Chapter

Neuroimaging for Epilepsy Diagnosis and Management

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Abstract

This chapter will cover the neuroimaging techniques and their application to the diagnostic work up and management of adults and children with new onset or chronic epilepsy. We will focus on the specific indications and requirements of different imaging techniques for the diagnosis and pre-surgical work up of pharmacoresistant focal epilepsies. We will discuss the sensitivity, specificity and prognostic value of imaging features, benign variants and artefacts, and the possible diagnostic significance of non-epileptogenic lesions. This chapter is intended to be relevant for day-to-day practice in average clinical circumstances, with emphasis on MRI and most commonly used functional neuroimaging techniques.

Keywords: MRI, epilepsy, temporal, extratemporal, SPECT, PET

1. Introduction

The advent of neuroimaging has provided powerful tools for the identification of epileptogenic lesions preoperatively. This has increased the number of surgical candidates and improved postsurgical outcomes [1–3]. The approach of presurgical evaluation in patients with potential epileptogenic lesions has also radically changed, absolving the need for invasive neurophysiologic techniques.

Magnetic resonance imaging is currently the best available tool for identification of epileptogenic lesions, newer scanning techniques such as 3T magnets, functional MRI (fMRI), and diffusion tensor imaging (DTI) are giving clinicians more insight into the presumptive pathology. More importantly these techniques allow precise 3D anatomic localization of the lesion and its relationship to adjacent structures and network connectivity (brain connectome). Novel imaging results are giving us more information about cortical function and/or dysfunction in patients with epilepsy in order to predict postoperative deficits and odds of seizure freedom. This has given a lot of hope to patients previously diagnosed with refractory epilepsy with no identifiable culprit.

2. MRI

3T MRI scanners are now widely available and replacing 1.5T scanners for epilepsy protocol imaging. Increase in the magnetic field strength in 3T MRI improves the signal-to-noise ratio and contrast-to-noise ratio, thereby improving the detection

of elusive lesions such as malformations of cortical development (MCD) [4–7]. Challenges of ultra-high-field imaging include far greater radiofrequency signal inhomogeneities, higher energy deposition in tissue, and more pronounced imaging artifacts at soft tissue–air and soft tissue–bone interfaces. 3T MRI also has increased device incompatibility [4, 8, 9] compared to older machines.

Most MRI studies for evaluation of epilepsy would first include a sagittal T1-weighted spin-echo acquisition in order to position the slices of the subsequent pulse sequences. Two kinds of protocols were commonly used in epilepsy imaging in the past, the temporal lobe protocol and extratemporal protocol. However, these protocols would often neglect substantial parts of the non-targeted area of the brain. Some centres now advocate a more comprehensive protocol [10, 11]. Supplementary imaging sequences include T2* gradient echo, DWI, sagittal 3D TSE T2/FLAIR, contrast imaging and post-processing techniques such as voxel based morphometry. FLAIR has a specific advantage over T2 for lesions in periventricular, hippocampal and subpial cortex locations due to proximity to the brain-CSF interface. Other lesions readily identified by FLAIR include subtle hyperintensities blurring the gray-white junction of MCD, subcortical foci of gliotic hyperintensity in areas of encephalomalacia, and the extent of infiltration of low-grade neoplasms. Limitations of FLAIR include CSF pulsation induced motion artifacts causing blurring of the medial temporal regions and contrast suppression obscuring visualization of small foci of heterotopic gray matter. Also of note is that contrast on fast FLAIR seems to be most limiting in patients with immature white matter i.e. young children (<2 years). Conventional spin density images tend to be more helpful in this age group.

Signal characteristics of immature myelin in infants and young children can pose significant challenges in interpretation of studies obtained in infancy. Lesions such as MCDs and cortical tubers have varying signal characteristics depending on the developmental stage of the myelin of the lesions and the surrounding brain. In infants, the dysplastic cortex and adjacent subcortical regions may appear hypointense on T2-weighted images and hyperintense on T1 sequences, contrary to the reverse pattern seen in older children and adults [12–14]. In some patients these lesions tend to become less obvious or rarely "vanish" on follow-up imaging [15] thus reviewing only the most recent images may fail to detect the lesions. Conversely, a "new lesion" of MCD may be detected on follow-up imaging due to the poor background contrast of the bright immature myelin on the T2 images [16]. Follow-up MRI during 2nd year of life or later may unmask areas of MCD with decreased or absent subcortical myelin. Cortical tubers of tuberous sclerosis may be more evident on follow-up imaging. Apart from changes in myelination, increased growth of tubers and dystrophic calcification may contribute to their better visibility on follow-up imaging. Serial MRIs are helpful in other epileptic disorders such as Rasmussen encephalitis and Sturge-Weber syndrome to demonstrate progressive regional or hemispheric cortical atrophy.

2.1 Susceptibility weight imaging (SWI)

SWI techniques exploit differences in magnetic susceptibility of tissue components such as deoxygenated blood, iron, and calcium to provide additional information in epileptogenic lesions containing blood products. This can be useful for cavernomas, certain posttraumatic epilepsies, and Sturge-Weber syndrome. SWI is superior to T2* Gradient Echo (GRE) in detection of remote hemorrhages. Cortical gyral abnormalities in Sturge-Weber syndrome can represent venous stasis-related

hypoxia, and their SWI findings seem to correspond to the hypometabolic areas detected on FDG-PET. Thus, SWI has the potential to show functional information in addition to anatomical details in Sturge-Weber syndrome [17, 18].

2.2 Diffusion weighted imaging (DWI)

One of the more commonly encountered techniques in MRI is DWI. DWI was initially introduced in clinical practice for the early detection of stroke as it is very sensitive to areas affected by ischemia [19]. Animal studies on status epilepticus have highlighted initial restricted diffusion due to cytotoxic edema and, after several days, to normalization or facilitated diffusion [20–23]. Diffusion imaging may, therefore, provide an opportunity to directly image the areas involved in seizure generation and possibly spread. Overall, the correlation between the presumed epileptogenic zone and the diffusion changes is quite variable. In focal epilepsies, peri-ictal isolated low ADC values without overt hyperintensity on DWI have been reported. Peri-ictal cytotoxic edema with foci of hyperintensity on DWI with decreased ADC values have also been reported [24–26]. Correlations seem closer in patients with longer seizures (or status) and short duration between seizure end and scan [24, 27]. In contrast, interictal neuronal loss and increased extracellular space have been reflected in increased ADC values. Other disorders related to epilepsy that may show DWI abnormalities include cortical and subcortical abnormalities in status epilepticus, antiseizure medications and transient lesions of splenium of corpus callosum related to seizures [28–30]. A significant increase in ADC has been reported in epileptogenic tubers in patients with tuberous sclerosis.

2.3 Diffusion tensor imaging (DTI) and tractography

Diffusion tensor imaging (DTI) allows measurement of water diffusion in order to provide information on microstructural changes and connections between different regions of the brain. Animal models have revealed myelin as the main barrier to water diffusion [31–34]. This allows interrogation of white matter architecture and morphological reconstruction of major tracts in vivo. This method is still quite crude, however, and cannot resolve distinct fibers that cross within a voxel. White matter tractography is generally done in two different ways, either with a method known as "deterministic" tractography or with a "probabilistic" method. Using deterministic methods, points are placed, and the tract grows in both directions along the dominant diffusion direction. The probabilistic method probe fiber orientation distributions at each voxel and is computationally more intensive but can more reliably reconstruct crossing fibers.

The objective of epilepsy surgery in pharmacoresistant focal epilepsies is complete resection or at least disconnection of the epileptogenic zone while preserving eloquent cortex [2, 35]. Exploring white matter changes in epilepsy can help us to understand epileptogenicity, they may also be a surrogate marker for cognitive difficulties and can inform clinicians about risks of epilepsy surgery procedures. Once successfully implemented into neuronavigation systems this information may also be used intraoperatively to tailor resections [36]. Extratemporal surgeries will also benefit from visualizing crucial connections and tracts such as the pyramidal tract. Implementation of DTI-based tractography has already been shown to benefit patients undergoing brain tumor surgeries and resections of vascular malformations [36–40] and will certainly be increasingly used in epilepsy surgery.

2.4 fMRI

The simultaneous recording of electroencephalogram (EEG) and functional MRI (fMRI) was first demonstrated in patients with epilepsy in the early 1990s and has since become an important research tool in epilepsy and beyond [41]. EEG-fMRI has been primarily used as a localization technique. In addition it can be combined with other more advanced modeling methodologies to study the networks connectivity. Together, both technologies may allow for novel insights in understanding the ictal-onset zone, irritative zone, and functional deficit zone (the connectome).

2.5 Ultra-high-field 7T MRI

The first 7T MRI scanner was FDA approved for clinical diagnostic use in October 2017. 7T MRI is currently available for use in few centers. Improved image resolution and contrast at 7T, especially with the MP2RAGE sequence [42] opens new possibilities for visualization of internal details of hippocampal subfields [43]. Although the clinical yield of 7T visual analysis on 3T-negative cases was still unclear in TLE, studies utilizing quantitative approaches have suggested promising results [44, 45]. 7T MRI can lead to better detection of FCD in ETLE, even in some cases with negative 3T MRI [46–52]. The availability of higher magnetic field strength does not preclude the combined use of advanced image postprocessing to optimize diagnostic yields.

2.6 MRI postprocessing techniques

Several commercial packages enable the quantification of MRI structural features and are currently used in routine clinical practice. FDA-approved software packages include NeuroQuant (Cortechs Labs, San Diego, CA), BrainReader (BrainReader, Denmark), and icobrain (icometrix, Leuven, Belgium). These softwares typically generate a report that details the volume and percentile of each parcellated cortical regions, with comparison to normative databases. In epilepsy, NeuroQuant has been shown to lateralize hippocampal atrophy in TLE patients with accuracy rates that could exceed those achieved with visual inspection of clinical MR imaging studies [53].

Incorporating postprocessing techniques into routine care requires the use of high-quality MRI acquisition with 3D volumetric sequences for optimal results. It also requires specialized expertise in computational anatomy and seamless communication within the multidisciplinary epilepsy team. These techniques can provide unapparelled power in the ability to detect significant epileptogenic brain lesions in surgical candidates. Discovering a previously undetected lesion can drastically change the presurgical planning and surgical outcome. In fact, the lack of a visible lesion has consistently been shown to predict surgical failure [54, 55], and MRI-positive surgical candidates are two times more likely to become seizure free after epilepsy surgery than MRI-negative patients [56].

MCD is generally regarded as the most common epileptogenic substrate that can evade detection. Sometimes the only MRI finding of MCD can just be subtle blurring at the gray–white junction without hyperintensity on T2 or FLAIR. Novel quantitative image analyses can increase the yield of detecting relevant structural lesions in a sensitive, replicable, and reader-independent fashion, significantly complementing conventional visual analysis. Image reconstruction by manual means in a curvilinear plane—a plane parallel to the cortical surface and perpendicular in relation to the gyri—can show progressively deeper surfaces of the brain. This will result in a more

uniform distribution of gray matter on both hemispheres assisting in comparison of homologous regions of the cortex [57–59]. In addition to improving the detection of subtle MCDs, such surface reconstructions can also more precisely assess the location of subdural grids and depth electrodes and aid in presurgical planning.

2.7 Voxel-based morphometry (VBM)

VBM is one of the most popular and most useful postprocessing algorithms to date. Large-population control averages are used as common reference [60], however, references for adults should not be used to study paediatric cohorts. This fully automated technique extracts gray matter and white matter maps from individuals to make statistical comparisons with respect to a normal database [61]. VBM is able to accentuate abnormalities in the gray-white junction [62], minimizing "false-positive" studies. When there is an a priori hypothesis based on clinical and EEG data to confine the analysis to a certain brain region, VBM can be used to aim for maximal specificity. Whereas when EEG or other functional imaging data do not point to a region of interest, it is essential to opt for maximal sensitivity.

VBM consistently reported gray matter abnormalities extending beyond the visible culprit, sometimes distant from the epileptogenic area [63–66]. These changes could be due to occult dysplastic regions undetectable by visual analysis or represent an abnormal gyration [63]. These clusters may indicate dysplastic abnormalities much more widespread across the hemispheres than the changes visible on the MRI and may explain, at least in part, why in some cases complete resection of MRI lesion does not always lead to seizure freedom. It is also conceivable that these changes may potentially become active at a later stage and cause seizure recurrence after surgery [67].

2.8 MRI volumetry

In temporal lobe epilepsy (TLE), the epileptogenic network causes variable degrees of neuronal loss and astrogliosis across hippocampal subfields, the amygdala, and the entorhinal cortex, namely mesial temporal sclerosis (MTS) [68]. In many patients, MTS can be visualized on MRI as noticeable hippocampal atrophy, increased T2-weighted signal, and loss of internal architecture. However, the visual identification of morphologic and signal characteristics of the hippocampus is highly subjective and depends heavily on the experience of the reader. Manual MRI volumetry is a commonly used quantitative technique to assess mesial temporal lobe atrophy, as it has been demonstrated to be more sensitive than visual evaluation [69]. Volumetry of the entorhinal cortex, amygdala, and temporopolar region as well as the thalamus may also assist in lateralization of the seizure focus [70]. Specifically, in patients with a normal-appearing hippocampal structure by visual inspection, volumetry of the entorhinal cortex atrophy can provide accurate lateralization of the seizure focus in 25% of cases [71]. Quantification of mesial temporal structures is strongly recommended in order to detect subtle atrophy or abnormal signal increases ipsilateral to the seizure focus and to assess objectively the integrity of the contralateral structures in preparation for epilepsy surgery. Indeed, bilateral mesial temporal lobe atrophy raises concern of markedly reduced chance of seizure freedom after surgery, and an increased risk of memory impairment.

Volumetry studies have consistently revealed gray matter reduction extending beyond the atrophic hippocampus to the adjacent parahippocampal, frontal and anterior temporal regions, suggesting a disruption of frontolimbic pathways. These

widespread abnormalities have been associated with seizure frequency [72], epilepsy duration [73, 74], and cognitive dysfunction [75–78]. Patients with persistent seizures after removal of the hippocampus may also have a more widespread neocortical grey matter volume loss [79, 80].

2.9 Sulcal morphometry

Sulcal and gyral abnormalities in ETLE patients are characterized by a spectrum of changes [81–83]. In some instances these sulcal morphologic signs may be the only marker for cortical dysgenesis. It was reported that 85% of small FCD lesions that elude visual inspection are found at the bottom of an abnormally deep sulcus [84]. Such preferential location can be explained by local weakness within the developing cortical mantle, co-occurrence of incomplete maturation, decreased neuronal density, and disrupted connectivity in areas surrounding the FCD [69, 85]. Automated extraction, identification, and statistical analysis of cortical sulci was tested in a small series and small FCDs not detected on routine MRI was found on histopathology, particularly in the depth of the posterosuperior and intermediate frontal sulci [86].

2.9.1 Shape analysis

Visualization of hippocampal shape may extend evaluation to details not evident by measurements of hippocampal volume. This technique showed significant inward deviation in the Sommer sector of the sclerotic hippocampi. The analysis of curvature in the hippocampus also revealed medial bending of the posterior hippocampus in patients with TLE, compared with a superomedial shift of the hippocampal body observed in patients with MCD [87].

An extension of shape analysis to adjacent convexities often shows a pathologic relationship. For example, hippocampal malrotation in TLE is associated with increased complexity of the temporolimbic cortices, encompassing parahippocampal, temporopolar, insular, and fronto-opercular regions. This implies that neurodevelopmental factors may play a role in the epileptogenic process [88].

2.9.2 Cortical thickness

Progressive neocortical thinning in the frontal lobes had been found in patients with ongoing seizures than in patients with controlled seizures [89]. This was subsequently echoed in a meta-analysis that showed more marked atrophy in the ipsilateral hippocampus, with moderate effect sizes, in patients with longer epilepsy duration and more frequent seizures [90].

2.9.3 Automatic segmentation

Increasingly sophisticated automatic segmentation algorithms are developed for the assessment of mesial temporal lobe structures. While the majority of them generally demonstrate an excellent performance in healthy subjects, accuracy in patients drops significantly due to the atypical shape, positioning, and size of the hippocampus secondary to incomplete unfolding (or malrotation which occurs in about 40% of TLE patients) [88, 91, 92]. Automated hippocampal segmentation algorithm which integrates deformable parametric surfaces and multiple templates in a unified framework have been developed [93]. This provides flexibility to model disease-related

shape deformations and atrophy and is important in maintaining a high-level performance regardless of the presence of abnormal morphology [94, 95].

2.9.4 T2 relaxation times

The sensitivity of VBM can be increased by directly mapping T2 relaxation times. In the vast majority of TLE patients with hippocampal atrophy, T2 relaxation times within the hippocampal gray matter ipsilateral to the focus increased by at least 10ms when compared to controls [96–98]. This may allow mapping of lateralizing information in patients with no evidence of atrophy on MRI [99].

2.9.5 Multicontrast frameworks

The sensitivity to detect lesions undetectable by conventional MRI has been shown to increase proportionally to the number of techniques employed, suggesting that each contrast interrogates specific aspects of tissue structure. The combined sensitivity of various contrasts can be assessed by multivariate framework [69]. This can be used in subtyping of FCD. This method showed that FCD type IIB was characterized by abnormal morphology, intensity, diffusivity, and function across all surfaces, while type IIA lesions presented only with increased FLAIR signal and reduced diffusion anisotropy close to the gray-white interface. This multimodal MRI profiling method shows that normal-appearing cortex surrounding the lesion presents with alterations resembling those found at the lesion center [100]. This may help inform proper estimation of lesion extent.

2.9.6 Multimodal framework

The advent of MRI has tremendously advanced the field of epilepsy surgery. Various MRI techniques providing information on function and connections of different areas of the brain have helped with surgical planning immensely. However, the clinical utility of these techniques in large patient population has not been studied. To this date, a significant number of patients with refractory partial epilepsy still do not have an identifiable lesion on MRI. In such cases results of structural MRI postprocessing need to be confirmed with modalities that can characterize the pathophysiologic features of suspicious imaging findings. Invasive intracranial monitoring is often required, despite which the outcome remains poor. In the context of presurgical evaluation, localization data acquired from seizure semiology, magnetic source imaging (MSI), EEG, MEG, PET and SPECT may help pinpoint the area of interest. Studies have shown combined features from MRI and PET outperformed MRI postprocessing by itself, PET postprocessing by itself, and multimodal visual analysis [101, 102]. Development of newer MR techniques in the future may also have the potential to improve the understanding of the cytoarchitectural and molecular abnormalities of the brain with a greater impact in the field of epilepsy. Understanding postprocessing-positive structural changes outside the assumed epileptogenic zone will require further correlative studies with electrophysiology, pathology, and long-term surgical follow-up.

3. Nuclear imaging (PET, SPECT)

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) utilizes radiotracers, and are performed primarily to identify or

confirm the ictal focus in preparation for surgery. PET and SPECT help to investigate the pathophysiology of partial and generalized seizure disorders. Occasionally, PET is performed to identify eloquent cortical regions to be spared during epilepsy surgery.

Radiotracer studies using PET or SPECT allow for in vivo assessment of physiologic function of the brain. Such studies include glucose consumption ([18F]fluoro-2-deoxyglucose; [18F]FDG), cerebral blood flow ([15O]water), neurotransmitter synthesis (dopamine and serotonin), receptor ligand binding (agonists or antagonists to benzodiazepine, opiate, serotonin, and N-methyl-d-aspartate [NMDA] receptors), transporter proteins, and microglia. PET has a practical resolution of 2–3 mm, which is superior to that of SPECT, and can be quantitated. Compound half-lives help decide the use and application of PET ligands: 18F-tagged compounds have a 110-minute half-life, 11C a 20-minute half-life, and 15O a 2-minute half-life. The long half-life of [18F]FDG makes it not a good candidate for assessing short-lived physiologic phenomena such as ictal states, whereas the very short half-life of [15O]water allows it to capture the brief activity of cognitive processes. Given the relatively short half-life of PET ligands, data acquisition must occur shortly or immediately after injection.

3.1 PET

The most clinical experience for evaluating patients with partial epilepsy is with [18F]FDG-PET. Studies have demonstrated interictal regional decreases in glucose consumption ipsilateral to the seizure focus that is most pronounced in the temporal lobe [103–105]. This figure is close to 90% on recent generation scanners [106–109]. The area of decreased glucose utilization is often more extensive than the epileptogenic zone, may extend into adjacent inferior frontal or parietal lobe neocortex [105, 110] and occasionally into ipsilateral thalamus [111] and contralateral cerebellum [105].

The reason for regional hypometabolism is incompletely understood. Cell loss resulting in synaptic loss and altered remote projections, or hippocampal atrophy in mesial temporal sclerosis, may account for a portion of regional hypometabolism in TLE [112–114]. Hypometabolism does not correlate with lifetime generalized tonic-clonic (GTC) seizures or complex partial seizure (CPS) frequency [115]. Dysplastic tissue with aberrant synaptic connectivity can have either decreased or normal glucose consumption [116]. In focal cortical dysplasia, mitochondrial complex IV function may be decreased in areas of hypometabolism [117]. The abnormalities in some circumstances appear to be functional, as some patients have profound decreases in glucose uptake and no discernible pathology. In patients with mesial temporal sclerosis, the predominant regions that may manifest decreased glucose consumption are the lateral neocortex and, to a lesser extent, the frontal cortex. This may reflect the distant projection of functional loss in mesial structures. Frontal hypometabolism and contralateral hypometabolism appears to be reversible with successful temporal lobectomy [118]. Patterns of hypometabolism may reflect seizure characteristics and seizure propagation. Nevertheless, there is sufficient variability that individual predictions of seizure focus within the temporal lobe cannot be made based on [18F]FDG-PET alone [119], whereas a combination of MRI and PET findings predicted outcome—those with persistent abnormalities fared less well [120].

Metabolic abnormalities are less common in patients with recent-onset, nonrefractory, or well-controlled partial epilepsy [121]. Regional hypometabolism was also found to be changed in relation to seizure frequency in children with worsening seizures [122]. Similar to adults, 70% of children with chronic partial epilepsy (duration 10 years) have focal metabolic abnormalities. There is evidence that adult

patients with a greater duration of epilepsy are more likely to have focal [18F]FDG-PET abnormalities [105, 123, 124]. Partial seizures of greater duration are also associated with a greater dissociation between metabolism and blood flow. These [18F]FDG and cerebral blood flow studies, along with cross-sectional studies using volumetric MRI, may be taken as evidence that TLE in some patients is associated with chronic and continued neuronal injury [106, 125].

Although glucose consumption in temporal cortex is decreased, perfusion is often maintained, especially in lateral neocortex [106, 123]. Interictal studies of cerebral blood flow using [15O]water find a decrease in perfusion in only 50% of patients [106]. These data suggest that vascular tone may be impaired in TLE and that there is dissociation between metabolism and perfusion, rendering interictal blood flow studies unreliable markers of the epileptogenic zone and surgical outcome [126].

Focal interictal regional hypometabolism can predict good surgical outcome [107, 127–129]. Additionally, extent of resection of PET abnormalities is found to correlate with post operative outcome [130]. Bilateral temporal hypometabolism is associated with a less optimistic surgical outcome and in 50% of patients reflects bilateral foci [131]. Patients with focal temporal abnormalities have more than 90% likelihood of good surgical outcome, and in those without, this figure is reduced to about 63% [128, 129]. The ability to confirm the focus and predict surgical outcome is better when quantitative means are used, typically when asymmetry indexes [AI; e.g., AI = 2(left – right)/(left + right)] are greater than two standard deviations from normative data. Cortical segmentation may also improve yield for FDG-PET but not SPECT [132]. Focal abnormalities on [18F]FDG-PET may reduce the need for or extent of, invasive monitoring [104, 128, 129]. Nonetheless, questions of frontal versus temporal focus may not always reliably be resolved by interictal [18F]FDG-PET studies, and invasive studies or other PET ligand studies may be needed. Conflicting localizing or lateralization data nearly always merit invasive monitoring. False lateralization by PET has been demonstrated after surgery [103], specifically when interpretation relied upon non-quantitative analysis, or occurred during subclinical seizures [103, 133, 134].

[18F]FDG-PET is less efficacious in identifying the epileptogenic zone in extratemporal lobe epilepsy [135]. Most extratemporal lobe epilepsy series include patients with structural lesions that show concordant hypometabolism. When patients with abnormal MRI findings are excluded, 11–50% of the relatively small patient populations remaining show regional decreases in glucose consumption [109, 126]. FDG-PET abnormalities remote from the lesion lessen prospects of good surgical outcome. Abnormal focal PET (or SPECT) findings should be followed by review of "normal" MRI, as focal MRI findings often ensue and will positively affect yield of epilepsy surgery [136–138].

In absence seizures, glucose consumption and perfusion are globally increased [139]. [15O]Water studies performed during electroencephalographic (EEG) bursts of spike and wave demonstrate not only an increase in global perfusion but also a preferential increase in the thalamic regions, supporting the notion of the thalamus as the facilitator of absence events [140]. Interestingly, there is some evidence that valproate decreases cerebral blood flow in the thalamus, which may explain the effect of valproate in controlling generalized epilepsies. In Juvenile myoclonic epilepsy, [(11)C]PE2I, a marker of dopamine transporter (DAT) activity is reduced in midbrain and the high-affinity dopamine (D2/D3) receptor ligand [18F]Fallypride ([(18) F]FP) is reduced in putamen [141].

Some children with a generalized EEG and normal MRI can exhibit regional metabolic abnormalities [142]. "Interictal" FDG-PET will show hypermetabolic areas in

2–6% of pediatric studies. Regional uptake is associated with frequent spike activity and originates from focal cortical dysplasia. Intracranial EEG finds these regions are effectively in status and, when resected, are associated with good outcome [143, 144]. In some children, however, the metabolic abnormalities seen at onset of infantile spasms may resolve or shift with time and thus may represent a functional state that is potentially reversible with successful medical therapy [145, 146]. In children with Rasmussen's encephalitis and hemimegalencephaly, widespread hemispheric hypometabolism is typically seen. PET has been advocated in some circumstances to assess the integrity of the good hemisphere before extensive cortical resection [116, 147]. Isolated hemispheric abnormalities are associated with excellent outcomes for hemispherectomy (90%) but contralateral abnormalities may also be associated with good outcomes (75%) [148]. In tuberous sclerosis, tubers are often hypometabolic, whereas there is some evidence that the more epileptogenic tubers have increased serotonin or kynurenic acid synthesis, reflected by increased [11C]AMT uptake [149, 150]. [11C]AMT uptake is also increased in focal cortical dysplasia when MRI (especially in children <2 years) and [18F]FDG-PET may be normal [149–151]. In hypothalamic hamartoma, remote frontal and parietal cortical hypometabolism appears to be associated with cognitive impairment [152].

3.2 SPECT

SPECT ligands used in epilepsy are primarily markers of perfusion, though some receptor ligands are also available, such as [123I]iomazenil ([123I]IMZ) for benzodiazepine receptor studies. The compounds that mark blood flow, HMPAO and ECD, have a distribution in the brain that is proportional to cerebral blood flow. Both ligands are lipophilic; they readily cross the blood-brain barrier on their first pass through brain tissue, become trapped, and exhibit little subsequent redistribution. A potential limitation is that neither ligand has linear uptake at high cerebral blood flow rates, and thus, cerebral blood flow is underestimated under certain circumstances [153]. The efficacy of HMPAO and ECD in epilepsy studies is comparable.

For an ictal SPECT study to be useful, injection of the ligand must occur no later than 30 seconds after cessation of the seizure. The earlier the injection (<20 seconds from seizure onset), the more reliable are the study results [154, 155]; injections after 20 seconds will result in image propagation from the seizure onset zone and lessen localization value [156, 157]. SPECT ligands have a longer half-life compared to PET. 99mTc-Hexamethyl-propyleneamine oxime (99mTc-HMPAO) or 99mTc-ethyl cysteinate dimer (99mTc-ECD) for cerebral perfusion has replaced 123I-based ligands such as [123I]iodoamphetamine and [123I]trimethyl-hydroxymethyl-iodobenzylpropane diamine, because these ligands have a rapid first-pass uptake and long half-life. The long half-life permits bedside injection at ictus and offers a longer window of injectability (from 30 minutes to 4 hours after composition) as well as time to arrange for data acquisition scanning within 4–6 hours after injection. During ictus, there is focal increase in cerebral blood flow to involved cortex, often with decreased perfusion in adjacent areas. After the seizure, there is postictal hypoperfusion, which may return to an interictal state rapidly [158]. Postictal hypoperfusion abnormalities are more reliable than interictal hypoperfusion (60–70% vs. 40–50%, respectively). After ligand injection, lorazepam is sometimes administered to diminish the likelihood of subsequent seizures. It is important to recall that if a patient has multiple seizure types, each type must be captured. Automated systems may be helpful to improve

timing (approximately 8 seconds) and reliability of ligand delivery; video-EEG monitoring is critical for interpretation of SPECT studies [159, 160].

The usefulness of SPECT ictal studies approaches that of [18F]FDG-PET in patients with TLE, and ictal studies are probably superior for extratemporal focus localization [161–163]. Partial seizures often show more reliable results than secondarily generalized seizures [164]. False localization is reported in 3–4% of studies, presumably because of seizure propagation, and is more likely to occur with later injection times [107]. Subtraction techniques with MRI co-registration provide enhanced comparison and semiquantitation of perfusion changes between the interictal and ictal states compared with visual comparison alone. Focal ictal SPECT can also predict whether surgical outcome will be good. SPECT is considered most useful in evaluating patients with nonlesional partial epilepsy, especially extra-temporal partial epilepsy. Ictal subtraction SPECT may also be useful in evaluating patients who have failed initial surgery.

Interictal SPECT studies demonstrate regional hypoperfusion in 40–50% of patients with partial epilepsy of temporal lobe origin. However, approximately 5–10% of studies are falsely lateralizing [106, 107, 109, 165, 166].

4. Neuroimaging and brain connectome

To date, structural connectivity analyses have been able to demonstrate abnormal networks in patients with epilepsy. There is decreased fiber density of connections in the limbic system among patients with medial TLE [130], which is paradoxically associated with increased nodal clustering and efficiency in the thalamus, insula, and superior temporal regions [131]. Other studies have further revealed atypically strong thalamic–limbic connections with aberrant linkages beyond the medial temporal lobes [167]. These atypical patterns of simultaneous brain activity appear to translate to a reorganization of the functional connectome [168–176]. Reorganization of the functional connectome in epilepsy also appears to be confounded by age [177], age of seizure onset [173, 178], and disease duration [179], reflecting the importance of understanding how disease burden can affect atypical functional patterns.

Identifying these deviant connectome patterns is important because it helps us understand the abnormal plasticity associated with epilepsy and what architectural changes to the brain network provide the substrate for hyperexcitable states. In addition, there is a potential role for identification of specific aberrant connections that may help phenotype different subgroups according to brain imaging parameters and clinical features. For instance, language difficulties in epilepsy have been associated with altered patterns in functional connectivity involving language areas [180], especially when hippocampal sclerosis occurs in the dominant hemisphere [119].

Connectome-based lesion-symptom mapping (CLSM) is a novel approach to lesion mapping that establishes relationships between behavioral measures and specific white matter tracts in the connectome using statistical methods [151]. At the individual level this has the potential to predict clinical outcomes and guide tailored treatments on a case-by-case basis [106, 149]. With approximately one-third of patients with seizures refractory to multiple antiseizure medications [181], and with epilepsy surgery now considered an effective treatment for drug-resistant focal epilepsy [182], it is paramount to identify the factors that may affect postoperative seizure control. Clinical variables alone, however, have been insufficient to predict postoperative outcome. This points to the direction that epilepsy is more of a network

disorder than a purely lesional one. It is in this context that network imaging may help to more accurately predict which patients are likely to benefit from epilepsy surgery.

Nowadays computational algorithm based on machine learning is capable of classifying patients who become seizure free postsurgically by analyzing fiber density values with an accuracy of 70% [144]. White matter tracts including the fimbria-fornix, the uncinate fasciculus, and the parahippocampal white matter bundle, have been suggested to contribute to seizure propagation. Reorganization of structural networks after surgery can affect seizure control outcomes [138]. Each patient exhibits different network patterns at the individual level. Features located in the contralateral hemisphere can contribute to prediction accuracy. Deep learning has been shown to be able to sieve through connectivity information derived from presurgical MRI of patients to identify biomarkers which can predict surgical outcome [183]. For example, in TLE patients with persistent postoperative seizures, circumscribed alterations in two regions were found in those with poor postoperative seizure control: the dorsal segment of the ipsilateral fornix and the contralateral parahippocampal white matter bundle [141].

In addition to predicting outcome, network imaging may prove useful in planning surgical targets. Utilization of diffusion measures to study white matter tracts can yield information on laterality of the lesion [184]. While promising, it is important to note that the aforesaid findings were all yielded from retrospective analyses and must therefore be validated in prospective studies.

5. Outlook for clinical translation: what lies ahead in the field of connectomics and epilepsy?

The vast amount of data generated by neuroimaging makes it a good candidate for computational methodological analysis. This has shed light on epilepsy as a disease of brain networks. While connectome-derived data have been instrumental thus far in improving and expanding our understanding of the pathophysiology of seizure propagation in difficult-to-treat epilepsy. The generation of personalized connectome is clearly the next step forward in presurgical epilepsy workup in the era of personalized medicine. In doing so our understanding of the brain network will be further expanded benefiting not only epilepsy patients but other neurological and neurosurgical patients alike.

6. Conclusions

Improving noninvasive localization is paramount in the surgical treatment of refractory epilepsies. MRI postprocessing techniques allow for more accurate identification of epileptogenic abnormalities, and in doing so they have the potential to increase the diagnostic yield, reduce the need for invasive electrophysiological investigations, and improve epilepsy surgical outcome in years to come. Patient centered connectome-based lesion-symptom mapping will be the future for epilepsy management where therapeutic options can be tailored in order to enable best informed management for both clinicians and patients in their lifelong journey with this disease.

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