A combined study of tumor-related brain lesions by using magnetoencephalography and $^1$H magnetic resonance spectroscopic imaging

Technical note

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The purpose of this study was to localize pathological magnetic brain activities and to analyze metabolic alterations in functionally abnormal lesions by using magnetoencephalography (MEG) and $^1$H magnetic resonance (MR) spectroscopy in patients with brain tumors. The authors studied 10 healthy volunteers and seven patients who harbored common brain tumors, namely astrocytic tumors and meningioma. In spontaneous MEG the pathological brain activities (slow waves, fast waves, and spikes) were localized using a single equivalent dipole model. After the results of MEG and $^1$H MR spectroscopy were superimposed onto the corresponding MR images, the signal intensities of spectroscopically visible metabolites were analyzed in the regions in which the dipoles of the pathological activities were concentrated. Increased slow-wave activity was observed in four cases, and fast-wave or spike activity was significantly increased in one case each, respectively. These pathological activities were localized at almost the same cortical areas adjacent to the bulk of tumors, where mild reduction of $\text{N}$-acetyl aspartate (NAA) and slight accumulation of lactate consistently existed. Preserved and metabolically active cortical areas, which are indicated by residual NAA, might be able to generate pathological magnetic activities under lactic acidosis. Such an area could be understood as a border zone between normal brain tissue and brain tissue that has been seriously damaged by tumors or associated edema, which should be intensively treated. This combination of imaging techniques gives insight into functional as well as metabolic aspects of pathological brain conditions.

Key Words * brain tumor * magnetic resonance spectroscopy * magnetoencephalography * $\text{N}$-acetyl aspartate

Major pathological conditions frequently encountered include brain tumors and associated brain edema. Although these conditions have been analyzed using various modalities such as electroencephalography (EEG), computerized tomography, magnetic resonance (MR) imaging, and positron emission
tomography, the relationship between radiological findings and neurological symptoms has not been clarified. Magnetic resonance imaging is best suited for estimating the size and location of structurally altered brain tissue, but it has been shown that areas of increased signal intensity detected on MR imaging are due to a variety of pathological changes ranging from colliquative necrosis to edema. Thus, MR imaging provides no information on the functioning of tissue that appears to be normal while adjacent to brain lesions.[8,11] Localized water-suppressed $^1$H MR spectroscopy is a powerful tool for investigating pathophysiological changes in the spatial distribution of spectroscopically visible metabolites within tissue in situ. Many investigators have applied $^1$H MR spectroscopy to determine the histological diagnosis of brain tumors and have found an increase in the ratio of choline-containing compounds (Cho) to creatine (Cr) and phosphocreatine, and a decrease in the ratio of N-acetyl aspartate (NAA) to Cr, with increasing histopathological grades of malignancy.[1,19] The metabolic profiles of the surrounding regions, however, have not yet been studied in detail.

Multichannel magnetoencephalography (MEG) reflects intracellular electrical current flow in the brain, providing direct information of neural activity. It has been mainly used for functional brain mapping of the primary cortex in which evoked magnetic fields are measured.[2] We have previously reported increased abnormal magnetic brain activities in the areas adjacent to cerebral infarction and have found that those lesions displaying the highest slow-wave activity showed significantly reduced NAA signal, which was well correlated with the dipole density of the slow waves.[13,21] Therefore we believe MEG could be a powerful tool with which to find functionally abnormal lesions that survive in pathological conditions.

To our knowledge, there have been no other studies in which the authors describe the changes of human brain function and metabolism in the presence of and in areas surrounding brain tumors. The purpose of this study was to investigate the increased abnormal magnetic brain activities and pathological metabolism in the border zone of tumor-related brain lesions by using spontaneous MEG and $^1$H MR spectroscopy.

**CLINICAL MATERIAL AND METHODS**

**Patient Population**

Studies were performed in patients who harbored an astrocytic tumor (four cases) or a meningioma (three cases). Table 1 summarizes all characteristics, symptoms, and histological diagnoses. Age-matched controls consisted of 10 volunteers in whom there was no history of cerebral events or MR imaging- or EEG-detected abnormality. Written informed consent was obtained from each patient and volunteer before participation in the studies.
Although detailed procedures have been described elsewhere,[13,21] we will briefly elucidate the methodological overview of this study.

### Proton MR Imaging and $^1$H Spectroscopy

Magnetic resonance images were acquired using a 1.5-tesla Magnetom Vision whole-body imager (Siemens AG, Erlangen, Germany). The volume of interest (VOI) within the brain was selected that contained the bulk of tumor and the surrounding region, but that excluded lipids of the skull and subcutaneous fat. The spin-echo signals were obtained using standard parameters (TE = 270 msec, TR = 1500 msec) and shorter echo time parameters (TE = 135 msec, TR = 1500 msec).

Raw data obtained using $^1$H MR spectroscopic imaging were reconstructed by standard postprocessing software, and four peaks (Cho, Cr, NAA, and lactate [Lac]) were assigned according to their positions as described in previous reports.[11,14] The signal intensity was measured by integrating each peak area in the complete stack of spectra. To avoid the uncertainties involved in absolute quantitation, the signal intensities were normalized to an internal standard, calculated from the peak integral of NAA, averaged over four voxels in the uninvolved occipital lobe, and expressed as relative metabolite concentrations.

### Spontaneous Magnetoencephalography

Spontaneous magnetic brain activity was measured in a magnetically shielded room by using a 2 X 37 channel biomagnetic system (Magnes II; Biomagnetic Technologies, San Diego, CA). The patient was placed supine on a bed with the head fixed between the two MEG dewars. In each case, a data set of 600 seconds was collected and then digitally filtered using a 2 to 6-Hz, 12.5 to 30-Hz, or 1 to 70-Hz bandpass notch filter for the analysis of slow- and fast-wave activities or spikes, respectively.

The customized program of principle component analysis automatically selected time sections in which only one component of interest was predominantly active[17] and spikes were manually selected. An equivalent current dipole was calculated every 2 msec over selected time sections, and only the dipoles in which there was a minimum correlation value of 0.8 were accepted. The highest dipole density of each abnormal brain activity was divided by the total number of the estimated dipoles to be standardized in each measurement, and it was three dimensionally projected onto MR images by using contour lines.[17,21] To superimpose the MEG results onto MR imaging and $^1$H MR spectroscopic imaging data, the digitized head surface data set was fitted to the reconstructed MR image headshape by using a surface-fit program.[16] To determine whether there were significant differences in dipole density between hemispheres (left and right), the Wilcoxon signed-ranks sum test was applied. The range

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**TABLE 1**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Diagnosis</th>
<th>Location</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54, M</td>
<td>GBM</td>
<td>It frontotemoral</td>
<td>rt hemiparesis, oromotor seizure, dysphasia</td>
</tr>
<tr>
<td>2</td>
<td>37, F</td>
<td>AA</td>
<td>It frontal</td>
<td>rt hemiparesis, generalized tonic-clonic seizure</td>
</tr>
<tr>
<td>3</td>
<td>61, M</td>
<td>AA</td>
<td>It parietooccipital</td>
<td>psychomotor seizure, hemianopsia, dysphasia</td>
</tr>
<tr>
<td>4</td>
<td>50, F</td>
<td>AA</td>
<td>It frontal</td>
<td>tonic-clonic seizure, dysphasia</td>
</tr>
<tr>
<td>5</td>
<td>53, M</td>
<td>menin</td>
<td>It frontoparietal</td>
<td>headache, generalized tonic-clonic seizure</td>
</tr>
<tr>
<td>6</td>
<td>42, F</td>
<td>menin</td>
<td>It frontoparietal</td>
<td>none</td>
</tr>
<tr>
<td>7</td>
<td>54, F</td>
<td>menin</td>
<td>It frontoparietal</td>
<td>none</td>
</tr>
</tbody>
</table>

* AA = anaplastic astrocytoma; GBM = glioblastoma multiforme; menin = meningioma.
between mean ± two standard deviations of normal volunteers was determined as normal limits of slow- and fast-wave magnetic activities.

RESULTS

**Spontaneous Magnetoencephalography**

In the 20 hemispheres of 10 normal volunteers, we confirmed that they had no spike activity, and no significant differences in slow-wave (p > 0.05) or fast-wave (p > 0.05) magnetic activities were shown (Table 2). The standardized highest density of dipoles fluctuated between 2.28 and 9.43 and between 1.77 and 6.16 in slow-wave and fast-wave magnetic activities, respectively (Table 2).

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Time (seconds)</th>
<th>Total Dipoles</th>
<th>Max Dipoles</th>
<th>D_{Standard}</th>
</tr>
</thead>
<tbody>
<tr>
<td>slow-wave activity</td>
<td>1</td>
<td>13</td>
<td>2841</td>
<td>232.25</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>13</td>
<td>1589</td>
<td>83.42</td>
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<td></td>
<td>3</td>
<td>10</td>
<td>1579</td>
<td>64.44</td>
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<tr>
<td></td>
<td>4</td>
<td>10</td>
<td>1763</td>
<td>26.79</td>
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<td></td>
<td>5</td>
<td>11</td>
<td>2497</td>
<td>59.51</td>
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<td></td>
<td>6</td>
<td>12</td>
<td>2500</td>
<td>54.8</td>
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<tr>
<td></td>
<td>7</td>
<td>10</td>
<td>1843</td>
<td>34.03</td>
</tr>
<tr>
<td>volunteers</td>
<td></td>
<td>±1.39</td>
<td>±363.14</td>
<td>±7.33</td>
</tr>
<tr>
<td>fast-wave activity</td>
<td>1</td>
<td>11</td>
<td>2167</td>
<td>36.86</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>11</td>
<td>2193</td>
<td>99.12</td>
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<td></td>
<td>3</td>
<td>12</td>
<td>1802</td>
<td>31.02</td>
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<td>4</td>
<td>12</td>
<td>2306</td>
<td>51.42</td>
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<td>5</td>
<td>12</td>
<td>2173</td>
<td>63.01</td>
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<td></td>
<td>7</td>
<td>13</td>
<td>2156</td>
<td>33.03</td>
</tr>
<tr>
<td>volunteers</td>
<td></td>
<td>±1.85</td>
<td>±496.65</td>
<td>±10.64</td>
</tr>
</tbody>
</table>

* Values for volunteers are expressed as the mean ± standard deviation. 
† Indicates that a value of \( D_{\text{Standard}} \) exceeds the normal range.

In four patients (Cases 1-3 and 5) highly concentrated dipoles of slow-wave components were shown and in one patient (Case 2) increased fast-wave magnetic activity was also observed. In three patients (Cases 4, 6, and 7) no significant differences in any activity were shown when compared with the volunteers. Although the bulk of every tumor (glioma or meningioma) was magnetically silent, the pathological activities (slow waves, fast waves, or spikes) were observed in cortical areas adjacent to the tumors. In the patient in Case 1 who harbored a glioblastoma multiforme, numerous spikes were disclosed in the identical area where slow-wave dipoles were concentrated (Fig. 1). Concerning the topographical relationship among slow waves, fast waves, and spikes, the source locations of fast-wave magnetic activity and spikes were nearly identical to those of slow-wave magnetic activity in each patient.
Fig. 1. Case 1. Monitoring and imaging studies. a: Actual MEG and electrocardiography recordings. Black bars drawn on slow-wave or spike selection indicate selected time intervals of slow wave component by principle component analysis or spikes by manual selection. b: An MEG isocontour map obtained at a selected time interval of a spike. The contour step is 500 femtotesla. c: An MEG isocontour map obtained at a different selected time interval of slow-wave component. d: Gadolinium-enhanced T₁-weighted MR image revealing ringlike enhanced tumor that exists mainly in the white matter. e: Dipole density plotting of spikes superimposed on the corresponding T₂-weighted MR image as isocontour lines. The maximum dipole density is observed in the left frontal region in the residual cortex invaded by the astrocytic tumor.
Findings on $^1$H MR Spectroscopy

Peaks corresponding to NAA, Cr, and Cho were readily assigned in the brains of healthy volunteers and were fairly constant in amplitude throughout the selected VOI (Table 3).

The bulk of the astrocytic tumor (voxel 1; Case 1) demonstrated relative increases of Cho and Lac, as well as an absence of NAA signal (Fig. 2). The surrounding cortical region of the tumor (voxel 2) showed remaining NAA signal, mild accumulation of Lac, and relatively decreased Cr signal compared with the other spectra. A color map of NAA demonstrated the heterogeneous distribution, especially the NAA signal that partly remained in the residual cortex (Fig. 2c).

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Cho$_{rel}$</th>
<th>Cr$_{rel}$</th>
<th>NAA$_{rel}$</th>
<th>Lac$_{rel}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.31</td>
<td>0.13†↓</td>
<td>0.44†↓</td>
<td>0.17††</td>
</tr>
<tr>
<td>2</td>
<td>1.14††</td>
<td>0.63</td>
<td>0.50†↓</td>
<td>0.16††</td>
</tr>
<tr>
<td>3</td>
<td>1.20††</td>
<td>0.44</td>
<td>0.59††</td>
<td>0.11††</td>
</tr>
<tr>
<td>5</td>
<td>0.31</td>
<td>0.39</td>
<td>0.42†↓</td>
<td>0.07††</td>
</tr>
<tr>
<td>volunteers</td>
<td>0.45</td>
<td>0.55</td>
<td>1.03</td>
<td>ND</td>
</tr>
</tbody>
</table>

* Values for volunteers are expressed as the mean ± standard deviation.
† Indicates that a value of $D_{Standard}$ exceeds the normal range.
Fig. 2. Case 1. a: Transverse T₂-weighted image obtained in the patient in whom glioblastoma multiforme is present. The large box within the image indicates the preselected region of interest (in the small squares 1 = the tumor itself and 2 = the residual cortex invaded by the tumor). In the unaffected brain region the averaged signal of four voxels ("N") is used as internal reference point. b: Proton MR spectrum revealing one of the voxels "N," (1), and (2). c: An NAA MR spectroscopic image demonstrating residual cortex along the cerebral hemisphere.

**Combination of ¹H MR Spectroscopy and Spontaneous MEG**

The patient in Case 1 was a 54-year-old man who had a 4-month history of focal oromotor seizures prior to undergoing ¹H MR spectroscopy and MEG. The tumor showed heterogeneous high intensity signals on T₂-weighted MR images and ringlike enhancement on contrast-enhanced T₁-weighted images, suggesting malignant glioma (Fig. 1). Frequent slow waves and spikes were found on a routine EEG study. Figure 3 shows the combined images obtained using ¹H MR spectroscopy and spontaneous MEG, as well as the continuous changes of dipole density of slow-wave activity and MR spectroscopic signal...
intensities along an indication line of interest. The indication line was drawn from the center of the highest density of slow-wave dipoles to the normal cortex. Markedly increased slow-wave magnetic activity (9.43 in dipole density) was observed in the frontal cortex where mild reduction of NAA (0.44 in NAA) and slightly elevated Lac (0.17 in Lac) were observed (Fig. 3). The tumor itself, however, was magnetically silent, demonstrating only Cho and Lac signals (Figs. 2 and 3). The estimated dipoles of the spikes were observed in the same region as those of the slow-wave activity. Histopathological evaluation of this patient's tumor revealed a glioblastoma multiforme.

Fig. 3. Case 1. Combined MEG and 1H MR spectroscopic images and DDP data. a: An NAA MR spectroscopic image (0-1.2-inch scale) and superimposed slow-wave magnetic activity in yellow isocontour lines of the DDP. b: A Lac MR spectroscopic image (0-0.3-inch scale) and slow-wave magnetic activity of the DDP. Slow-wave magnetic activity is seen in the residual cortex in the left frontal region where a mild reduction of NAA and slightly elevated Lac existed. The color map is coded on a scale comprising blue
The patient in Case 5 was a 53-year-old man who harbored a meningioma associated with brain edema in the left frontoparietal region. Three days before undergoing the imaging studies, he experienced a generalized tonic-clonic seizure and was transferred to our hospital. A routine EEG recording demonstrated frequent slow waves in the left hemisphere without any fast-wave or spike activity. The dipoles of slow-wave activity were highly concentrated in the cortical region adjacent to the edema that was associated with the meningioma. Residual NAA (0.42 in NAA) and mild accumulation of Lac (0.07 in Lac) were present in the lesion in which the estimated dipoles were concentrated (Fig. 4).

Fig. 4. a and b: T1- and T2-weighted transverse images of a patient with a meningioma. c: Serial changes in DDP of slow-wave component (yellow), NAA (green), and Lac (red) along a yellow indication line from "normal" tissue across the tumor, showing concentrated slow-wave magnetic activity at the center of brain edema in which mild reduction of NAA and slightly elevated Lac are present.

The regions of interest in which the highest slow wave in the MEG study existed were selected for comparison with metabolites (Cho, Cr, NA, and Lac) on 1H MR spectroscopy, because the dipoles of fast waves and spikes were concentrated in the same area as those of slow waves. Three patients (Cases 4, 6, and 7) in whom no abnormality was demonstrated on MEG study were omitted from further 1H MR spectroscopy data analysis. Table 3 provides the results obtained in the four remaining patients (Cases 1-3, and 5) in whom 1H MR spectroscopy demonstrated increased abnormal activities.

Consistent 1H MR spectroscopy findings of the lesions in all four patients consisted of mild reduction of...
NAA and slight accumulation of Lac. In two patients harboring anaplastic astrocytic tumors (Cases 2 and 3) an increased Cho signal was revealed in the area where the estimated dipoles of the slow waves were concentrated. The patient in Case 1 manifested significantly decreased Cr in the lesion without any change of Cho.

**DISCUSSION**

There have been no published reports in which the authors studied the pathological focal activities and simultaneously analyzed metabolic changes of functionally abnormal lesions in patients harboring brain tumors. In our analyses, increased slow-wave activity was observed in four cases, and fast-wave or spike activity was significantly increased in another case. Fast waves and spikes as well as slow waves were localized at almost the same cortical areas adjacent to the bulk of tumors, where mild reduction of NAA and slight accumulation of Lac were present in all patients in whom pathological activities existed.

There have been numerous EEG studies in which the investigators analyzed the relationship between pathological brain activity and brain lesions.[3,4] To verify the origins of slow waves, Gloor, et al.,[4] recorded brain activities and produced brain lesions by electrical coagulation in the cortex or white matter. They reported that slow-wave activity was observed only in cases of white matter lesions and concluded that the slow-wave activity is more likely generated by the disturbance of the afferent volley of activity from the thalamus to the cortex than by the disturbance of the activity in the cortex itself. In the patient in our Case 1 a slow-wave component was localized in the residual cortex, and a ringlike enhanced tumor containing necrotic tissue existed mainly in the white matter. In the patient in Case 5 the concentrated dipoles of slow waves were demonstrated in the cortical area adjacent to the edema existing mainly in the white matter. On the basis of these findings, white matter lesions, such as the tumors and peritumoral edema that spared serious cortical invasion, might possibly play a role in generating pathological brain activities.

Klatzo[15] has classified brain edema into two different types depending on pathophysiological mechanism: the "cytotoxic" type (due to a severe disturbance of cell metabolism associated with anoxia and ischemia) and the "vasogenic" type (occurring in association with brain tumors that result from a breakdown of the blood-brain barrier to macromolecules). The edema fluid leaks from brain vessels into the extracellular space and concentrates mostly in the white matter. Peritumoral edema consists mainly of the vasogenic edema, and it might not directly damage the cortical tissue.[10,11] Although these different types of the edema uniformly demonstrate high intensity on T2-weighted MR images, Kamada and associates[11] have reported that 1H MR spectroscopy is capable of revealing characteristic metabolic differences between peritumoral edema and ischemic stroke. They showed that slightly decreased NAA and elevated Lac are typical 1H MR spectroscopy-demonstrated patterns of peritumoral edema and that the edematype MR spectra completely recovered after successful treatment. In one of our patients (Case 5) similar MR spectroscopy profiles were shown with the metabolic pattern of vasogenic edema in the lesion where the dipoles were concentrated. Therefore, it was expected that the metabolic and functional profiles of the lesion would recover completely after successful removal of the meningioma.

In the edematous lesion Lac is the endproduct of anaerobic metabolism and generally serves as a marker of glycolysis. Hanstock, et al.,[6] and Hossman[7] found the accumulation of Lac in the experimental vasogenic edema as demonstrated by 1H MR spectroscopy[6] and biochemical analysis.[7] These findings suggested that peritumoral edema might cause energy failure and functional disruption of the
white matter in which the edematous fluid mainly exists and, therefore, that peritumoral edema might play an important role in generating slow waves.

Cerebral NAA was found in a higher concentration in gray matter than in white matter, and it rapidly disappeared when the neurotoxin kainic acid was injected into neurons.[9,20] The presence of an NAA signal was therefore considered a neuronal marker, and decreases in the NAA signal have been shown to be an indication of neuronal loss on 1H MR spectroscopy studies.[8,18] Graham, et al.[5] have recently demonstrated that NAA and Lac levels can be used to predict clinical prognosis. Kamada and coworkers[12] have pointed out that various intensities of NAA in the lesions involving the motor cortex could reflect the severity of paresis. In this study, consistent 1H MR spectroscopy findings, which were obtained in the lesions in which the estimated dipoles of pathological activities were concentrated, were mild reduction of NAA and slight accumulation of Lac; these findings suggest the functional disruption of brain tissue. In the patient in Case 1 numerous slow waves and spikes were clearly demonstrated in the residual cortex, where a reduced NAA signal still remained. On the basis of these findings, a residual NAA signal in those lesions in which abnormal activities are displayed, as we observed, suggests that surviving and viable neurons, which produce NAA signal, are able to function and also to generate pathological activities. The NAA signal might, therefore, reflect neuronal function as well as the numbers of damaged but still surviving neurons. It is inferred from this that mild accumulation of Lac and slightly decreased NAA might be fundamental changes in the brain metabolism that produce pathological activities.

Because the spatial resolution in this 1H MR spectroscopy study was 12.5 x 12.5 x 15 mm in the X, Y, and Z direction, each VOI might possibly contain partial volume effect. We acquired three orthogonal T2-weighted images to delineate an area around a tumor and by which, estimate the proportion of the lesion within a VOI so as to avoid this effect. Our study demonstrated that the intensity of the VOI was relatively homogeneous, which in one patient (Case 5) was high on T2-weighted images, indicating edematous tissue; in another patient (Case 1) there was iso- and no enhancement on T1-weighted, and slightly high intensity on T2-weighted images, indicating residual cortical tissue. Thus, we believe we could minimize this effect in the VOI. In addition, the estimated dipoles were concentrated in an area to a certain extent in each MEG experiment. It is, therefore, reasonable to select the VOI size (12.5 x 12.5 x 15 mm) for this combined study, taking the distribution of estimated MEG dipoles into account.

Although EEG can sometimes be used to detect the affected neurological function, localization is difficult because of the different conductivities of the skull, the brain, and inhomogeneities in the head. Previous EEG studies have revealed an increase in pathological activities such as slow and fast waves and spikes in association with brain tumors.[3,4]

In our analysis of spontaneous MEG data, we observed increased pathological activities, and the ability of MEG to localize the sources of the abnormal brain activities was clearly demonstrated. The customized principle component analysis can be used to determine, for each time section, the number of components and the contribution of each component to the signal. Because those time sections are used to localize single equivalent dipoles in which one component dominates the signal, the single equivalent dipole should be a relatively adequate source model. As a result, the increased abnormal activities were exactly localized only in border zones of tumors. However, a single equivalent dipole model is still an insufficient method for localizing more complex activities.
In this combined method the MEG, $^1$H MR spectroscopy and MR imaging data can be easily and readily fused on the same planes, and the relationships among them can be easily obtained. Preserved and metabolically active cortical tissue with a remaining NAA signal and increased pathological magnetic activities under lactic acidosis (mild accumulation of Lac) may be interpreted as a border zone between normal brain tissue and brain tissue that has been seriously damaged by tumors or associated brain edema. Future studies will need to be focused on identifying the border zone as a region of reversible brain damage, which should be intensively treated and carefully observed. We believe that the combined implementation of these two different modalities gives insight into functional as well as metabolic aspects of pathological brain conditions including the border zones of brain lesions.

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References


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