Magnetic resonance spectroscopy (MRS) can detect in vivo cerebral metabolites non-invasively. Principles underlying MRS are basically the same as those of magnetic resonance imaging (MRI). The results of MRS measurement are always presented in terms of semi-quantitative ratios or quantitative intensities of metabolites. Technique differences, parameter inconsistency and regional variations will influence the spectral profiles and significantly change the results. Therefore, it is very important to keep the sequences and parameters used for spectral acquisition consistent in order to make the measurements reproducible and longitudinal studies comparable. The effects of different acquisition techniques and parameters must be considered when interpretation or comparison of MRS data is made.

In vivo MRS is increasingly used for clinical study in seizure patients, especially in those with temporal lobe epilepsy. Phosphorus MRS can detect the levels of high-energy phosphates in the brain, but has the disadvantages of low signal-to-noise ratio, poor spatial resolution and unavailability on clinical MR systems. Proton MRS can be performed together with MRI during the same examination session, providing biochemical data in addition to structural information. Reduced intensity of N-acetylaspartate on proton spectra is consistently identified in the mesial temporal lobe or hippocampus of patients with temporal lobe epilepsy, reflecting underlying neuronal loss or dysfunction. Pre-surgical lateralization, post-ictal metabolite changes, prediction of surgical outcome, post-treatment features, and differences between temporal and extra-temporal epilepsy are under intensive investigation using in vivo proton MRS. Despite being regarded as a research imaging modality for patient evaluation, proton MRS has the promising potential to be helpful in seizure management.

Key words: Brain, Epilepsy, Magnetic resonance spectroscopy

Because magnetic resonance spectroscopy (MRS) has the advantage to measure in vivo cerebral metabolites non-invasively, it has been increasingly used for epilepsy study over the last decade [1]. For example, phosphorus (\(^{31}\)P) MRS can detect the levels of adenosine triphosphate, phosphodiesters, phosphomonoesters, phosphocreatine, and inorganic phosphate in the brain and yield pH values [2]. Proton (\(^{1}\)H) MRS can detect N-acetylaspartate (NAA), choline-containing compounds (Cho), creatine-phosphocreatine (Cr), and lactate [2]. NAA is located primarily in the neurons, and reduction of NAA intensity or its ratio to other metabolites is a marker for neuronal loss or dysfunction [3]. Advanced proton MRS techniques can detect myo-inositol (a putative glial marker) and several neurotransmitters, such as glutamine/glutamate and gamma-aminobutyric acid (GABA) [2]. Due to its high magnetic sensitivity and easy incorporation into clinical MR systems, proton MRS is becoming the mainstream in the clinical field of epilepsy study [4].

Most neuro-imaging studies in seizure patients were focused on temporal lobe epilepsy, because surgical treatment can provide excellent outcome in many patients with medically intractable disease [5]. In addition to the physiological and anatomical information obtained by single photon emission computed tomography (SPECT), positron emission tomography (PET) and magnetic resonance imaging (MRI), in vivo cerebral biochemistry added by MRS is a promising parameter to evaluate the epileptic brain. Increased inorganic phosphate, elevated pH and reduced phosphomonoesters in temporal lobe epilepsy were found in several phosphorus MRS studies [6-9]. However, no difference in pH or phosphomonoesters between
Figure 1. Proton magnetic resonance spectroscopy of left hippocampal region in a normal 28-year-old woman. 

**a.** The proton spectrum was acquired from a 20 × 20 × 15 mm volume of interest, using single voxel spectroscopy, point-resolved spatial selection, and a long echo time (135 msec). 

**b.** There are 3 major peaks easily identified: N-acetylaspartate at 2.0 ppm, creatine-phosphocreatine at 3.0 ppm, and choline-containing compounds at 3.2 ppm.

Figure 2. Proton magnetic resonance spectroscopy of left hippocampal region in a normal 32-year-old man. 

**a.** Proton spectra were acquired from a 20 × 40 × 15 mm volume of interest (the rectangular area bounded by thick white lines), using chemical shift imaging technique, point-resolved spatial selection, and a long echo time (135 msec). 

**b.** There are 8 spectra obtained simultaneously during one measurement. Each voxel is 10 × 10 × 15 mm in size, carrying metabolite information of the corresponding anatomical region shown on the overlaid spectral map.
patients and controls was reported by others [10, 11]. Owing to small cohorts and conflicting results, the metabolite profiles in temporal lobe epilepsy detectable by in vivo phosphorus MRS remained elusive. On the other hand, decreased NAA intensity was consistently identified in the patients with temporal lobe epilepsy, using both in vivo and in vitro proton MRS [12-15]. Decreases in NAA intensity measured by in vivo proton MRS correlate with the severity of hippocampal sclerosis or mesial temporal sclerosis [16], which is responsible for a major proportion of temporal lobe epilepsy [17]. Pre-operative lateralization of the seizure focus is the main goal of MRS studies in temporal lobe epilepsy. Other research interests include MRS changes after surgical or medical treatment, relationship between pre-operative MRS findings and post-operative prognosis, association between MRS data and neuropsychological functions, and differentiation of temporal from extra-temporal epilepsy. This review article will first address mandatory issues that should be sincerely considered before applying in vivo proton MRS for epilepsy study, then summarize important proton MRS findings in temporal lobe epilepsy, and finally describe briefly the MRS differences between temporal lobe epilepsy and other type of seizures.

TECHNICAL CONSIDERATIONS

There are basically two different techniques for spatial encoding in MRS measurements: single-voxel spectroscopy (SVS) and chemical shift imaging (CSI), also known as magnetic resonance spectroscopic imaging (MRSI) [18, 19]. Generally speaking, SVS has the advantages of more explicit spatial localization, more homogeneous shimming, better water suppression, and shorter operation time as compared with CSI; but only one spectrum can be obtained from one data acquisition. On the other hand, CSI can obtain spectra from multiple voxels of about 1 ml in size during one measurement; but field inhomogeneity, voxel contamination, and sophisticated post-processing procedures are the main disadvantages of CSI technique. Proton MRS studies in temporal lobe epilepsy using either SVS or CSI revealed consistent and promising results. Because CSI allows multivoxel acquisition and metabolic image display, and user-friendly hardware and software are now available, there is an increasing number of epilepsy studies using CSI technique.

There are two pulse sequences commonly used for MRS measurements: point-resolved spatial selection (PRESS) and stimulated echo acquisition modes (STEAM) [20, 21]. PRESS has higher signal-to-noise ratio than STEAM at the same echo time (TE), and is preferred at long TEs. The signal-to-noise ratio somewhat reduces at long TE but peaks of NAA, Cho, Cr, and lactate can be easily detected without overlapping with short-T2 biochemicals. Contrarily, STEAM allows short TE (20-30 msec) to be used and can detect signals from lipids, myo-inositol, glutamine/glutamate, and GABA. However, signal overlaps of these short-T2 metabolites cause interpretation and quantification more difficult. For obtaining adequate spectral resolution and accurate peak integration, it is reasonable to use PRESS technique with a long TE (135 or 270 msec) for in vivo proton MRS studies in temporal lobe epilepsy, especially when conducted on a clinical 1.5-tesla MR scanner.

There is a tremendous difference in the relative concentrations between cerebral metabolites and water. The high intensity of water needs to be suppressed before the other metabolites can be seen on the spectra [22]. In addition to an optimized suppression of water signals, repeated acquisitions are necessary to improve the relatively low signal-to-noise ratios of cerebral metabolites. Consequently, the time necessary for a single proton MRS measurement on a 1.5-tesla scanner is always longer than conventional MRI. Therefore, patient cooperation and immobilization are essential for a successful MRS study. Furthermore, measurement sequence, parameters, and the volume of interest are also important for data collection. Results of CSI and SVS are significantly different even acquired from the same region of anterior temporal lobe [23]. The size of volume of interest also has significant contribution to the variation of metabolite ratios, either measured by SVS [24] or CSI [23]; most likely due to partial volume effects and various field inhomogeneity. Additionally, there is regional variation of metabolite ratios between anterior and posterior hippocampal regions [23, 25]. Accordingly, application of consistent acquisition technique, pulse sequence, and measurement parameters should never be over-emphasized while applying proton MRS for epilepsy study.

The last, but never the least, important thing to be addressed is that there are various criteria used for identification of metabolite abnormalities or definition of lateralization. Either a single threshold value [26-28], an asymmetric index [29, 30], or their combination [31, 32] has been used in different studies. For each method, whether the lowest normal value or the mean value minus 1 or 2 standard deviations should be selected as the threshold value is still an open question. Refining the methods for identification and local-
Lateralization of seizure focus using MRS

Promising seizure control and cure of the disease can be obtained via surgical treatment in patients with intractable temporal lobe epilepsy [5]; consequently, pre-operative lateralization of epileptogenic focus is the major goal of many clinical MRS studies. Compared with the control group, reduction in NAA intensity or ratios between NAA and other metabolites in the temporal lobe was consistently identified using SVS [13, 35-37] or CSI [32, 38-41]. Correlation between NAA reduction and disease duration or inter-ictal spike frequency was noted [42, 43]. Pre-operative lateralization of seizure focus using proton MRS has been under intensive investigation using different parameters, including quantitative metabolite intensities [30], semi-quantitative metabolite ratios [27-29, 31, 32, 44] and qualitative visual inspection of spectral imaging [45, 46]. According to the findings of 24-hour video electroencephalogram (EEG) or the results of operation, most in vivo proton MRS studies using SVS or CSI can provide accurate lateralization in more than 80% of patients with temporal lobe epilepsy [27-32, 44-46]. NAA intensity is the most common parameter for MRS lateralization using spectral quantification. Various metabolite ratios, such as NAA/Cho, NAA/Cho and NAA/(Cho+Cr), have generally comparable efficacy for MRS lateralization [27-32, 44]. Proton MRS obtained with higher magnetic field has the advantages of better spectral resolution, and provides concordant pre-surgical lateralization in more than 90% of patients [47, 48]. MRS lateralization by visual inspection of metabolite images was determined correctly in about 70% of patients with temporal lobe epilepsy [45, 46]. Confidence of visual interpretation increased as the difference in NAA intensity between the temporal lobes increased [45]. Although the lateralization accuracy of qualitative reading is generally lower than that of quantitative or semi-quantitative methods, reading of metabolite images provides a feasible and fast means for clinical evaluation of patients with temporal lobe epilepsy [46].

Volumetric MRI revealed hippocampal atrophy in patients with temporal lobe epilepsy, which helped to correctly lateralize seizure focus in as much as 83% of patients [32]. Combination of MRS with volumetric MRI had better lateralization accuracy than using either method alone [32]. Interestingly, it has been shown that reduction of NAA intensity or ratios did not correlate with hippocampal volume losses, indicating proton MRS disclosed specific metabolic abnormalities other than anatomic changes [28]. In vivo proton MRS has the potential to identify metabolic abnormalities before structure changes occur, as shown in many studies that MRS detected abnormalities or determined lateralization in patients with normal MRI exams [32, 49, 50]. However, impacts of MRS on the management of temporal lobe epilepsy with negative MRI findings need further evaluation.

It has been shown in patients with temporal lobe epilepsy that NAA/(Cho+Cr) ratios on MRS correlated significantly with the inter-ictal glucose metabolism on PET [51]. Comparing the efficacy of seizure lateralization between proton MRS and ¹⁸F-fluorodeoxyglucose PET, several small cohort studies showed conflicting results [52-54]. Controversial findings were also noted when comparing the ability of pre-surgical lateralization between MRS and inter-ictal SPECT [15, 55]. Nevertheless, MRS has the advantage to identify bilateral abnormalities over PET and SPECT. MRS can easily detect reduction of bitemporal NAA intensities or ratios in 20 ~ 54% of patients [26, 27, 29, 32, 41, 53], consistent with the fact that bilateral asymmetric hippocampal sclerosis is always found in patients with temporal lobe epilepsy [17]. This additional biochemical information may provide an insight into the underlying pathophysiology and give clues to the prognosis.

Peri-ictal MRS

Studies reporting peri-ictal proton MRS metabolite changes in temporal lobe epilepsy are few and the results are contradictory [56-58]. Lipid and lactate intensities were found in the hippocampi of patients with acute temporal lobe seizure within 24 hours [57], and higher glutamate/glutamine concentrations found in the epileptic focus during post-ictal state [56]. Contrarily, absence of significant changes in metabolite ratios between inter-ictal and post-ictal state was reported in a recent study [58]. Further evaluation using standard measurement and inclusion criteria in large groups of subjects is necessary to resolve the controversy.
Post-surgical outcome and pre-operative MRS

Usefulness of proton MRS in prediction of post-surgical outcome has been investigated in terms of NAA relative to other metabolite ratios, such as NAA/Cr and NAA/(Cho+Cr), or NAA intensities of the hippocampus [41, 59, 60]. Several studies showed that ipsilateral MRS lateralization and normal metabolite profile in contralateral side were significantly associated with favorable surgical outcome [41, 59]. Other researchers did not show the same association, but found a relationship between elevated Cr/NAA ratios in contralateral temporal lobe and surgical failure [60]. Despite bilateral MRS abnormalities do not preclude good surgical outcome in patients with temporal lobe epilepsy [53]; in patients with severe bilateral metabolic changes, poor seizure outcome is a likely result [61].

Post-treatment MRS

In patients with temporal lobe epilepsy who became seizure free after surgical treatment, post-operative recovery of NAA/Cr ratios to the normal range on the side of surgery, or on both sides in patients with bitemporal abnormalities was noted [62]. Contrarily, NAA/Cr ratios did not change in those patients who continued to have seizures after surgery [62]. Recently, the time course of post-operative recovery of NAA/Cr in temporal lobe epilepsy was characterizing as an exponential curve with a half-time of 6 months and a 95% recovery after 25 months [63]. Despite metabolite dysfunction recovery in patients with successful surgical treatment has been reported, there is no significant increases of NAA/Cr ratios in seizure-free patients controlled with anti-epileptic drugs [64].

Recent developments involving proton MRS editing techniques have allowed in vivo measurements of the effects of vigabatrin, an anti-epileptic drug that increases GABA in human brain by irreversibly inhibiting GABA transaminase, in patients with temporal lobe epilepsy [65-67]. Prompt elevation of GABA in the occipital cortex after administration of vigabatrin could be detected using in vivo proton MRS [65, 66]. Dose- and time-dependent changes of occipital GABA levels after vigabatrin administration were well demonstrated using proton MRS [65, 66]. Furthermore, in patients with temporal lobe epilepsy and good response to vigabatrin, a lower ipsilateral GABA level at baseline and a significant increase of GABA during the whole treatment phase were noted [67]. Contrarily, in patients without response to vigabatrin, there was no significant change in the GABA intensity during the treatment compared with baseline [67]. Occipital lobe GABA measured by proton MRS may be predictive of improved seizure control among patients taking anti-epileptic drugs designed to increased cerebral GABA levels [66]. The post-treatment biochemical changes detected by in vivo proton MRS may be helpful in management of seizure patients and development of new anti-epileptic therapy.

Neuropsychology and MRS

Hippocampal neuron loss and associated memory deficits are characteristics of intractable temporal lobe epilepsy [68]. The correlation between memory functions and NAA changes measured by MRS was frequently investigated [68-72]. Most studies found that left hippocampal NAA ratios were strongly correlated with verbal memory functions [68-70]; whereas right hippocampal NAA ratios were strongly correlated with non-verbal functions [69, 70]. The same association was also demonstrated in children with temporal lobe epilepsy [71]. An association between left hippocampal NAA ratios and visual confrontation naming function was also noted [69, 72]. These findings indicate that proton MRS may enhance understanding the role of hippocampal function in complex cognitive system.

Extra-temporal Epilepsy

In addition to temporal lobe epilepsy, there are also reports concerning proton MRS in other types of seizures [73-80]. For example, the metabolite ratio NAA/Cr is decreased in the seizure focus of frontal lobe epilepsy [73]. But the coincidence rate between seizure focus and reduction in NAA/Cr is much lower in frontal than in temporal lobe epilepsy [74]. Phosphorus MRS of frontal lobe epilepsy was seldom reported [75].

Patients with extra-temporal epilepsy have reduced NAA intensities or ratios in the EEG-identified seizure focus as compared with controls, and the reduction is greater in the epileptogenic region than in the non-epileptogenic regions defined by EEG [76]. Metabolite changes in extra-temporal epilepsy extends beyond the epileptogenic zone delineated on EEG or MRI [76, 77], indicating in vivo MRS detects widespread neuronal damage or dysfunction that is greatest in the region of seizure focus.

In contrast to mesial temporal lobe epilepsy where hippocampal NAA is reduced, a recent study showed that NAA was not reduced in the hippocampus of patients with neo-cortical epilepsy, neither ipsilateral nor contralateral to the seizure focus [78].
These results suggest that repeated seizures do not cause secondary damage to the hippocampus [78]. Proton MRS has also been applied for discrimination of complex partial seizures and absence [79], showing inter-ictal NAA decreases and ictal or post-ictal lactate elevation in patients with complex partial seizure, but not in patients with absence [79]. Despite all these promising findings, additional studies are necessary to solidify these preliminary results.

**CONCLUSION**

In addition to the other neuro-imaging modalities for pre-surgical lateralization of seizure focus, proton MRS provides a non-invasive and complimentary technique to detect biochemical abnormalities in terms of metabolite intensities or ratios. Even though in vivo proton MRS is regarded as a research tool rather than an essential examination for seizure evaluation at present, promising results in the literature indicate that proton MRS may be helpful in the management of seizure patients and included as a key imaging modality in the near future.

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癲癇之磁振頻譜

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磁振頻譜（magnetic resonance spectroscopy）不具侵襲性，並且可以測量人體腦部的代謝物，其基本原理與磁振造影相同。磁振頻譜的測量結果，一般是以半定量的代謝物比率或定量的代謝物強度來表示。不同的測量技術、測量條件和測量區域，都會影響頻譜的表現而改變檢測的結果。因此，為了使磁振頻譜的測量有可重覆性，並且能做長期追蹤的比較，保持固定一致的測量方式是非常重要的。在判讀或比較磁振頻譜的數據時，一定要考量不同檢測條件可能會有的影響。

近年來，利用磁振頻譜研究癲癇病患日益增多的趨勢，尤其是顳葉癲癇。磷磁振頻譜能測量腦部高能磷酸鹽的含量；但是其信號-雜訊比率低，空間解析度差，而且在一般臨床磁振系統無法進行。而質子磁振頻譜則可和一般的磁振造影在同一檢查中進行，同時提供解剖影像以及生化數據。質子磁振頻譜可在顳葉癲癇病人的內側顳葉或海馬區測得N-乙醯天門冬胺酸（N-acetylaspartate）減少的現象，表示病灶處有神經元喪失或功能不良的情形。質子磁振頻譜已廣泛應用於許多有關顳葉癲癇的研究領域，包括手術前的病灶定位，癲癇發作前後代謝狀態的改變，預測手術的結果，治療造成的代謝改變，以及與其他不同類型癲癇之間的差異。雖然磁振頻譜目前仍被視為研究工具，但是許多文獻報告顯示磁振頻譜當有助於吾人對癲癇之瞭解與治療。

關鍵詞：腦，癲癇，磁振頻譜