Chapter 12
Magnetic Resonance Spectroscopy in Epilepsy

Jullie W. Pan

Abstract This review discusses the utilization of MR spectroscopy and spectroscopic imaging for epilepsy from a clinical localization and research perspective. As a relatively common neurological problem that affects the entire age range, the understanding and management of epilepsy has benefited substantially from the recent past improvements in anatomical MRI quality and resolution. With multiple facets of epilepsy dysfunction identified metabolically and neurophysiologically, the sensitivity of metabolic and functional MR imaging to such processes suggest that continued MR development can be important as well. Metabolically and spectroscopically, much of the challenge for the most common type of clinical epilepsy (localization related) is the sizable interpatient variability for both location of abnormality and severity of injury as well as the need to adequately evaluate the neocortical ribbon. These factors combine to place emphasis on developments at high field for SNR and voxel size, acceleration, and adequate lipid suppression. From a basic science perspective, substantial work has shown that metabolic and cellular changes are well detected by MRS early and late in the process of epileptogenesis, consistent with major shifts in neuronal and astrocytic processes. Thus, the role of MR spectroscopy has much room to progress for clinical and research applications in epilepsy.

Keywords Localization-related epilepsy • Primary generalized epilepsy • Medial temporal lobe • Bioenergetics • Glial/neuronal unit • GABA • Glutamate

Epilepsy: The Role for MR Spectroscopy in the Clinic and the Bench

Epilepsy is a chronic neurological disorder characterized by spontaneous recurrent seizures. It has a prevalence of about 6–7/1000 people, varying between 0.5 and 0.8 % in developed countries to less affluent countries, respectively [1, 2]

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Jallon P, 1997. Multiple types of epilepsy exist, and in its more common form of "localization related" or focal epilepsy, seizures are typically believed to arise from a discrete cerebral location. This nomenclature is used to distinguish it from "primary generalized epilepsy," which is substantially less common than focal epilepsy (15–20 % of all the epilepsies), [2]. In primary generalized epilepsy, the seizures are not thought to arise from any specific brain region and can instead appear to involve the entire brain simultaneously. However, it should be noted that many focal onset seizures can evolve into what appears to be a generalized seizure. In focal epilepsy, the transient behavior that is seen in a seizure is variable between patients, depending on the location of seizure onset, e.g., a momentary lapse of attention, staring to whole body convulsive events. Importantly, the region of seizure onset is believed to be at, adjacent or linked to a direct site of brain dysfunction or injury. Through this region, the brain's electrical activity is abnormal, and the overt rapid appearance of the seizure results from propagation of abnormal electrical activity through the brain.

While the majority of patients with epilepsy can be managed with medications, ~35 % of patients find that medications are insufficient for seizure control [2, 3]. In these medically intractable cases, many studies have shown that if the region of seizure onset can be identified, surgical resection of that region can be highly effective to treat and possibly cure the epilepsy. One of the most common types of focal epilepsy that is readily identified as such is medial temporal lobe epilepsy, MTLE. MTLE has a characteristic seizure semiology and with improvements in high field (3 T) structural imaging, is generally well identified with T1-weighted and FLAIR imaging, especially as it is also anatomically restricted to the regions of the hippocampi and amygdala. Success of temporal lobe epilepsy surgery is excellent, at approximately ~66 % with a range of 50–85 % seizure freedom at 2 years follow-up [6, 7].

Thus, as MTLE is relatively straightforward to identify and has an outstanding response to surgery, the belief is that other localization-related epilepsies may or should be similarly responsive. Data have supported this view (e.g., Hauptman and Mathern [8] with focal cortical dysplasias); however, in non-MTLE or extratemporal epilepsy, structural imaging can be commonly negative or ambiguous for identification of seizure onset. With careful clinical description of seizure behavior, the lobe or region of seizure onset can generally be hypothesized; however, extensive testing is still required for adequate surgical planning. Multiple imaging methods are used to attempt to identify the region of greatest cerebral "irritability," now commonly including FDG-PET, magnetoencephalography (MEG), SPECT, and MR spectroscopy. For this goal, our group and others have suggested that MRSI can provide pertinent data. While this role is clearest on the major question of clinical localization, it should be noted that other spectroscopic measurements such as GABA and glutamate are also of obvious interest for human epilepsy research.

From a basic science perspective, metabolic dysfunction has been continually considered in the evaluation of epilepsy, seizures, and epileptogenesis. A seizure, defined as that acute process of aberrant cerebral electrical propagation, has long

been known to be an energetically demanding event (e.g., [9] and earlier). The fact that the ketogenic diet, which shifts the brain from its normally preferred fuel of glucose to ketone bodies, can strongly affect seizure frequency and severity, has been a very compelling basis to better understand the interaction between metabolic function and seizures. It is therefore not surprising that MR spectroscopy is of particular interest for basic science studies of epilepsy. This is exemplified by early animal model studies, e.g., [10–12], finding that seizures induce specific changes in lactate, NAA, myo-inositol, and also possibly in high energy phosphates.

In studying the development of epilepsy, it is important to recall that from both human and animal model experience, the pathophysiology of most focal epilepsy is initiated by a cerebral insult (e.g., the fairly common event of fever-induced or febrile seizures, head trauma or infection), followed by a latent period that precedes the onset of overt spontaneous recurrent seizures, i.e., epilepsy. Given several clinical studies (e.g., [13]) that have shown that treating the immediate seizure or status epilepticus (i.e., a prolonged seizure, occasionally less responsive to medications) does not necessarily prevent the subsequent development of epilepsy, it is clear that epileptogenesis is not identical to ictogenesis, i.e., the process that leads to spontaneous recurrent seizures is not the same as the acute process that leads to the occurrence of any given seizure. Thus in animal models, much interest is focused on epileptogenesis, hypothesized to occur during the latent period between insult to recurrent seizures. Several physiologic and pathophysiologic processes have been identified, including development of novel aberrant circuits (e.g., mossy fiber sprouting), abnormal neuroregeneration, GABA receptor shifts, inflammation, glial dysfunction and mitochondrial injury (for review, see [14, 15]), or a combination therein. Given the brain's obvious complexity, its endogenous regulation and the variety of insults that can all result in epilepsy, the response to a major injury of this kind may very well be multifactorial, exhibiting several of these pathophysiologic processes. From an imaging and spectroscopic perspective, there is interest in studying the process from a metabolic dysfunction viewpoint, although it is clear that identification of an imaging biomarker that characterizes this process is also of obvious importance.

Thus overall, the role of MR spectroscopy in epilepsy has at least two major aspects. First, several groups [16–20] have suggested that MR spectroscopic imaging can contribute toward the challenging problem for localization of regions of brain dysfunction, i.e., identify possible regions of seizure onset. It is also clear that in human research, measurements of GABA, glutamate may provide similar localization information and/or clarify the nature of seizure control or drug effect. Second, from a basic science view, evaluating the role and consistency of MR detectable dysfunction in epileptogenesis may also be of major importance [21, 22]. Not only might it better define the metabolic distortions in epileptogenesis, it and other MRI methods of early detection of epileptogenesis [23] may be especially useful given the recent developments of novel neuroprotective therapies that target epileptogenesis. For both of these avenues, an interdisciplinary approach is needed, given that the scientific, clinical, and imaging aspects of the problem are still evolving.

Epilepsy as a Neurodegenerative Disorder

Before further discussion on MR spectroscopic imaging in epilepsy, it should be stated that the classification of epilepsy as a neurodegenerative disorder, characterized by progressive neuronal death commonly linked with mitochondrial dysfunction, can be debated. To address this, two factors may be considered. First, as stated earlier, mitochondrial dysfunction with its attendant abnormalities in calcium handling and free radical oxygen species generation (for review, [24]) is hypothesized as a contributing factor in epileptogenesis which with its key function for cellular bioenergetics has been strongly implicated in a self-sustaining cycle that can propagate into progressive injury. While a single brief seizure itself is not strongly associated with neuronal death (for review, [25]), recurrent and severe seizures (e.g., status epilepticus) are. Thus, even during the latent period before onset of spontaneous recurrent seizures, clinical experience and many animal models of epilepsy require a sustained period or multiple episodes of seizures or status to initiate the process of epileptogenesis. Second, it is clear that under conditions of mitochondrial disease such as Leigh syndrome, MELAS, MERRF, epilepsy is commonly a key phenotype, implying that epilepsy and recurrent seizures can be considered a symptom of mitochondrial dysfunction.

Thus, in either the development of epilepsy or the recurrent seizure condition, neuronal injury is present. Given that many clinical research and animal studies have shown there to be a strong correlation between seizure frequency and several pertinent indices, e.g., subsequent seizure control [26] and cognitive performance [27, 28], these data suggest that the injury from continuing seizures has broad impact, for both the epilepsy and brain function itself. As a result, approaches that can evaluate and quantify such degenerative injury remain of significant interest.

What Can Be Evaluated

In this chapter, we review the state of the art for MR spectroscopy in epilepsy. We stay with ^{1}H MR spectroscopy, as the availability of X-nucleus channels is generally limited with many human spectrometers. It should already be apparent that with the detection sensitivity of MR spectroscopy being in the range of 1–10 mM of small molecules, this means that the compounds of interest are most frequently components of metabolic pathways. Given the hypothesized dysfunction of neuronal, astrocytic, and mitochondrial associated injury in epilepsy [21, 29, 30], the interest in the MR spectroscopic evaluation of epilepsy is logical.

The most commonly studied ^{1}H spectroscopic compounds in MRSI are *N*-acetyl aspartate (NAA), creatine, myo-inositol, glutamate, glutamine, and GABA. As stated in earlier chapters, NAA is synthesized only in neuronal mitochondria [31, 32] and is strongly correlated with oxidative metabolism [33–35]. As a result, many studies of a variety of brain disorders have found NAA to be an informative

measure of neuronal function. Creatine, as a key component of phosphocreatine, is highly useful as a normalization factor for many bioenergetic parameters, being consistent over a cross section of species and within a given tissue type, as discussed by Connett [36]. While found in both neurons and astrocytes, the highest concentration of creatine is in astrocytes and thus when considering an integrated unit of neuronal function, many groups have used the ratio of NAA/Cr as a normalized parameter. We characterize NAA/Cr as reflecting the bioenergetics of the glial/neuronal unit ("bGNU"), finding it to be very informative for identifying regions of energetic and neuronal dysfunction [37–39].

The comparison between MRSI and 18-fluoro-deoxyglucose-PET (FDG-PET) is inevitable, and while these are clearly complementary measurements, it is worthwhile considering some of the pertinent differences and similarities. FDG-PET evaluates total glucose consumption and has been long used to measure differences in glucose consumption in varying tissue types (FDG uptake in gray matter is approximately 3× that of white matter [40]) and with various states of activation. The amount of uptake reflects the amount of tissue present in the voxel of interest, and thus decreases in uptake can result from both decreased cerebral consumption and/or tissue atrophy (with potential for distortion of white and gray matter contributions). There is commonly variation in voxel size or point spread function with location in PET, but given improvements with human high resolution research tomograph (HRRT) cameras, the voxel resolution has improved to better than 2–3 mm in-plane resolution [41]. For application to epilepsy, the success rate of FDG-PET in identifying the region of seizure onset very much depends on the population studied with the best localization rates of ∼80–90 % in temporal lobe epilepsy, although it is probably less successful in the nonlesional neocortical epilepsy patients (for review, [6, 42, 43]). This lesser success rate reflects the challenge in neocortical epilepsy, with the region of seizure onset commonly much less well defined, with variations in propagation paths and volume of injury.

In MRSI, the use of the NAA/Cr ratio largely eliminates the sensitivity of the parameter to tissue volume due to minimal NAA and Cr in the CSF; however, there is sensitivity to tissue type (gray, white matter), with the majority of workers finding that NAA/Cr is smaller in gray than in white matter (reflecting primarily a higher creatine concentration in gray [44–46]). With most sampling strategies, the sampling volume of MRSI is regionally constant, and for practicable time limits of study, are typically 0.64–2 cc. Thus in epilepsy, where tissue atrophy can be variably gross or subtle, the ability of MRSI to detect dysfunction using the bGNU with tissue type correction is potentially excellent as it does not require use of asymmetry indices and is relatively independent of tissue atrophy.

MRSI of Medial Temporal Lobe Epilepsy

Studies initially performed in the 90s established the ability of ^{1}H-MRS to lateralize the seizure focus in temporal lobes and to test the validity of MRSI to already established methods of localization, using video-EEG as gold standard as well as MRI-volumetry (MRIV), FDG-PET, and SPECT. Hugg et al. [47] initially demonstrated a significant asymmetry of NAA left/right metabolite ratios and further studies have demonstrated comparable results, e.g., Cendes et al. [48] and Kuzniecky et al. [49] in larger patient groups. In addition, ^{1}H-MRS was also sensitive in detecting bilateral dysfunction. The degree of asymmetry in NAA/Cr ratios correlated with the degree of one sidedness of EEG abnormalities. These results support the fact that ^{1}H-MRS is a valid method even in bilateral cases presenting a high concordance to the degree of bilateral EEG findings in patients with TLE. Our recent data [50–52] in temporal lobe epilepsy has demonstrated that the decrements in NAA are not just localized to the ipsilateral hippocampus, but consistent with existing PET studies, are also found in a network of involved limbic and subcortical nuclei.

Such studies, pertinent for seizure localization, have also been integrated with physiological research studies of epilepsy. For example from animal studies of mitochondrial dysfunction, it has been known that mild to moderate oxidative stress can also cause major abnormalities in GABA (and glutamate). Saransaari and Oja [53] studied the mouse hippocampus with variable levels of peroxide stress to show increases in basal GABA release, ranging from 30 to more than 550 %. These observations are of particular interest for epilepsy where GABA is thought to be a key component underlying the abnormal hyperexcitability. Given this and the known high energetic cost of neurotransmission and synaptic activity [54], we anticipated that GABA neurotransmission and metabolic function might be correlated, certainly in the seizure onset zone. This may be especially important given the recent in vitro work that has suggested GABA function may be either anti- or proconvulsant [55, 56]. This was evaluated in human epilepsy patients undergoing intracranial EEG and microdialysis analysis. Their microdialysis measurements of extracellular GABA (ecGABA) were compared to preoperative measures of the bGNU or NAA/Cr. All data from this study were acquired from the hippocampus, including patients with either hippocampal epilepsy or nonhippocampal (neocortical) epilepsy. Figure 12.1 shows the correlations from this study, finding very strong correlations between ecGABA and NAA/Cr. In the MTLE patients, ecGABA strongly negatively correlated with decreasing NAA/Cr, $R = -0.94$, $p < 0.001$ (Fig. 12.1) and implies that ecGABA and mitochondrial function are largely representing parallel processes, and appears consistent with the conclusions from Saransaari and Oja [53], and Woo et al. [56]. In contrast, with the neocortical epilepsy patients (and outside of the seizure onset zone), the relationship between ecGABA and NAA/Cr is also significant but positive with $R = +0.70$, $p < 0.015$. In these neocortical patients, the hippocampus being studied was ipsilateral to the cortical seizure onset region and thus may be a site of proximal propagation.

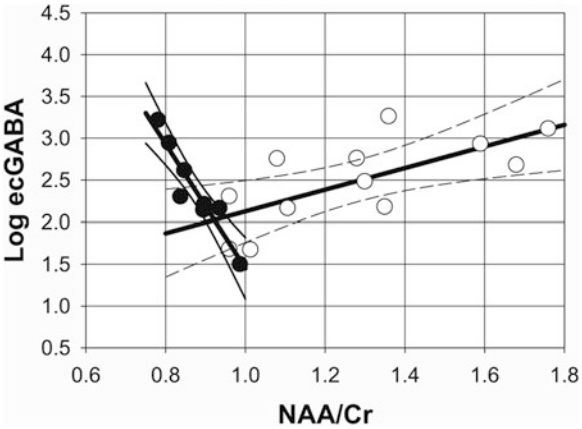

Fig. 12.1 Interictal extracellular GABA (ecGABA) levels are measured by quantitative zero flow microdialysis, which estimates the true basal concentrations of extracellular fluid neurochemicals such as glutamate, glutamine, and GABA [57]. *Closed circles* from hippocampal epilepsy patients; *open circles* from nonhippocampal (neocortical) epilepsy patients

Nonetheless, as it is not the seizure focus, these data remain conceptually similar to the results of Petroff et al. [58], who found that well outside the seizure focus (studying the occipital lobe), patients with better seizure control have higher tissue GABA levels.

While these data cannot specify which or several of these injurious processes may be ongoing in the seizure onset zone, it is evident that the relationship of ecGABA with NAA/Cr within the ipsilateral hippocampus is distinctive in comparison to ecGABA correlations in the non-MTLE group. It is notable that these two groups are largely separated by the NAA/Cr measurement, given that the dynamic range of ecGABA is similar. This suggests in the healthier (non-MTLE) vs. the diseased (MTLE) hippocampus, there is a real change in the function of ecGABA, e.g., potentially proconvulsant as suggested by Woo et al. [56].

Neocortical Epilepsy

The localization of extra-temporal and neocortical epilepsies is commonly much more challenging than solely temporal and medial temporal lobe epilepsy, much in part due to given the large volume of neocortex that has potential for seizure onset, which can be MRI negative or MRI ambiguous. Furthermore, there is also the potential for variable propagation paths and variation between different subjects for volume of seizure onset. Nonetheless, given that the success of surgery is high with accurate identification of seizure onset zone [6, 43, 59, 60], additional information that can help guide the localization process is desirable. As now routinely performed between neurosurgery and neurology, intracranial EEG monitoring is

used to more accurately localize seizure onset; however, it is clear that positioning of electrodes is a critical step. If electrodes do not adequately sample the seizure onset zone, the likelihood for success for seizure localization is low.

Thus, it is obvious that for such challenging cases, there is a potential strong role for spectroscopic imaging to assist in the identification of candidate regions of seizure onset. As discussed earlier, the high sensitivity of the bGNU measure is a robust parameter to develop for this target. However starting from the relative success in studies of medial temporal lobe epilepsy, the required jump to neocortical epilepsy poses a major technologic challenge. The challenges include a commonly large target region that varies between different patients, thus requiring extended volume coverage. For example, temporal lobe (with its functions for memory and learning) seizure onset is a very common site for epilepsy (>50 % of all cases), but even so, is frequently not well distinguished from frontal lobe onset. The size of the seizure onset zone is variable and unknown as to the requisite voxel size of MRSI measurement, implying that to maintain adequate SNR, studies may use larger voxel sizes that can then dilute the metabolic abnormality. The requirement to visualize the cortical ribbon imposes a need for outstanding extracerebral lipid suppression which can be difficult for large volume spectroscopic imaging. While overall, epilepsy patients span the entire age range and are a highly cooperative patient group, very lengthy acquisition times commonly considered for spectroscopic imaging studies are intrinsically difficult. In spite of these many significant challenges, there have been a few groups that have targeted work in large volume spectroscopic imaging for epilepsy [17–19, 61, 62]. Maudsley et al. [17] developed whole brain echo-planar spectroscopic imaging in epilepsy at 3 T, achieving study durations of 25 min, FOV $280 \times 280 \times 180$ with a final sampling matrix of $50 \times 50 \times 18$, giving 70 ± 6 % coverage of the whole brain. The approach uses a moderate echo (TE 70 ms), global inversion recovery for lipid suppression (TI 198 ms) supplemented with a *k*-space extrapolation based on a scalp mask to reduce lipid ringing artifact. However after filtering the data based on spectral quality (<13 Hz linewidth), much of the entire temporal and inferior frontal lobes is excluded, explained as resulting from the well-known problems in field homogeneity with consequent difficulties for linewidth and spectral quality. This report on $n = 14$ patients concluded that the MRSI was helpful although varied substantially between patients, with detected dysfunction found in 7/14 subjects, the other 7 subjects with inconclusive findings. A figure from Maudsley et al. [17] is reshown here (Fig. 12.2) and shows the spectral variations in the temporal and parietal lobes.

Whether the 50 % detection result is due to the variability in patient severity of bGNU abnormality or sensitivity of the study is unknown. However, it is known that more than 50 % of surgical epilepsy patients have their seizure onset in the temporal lobe, with either initiation from or propagation into the medial temporal region and thus methods need to be able to consistently evaluate this region. This challenge is still present even at 1.5 T where the residual inhomogeneity is less; however, as reported by Mueller et al. [61], there can be problematic spectra in up to 50 % of all pixels in the temporal region.

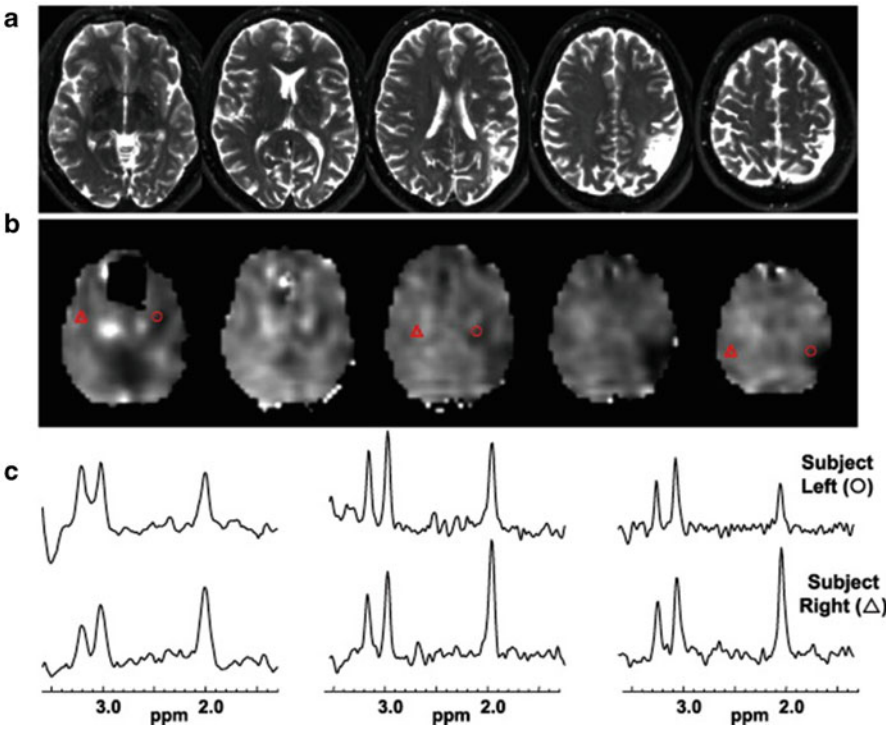

Fig. 12.2 From Maudsley et al. [17]. Results for subject 17 that exhibits a clearly defined left parietal lesion seen on the T2-weighted MRI (**a**) and by decreased NAA/Cr (**b**). Spectra selected from contralateral anatomical locations indicated by the *triangle* (subject right) and *circle* (subject left) symbols are shown in (**c**) for the *left*, *middle*, and *rightmost slices* shown

With the demonstrated improvement of SNR available at 7 T and the uncertainty on the severity of metabolic dysfunction in epilepsy, our group has developed 7 T MRSI for neocortical epilepsy. This initial work, performed to establish the methodology and to assess the range of severity of dysfunction, performed targeted whole slice MRSI studies from regions determined with available clinical information. The extent of overlap between the NAA/Cr abnormality with surgical resection (none, partial, or complete) was compared with patient outcome (International League Against Epilepsy (ILAE) classification dichotomized to I–III and IV–VI). These studies used TE/TR 40 ms/1.5 s and single slice acquisitions (acquisition time 14 min/slice), with high degree and order (3rd and 4th) B_0 shimming to accommodate large volumes of study as well as B_1 RF shimming to overcome known problems with B_1 inhomogeneity and amplitude present at 7 T [63, 64]. Figure 12.3a shows data from a patient with neocortical epilepsy with a history of meningitis who had unilateral (left) intracranial EEG coverage based on semiology. The resulting resection surgery included the L precuneus, which did overlap with the bGNU abnormality. Postoperatively this patient did well initially for 3 months

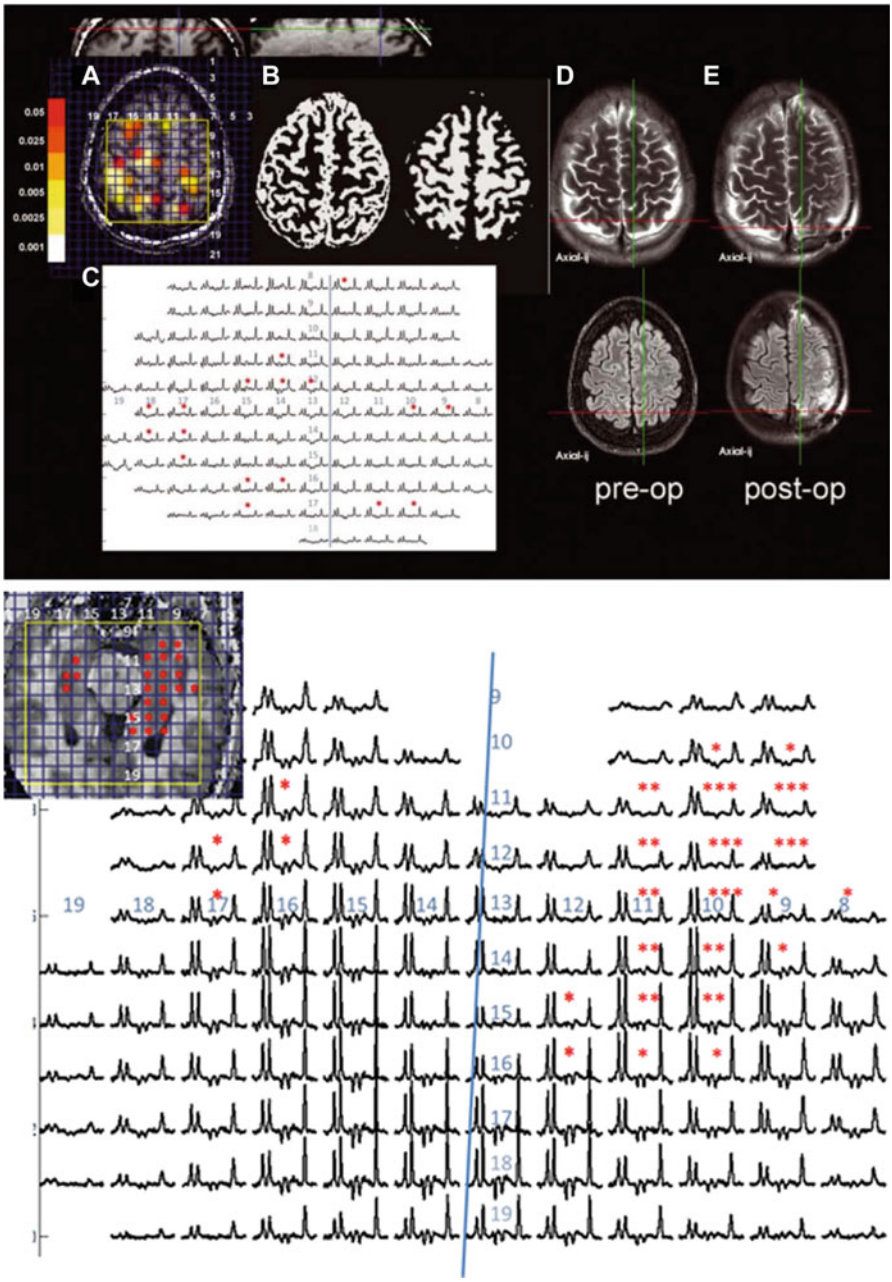

Fig. 12.3 (**a**) With permissions from Pan et al. [18, 19]. Data from a neocortical epilepsy patient: (*A*) scout with statistical overlay, (*B*) segmentation data showing gray and white matter masks, (*C*) spectra and (*D* and *E*) pre-op and post-op clinical imaging showing the area of resection in the precuneus. There are multiple areas of NAA/Cr abnormality seen in both hemispheres (shown with *stars*). (**b**) An MTLE patient who was MRI negative with a large extent of metabolic dysfunction over the left MTL greater than right MTL

but had an ILAE class IV outcome. Figure 12.3b shows temporal lobe data from a MTLE patient with a negative MRI, having had intractable epilepsy for a relatively short 3 years. These data were consistent with intracranial monitoring results, and as a group, all of the MTLE patients undergoing anterior temporal lobectomy resection had ILAE class I or II outcomes. In this initial group of 25 patients all of whom eventually underwent resective surgical treatment, we have assessed the coherence of the bGNU with resection region (i.e., did the region of resection overlap with metabolic abnormality or not) and eventual outcome. While it is clear that this is a small patient group, a Fisher's exact 3×2 contingency statistical test found that the concordance between MRSI and surgical resection was significantly related to good outcome, $p < 0.001$ [18, 19].

Thus, the question on whether the spectroscopic imaging of NAA/Cr has the adequate sensitivity to detect pertinent dysfunction in neocortical epilepsy seems promising. Nonetheless, it seems to be highly variable; in this short literature review, recent studies seem to range from ~50 % detection of abnormality [17] to higher rates of dysfunction detection [18, 19, 62]. In fact, as suggested by Mueller et al. [62], the widespread distribution of injury seen by MRSI in fact raises the possibility that the bGNU parameter could be too sensitive for seizure localization. As stated, at least part of this wide variability may be due to acquisition methodology; however, it is also clear that epilepsy patients can be highly variable. Depending on the nature of the epilepsy type (e.g., malformations, meningitis, traumatic, mesial temporal lobe, etc.) the extent and nature of metabolic aberrancy may be expected to differ. For example, as a group, malformations can be highly variable from both a structural imaging as well as etiologic view, some are subtly MRI detectable vs. those with multiple and large lesions, some are highly familial while others are most likely due to in utero insult. Large systematic MRSI studies of various epilepsy etiologies have not been done but an eight patient study [65] of several types of malformations (including polymicrogyria, dysplasias, heterotopia) found variable NAA/Cr abnormalities within and surrounding the lesion. Another cause for variability is the reasonably well-established view of epilepsy as a network disorder [50, 66] which could be expected to manifest in a distribution of injury that includes the propagation path(s) for the seizure. The practical relevance of this network is pertinent; e.g., propagated injury through the seizure network (which can be hypothesized as a deviant form of normal brain connectivity) is possibly a key basis for the relatively common presence of dual pathology, that condition in which medial temporal lobe epilepsy is identified in concert with a separate (typically ipsilateral) neocortical lesion. Thus, while not all abnormalities of the bGNU are necessarily epileptic, it is not surprising that a widespread distribution of abnormalities is seen and needs to be assessed individually in the context of the patient and their epilepsy. The data thus far have suggested that the identified abnormal NAA/Cr regions are informative and may be more viewed as candidate regions of seizure onset with additional study needed for their classification (e.g., seizure onset, multiple seizure onset vs. propagation vs. unrelated injury).

Measurements of GABA and Glutamate

Other important resonances identified for epilepsy include glutamate, GABA, myo-inositol, lactate, and glutamine. Glutamate and GABA, in particular, are important targets given their neurotransmission roles. However as coupled resonances, these compounds generally require more care in detection and analysis, either via short echo spectroscopy or through editing sequences. While short echo spectroscopy is a relatively successful approach, there are potential significant problems due to the variable macromolecule baseline that is present [67, 68]. Our group has targeted the detection of coupled resonances using a J-refocused coherence transfer (double echo) sequence that enables longer echo times, which minimizes the macromolecule baseline due to T2 decay and yet retains excellent sensitivity to coupled resonances. Figure 12.4a shows the performance of the coherence transfer sequence in comparison to a short echo acquisition and shows the elevated glutamine resonance in an epilepsy patient being treated with valproic

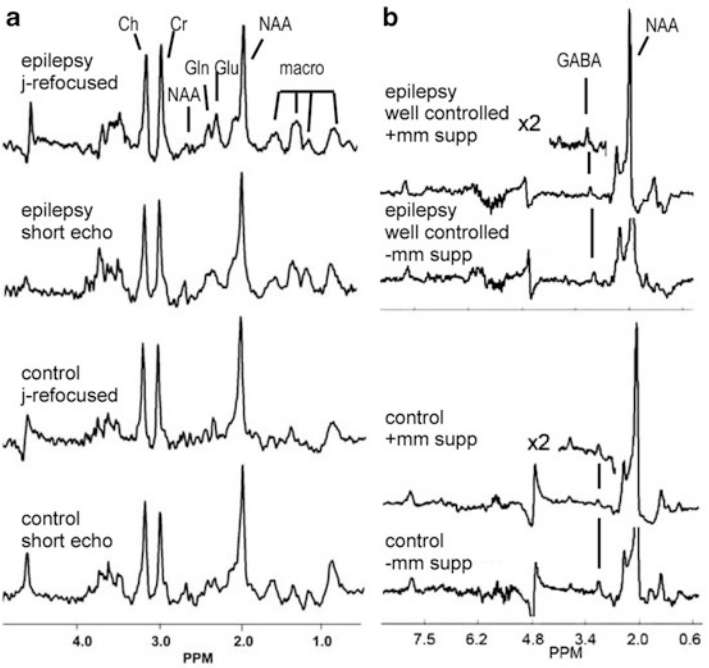

Fig. 12.4 (**a**) (*left*) J-refocused spectra from a control (*bottom*) and epilepsy patient on valproic acid (*top*). For both the control and patient, short echo and j-refocused spectra are shown. Key resonances are identified. The epilepsy patient shows a substantially increased glutamine resonance in comparison to control. (**b**)(*right*) GABA spectra from a control (*bottom*) and epilepsy patient whose seizures are well controlled (*top*). For both control and patient spectra, macromolecule (mm) suppressed and nonsuppressed spectra are shown. The epilepsy patient shows a substantially increased GABA resonance

acid. This glutamine change is consistent with the known hyperammonemia and hepatic changes that occur with use of valproic acid.

As the major inhibitory neurotransmitter, GABA detection is also of obvious interest for epilepsy. However, with its resonances obscured by many other metabolites (creatine 3.0 ppm, NAA 1.9 ppm, and amino acids 2.28 ppm) and relatively low concentrations of typically 0.8–2 mM, for optimal detection, a selection process such as spectral editing or a multiple quantum selection is preferred. Spectral editing has been used by several groups in epilepsy, such as Petroff et al. [58], finding that tissue GABA is increased in patients whose seizures are well controlled in comparison to poorly controlled patients. We have adapted the J-refocused approach to select for the C4 3.0 ppm resonance of GABA. Based on an initial inversion recovery suppression of the 3.0 ppm region, the coherence transfer sequence induces magnetization transfer from the C3 1.9 ppm to its coupled partner at C4 3.0 ppm. The GABA C4 3.0 ppm resonance is therefore detected without the overlapping creatine resonance. As a single shot acquisition (no scan-to-scan differencing needed) GABA is detected with an efficiency of ~50 %. As studied in the thalamus in a small epilepsy group (example spectra Fig. 12.4b), this study found that the thalamic GABA/Cr in well controlled, poorly controlled epilepsy patients vs. controls was 0.119 ± 0.013, 0.054 ± 0.013, and 0.071 ± 0.015, respectively [51, 52].

Animal Models of Epileptogenesis

MR spectroscopy has long been proposed to be useful to noninvasively evaluate the process of epileptogenesis [11, 12, 69]. The more recent work of Filibian et al. [21] used a pilocarpine rat model to study the process of epileptogenesis, using TE 10 ms PRESS and 16 μl voxel sizes in the hippocampus. This report found progressive increases in myo-inositol, glutathione with decreases in NAA in the immediate days after status epilepticus, most likely characterizing glial activation, edema, and neuronal injury (Fig. 12.5). In the chronic epileptic rat, similar findings were reported. It is clear that in this time course, many of the changes are metabolic, with comparatively less change seen in GABA and glutamate. This would be reasonably expected, given the known metabolic demands of seizures. However the NAA changes, interpreted as abnormalities in neuronal mitochondrial function, when taken in comparison with the myo-inositol changes, suggest a difference in the temporal response of neuronal vs. glial processes. This interesting study raises the question on what these changes may mean for epileptogenesis as a better understanding these early processes will suggest which cellular pools are most dynamic and may suggest avenues of approach and prediction for epileptogenesis. Given these well-established methods in animals, it will become more compelling to consider evaluating these metabolites in patients who are at risk for development of epilepsy.

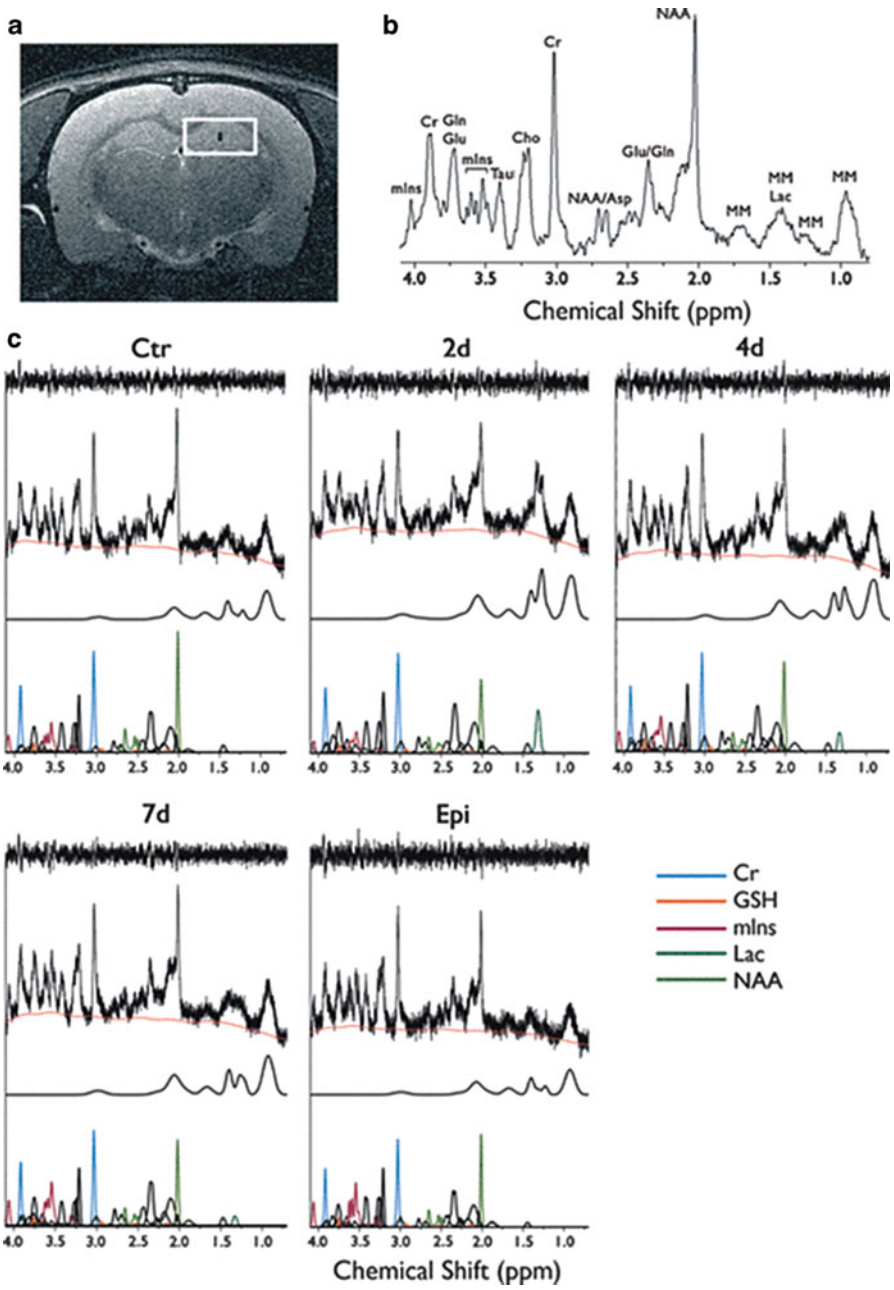

Fig. 12.5 From Filibian et al. [21]: ^{1}H spectra (7 T 16 μl single voxel TE10ms PRESS) from a pilocarpine rat model of epilepsy, showing progression of abnormalities. Fitted data from Panel (**c**): spectrum, macromolecule, fitted resonances (*top noise line* represents difference residual)

Conclusions: Imaging Challenges in Humans and Animals and Promises

Altogether, there are many aspects to the metabolic dysfunction seen in the brain injury of seizures and epilepsy that result from the close physiological relationship between brain function and metabolism. From a basic science view, it is clear that there are sizable metabolic shifts occurring early in the process of seizures and epileptogenesis. The changes seen by MR spectroscopy are consistent with dynamic glial and neuronal responses to seizure injury [11, 21]. This type of work opens an avenue toward defining and understanding the pathologic and pathophysiologic responses (e.g., the roles of NAA, myo-inositol, glutamine, and/or glutathione) to epileptogenic injury which may lead to a better understanding of the in vivo target for therapeutic intervention and to establish potential biomarkers for predicting the development of epilepsy.

From a human imaging perspective, the use of the MRSI measures for purposes of seizure localization in surgical planning remains an important question with both technological and clinical epilepsy aspects. While measurements of GABA, glutamate, and myo-inositol remain of high clinical interest for their roles in epilepsy toward neurotransmission and astrocytic function, consistent measurements of these require substantially more care because of their j-modulating signal and spectral overlap. With its robustness of acquisition and sensitivity to injury, the utility of NAA/Cr remains strong for its use for seizure localization. Given the variable nature of epilepsy, it is clear that spectroscopic imaging, rather than single voxel spectroscopy is necessary; that high SNR needs to be maintained; and finally, given that seizures are not thought to arise from white matter and subcortical nuclei, studies need to achieve excellent coverage of the cortical ribbon. These basic requirements make consistent human studies challenging.

Technologically, there has been variability on how such studies are being and will be performed, specifically with regards to field strength, hardware, pulse sequences, and analysis methods. The SNR at 7 T is clearly at least linearly better than 3 T; however whether the increased SNR is requisite for the singlet NAA/Cr measurements in comparison to the much more commonly available 3 T platform will depend on the severity and volume extent of metabolic dysfunction seen in epilepsy (e.g., it is possible that in some malformations, the volume extent of NAA/Cr decline may be very small). This needs to be balanced against the push to accelerate the acquisitions (e.g., $<$15 min) which if incurred at the sacrifice of SNR will make detection difficult and may ultimately come back and make the case for needing greater field strength. As discussed earlier [17, 70] and well known by MRS practitioners, at 7 T and even at 3 T, a major challenge facing consistent epilepsy MRSI is field homogeneity, with problems in the temporal lobe, inferior frontal, and lower brain regions. It should be noted however that the high degree and order shim inserts that have been developed for 7 T field homogeneity have immediate impact for 3 T, and at the present writing, developments are under way to implement additional shim hardware for 3 T. Nonetheless whether for 3 or 7 T,

the field distortions for the temporal region are substantially different from the frontal–parietal regions and thus ability to obtain true simultaneous and equivalent performance in temporal and frontal–parietal regions from whole brain acquisitions will be difficult. Finally, pulse sequence design and analysis approaches substantially depend on the above factors and local equipment, with many groups finding lipid suppression provided most robustly through inversion recovery and moderate echo times to reduce j-modulating coherences while maintaining sensitivity. Accelerated methods (e.g., EPSI, spiral, multiband SI) will depend on gradient, RF coil equipment, and experience; however, it is noted that acceleration performed at the cost of SNR is likely to reduce sensitivity of detection.

So the dilemma for epilepsy is therefore reasonably clear. As a disorder that can vary substantially between different patients, commonly requires clinical and imaging scrutiny over large portions of the brain, requires high performance imaging equipment and expertise for acquisition and analysis, MRSI for epilepsy is challenging. In comparison with other difficult neurological problems, many of these other conditions are more forgiving, e.g., the disorder is generally found in the same locus in all patients, does not require visualization in the cortical ribbon and/or caudal brain regions, and is not surgically quickly verifiable. Thus, at this writing MRSI is performed for epilepsy localization only in a handful of interested academic imaging centers. For the difficult problem of neocortical epilepsy, we have taken a positive position, that MRSI can be highly informative. However, we also recognize that typical for any complex multicomponent undertaking, MRSI is demanding in that each component needs to have a high rate of success. In all reality, whether or not MRSI can be implemented for broader use in epilepsy will depend on not just the above clinical and imaging requirements, but also multiple economic factors from within neurology, neurosurgery, and radiology.

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