Improved cerebral function in mesial temporal lobe epilepsy after subtemporal amygdalohippocampectomy

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The functional changes that occur throughout the human brain after the selective removal of an epileptogenic lesion remain unclear. Subtemporal selective amygdalohippocampectomy (SAH) has been advocated as a minimally invasive surgical procedure for patients with medically intractable mesial temporal lobe epilepsy (MTLE). We evaluated the effects of subtemporal SAH on cerebral glucose metabolism and memory function in 15 patients with medically intractable MTLE with hippocampal sclerosis using [18F]-fluorodeoxyglucose PET (FDG-PET) and the Wechsler Memory Scale-Revised. The patients were evaluated before and 1–5 years (mean 2.6 years) after surgery. In patients with MTLE of the language-dominant hemisphere, the basal temporal language area was preserved by this surgical approach. Voxel-wise comparison of FDG-PET images was conducted using SPM5 to identify the brain regions showing postoperative changes in glucose metabolism (height threshold, \(P = 0.01\) corrected for multiple comparisons; extent threshold, 100 voxels). During spatial normalization of the postoperative FDG-PET images, we used cost-function masking to minimize any inappropriate image distortion as a result of the abnormal signal within the surgically resected region. Postoperative glucose metabolism increased in extratemporal areas ipsilateral to the affected side, such as the dorsolateral prefrontal cortex, and the dorsomedial and ventromedial frontal cortices. Glucose metabolism also increased in the bilateral inferior parietal lobules and in the remaining temporal lobe regions remote from the resected mesial temporal region, such as the superior temporal gyrus and the temporal pole. By contrast, postoperative glucose metabolism decreased only in the mesial temporal area adjacent to the resected region. Postoperative verbal memory, delayed recall and attention/concentration scores were significantly better than preoperative scores regardless of the resected side. This study suggests that the selective removal of the epileptogenic region in MTLE using a subtemporal approach improved cerebral glucose metabolism in the areas receiving projections from the affected mesial temporal lobe. Cognitive improvement might result from a combination of good seizure control and minimizing the regions of the brain with postoperative functional impairment.
Keywords: FDG-PET; memory; postoperative change; selective amygdalohippocampectomy; temporal lobe epilepsy

Abbreviations: AED = antiepileptic drug; FDG = $[^{18}F]$-fluorodeoxyglucose; IQ = intelligence quotient; MTLE = mesial temporal lobe epilepsy; SAH = selective amygdalohippocampectomy

Introduction

Mesial temporal lobe epilepsy (MTLE) with hippocampal sclerosis is the most common localization-related epilepsy in adults. MTLE is characterized by epileptic activity arising from the mesial temporal region where there are neuropathological changes. MTLE is also associated with broad temporal lobe functional abnormalities, shown by an alteration of cerebral glucose metabolism and neuropsychological deficits such as memory dysfunction. Moreover, neuroimaging studies using $[^{18}F]$-fluorodeoxyglucose (FDG), $[^{11}C]$-flumazenil PET or magnetic resonance spectroscopy have shown that functional abnormalities extend beyond the temporal lobe (Arnold et al., 1996; Hammers et al., 2002; Mueller et al., 2004).

For patients with medically intractable MTLE, surgery is one of the more favourable options in order to achieve good seizure control (Wiebe et al., 2004). Anterior temporal lobectomy, where the anterior one-third of the temporal lobe is resected, has been a standard surgical procedure because the anterior part of the temporal lobe was considered to be a functionally `silent area’ (Gibbs et al., 1948; Falconer et al., 1955). However, recent FDG-PET and neuropsychological studies have described a postoperative decrease in cerebral glucose metabolism and associated cognitive impairments following anterior temporal lobectomy (Lee et al., 2002; Joo et al., 2005; Tellez-Zenteno et al., 2007). Decreased glucose metabolism inside and outside the remnant temporal lobe is assumed to be the result of deafferentiation following the massive resection of anterior temporal structures (Joo et al., 2005).

Selective amygdalohippocampectomy (SAH) has been advocated as a less-invasive surgical procedure in order to preserve postoperative cerebral functions. Trans-sylvian SAH, however, resulted in postoperative verbal memory decline in patients with MTLE of the language-dominant hemisphere (Gleissner et al., 2002; Gleissner et al., 2004; Morino et al., 2006; Helmstaedter et al., 2008). One hypothesis is that the procedure disconnects the long-tract fibres that pass through the white matter of the temporal stem, such as the uncinate fasciculus or the cholinergic projection fibres from the nucleus basalis of Meynert (Selden et al., 1998; Ikeda et al., 2005; Helmstaedter et al., 2008).

It is thought that subtotal SAH could offer an alternative procedure that prevents damage to the lateral temporal neocortex and temporal stem white matter (Hori et al., 1993; Park et al., 1996). Recent studies indicate that subtotal SAH results in the preservation or improvement of postoperative cognitive function in patients with intractable MTLE (Hori et al., 2003; Mikuni et al., 2006; Hori et al., 2007). A preliminary study suggested that subtotal SAH preserving the basal temporal language area achieved good seizure control and improved verbal memory in patients with MTLE in the language-dominant hemisphere (Mikuni et al., 2006). Although such neuropsychological studies suggest that cerebral function improves after subtemporal SAH, the neural substrate for this remains unclear.

The purpose of the current study was to evaluate the effects on cerebral glucose metabolism and memory function of subtemporal SAH that preserved the basal temporal language area in patients with medically intractable MTLE. Elucidating the functional changes in the human brain after the selective removal of an epileptogenic lesion is of both clinical and neuroscientific interest.

Patients and Methods

Patients

All patients over the age of 16 years who underwent subtemporal SAH for intractable MTLE with hippocampal sclerosis between 2002 and 2006 at Kyoto University Hospital were considered potential candidates for the study. Among them, 15 patients met the inclusion criteria for this study (8 left MTLE patients and 7 right MTLE patients). All patients underwent preoperative and postoperative neuropsychological testing. All but two patients (Patients 6 and 14) consented to undergo postoperative FDG-PET. The interval between surgery and postoperative assessment was 1–5 years (mean 2.6 years). The results of the neuropsychological tests 1 year after surgery in five patients with dominant-side MTLE have been reported elsewhere (Mikuni et al., 2006).

The inclusion criteria were as follows: (i) medical history and seizure semiology consistent with MTLE, such as epigastric, autonomic or psychic aura, followed by motor arrest, progressive clouding of consciousness, oro-alimentary or manual automatisms and autonomic phenomena; (ii) a unilateral epileptic focus in the anterior temporal regions confirmed by prolonged video-electroencephalography (EEG) monitoring and (iii) unilateral hippocampal sclerosis detected by conventional 1.5 T MRI and glucose hypometabolism determined by FDG-PET in the affected side of the temporal lobe in accordance with the EEG findings. The exclusion criteria were as follows: (i) focal neurological abnormalities on physical examination or psychiatric diseases; (ii) significant past medical history suggesting causes of temporal lobe epilepsy other than MTLE with hippocampal sclerosis (that is, encephalitis or severe head trauma); (iii) MRI abnormalities including significant brain atrophy outside the mesial temporal lobe; (iv) epileptic paroxysms in the extratemporal area on EEGs and (v) a full-scale intelligence quotient (IQ) <65.

The preoperative full-scale IQ was significantly lower in patients with dominant-side MTLE than in those with non-dominant-side MTLE. There were no statistical differences between the two groups with respect to the male/female ratio, level of education (number of years), duration of the disease, age at surgery, postoperative interval or number of seizure-free patients within each group. At postoperative evaluation, the numbers or dosages of antiepileptic drugs (AEDs) remained unchanged from the preoperative state in seven patients, decreased in six patients (based on >2 years freedom from seizures) and increased in two patients because of poor seizure control.
This study was approved by the Ethics Committee of the Kyoto University Graduate School of Medicine, and written informed consent was obtained from all patients (Tables 1 and 2).

Surgical procedures and outcome

The language-dominant hemisphere was determined pre-surgically by the Wada test. In one patient, the right hemisphere was language-dominant; as she was to undergo surgery on the left hemisphere, she was classified into the non-dominant MTLE group. In patients with dominant-side MTLE, the basal temporal language area was defined using long-term subdural electrodes (Usui et al., 2003). All patients underwent SAH by a combined subtemporal, transventricular, transchoroidal fissure approach. When the temporal horn was opened from the basal surface of the temporal lobe, the basal temporal language area was preserved and a transsulcal approach was used as much as possible to avoid damage to the surrounding cortices. The details of the surgical procedure are provided elsewhere (Miyamoto et al., 2004; Mikuni et al., 2006). Intraoperative electrocorticograms were performed and additional corticotomies were conducted in the small, potentially epileptogenic areas adjacent to the hippocampus. In all patients, hippocampal sclerosis was confirmed by pathological examination.

At the postoperative evaluation, 13 of the 15 patients were seizure-free following subtemporal SAH. The overall seizure-free ratio (Engel class I) was 87% (95% confidence interval 62–96%). This is comparable with the seizure-free rates achieved using other surgical procedures for patients with MTLE with MRI-defined hippocampal sclerosis; freedom from disabling seizures has been reported in 66–89% of patients 2–3 years after a non-subtemporal SAH or anterior temporal lobectomy (Wieser et al., 2003; Paglioli et al., 2004; Janszky et al., 2005; Paglioli et al., 2006).

Image data acquisition

Preoperative and postoperative FDG-PET scans were performed using a PET scanner (Advance, General Electric Medical Systems, Milwaukee, WI, USA). [18F]-FDG at 370 MBq (10 mCi) was injected intravenously.
into patients who had been fasting for at least 4 h. Then, 40 min after the administration of the radiotracer, 35 slices of brain-emission images were acquired over a 20-min period. The patients were studied in an awake, resting state, with their eyes closed and their ears unplugged in a dimly lit environment. Although EEG was not performed during the FDG-PET study, ictal studies were unlikely, because no abnormal behaviours were observed, and patients did not report any subjective manifestations of seizures during the examination. Emission images were reconstructed into a 128 × 128 matrix image with a pixel size of 1.95 × 1.95 mm² and a slice thickness of 4.25 mm. All reconstructed images were corrected for attenuation using ⁶⁸Ge-⁶⁸Ga transmission scans performed before the actual scan.

To increase the accuracy of the spatial normalization in the post-operative FDG-PET images when performing voxel-wise analysis using mask images for the surgically resected region, three-dimensional anatomical MRI images were obtained on the same day as the postoperative FDG-PET scanning. The scans were performed using a 3 T MRI scanner (Trio, Siemens, Erlangen, Germany) with the following sequence: magnetization-prepared rapid-acquisition gradient-echo; repetition time (TR)/echo time (TE) = 2000/4.38; matrix size, 240 × 256; field of view, 24 cm; slice thickness, 1.0 mm.

FDG-PET data analyses

In order to increase the statistical power of the group analyses, the FDG-PET images from the patients with right MTLE were flipped horizontally so that the epileptogenic zone was lateralized to the left side in all of the images. The voxel-wise analysis of the FDG-PET images was performed using SPM5 (Wellcome Department of Imaging Neuroscience, UCL, London, UK).

The preoperative FDG-PET images were spatially normalized to fit the standard FDG-PET template using affine and nonlinear warping. In the presence of a focal brain lesion, automated methods for spatial normalization are liable to cause inappropriate image distortion due to the abnormal signal within the lesion, particularly during nonlinear transformation; furthermore, cost-function masking provides better and more reliable matching to the standard template (Brett et al., 2001). Thus, we used cost-function masking with a mask image for the surgically resected lesion when normalizing the postoperative FDG-PET images. The procedure was as follows. The surgically resected region was defined in the anatomical postoperative MRI of each individual using MRICron (http://www.sph.sc.edu/comd/rorden/mricron/), as shown in Fig. 1B. This mask image was modified with a value of 0 within the resected region and a value of 1 elsewhere (Fig. 1C). The mask image was smoothed and expanded using a Gaussian filter of a full-width at a maximum (FWHM) of 8 mm with a 0.1% threshold border. This resulted in the expansion of 9.6 mm of the masked area (Fig. 1D). Then, the anatomical MRI was co-registered onto the postoperative FDG-PET image of each individual using the mutual information algorithm implemented in SPM5, and the transformation matrix was adjusted to the expanded mask image of the same subject. The result was used for the cost-function masking during the spatial normalization of the postoperative FDG-PET image of each individual. Note that this process does not imply that the areas under the mask remained untransformed, but rather that a continuation of the solution for the unmasked portion of the image was applied to the masked regions.

The spatially normalized images were smoothed with an isotropic Gaussian kernel with 16 mm FWHM to increase the signal-to-noise ratio and to account for normal inter-individual variation in macroanatomy. To remove the effects of global activity, each voxel count was normalized to the total count of the whole brain using proportional scaling (Van Bogaert et al., 2000). A paired t-test was used for the voxel-wise group comparison of the FDG-PET images before and after surgery. We investigated brain regions showing increases and decreases in glucose metabolism after surgery, at a height threshold of P = 0.01 corrected for multiple comparisons using the false discovery rate (FDR) algorithm and an extent threshold of 100 voxels (Genovese et al., 2002). Regional glucose hypometabolism adjacent to the surgically resected region—due to deafferentation or the partial volume effect—could reduce the global count in the postoperative FDG-PET images. This might result in the overestimation of increases and the underestimation of decreases in postoperative regional glucose metabolism. To minimize this effect, we first confirmed the region of the brain showing a postoperative decrease in glucose metabolism, which was located in a restricted area adjacent to the resected region (Fig. 2). This area was expanded as described above and used as an explicit mask in the group-comparison analysis. Again, each voxel count was normalized to the total count by masking this area, and the second analysis was conducted to find the brain regions that showed either an increase or a decrease in glucose metabolism.

Fig. 1 Process of constructing the cost-function masking images for the spatial normalization of the postoperative FDG-PET images in a representative case. (A) A postoperative anatomical MRI of each individual was obtained. (B) The surgically resected region was defined manually. (C) The mask image was made with the value of 0 within the resected region and 1 elsewhere. (D) The mask image was expanded using a Gaussian filter of 8 mm FWHM with a 0.1% threshold border and then was coregistered onto the postoperative FDG-PET image of each individual.
For visualization, the significant clusters were projected onto a surface-rendered anatomical template provided by SPM5. The spatial coordinates of the local maxima from the $t$-statistics were used to identify the corresponding brain areas according to the atlas of Talairach and Tournoux (Talairach and Tournoux, 1988). The non-linear transformation of the Montreal Neurological Institute (MNI) coordinates to the Talairach coordinates was performed using appropriate converter software (mni2tal.m; http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml).

**Neuropsychological tests**

Preoperative general intelligence was assessed using the Japanese version of the Wechsler Adult Intelligence Scale-Revised (WAIS-R). Preoperative and postoperative memory function was evaluated using the Wechsler Memory Scale-Revised (WMS-R). Postoperative WMS-R testing and the FDG-PET scanning were conducted within a 1-week interval. The memory scores were evaluated in each of four domains: verbal memory, visual memory, delayed recall and attention/concentration.

**Statistical analyses**

A two-sample $t$-test and Fisher’s exact test were used for the statistical analyses of the clinical features. To evaluate the effect of surgery on memory function at the group level, we evaluated the changes in the WMS-R memory scores using a repeated-measures analysis of variance (ANOVA), with time (before or after surgery) as the within-subject variable, and group (MTLE in the dominant or non-dominant hemisphere) as the between-group variable. To assess the change in memory function at the individual level, we counted the number of patients showing an increase or a decrease of 1 SD or more of the preoperative scores on each memory variable in WMS-R. We used SPSS 16.0J for Windows for these statistical analyses.

**Results**

**FDG-PET**

The postoperative glucose metabolism decreased only in the mesial temporal lobe ipsilateral to the resection, in regions such as the parahippocampal gyrus and the area immediately adjacent to the resected hippocampus (Fig. 2 and Table 3). When we reanalysed the data using this region as an explicit mask, no additional areas were detected that showed decreased glucose metabolism. The group comparison using the explicit mask revealed that postoperative glucose metabolism increased in the middle and inferior frontal gyri (BA 9, 46, 44 and 45), the dorsomedial and ventromedial frontal gyri (BA 8, 10, 9, 6 and 11), the posterior part of the superior temporal gyrus (BA 22/42) and the temporal pole (BA 38) ipsilateral to the resection, and bilaterally in the inferior parietal lobules (BA 7/40) (Fig. 3 and Table 4). Even in the analysis conducted without the explicit mask, no increase in glucose metabolism was detected adjacent to the surgically resected region.

**Neuropsychological tests**

In both the dominant and non-dominant MTLE groups, there was a trend towards postoperative improvement in all domains of memory function. For verbal memory, delayed recall and attention/concentration, the repeated-measures ANOVA demonstrated significant effects of time of testing ($P<0.005$ for verbal memory and delayed recall; $P<0.05$ for attention/concentration), but did not show a time $\times$ group interaction ($P=0.94$ for verbal memory; $P=0.94$ for overall delayed recall; $P=0.77$ for attention/concentration). For visual memory, there was no significant effect of time of testing ($P=0.09$) and no time $\times$ group interaction ($P=0.98$) (Fig. 4). At the individual level analyses, postoperative improvement was more frequent in the dominant side MTLE group for delayed recall and in the non-dominant side MTLE group for attention/concentration, although it did not reach significance (Table 5).

**Discussion**

This study had three main findings related to the change in human cerebral function after the selective removal of the epileptogenic region in the mesial temporal lobe using a subtemporal

### Table 3 Brain regions showing significant decrease in glucose metabolism after subtemporal amygdalohippocampectomy. $P<0.01$, FDR-corrected; without an explicit mask

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Side</th>
<th>Coordinate of the peak</th>
<th>T-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>x y z</td>
<td></td>
</tr>
<tr>
<td>Hippocampus</td>
<td>L</td>
<td>-24 -15 -19</td>
<td>14.07</td>
</tr>
<tr>
<td>Parahippocampal gyrus</td>
<td>L</td>
<td>-30 -7 -23</td>
<td>12.10</td>
</tr>
</tbody>
</table>

L = ipsilateral side to the focus.
approach: first, compared to the preoperative state, glucose metabolism increased in many extratemporal regions as well as in the remnant temporal lobe; second, the postoperative decrease in glucose metabolism was limited to the area around the resected region and third, memory function improved regardless of the resected side.

**Fig. 3** Brain regions showing a significant increase (red) and decrease (blue) in glucose metabolism after subtemporal SAH. The epileptogenic zone was lateralized to the left side. Note that the results of the group-comparison analysis without an explicit mask are displayed for decrease in glucose metabolism, because when the data were reanalysed with an explicit mask no additional brain regions were detected. Height threshold was set at $P = 0.05$, FDR-corrected for display purposes. Even at the lower statistical threshold, the postoperative decrease in glucose metabolism was limited to the mesial temporal area adjacent to the resected region. $n = 13$; paired $t$-test; extent threshold of 100 voxels.

**Table 4** Brain regions showing significant increase in glucose metabolism after subtemporal amygdalohippocampectomy. $P < 0.01$, FDR-corrected; with an explicit mask

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Brodmann area (BA)</th>
<th>Side</th>
<th>Coordinate of the peak $xyz$</th>
<th>$T$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle and inferior frontal gyri</td>
<td>[9/46/44/45]</td>
<td>I</td>
<td>$-61$ 11 27</td>
<td>10.76</td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>[22/42]</td>
<td>I</td>
<td>$-57$ 23 25</td>
<td>5.58</td>
</tr>
<tr>
<td>Inferior parietal lobule</td>
<td>[7/40]</td>
<td>I</td>
<td>$-55$ 22 20</td>
<td>7.75</td>
</tr>
<tr>
<td>Dorsomedial frontal gyrus</td>
<td>[8/10/9/6]</td>
<td>I</td>
<td>$-30$ 46 50</td>
<td>7.25</td>
</tr>
<tr>
<td>Temporal pole</td>
<td>[38]</td>
<td>C</td>
<td>24 $-52$ 47</td>
<td>7.70</td>
</tr>
<tr>
<td>Orbitofrontal gyrus</td>
<td>[11]</td>
<td>I</td>
<td>$-8$ 50 $-13$</td>
<td>5.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I</td>
<td>$-68$ 48 $-19$</td>
<td>4.68</td>
</tr>
</tbody>
</table>

$I = \text{ipsilateral side to the focus, } C = \text{contralateral side to the focus.}$
Increased glucose metabolism in the projection areas

Animal studies have shown that cortical hypometabolism in remote brain regions is not present when the putative neural pathway from the epileptic focus is destroyed before the epileptic focus is produced (Bruehl et al., 1998). Thus, the transmission of the epileptic activity via the neural connections from the focus is thought to suppress cerebral glucose metabolism in regions remote from the epileptic focus. Although such clear evidence has not been found in human studies, the combination of FDG-PET and EEG in humans has revealed that both clinical and subclinical epileptic activity coincides with interictal glucose hypometabolism outside the focus region (Merlet et al., 1996; Chassoux et al., 2004).

In the present study, glucose metabolism increased compared to the preoperative state in many extratemporal areas in the frontal and parietal lobes. These particular areas are thought to receive direct projections from the area adjacent to the resected mesial temporal region. The projection fibres from the parahippocampal gyrus to the frontal lobe consist of two pathways: the ventral limbic pathway and the dorsal limbic pathway (Petrides and Pandya, 2002). The ventral pathway includes two groups of fibres: the caudal pathway, which enters the extreme capsule and terminates in the dorsolateral prefrontal cortex (BA 9, 46); and the rostral pathway, which runs through the uncinate fasciculus towards the ventromedial prefrontal cortex (BA 10, 11). By contrast, the dorsal limbic pathway runs as a part of the cingulum bundle, with branches to the dorsomedial frontal regions, and directs its fibres towards the frontal pole (Mori et al., 2005). Another contingent of parahippocampal efferent fibres project to the inferior parietal lobule (Van Hoesen, 1982). In addition, the anterior region of the inferior temporal cortex (area TE) and the posterior region of the inferior temporal cortex (area TEO) in macaque monkeys connect with the inferior frontal gyrus, including the homologue of BA 45, and these areas also project to the inferior parietal lobule (Ungerleider et al., 1989; Webster et al., 1994). Among these areas, the prefrontal region was shown to be a major route of seizure propagation from the mesial temporal focus in a depth EEG study (Lieb et al., 1991). Particularly, the dorsolateral prefrontal cortex is the region in which interictal glucose hypometabolism was detected in association with high seizure-frequency and the same region showed ictal hyperperfusion in patients with MTLE (Van Paesschen et al., 2003; Takaya et al., 2006). The present results indicate that a decrease in the epileptic activity emanating from the seizure focus in the mesial temporal lobe improved interictal cerebral glucose metabolism in a wide range of projection areas.

Table 5 Individual changes in memory scores after subtemporal SAH

<table>
<thead>
<tr>
<th>Memory variable</th>
<th>Dominant side (n = 7)</th>
<th>Non-dominant side (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gain</td>
<td>Loss</td>
</tr>
<tr>
<td>Verbal</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Visual</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Delayed (verbal + visual)</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Attention/Concentration</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Cells provide the number of patients showing an increase or a decrease of one standard deviation or more of the preoperative scores on each memory variable in WMS-R.

Increased glucose metabolism in the projection areas

In the present study, glucose metabolism increased compared to the preoperative state in many extratemporal areas in the frontal and parietal lobes. These particular areas are thought to receive direct projections from the area adjacent to the resected mesial temporal region. The projection fibres from the parahippocampal gyrus to the frontal lobe consist of two pathways: the ventral limbic pathway and the dorsal limbic pathway (Petrides and Pandya, 2002). The ventral pathway includes two groups of fibres: the caudal pathway, which enters the extreme capsule and terminates in the dorsolateral prefrontal cortex (BA 9, 46); and the rostral pathway, which runs through the uncinate fasciculus towards the ventromedial prefrontal cortex (BA 10, 11). By contrast, the dorsal limbic pathway runs as a part of the cingulum bundle, with branches to the dorsomedial frontal regions, and directs its fibres towards the frontal pole (Mori et al., 2005). Another contingent of parahippocampal efferent fibres project to the inferior parietal lobule (Van Hoesen, 1982). In addition, the anterior region of the inferior temporal cortex (area TE) and the posterior region of the inferior temporal cortex (area TEO) in macaque monkeys connect with the inferior frontal gyrus, including the homologue of BA 45, and these areas also project to the inferior parietal lobule (Ungerleider et al., 1989; Webster et al., 1994). Among these areas, the prefrontal region was shown to be a major route of seizure propagation from the mesial temporal focus in a depth EEG study (Lieb et al., 1991). Particularly, the dorsolateral prefrontal cortex is the region in which interictal glucose hypometabolism was detected in association with high seizure-frequency and the same region showed ictal hyperperfusion in patients with MTLE (Van Paesschen et al., 2003; Takaya et al., 2006). The present results indicate that a decrease in the epileptic activity emanating from the seizure focus in the mesial temporal lobe improved interictal cerebral glucose metabolism in a wide range of projection areas.

The topography of the improved glucose metabolism in the affected temporal lobe is another point of interest in the present study. The cerebral glucose metabolism increased as compared to the preoperative state in areas in the remnant temporal lobe distant from the resected epileptogenic lesion, such as the superior temporal gyrus and the temporal pole. These areas have reciprocal connections to the parahippocampal gyrus (Van Hoesen, 1982). However, glucose metabolism remained unchanged in the other areas around the mesial temporal region. FDG-PET and diffusion MRI studies have shown that functional abnormalities extend to a wide area around the epileptogenic region in the temporal lobe in patients with intractable MTLE (Arnold et al., 1996; Chassoux et al., 2004; Concha et al., 2005). The two-hit hypothesis has been proposed to explain the generating mechanism of MTLE, in which a combination of inherent pre-existing abnormalities in the temporal lobe, due to genetic factors or developmental abnormalities, and precipitating events, such as prolonged febrile seizures, eventually cause an epileptogenic lesion in the hippocampus (Velisek and Moshe, 2003; Wieser, 2004; Love, 2005). According to this hypothesis, pre-existing abnormalities in the affected temporal lobe remain even after the epileptogenic lesion is selectively removed and seizures cease. In fact, a recent diffusion MRI study revealed that the abnormal integrity of the axonal microenvironment persisted even after the cessation of epileptic activity in the major limbic white-matter pathways such as the fornix and cingulum adjacent to the mesial temporal lobe (Concha et al., 2007). The present findings suggest that functional abnormalities in the cortex around the hippocampus also remain after the selective removal of the epileptogenic region in MTLE.

AEDs cause a variable degree of reduction in global glucose metabolism, but no consistent region-specific cortical effects have been noted (Theodore et al., 1986a, b, 1989; Gaillard et al., 1996). In the present study, the dose or number of AEDs remained unchanged or decreased postoperatively in all but two patients, which we assume would increase the postoperative global glucose metabolism in each patient. To control for this, we normalized the value of each voxel to the global mean in each scan. This method is thought to remove the effects of the inter-scan variation in global counts on the patterns of regional glucose metabolism. However, in the present study, it is probable that there was an underestimation of the increase and an overestimation of the decrease in postoperative regional glucose metabolism. Thus, the brain regions showing a postoperative improvement in glucose metabolism are likely to be more extensive.

Decreased glucose metabolism is limited to the mesial temporal region

In the present study, while a broadly distributed improvement in glucose metabolism was seen, the postoperative decrease in glucose metabolism was limited to the mesial temporal area adjacent to the resected region. After anterior temporal lobectomy, glucose
metabolism decreased widely in remote areas such as the basal ganglia, thalamus, fusiform gyrus, lingual gyrus and posterior insular cortex (Joo et al., 2005b). These metabolic changes are assumed to be the result of deafferentiation following the resection of anterior temporal structures. A study using a region-of-interest method reported decreased glucose metabolism in the ipsilateral temporal pole after trans-sylvian SAH (Dupont et al., 2001). This could be attributed to the disconnection of the fibre tracts that project to the temporal pole through the deep white matter of the temporal lobe, such as the uncinate fasciculus or the lateral cholinergic pathway from the nucleus basalis of Meynert (Selden et al., 1998; Ikeda et al., 2005; Helmstaedter et al., 2008). In the present study, the sparing of these dense bundles by the subtemporal approach might have led to the preservation of glucose metabolism in the remote projection areas of the brain. However, FDG-PET analyses are substantially different between the two studies. Thus, a direct comparison of the two surgical procedures (trans-sylvian SAH versus subtemporal SAH) using the same FDG-PET analyses is expected to yield conclusions.

Improved memory function

The postoperative decline in verbal memory impairs cognitive performance in patients with MTLE. Verbal memory function after anterior temporal lobectomy or trans-sylvian SAH deteriorates at the group level in patients with dominant-side MTLE, whereas it tends to improve in patients with non-dominant-side MTLE (Novelly et al., 1984; Lee et al., 2002; Morino et al., 2006). In the present study, an improvement in verbal memory was observed regardless of the resected side. Previous studies have reported that subtemporal SAH might spare verbal memory decline in patients with dominant-side MTLE (Mikuni et al., 2006; Hori et al., 2007). Preservation of the basal temporal language area resulted in improved verbal memory 1 year after the operation, even when the AED dosage remained unchanged (Mikuni et al., 2006). The present study also shows a long-lasting improvement in verbal memory following subtemporal SAH. Although functional neuroimaging studies have emphasized the contribution of frontal and mesial temporal regions to memory, a study using recordings of microelectrodes placed on the human cortex revealed that the inferior lateral and basal temporal cortices were involved in verbal memory tasks (Ojemann et al., 2002). In fact, a broader resection of the inferior or basal temporal gyri of the language-dominant hemisphere was associated with postoperative decline in the verbal delayed recall score in patients with MTLE (Joo et al., 2005a). The basal temporal language area is located between 10 mm and 75 mm posterior to the temporal tip, and is important in processing verbal information (Lüders et al., 1991; Schaffler et al., 1996). In the Japanese language, this area has been associated with the processing of both kanji (Japanese morphograms) and kana words (Japanese syllabograms) (Nakamura et al., 2000; Usui et al., 2003, 2005). In the present study, the seizure activity ceased in the language-dominant side of the temporal lobe following surgical treatment in which the basal temporal language area and the fibre tracts passing through the temporal stem were preserved. This could result in the improvement of verbal memory processing in patients with dominant-side MTLE.

An alternative explanation for the memory improvement observed in the present study is simply the non-specific improvement of cerebral function resulting from decreased seizure frequency and AED intake. A long-term follow-up study in temporal lobe epilepsy has shown that good seizure control after surgery is an important factor for improved cognitive function (Helmstaedter et al., 2003). In the present study, this was corroborated by the improvement in multiple WMS-R domains, including verbal memory, delayed recall and attention/concentration, and these improvements were present regardless of the resected side. In addition, the dominant side MTLE group in the present study consisted of relatively young adult patients with the borderline impaired range of mean IQ and verbal memory scores. Age of surgery and preoperative cognitive function are associated with postoperative cognitive outcome (Helmstaedter et al., 2002; Rausch et al., 2003; Gleissner et al., 2005; Baxendale et al., 2006). A longitudinal study with a larger number of patients that evaluates the multivariate effects on neuropsychological results and the specific brain regions that contribute to cognitive improvement is now warranted.

Conclusion

Subtemporal SAH preserving the basal temporal language area in patients with intractable MTLE improved cerebral glucose metabolism in the extratemporal projection areas and the remote regions of the remnant temporal lobe, and improved memory function. In addition, the postoperative decrease in glucose metabolism was restricted to the mesial temporal region. This implies that the brain regions with postoperative functional impairments can be minimized by the use of subtemporal SAH in patients with intractable MTLE with hippocampal sclerosis.

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REFERENCES


