Published in final edited form as:

Ann Neurol. 1997 August ; 42(2): 194–199. doi:10.1002/ana.410420210.

Hippocampal *N*-Acetylaspartate in Neocortical Epilepsy and Mesial Temporal Lobe Epilepsy

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Abstract

Previous magnetic resonance spectroscopy (MRS) studies have shown that *N*-acetylaspartate (NAA) is reduced not only in the ipsilateral but also in the contralateral hippocampus of many patients with mesial temporal lobe epilepsy (mTLE). The reason for the contralateral damage is not clear. To test whether the hippocampus is also damaged if the focus is outside the hippocampus, we have measured patients with neocortical epilepsy (NE). Therefore, the goals of this study were to determine if hippocampal NAA is reduced in NE and if hippocampal NAA discriminates NE from mTLE. MRS imaging (MRSI) studies were performed on 10 NE patients and compared with MRSI results in 23 unilateral mTLE patients and 16 controls. The results show that, in contrast to mTLE, NAA was not reduced in the hippocampus of NE patients, neither ipsilateral nor contralateral to the seizure focus. These results suggest that repeated seizures do not cause secondary damage to the hippocampus. The absence of spectroscopic differences in NE may help to distinguish NE from mTLE.

Approximately 30% of epilepsy patients have neocortical epilepsy (NE) [1] in which, in contrast to mesial temporal lobe epilepsy (mTLE), the focus is outside the hippocampus. Although these patients respond much less well than mTLE patients to medical treatment, neurosurgical removal is performed only rarely and with less success than in mTLE [2].

This laboratory and others have previously shown that proton magnetic resonance spectroscopy (¹H MRS) can be used to lateralize the seizure focus in mTLE [3–11]. The correlation to the epileptogenic focus as defined by electroencephalography (EEG) was done on the basis of reduced *N*-acetylaspartate (NAA) in the hippocampus and/or the temporal lobe. The reduction was reported either in absolute units or as a ratio to choline-containing compounds (Ch) and/or creatine/phosphocreatine (Cr). Several recent reports have shown that NAA in the contralateral side is also reduced in many mTLE subjects [8,10,11], suggesting contralateral damage. Structural abnormalities of both hippocampi have also been detected in an autopsy study of TLE [12].

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The following are the three possible explanations for the contralateral reduction of NAA in mTLE: (1) bilateral presence of mesial temporal sclerosis, (2) seizures in one hippocampus causing secondary damage to the opposite hippocampus due to preferential pathways, and (3) damage to the contralateral hippocampus as a result of repeated seizure activity. If repeated seizure activity is responsible for reduced contralateral NAA, hippocampal NAA might also be reduced in NE. Therefore, the primary goal of our study was to determine if hippocampal NAA is reduced in NE. The finding may lead to a better understanding of contralateral damage in mTLE, or point to mechanistic differences between mTLE and NE.

In some circumstances it can be difficult to distinguish NE from mTLE. Hence, a secondary goal was to test if hippocampal NAA results could be used to discriminate NE from mTLE patients.

Subjects and Methods

To meet the goals of the study, hippocampal metabolites were measured by magnetic resonance spectroscopic imaging (MRSI) and compared in three different groups, in NE patients, in mTLE patients, and in normal subjects.

Neocortical Epilepsy Patients

Ten patients with medically refractory NE (based on seizure semiology and ictal EEG recordings) were studied (Table 1). The age range was 25 to 51 years (mean age, 34.4 ± 7.4 years). All patients were evaluated at the Northern California Comprehensive Epilepsy Center, and none of the patients had clinical or EEG evidence to suggest a second seizure focus. The seizure focus was localized by scalp (including sphenoidal electrodes) and, as necessary, subdural electrode recordings. Only patients whose ictal recordings demonstrated either localized voltage attenuation or rhythmic sharp activity that preceded or coincided with the onset of the clinical seizure were included. Four patients had their seizures arise from the frontal lobes, 2 from the occipital lobe, 1 from the parietal lobe, and 3 patients had their seizures arise from the lateral–neocortical regions of the temporal lobes. The severity and frequency of seizures in the NE patients was similar or greater to the group of mTLE patients that was used for comparison (see below). None of the patients had simple partial seizures only, with each patient experiencing complex partial seizures with all but 2 patients also experiencing secondarily generalized convulsions as well (see Table 1).

All NE patients had normal magnetic resonance images (MRIs), with hippocampi that were normal in appearance, shape, and volume.

Mesial Temporal Lobe Epilepsy Patients

This comparison group consisted of 23 unilateral medically refractory mTLE patients (16 of whom were previously reported [11]). The age range was 14 to 49 years (mean age, 35.0 ± 9.7 years).

Normal Subjects

Both patient groups were compared with 16 healthy age- and sex-matched controls (age range, 23–56 years; mean age, 33.3 ± 7.9 years).

Written informed consent was obtained from all subjects before MRSI studies.

MRI and MRSI Methods

All studies were performed on a 1.5-T Magnetom VISION (Siemens Erlangen), using a standard circularly polarized head coil. Two-dimensional fast low-angle shot (2D FLASH)

images in coronal, sagittal, and oblique transverse orientations were acquired. The transverse images were angulated parallel to the long axis of the hippocampus.

A 2D MRSI sequence with double spin-echo (PRESS) volume preselection was used with typical dimensions of 15 mm axial, 70 mm left–right, and 90 mm anterior–posterior (Fig 1). The volume was angulated parallel to the transverse images and included both hippocampi. The equivalent of 24×24 phase-encoding steps over a circular k-space region was used [4] with a 210-mm² field of view. The data were acquired with repetition time (TR) = 1.8 seconds and echo time (TE) = 135 msec, resulting in a measurement time of 13 minutes. The unsuppressed water signal was used as an internal standard and acquired in a second MRSI examination with otherwise identical measurement parameters [13]. Total measurement time for MRI and MRSI studies was approximately 60 minutes.

Data Processing

Postprocessing of the MRSI data included zero-filling to 32×32 k-space points and k-space apodization that produced an effective voxel size of approximately 2 ml. The time domain data was zero-filled to 1,024 data points and apodized with a Gaussian function corresponding to 2-Hz line broadening in the frequency domain. Spectral phasing and a polynomial baseline correction were also performed. In the plane parallel to the long axis of the hippocampus, in general, 10 to 12 nominal voxels were located (in two dimensions) within each hippocampus (see Fig 1). To reduce major contributions from adjacent tissue, an average of five voxels centered primarily on hippocampal gray matter were selected. The summed spectra contained mainly contributions from the hippocampus. However, adjacent tissue also contributed to the spectra to a minor degree because the thickness of the SI slice (15 mm) exceeded the thickness of the hippocampus. The signals of NAA, Cr, and Ch were quantitated by curve fitting.

In 8 of 10 patients, absolute concentrations were calculated by using the unsuppressed water resonance as a reference. The concentration calculations included corrections of metabolite and water signals for T_1 and T_2 relaxation, and corrections for the number of protons belonging to the metabolite resonances [13].

EEG findings were used as the standard for localization and lateralization of the seizure focus. Lateralization by MRSI was performed in several ways: The NAA, Ch, and Cr concentrations ([NAA], [Ch], and [Cr]) and metabolite ratios [NAA/Cr, NAA/Ch, and NAA/(Cr + Ch)] were compared for left and right hippocampi in patients. Furthermore, the patient values were compared with control values.

Asymmetry indices were calculated by $(M_{\text{contra}} - M_{\text{ipsi}})/(M_{\text{contra}} + M_{\text{ipsi}}) \times 100$ for patients and $(M_{\text{left}} - M_{\text{right}})/(M_{\text{left}} + M_{\text{right}}) \times 100$ for controls, with the metabolite concentration or metabolite ratio designated by M .

Statistical Analyses

Statistical analyses of the MRSI data comparing metabolite concentrations and ratios between NE and mTLE patients and controls were done using a one-tailed unpaired t test. A probability value of $p < 0.05$ was considered significant for each analysis. To also detect smaller metabolite changes, we did not correct for multiple comparisons. All data are presented as mean $\pm$ SD values.

Results

Figure 1 shows a transverse FLASH image with an outline indicating the typical PRESS volume superimposed. In addition, spectra from right and left hippocampi are shown, and the regions from which each spectrum originates are indicated.

In our previous study of mTLE patients, [NAA] and NAA/(Cr + Ch) values proved to be most predictive [11] and are, therefore, mainly used in this study and are presented in Table 2 for NE, mTLE, and controls. In addition, [Cr] and [Ch] were calculated. The mean ipsilateral values for [NAA], [Cr], and [Ch] in the NE patients was 12.3 ± 1.9 , 9.8 ± 1.2 , and 2.9 ± 0.7 , respectively, and for the mTLE patients, 8.3 ± 1.3 , 8.6 ± 1.6 , and 2.6 ± 0.4 .

The major finding of this study was that, in contrast to mTLE, there were no significant changes in any ratio or metabolite concentration in NE compared with controls (see Table 2). In Figure 2, the ipsilateral and contralateral values of [NAA] and NAA/(Cr + Ch) ratios are plotted for the individual patients. In 19 of 23 mTLE patients, the ipsilateral [NAA] and NAA/(Cr + Ch) values were lower than the contralateral values. In contrast, there was no uniform tendency between ipsi- and contralateral values for NE patients.

A comparison of ipsilateral values with controls shows that for mTLE, ipsilateral [NAA] and NAA/(Cr + Ch) are significantly reduced ($p < 0.001$), whereas for NE the mean values are not different from controls (see Table 2).

Furthermore, Figure 2 shows that mTLE patients also had significantly reduced values in the contralateral hippocampus. [NAA] values and NAA/(Cr + Ch) ratios were reduced at least 1 SD below the control mean in 16 patients (70% of all patients, $p < 0.001$) and in 13 patients (57%, $p < 0.002$), respectively.

The asymmetry index defined above was calculated to determine the degree of asymmetry between ipsi- and contralateral values of [NAA] and NAA/(Cr + Ch) in NE compared with controls and mTLE (Table 3). In contrast to mTLE, the asymmetry of the NE group did not differ significantly from controls. To detect any asymmetries (independent of the location of the seizure focus) between left and right side in patients, absolute asymmetry indices were also calculated (see Table 3). Although these asymmetry values were slightly higher in NE than in controls, this difference was not significant, in contrast to the highly significant difference between mTLE and controls.

The second goal of our study was to determine if any metabolic features distinguished NE from mTLE. Figure 3 shows the ipsilateral values of [NAA] and NAA/(Cr + Ch) for NE and mTLE patients. For single-patient comparisons, values of >2 SD from either group (NE or mTLE) were considered to be abnormal. Ipsilateral [NAA] values were reduced in 13 of 23 mTLE patients and NAA/(Cr + Ch) values were reduced in 9 mTLE patients >2 standard deviations below the mean values of NE patients. On the other hand, 6 of 8 NE patients had higher [NAA] and 4 of 10 NE patients had higher NAA/(Cr + Ch) values of >2 SD above mTLE. Therefore, despite the overlap between the two groups, the metabolite values may help discriminate mTLE from NE. Although there appears to be a clustering of the neocortical patients NAA/(Cr + Ch) into two subgroups (ie, low values similar to mTLE and slightly increased values), there were no clinical differences between these patients in terms of age, years seizing, seizure frequency, or seizure types.

To see if the location of the focus influenced the NE metabolite values, the patients were divided into three groups based on the relationship of their seizure focus to the hippocampus (Fig 4). Patients whose seizures arose from neocortical structures within the ipsilateral temporal lobe but that were outside the hippocampus were classified as “same.” Patients whose seizures arose from the ipsilateral frontal lobe were looked at separately because of the rich, profuse, and preferred pathways between the frontal lobe and the medial temporal lobe structures (“frontal”). All other patients were grouped together because the location of their seizure foci would be expected to have less influence on the hippocampus (“other”). No relationship between the distance of the seizure focus from the ipsilateral hippocampus (either anatomical or in terms of preferential pathways) was found for the metabolites (see Fig 4). The 2 patients

without convulsions were not distinguishable from the others with respect to [NAA] or NAA ratios.

Discussion

The goal of this study was to determine if seizures arising from outside the hippocampal region cause metabolite change in the hippocampus. NE is a more heterogeneous disorder than mTLE because the seizure focus may be anywhere in the neocortex, but seizures in these patients do not originate from the hippocampus and frequently involve the brain in a diffuse and bilateral fashion. Therefore, this patient population is well suited to test the primary hypothesis.

Our results clearly show that, in contrast to mTLE, patients with NE do not have reduced hippocampal NAA, either ipsilateral or contralateral to the seizure focus. The asymmetry between ipsi- and contralateral was not significant and the absolute asymmetry index was not significantly different from controls. Furthermore, there was no correlation between the spectroscopic results and the distance of the seizure focus from the ipsilateral hippocampus. In an MRI study, Cook and associates [14] reported unchanged hippocampal volume in NE patients, in contrast to the volume loss they detected in the hippocampus of mTLE patients. This is consistent with our finding of unchanged hippocampal [NAA]. Therefore, the current results, taken together with those of Cook and associates [14] strongly suggest that seizures that arise from outside the hippocampus do not damage the hippocampus.

On the other hand, contralateral abnormalities have been repeatedly seen in several published studies of unilateral mTLE [8–12]. This laboratory previously found reduced [NAA] and NAA/(Cr + Ch) in 50% of the contralateral hippocampi of unilateral mTLE patients [11], suggesting that bilateral hippocampal abnormalities are more common than was previously assumed. Contralateral abnormalities in proton spectra from the temporal lobe were also found by Connelly and associates [8] in 40% and Ng and colleagues [10] in 18% of their unilateral TLE patients. In an autopsy study, Margerison and Corsellis [12] found structural abnormalities of both hippocampi in 30% of mTLE patients. The reason for these contralateral abnormalities is still not clear. The pathological mechanisms that are producing the contralateral damage could be due to either bilateral presence of mesial temporal sclerosis and/or damage to the contralateral hippocampus because of repeated seizure activity arising from the ipsilateral hippocampus.

However, the finding that [NAA] is not reduced in the hippocampus of NE patients strongly suggests that repeated seizures do not cause secondary damage to the hippocampus. Therefore, the present results suggest that the contralateral reductions of NAA in mTLE are probably not the result of repeated seizures. These reductions are presumably caused by bilateral mesial temporal sclerosis. Alternatively, the possibility remains that, because of their proximity, or due to preferential activation of neural connections, seizures in one hippocampus cause secondary damage to the opposite hippocampus.

The MRSI measurements indicate that hippocampal NAA in mTLE is significantly lower than in NE; however, there remains substantial overlap between the two groups. Notwithstanding this overlap, the finding that hippocampal NAA is not reduced in NE suggests that MRSI may help discriminate NE from mTLE. Another important clinical problem is to localize the seizure focus in NE. Studies in this laboratory are in progress to determine if multislice MRSI that obtains spectra from cortical regions [15,16] can be used to localize the seizure focus in NE.

In conclusion, the results show, first, that the hippocampus is not affected in NE patients, suggesting that reduced contralateral NAA in mTLE reflects extension of mesial temporal sclerosis and, second, that hippocampal NAA measurements may help to clinically distinguish mTLE from NE.

Acknowledgments

This study was supported by NIH grant ROI-NS31966 and by DFG Forschungsstipendium.

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Fig 1. Transverse image angulated parallel to the long axis of the hippocampus with a typical localization of the magnetic resonance spectroscopy imaging measurement superimposed. The region from which right and left spectra originate is indicated.

Fig 2.

Comparison of ipsilateral and contralateral N-acetylaspartate concentration ([NAA]) and NAA/(creatine + choline) [NAAI (Cr + Ch)] for neocortical epilepsy (NE) and mesial temporal lobe epilepsy (mTLE). The dashed lines indicate normal mean ± 1 SD. The p values compare ipsi- with contralateral.

Fig 3.

Comparison of ipsilateral N-acetylaspartate concentration ([NAA]) and NAA/(creatine + choline) [NAA/(Cr + Ch)] for neocortical epilepsy (NE) and mesial temporal lobe epilepsy (mTLE). The dashed lines indicate mean + 2 SD and mean - 2 SD of TLE and NE patients, respectively

Fig 4. Ipsilateral N-acetylaspartate concentration ([NAA]) and NAA/(creatine + choline) [NAA/(Cr + Ch)] of neocortical epilepsy (NE) compared with the distance of the seizure focus from the hippocampus. The dashed lines indicate normal mean ± 1 SD.

Table 1

Patient Characteristics

Patient No.	Localization	Age (yr)	Sex	Years of Seizing	Seizure Frequency/Week	Lifetime GTCs ^a
1	Lt neotemporal	38	M	13	1 CPS	2
2	Rt occipital	36	F	18	21 CPS	0
3	Lt neotemporal	27	F	11	7 CPS	25
4	Rt occipital	37	F	26	7 CPS	69
5	Rt parietal	51	M	31	2 CPS	0
6	Rt frontal	37	F	10	0.25 CPS, 0.5 GTC	78
7	Rt neotemporal	29	F	24	5 CPS	1
8	Rt frontal	30	F	19	49 CPS	10
9	Lt frontal	37	M	26	28 CPS	3
10	Rt frontal	25	M	6	14 CPS, 1 GTC	209

Lt = left; Rt = right; CPS = complex partial seizure; GTC = secondarily generalized tonic clonic seizure.

^a Estimate of the total lifetime number of GTCs experienced by the patient.

Table 2
Ipsi- and Contralateral NAA Concentrations and NAA/(Cr + Ch) Ratios (Mean ± 1 SD) in the Hippocampus of NE and mTLE Patients in Comparison with Controls

			[NAA] (mM)	NAA/(Cr + Ch)	
Controls	n = 16		11.6 ± 1.3	0.81 ± 0.06	
NE	n = 8/10	Ipsi	12.3 ± 1.9	0.79 ± 0.11	<i>p</i> = NS
		Contra	11.4 ± 2.7	0.77 ± 0.10	<i>p</i> = NS
mTLE	n = 23	Ipsi	8.3 ± 1.3	0.62 ± 0.11	<i>p</i> < 0.001
		Contra	9.6 ± 1.3	0.72 ± 0.11	<i>p</i> < 0.001

p values compare patients with controls.

NAA = *N*-acetylaspartate; Cr = creatine/phosphocreatine; Ch = choline; NE = neocortical epilepsy; mTLE = mesial temporal lobe epilepsy.

Table 3
[NAA] and NAA/(Cr + Ch) Asymmetry Indices (Mean $\pm$ 1 SD) of NE and mTLE Patients in Comparison with Controls

	Asymmetry [NAA]	Asymmetry NAA/(Cr + Ch)	Absolute Asymmetry [NAA]	Absolute Asymmetry NAA/(Cr + Ch)
Controls	-0.19 $\pm$ 4.87	0.62 $\pm$ 6.24	3.12 $\pm$ 3.66	4.73 $\pm$ 3.92
NE	-4.61 $\pm$ 7.79	-1.15 $\pm$ 8.05	5.72 $\pm$ 6.89	6.76 $\pm$ 3.95
mTLE	7.43 $\pm$ 8.28	7.40 $\pm$ 8.65	8.95 $\pm$ 6.53	9.08 $\pm$ 6.78

p values compare patients with controls.
NAA = *N*-acetylaspartate; Cr = creatine/phosphocreatine; Ch = choline; NE = neocortical epilepsy; NS = not significant; mTLE = mesial temporal lobe epilepsy.