# A single-voxel spectroscopy study of hippocampal metabolic dysfunction in patients with juvenile myoclonic epilepsy, frontal lobe epilepsy, and psychogenic nonepileptic seizures

Epilepsy Center, National Hospital Organization, Nara Medical Center
Tohru HOSHIDA, Nobuyuki Maruyama, Yasuko Sawai, Kazuhiro Kawata, Hidehiro Hirabayashi

<Purpose>
Proton magnetic resonance spectroscopy (MRS) studies have shown neuronal dysfunction with differing patterns of abnormality in various types of epilepsy pathogenesis. Our aim was to identify metabolic differences in the hippocampi of patients with juvenile myoclonic epilepsy (JME), frontal lobe epilepsy (FLE), and psychogenic nonepileptic seizure (PNES) compared to normal healthy subjects by using single-voxel MRS.
<Methods>
The study included 18 patients with JME, 38 with FLE, and 15 with PNES who had no true epileptic seizures. The control group consisted of 24 age-matched healthy volunteers (mean age: JME, 22.3; FLE, 23.7; PNES, 25.0; controls, 25.8). All patients and controls underwent normal neurological examinations and magnetic resonance imaging.
Quantitative single-voxel MRS was conducted at 1.5 Tesla with a sequence of TR/TE = 1,323/136 ms with a voxel size of 30 × 15 × 15 mm in both hippocampi. LC-Model was used to estimate the absolute concentrations of *N*-acetyl-aspartate (NAA), choline (Cho), creatine (Cr), and the ratio of NAA to Cho + Cr (NAA ratio).
<Results>
Significant reductions in NAA and the NAA ratio were observed in the left hippocampus in the JME group compared to controls (NAA: 8.22 vs. 8.89, $p < 0.05$; NAA ratio: 0.92 vs. 1.03, $p < 0.01$). Furthermore, significant reductions in NAA were found in both hippocampi in the FLE group compared to controls (right: 7.79 vs. 8.28, $p < 0.05$; left: 8.14 vs. 8.89, $p < 0.01$). The bilateral hippocampal NAA ratios were not reduced significantly in the FLE patients. In PNES patients, NAA and the NAA ratio in both hippocampi were not significantly lower than in the

controls.

<Conclusions>

These data support the hypothesis that JME and FLE involve neuronal dysfunction within the temporal lobe as well as the frontal lobe. However, neuronal dysfunction in PNES might demonstrate normal hippocampal metabolism and differ from epileptic pathogenesis.

# A single-voxel spectroscopy study of hippocampal metabolic dysfunction in patients with juvenile myoclonic epilepsy, frontal lobe epilepsy, and psychogenic nonepileptic seizures

Epilepsy Center, National Hospital Organization,
Nara Medical Center

Tohru HOSHIDA, Nobuyuki Maruyama,
Kazuhiro Kawata, Hidehiro Hirabayashi

NARA MEDICAL CENTER

# <Purpose>

Proton magnetic resonance spectroscopy (MRS) studies have shown neuronal dysfunction with differing patterns of abnormality in various types of epilepsy pathogenesis. Our aim was to identify metabolic differences in the hippocampi of patients with juvenile myoclonic epilepsy (JME), frontal lobe epilepsy (FLE), and psychogenic nonepileptic seizure (PNES) compared to normal healthy subjects by using single-voxel MRS.

## Choline

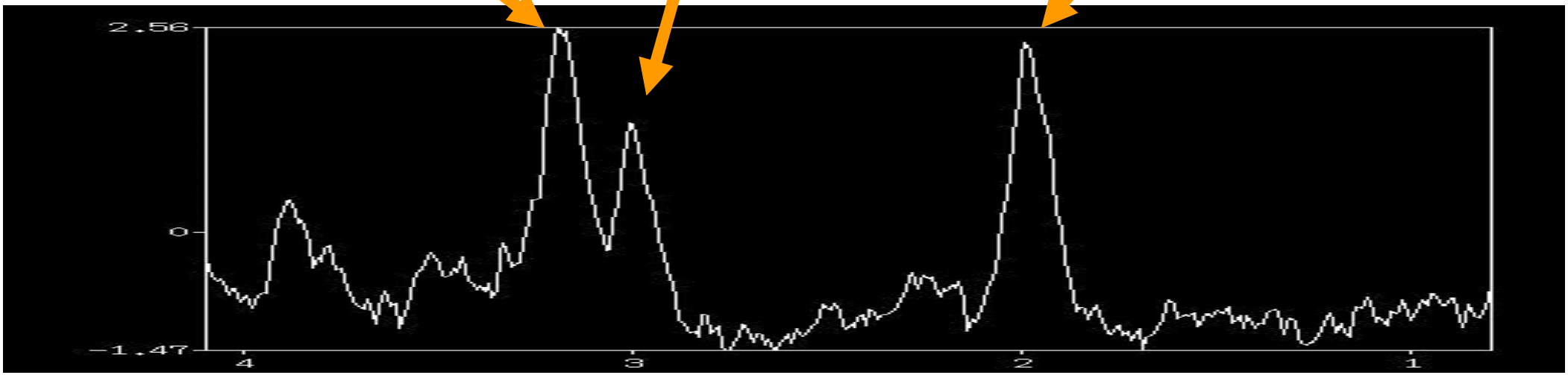
- peak at 3.24ppm
- metabolism of phospholipid
- cell membrane and synaptic terminal of cholinergic nerve fiber
- neuron＜glia
- increased in tumor tissue and plaque of multiple sclerosis

## Creatine

- peak at 3.04ppm
- sum of creatine and phosphocreatine
- relatively stable in brain tissue
- neuron＜glia
- decreased in metastatic brain tumor and infectious disease

## N-acethyl aspartate（NAA)

- peak at 2.02ppm
- only in central nervous system
- white matter＜grey matter
- possibility of regulate action of neuronal protein synthesis
- indicator of neuronal function
- decreased in neuronal cell loss or dysfunction

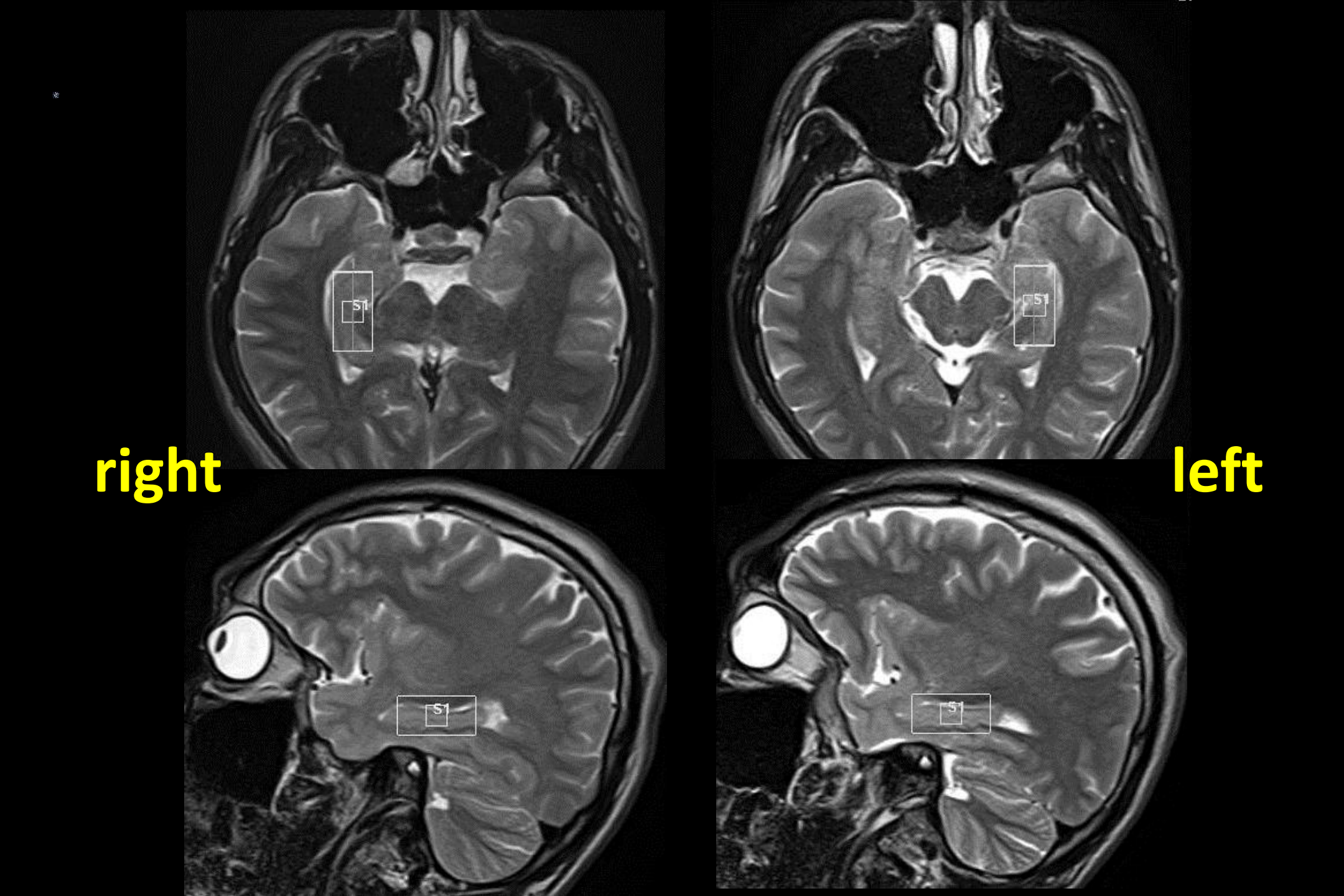


# <Methods>

The study included 18 patients with JME, 38 with FLE, and 15 with PNES who had no true epileptic seizures. The control group consisted of 24 age-matched healthy volunteers (mean age: JME, 22.3; FLE, 23.7; PNES, 25.0; controls, 25.8). All patients and controls underwent normal neurological examinations and magnetic resonance imaging.

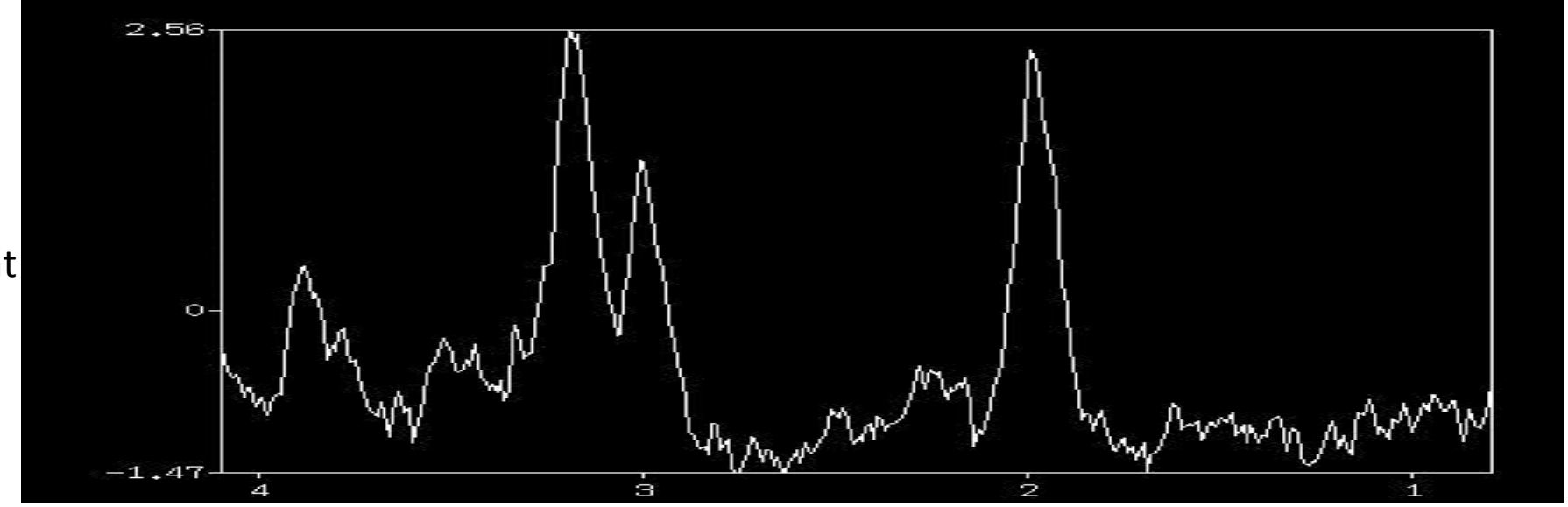
Quantitative single-voxel MRS was conducted at 1.5 Tesla with a sequence of TR/TE = 1,323/136 ms with a voxel size of 30X15X15 mm in both hippocampi.

LC-Model was used to estimate the absolute concentrations of *N*-acetyl-aspartate (NAA), choline (Cho), creatine (Cr), and the ratio of NAA to Cho + Cr (NAA ratio).


right
left

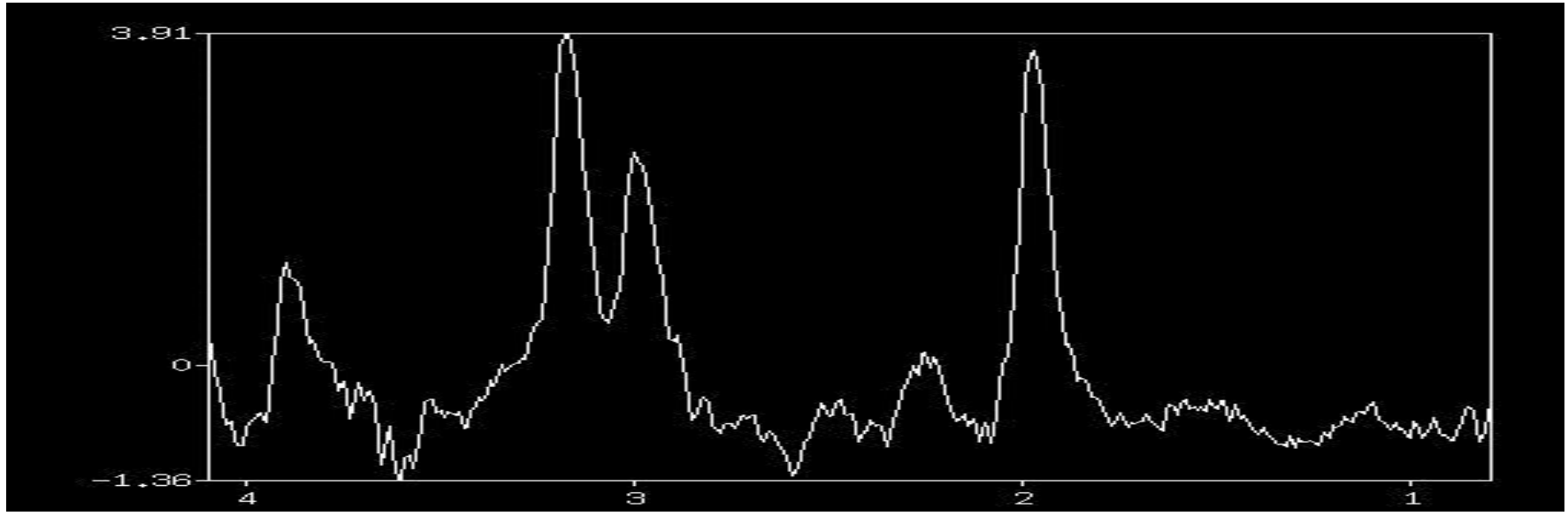
right

18.9 y.o.
male
JME




| 1.50 | 2.49 | 5.11 | 7.67 | 1.01 |
|---|---|---|---|---|
| **NAA/Cr** | **Choline** | **Creatinine** | **NAA** | **NAA/Cho+Cr** |
| 1.41 | 2.89 | 5.37 | 7.57 | 0.92 |

left



# <Results>

**1.** In normal control, there is no difference between male and female in hippocampal NAA value and ratio.
**2.** Left hippocampal NAA value is higher than right in normal control, and no difference in NAA ratio.
**3.** Significant reductions in NAA and the NAA ratio were observed in the left hippocampus in the JME group compared to controls (NAA: 8.22 vs. 8.89, $p < 0.05$; NAA ratio: 0.92 vs. 1.03, $p < 0.01$).
**4.** Significant reductions in NAA were found in both hippocampi in the FLE group compared to controls (right: 7.79 vs. 8.28, $p < 0.05$; left: 8.14 vs. 8.89, $p < 0.01$). The bilateral hippocampal NAA ratios were not reduced significantly in the FLE patients.
**5.** In PNES patients, NAA and the NAA ratio in both hippocampi were not significantly lower than in the controls.

# Result 1

**Normal control (n=24)**

No neurological deficit, negative MRI findings, MMSE : 27>/30, WMS-R : 85>

| | mean+/-SD | range | significance |
|---|---|---|---|
| Male (n=13) | 25.8 +/- 4.9y.o. | 17~35y.o. | |
| Female (n=11) | 25.8 +/- 6.1 | 15~33 | p=0.99 |
| **Male** | | | |
| r-NAA | 8.27 +/- 0.76 | 6.77~9.95 | |
| l-NAA | 8.81 +/- 1.13 | 6.77~10.46 | p=0.07 |
| r-NAA/Cho+Cr | 1.02 +/- 0.08 | 0.87~1.12 | |
| l-NAA/Cho+Cr | 1.02 +/- 0.09 | 0.86~1.14 | p=0.94 |
| **Female** | | | |
| r-NAA | 8.30 +/- 0.78 | 6.96～9.38 | |
| l-NAA | 8.99 +/- 0.84 | 7.72～10.29 | p=0.07 |
| r-NAA/Cho+Cr | 1.03 +/- 0.11 | 0.85～1.16 | |
| l-NAA/Cho+Cr | 1.03 +/- 0.11 | 0.87～1.28 | p=0.96 |
| **Gender difference** | | | |
| r-NAA | | | p=0.93 |
| l-NAA | | | p=0.66 |
| r-NAA/Cho+Cr | | | p=0.79 |
| l-NAA/Cho+Cr | | | p=0.70 |

# Result 2

| | No | male/female | age mean+/-SD | age range | |
|---|---|---|---|---|---|
| JME | 18 | 6/12 | 22.3 +/- 9.9 | 12～35 | 0.07 |
| FLE | 38 | 18/20 | 23.7 +/- 5.5 | 15～35 | 0.15 |
| PNES | 15 | 7/8 | 25.0 +/- 6.0 | 16～34 | 0.66 |
| Control | 24 | 13/11 | 25.8 +/- 5.4 | 15～35 | |

| | mean+/-SD | range | right-left difference |
|---|---|---|---|
| control (n=24) | | | |
| r-NAA | 8.28 +/- 0.75 | 6.77~9.95 | |
| l-NAA | 8.89 +/- 0.99 | 6.77~10.46 | p=0.008 |
| r-NAA/Cho+Cr | 1.03 +/- 0.09 | 0.85~1.16 | |
| l-NAA/Cho+Cr | 1.03 +/- 0.10 | 0.86~1.28 | p=0.99 |

# Result 3,4,5

| | right | | left | |
|---|---|---|---|---|
| | NAA | NAA/Cho+Cr | NAA | NAA/Cho+Cr |
| JME | 7.98 | 0.99 | 8.22* | 0.92** |
| FLE | 7.79* | 1.00 | 8.14** | 0.99 |
| PNES | 8.21 | 1.04 | 8.73 | 1.01 |
| Control | 8.28 | 1.03 | 8.89 | 1.03 |

* p<0.05
** p<0.01

| | mean+/-SD | range | right-left difference |
|---|---|---|---|
| **JME** (n=18) | | | |
| r-NAA | 7.98 +/- 1.01 | 6.19~9.60 | |
| l-NAA | 8.22 +/- 0.85 | 6.72~9.75 | p=0.20 |
| r-NAA/Cho+Cr | 0.99 +/- 0.11 | 0.78~1.26 | |
| l-NAA/Cho+Cr | 0.92 +/- 0.07 | 0.80~1.04 | **p=0.014** |
| **FLE** (n=38) | | | |
| r-NAA | 7.79 +/- 1.01 | 5.06~9.99 | |
| l-NAA | 8.14 +/- 1.00 | 5.69~10.41 | **p=0.026** |
| r-NAA/Cho+Cr | 1.00 +/- 0.12 | 0.65~1.39 | |
| l-NAA/Cho+Cr | 0.99 +/- 0.10 | 0.75~1.18 | p=0.71 |
| **PNES** (n=15) | | | |
| r-NAA | 8.21 +/- 1.18 | 5.63~9.90 | |
| l-NAA | 8.73 +/- 1.14 | 6.24~10.48 | p=0.07 |
| r-NAA/Cho+Cr | 1.04 +/- 0.10 | 0.90~1.25 | |
| l-NAA/Cho+Cr | 1.01 +/- 0.14 | 0.75~1.24 | p=0.67 |

# Discussion

Duncan JS: Imaging Idiopathic Generalized Epilepsy. Clinical EEG and Neuroscience 2004;35:168-172

- MRS indicates neuronal dysfunction with differing patterns of abnormality in the IGE sub-syndrome.

Haki C et al: Proton magnetic resonance spectroscopy study of bilateral thalamus in juvenile myoclonic epilepsy. Seizure 2007;16:287-295

- Thalami NAA/Cr ratios were significantly decreased in JME patients as compared with controls.

Savic I et al: MR spectroscopy shows reduced frontal lobe concentrations of N-acetyl aspartate in patients with JME. Epilepsia 2000;41:290-296

- JME had significantly reduced prefrontal concentrations of NAA in relation to controls
- The other regions showed normal NAA values, as did the other metabolites.
- The observed reduction in NAA levels suggests a prefrontal neuronal lesion in patients with JME.

Ristić AJ et al: Hippocampal metabolic dysfunction in JME: 3D multivoxel spectroscopy study. Journal of the Neurological Sciences 2011;305:139-142

- Significant differences of NAA/Cr in the head, body and tail, NAA/Cho+Cr in the body and tail of
- The left hippocampus, and NAA/Cho+Cr in the body and tail of the right hippocampus.
- The hippocampus may have a certain role in the pathogenesis of JME.

# <Conclusions>

These data support the hypothesis that JME and FLE involve neuronal dysfunction within the temporal lobe as well as the frontal lobe. However, neuronal dysfunction in PNES might demonstrate normal hippocampal metabolism and differ from epileptic pathogenesis.