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Neuroimaging Biomarkers for Epilepsy: Advances and Relevance to Glial Cells

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Abstract

Glial cells play an important role in normal brain function and emerging evidence would suggest that their dysfunction may be responsible for some epileptic disease states. Neuroimaging of glial cells is desirable, but there are no clear methods to assess neither their function nor localization. Magnetic resonance imaging (MRI) is now part of a standardized epilepsy imaging protocol to assess patients. Structural volumetric and T2-weighted imaging changes can assist in making a positive diagnosis in a majority of patients. The alterations reported in structural and T2 imaging is predominately thought to reflect early neuronal loss followed by glial hypertrophy. MR spectroscopy for myo-inositol is a being pursued to identify glial alterations along with neuronal markers. Diffusion weighted imaging (DWI) is ideal for acute epileptiform events, but is not sensitive to either glial cells or neuronal long-term changes found in epilepsy. However, DWI variants such as diffusion tensor imaging or q-space imaging may shed additional light on aberrant glial function in the future. The sensitivity and specificity of PET radioligands, including those targeting glial cells (translocator protein) hold promise in being able to image glial cells. As the role of glial function/dysfunction in epilepsy becomes more transparent, neuroimaging methods will evolve to assist the clinician and researcher in visualizing their location and function.

Keywords

MRI; DTI; MRS; T2; limbic; seizures; astrocytes; PET; SPECT

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Introduction

The diagnosis of epilepsy and its associated syndromes has been traditionally undertaken using scalp electroencephalograms (EEG). This clinical gold standard is increasingly being supplemented by significant advances within the last decade of existing and emerging noninvasive neuroimaging modalities. The range of clinically relevant imaging modalities is rapidly expanding and includes magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission computed tomography (SPECT), computed tomography (CT) and ultrasound for neonatal and pediatric seizures. Clinically, the most prevalent of these imaging modalities is MRI, including magnetic resonance spectroscopy (MRS) (Table 1). The importance of MRI in epilepsy diagnosis is underscored by the 1997 International League Against Epilepsy (ILAE) recommendations and guidelines for a dedicated epilepsy MR imaging protocol when patients are being clinically assessed (1997). More recently, a specific set of guidelines for neuroimaging of infants and children with epilepsy has also been proposed that includes MRI, to primarily assess structural abnormalities (Gaillard, Chiron et al. 2009).

Animal models of experimental epilepsy combined with the increased availability of dedicated animal imagers have also advanced our understanding of the physiology of epilepsy and epileptogenesis. A variety of neuroimaging methods, including MRI (Grohn, Sierra et al. 2011; Otte, Bielefeld et al. 2012) and PET (Jupp, Williams et al. 2012; Lee, Park et al. 2012) have been used with success, not only to assess structural alterations but also to determine the pathophysiological basis for disease onset and progression. Many of these studies have been undertaken with an eye towards clinical translatability for improved diagnosis and assessment of current and new therapeutics.

The importance of glial cells in epilepsy is slowly coming into view from its previous categorization of being solely reactive to ongoing neuronal injury (Wolf, Dyakin et al. 2002; Das, Wallace et al. 2012). It is increasingly now thought to play a significant role in localized excitability (Rodgers, Hutchinson et al. 2009; Zheng, Zhu et al. 2010), as well as other active and supportive roles (Coulter and Eid 2012). The importance of glial cells in epilepsy and their roles are reviewed by XXX in this special issue (REFS). Given their importance and significance not only in response to epilepsy-induced injury, but also in their putative roles in causing local tissue disturbances that may initiate epileptiform activity, there is some hope that current and forthcoming neuroimaging methods may identify the evolution of abnormal glial changes within the brain.

Extensive reviews of current advances in neuroimaging in epilepsy have been previously published for MRI (Beers and Federico 2012; Jones and Rabiner 2012; Laufs 2012; Malmgren and Thom 2012; Urbach 2012) and PET (la Fougere, Rominger et al. 2009; Horky and Treves 2011; Jones and Rabiner 2012). The primary focus of the current review is to identify current imaging modalities that may yield insights into the role of glial cells in epilepsy both clinically and in studies using experimental models.

Magnetic Resonance Imaging (MRI)

MRI is the imaging modality of choice to evaluate patients for structural abnormalities, particularly for assessment as surgical intervention candidates. However, the successful interpretation and diagnosis of seizure foci is dependent on specialized MRI epilepsy protocols (1997). Studies have previously reported that routine MRI sequences read by expert radiologists failed to detect 57% of epileptogenic lesions (Von Oertzen, Urbach et al. 2002). These findings and those by others provided the impetus to develop clinically dedicated epilepsy MRI protocols at medical centers for evaluating these patients. Such dedicated MR protocols can significantly improve detection of abnormalities on structural imaging, usually in the form of unilateral and bilateral focal lesions as a result of epilepsy.

Structural MRI

The long-term effects of epilepsy, including anatomical and morphological changes within the brain can be visualized using structural MRI (Jackson, Calamante et al. 2010; Jackson and Badawy 2011). Clinically, in mesial temporal lobe sclerosis (MTS), a common finding is that of altered hippocampal and temporal lobe volumes. As noted above, an epilepsy protocol comprised of coronal MRI perpendicular to the long axis of the hippocampus is invaluable for making a definitive structural diagnosis. The predominant findings in structural imaging of MTS include reduced hippocampal volumes using either T1- or T2 weighted imaging (T2WI) and increased T2WI signal intensities within the hippocampus (Jackson, Berkovic et al. 1990; Jackson, Berkovic et al. 1993). T2-relaxometry was also found to aid in the diagnosis of hippocampal sclerosis (Jackson, Connelly et al. 1993). Similar findings have been reported in animal models of epilepsy (Jupp, Williams et al. 2006). A critical caveat is that the volumetric loss of brain anatomy that has been reported from both MRI and histological studies occurs late after the onset of seizures and thus reflects tissue level neuropathology which limits therapeutic intervention. However, one strength of non-invasive imaging modalities is their ability to repeatedly image the subject of interest, such as the temporal evolution of the reported T2 changes. Parekh and colleagues reported early decrements in T2 values within the hippocampus in all rats during the acute phase (Parekh, Carney et al. 2010). However, T2 values were then increased during the chronic (>40 days) phase but only in rats exhibiting spontaneous seizures. In addition, there appeared to be anatomically sensitive changes with the hippocampal regions that were predominately affected acutely, while piriform and entorhinal cortices along with the thalamus exhibited chronic increases or decreases in T2, respectively (Parekh, Carney et al. 2010). While T2 may be a useful biomarker for emerging epileptogenesis, the significance of these T2 alterations is still speculative (Bhagat, Obenaus et al. 2001; van Eijsden, Notenboom et al. 2004).

The reduced hippocampal volumes reported in epilepsy patients using hippocampal volumetry has been shown to be related to neuronal loss (Van Paesschen, Revesz et al. 1997), similar to numerous animal studies (Wolf, Dyakin et al. 2002). A common feature both clinically and experimentally is that following neuronal loss there is substantial gliosis (Lockwood-Estrin, Thom et al. 2012) (see also XXX this issue). The elevation of T2WI signal intensities are thought to be due to increased edema and evolving gliosis (Van

Paesschen, Revesz et al. 1997; Jupp, Williams et al. 2006). In a model of febrile seizures (FS), Dube and colleagues reported increased T2 values within limbic structures in 75% of the animals studied (Dube, Yu et al. 2004). However, these increases in T2 were not associated with neuronal injury. In another study, T2 increases were found in FS animals that had cognitive disabilities (Dube, Zhou et al. 2009), suggesting that T2 alterations may provide a biomarker in human febrile seizures for altered brain function (Gomes and Shinnar 2011). More recently, we have reported within the amygdala, decreases in T2 relaxometry within hours after the onset of febrile seizures which was able to differentiate between those rats that went on to become epileptic from those that did not (Choy, Dube et al. 2012). We have hypothesized that these T2 decrements maybe related to increased metabolic demand during the febrile status period.

Other models of epilepsy and seizures, including pentylenetetrazol (PTZ) induced seizures have reported similar increases in T2 accompanied by hippocampal atrophy, neuronal loss and gliosis (Fang and Lei 2010).These authors were able to demonstrate that the T2 increases positively correlated to seizures. Virtually similar T2 and histological observations were found in a temporal lobe model of adult epilepsy, during both the acute and chronic phases of the disease (Parekh, Carney et al. 2010). We have also reported similar T2 increases within limbic regions following pilocarpine induced status epilepticus that coincided with gliosis (Wall, Kendall et al. 2000).

Thus, both in clinical patients and in a variety of experimental models hippocampal volume loss with acute and chronic alterations in T2 are common features. Numerous studies have made careful inferences that the increases in T2 appear to be related to increased glial hypertrophy within the affected tissues. Certainly, during the acute phase of epileptiform activity glial cells are actively involved in clearance of edema (via glial water channels, aquaporin 4) (Binder, Nagelhus et al. 2012; Lee, Amini et al. 2012) and appear to be directly associated with the observed T2 increases. However, the underlying late and more chronic elevations in T2 and its relationship to glial hypertrophy are less well understood and additional studies are warranted.

Diffusion-weighted (DWI) and Diffusion Tensor Imaging (DTI)

Several decades ago diffusion weighted imaging (DWI) and its quantitative parameter, the apparent diffusion coefficient (ADC), were found to be uniquely sensitive to rapid onset pathophysiology in stroke and other central nervous system disorders, including seizures (Forster, Griebe et al. 2012). Extensive studies in a broad range of experimental models have described DWI (and ADC) alterations within selected brain regions following status epilepticus. We (Wall, Kendall et al. 2000) and others (Engelhorn, Hufnagel et al. 2007) have described ADC reductions within the hippocampus, amygdala and piriform, parietal and temporal cortices (Figure 1). These decrements start within minutes and then over the next 24-72 hours begin to normalize to control levels within the affected brain tissues. DWI/ADC correlations with histopathology demonstrate neuronal loss and glial hypertrophy. The injury cascade seen on DWI/ADC is reflective of neuronal swelling, followed by rapid neuronal loss and death with ensuing glial activation (Wall, Kendall et al. 2000). In experimental models of epilepsy, hippocampal ADC, decreases very rapidly over

the first several hours (Engelhorn, Hufnagel et al. 2007) that then return to control levels which is then followed by slow ADC increases at 7 days post seizure induction (Figure 1) (Wall, Kendall et al. 2000). These ADC increases in limbic structures progressively increase even further, up to 60 days after status epilepticus (Parekh, Carney et al. 2010). The chronic DWI increases were observed only in spontaneously seizing rats and existed predominately within the hippocampus, the fimbria and the piriform cortex. A constellation of cellular injury cascades, including altered perfusion, increased microglial and astroglial proliferation with concomitant changes in tissue tortuosity very likely underlie these biphasic DWI changes (Sykova and Nicholson 2008; Vargova, Homola et al. 2011). We have previously suggested a linkage between changes in extracellular water mobility and T2 relaxation times (Bhagat, Obenaus et al. 2001), particularly within the first 24 hrs following seizures. Swelling of glial and neuronal cells modify the extracellular space which is an important determinant for propagation of seizure activity, particularly via non-synaptic mechansims (Dudek, Obenaus et al. 1990).

A variant of DWI, q-space imaging, can probe more accurately water compartments within the brain (intra- vs. extracellular, glial vs. neuronal) and has also been applied to epilepsy. The sensitivity of water diffusion at the cellular and sub-cellular level can be probed even more finely leading to inferences of the statistical probabilities of water displacement (Cohen and Assaf 2002). We extended our original DWI findings (Wall, Kendall et al. 2000) by applying q-space imaging in an animal model of status epilepticus (Eidt, Kendall et al. 2004) to further attempt separation of neuronal and glial tissue fractions. Within the piriform cortex, we observed decrements in the mean free diffusion path early after status epilepticus that slowly returned to control values. These chanages were accompanied by decrements in the water probability of zero displacement which coincided with glial invasion and hypertrophy. More recent advances in q-space imaging have probed cellular and tissue microstructures within the brain and spinal cord which could be readily applied to epilepsy studies (White, Leergaard et al. 2012). A potential limitation of these studies to clinical translation is related to hardware limits in both ramp- and dwell time of the gradients. It is conceivable that non-invasive imaging of glial cell populations, particularly following onset of epilepsy could be undertaken using emerging variants of diffusion weighted imaging, such as q-space.

At the present time clinical neuroimaging of epilepsy using DWI is not used extensively, due in part that many patients undergo MRI evaluation as potential surgical candidates. Temporally, by this time after pharmacological therapy has proved to be ineffective, many of the structural changes we noted above have appeared. Thus, in order to fully utilize DWI's sensitivity for early changes (< 24 hours) following epileptiform activity, neuroimaging should be performed early after the seizure onset. Given DWI's sensitivity for cellular swelling and neuronal death, several clinical studies have utilized DWI to examine in tissue level alterations early after status epilepticus (Chatzikonstantinou, Gass et al. 2011; Forster, Griebe et al. 2012). Chatzikonstantinou and colleagues imaged a heterogenous group of patients within 24 hours of presenting with status epilepticus in the emergency room (Chatzikonstantinou, Gass et al. 2011). They found peri-ictal DWI changes in all status epilepticus patients, but 67% of the patients with symptomatic seizures had underlying pathology (e.g. tumors, ischemia etc). Many of the patients in this report were cases of

known epilepsy (37%) (Chatzikonstantinou, Gass et al. 2011). Clinically, there have not been clear associations between the DWI parameters and histological measures of gliosis nor neuronal loss in either gray or white matter (Lockwood-Estrin, Thom et al. 2012). More often, DWI has been used to evaluate surgical candidates but it is not typically considered part of a standardized epilepsy imaging protocol. What is lacking are clinical studies that temporally evaluate the ability of DWI to define early changes following seizures, similar to those undertaken in the FEBSTAT studies (Nordli, Moshe et al. 2012; Shinnar, Bello et al. 2012). More often DWI is used to evaluate the late progression of the disease.

In contrast an extension of DWI, diffusion tensor imaging (DTI), is gaining significance in clinical evaluation of epilepsy patients to investigate microstructural changes in white matter (Lockwood-Estrin, Thom et al. 2012). Particularly those deemed as candidates for tissue resection (Chen, Weigel et al. 2009). Altered white matter tracts have been reported following various forms of epilepsy and may be indicative of the progression of injury (Figure 2) (Kim, Suh et al. 2012; Liacu, Idy-Peretti et al. 2012; Otte, van Eijsden et al. 2012). The majority of DTI studies have studied white matter structure due to its uniform anatomical structure (axons, myelin sheaths etc). However, an interesting recent study of multiple sclerosis patients found that gray matter DTI changes preceded those found in white matter (Geurts, Calabrese et al. 2012). Additional investigations into gray matter alterations (neuronal and glial) could potentially provide some insights into the role of glial cells in evolving epilepsy syndromes. However, the use of DTI to specifically image glial cells and or the hypertrophy of these cells in response to epileptiform activity and seizures have not been explicitly studied. In the future, investigations need to be undertaken into the clinical utility of DTI for epilepsy diagnosis and ultimately, as a biomarker for glial cells underlying the pathology of seizures.

Experimentally in animal models of epilepsy, DTI has been predominately utilized to assess white matter injury (Obenaus and Jacobs 2007; Grohn, Sierra et al. 2011). Praekh and colleagues found significant decrements in fractional anisotropy (FA), a measure of directionality of water movement within the fimbria, entorhinal cortex and thalamus (Parekh, Carney et al. 2010). These decreases were preceded by increases in FA within the hippocampus during the acute phase of the seizures. Thinning of the fimbria was also observed in all rats that exhibited spontaneous seizures and was hypothesized to contribute to the observed decreases in FA. Further, DTI combined with tract-based spatial statistics have also been reported to identify hereto unknown brain regions that that were correlated to myelin alterations in the kainic acid model of epilepsy (Sierra, Laitinen et al. 2011). It is clear that additional research into usefulness of DTI imaging for epilepsy diagnosis and its relevance for imaging glial cells is desirable, particularly for oligiodendrocytes.

Emerging techniques such as diffusion spectrum imaging (Kuo, Lee et al. 2008) and diffusion basis spectrum imaging (Wang, Wang et al. 2011) appear to have increased sensitivity for identification of tissue level alterations. For example, Song and colleagues devised an extension of DTI that also reports increased cellularity following inflammation-induced demyelination. Such techniques can be readily applied to imaging of glial cells in epilepsy (Wang, Wang et al. 2011). Confirmatory studies are clearly required to assess if these emerging technologies have a role in epilepsy diagnosis and management beyond

confirming tissue related abnormalities, particularly for imaging the status and activation of glial cells.

Magnetic Resonance Spectroscopy (MRS)

Proton MRS allows anatomical and regional measurements of brain metabolites, including N-acetyl-aspartate (NAA, a neuronal marker), choline (Cho, a marker for cell membranes and brain lipids) and creatine (Cr, a marker for energy metabolism). Numerous studies, both clinically (Cendes, Andermann et al. 1994; Fountas, Tsougos et al. 2012) and in animals (Filibian, Frasca et al. 2012; Lee, Park et al. 2012) have reported decreases in NAA that are associated with either neuronal dysfunction (Kuzniecky, Palmer et al. 2001) or frank neuronal loss (Tasch, Cendes et al. 1999). In 15 MTS patients there was a 65% reduction in NAA along with increased (56%) concentrations of Cho and Cre (Fountas, Tsougos et al. 2012). Unlike other studies, these authors did not find contralateral alterations in metabolite levels in their MTS patient cohort. A significant confound in many of these clinical studies is that when sclerotic tissues are excised, the MRS findings seldom quantitatively correlate to histological measures, including glial cells. An assumption is often made that the oft reported increase in Cho is related to gliosis within the affected tissues, either in hippocampus or temporal cortices. It should be noted that some studies have suggested that their MRS findings have been able to localize unilateral and bilateral seizure foci using NAA metabolism, as accurately as EEG (Cendes, Andermann et al. 1997; Simister, McLean et al. 2009). These studies also found that MRS abnormalities, notably NAA and Cr may normalize and therefore may not be entirely reflective of ongoing cell death or gliosis (Cendes, Andermann et al. 1997). Thus, clinical application of MRS has been found to be very useful, particularly when combined with other imaging modalities and EEG to assist in the diagnosis of epilepsy (Cendes, Caramanos et al. 1997).

Animal studies of epilepsy have reported similar changes in NAA, Cho and Cre (Tokumitsu, Mancuso et al. 1997; Filibian, Frasca et al. 2012; Lee, Park et al. 2012). In contrast to clinical studies, several recent studies have proposed that MRS can identify glial related alterations within the brains of epileptic rodents (Filibian, Frasca et al. 2012; van der Hel, van Eijsden et al. 2012). Evaluation of putative markers for astrocytes including myo-inositol (mIno) and glutathione (GSH), by MRS confirmed a progressive increase in both glial markers in epileptic rats that were sustained over the 7 day study period (Filibian, Frasca et al. 2012). Immunohistochemical scoring for glial cells found significant correlations between elevations in MRS markers and increased numbers of glial cells; these findings were strengthened by significant correlations between MRS data and spontaneous seizure frequency. The increased mIno from animal studies have not been confirmed in patients with epilepsy (Garcia, Huppertz et al. 2009; Doelken, Mennecke et al. 2010). Thus, high-field MRS shows promise as a potential epilepsy imaging modality for assessment of glial cells but future studies are necessary to evaluate its clinical and experimental potential.

Functional MRI (fMRI)

Functional MRI is an imaging modality based on visualizing deoxyhemoglobin/ oxyhemoglobin concentrations that are a consequence of neuronal activation (Limotai and Mirsattari 2012). Numerous studies have utilized fMRI to assess brain structure-function

relationships as a prelude to surgical intervention for epilepsy treatment in patients (Beers and Federico 2012; Laufs 2012) and in experimental studies (Blumenfeld 2007; Englot, Modi et al. 2009). In most epilepsy studies fMRI has been used to identify specific brain regions and pathways that are activated in response to a stimuli (e.g. finger tapping, visual cues, etc) (Beers and Federico 2012). Assessment of memory and white matter reorganization studies is often the primary focus to identify functional regions within the brain prior to surgical intervention. A more recent extension of fMRI is resting state MRI (rsMRI) where baseline connectivity within the brain between anatomically distinct regions is assessed and can provide novel insights into the progressive nature of CNS injury (Loitfelder, Filippi et al. 2012). Interestingly, increased compensatory connectivity appears to be a consequence of long-term seizures (Holmes, Folley et al. 2012; Lee, Smyser et al. 2012; Wurina, Zang et al. 2012). At the present time, while a powerful tool for evaluation of epilepsy patients, it is unclear how fMRI or rsMRI could be utilized to identify glial cells non-invasively.

Other MRI Modalities

There are a number of MR imaging modalities that have been applied to the study of epilepsy, including manganese-enhanced MRI (MEMRI) and susceptibility weighted imaging (SWI). Each of these imaging techniques exploits unique features of brain physiology that could be applied to investigating the role of glial cells in epilepsy.

MEMRI has been used extensively in a broad range of animal studies including epilepsy (Obenaus and Jacobs 2007; Grohn, Sierra et al. 2011; Inoue, Majid et al. 2011). Manganese enters various cell types through voltage gated calcium channels and has been used as a T1-weighted contrast agent to map brain function. Several studies have now applied MEMRI to the study of epilepsy to study activity dependent alterations in hippocampus, amygdala and entorhinal cortex (Nairismagi, Pitkanen et al. 2006; Alvestad, Goa et al. 2007; Immonen, Kharatishvili et al. 2008; Dedeurwaerdere, Fang et al. 2013). Most recently, MEMRI has been used to evaluate the presence of mossy fiber sprouting (MFS) in the hippocampus (Alvestad, Goa et al. 2007; Malheiros, Polli et al. 2012; Dedeurwaerdere, Fang et al. 2013). The majority of studies report a relationship between MRI signal enhancement and subsequent MFS (Nairismagi, Pitkanen et al. 2006; Immonen, Kharatishvili et al. 2008; Malheiros, Polli et al. 2012). But, a recent study did not find such a relationship between manganese enhancement and MFS (Dedeurwaerdere, Fang et al. 2013), but interestingly found increased signal intensity in mildly seizing rats compared to severe seizures. While glial cells, including microglia, are cells that take up manganese, virtually all epilepsy MEMRI studies have not found a correlation between signal enhancement and astrogliosis (Alvestad, Goa et al. 2007; Immonen, Kharatishvili et al. 2008; Dedeurwaerdere, Fang et al. 2013). A caveat is that no studies have been designed specifically to assess glial physiology in response to seizure induction or epileptogenesis but additional targeted studies may resolve this question. Further, MEMRI is unlikely to have clinical applicability due to its toxic profile.

SWI is an MRI sequence that is uniquely sensitive to calcifications and iron content within the brain (Haacke, Mittal et al. 2009; Mittal, Wu et al. 2009). To date no animal studies have

been performed evaluating the ability of SWI to identify tissue level abnormalities in epilepsy models. However, clinical studies have suggested that imaging calcifications in a subset of epilepsy patients provides additional diagnostic information not gleaned from current epilepsy protocols (Saini, Kesavadas et al. 2009). SWI identified calcifications have also been used to identify perfusion deficits in white matter from children with Sturge-Weber Syndrome (Wu, Mittal et al. 2009). No studies have correlated SWI to glial cells, but it may hold some potential particularly with glial cells ability to sequester iron (Skjorringe, Moller et al. 2012).

Positron Emission Tomography (PET) / Single Photon Emission Tomography (SPECT)

PET imaging has been utilized for over a quarter century to identify seizure foci in temporal lobe epilepsy patients. PET imaging requires the injection of a radioactive tracer attached to a compound or receptor of interest to visualize modifications in brain function. A classic radiotracer in epilepsy studies has been a non-metabolizable glucose analog, fluorodeoxyglucose that is labeled with fluorine 18 (18F-FDG). 18F-FDG has been routinely used to identify regional glucose hypo- and hypermetabolism in human (Malmgren and Thom 2012) and in animal (Lee, Park et al. 2012) studies of epilepsy. A common feature of 18F-FDG PET in clinical studies is hypometabolism (Knowlton, Laxer et al. 2001; Knowlton, Abou-Khalil et al. 2002). A recent study reported that FDG PET was the most accurate for lateralization of seizure foci when compared to ictal SPECT or DWI (Pillai, Williams et al. 2012) which confirmed an earlier study using O-15 water PET imaging (Tatlidil, Xiong et al. 2000). Similarly, animal studies have reported hypometabolism in limbic structures including the hippocampus (Jupp, Williams et al. 2012). However, the decreased glucose metabolism was reported not to be a consequence of cell death or structural atrophy, but was rather thought to reflect ongoing cellular processes related to the development of epilepsy. However, other studies have concluded that the observed hypometabolism appears to be linked to decreased NAA as assessed by MRS (Lee, Park et al. 2012). While decreases in NAA would suggest neuronal loss, several studies have reported NAA decreases that normalized over time (Cendes, Andermann et al. 1997). Clearly, the use of non-invasive biomarkers, be they PET or MRS, are at times not entirely indicative of the underlying pathological and cellular processes that are a consequence of seizures.

Synthesis of novel tracers for PET has greatly aided diagnosis in numerous diseases including those related to epilepsy (la Fougere, Rominger et al. 2009; Jones and Rabiner 2012). The specificity and sensitivity of these tracers allows accurate and unequivocal localization, for example of dopamine receptors (Landvogt, Buchholz et al. 2010; Yakushev, Dupont et al. 2010). At the present time, there are no direct PET ligands for use clinically nor experimentally that can directly image glial cells, a void that is noted by Jones and Rabiner (Jones and Rabiner 2012). However, translocator protein (TSPO, and its former designation as 11C-PK-11195) are known to target microglial cells (Chauveau, Boutin et al. 2008; Dedeurwaerdere, Callaghan et al. 2012). A recent publication elegantly demonstrates that reactive astrocytes can also express TSPO and can be imaged using 18F and 11C PET

analogs (Lavisse, Guillermier et al. 2012). However, the relative amounts of TSPO expressed by reactive microglia or astrocytes is not well known, so caution must be used in interpreting these novel TSPO PET results.

It is clear that new and more specific glial ligands are needed for PET imaging to succeed as a biomarker for glial cells. The advent of additional radioligands targeting glial cells will aid in elucidating the role of these cells in the diagnosis and disease progression of epilepsy. Only then, can the recent advances of combining both PET and MRI scanners come to the fore to significantly aid in accurate and timely diagnosis of altered brain function, either as a consequence of long-term seizure activity or in cases of new epilepsy onset (Vargas, Becker et al. 2012). Clinically, repeated radioactive ligand imaging to study the time course of injury is less attractive, particularly in children. Other molecular imaging modalities, such as single photon emission computed tomography (SPECT) (Horky and Treves 2011; Jayalakshmi, Sudhakar et al. 2011) are able to directly image brain perfusion either ictally or interictally, but not glial cells. However, experimentally, research efforts are focused on using TSPO attached to 123I ([123I]-CLINDE) for SPECT imaging (Mattner, Bandin et al. 2011).

Conclusion

The use of neuroimaging to aid in the diagnosis and treatment of epilepsy has made great strides over the last several decades. While EEG remains the primary diagnostic tool, assessment by MRI using volumetric and T2 relaxometry analysis of limbic structures is now routinely used for epilepsy. PET and SPECT provide additional diagnostic tools to confirm MR observable changes or in the cases where no alterations are found on MRI. High resolution MR spectroscopy at the present time appears to have the greatest sensitivity in monitoring progressive gliosis which can be subsequently confirmed on DWI.

Imaging has become a corner stone for the diagnosis of epilepsy and as a tool for identifying surgical candidates. However, an important consideration for the success of any imaging modality is that can be used to detect ongoing alterations within the brain, particularly during the early acute stages. Thus, early imaging (MRI, PET or SPECT) that is sensitive to physiological alterations that ensue from seizures would be extremely important and potentially could provide the basis for early therapeutic intervention. As such, our own work and that of others in using MR signatures within hours of seizure onset are crucial for advancing treatment options, irrespective of glial cell contributions to seizures.

In the future as tailored radioligands become available for PET imaging, molecular imaging of glial cells will be able shed some light on their role in epilepsy. Thus, while there are no conclusive or specific imaging markers for glial cells, advances in MRI and PET continue to make inroads for the diagnosis, assessment of therapeutics and treatment of epilepsy and its associated syndromes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Volumetric and T2 MRI can identify structural alterations following epilepsy
- MRS shows significant promise in imaging glial changes in the epileptic brain
- PET/SPECT imaging using translocator protein (TSPO) radioligands are promising
- No single imaging modality can unequivocally identify glial cells within the brain

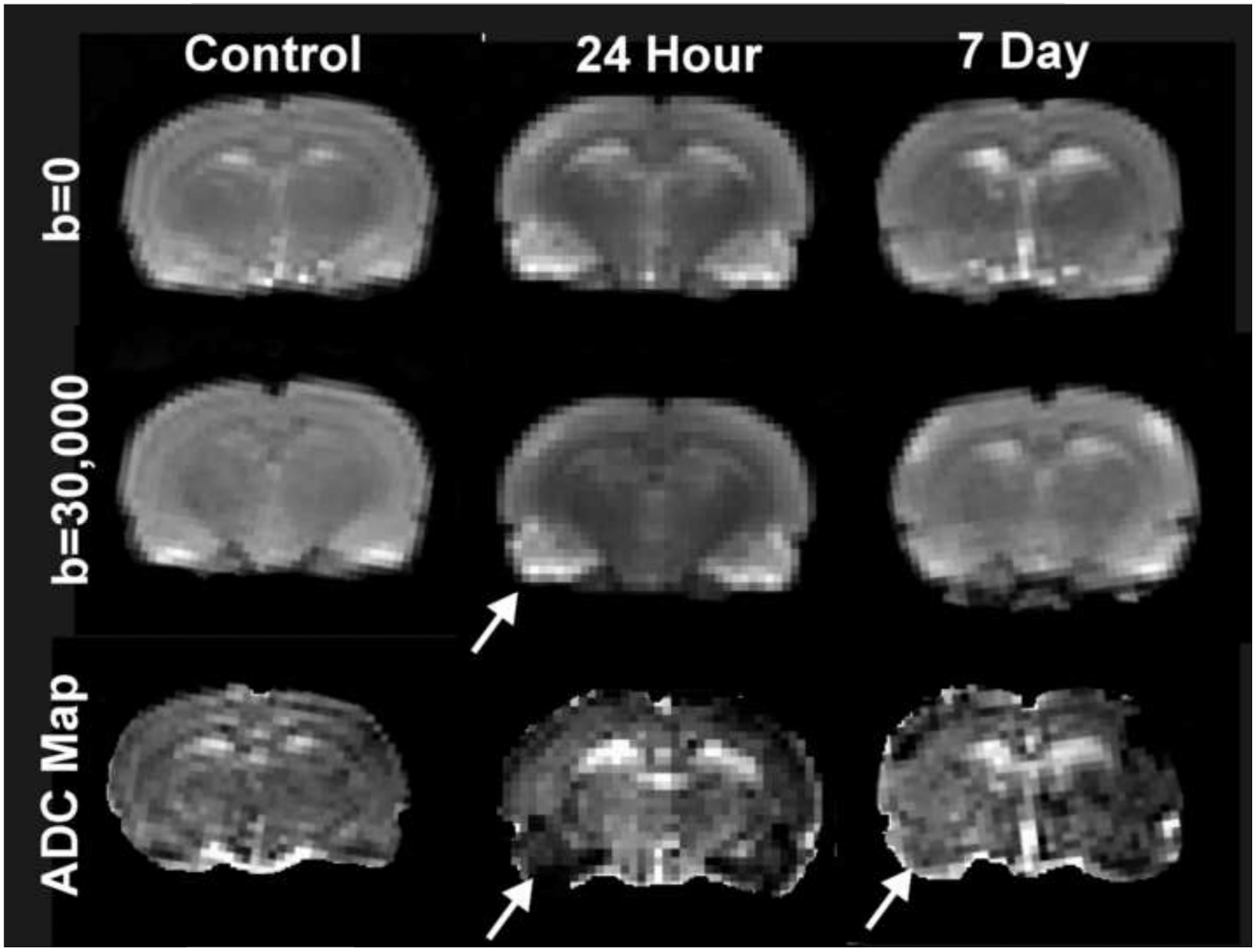

Figure 1.

Diffusion weighted imaging (DWI) maps spatial and temporal evolution of injury following pilocarpine induced seizures. The piriform cortex and amygdala reveal increased signal intensities at 12 and 24hr post status epilepticus that then returns to control levels by 7 days. Apparent diffusion coefficient maps (ADC) were generated from unweighted (b = 0, predominately T2) and weighted (b= 30000 s/cm^2) images. Note the increased signal intensity in the piriform cortex (arrows) and their corresponding hypointensities are seen on the ADC maps. In addition, pseudo-normalization of the ADC occurs within the piriform cortex (arrow) at 7 days post status epilepticus. (Data acquired on a 1.5T clinical scanner with a surface coil)

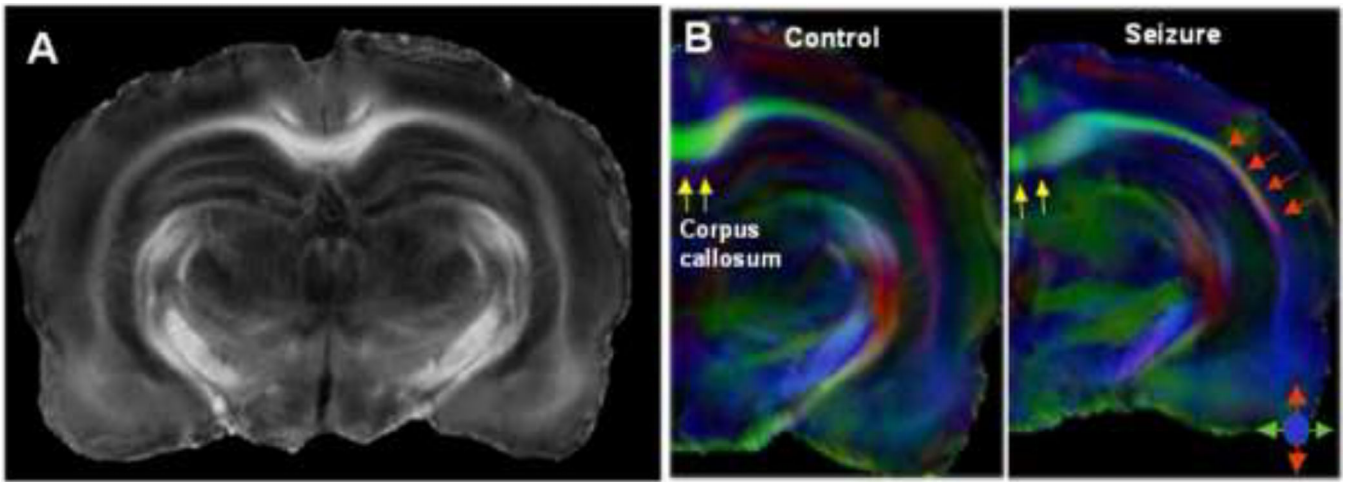

Figure 2.

Diffusion tensor imaging 30 days after febrile seizures reveals altered white matter structures. A) Relative anisotropy maps can be used to visualize and extract quantative data from a multitude of anatomical regions. B) Pseudo-colored relative anisotropy images illustrate the alterations within the corpus callosum of a rat following febrile seizures (yellow and red arrows). Other tissue level alterations are also observable (i.e. thalamus). (Data were acquired at 11.7T using a volumetric coil).

Table 1

Diagnostic modalities for epilepsy

Modality	Pros	Cons	Image glial cells
Electroencephalogram (EEG)	Non-invasive Easy and quick application Excellent sensitivity Ability to do continuous long-term monitoring	Low spatial resolution Quantitative analysis is difficult	No
Magnetic Resonance Imaging	Excellent anatomical resolution Multimodal imaging modalities (MRS, DTI etc)	Expensive High magnetic field	Yes, with MRS and potentially q-space
Single Photon Emission CT (SPECT)	Excellent for ictal events	Poor anatomical localization	Yes with TSPO ligands*
Positron Emission Tomography (PET)	High sensitivity & specificity Development of targeted radioligands	Requires synthesis laboratory for novel radioligands Requires a cyclotron	Yes with TSPO ligands**

* 123I radioligands

** −11C, 18F radioligands