fMRI and DTI assessment of patients undergoing radical epilepsy surgery

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Hemispherectomy; Surgical evaluation; fMRI; DTI; Functional reorganization

Summary  Hemispherectomy is effective for young patients suffered from unilateral cortical disease and severe drug-resistant epilepsy, but a major concern for hemispherectomy is the remaining brain functions and function recovery in patients after such surgery. In this study, seven patients were evaluated with clinical and imaging assessment pre- and post-surgery. Among them, four underwent anatomic hemispherectomy (AH) and three underwent subtotal hemispherectomy (functional hemispherectomy, FH). After the surgery, 71.4% (5/7) patients [(4/4) with AH and (1/3) with FH] became seizure free (Engel class I). Motor function of the paretic upper extremity unchanged in 4 patients and deteriorated in 3. Functional imaging results indicated that relocation of hand motor function (to the ipsilateral hemisphere) could take place before or after the surgery, or did not occur. Similar observations were made in the motor cortex activation on the paretic foot movement. In addition, both the affected and unaffected hemispheres underwent post-surgical changes in the corticospinal tracks (CST) in various degrees, but significant reinforcement of the CST in the remaining unaffected hemisphere was not evident. Further research is needed to reveal the true functional and structural changes of the remaining brain after surgery and to explore the mechanisms of such functional relocation and reorganization in patients underwent hemispherectomy.

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Introduction

For patients with severe or progressive unilateral cortical disease and continued drug-resistant epilepsy, hemispherectomy is an effective treatment for relieving constant seizures (Choi et al., 2010). Hemispherectomy is performed to treat patients with severe drug-resistant epilepsy arising from conditions such as Rasmussen's encephalitis, infantile hemiplegia, Sturge–Weber syndrome, hemimegalencephaly.
and extensive hemispheric infarct (Peacock et al., 1990; Tuxhorn et al., 1997). Anatomic hemispherectomy (AH) is a drastic procedure that removes the entire (or nearly entire) affected hemisphere. When a patient in such condition has brain functions in both hemispheres and the functional cortex does not overlap with either the lesion or the seizure focus, often rather than an en bloc AH, a piecemeal or subtotal hemispherectomy—functional hemispherectomy (FH) may be considered instead in order to avoid over-resection and to protect brain functions.

Although hemispherectomy is effective in relieving seizures, a major concern for such surgery is neurological function deterioration and recovery after the surgery (Govindan et al., 2010), e.g., function deterioration of the extremities contra-lesion. For example, it has been reported that patients who had increased hemiparesis after hemispherectomy (Kwan et al., 2010) and children with contralateral MRI abnormalities more often were severely retarded after surgery (Boshuisen et al., 2010). In addition, the emergence of a hemianopic field defect in patients after hemispherectomy is an acknowledged surgical consequence (Krynauw, 1950; Wilson, 1970; Duchowny et al., 1998). Thus, it was suggested that in order to minimize the functional impact of the removal of the sensorimotor cortex (Graveline, 1999), candidates for such surgery have to show weakness of one side of body with loss of dexterity of hand, or the development of a clinical hemiparesis on the contra-surgical side (Hwang, 1993). In addition, hemispherectomy is mainly performed in children due to strong neuroplasticity of their nervous system. On the other hand, since the remaining brain is released from epileptic influences from the affected hemisphere, improved function in patients after hemispherectomy has also been reported (Krynauw, 1950; Smith and Sugar, 1975; Damasio et al., 1975; Lindsay et al., 1987; Battaglia et al., 1999; Boatman et al., 1999; Jonas et al., 2004). Nevertheless, most studies have indicated that the hemiparesis is likely to remain unchanged in the majority of patients underwent hemispherectomy, with fewer improved or deteriorated (Krynauw, 1950; Wilson, 1970; Vining et al., 1997; Devlin et al., 2003). Taken together, surgical outcome of neurological functions such as motor, visual and language is an important criterion for hemispherectomy. In fact, due to high hemiparesis rate in patients receiving hemispherectomy, function recovery (e.g., motor function recovery) is one of the most important aspects of such surgery.

A number of studies have reported residual motor function in the contralateral extremities in patients underwent hemispherectomy (Beckung et al., 1994; Peacock et al., 1996; Vargha-Khadem et al., 1997; de Bode et al., 2005; Dijkerman et al., 2008). In addition, relocation of sensorimotor function (to the unaffected ipsilateral hemisphere) and cerebral reorganization in the remaining hemisphere after hemispherectomy has also been observed (Graveline et al., 1998; Holloway et al., 2000; Olausson et al., 2001; Rutten et al., 2002; Honda et al., 2010). Residual motor functions may be explained by reinforcement of the ipsilateral uncrossed corticospinal tract (CST) and bilateral cortico-reticulospinal pathways (Holloway et al., 2000; Choi et al., 2010). However, the following questions remain unclear: When did such functional relocation happen? What affects specific motor functions in this process? And how do motor neural pathways relate to motor function recovery? Therefore, a longitudinal study might be necessary to provide a clearer picture of the interactions between development and recovery (Choi et al., 2010).

In this study, a group of seven patients underwent AH or FH were investigated with fMRI pre- and post- surgery in order to understand the timing and possible patterns of function relocation/reorganization. Clinical assessment was also included in the study in order to understand what may possibly affect or relate to specific motor functions. In addition, CST was investigated with DTI for some of the patients pre- and post-surgery in order to understand the changes in the motor neural pathways and how these pathways relate to motor function recovery.

Methods

Subjects

Seven patients (mean age: 13.3 year, age range: 7—19 years, four males, three females) were included in this study: four (namely, patient 1 to patient 4) had undergone AH and three (patient 5 to patient 7) had undergone FH or unilateral multiple lobectomies (UML) for alleviation of drug-resistant seizures (Table 1A). AH excises the entire epileptic hemisphere sparing the basal ganglia and thalamus; while FH or UML resects the extended epileptic cortical regions across multiple brain lobes unilaterally (e.g., frontal and temporal lobes, depending on the patient’s condition) and spares the sensorimotor cortex. Among those who underwent FH, the right frontal and temporal lobes were resected for patient 5; Patient 6 underwent left FH of the frontal, temporal, parietal and occipital lobes except for the left central sulcus; The left frontal, temporal and occipital lobes were resected for patient 7. Details of the demographic and clinical characteristics of the patients are listed in Table 1A.

The seven patients had undergone clinical and imaging (MRI and fMRI for all patients, DTI for 5 patients) assessments pre- and post-surgery. The mean interval between pre-surgery imaging and surgery was 7.9 days before surgery (range: 2—15 days) and the mean interval between surgery and post-surgery imaging was 6.4 months (range: 3.5—13.5 months) after surgery (Tables 1A and 1B). The seven patients were selected from a much larger sample (n = 34). Patients who could not perform the fMRI tasks or who had undergone pre-surgery imaging assessment alone were excluded from the study. This research (under grant no. 81071211) was approved by the IRB at the Capital Medical University.

Clinical assessment

The motor function of the paretic upper extremity for these patients was evaluated by neurologists pre- and post-surgery. Motor function on the paretic extremities was assessed using the Medical Research Council scale (Medical Research Council, 1981) with grade 5 being normal motor function and muscle strength, grade 4 reduced motor function and muscle strength, grade 3 further reduced motor function, grade 2 and 1 severe deficit (movement only if without resistance of gravity and a trace of detectable movement for grade 2 and 1 respectively), and grade 0 no detectable motor function.
**Imaging assessment**

MRI images were acquired by a Trio 3-T scanner (Siemens) at Beijing MRI Center for Brain Research with a standard birdcage head coil. Patients’ head movement in the scanner was minimized by two pieces of foam surrounding the patient’s head. The stimuli were presented centrally at the viewing distance of about 60 cm through an LCD projector onto a rear projection screen, which was located before the patient’s head inside the magnet core. Functional images were acquired using a T2*-weighted gradient-echo, echo-planar pulse sequence (25 axial slices (4 mm thick with 1 mm gap); echo time (TE) = 30 ms; repetition time (TR) = 2000 ms; flip angle (FA) = 90°; matrix = 64 × 64; in-plane resolution 3.4 mm × 3.4 mm). Immediately after the functional scanning, a high-resolution (1.0 mm × 1.0 mm × 1.0 mm) T1-weighted anatomic scan (MP-RAGE, 176 sagittal slices; TE = 3.37 ms; TR = 2560 ms; flip angle = 7°; matrix = 256 × 256) was acquired for each patient as a reference volume to allow functional signal strengths to be superimposed on.

The fMRI was a block-design study that consisted of 6 tasks (left fist flexion and extension, right fist flexion and extension, left foot movement, right foot movement, tongue movement and silent reading). There were 120 s per task: two 30-s blocks of task interleaved with three 20-s blocks at rest (baseline). Due to the availability of the facility and patients’ conditions, the tasks that the patients performed varied. For normal hand and foot, active movement was performed. For paretic hand and foot, passive movement was performed in two patients (patient 4 and 7, due to weak motor functions) pre- and post-surgery, while the rest performed active movement. Tongue movement and silent reading were performed according to the availability of the patients’ remaining functions. In addition, patient 2 underwent pre-surgery fMRI (with hand movement) in the Department of Radiology, Beijing Fuxing Hospital where he was scanned with a GE scanner (which generated an activation map of correlation coefficient). After the fMRI images were acquired, they were realigned, smoothed, normalized and analyzed with SPM8 (Wellcome Department of Neurology, London, UK) (Friston et al., 1995).

Table 1A  The demographic information and surgical outcomes of the patients.

(A) Demographic and clinical characteristics of the patients

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age</th>
<th>Gender</th>
<th>Etiology</th>
<th>Location of resection</th>
<th>Interval between imaging and surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>F</td>
<td>Febrile seizures AB</td>
<td>L hemisphere</td>
<td>Pre. 4 d, Post. 8.5 m</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>M</td>
<td>Stroke AB</td>
<td>R hemisphere</td>
<td>Pre. 10 d, Post. 13.5 m</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>F</td>
<td>Stroke AB</td>
<td>L hemisphere</td>
<td>Pre. 6 d, Post. 3.5 m</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>M</td>
<td>Stroke AB</td>
<td>L hemisphere</td>
<td>Pre. 13 d, Post. 4 m</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>M</td>
<td>Stroke AB</td>
<td>F and T in R hemisphere</td>
<td>Pre. 5 d, Post. 3.5 m</td>
</tr>
<tr>
<td>6</td>
<td>17</td>
<td>F</td>
<td>Purulent meningitis AB</td>
<td>F, T, P and O in L hemisphere</td>
<td>Pre. 15 d, Post. 4.0 m</td>
</tr>
<tr>
<td>7</td>
<td>17</td>
<td>F</td>
<td>AB asphyxia, hypoxia, scalp hematoma</td>
<td>F, T and O in L hemisphere</td>
<td>Pre. 2 d, Post. 7.5 m</td>
</tr>
</tbody>
</table>

Pt.: patient; Age: age at surgery; F: female; M: male; AB: after birth; L: left; R: right; F: frontal; T: temporal; P: parietal region; Pre: pre-surgery; Post: post-surgery; d.: days; m.: months.

Table 1B  The demographic information and surgical outcomes of the patients.

(B) Surgical outcomes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Surgery Type</th>
<th>Seizure outcome (Engel class)</th>
<th>Paretic side</th>
<th>Motor function of the paretic upper extremity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Arms Wrist Hand (fingers) Overall</td>
</tr>
<tr>
<td>1</td>
<td>L AH</td>
<td>I</td>
<td>R</td>
<td>5 → 4.5 2 → 1 1 → 1 Deteriorated</td>
</tr>
<tr>
<td>2</td>
<td>R AH</td>
<td>I</td>
<td>L</td>
<td>5 → 5 3 → 3 2 → 2 Unchanged</td>
</tr>
<tr>
<td>3</td>
<td>L AH</td>
<td>I</td>
<td>R</td>
<td>4 → 4 3 → 3 3 → 3 → 3 → 4 Unchanged</td>
</tr>
<tr>
<td>4</td>
<td>L AH</td>
<td>I</td>
<td>R</td>
<td>4 → 3 4 → 3 1 → 1 Deteriorated</td>
</tr>
<tr>
<td>5</td>
<td>R FH (F,T)</td>
<td>II</td>
<td>L</td>
<td>4 → 4 3 → 3 3 → 3 Unchanged</td>
</tr>
<tr>
<td>6</td>
<td>L FH * (F,T,P,O)</td>
<td>III</td>
<td>R</td>
<td>4 → 4 3 → 3 3 → 3 Unchanged</td>
</tr>
<tr>
<td>7</td>
<td>L FH (F,T,O)</td>
<td>I</td>
<td>R</td>
<td>4 → 3 → 3 → 4 → 0 → 2 1 → 2 → 1 → 2 Deteriorated</td>
</tr>
</tbody>
</table>

AH: anatomical hemispherectomy; FH: functional hemispherectomy; L: left; R: right; (F,T): The frontal and temporal lobes were resected; * (F,T,P,O): Patient 6 underwent left FH of the frontal, temporal, parietal and occipital lobes except for the left central sulcus; (F, T, O): The frontal, temporal and occipital lobes were resected.
Table 2  fMRI activation on the movement of the paretic extremity (hand and foot).

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Activation on paretic hand movement</th>
<th>Activation on paretic foot movement</th>
<th>Pre. → Post. Activation change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.65(L)</td>
<td>2.37(R)</td>
<td>0.47(L)</td>
</tr>
<tr>
<td>2</td>
<td>0.43*(L)</td>
<td>4.13(L)</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>0.80(R)</td>
<td>2.80(R)</td>
<td>2.12(L)</td>
</tr>
<tr>
<td>4</td>
<td>2.00(R)</td>
<td>2.00(R)</td>
<td>2.66(R)</td>
</tr>
<tr>
<td>5</td>
<td>0.50(R)</td>
<td>2.77(L)</td>
<td>2.17(R)</td>
</tr>
<tr>
<td>6</td>
<td>1.79(L)</td>
<td>2.65(L)</td>
<td>2.63(L)</td>
</tr>
<tr>
<td>7</td>
<td>2.64(R)</td>
<td>2.00(R)</td>
<td>2.79(L)</td>
</tr>
</tbody>
</table>

Pt.: patient; L: left; R: right; Pre.: pre-surgery; Post.: post-surgery; NA: not available; Time A.S.: The time point after surgery for post-surgery fMRI; C: contralateral hemisphere; I: ipsilateral hemisphere; *: measured in correlation coefficient (0–1), the rest without * were measured in t-values where t-value > 1.96 corresponds to p < 0.05 (uncorrected).

The results of functional imaging were used to support clinical decisions on surgery type. The following rule was applied to the surgical decision on surgery type: if a patient completely loses brain function in the affected hemisphere, then consider AH; otherwise, consider FH to protect the remaining brain function in the affected hemisphere.

DTI acquisition and analysis

5 patients had undergone DTI: 3 of them with FH (i.e., patient 5, 6 and 7) took DTI pre- and post-surgery, the other two with AH (i.e., patient 1 and 4) took DTI post- and pre-surgery respectively. The DTI acquisition was performed in the axial plane using a two-dimensional (2D) echo planar imaging (EPI) diffusion-weighted sequence with TR/TE = 3000/93 ms, flip angle = 90°, two b values = 0 and 1000 s/mm², 12 directions, and 4 averages. Twenty-two 4-mm continuous slices were acquired with FOV = 22 cm and matrix = 128 × 128, resulting in a voxel size of 1.719 mm × 1.719 mm × 4 mm. Diffusion weighted images were processed using FSL eddy correction and DTIFIT tools (FSL Diffusion Tools, FDT 2.0, http://www.fmrib.ox.ac.uk/fsl/fdt/index.html). Corticospinal tracks (CST) were traced with MedINRIA (version 1.9.4, INRIA-Asclepios Research Team). Seed ROI placement for CST tracing was based on the approach described in (Yu et al., 2007). 3 seed ROIs were placed on axial slices of FA maps at the cerebral peduncle, internal capsule, and pre- and post-central gyrus where the CST can be identified. CST was traced many times for each subject’s pre- or post-surgery DTI in order to check the reproducibility of CST tracing and high reproducibility was achieved partially due to the ability of MedINRIA to filter out irrelevant fibers. The number of fibers, fiber length, fractional anisotropy (FA) and apparent diffusion coefficient (ADC) of the CST traced, as well as FA and ADC at the cerebral peduncle level were measured with MedINRIA.

Statistical analysis

T-statistics was performed on the fMRI data to obtain the activation maps except for the fMRI images of patient 2 (an activation map of correlation coefficient was obtained instead for patient 2 who was scanned in Beijing Fuxing Hospital). Due to relatively weak fMRI responses to paretic extremities, significance of p < 0.05 or threshold t = 2.0 was set (uncorrected for multiple comparisons). Non-parametric Wilcoxon rank sum tests were performed on the DTI data of the traced CST, i.e., the number of fibers, fiber length, FA and ADC.

Results

Clinical assessment and surgical outcome

All 7 patients had residual motor function in the paretic hands. Among them, 4 patients (2 with AH, 2 with FH) had unchanged motor function of the paretic upper extremity post-surgery. 3 patients (2 with AH, 1 with FH) had deteriorated motor function in the paretic upper extremity after surgery. Details of the clinical evaluation results are listed in Table 1B.

Complete seizure freedom was obtained in 4 patients with AH (4/4) and 1 with FH (1/3), and partial seizure control was obtained in 2 patients with FH. Taken together, 71.4% (5/7) of the patients achieved Engel class I outcome, 14.3% (1/7) Engel class II and 14.3% (1/7) Engel class III (Table 1B).

fMRI assessment

In pre-surgery fMRI, 4 patients had significant unilateral fMRI activation for the tasks performed (hand, foot, tongue movements and silent reading), while the other 3 patients had significant bilateral fMRI activation. These functional imaging results provided evidence to support clinical decisions on surgery type. Consequently, the 4 patients who had unilateral fMRI activation underwent AH, and the other 3 patients who had bilateral fMRI activation underwent FH in order to protect eloquent brain regions and avoid over-resection. In addition, mirror movements were observed in patients (such as patient 1) who had remaining motor function and performed active movement of the paretic hand or foot.
Figure 1  Motor cortex activation in patient 4 and patient 7 for paretic hand movement. Activated brain regions are indicated in red (voxels with light red are more significant than those with dark red). (A) Cortical activation of patient 4 (with left AH) on passive movement of the paretic (right) hand. (B) Cortical activation of patient 7 (with left FH) on passive movement of the paretic (right) hand.

Hand movement

All patients showed normal contralateral primary motor cortex activation on healthy hand movement before and after the surgery. Six patients (patients 1, 2, 3 and 4, and patients 5 and 7) demonstrated ipsilateral motor cortex activation on paretic hand movement post-surgery (Table 2). Among them, patients 2, 3, 4 and 7 had ipsilateral motor cortex activation pre-surgery suggesting that such motor relocation occurred before the surgery, while patients 1 and 5 had contralateral motor cortex activation pre-surgery suggesting that motor relocation occurred after the surgery. In contrast, patient 6 showed contralateral fMRI activation on the paretic hand movement after the surgery suggesting that functional relocation to the ipsilateral hemisphere did not take place in this patient. Examples of the ipsilateral responses on the paretic hand movement (patients 4 and 7) are illustrated in Fig. 1 where the intensities of the motor cortex activation on paretic hand movement did not improve post-surgery in both patients and the locations were slightly different pre- and post-surgery in both of them.

Foot movement

All patients except for patient 3 showed normal contralateral primary motor cortex activation on healthy foot movement before and after the surgery. Four patients (patients 2–5) demonstrated ipsilateral motor activation on the paretic foot movement after the surgery (Table 2). One of them (patient 4) had ipsilateral motor cortex activation pre-surgery suggesting that relocation of foot motor function occurred before the surgery, while two of the patients (patients 3 and 5) had contralateral motor cortex activation pre-surgery indicating that relocation of foot motor function occurred after the surgery. In contrast, patients 6 and 7 showed contralateral motor cortex activation on the paretic foot movement pre- and
post-surgery suggesting that function relocation to the ipsilateral hemisphere did not take place in these two patients. Examples of the ipsilateral and contralateral responses on the paretic foot movement (patients 4 and 7) are illustrated in Fig. 2 where the intensities of the motor cortex activation on paretic foot movement improved post-surgery in both patients and the locations were similar pre- and post-surgery in patient 4, but differed more in patient 7.

### Tongue movement

Most patients could move tongue pre- and post-surgery. fMRI activation on tongue movement was in the remaining unaffected hemisphere. While the intensity and location of fMRI activation on tongue movement were similar pre- and post-surgery for most patients, the intensity of activation largely increased for three patients (patients 1, 4 and 5) after the surgery.

### Silent reading

Few patients performed silent reading, especially for those who underwent left hemispherectomy (patients 1, 3 and 4) and left occipital lobectomy (patients 6 and 7). The regions of activation on silent reading were in occipital and frontal areas, mainly in the unaffected hemisphere. Two patients (patients 5 and 6) had improved fMRI activation on silent reading after the surgery at the point of postoperative assessment.

### DTI assessment

Compared with the unaffected hemisphere, the CST fibers of the affected side in patients who took DTI showed abnormalities: the ADC values of the CST fibers on the affected side were significantly higher than those of the unaffected side ($p < 0.05$) (Table 3).

In addition, compared with pre-surgical CST, the affected hemisphere demonstrated some changes in the CST.
### Table 3 DTI CST fiber tracking results.

<table>
<thead>
<tr>
<th>Patient</th>
<th>N of fibers</th>
<th>Fiber length</th>
<th>FA</th>
<th>ADC</th>
<th>Wilcoxon Signed Rank Sum-test Sig. (Pre. vs. Post.)</th>
<th>Wilcoxon 2 Sample -test Sig. (Affected hemi. vs. Unaffected hemi.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Affected hemi. Pre-surgery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P4</td>
<td>20</td>
<td>62.2</td>
<td>0.38</td>
<td>3.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P5</td>
<td>204</td>
<td>97.3</td>
<td>0.40</td>
<td>3.24</td>
<td>0.109</td>
<td>0.686</td>
</tr>
<tr>
<td>P6</td>
<td>127</td>
<td>72.4</td>
<td>0.44</td>
<td>3.28</td>
<td>0.285</td>
<td>0.886</td>
</tr>
<tr>
<td>P7</td>
<td>197</td>
<td>97.4</td>
<td>0.45</td>
<td>3.24</td>
<td>0.564</td>
<td>0.343</td>
</tr>
<tr>
<td>Wilcoxon Signed Rank Sum-test Sig. (Pre. vs. Post.)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Wilcoxon 2 Sample -test Sig. (Affected hemi. vs. Unaffected hemi.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Affected hemi. Post-surgery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P4</td>
<td>4</td>
<td>14.5</td>
<td>0.43</td>
<td>3.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P5</td>
<td>101</td>
<td>84.1</td>
<td>0.41</td>
<td>3.17</td>
<td>0.486</td>
<td>0.114</td>
</tr>
<tr>
<td>P6</td>
<td>38</td>
<td>72.5</td>
<td>0.45</td>
<td>3.02</td>
<td>0.114</td>
<td>1.000</td>
</tr>
<tr>
<td>P7</td>
<td>179</td>
<td>78.8</td>
<td>0.44</td>
<td>3.06</td>
<td>0.114</td>
<td>0.029</td>
</tr>
<tr>
<td>Wilcoxon Signed Rank Sum-test Sig. (Pre. vs. Post.)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Wilcoxon 2 Sample -test Sig. (Affected hemi. vs. Unaffected hemi.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Unaffected hemi. Pre-surgery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>P4</td>
<td>94</td>
<td>96.7</td>
<td>0.46</td>
<td>2.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P5</td>
<td>291</td>
<td>100.6</td>
<td>0.42</td>
<td>2.50</td>
<td>0.109</td>
<td>1.000</td>
</tr>
<tr>
<td>P6</td>
<td>68</td>
<td>70.5</td>
<td>0.48</td>
<td>2.35</td>
<td>0.109</td>
<td>1.000</td>
</tr>
<tr>
<td>P7</td>
<td>237</td>
<td>79.7</td>
<td>0.43</td>
<td>2.47</td>
<td>0.109</td>
<td>1.000</td>
</tr>
<tr>
<td>Wilcoxon Signed Rank Sum-test Sig. (Pre. vs. Post.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilcoxon 2 Sample -test Sig. (Affected hemi. vs. Unaffected hemi.)</td>
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<td><strong>Unaffected hemi. Post-surgery</strong></td>
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<tr>
<td>P4</td>
<td>70</td>
<td>86.6</td>
<td>0.45</td>
<td>2.31</td>
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<tr>
<td>P5</td>
<td>138</td>
<td>96.4</td>
<td>0.41</td>
<td>2.49</td>
<td>0.010</td>
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<td>P6</td>
<td>65</td>
<td>87.5</td>
<td>0.46</td>
<td>2.46</td>
<td>0.010</td>
<td>1.000</td>
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<tr>
<td>P7</td>
<td>185</td>
<td>77.1</td>
<td>0.41</td>
<td>2.45</td>
<td>0.010</td>
<td>1.000</td>
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N of fibers: Number of fibers; hemi.: hemisphere; P1…P7: patient 1…patient7; Pre.: pre-surgery; Post.: post-surgery; Sig.: Significance; Sig. in bold are significant at p < 0.05 (2-tailed).

Post-surgery, while the length of CST fibers in the affected hemisphere shortened after the surgery (but the change was not significant). In the unaffected hemisphere, the FA values of the CST fibers dropped in the patients after the surgery and the number of CST fibers also dropped insignificantly. These results indicated that the affected and unaffected hemispheres underwent post-surgery changes in different degrees.

Moreover, except for patient 6 whose CST in the unaffected hemisphere was outnumbered by that in the affected hemisphere pre-surgery, asymmetry was found in the CST with more CST in the unaffected hemisphere than in the affected hemisphere in these patients pre- and post-surgery, although such asymmetry was not significant (Fig. 3).

**Discussion**

In this study, we found that for patients underwent radical epilepsy surgery (AH or FH), some had ipsilateral responses
on the paretic hand movement pre- and post-surgery (e.g., patient 2 and 4) suggesting that motor relocation (to the ipsilateral unaffected hemisphere) occurred before the surgery, while some patients (e.g., patient 1 and 5) had contralateral responses pre-surgery and ipsilateral responses post-surgery indicating that motor relocation occurred after the surgery, whereas other patients (e.g. patient 6) had contralateral responses pre- and post-surgery suggesting that motor relocation did not occur (Table 2B). The similar or different locations of motor cortex activation on hand movement before and after surgery may be due to functional reorganization post-surgery. Similar findings (e.g., ipsilateral activation pre- and post-surgery) were obtained in the motor cortex activation on the paretic foot movement (Table 2).

Motor relocation and cerebral reorganization

When the affected hemisphere is surgically removed, the remaining unaffected hemisphere may gradually take over the functions of the affected side whose control has been lost (Honda et al., 2010). Postoperative and serial neuropsychological assessments suggest that the functional reorganization process begins very early after surgery but can continue for as long as 1 year (Boatman et al., 1999). This study demonstrated that functional reorganization and relocation to the ipsilateral hemisphere may occur before or after the surgery, or even not occur, depending on the characteristics of the patient’s brain disorder (etiology, structural properties of the lesion and its damage to the brain, timing of the brain disorder, etc.) and the surgery performed (type of the surgery, timing of the surgery, etc.). In other words, epilepsy surgical outcomes were much influenced by etiology and surgery type, which was supported by a number of recent studies (van der Kolk et al., 2012; Schramm et al., 2012).

First, the characteristics of the patient’s brain disorder such as etiology have much impact on surgical outcomes (de Bode et al., 2005) and the pathologic substrate predicts pre- and post-surgery differences in outcomes (Jonas et al., 2004). Brain diseases acquired early in life or congenital diseases with continued seizures that affects one hemisphere and causes damage to unilateral brain functions may trigger ipsilateral development and responses (i.e., brain function learning, plasticity and cerebral reorganization in the ipsilateral hemisphere) years before the surgery. This was seen in the ipsilateral responses to paretic hand movement in patients 2 and 4. In this case, the structural and functional integrity of the remaining hemisphere may be a key factor in the function reorganization and recovery process because functional processes relocate to ipsilateral regions (with integrated neural networks) before plasticity of higher cortical function proceeds (Duchowny, 2004). Presurgical PET evaluation has revealed functional deficit in the apparently healthy hemisphere in patients underwent hemispherectomy, which suggests that it is possible that intrinsic abnormalities of the remaining hemisphere could affect brain reorganization after surgery (Wakamoto et al., 2006). On the other hand, if brain diseases did not cause severe damage to the contralateral motor cortex, contralateral motor responses and functions on paretic hand movement could be preserved in various degrees, which was seen in the contralateral responses to paretic hand movement pre-surgery in patients 1, 5 and 6.

Second, the radical surgery hemispherectomy (AH or FH) may serve as another catalyst to further trigger the ipsilateral responses and functional reorganization in the remaining brain. The surgery type (AH or FH) is also critical. If such surgery resects an entire cerebral hemisphere and removes the eloquent cortex and/or its related pathways in the affected hemisphere (which may already be affected and weak), then ”the remaining healthy side of the brain may gradually take over the functions whose control has been lost (Honda et al., 2010)”, which was seen in the post-surgery motor relocation (to the ipsilateral hemisphere) in patients 1 and 5. On the other hand, if the surgery resects partial hemisphere and leaves the eloquent cortex as well as its related pathways intact, functional relocation to
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the ipsilateral hemisphere may not be necessary depending on functional demand and thus the original eloquent cortex in the contralateral hemisphere may still be used. This was seen in the contralateral responses to paretic hand movement post-surgery in patient 6.

In addition, the timing of surgery or patient’s age at surgery is another critical factor for functional reorganization post-surgery. During cortical maturation through childhood, ipsilateral pathways become functionally suppressed by an inhibitory influence from the opposite hemisphere through the corpus callosum (Netz et al., 1997) and the associated movements or ipsilateral motor evoked potentials could be detected in children until callosal maturation at the age of ~10 years (Yakovlev and Lecours, 1967; Lazarus and Todor, 1987; Müller et al., 1997). It is believed that early hemispherectomy or brain damage may escape from such inhibition and the ipsilateral pathways may keep functioning through callosal maturation, which may cause mirror movements displayed in patients with remaining motor function (Holloway et al., 2000). This study showed that such functional relocation to the ipsilateral hemisphere still could take place for young adult, although motor function declined post-surgery (e.g., for patient 1 and 7), which may be due to the decrease of neuroplasticity after callosal maturation.

The location of ipsilateral cortical activation in response to the movement of the paretic extremity may be similar to or a little different from (e.g., a little anterior) that of the contralateral activation (Benecke et al., 1991; Roth et al., 1996; Pascual-Leone et al., 1992). This may be explained by the strengthening and reorganization of the ipsilateral connections through the ipsilateral pathways or nerve tracks.

Neural pathways for motor relocation and reorganization

The responses that occur in the primary motor cortex and premotor cortex may result from two distinct pathways that may serve ipsilateral function: the uncrossed corticospinal (primary motor cortex) and corticoreticulospinal (premotor cortex) pathways (Holloway et al., 2000). Ipsilateral pathways may persist after cortical maturation and ipsilateral fibers in the motor system may account for ~25% of all ascending fibers in the normal human brain (Nyberg-Hansen and Rinvik, 1963). It is possible that the ipsilateral activation in the patient with acquired disease may be due to the activation of the corticoreticulospinal pathway, while the ipsilateral CST may be responsible for the ipsilateral activation in the patient with congenital disease (Benecke et al., 1991). After severe brain disease developed or hemispherectomy was performed early in life (infancy, childhood, adolescence or young adulthood), the cortico-reticulospinal or corticospinal track undergoes reorganizational changes that strengthens the ipsilateral connections or develops new functional pathways driven by functional demand (Benecke et al., 1991). This induces enhanced function of the motor pathway and mediates partial recovery of motor function (Jonas et al., 2004).

In this study, although the sample size was small (n = 7) and DTI was not acquired for all patients pre- and post-surgery, the asymmetry of the CST observed in the study indicated that the structural connectivity was reduced in the affected hemisphere in most patients, which is consistent with the findings in Choi et al. (2010). In addition, the white matter property changes of CST fibers were observed in both the affected and unaffected hemisphere post-surgery. These changes together with the abnormalities in the CST of the affected hemisphere (compared with the CST in the unaffected hemisphere) suggested that wallerian degeneration occurred in the motor pathway post-surgery. However, the DTI results in this study did not provide evidence for significantly improved or strengthened white matter properties of CST in the unaffected hemisphere, which was consistent with the report of Wakamoto et al. (2006) (n = 7). The results might potentially be influenced by a number of factors such as the presence and duration of seizures, the medication effects, the time intervals between surgery and imaging (Wakamoto et al., 2006), and the structural integrity of the remaining hemisphere. Such results may indicate that motor recovery may rely less on structural changes in the direct uncrossed CST and possibly more on the use of the indirect corticoreticulospinal pathways (Choi et al., 2010). Further, ipsilateral motor recovery may be due to the strengthening of ipsilateral functional connections. Future study with a larger sample may be necessary to further explore this.

Rehabilitation may result in the experience-driven expansion of maps and related improvements in motor performance (Williams et al., 2006). Differences in motor recovery could depend on plasticity in the remaining cerebral hemisphere and activity from the intact hemisphere may control ipsilateral muscles less via the direct uncrossed CST and more via indirect corticoreticulospinal pathways (Choi et al., 2010). Decreased FA in the ‘ipsi-lesional CST’ and asymmetry in brainstem corticospinal tracts were found in patients who underwent hemispherectomy, which suggested that post-surgery motor recovery might be facilitated by improved use of the indirect corticoreticulospinal pathways (Choi et al., 2010).

A trade-off in surgical outcomes

The results of this study showed that good seizure control (Engel Class I) does not necessarily go together with good motor outcome. Actually, there is a trade-off between seizure control and neurological function outcome in radical epilepsy surgery such as hemispherectomy. New surgical techniques such as hemispherotomy have been reported to optimize patient outcomes in recent years (Limbrick et al., 2009; Marras et al., 2010), which could be explored in the future.

Limitations

Major limitations of this study include the small sample size and the relatively low threshold for fMRI activation (possibly due to the paradigms used including 6 different activation tasks with few blocks of activation period for each task). In addition, the time points after surgery for functional imaging scans varied from patient to patient because most patients
live in other cities (or rural areas) in other provinces far away from the Epilepsy Surgery Center and their clinical revisit largely depends on these patients (their recovery status, etc.) and their family (economic status, availability of family members as company for the trip, etc.). The variation in the post-surgery time points for functional imaging added a variant (due to plasticity) to the post-surgical evaluation and made it difficult to compare the outcomes between patients (especially with different surgery types). To overcome these limitations, more patients need to be recruited, the fMRI paradigm needs to be optimized and standardized time point (such as half a year, one or two years) post-surgical evaluation could be introduced in the future. Furthermore, possible relationships between patients' features (such as etiology and age at surgery), motor function and imaging results could be investigated in future studies with more specific pathologic substrate.

Summary

In summary, this study found that for patients underwent AH or FH, motor relocation (to the ipsilateral hemisphere) occurred before the surgery, after the surgery, or even did not occur in individual patients. Similar observations were made in the motor cortex activation on paretic foot movement. Motor function of the upper paretic extremity unchanged in 4 patients and deteriorated in 3. In addition, both the affected and unaffected hemispheres underwent post-surgery changes in the CST in various degrees, but significant reinforcement of the CST in the healthy hemisphere was not evident, which might suggest that strengthening the ipsilateral connections may be through other neural pathways or through functional connections. Although age at surgery, motor function and fMRI activation of the paretic hand and imaging time after surgery were not correlated at p < 0.05, the 1-tailed (p < 0.10) significant correlation between age at surgery and motor activation on the paretic hand indicated that the earlier the surgery, the higher post-surgery motor activation. Further studies with a larger sample and improved imaging measures are necessary to reveal the true changes of the remaining brain post-surgery and to explore the mechanisms of the functional relocation and reorganization in patients with hemispherectomy, which hopefully will contribute to the motor recovery and rehabilitation of patients underwent hemispherectomy.

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References


