsy Curr. 2014;14(3):121-4.

4. Cendes F, Knowlton RC, Novotny E, et al. Magnetic resonance spectroscopy in epilepsy: clinical issues. Epilepsia. 2002;43(Suppl. 1):32–39.

5. Jellison BJ, Field AS, Medow J, Lazar M, Salamat MS, Alexander AL. Diffusion Tensor Imaging of Cerebral WhiteMatter: A Pictorial Review of Physics, Fiber Tract Anatomy, and Tumor Imaging Patterns. AJNR Am J Neuroradiol 2004; 25:356–369

6. Duncan JS. Imaging the brain's highways-diffusion tensor imaging in epilepsy. Epilepsy Curr. 2008;8(4):85-9

7. Tournier JS, Mori S, Leemans A. Diffusion Tensor Imaging and Beyond. Magnetic Resonance in Medicine 2011;65:1532–1556

8. Al-Otaibi F, Baeesa SS, Parrent AG, Girvin JP, Steven D. Surgical techniques for the treatment of temporal lobe epilepsy. Epilepsy Res Treat 2012;2012:374848

9. Piper RJ, Yoong MM, Kandasamy J, Chin RF. Application of diffusion tensor imaging and tractography of the optic radiation in anterior temporal lobe resection for epilepsy: a systematic review. Clin Neurol Neurosurg 2014;124:59-65

10. de Tisi J, Bell GS, Peacock JL, McEvoy AW, Harkness WF, Sander JW, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. Lancet 2011; 378:1388–95.

11. Pathak-Ray V, Ray A, Walters R, Hatfield R. Detection of visual field defects in patients after anterior temporal lobectomy for mesial temporalsclerosis-establishing eligibility to drive. Eye (Lond). 2002;16(6):744-8.

12. Zhang H, Wu W, Fang Y, Zhou D, Lei D. Changes in optic radiation integrity and visual fields afer three different temporal lobe epilepsy surgeries. 30th International Epilepsy Conference. p. 179.

13. Nilsson D, Starck G, Ljungberg M, Ribbelin S, Jönsson L, Malmgren K, et al. Intersubject variability in the anterior extent of the optic radiation assessed by tractography. Epilepsy Res 2007;77:11–6.

14. James JS, Radhakrishnan A, Thomas B, Madhusoodanan M, Kesavadas C, Abraham M, et al. Diffusion tensor imaging tractography of Meyer's loop in planning resective surgeryfor drug-resistant temporal lobe epilepsy. Epilepsy Research 2015;110:95-104

15. Yogarajah M, Focke NK, Bonelli S, Cercignani M, Acheson J, Parker GJM, et al. Defining Meyer's loop–temporal lobe resections, visual field deficits and diffusion tensor tractography. Brain 2009:132;1656–1668

16. Sivakanthan S, Neal E, Murtagh R , Vale FL. The evolving utility of diffusion tensor tractography in the surgical management of temporal lobe epilepsy: a review. Acta Neurochir 2016; 158:2185–2193

17. Ahmadi ME, Hagler DJ, McDonald CR, Tecoma E, Vicente Iragui, et al. Side Matters: Diffusion Tensor Imaging Tractography in Left and Right Temporal Lobe Epilepsy.AJNR Am J Neuroradiol. 2009;30(9): 1740–1747

18. Rutten GJ, Ramsey NF. The role of functional magnetic resonance imaging in brain surgery. Neurosurg Focus.2010;28(2):E4

19. Middlebrooks EH, Hoef LV, Szaflarski JP. Neuroimaging in Epilepsy. Curr Neurol Neurosci Rep 2017;17:32

20. van Graan LA, Lemieux L, Chaudhary UJ.Methods and utility of EEG-fMRI in epilepsy.Quant Imaging Med Surg 2015 Apr;5(2):300-12

21.Bernasconi A, Bernasconi N, Bernhardt BC, Schrader D.Advances in MRI for 'cryptogenic' epilepsies.Nat Rev Neurol. 2011 Feb;7(2):99-108.

22. Duncan JS. Imaging in the surgical treatment of epilepsy.Nat Rev Neurol. 2010 Oct;6(10):537-50

23. Abou-Khalil B, Schlaggar BL. Is it time to replace the Wada test? Neurology. 2002;59(2):160–1.

24. Binder JR, Swanson SJ, Hammeke TA, Morris GL, Mueller WM, Fischer M, et al. Determination of language dominance using functional MRI: a comparison with the Wada test. Neurology. 1996;46(4):978–84.

25. Szaflarski JP, Holland SK, Jacola LM, Lindsell C, Privitera MD, Szaflarski M. Comprehensive presurgical functional MRI language evaluation in adult patients with epilepsy. Epilepsy Behav. 2008;12(1):74–83.

26. Janecek JK, Swanson SJ, Sabsevitz DS, Hammeke TA, Raghavan M, E Rozman M, et al. Language lateralization by fMRI and Wada testing in 229 patients with epilepsy: rates and predictors of discordance. Epilepsia 2013 Feb;54(2):314-22.

27. Szaflarski JP, Gloss D, Binder JR, Gaillard WD, Golby AJ, Holland SK, et al.Practice guideline summary: Use of fMRI in the presurgical evaluation of patients with epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology.Neurology. 2017 Jan 24;88(4):395-402.

28. Pittau F, Dubeau F, Gotman J. Contribution of EEG/fMRI to the definition of the epileptic focus. Neurology 2012;78:1479–1487.

29. Kobayashi E, Bagshaw AP, Jansen A, Andermann F, Andermann E, Gotman J, et al. Intrinsic epileptogenicity in polymicrogyric cortex suggested by EEG-fMRI BOLD responses. Neurology.

2005;64(7):1263–6.

30. Kobayashi E, Bagshaw AP, Benar CG, Aghakhani Y, Andermann F, Dubeau F, et al. Temporal and extratemporal BOLD responses to temporal lobe interictal spikes. Epilepsia. 2006;47(2):343–54.

31. Kobayashi E, Bagshaw AP, Grova C, Gotman J, Dubeau F. Grey matter heterotopia: what EEG-fMRI can tell us about epileptogenicity of neuronal migration disorders. Brain.2006;129(Pt 2):366–74.

32. Lapalme-Remis S, Cascino GD. Imaging for Adults With Seizures and Epilepsy. Continuum. 2016;22:1451-1479.

33. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55:475-82.

34. Von Oertzen J, Urbach H, Jungbluth S, Kurthen M, Reuber M, Fernandez G, et al. Standard magnetic resonance imaging is inadequate for patients with refractory focal epilepsy. J Neurol Neurosurg Psychiatry. 2002;73:643–647.

35. Carne RP, O'Brien TJ, Kilpatrick CJ, et al. MRI-negative PET-positive temporal lobe epilepsy: a distinct surgically remediable syndrome. Brain 2004;127:2276-2285.

36. Beleza P. Acute symptomatic seizures: a clinically oriented review. Neurologist. 2012;18(3):109-19.

37. Desai A, Bekelis K, Thadani V, Roberts D, Jobst B, Duhaime A, et al. Interictal PET and ictal subtraction SPECT: Sensitivity in the detection of seizure foci in patients with medically intractable epilepsy. Epilepsia. 2013;54(2):341–350.