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Neuroimaging biomarkers of epileptogenesis

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Abstract

Much progress has been made in the field studying the process of epileptogenesis via neuroimaging techniques. Conventional imaging methods include magnetic resonance imaging with morphometric analysis, magnetic resonance spectroscopy and positron emission tomography. Newer network-based methods such as diffusion tensor imaging and functional magnetic resonance imaging with resting functional connectivity are being developed and applied to clinical use. This review provides a brief summary of the major human and animal studies in both partial and generalized epilepsies that demonstrate the potential of these imaging modalities to serve as biomarkers of epileptogenesis.

Keywords

Epileptogenesis; Spike-wave seizure; Neuroimaging; Biomarker

1. Introduction

Epilepsy affects 2–3 million people in the United States [47] and exerts a huge toll on our society [117]. Currently, epilepsy can only be treated by medications or surgery upon diagnosis. Epileptogenesis is difficult to study in human patients because patients usually present with established epilepsy rather than at an early stage of the disease.

Neuroimaging has played an important role in measuring long-term changes in the brains of both partial and generalized epilepsy patients. Conventional imaging methods include magnetic resonance imaging (MRI) morphologic analysis, proton magnetic resonance spectroscopy (PMRS) and positron emission tomography (PET). Recently, network-based approaches, such as diffusion tensor imaging (DTI) and resting functional connectivity functional MRI (fMRI) are also being developed to measure structural and functional changes in the brain, even when seizures are not occurring.

The first section of this article reviews neuroimaging biomarkers of epileptogenesis in partial epilepsy and the second section, generalized epilepsy. We will review studies from both animal models and human patients, as each neuroimaging technique is discussed in

turn. Partial onset seizures discussed in this review will include febrile seizures, posttraumatic epilepsy (PTE), tuberous sclerosis, and various forms of temporal lobe epilepsy (TLE) including hippocampal sclerosis and mesial temporal sclerosis, as well as others in both animal models and human patients. Our discussion of idiopathic generalized epilepsy is divided into the following subsyndromes: childhood and juvenile absence epilepsy, juvenile myoclonic epilepsy, and generalized tonic-clonic seizures.

2. Partial epilepsy

2.1. Magnetic resonance imaging

Magnetic resonance imaging (MRI) was first introduced in the diagnostic evaluation of epilepsy in the 1980s and has since become a mainstay of clinical care [33,103]. In addition to detecting structural abnormalities, by measuring the variations in signals produced by protons in the brain, MRI can detect pathological changes in certain type of seizures, such as febrile seizures (FSs). Associated with a sudden rise in body temperature, febrile seizures are the most common type of seizure seen in children [31]. While FSs often do not pose subsequent threat to an individual's health, patients with prolonged FSs were demonstrated to be at a higher risk for developing TLE later in life [102]. In a rat model of experimentally induced prolonged FSs by way of hyperthermia, T2 signals taken from serial MRIs before and after seizure onset were abnormal in the dorsal hippocampus, piriform cortex and amygdala in 75% of these rats one day after seizures and in 87.5% of rats eight days after the induced febrile seizures [30] (Fig. 1). Although these abnormal MR signals in temporal lobe structures do not signify cell death, they may indicate underlying changes in neuronal integrity that promote epileptogenesis and provide early markers for subsequent TLE development.

In human patients with febrile status epilepticus, hyperintense hippocampal signal intensity on T2-weighted MRI and hippocampal volume changes were the most predictive indicators of subsequent development of mesial temporal sclerosis (MTS) [63,90,105,111]. In one study of 11 children with prolonged febrile seizures, seven cases developed severe hippocampal T2 signal abnormalities [63,111]. Five of these seven developed anatomical indicators of MTS, while none of the other 4 children with normal MRI signals demonstrated any evidence of MTS [90].

Posttraumatic epilepsy results from traumatic brain injury (TBI) caused by physical trauma to the brain and constitutes 5% of all cases of epilepsy [43]. In posttraumatic epileptogenesis, periods of enhanced abnormal plasticity occur, which mimic the critical period of development [83,89]. More recently, quantitative T2 signal evaluation has been used to analyze the severity of cortical damage and neuro-motor impairment soon after TBI. In a rat lateral fluid percussion injury (LFPI) model, T2 values were found not only to correlate with motor deficits and histological lesion volume, but also to successfully differentiate the moderate from the severe TBI groups [54]. Multiparametric quantitative MRI changes (such as T2, T1 ρ , diffusion tensor trace, the extent of hyperintense lesion and intracerebral hemorrhage) acquired shortly after TBI in the LFPI rat model were able to predict functional and histopathological changes 6–12 months post-LFPI [49]. These results demonstrate that early changes in the hippocampus and perifocal areas may be an indicator of the long-term outcome after TBI. These abnormal MRI changes can potentially serve as a useful clinical marker for identifying individuals with an elevated risk of developing PTE.

MRI has been used as a biomarker of epileptogenesis in other animal models of partial epilepsy. For instance, Roch et al. found that lithium-pilocarpine induced status epilepticus rats without MRI abnormalities or altered T2 relaxation times did not end up developing epilepsy, whereas those with increases in T2 relaxation times and abnormalities in the T2-

weighted images, specifically at the level of piriform and entorhinal cortices, subsequently developed epilepsy [93]. Transient MRI changes in the hippocampus and piriform cortex after lithium-pilocarpine induced seizure have been shown to correctly predict the severity of later hippocampal damage [21]. With further study, these MRI signal changes have the potential to become a clinically useful prognostic biomarker for at-risk patients.

2.2. MRI morphometric analysis

MRI volumetry and morphometry are involved in comparing the size and shape of brain structures. In the case of voxel-based morphometry (VBM), this is done by spatially normalizing all images, segmenting gray matter from images, and then performing voxelwise parametric statistical tests to produce a parametric map of structural regions [2]. One of first studies using morphometric analysis that received mainstream media attention was the VBM analysis of hippocampi of London taxi drivers. The hippocampus has long been associated with spatial navigational skills. It was found that the posterior hippocampal regions of taxi drivers were larger than those of normal people, while the anterior hippocampal regions were smaller [69]. Subsequently, VBM analysis has been applied to epilepsy research and other brain disorders. In other forms of analysis, only the volume of regions of interest (ROIs) are evaluated.

MRI volumetry has revealed smaller ipsilateral thalamic volumes in TLE patients with febrile seizures than in those without [77]. Using VBM analysis, Labate et al., has concluded that patients with TLE exhibit gray matter volume reduction and other structural abnormalities in the hippocampus and thalamus [62]. These abnormalities were more severe in those who also had MTS [62]. However, there was no gray matter difference between refractory TLE and milder TLE with MTS [61]. These gray matter volume differences in patients with partial epilepsy makes morphometric analysis a potential biomarker to study changes in the brain during epileptogenesis.

2.3. Proton magnetic resonance spectroscopy

Proton magnetic resonance spectroscopy (PMRS) and imaging (PMRSI) are noninvasive techniques for exploring the metabolic status of the brain in health and in disease [1,40,75]. The four major metabolites detected by PMRS at long echo times are N-acetylaspartate (NAA), creatine (Cr), choline-containing phospholipids (Cho) and lactate (Lac) [95]. NAA is a neuronal and axonal marker that decreases with neuronal loss or dysfunction; Cr, either alone or as phosphocreatine, is a marker for intact brain energy metabolism; Cho is a marker for membrane synthesis or repair, inflammation, or demyelination; Lac is a metabolite of anaerobic glycolysis [95]. Using PMRS to measure in vivo temporal lobe metabolite concentrations in patients with TLE attributable to unilateral hippocampal sclerosis (HS), Sinister et al. found a bilateral reduction of NAA + N-acetyl aspartyl-glutamate (NAAt) to creatine plus phosphocreatine (Cr) ratio (NAAt/Cr) in the temporal lobe; normalization of NAAt/Cr in the contralateral temporal lobe was seen following successful temporal lobe resection [104]. PMRS has also been used in the preoperative evaluation of patients with mesial temporal lobe epilepsy (mTLE): a decrease of NAA or more frequent presence of lactate provided diagnostic clues for the lateralization of the epileptogenic zone, while significant bilateral metabolic alterations in the mesial temporal lobe structures were associated with worse postoperative seizure control [20]. PMRSI in patients with medically intractable TLE was abnormal and predicted lateralization in 86% patients using PMRSI alone [17]. The combination of PMRSI and MRI volumetry can accurately and non-invasively lateralize TLE in the majority of patients [17]. Stefan et al. found that PMRS could detect subtle abnormalities that were not apparent on MRI [107]. Another study indicated that hippocampal structural damage may be depicted by PMRS [36]. In intractable TLE, correlation analysis showed significant linear correlation between the midtemporal

NAA/Cr relative asymmetry ratio and surgical outcome; the greater the asymmetry, the better the outcome [64]. PMRS has provided new and important biological brain markers able to predict clinical outcomes and identify subjects at high risk for the poorer outcomes.

2.4. Positron emission tomography

Positron emission tomography (PET) was developed during the mid-1970s [88]. Various PET studies using several different radiotracers have been used to visualize and quantify changes in receptor density.

The most common PET radiotracer used is FDG (fluorodeoxyglucose (^{18}F)), a glucose analogue. FDG-PET signal intensity is related to glucose uptake and metabolism in the brain. In a study of 11 children with focal epilepsy associated with tuberous sclerosis complex, Nishida et al. found that glucose hypometabolism was associated with increased delta wave-slowing and frequent spike activity on electrocorticography [80]. However, Liew et al. recently showed that (^{18}F)-FCWAY-PET may show more specific binding reduction of serotonin receptor in seizure initiation regions [66]. It was found that when compared with controls, MRI-negative TLE patients had significantly reduced free fraction-corrected volume of distribution and significantly greater asymmetry indices in fusiform gyrus, hippocampus and parahippocampus ipsilateral to epileptic foci [66].

Various PET studies using several different radiotracers have been used to visualize and quantify changes in receptor density. Serotonin mediates an antiepileptic and anticonvulsant effect via 5-hydroxytryptamine-1A (5-HT_{1A}) receptors, which are predominantly located in limbic areas [84]. PET studies using 5-HT_{1A} receptor antagonist [^{18}F] MPPF, [(11C)]WAY-100 635 or 18F-FCWAY have demonstrated that a decreased 5-HT_{1A} receptor binding (or availability) correlated with the degree of epileptogenicity in regions involved in seizure onset and where discharges propagated (e.g., hippocampus and amygdala) [35,71,99,109]. In children with intractable partial epilepsy following cortical resection, Chugani et al. found an increased alpha[(11C)]methyl-L-tryptophan uptake in the lentiform nucleus ipsilateral to the resection as compared to the contralateral side (suggesting increased serotonin synthesis), and these asymmetries were higher than those measured in controls [22]. PET-detected changes in receptor binding or metabolite metabolism can be applied in the future to study the epileptogenic process in human patients with partial epilepsy.

2.5. Functional magnetic resonance imaging

In 1936, Pauling and Coryell found that deoxyhemoglobin was paramagnetic [86]. Ogawa et al. used this properties of hemoglobin to develop a new MRI image contrast named blood-oxygen-level dependent (BOLD) functional MRI (fMRI) [82]. BOLD fMRI provides a non-invasive measure of brain function and has been applied to epilepsy research. EEG-correlated fMRI has been used to investigate epileptogenic networks in patients with focal epilepsy. Several studies have looked at BOLD signal changes preceding focal EEG spikes [50,92]. Jacobs et al. were able to conclude that prespike BOLD fMRI responses in patients with focal epilepsy were more localized than late responses and were strongly related to the spike field [50].

EEG-fMRI has proven to be a valuable tool in the presurgical evaluation of patients with medically refractory epilepsy [120]. It also provides a noninvasive method for selecting tubers in patients with tuberous sclerosis complex [51]. These studies laid the foundation for its future use as a suitable imaging biomarker to track disease progression and treatment efficacy in partial epilepsy patients.

2.6. Resting functional connectivity with fMRI

Functional connectivity is the temporal correlation of a neuro-physiological index measured in different brain areas [34]. Using fMRI, Biswal et al. demonstrated correlation of low frequency (<0.1 Hz) fluctuations in the primary sensory cortex secondary to hand movement both within and between hemispheres [12]. mTLE is a neural network disorder involving widespread brain regions. Seeding the anterior hippocampal region of resection, Morgan et al. found increased negative connectivity across a network including thalamic, brainstem, frontal and parietal regions in left mTLE patients as compared to controls via full brain connectivity analysis [76]. This result supports theories of inhibited function in subcortical and cortical structures during ictal propagation.

Using resting-state fMRI with independent component, Zhang et al. demonstrated that mTLE patients had decreased functional connectivity in the dorsal mesial prefrontal cortex, mesial temporal lobe and inferior temporal cortex [119]. In addition, only mTLE patients with right, but not left, hippocampal sclerosis had bilaterally decreased functional connectivity in the mesial temporal lobe and increased functional connectivity in the posterior cingulate cortex [119]. Looking at perceptual function, Zhang et al. found that compared with controls, mTLE patients presented with decreased functional connectivity in the auditory and sensorimotor networks, but increased functional connectivity in the primary visual cortex [118]. Left TLE patients also have reduced functional connectivity in the language areas [113]. Furthermore, in mTLE patients, left hippocampal sclerosis causes a greater reduction of functional connectivity in large parts of the limbic lobes (especially the mesial temporal lobe), than right hippocampal sclerosis [87] (Fig. 2).

fMRI with resting state functional connectivity may also be useful in the presurgical assessment of mTLE patients. Bettus et al. demonstrated that basal functional connectivity increases in the non-epileptic side was the most specific marker for lateralizing/localizing the epileptogenic zones [11]. These results suggest that fMRI-based resting functional connectivity is a powerful technique for detecting abnormal network function, and may be a useful biomarker for epileptogenesis and its prevention by early treatment.

2.7. Diffusion tensor imaging

Diffusion tensor imaging (DTI) measures diffusion properties of water protons in tissue [6] and can detect subtle white matter changes in the pathological state [18,52]. Apparent diffusion coefficient (ADC) is an average measure of water diffusion and fractional anisotropy (FA) measures the degree of alignment of cellular structures within a tissue (e.g., white matter fiber tracts), with 0 being the least anisotropic and 1 being highly anisotropic [6,7]. There have been many studies supporting DTI as a promising noninvasive biomarker. In animal studies, quantitative diffusion-weighted imaging (DWI) has been used in the prediction of increased seizure susceptibility [53] and in the diagnosis of subtle changes in brain water in other brain diseases [52,91] including epilepsy animal models [18]. In a rat model of moderate traumatic brain injury (TBI) induced by lateral fluid percussion, DWI correlated with mossy fiber sprouting density and EEG parameters such as spike count, epileptiform discharge number and first spike latency in the ipsilateral hippocampus at both early and chronic time points after TBI [53].

DTI is a sensitive method for detecting abnormalities in patients with partial epilepsy, even in structures without apparent changes on conventional MRI. For instance, in children with TLE, decreased FA and increased ADC were found in the hippocampi ipsilateral to the seizure focus, and significantly decreased FA was also found in the contralateral hippocampi of these patients [57]. In patients with mTLE accompanied by hippocampal sclerosis (HS), Thivard et al. showed that diffusion abnormalities were not restricted to the pathologic

hippocampus but involved a larger network (i.e., the temporal lobe and extratemporal regions) [108]. DTI has also been used to evaluate thalamic differences between TLE patients with and without hippocampal sclerosis [55]. The mean diffusivity (MD) of the thalamus ipsilateral to the epileptogenic side was higher in TLE patients with HS than those without [55].

Many human studies have used DTI to study changes in the underlying connectivity of the epileptic brain. In TLE patients with mesial temporal sclerosis (MTS), DTI showed decreased FA in the genu of the corpus callosum and external capsule and increased MD in the genu and splenium of corpus callosum and external capsule [25,38]. Only TLE patients with unilateral MTS (relative to TLE patients without MTS) had abnormal DTI parameters of the fimbria-fornix and decreased anisotropy in the cingulum [25]. On electron microscope, the fimbria-fornix of these patients showed increased extra-axonal fraction, and reduced myelin area and cumulative axonal membrane circumference, which correlated strongly with water diffusion anisotropy over the crus of the fimbria-fornix [26] (Fig. 3). This demonstrates a correlation between histology and human in vivo DTI and validates DTI as a noninvasive marker of white matter pathology.

3. Generalized epilepsy

Blumenfeld et al. recently found that early treatment with ethosuximide given continuously in drinking water from P21 to age five months in a rat model of absence seizures blocked the expression of ion channels that are characteristic of seizure development [13,58] (Fig. 4). The treatment suppressed seizures, an effect that lasted 90 days after stopping the medication. These results suggested that there may be a “critical period” early in development during which treatment can result in both molecular and electrophysiological inhibition of epileptogenesis. This raises the hope that once genetics allows identification of those patients at risk, we can predict disease onset and eventually cure the underlying disease via primary prevention. In order to achieve this goal, non-invasive biomarkers to monitor disease progression, severity and efficacy of therapy, are urgently needed.

3.1. MRI morphometric analysis: voxel-based morphometry

In idiopathic generalized epilepsy (IGE), MRI-VBM can reveal subtle structural abnormalities, even when MRI scans are normal on visual assessment. In patients with juvenile myoclonic epilepsy (JME), an increased gray matter volume in the mesiofrontal lobes and a reduced gray matter volume in the thalamus were detected by VBM analysis [10,56,67,114,115]. Reduced bilateral gray matter volume of visual cortices were found in JME patients with photosensitivity [67]. Using VBM, Helms et al. found decreased thalamic gray matter fraction and increased white matter fraction in brains of IGE patients [44] (Fig. 5A). These changes were greatest in the dorso-medial thalamus. In childhood absence epilepsy (CAE) patients, optimized voxel-based morphometry revealed gray matter decrease in both thalami and the subcallosal gyrus and white matter decrease in the extranuclear subcortical area and the basal forebrain [19,85]. Recently, Caplan et al. reported lower gray matter volumes in the left orbital frontal gyrus and bilateral temporal lobes of CAE patients [16]. These abnormal gray and white matter changes in the thalamus and frontal cortex emphasize the role of the thalamocortical network as the underlying mechanism of absence seizures and other generalized epilepsies [116].

The ability to track these changes with VBM during epileptogenesis may make it a clinically useful biomarker to monitor the course of the disease. However, it has been pointed out that changes in VBM processing methods such as type and level of statistical correction, modulation, smoothing kernel, adjustment for brain size, subgroup analysis and software version can mimic biological differences and lead to misinterpretation [15,45]. For instance,

a recent multi-site VBM study found site-specific differences between controls [85]. If VBM is to be used clinically as a biomarker, consistency in these user-specific parameters needs to be reinforced.

3.2. MRI morphometric analysis: surface-based morphometry

Other variants of morphometric analysis in neuroimaging include deformation-based morphometry and surface-based morphometry. Using surface-based morphometry, Tosun et al. showed that CAE children, when compared to normal subjects, did not undergo such normal age-related changes as a decrease in cortical thickness and an increase in the depth of sulci [110]. Lower IQ scores (although still in the average range) in CAE children when compared to controls were associated with less cortical thinning in the left middle frontal, left medial superior frontal gyrus, and right inferior temporal cortices, and smaller sulcal depth in the left superior temporal, middle frontal, superior frontal and parieto-occipital regions [110]. These morphometric differences between CAE and normal children demonstrate the diverse nature of neurodevelopmental abnormalities in CAE and their possible association with cognitive function.

3.3. Proton magnetic resonance spectroscopy

PMRS has evolved from a technique in chemistry (i.e., NMR spectroscopy) to determine the structure of molecules to one that measures the level of different metabolites in the brain in vivo [94]. Using quantitative single volume PMRS in IGE patients, two groups found increased absolute concentration of glutamate and glutamine (Glx) and decreased NAA in the thalamus [9,44] (Fig. 5B). The concentration of these metabolites can be predictive of progressive thalamic dysfunction in these patients. In photosensitive IGE, PMRS showed decreased NAA in the right frontal lobe and left thalamus, decreased NAA/creatine (Cr) ratio in the left thalamus, increased choline (Cho)/Cr ratio in the right frontal lobe and increased NAA/Cr ratio in the left occipital lobe [3]. Using MRS, Savic et al. found decreased thalamic NAA, Cho and myo-inositol in both JME and generalized tonic clonic epilepsy (GTCS) patients, but decreased frontal lobe NAA only in JME patients. This showed the involvement of the thalamus in GTCS and differentiated alterations within the thalamocortical loop between the two types of seizure [98,100]. All of these studies indicate that there could potentially be a role for MRS to evaluate the type, severity and development of epilepsy in individual patients.

3.4. Positron emission tomography

As discussed earlier, PET was applied to epilepsy research several years after it was first developed in the 1970s [59]. One advantage of PET is the large number of radioactive tracers that can be used to study various metabolic processes in the brain. Using FDG-PET, Hikima et al. demonstrated that there was significant interictal glucose hypometabolism in bilateral basal ganglia only during generalized epilepsy but not during localization-related epilepsy [46]. In children with continuous spike-and-wave activity during slow-wave sleep, Luat et al. found a concordance between lateralized glucose hypermetabolism and the presumed origin of generalized interictal spike activity delineated by quantitative EEG analysis in five of the six patients studied [68].

PET and a dopamine (DA) transporter ligand [(11C)PE2I] have been used to investigate the regional binding potential (BP) to dopamine transporter in JME and GTCS patients. It was found that JME patients had lower tracer binding in the midbrain and substantial nigra, whereas GTCS patients had reduced tracer binding in the putamen [23,24]. In addition, these changes in BP were correlated with performance in neuropsychological tests [23]. Furthermore, the serotonin system was also altered in JME patients, with a reduced BP in the dorsolateral prefrontal cortex, raphe nuclei, and hippocampus [72]. The ability of PET to

detect glucose hypometabolism in IGE patients and to differentiate among different IGE subsyndromes based on changes in receptor binding could make it useful as a biomarker to study these diseases and their epileptogenic processes.

3.5. Functional magnetic resonance imaging

Using BOLD fMRI to study spike-wave discharges of WAG/Rij rats, a genetic absence model of epilepsy, it has been shown that increases were most prominent in focal regions of somatosensory cortex, motor cortex and thalamus, while the occipital region was spared [70,74,79]. These regions were shown to have both increased neuronal firing and increased CBF during SWD [78]. During bicuculline-induced generalized tonic-clonic seizures, the BOLD fMRI increases were still largest in somatosensory cortex, while decreases were seen in the hippocampus [29,79,101].

In human CAE patients, fMRI increases were observed in the bilateral thalamus and occipital cortex, while decreased fMRI signals were observed in the bilateral lateral parietal cortex, precuneus, cingulate gyrus, and basal ganglia [4,8,37,41,60] (Fig. 6). The fMRI time course of human absence seizure is characterized by small early fMRI increases in the orbital/medial frontal and medial/lateral parietal cortex >5 s before seizure onset, followed by profound fMRI decreases continuing >20 s after seizure offset [5]. This dynamic sequence of fMRI changes offered a view of the temporal complexity of seizure-related fMRI changes, which was not detected by hemodynamic response function modeling. Furthermore, identification of a seizure network via these fMRI changes provides potential targets for therapy, and for monitoring of therapeutic efficacy.

3.6. fMRI with resting functional connectivity

fMRI-based resting functional connectivity is a noninvasive method for assessing connectivity [12,113], which can readily be translated from animal studies to use in human epilepsy patients. Since generalized epilepsy such as absence seizure involves the thalamocortical network, neuroimaging methods geared toward long-range interactions, such as DTI and resting functional connectivity, may be robust methods for measuring long-term changes, even when seizures are not occurring or are blocked by medication. In WAG/Raj rats, the regions most intensely involved by seizures (i.e., bilateral cortical regions including the somatosensory cortex) showed markedly increased resting functional connectivity when compared with controls [73]. Further studies are needed to determine whether preventing epileptogenesis will also prevent abnormal functional connectivity in epileptic networks in this rat model [13]. In a study of human CAE patients, there was a significantly increased interhemispheric correlation between orbitofrontal cortex regions [4]. These abnormalities were observed in both animal and human subjects, even when seizures were not occurring, and have the potential to serve as an interictal biomarker of disease severity in childhood absence epilepsy and other generalized epilepsies.

3.7. Diffusion tensor imaging

Water diffusion is highly anisotropic (i.e., have a directional dependence) in nerves and white matter structures [7]. Water molecules preferentially diffuse along the length of the densely packed axons. They are hindered in the perpendicular direction by the axonal membrane and myelin sheath, which modulate the degree of anisotropy. DTI measures diffusion properties of water protons in tissue and can detect subtle white matter changes in different pathological states including epilepsy [14,81,106]. In children and adults with malformations of cortical development and different forms of epilepsy, there is often reduced white matter FA [32,96,108] and DTI may detect abnormalities in these patients even when conventional MRI is normal. Several studies using DTI in human patients with idiopathic generalized epilepsy have now been published. Investigating the white matter

abnormalities underlying IGE, Li et al. found significantly decreased FA values in the cerebellum of 14 young male patients with GTCS only [65]. A decreased FA was found in the anterior thalamic radiations (i.e., fibers connecting the anterior thalamus with prefrontal cortical areas) of patients with JME when compared to both healthy controls and patients with cryptogenic partial epilepsy [28]. The FA reductions in these patients correlated with the frequency of generalized tonic-clonic seizures, but not with the duration of antiepileptic medication [28,112].

In WAG/Rij rats, there was reduced FA and increased perpendicular diffusivity in the anterior corpus callosum, which was not observed in young rats before seizure onset or nonepileptic controls [18] (Fig. 7). Genetic absence epilepsy rats from Strasbourg (GAERS) has more pronounced changes [18]. The white matter abnormalities can be due to reduction in myelin [39,42] and/or decreased axon fiber density [27,48] or due to changes in the density and orientation of crossing fibers in pathways connecting regions of seizure activity. The animal models will enable histological studies to determine the mechanisms for these observed DTI changes. DTI can also be a potential noninvasive biomarker for monitoring treatment by visualizing structural recovery in affected brain regions.

4. Conclusions

MRI with morphometric analysis, MR spectroscopy and PET are established imaging methods to study chronic changes in partial and generalized epilepsy. Newer methods such as DTI and fMRI with resting functional connectivity emphasize the network interaction in the thalamocortical circuitry and are currently being tested in both animal models and human subjects. These noninvasive biomarkers allow for the investigation of treatment effects on epileptogenesis and present the possibility of early intervention and predictive potential in the future management of epilepsy patients.

5. Summary of implications and future directions

It was recently shown that early treatment can beneficially alter the phenotype of genetic epilepsy in rodents [13,97]. These animal models appear to demonstrate a critical period in epileptogenesis, during which spike-and-wave seizures can be suppressed, leading to long-term changes in the brain. It is important to know if such a “critical period” exists in human epilepsy patients and if so, whether intervening before disease onset could lead to suppression of symptoms later in life. Once our genetic knowledge grows, primary prevention by therapy will soon be a realistic goal. Prevention of epilepsy in individuals susceptible to epilepsy would have a major impact on patient quality of life. The neuroimaging biomarkers of epileptogenesis reviewed in this paper may be useful to monitor disease progression and treatment effectiveness, allowing important proof-of-principle animal and human studies to be carried out. Studies in animals and humans with these new neuroimaging biomarkers of epileptogenesis will pave the way for future treatment trials in human patients.

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Fig. 1.

T2-weighted MRI signal intensities after prolonged experimental febrile seizures (FSs). (A) The control and the seizure animal groups were imaged before the seizures on postnatal day 10, P10, to provide baseline intensities, and on P12 (24 h after seizure, seizure group) as well as 8 days after the seizures. Regions used for analysis are delineated in white in baseline image. Increased signal intensity is evident in the dorsal hippocampus (white arrows), piriform cortex (white arrowheads), and amygdala (asterisk). (B) T2 signal intensity modulation by prolonged experimental FSs: (i) a significant increase of T2 signal occurred in dorsal hippocampus, by 8 days after the seizures, (ii) in piriform cortex, signal intensity increased significantly at 24 h and 8 days, (iii) in the medial ventroposterior thalamic nucleus, signal intensity increased significantly at 8 days and there was a strong trend for increased signal at 24 h (diamond).

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Fig. 2.

Comparison of functional connectivity among right MTLE group, left MTLE group, and controls. Functional connectivity maps were generated by placing the seed in the left (A) and right hippocampus (B): (i) control group versus patients with right MTLE, (ii) control group versus patients with left MTLE, (iii) patients with right MTLE versus patients with left MTLE. Abbreviations—s1: first sagittal image; s2: second sagittal image; s3: third sagittal image; a1: first axial image; a2: second axial image; a3: third axial image; c1: first coronal image; c2: second coronal image. Statistical maps with t -scores higher than 6. This figure is reproduced with permission from Pereira et al. [87].

Fig. 3.

DTI tractography and electron microscopy of the fimbria-fornix. Histological fields of the fimbria-fornix resected during surgery from two patients with TLE are shown with their corresponding FA maps (A and D, with the left fimbria-fornix marked as green) and tractography of the fimbria-fornix (B and E). The patient with MTS shows lower diffusion anisotropy of the fimbria-fornix (B) than the patient without MTS (E). This corresponds to lower axonal density and higher extra-axonal fraction for the patient with MTS (C) than for the patient without MTS (F).

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Fig. 4.

Early ethosuximide (ESX) treatment persistently suppressed the development of Spike-wave discharges (SWDs) in WAG/Rij rats, even after cessation of treatment. (A) Epileptic WAG/Rij rats were given either normal drinking water (H₂O group), ESX 300 mg/kg/day from age p21 through age 5 months and then normal drinking water from age 5 to 8 months (ESX 4 month group), or ESX 300 mg/kg/day continuously from age p21 through 8 months (ESX continuous group). EEG was recorded 1 day before stopping ESX, and 1, 14, 30, 60, and 90 days after stopping ESX. (B) Quantification of effects of early ESX treatment on percent time in SWD. Even after stopping ESX, percent time in SWD remained markedly reduced in the treated rats (ESX 4 months group) when comparing all time points for days 1 through 90 to rats on normal H₂O.

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Fig. 5.

Decreased N-acetyl aspartate (NAA) and increased glutamate and glutamine (Glx) and reduced gray matter fraction in the thalamus of idiopathic generalized epilepsy (IGE) patients when compared with controls. (A) VBM showing decreased thalamus gray matter fraction in patients compared to controls. The white areas in the center of each image indicate z scores of ≤ -4 . (B) Absolute concentrations of thalamic NAA and Glx in IGE (shaded) and controls (blank). The boxes indicate inner quartiles, the vertical lines the outer quartiles. Outliers are shown as circles.

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Fig. 6.

Increases in thalamus and decreases cortical regions are the most prominent changes with conventional HRF modeling in CAE patients. Functional data are superimposed on the MNI brain template “colin27” (sing subj T1 in SPM2) displaced in radiological right–left convention. In total, 54 seizures in nine patients were analyzed using GLM with canonical HRF in SPM2. fMRI increases were seen in bilateral thalamus, occipital cortex, and to a lesser extent the midline cerebellum, anterior and lateral temporal lobes, insula, and adjacent to the lateral ventricles. fMRI decreases were seen in the bilateral parietal, medial parietal, and cingulate cortex and basal ganglia.

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Fig. 7.

Epileptic adult WAG/Rij (8 months) and GAERS (1.7 months) rats, but not young WAG/Rij rats (1.7 months) have decreased fractional anisotropy in anterior corpus callosum compared to controls. *t*-Maps at -1.3 mm are shown, with warm colors representing decreased FA when compared with nonepileptic controls, and cool colors the opposite. (A) In adult epileptic WAG/Rij rats, decreased FA was observed in the anterior corpus callosum (CC). (B) In young WAG/Rij rats, anterior corpus callosum does not show decreased FA when compared with controls. (C) In adult epileptic GAERS, extensive decreased FA was observed in the anterior corpus callosum. Unlike the WAG/Rij rats, the fornix showed increased FA in GAERS when compared with controls, which may represent a strain difference not directly related to seizures. *t* value threshold = 2.00, extent threshold = 50 voxels (voxel dimension $0.234 \text{ mm} \times 0.234 \text{ mm} \times 0.5 \text{ mm}$), and FA threshold = 0.30. This figure is reproduced from Chahboune et al. [18] with permission.