Published in final edited form as:

Future Neurol. 2009 May 1; 4(3): 295–304. doi:10.2217/fnl.09.12.

Novel approaches to imaging epilepsy by MRI

Hoby Hetherington

Departments of Neurosurgery and Diagnostic Radiology, Yale University, 404 Tompkins East, 333 Cedar St, New Haven, CT 06525, USA ■ hoby.hetherington@yale.edu

Abstract

As the concept of a network of injury has emerged in the treatment of epilepsy, the importance of evaluating that network noninvasively has also grown. Recently, studies utilizing magnetic resonance spectroscopic imaging, manganese-enhanced MRI and functional (f)MRI measures of resting state connectivity have demonstrated their ability to detect injury and dysfunction in cerebral networks involved in the propagation of seizures. The ability to noninvasively detect neuronal injury and dysfunction throughout cerebral networks should improve surgical planning, provide guidance for placement of devices that target network propagation and provide insights into the mechanisms of recurrence following resective surgery.

Keywords

epilepsy; magnetic resonance; spectroscopic imaging; manganese-enhanced MRI; neuronal networks; resting state connectivity

Brain imaging, including MRI, PET and single positron emission computed tomography (SPECT), has revolutionized the treatment of human epilepsy. The ability to identify anatomical (MRI) and functional (PET and SPECT) deficits has dramatically enhanced our ability to lateralize, localize and identify epileptogenic regions for surgical intervention. Despite the success of surgery for many forms of epilepsy, it is clear that focal epilepsies can involve brain regions that are distant from the region of onset [1]. With improvements in imaging technologies, it has been demonstrated that these effects can be visualized noninvasively and involve networks of brain structures, including cortical and subcortical structures [2-7]. With the advent of various devices that target suppression and interruption of epileptic circuits in the brain [8-10], a better understanding of the networks involved in epilepsy is of growing importance. However, many of the structures, including the onset region and regions that are involved in the propagation of seizures, may show minimal or no overt anatomical changes. Thus, new imaging methods that can identify individual abnormal brain regions or networks of these regions are critical to a better understanding of the role of these individual regions and the networks they comprise in human epilepsy. In this review we will focus on three aspects of MRI: magnetic resonance spectroscopic imaging (MRSI), manganese-enhanced MRI (MEMRI) and functional MRI (fMRI) measures of resting state connectivity. However, it is also important to acknowledge the critical role that high resolution

© 2008 Future Medicine Ltd

hoby.hetherington@yale.edu.

Financial & competing interests disclosure The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

anatomical MRI and diffusion tensor imaging play in providing visualization of the anatomical substrates that form the network.

Magnetic resonance spectroscopic imaging

Unlike conventional MRI studies, which detect the concentration of water and are sensitive to its cellular environment, magnetic resonance spectroscopy (MRS) enables different chemical compounds to be identified by their unique family of frequencies. In the brain the most widely studied compounds include *N*-acetylaspartate (NAA; a compound synthesized only in neuronal mitochondria) [11], creatine (both phosphorylated and non-phosphorylated compounds) and choline (elevated in cells with increased membrane turn-over) (FIGURE 1). Initially, MRS studies were carried out by selecting a moderately small location within the brain and acquiring data from that region. However, with improvements in both hardware and methods, a variety of techniques based on the concepts used for MRI have been developed to acquire spectra from multiple locations simultaneously (i.e., imaged). By integrating the signal intensity over a frequency range characteristic of a specific compound, metabolic images can be constructed (FIGURE 1). These methods provide a highly efficient method for probing for focal changes in metabolism characteristic of pathology.

The quality of MRSI data is largely dependent upon two factors: first, adequate sensitivity; and second, the ability to obtain a homogeneous magnetic field over the region to be imaged. Owing to the low concentration of most ^1H metabolite signals, 1–10 mM, in comparison with tissue water 35–55 M, attaining adequate sensitivity is critical for achieving high spatial resolution (small voxel sizes, e.g., <1 cc) and sensitivity to small changes in metabolite content. Advances in magnet technology (3 T and higher field systems) and detector technology (phased arrays) have significantly improved sensitivity. In the case of higher field systems, typically signal-to-noise ratio (SNR) has been reported to be increased at least linearly with field strength, while gains of a factor of greater than four in sensitivity have been reported for cortical locations when using phased arrays.

In MRSI studies, the observed width of the resonances is primarily determined by the homogeneity of the local magnetic field. Owing to the ubiquity of the ^1H nucleus in biologically active molecules, the ^1H spectrum suffers from significant spectral overlap. Increasing magnetic field inhomogeneity results in increased spectral overlap, which in turn makes interpretation and quantification of the spectra difficult. Initial studies using single-voxel methods minimized this effect by limiting the region of interest spatially to relatively small volumes (~1–8 cc). However, when MRSI studies are carried out, much larger regions are sampled (~100–1000 cc), placing significant demands on the hardware (shim coils) required to compensate for the magnetic field distortions induced by the human head. In recent years, significant improvements in technology both in hardware (third-order shim coils) and methods to map and noniteratively determine the appropriate shim corrections have dramatically enhanced the ability to attain homogeneous fields within the human head.

Localization of epileptogenic regions with ^1H MRS

In the mid-1990s, a number of investigators from different laboratories demonstrated the sensitivity of MRS measurements of NAA for the lateralization of the epileptogenic region in patients with temporal lobe epilepsy (TLE) [12–17]. Specifically, decreases in NAA content [12], and its ratio to other metabolites, such as creatine (NAA/Cr) [15–17], choline (NAA/Ch) [14] and the sum of creatine and choline (NAA/[Cr+Ch]) [13], were used to lateralize the seizure focus in patients with intractable temporal lobe seizures (FIGURE 2). As a lateralization and localization tool, the reported sensitivities have ranged from 60 [13] to 97% [18], somewhat higher than the 70–80% typically reported for conventional MRI studies. The ability of MRS to attain higher sensitivities in comparison with standard imaging is most likely the result of

the following factors: first, that the metabolic perturbation seen in TLE is widespread, affecting not only the hippocampus but also surrounding temporal gray and white matter; and second, detectable decreases in hippocampal volume by conventional MRI may require neuronal losses of up to 50%. Thus, for TLE the biochemical specificity afforded by spectroscopy outweighs the superior resolution afforded by MRI.

The finding of decreased NAA is not restricted to TLE. Reduced NAA levels have been reported in a variety of epileptic subtypes, including frontal lobe epilepsy [19,20] and malformations of cortical development [21,22].

³¹P spectroscopy & epilepsy

Although the majority of studies using spectroscopic imaging in epilepsy have focused on ¹H resonances, prior to the development of ¹H spectroscopy for studies of the human brain, Weiner and colleagues evaluated the use of ³¹P spectroscopy to localize epileptogenic regions. ³¹P spectroscopic imaging allows the distributions of high-energy phosphate resonances, including ATP, PCr and inorganic phosphate, to be imaged noninvasively (FIGURE 3). In their initial studies at 2.0 T, Weiner and colleagues reported significant increases in inorganic phosphate, suggesting increased hydrolysis of high-energy compounds, such as ATP and PCr [23,24]. Subsequent studies at 1.5 and 4 T demonstrated that significant declines in PCr/ATP were present in the ipsilateral [25] and contralateral temporal lobes [26]. Within this group, 73% of the patients were correctly lateralized using the PCr/Pi ratio. Similar to that seen in the ¹H spectrum, these effects are also seen throughout the network involving the thalamus [27]. Since patients with recent seizures (less than 24 h previous) were excluded, the decreased PCr/Pi was interpreted to reflect a chronic impairment of bioenergetics as opposed to an acute seizure-induced effect. Declines in bioenergetics are also seen in a variety of other forms of epilepsy, including children with Lennox—Gastaut syndrome, absence seizures and in adults with frontal lobe epilepsy [28,29]. Thus the finding of bioenergetic impairment is not restricted solely to TLE, but may reflect a basic mechanism underlying epilepsy as a whole.

Imaging networks of bioenergetic impairment in epilepsy

The presence of significant decreases in NAA in patients with TLE is also not restricted to the temporal lobe and reductions in NAA have been reported in the frontal and parietal lobes [30]. In studies using fluorodeoxyglucose (FDG) PET reductions in cerebral metabolic rate for glucose (CMRglucose) have been reported that correlate with neuronal loss in the ipsilateral hippocampus [31]. This latter work suggested that damage caused by the seizures originating in the ipsilateral hippocampus was being propagated to the thalamus resulting in hypometabolism. However, the origin of the decreased CMRglucose in the thalamus could be due to either metabolic dysfunction/injury in the thalamus or downregulation of activity due to deafferentation of hippocampal projections. To evaluate the relationship between various components of the macroscopic network, individual loci within the hippocampus, thalamus and basal ganglia were averaged and a correlation analysis was then performed evaluating the relationships between the ipsilateral and contralateral hippocampi with the other structures (FIGURE 4) [32]. This analysis identified highly significant correlations in decrements in NAA/Cr between the ipsilateral hippocampus and the bilateral thalamus and basal ganglia. An exceptionally strong correlation was detected between the ipsilateral hippocampus and the anterior thalamus ($R: +0.76; p < 1 \times 10^{-5}$). The contralateral hippocampus showed generally weaker correlations and primarily with ipsilateral structures (ipsilateral hippocampus, ipsilateral anterior thalamus and ipsilateral putamen) ($p < 10^{-3}$ -0.04). The only significant correlation within the same hemisphere for the contralateral hippocampus was the correlation with the contralateral anterior thalamus ($p < 0.03$). In contrast to the very strong correlations between the hippocampi, thalamus and putamen in patients, no significant correlations were observed in controls between the hippocampi and thalamus within the same hemisphere or

across hemispheres. Similar work investigating PCr/ATP correlations in TLE patients revealed significant correlations between PCr/ATP in the thalamus, basal ganglia and contralateral hippocampus [33].

Clinical implications & caveats

Unlike TLE, where the loci involved are well defined, in patients with neocortical epilepsy, the epileptogenic regions are often poorly defined anatomically and may have no accompanying MRI abnormality. This poses significant additional demands with regards to data acquisition and analysis. In addition to evaluating the observed ratios of NAA, Cr and Ch in hundreds if not thousands of locations, natural tissue-specific alterations must also be considered. For example, white matter concentrations of Cr have been reported to be approximately 6 mM [34,35], while gray matter values are approximately 8–9 mM. Additionally, variations in the content of these same compounds have also been reported between different lobes [36]. Thus, depending upon the location of the region of interest and its mixture of gray and white matter, the ‘normal’ levels of these metabolites will vary, complicating detection of ‘abnormal’ regions.

Although it is tempting to interpret decreases in NAA as reflecting solely neuronal loss, quantitative studies correlating NAA loss with neuronal loss have failed to demonstrate a significant relationship [37,38]. Furthermore, NAA changes in TLE have been demonstrated to be reversible [39–42]. The reversibility of decreased NAA in the contralateral hippocampus with successful surgical outcome, that is to say cessation of seizures, suggests that the recovering NAA levels reflect a ‘healing’ or ‘normalization’ of cellular process in the contralateral hippocampus. The fact that NAA normalization is associated with ‘normalization’ of neuronal function, that is to say cessation of seizures, suggests that the processes that link the balance between NAA synthesis and degradation directly reflect the dysfunction seen in epilepsy. Notably, NAA and ATP synthesis are also strongly correlated and can be modulated by mitochondrial inhibitors [43,44], suggesting a possible linkage between bioenergetic impairment and epilepsy.

Similar to the ^1H data, an analysis of the relationship between the bioenergetics (PCr/ATP) and neuropathology in TLE patients yielded no significant relation between the PCr/ATP in the ipsilateral hippocampus and neuronal loss [33]. However, significant correlations between thalamic and striatal PCr/ATP and total glial count in the hippocampus were found. This is similar to the data of Dlugos *et al.* [45], who reported no significant relationship between neuronal loss and FDG uptake in the hippocampus of TLE patients, but did find significant correlations between thalamic and striatal FDG uptake with neuronal loss in the ipsilateral hippocampus. Thus, similar to the ^1H data above, the PCr/ATP correlation with total glial count can also be interpreted as a result of chronic impairment and sublethal injury, possibly resulting from mitochondrial deficits.

However, it is not clear if the impairment in bioenergetics as reflected by decreased NAA/Cr and PCr/ATP is merely a secondary effect of the presence (reduced NAA and PCr) or absence (normalization of NAA and PCr) of seizures or rather, an underlying cause of the seizures. Finally, the extent to which NAA changes in network-related structures (e.g., NAA in the thalamus and basal ganglia) are reversible is unknown at this time. However, it is clear, that MRSI is sensitive to the injury induced by repeated seizures both at the site of onset and regions involved in propagation.

Mapping neuronal plasticity with MEMRI

Although the ^1H and ^{31}P spectroscopic imaging studies clearly demonstrate the role of networks of metabolic injury in patients with TLE, they are based on group statistics and

correlations. An imaging measure that is able to visualize functional changes within a given subject or animal over time would be immensely useful. Recently, MEMRI has emerged as a tool capable of visualizing neural connectivity and activity [46-51]. In the mammalian nervous system, Mn^{2+} mimics Ca^{2+} in a variety of ways, including transport by voltage-gated Ca^{2+} channels, exchange with Na^{+} through the Na^{+}/Ca^{2+} exchanger and active uptake by Ca^{2+} transporters in the mitochondria. As such, Mn^{2+} can serve as a marker for Ca^{2+} transport and uptake. After uptake into neurons Mn^{2+} moves along the axon and is eventually released into the synaptic cleft for reuptake and continued passage. Mn^{2+} is also a powerful paramagnetic relaxation agent, causing dramatic decreases in the T1 and T2 of the 1H MRI signal of water. Thus, T1-weighted images acquired after introduction of Mn^{2+} to the nervous systems will show enhanced signal intensity reflecting the uptake of Mn^{2+} . To date, MEMRI has been used for a wide variety of purposes [52] in animal models, including: first, the improvements in the visualization of neuronal architecture [53]; second, the tracking neuronal pathways in the visual and olfactory system following local administration [46,47]; and third, the alterations in neuronal plasticity following systemic administration [54-56].

MEMRI & plasticity in epilepsy

In the kainate model of epilepsy Nairismagi *et al.* [54], Immonen *et al.* [55] and Alvestad *et al.* [56] have investigated the spatial and temporal dynamics of MEMRI and its histological correlates. The kainate model of epilepsy is characterized by several distinct periods over which epileptogenesis occurs. After a brief period of status epilepticus induced by kainate (1 to several hours), seizure activity halts and the animals are seizure-free for a period of one to several weeks. During this period, the latent period, a series of complex changes occur, including mossy fiber sprouting, glial proliferation and neuronal loss. These changes lead to spontaneous seizures and signal the beginning of a period of chronic spontaneous seizures and epilepsy. Nairismagi *et al.* demonstrated that following direct injection of Mn^{2+} into the entorhinal cortex, the number of Mn^{2+} enhanced pixels in the dentate gyrus and CA3 subfield of the hippocampus was increased relative to controls and significantly correlated with Timm staining during the latent period [54]. This was consistent with mossy fiber sprouting leading to enhanced connectivity between these structures.

Alvestad *et al.*, investigated the temporal dynamics of MEMRI enhancement following subcutaneous injection of $MnCl$ at various times following kainate-induced seizures in the rat [56]. Mn^{2+} enhancement followed a complex pattern of spatial and temporal changes during the initial recovery period (2 days), latent period (15 days) and chronic period (11 weeks). In the hippocampus (CA3 and dentate gyrus) a biphasic response was observed, with initial declines during the recovery period relative to control followed by increased signal intensity in the latent period, with relatively small increases in the chronic period. This was in contrast to the thalamus and cerebellum, which showed minimal changes during the early and latent periods followed by large declines in signal intensity during the chronic period, indicating the specificity of the response. These changes can be understood in the context of balance between possible effects leading to decreased enhancement (neuronal loss and decreased activity) and increased enhancement (mossy fiber sprouting and increased activity). In the hippocampal structures, the initial decreases in enhancement primarily reflect neuronal injury and decreased activity during the initial period following status epilepticus. During the latent and chronic periods, a balance between mossy fiber sprouting, increased activity and neuronal loss leads to increases in enhancement. By contrast, for the thalamus and cerebellum, large decreases in enhancement are seen only in the chronic period most likely reflecting the downstream effects of the seizure resulting in neuronal injury and dysfunction. This would be in agreement with the spectroscopic imaging studies discussed earlier, where the extent of neuronal injury as visualized by decreased NAA in the thalami and hippocampi is correlated. This is also

consistent with the increase in the thalamic enhancement observed by Nairismagi following local injection of MnCl into the entorhinal cortex.

To better define the origin of the MEMRI enhancement, Immonen *et al.* evaluated the histologic correlates of MEMRI-based contrast enhancement and EEG activity in the kainate model [55]. A statistically significant correlation was observed between the degree of mossy fiber sprouting and MEMRI enhancement, while no such correlation was found with the degree of neural degeneration, gliosis or EEG activity. Thus the predominant factor leading to enhancement during the latent and chronic periods is likely due to the presence of mossy fiber sprouting. Thus, in the kainate model of epilepsy, MEMRI provides a highly sensitive probe for the reorganization that occurs during the latent period.

Implications & caveats

As described, MEMRI provides the ability to track neuronal networks when applied locally and alterations in neuronal activity when applied systemically. In contrast to fMRI and MRSI measurements, which visualize long-range anatomical networks involved in seizure propagation, the ability to visualize mossy fiber sprouting may provide an *in vivo* noninvasive surrogate marker for the local processes and networks involved in seizure initiation. If this is validated in additional studies, it would provide a powerful tool for evaluating various therapeutic interventions in preclinical models of human epilepsy. This has the potential to dramatically accelerate the evaluation of anti-epileptogenic therapies by allowing longitudinal studies to be carried out in the same animals and reducing variability due to interanimal differences. However it should also be noted that, owing to the myriad of factors that can potentially affect Mn²⁺ uptake, it will be important to determine the relative contributions of altered EEG activity, mossy fiber sprouting and other histologic changes as different experimental models of epilepsy are employed. Although Mn²⁺ has been extensively used in animal models, and is present naturally in the brain, it is highly toxic when elevated [52]. Thus the feasibility of extensive use in patients is unclear. However, its careful use in animal models offers a unique contrast agent for changes in neuronal activity.

Resting-state connectivity by fMRI

Over the past 10 years, fMRI has gained immense popularity for anatomical localization of different brain functions. For conventional applications, fMRI involves the analysis of images acquired in the presence and absence of a specific set of stimuli or task performance. During the 'activated' image, increased blood flow to active brain regions exceeds O₂ utilization, decreasing venous deoxyhemoglobin content and thereby increasing the transverse relaxation time, T2*, of water. For T2*-weighted images this results in an increase in intensity and a difference between the activated and nonactivated images. These methods have been widely used in presurgical planning for patients with epilepsy [57-59]. Most recently, this methodology has been applied to the evaluation of cerebral networks, via assessing their connectivity during rest. This connectivity manifests itself as a series of temporally correlated fluctuations in signal intensity from the brain regions participating in the network [60-62]. The network is typically identified by selecting an initial target region and then correlating the temporal evolution of the fMRI signal from this region with the rest of the brain. In this case the changes in signal intensity are due to changes in venous oxygenation caused by spontaneous fluctuations in activity of the cerebral network. These changes are at extremely low frequencies of approximately 0.1 Hz. Under this paradigm, larger correlation coefficients are interpreted to reflect stronger networks. Owing to the ease of performing the measurement, resting-state connectivity measurements have found widespread use in probing networks in normal development [63] and a variety of disease pathologies, including Alzheimer's [64], multiple sclerosis [65] and schizophrenia [66].

Resting-state connectivity in epilepsy

In a study of 17 patients with left TLE and eight controls, Waites *et al.* evaluated both resting-state connectivity and task-based activity for a language paradigm [67]. Although the task-based activation study showed similar responses between patients and controls, the resting-state connectivity maps showed dramatic differences. Specifically, the patients showed a reduction of the number of brain regions showing correlation with seed areas selected in the left inferior frontal gyrus, left middle frontal gyrus, anterior and posterior cingulate cortex. The authors interpreted the changes as being due to ongoing aberrant electrical activity (similar to dysfunction caused by interictal discharges) and alterations in the pathways themselves (consistent with the increased number of epilepsy patients with atypical language dominance). Bettus *et al.* used resting-state fMRI to evaluate the relationship between the epileptogenic regions (anterior and posterior hippocampus, amygdala, temporal pole and entorhinal cortex) in patients with TLE [68]. Similar to that seen by Waites, functional connectivity within the epileptogenic temporal lobe was reduced in patients relative to controls. However, connectivity within the contralateral temporal lobe in patients was increased and correlated with measures of working memory. This latter finding was interpreted to reflect a compensatory mechanism associated with the ipsilateral dysfunction.

Caveats & clinical implications

As described, the measurements rely on a three-stage process in which: first, the spontaneous events in one brain region cause a hemodynamic response that results in a change in MRI signal intensity; second, the functional activity in this brain region evokes activity in a distant brain region (next component of the network); and third, the activity generated in this distant brain region results in a hemodynamic change that manifests as an MRI signal change. As such, the strength and presence of various networks as suggested by resting-state connectivity is dependent upon a number of factors that may be altered in various pathologic states. For example, decreased interictal FDG uptake and neuronal loss in the epileptogenic focus is a common finding, indicating an overall lower level of activity. This lower level of activity may decrease spontaneous activity making existing connectivities difficult to measure, independent of the actual strength of the network being investigated. Alternately, constant spiking may accentuate a correlation by increasing the overall state of activity originating from the epileptogenic focus. In addition to activity-based changes, pathologic changes in bioenergetics may also modulate how the network expresses its connectivity. Specifically, even in the presence of a hemodynamic change, the MRI signal change remains largely dependent upon a change in venous blood oxygenation, which requires O₂ delivery to exceed demand. However, epileptogenic regions are characterized by impairments in oxidative metabolism (decreased NAA and PCr) such that the normal responses coupling metabolism and function are altered. Similarly, the use of specific anti-epileptic drugs may alter both the coupling between metabolism and function and alter the connectivities themselves. Thus, the absence or a decrement in resting-state connectivity in a given network involving epileptogenic regions may not reflect a reduction in strength of connectivity. Finally, owing to hardware limitations in many 3 T systems, fMRI measurements of the anterior temporal lobe and inferior frontal lobe can be compromised by static magnetic field inhomogeneity resulting in low quality measurements and spatial distortions. However, given the immense value of a noninvasive method for mapping functional connectivity, additional research to evaluate this methodology in epilepsy patients is critically needed.

Ultra-high-field MRI

With recent advances in magnet technology, ultrahigh field magnets (7 T and higher) with bore sizes capable of accommodating the adult human head have become available from a variety of research and clinical vendors. The increased field strength confers the intrinsic advantages

of: first, the increased SNR; second, the increased sensitivity to changes in deoxyhemoglobin content for small vessels; and third, the increased spectral resolution and spectral simplification for J-coupled resonances. Although measurements of NAA, creatine and choline have been highly successful at conventional field strengths (3 T and lower), the measurements of amino acids such as glutamate and glutamine in high-resolution spectroscopic images has been difficult owing to spectral overlap and SNR limitations. Thus, spectroscopic imaging at 7 T should provide an ideal platform for evaluating these compounds. With regard to resting state connectivity, owing to the relatively small size of the BOLD effect, increased SNR will also be of significant benefit, likely enhancing our ability to identify networks and reducing the number of acquisitions required to achieve statistical significance for any specific network. Additionally, the sensitivity for the detection of BOLD fMRI changes from small vessels increases dramatically at 7 T, enhancing spatial specificity [69]. However, to achieve these advantages, limitations due to increased power deposition [70] and increased magnetic field inhomogeneity have to be overcome. Specifically, required power levels increase as the third power of field strength for equivalent sequence performance, resulting in a factor of 12 increase in required power. Similarly, the absolute increase in inhomogeneity (Hz/cmⁿ) grows linearly with field strength. Fortunately, recent advances in RF coil design, including highly efficient independent multi-element transmission systems, transceiver arrays [71], methodologies utilizing their unique capabilities to spatially tailor the distribution of RF [72] to minimize power deposition and ultra strong higher order shim systems, provide a clear path to overcome these limitations.

Conclusion

As the concept of a network of injury has emerged in the treatment of epilepsy, the importance of evaluating that network noninvasively has also grown. Although high-resolution MR anatomical imaging is capable of identifying regions of significant neuronal loss, MRS has been demonstrated to be sensitive to neuronal injury, even in the absence of significant neuronal loss. Using ¹H and ³¹P MRSI it is clear that the injury associated with a variety of forms of epilepsy manifest themselves as bioenergetic impairment. This impairment appears to be propagated along the network of anatomical structures involved in epilepsy. Thus, MRSI has the potential to provide noninvasive assessments of neuronal injury throughout the network. For experimental animal models, the use of MEMRI provides direct visualization of the passage of Mn²⁺, an analog of Ca²⁺, along active neuronal tracts. In epilepsy this method allows visualization of neuronal sprouting, a key process in epileptogenesis. Finally, measures of resting-state connectivity provide the ability to monitor coordinated activity across large regions of the brain. To date this methodology has demonstrated decreased activity associated with functional declines in patients with TLE.

Future perspective

With the advent of higher field systems, 7 T for humans, improvements in SNR have the potential to make ¹H and ³¹P spectroscopic imaging studies routine for clinical evaluation of metabolic and bioenergetic impairment. These measures should provide better characterization of the networks involved in epilepsy, and how they respond to therapy. This latter issue may provide new insights into how and why epilepsy recurs in patients undergoing resective surgery. In animal models of epilepsy, the ability to detect neuronal sprouting non-invasively may significantly augment our ability to test new therapies. Specifically, the ability to monitor neuronal sprouting noninvasively will allow the time course in individual animals to be evaluated. Finally, resting-state connectivity measures may provide an additional means for evaluating network impairment in epilepsy. This may provide an additional tool for localizing and characterizing more difficult forms of epilepsy.

Executive summary

Magnetic resonance spectroscopic imaging

- ^1H and ^{31}P magnetic resonance spectroscopic imaging provide measures of injury and bioenergetic impairment in epilepsy.
- Decreases in *N*-acetylaspartate/creatine and phosphocreatine/ATP are not due to neuronal loss, but are correlated with neuronal dysfunction.
- Magnetic resonance spectroscopic imaging reveals a network of injury in temporal lobe epilepsy.

Manganese-enhanced MRI

- Manganese-enhanced MRI enables tracing of neuronal tracts.
- In epilepsy models manganese-enhanced MRI is sensitive to neuronal sprouting.
- Mn^{2+} toxicity may limit eventual application to patients.

Resting-state connectivity

- Low-frequency fluctuations in hemodynamics due to neuronal activity can be used to detect neuronal networks.
- In epilepsy patients, measures of resting-state connectivity demonstrate impaired network connectivity, which is consistent with dysfunction.

Bibliography

Papers of special note have been highlighted as:

■ of interest

■ of considerable interest

1. Margerison JH, Corsellis JAN. Epilepsy and the temporal lobes. *Brain* 1968;91:499–531.
2. Blumenfeld H, McNally KA, Vanderhill SD, et al. Positive and negative network correlations in temporal lobe epilepsy. *Cereb. Cortex* 2004;14(8):892–902. [PubMed: 15084494]
3. Labate A, Cerasa A, Gambardella A, Aguglia U, Quattrone A. Hippocampal and thalamic atrophy in mild temporal lobe epilepsy: a VBM study. *Neurology* 2008;71(14):1094–1101. [PubMed: 18824674]
4. Riederer F, Lanzenberger R, Kaya M, et al. Network atrophy in temporal lobe epilepsy: a voxel-based morphometry study. *Neurology* 2008;71(6):419–425. [PubMed: 18678824]
5. Gong G, Concha L, Beaulieu C, Gross DW. Thalamic diffusion and volumetry in temporal lobe epilepsy with and without mesial temporal sclerosis. *Epilepsy Res* 2008;80(2–3):184–193. [PubMed: 18490143]
6. Guye M, Régis J, Tamura M, et al. The role of corticothalamic coupling in human temporal lobe epilepsy. *Brain* 2006;129(Pt 7):1917–1928. [PubMed: 16760199]
7. Kimiwa T, Juhász C, Makki M, et al. Hippocampal and thalamic diffusion abnormalities in children with temporal lobe epilepsy. *Epilepsia* 2006;47(1):167–175. [PubMed: 16417545]
8. Salanova V, Worth R. Neurostimulators in epilepsy. *Curr. Neurol. Neurosci. Rep* 2007;7(4):315–319. [PubMed: 17618538]
9. Pollo C, Villemure JG. Rationale, mechanisms of efficacy, anatomical targets and future prospects of electrical deep brain stimulation for epilepsy. *Acta Neurochir. Suppl* 2007;97(Pt 2):311–320. [PubMed: 17691317]
10. Halpern CH, Samadani U, Litt B, Jaggi JL, Baltuch GH. Deep brain stimulation for epilepsy. *Neurotherapeutics* 2008;5(1):59–67. [PubMed: 18164484]

11. Goldstein FB. The enzymatic synthesis of *N*-acetyl-aspartic acid by sub-cellular preparation of rat brain. *J. Biol. Chem* 1969;244:4257–4260. [PubMed: 5800445]
12. Hugg JW, Laxer KD, Matson GB, Maudsley AA, Weiner MW. Neuron loss localizes human temporal lobe epilepsy by *in vivo* proton magnetic resonance spectroscopic imaging. *Ann. Neurol* 1993;34:788–794. [PubMed: 8250527]
13. Connelly A, Jackson GD, Duncan JS, King MD, Gadian DG. Magnetic resonance spectroscopy in temporal lobe epilepsy. *Neurology* 1994;44:1411–1417. [PubMed: 8058140]
14. Ng TC, Comair YG, Xue M, et al. Temporal lobe epilepsy: presurgical localization with proton chemical shift imaging. *Radiology* 1994;193:465–472. [PubMed: 7972764]
15. Cendes F, Andermann F, Preul MC, Arnold DL. Lateralization of temporal lobe epilepsy based on regional metabolic abnormalities in proton magnetic resonance spectroscopic images. *Ann. Neurol* 1994;35:211–216. [PubMed: 8109901]
16. Hetherington HP, Kuzniecky R, Pan JW, et al. Proton nuclear magnetic resonance spectroscopic imaging in temporal lobe epilepsy at 4.1 T. *Ann. Neurology* 1995;38:396–404.
17. Constantinidis I, Malko JA, Peterman SB, et al. Evaluation of magnetic resonance spectroscopic imaging as a diagnostic tool for the lateralization of epileptogenic seizure foci. *Br. J. Radiol* 1996;69:15–24. [PubMed: 8785617]
18. Kuzniecky R, Hugg JW, Hetherington H, et al. Relative utility of spectroscopic imaging and hippocampal volumetry in the lateralization of mesial temporal lobe epilepsy. *Neurology* 1998;51(1):66–71. [PubMed: 9674780] Garcia PA, Laxer KD, van der Grond J, et al. Correlation of seizure frequency with *N*-acetyl-aspartate levels determined by magnetic resonance spectroscopic imaging. *Magn. Reson. Imaging* 1997;15(4):475–478. [PubMed: 9223048]
19. Lundbom N, Gaily E, Vuori K, et al. Proton spectroscopic imaging shows abnormalities in glial and neuronal cell pools in frontal lobe epilepsy. *Epilepsia* 2001;42(12):1507–1514. [PubMed: 11879360]
20. Kuzniecky RI, Hetherington HP, Pan JW, et al. Proton spectroscopic imaging in patients with malformations of cortical development and epilepsy. *Neurology* 1997;48:1018–1024. [PubMed: 9109893]
21. Li LM, Cendes F, Bastos AC, et al. Neuronal metabolic dysfunction in patients with cortical developmental malformations. *Neurology* 1998;50:755–759. [PubMed: 9521269]
22. Laxer KD, Hubesch B, Sappey-Marini D, Weiner MW. Increased pH and inorganic phosphate in temporal seizure foci demonstrated by ³¹P MRS. *Epilepsia* 1992;33:618–623. [PubMed: 1628574]
23. Hugg JW, Laxer KD, Matson GB, et al. Lateralization of human focal epilepsy by ³¹P magnetic resonance spectroscopic imaging. *Neurology* 1992;42(10):2011–2018. [PubMed: 1407585]
24. Kuzniecky R, Elgavish GA, Hetherington HP, Evanochko WT, Pohost GM. *In vivo* ³¹P nuclear magnetic resonance spectroscopy of human temporal lobe epilepsy. *Neurology* 1992;42(8):1586–1590. [PubMed: 1641155]
25. Chu WJ, Hetherington HP, Kuzniecky RI, et al. Lateralization of human temporal lobe epilepsy by ³¹P NMR spectroscopic imaging at 4.1 T. *Neurology* 1998;51:472–479. [PubMed: 9710021]
26. Pan JW, Kim JH, Cohen-Gadol A, et al. Regional energetic dysfunction in hippocampal epilepsy. *Acta Neurol. Scand* 2005;111(4):218–224. [PubMed: 15740571]
27. Pan JW, Bebin EM, Chu WJ, Hetherington HP. Ketosis and epilepsy: ³¹P spectroscopic imaging at 4.1 T. *Epilepsia* 1999;40(6):703–707. [PubMed: 10368066]
28. Garcia PA, Laxer KD, van der Grond J, et al. Phosphorus magnetic resonance spectroscopic imaging in patients with frontal lobe epilepsy. *Ann. Neurol* 1994;35(2):217–221. [PubMed: 8109902] Vermathen P, Laxer KD, Schuff N, Matson GB, Weiner MW. Evidence of neuronal injury outside the medial temporal lobe in temporal lobe epilepsy: *N*-acetyl aspartate concentration reductions detected with multi-section proton MR spectroscopic imaging-initial experience. *Radiology* 2003;26:195–202. [PubMed: 12511690]
29. Dlugos DJ, Jaggi J, O'Connor WM, et al. Hippocampal cell density and subcortical metabolism in temporal lobe epilepsy. *Epilepsia* 1999;40:408–413. [PubMed: 10219265]
30. Hetherington HP, Kuzniecky RI, Vives K, et al. A subcortical network of dysfunction in TLE measured by magnetic resonance spectroscopy. *Neurology* 2007;69(24):2256–2265. [PubMed: 18071146] .Use of magnetic resonance spectroscopic imaging to detect a thalamo—hippocampal network of injury in patients with temporal lobe epilepsy.

31. Pan JW, Kim JH, Cohen-Gadol A, Pan C, Spencer DD, Hetherington HP. Regional energetic dysfunction in hippocampal epilepsy. *Acta Neurol. Scand* 2005;111(4):218–224. [PubMed: 15740571]
32. Michaelis T, Merboldt KD, Bruhn H, Hanicke W, Frahm J. Absolute concentrations of metabolites in the adult human brain *in vivo*: quantification of localized proton MR spectra. *Radiology* 1993;187(1):219–227. [PubMed: 8451417]
33. Hetherington HP, Pan JW, Mason GF, et al. Quantitative spectroscopic imaging of human brain at 4.1 T using image segmentation. *Magn. Reson. Med* 1996;36(1):21–29. [PubMed: 8795016]
34. Wiedermann D, Schuff N, Matson GB, et al. Short echo time multislice proton magnetic resonance spectroscopic imaging in human brain: metabolite distributions and reliability. *Magn. Reson. Imaging* 1996;19(8):1073–1080. [PubMed: 11711231]
35. Kuzniecky R, Palmer C, Hugg J, et al. Magnetic resonance spectroscopic imaging in temporal lobe epilepsy: neuronal dysfunction or cell loss? *Arch. Neurol* 2001;58(12):2048–2053. [PubMed: 11735779]
36. Cohen-Gadol AA, Pan JW, Kim JH, Spencer DD, Hetherington HP. Mesial temporal lobe epilepsy: a proton magnetic resonance spectroscopy study and a histopathological analysis. *J. Neurosurg* 2004;101(4):613–620. [PubMed: 15481715] Relationship between neuronal injury and changes in *N*-acetylaspartate in patients with temporal lobe epilepsy.
37. Hugg JW, Kuzniecky RI, Gilliam FG, Morawetz RB, Faught RE, Hetherington HP. Normalization of contralateral metabolic function following temporal lobectomy demonstrated by ¹H magnetic resonance spectroscopic imaging. *Ann. Neurol* 1996;40:236–239. [PubMed: 8773605]
38. Cendes F, Andermann F, Dubeau F, Matthew PM, Arnold DL. Normalization of neuronal metabolic dysfunction after surgery for temporal lobe epilepsy. *Neurology* 1997;49:1525–1533. [PubMed: 9409340]
39. Vermathen P, Ende G, Laxer KD, Weiner MW. Temporal lobectomy for epilepsy: recovery of the contralateral hippocampus measured by MRS. *Neurology* 2002;59(4):633–636. [PubMed: 12196667]
40. Serles W, Li LM, Antel SB, et al. Time course of postoperative recovery of *N*-acetyl-aspartate in temporal lobe epilepsy. *Epilepsia* 2001;42(2):190–197. [PubMed: 11240588]
41. Heales SJR, Davies SEC, Btes TE, Clark JB. Depletion of brain glutathione is accompanied by impaired mitochondrial function and decreased *N*-acetylaspartate concentration. *Neurochem. Res* 1995;20:31–38. [PubMed: 7739756]
42. Bates TE, Strangward M, Keelan J, Davey GP, Munro PMG, Clark JB. Inhibition of *N*-acetylaspartate production: implications for MRS studies *in vivo*. *Neuroreport* 1996;7:1397–1400. [PubMed: 8856684]
43. Dlugos DJ, Jaggi J, O'Connor WM, et al. Hippocampal cell density and sub-cortical metabolism in temporal lobe epilepsy. *Epilepsia* 1999;40:408–413. [PubMed: 10219265]
44. Pautler RG, Koretsky AP. Tracing odor-induced activation in the olfactory bulbs of mice using manganese-enhanced magnetic resonance imaging. *Neuroimage* 2002;16(2):441–448. [PubMed: 12030829]
45. Pautler RG, Silva AC, Koretsky AP. *In vivo* neuronal tract tracing using manganese-enhanced magnetic resonance imaging. *Magn. Reson. Med* 1998;40:740–748. [PubMed: 9797158]
46. Pautler RG, Mongeau R, Jacobs RE. *In vivo* trans-synaptic tract tracing from the murine striatum and amygdala utilizing manganese enhanced MRI (MEMRI). *Magn. Reson. Med* 2003;50(1):33–39. [PubMed: 12815676]
47. Pautler RG. Biological applications of manganese enhanced magnetic resonance imaging. *Methods Mol. Med* 2006;124:365–386. [PubMed: 16506430]
48. Tucciarone J, Chuang KH, Dodd SJ, et al. Layer specific tracing of corticocortical and thalamocortical connectivity in the rodent using manganese enhanced MRI. *Neuroimage* 2009;44(3):923–931. [PubMed: 18755280]
49. Simmons JM, Saad ZS, Lizak MJ, Ortiz M, Koretsky AP, Richmond BJ. Mapping prefrontal circuits *in vivo* with manganese-enhanced magnetic resonance imaging in monkeys. *J. Neurosci* 2008;28(30):7637–7647. [PubMed: 18650340]

50. Silva AC, Bock NA. Manganese-enhanced MRI: an exceptional tool in translational neuroimaging. *Schizophr. Bull* 2008;34(4):595–604. [PubMed: 18550591] Review of the applications of manganese-enhanced MRI (MEMRI).
51. Silva AC, Lee JH, Wu CW, et al. Detection of cortical laminar architecture using manganese-enhanced MRI. *J. Neurosci. Methods* 2008;167(2):246–257. [PubMed: 17936913]
52. Nairismägi J, Pitkänen A, Narkilahti S, et al. Manganese-enhanced magnetic resonance imaging of mossy fiber plasticity *in vivo*. *Neuroimage* 2006;30(1):130–135. [PubMed: 16246593]
53. Immonen RJ, Kharatishvili I, Sierra A, et al. Manganese enhanced MRI detects mossy fiber sprouting rather than neurodegeneration, gliosis or seizure-activity in the epileptic rat hippocampus. *Neuroimage* 2008;40(4):1718–1730. [PubMed: 18328732] Correlation between mossy fiber sprouting and MEMRI enhancement in a model of temporal lobe epilepsy.
54. Alvestad S, Goa PE, Qu H, et al. *In vivo* mapping of temporospatial changes in manganese enhancement in rat brain during epileptogenesis. *Neuroimage* 2007;38(1):57–66. [PubMed: 17822925]
55. Medina LS, Bernal B, Dunoyer C, et al. Seizure disorders: functional MR imaging for diagnostic evaluation and surgical treatment — prospective study. *Radiology* 2005;236(1):247–253. [PubMed: 15987978]
56. Tharin S, Golby A. Functional brain mapping and its applications to neurosurgery. *Neurosurgery* 2007;60(4 Suppl 2):185–201. [PubMed: 17415154]
57. Chakraborty A, McEvoy AW. Presurgical functional mapping with functional MRI. *Curr. Opin. Neurol* 2008;21(4):446–451. [PubMed: 18607205]
58. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn. Reson. Med* 1995;34(4):537–541. [PubMed: 8524021] One of the first descriptions of resting-state connectivity.
59. Lowe MJ, Mock BJ, Sorenson JA. Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. *Neuroimage* 1998;7(2):119–132. [PubMed: 9558644]
60. Auer DP. Spontaneous low-frequency blood oxygenation level-dependent fluctuations and functional connectivity analysis of the ‘resting’ brain. *Magn. Reson. Imaging* 2008;26(7):1055–1064. [PubMed: 18657923]
61. Fair DA, Cohen AL, Dosenbach NU, et al. The maturing architecture of the brain’s default network. *Proc. Natl Acad. Sci. USA* 2008;105(10):4028–4032. [PubMed: 18322013]
62. Sorg C, Riedl V, Mühlau M, et al. Selective changes of resting-state networks in individuals at risk for Alzheimer’s disease. *Proc. Natl Acad. Sci. USA* 2007;104(47):18760–18765. 20. [PubMed: 18003904]
63. Lowe MJ, Phillips MD, Lurito JT, et al. Multiple sclerosis: low-frequency temporal blood oxygen level-dependent fluctuations indicate reduced functional connectivity initial results. *Radiology* 2002;224(1):184–192. [PubMed: 12091681]
64. Liang M, Zhou Y, Jiang T, et al. Widespread functional disconnectivity in schizophrenia with resting-state functional magnetic resonance imaging. *Neuroreport* 2006;17(2):209–213. [PubMed: 16407773]
65. Waites AB, Briellmann RS, Saling MM, Abbott DF, Jackson GD. Functional connectivity networks are disrupted in left temporal lobe epilepsy. *Ann. Neurol* 2006;59(2):335–343. [PubMed: 16404743] Describes how dysfunctional networks in epilepsy can be detected using measures of resting-state connectivity.
66. Bettus G, Guedj E, Joyeux F, et al. Decreased basal fMRI functional connectivity in epileptogenic networks and contralateral compensatory mechanisms. *Hum. Brain Mapp.* 2008 DOI: 10.1002/hbm.20625. (Epub ahead of print).
67. Yacoub E, Duong TQ, Van De Moortele PF, et al. Spin-echo fMRI in humans using high spatial resolutions and high magnetic fields. *Magn. Reson. Med* 2003;49(4):655–664. [PubMed: 12652536]
68. Vaughan JT, Garwood M, Collins CM, et al. 7T vs. 4T: RF power, homogeneity, and signal-to-noise comparison in head images. *Magn. Reson. Med* 2001;46(1):24–30. [PubMed: 11443707]
69. Adriany G, Van de Moortele PF, Ritter J, et al. A geometrically adjustable 16-channel transmit/receive transmission line array for improved RF efficiency and parallel imaging performance at 7 Tesla. *Magn. Reson. Med* 2008;59(3):590–597. [PubMed: 18219635]

70. Van de Moortele PF, Akgun C, Adriany G, et al. B(1) destructive interferences and spatial phase patterns at 7 T with a head transceiver array coil. *Magn. Reson. Med* 2005;54(6):1503–1518. [PubMed: 16270333]

Figure 1. ^1H magnetic resonance spectra from a column along the hippocampus from a control subject

The labeled resonances are water, Cr, MI, Ch and NAA. The locations of the magnetic resonance spectra are indicated by the red box overlaid on the anatomical image. Ch: Choline; Cr: Creatine; MI: Myoinositol; NAA: *N*-acetylaspartate.

Figure 2. ^1H magnetic resonance spectra from a patient with temporal lobe epilepsy

Note the decreases in NAA/Cr in the ipsilateral hippocampus are greater than that seen in the contralateral hippocampus, and that seen in controls (FIGURE 1). The spectra are overlaid on the anatomical image.

Ch: Choline; Contra: Contralateral; Cr: Creatine; Ipsi: Ipsilateral; NAA: *N*-acetyl aspartate; MI: Myoinositol.

Figure 3. ^{31}P spectrum from a control subject displaying the resonance of inorganic phosphate, phosphocreatine & ATP

Shown below is an image from a patient with temporal lobe epilepsy showing the decrease in PCr/ATP from the ipsilateral hippocampus.

Contra: Contralateral; Ipsi: Ipsilateral; PCr: Phosphocreatine; Pi: Phosphatidylinositol.

Figure 4. Network of correlations (Pearson) of *N*-acetylaspartate/creatine between the hippocampus, anterior & posterior hippocampus and basal ganglia in patients with temporal lobe epilepsy.