Brain Reorganization after Bilateral Arm Training and Distributed Constraint-induced Therapy in Stroke Patients: A Preliminary Functional Magnetic Resonance Imaging Study

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Background: Bilateral arm training (BAT) and constraint-induced therapy (CIT) have shown beneficial effects in improving motor control and function of the upper extremities (UE) for patients with stroke. Thus far, no study has directly investigated the relative effects of BAT versus CIT on brain reorganization. This study compared the effects of BAT with distributed CIT (dCIT) on brain reorganization and motor function in 6 stroke patients.

Methods: In a pre-post randomized controlled trial, 6 stroke patients received BAT (intensive bilateral simultaneous and symmetrical training) or dCIT (restraint of the unaffected UE combined with intensive training of the affected UE) for a period of 3 weeks, 5 days per week. Functional magnetic resonance imaging (fMRI) examination and 3 clinical measures (Fugl-Meyer Assessment, Action Research Arm Test, and Motor Activity Log) were administered before and after the intervention.

Results: After intervention, patients showed varied patterns of fMRI changes and improved motor function. Two well-recovered patients, one from each group, showed large increases in bilateral hemisphere activation, especially in the ipsilesional hemisphere during affected hand movement and in the contraleisional hemisphere during unaffected hand movement. During bilateral elbow movement, 3 of the 4 BAT patients showed increased bilateral cerebellum activation, especially in the left cerebellum, whereas 2 dCIT patients showed decreased cerebellar activation.

Conclusions: The findings of this preliminary research revealed that neuroplastic changes after stroke motor rehabilitation may be specific to the intervention. Further research using a larger sample and more complex fMRI tasks is warranted to validate the findings.

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Key words: stroke, rehabilitation, functional magnetic resonance imaging, neuroplasticity
Upper extremity (UE) motor deficits after stroke are a special concern because more than half of patients continue to have UE dysfunction at 6 months after onset.\(^1\),\(^2\) Two active rehabilitation approaches, bilateral arm training (BAT) and constraint-induced therapy (CIT), have gained increasing attention in stroke rehabilitation.\(^3\),\(^4\) Active rehabilitation approaches reflect the principle that patients can benefit most when they are actively involved in their treatment (eg, selection of treatment tasks and setting goals). Recent evidence supports the efficacy of active rehabilitation.\(^5\),\(^6\)

BAT and CIT share similar therapeutic elements of task-specific and repetitive exercise. BAT emphasizes both UEs, which simultaneously practice functional tasks. Possible rationales include interhemispheric coupling and neural cross-talk.\(^9\) CIT and its distributed form (dCIT), an alternate form of the original CIT in which treatment is done for a longer period with fewer training hours per day, involve restriction of the unaffected UE and intensive training of the affected UE to overcome learned nonuse.\(^3\),\(^6\),\(^7\)

The relative effects of BAT versus dCIT on motor and functional performance have been studied,\(^8\) but thus far, no study has directly compared the effects of BAT and dCIT on brain reorganization. Emerging neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), have an important use in the study of plastic reorganization in the brain after stroke.\(^9\) A fMRI study of stroke patients undergoing BAT showed that in 6 of 9 patients, activations were increased in the contralesional hemisphere of the cerebrum and ipsilesional hemisphere of the cerebellum during affected arm movement.\(^10\) The number of studies on cortical reorganization after CIT or BAT in stroke patients is growing.\(^10\)\(^–\)\(^17\) Most fMRI studies have shown that gains in motor function of the affected hand after CIT are accompanied by increased activation in the ipsilesional hemisphere,\(^12\)\(^–\)\(^15\),\(^17\) whereas others observed increased activation in the contralesional hemisphere or in the bilateral association motor cortices.\(^12\)\(^–\)\(^17\)

These fMRI studies of paretic arm movement have shown varied patterns of cortical recruitment after BAT or CIT. The factors affecting brain reorganization depend on the severity of impairment,\(^18\) lesion location,\(^19\) and time since the stroke.\(^20\) The underlying mechanisms of plastic changes might be different between BAT and CIT because one involves unilateral training and the other emphasizes bimanual movement. Bilateral training might have positive neural effects for both hemispheres, whereas unilateral training might result in reorganization of the ipsilesional hemisphere.\(^21\) To date, there is no empirical evidence to unravel the similarities or differences in brain plastic changes between BAT and CIT in stroke patients. It is important to contrast the patterns of neuroplasticity between these regimens to provide information on brain reorganization and to optimize rehabilitative strategies.\(^22\),\(^23\) This pilot study evaluated the patterns of brain reorganization and examined motor and functional performance after BAT versus dCIT in stroke patients.

**METHODS**

**Participants**

Six stroke patients who participated in outpatient rehabilitation programs at a medical center in Taiwan were screened. Patients in this study were recruited from a randomized controlled trial to investigate the effectiveness of dCIT and BAT (Fig. 1). These patients met the following criteria: more than 6 months since the stroke, Brunnstrom stage exceeding III for the proximal and distal parts of the UE,\(^24\) considerable nonuse of the affected UE and amount of use score < 2.5 on the Motor Activity Log,\(^25\) no serious cognitive deficits (score ≥ 24 on the Mini-Mental State Examination),\(^26\) no excessive spasticity in any joints of the affected UE (Modified Ashworth Scale score ≤ 2 in all joints), no participation in any experimental rehabilitation or drug studies within the past 6 months, no balance problems sufficient to compromise safety when wearing a constraint mitt, no seizures within the last 6 months, no metal implants, no claustrophobia, and able to perform fMRI motor tasks. All participants signed an informed consent form approved by the Institutional Review Board.

**Interventions**

Participants were randomized to receive BAT or dCIT. Both groups received equivalent treatment for 2 hours a day, 5 days a week, for 3 weeks. The 4 participants who received BAT concentrated on simultaneous movement of the UEs in functional
tasks in symmetric or alternating patterns that emphasized both UEs moving synchronously, such as lifting 2 cups, picking up 2 pegs, reaching forward or upward to move blocks, and grasping and releasing 2 towels. The 2 participants in dCIT focused on restriction of the unaffected hand with a mitt and intensive training of the affected UE with functional activities and behavioral shaping. The functional tasks included reaching forward or upward to move a cup, picking up coins, picking up a utensil to eat food, and grasping and releasing various blocks.

**Clinical outcome measures**

Three clinical measures were administered at baseline and after the 3-week training period. We used the UE subscale of the Fugl-Meyer Assessment to evaluate motor impairment. The 33 items, scored on a 3-point scale, measure movements and reflexes of the shoulder/elbow/forearm, wrist, and hand, as well as coordination and speed. The reliability and validity of the Fugl-Meyer Assessment are well established.

The Action Research Arm Test was designed to evaluate UE function. It consists of 19 items scored on a 4-level scale and grouped into 4 subscales: grasp, grip, pinch, and gross movement. The psychometric properties of the Action Research Arm Test are well established.

The Motor Activity Log was used to assess the amount of use and quality of movement of the affected UE in 30 daily activities using a 6-point scale. This scale has good reliability and validity.

**Functional MRI examination**

The fMRI was performed on a 1.5T Magnetom Vision MRI scanner (Siemens, Erlangen, Germany) before and immediately after intervention. Blood oxygenation level-dependent functional images were collected using a T2-weighted gradient-echo sequence. Structural images were collected using a T1-weighted spin-echo sequence. Slices were oriented parallel to the anterior-posterior commissural line and covered the cerebral and cerebellar hemispheres.

Before imaging, participants were introduced to the motor tasks. Participants performed finger flexion/extension of the affected hand or unaffected hand at two-thirds Hz with six 21-second rest epochs and six 21-second movement epochs. Patients also performed bilateral elbow flexion/extension at one-third Hz with three 30-second rest epochs and three 30-second movement epochs. A head coil, a customized splint mask, and a wooden apparatus with straps were used to stabilize the head and UEs during imaging.

Imaging processing and analysis were per-
formed on a Sun Blade 1000 workstation (Sun Microsystems Inc, Santa Clara, CA, U.S.A.). Statistical activation maps were generated voxel-by-voxel using the t test, which contrasted the images acquired during the rest epochs with those acquired during the movement epochs. The averaged activation maps of each group with a t-value threshold of 3.6 and a cluster threshold of 250 mm$^3$ ($p < 0.05$, corrected) were calculated and then overlaid on the corresponding T1 images. All images were normalized to the anatomic images.

Quantification of activation was conducted by 4 region-of-interest (ROI) analyses, including the primary sensorimotor cortex, premotor cortex, supplementary motor area, and cerebellum. Cerebral ROIs activation is the sum of the activation values of the primary sensorimotor cortex, the premotor cortex, and the supplementary motor area. The cerebellum was taken as a whole.\(^{(35)}\) The total ROIs included cerebral and cerebellar activation. The laterality index (LI) was calculated to estimate the relative hemispheric activation. The LI was defined as $\left[\frac{I - C}{I + C}\right]$, where $I$ and $C$ represent the number of activated voxels in the ipsilesional and contralesional ROIs, respectively.\(^{(22,36)}\) LI values ranged from +1, indicating that all activation occurred in the ipsilesional hemisphere, to –1, indicating that all activation occurred in the contralesional hemisphere.

**RESULTS**

Demographic and clinical characteristics of the participants are summarized in Table 1. The participants had a mean age of 56.0 years and participated in this study an average 23.5 months after a stroke. Table 2 reports the clinical assessment scores before and after the intervention. Patients 2 and 5 appeared to have better motor and functional improvement after treatment, whereas patient 1 had less benefit from the training. Patient 3 showed only modest changes in the Fugl-Meyer Assessment and Motor Activity Log scores. Patient 4 exhibited improvement in the Fugl-Meyer Assessment, Action Research Arm Test, and Motor Activity Log-amount of use scores, but not in the Motor Activity Log-quality of movement score. Patient 6 showed improvement in the Fugl-Meyer Assessment and Motor Activity Log scores after dCIT. Brain activation patterns before and after treatment are shown in Fig. 2 for patient 2 (BAT group) and in Fig. 3 for patient 5 (dCIT group). Table 3 summarizes the mean number of activation voxels and the mean LIs of the BAT and dCIT groups during movement of the affected hand, unaffected hand, and bilateral elbow before and after treatment.

During affected hand movement, the BAT and dCIT groups showed increased activation in the bilateral hemispheres (total ROIs). Patient 1 showed no activation at baseline and slightly increased activation in the ipsilesional cerebellum after treatment. Patient 2 exhibited increased activation in the bilateral hemispheres after BAT, especially in the ipsilesional hemisphere (Fig. 2A). The LI of the total ROIs for patient 2 shifted from –0.02 to 0.44. Patient 3 showed slightly increased activation in the ipsilesional cerebrum, slightly decreased activation in the

<table>
<thead>
<tr>
<th>Patient (group)</th>
<th>Side of lesion</th>
<th>Lesion type</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Time since stroke (months)</th>
<th>MMSE score</th>
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<tr>
<td>1 (BAT)</td>
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<td>Putaminal and corona radiata infarction</td>
<td>Male</td>
<td>54</td>
<td>11</td>
<td>30</td>
</tr>
<tr>
<td>2 (BAT)</td>
<td>L</td>
<td>Corona radiata ischemia</td>
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<td>55</td>
<td>57</td>
<td>30</td>
</tr>
<tr>
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<td>Male</td>
<td>57</td>
<td>14</td>
<td>30</td>
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<tr>
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<td>Thalamus and corona radiata hemorrhage</td>
<td>Male</td>
<td>45</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>5 (dCIT)</td>
<td>R</td>
<td>Thalamic hemorrhage</td>
<td>Male</td>
<td>57</td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td>6 (dCIT)</td>
<td>R</td>
<td>Thalamic hemorrhage</td>
<td>Female</td>
<td>68</td>
<td>40</td>
<td>25</td>
</tr>
</tbody>
</table>

**Table 1.** Demographic and Clinical Characteristics of the Participants

**Abbreviations:** BAT: bilateral arm training; dCIT: distributed constraint-induced therapy; MMSE: Mini-Mental State Examination.
Table 2. Clinical Assessment Scores before and after Intervention

<table>
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<tr>
<th>Patient (group)</th>
<th>FMA</th>
<th>ARAT</th>
<th>MAL-AOU</th>
<th>MAL-QOM</th>
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<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>1 (BAT)</td>
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<td>2 (BAT)</td>
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<tr>
<td>3 (BAT)</td>
<td>50</td>
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<td>49</td>
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<td>4 (BAT)</td>
<td>52</td>
<td>57</td>
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<td>42</td>
</tr>
<tr>
<td>5 (dCIT)</td>
<td>48</td>
<td>54</td>
<td>33</td>
<td>50</td>
</tr>
<tr>
<td>6 (dCIT)</td>
<td>39</td>
<td>49</td>
<td>28</td>
<td>29</td>
</tr>
</tbody>
</table>

**Abbreviations:** BAT: bilateral arm training; dCIT: distributed constraint-induced therapy; FMA: Fugl-Meyer Assessment; ARAT: Action Research Arm Test; MAL: Motor Activity Log; AOU: amount of use; QOM: quality of movement; pre: pretreatment; post: posttreatment.

Fig. 2 Brain activation patterns in patient 2 (left corona radiata ischemia) before and after bilateral arm training. (A) During affected hand movement, activation in both cerebral hemispheres is substantially increased after treatment, especially in the ipsilesional hemisphere (blue arrow). (B) During unaffected hand movement, activation in both cerebral hemispheres is increased after treatment, particularly in the contralesional hemisphere (blue arrow). (C) During bilateral elbow movement, activation in both cerebellar hemispheres is increased after treatment (blue arrow).
contralateral cerebrum, and substantially decreased activation bilaterally in the cerebellum after BAT. The LI of the total ROIs for patient 3 changed from 0.14 to −0.03. In patient 4, increased activation bilaterally in the cerebrum and cerebellum, especially the ipsilesional hemisphere, was noted after BAT. The LIs of the total ROIs were positive before and after treatment. Patient 5 showed a substantial increase in the bilateral hemispheres, particularly in the ipsilesional hemisphere (Fig. 3A). The cerebral activation of patient 6 did not show clear changes after dCIT, with only a slight increase in contralateral cerebellar activation. The LIs for the total ROIs for patients 5 and 6 were positive before and after dCIT.

During unaffected hand movement, the BAT group showed slightly increased activation in the bilateral cerebrums, whereas the dCIT group had a marked increase in the contralateral hemisphere. Individually, patient 1 showed no activation before and after treatment. Patient 2 exhibited increased activation in the bilateral hemispheres of the cerebrum after BAT, especially in the contralateral hemisphere (Fig. 2B). Patient 3 showed slightly decreased ipsilesional cerebral activation, and no activation in the bilateral hemispheres of the cerebellum after BAT. Patient 4 exhibited a slight decrease in ipsilesional cerebral activation, an

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**Fig. 3** Brain activation patterns in patient 5 (right thalamic hemorrhage) before and after distributed constraint-induced therapy. (A) During affected hand movement, activation is increased in both cerebral hemispheres after treatment, particularly in the ipsilesional hemisphere (blue arrow). (B) During unaffected hand movement, activation in both cerebral hemispheres shows substantial increases after treatment, especially in the contralateral hemisphere (blue arrow). (C) During bilateral elbow movement, activation is decreased in both cerebellar hemispheres after treatment (blue arrow).
increase in contralesional cerebral activation, and a decrease in bilateral cerebellar activation after BAT. The LIs of the total ROIs for patients 2, 3, and 4 were all negative before and after BAT. Patient 5 showed a substantial increase in the bilateral hemispheres after dCIT, particularly in the contralesional hemisphere (Fig. 3B). The LIs of the total ROIs were negative before and after dCIT. Patient 6 showed a slight increase in ipsilesional cerebral and cerebellar activation and an obvious increase in contralesional cerebral and cerebellar activation. The LI of the total ROIs changed from 1 to –0.83 after dCIT.

During bilateral elbow movement, the BAT group showed increased activation in bilateral cerebellums, especially in the left cerebellum, whereas the dCIT group had decreased activation in the bilateral cerebellums. Patients 1, 3, and 4 showed no activation at baseline. Patient 1 still had no clear activation after treatment. Patient 2 exhibited increased activation in the ipsilesional cerebrum and bilateral cerebellums after BAT (Fig. 2C). Patient 3 showed no clear change in the cerebrum and slightly increased activation in the ipsilesional cerebellum after BAT. Patient 4 exhibited an increase in bilateral cerebral and cerebellar activations after BAT. Patient 5 showed a slight increase in bilateral cerebral activation and a decrease in bilateral cerebellar activation after dCIT (Fig. 3C). Patient 6 showed an activation pattern similar to patient 5 after dCIT.

DISCUSSION

To our knowledge, this study is the first to compare brain reorganization patterns after BAT and dCIT in stroke patients. The patients in this case series showed improved motor and daily function after interventions. Brain reorganization was displayed on fMRI after BAT and dCIT in 5 of the 6 stroke patients, but the patterns of plastic changes were patient-dependent. Our findings showed that neuroplasticity changes may mediate the efficacy of BAT and dCIT. Patients 2 and 5, who benefited most
in clinical outcomes, showed large activation increases in both hemispheres, particularly in the ipsilesional hemisphere during affected hand movement and in the contralesional hemisphere during unaffected hand movement. This indicates that the ipsilateral motor pathway may be important in recovery. Affected hand movement relied mainly on the ipsilesional hemisphere, and the contralesional hemisphere predominantly controlled the unaffected hand. This finding was in agreement with previous work in which more normal task-related ipsilesional activation during affected hand movement was noted in well-recovered patients.\(^{(21,27)}\)

BAT facilitates balanced interhemispheric interaction through transcallosal pathways and reduces intracortical inhibition in both hemispheres,\(^{(15,21)}\) which may lead to increased activation in both hemispheres. This finding supports the notion that neural cross-talk may underlie bimanual movement by way of callosal connections to mediate interaction between the hemispheres. One study found that movement of the affected elbow increased activation in the contralesional cerebral and ipsilesional cerebellum after BAT with rhythmic auditory cueing, which was not congruent with our results.\(^{(15)}\)

Differences in treatment protocols, fMRI motor tasks, and participant characteristics (eg, chronicity and loci of stroke lesions) may have contributed to the inconsistent results.

In addition, previous studies showed that functional gains were accompanied by increased activation in the bilateral hemispheres after CIT/dCIT.\(^{(15,17)}\)

Increased use of the affected hand in CIT/dCIT may increase ipsilesional activation, enlarge cortical representation of the affected hand,\(^{(38,39)}\) and facilitate ipsilateral pathways in the contralesional hemisphere.\(^{(16)}\) CIT/dCIT thereby resulted in use-dependent brain reorganization.\(^{(40)}\)

During unaffected hand movement, the dCIT group exhibited increased activation in the bilateral hemispheres, especially in the contralesional hemisphere. One possible reason is that restriction of the unaffected hand during the training period may result in a reduction of motor representation for the unaffected hand in the contralesional hemisphere,\(^{(38,39)}\) possibly leading to the recruitment and activation of more neurons. This phenomenon was a functional and temporary change rather than a permanent change, because the activation areas recovered 2 weeks after disengagement of the restriction.\(^{(42)}\)

During bilateral elbow movement, the BAT group showed no change or slightly increased activation in the bilateral cerebrum and increased activation in the bilateral cerebellums, especially in the left cerebellum. In contrast, the dCIT group showed slightly increased activation in the bilateral cerebrums, and decreased activation in the bilateral cerebellums. Evidence from lesion and fMRI studies shows that the cerebellum is a critical site involved in bimanual movement.\(^{(42-44)}\) Moreover, the left hemisphere shows a greater involvement and has a more profound effect than the right hemisphere during bimanual coordination.\(^{(42,45)}\) Movement of the bilateral UEIs in the BAT program and unilateral affected arm movement in the dCIT regimen explain the differential change in cerebellar activation. The dCIT training protocol might be below the threshold to induce cerebellar activation after treatment.

Our preliminary findings may have some clinical implications. For instance, the neuroimaging and functional data showed that neuroplastic changes after stroke motor rehabilitation remain possible in patients with chronic stroke (> 6 months). Additionally, the activation patterns of the patients who benefited most from the two interventions showed a trend to change toward those of neurologically intact people, which provides evidence of the efficacy of BAT or dCIT intervention and supports their clinical use in stroke patients. Moreover, the differential neural plastic changes in the cerebellum between the BAT and dCIT interventions indicate the changes may be specific to different interventions. Further research is needed to study the role of cerebellar activation in mediating the effects of rehabilitation intervention.

This study had several limitations that warrant consideration. First, given the small sample size, this preliminary study is exploratory and requires further research using a larger sample to validate the findings. Second, most of the ROIs in patient 1 showed nearly no activation on the 1.5-T MRI. Further research with higher-resolution MRI would provide more sensitive images. Third, this study did not recruit patients who received conventional intervention. Further studies to compare the fMRI findings of the BAT and dCIT groups with a control intervention group are needed. Finally, the task movements may not have been challenging enough to generate activa-
nation in some patients. Further studies may need to use more complex fMRI tasks (eg, unfamiliar motor tasks) for higher-functioning patients.

**Conclusion**

This preliminary study revealed that BAT and dCIT might induce neural plasticity changes and produce motor and functional gains in stroke patients. Two well-recovered patients showed increased activation in the bilateral cerebral hemispheres, especially in the ipsilesional hemisphere, during affected hand movement and in the contralesional hemisphere during unaffected hand movement. Bilateral elbow movement resulted in differential changes between the BAT and dCIT groups in activation of the cerebellum. Cerebellar activation increased in the BAT group, but decreased in the dCIT group. Further research should use larger samples and more complex fMRI tasks to validate the findings.

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Brain reorganization after stroke rehabilitation

中風病患雙側動作訓練及
侖限誘發治療後腦重組的功能性磁振造影初探

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劉鈴1 陳嘉玲1 林光華2 衛優遊3

背 景：雙側動作訓練及侖限誘發治療有助於改善中風病患之上肢動作控制及動作功能，但至今尚無研究直接對照这两种療法對中風後腦重組的效應。本文旨在對照雙側動作訓練與侖限誘發治療對6名中風病患腦重組及動作功能的影響。

方 法：本研究採用隨機控制臨床試驗設計，將6名單側腦中風患者分派至雙側動作訓練組
與侖限誘發治療組。為期三週之治療期間，4名雙側動作訓練個案，每週五天、每天
二小時以雙側上肢兩肢對稱性動作；2名侖限誘發治療組的患者接受每週五天、每天
二小時的患肢適用訓練，另於治療以外時間接受每日六小時的健側上肢侖限。治療
前、後，以功能性磁振造影檢查患側手及雙側手執行重複動作時的區域腦活化，並
以三種臨床評量（傅格—梅爾評估量表，動作研究手臂測試，及動作活動量表）評估
動作恢復與日常功能之改變。

結 果：治療結束後，病患於功能性磁振造影檢查上呈現不同型態的改變。兩名動作恢復良
好的患兒雙側腦活化明顯增加，特別是患側手執動作時，腦傷側的腦活化增
強；以健側手執動作時，呈現健側腦的活化增加。當雙側手動動作時，三名雙側
動作訓練組病患雙側小腦活化增加，特別是在左小腦；侖限誘發療法組病患則呈現
小腦活化減低。

結 論：此初步研究結果顯示中風後動作復健的神經塑性改變可能與治療型態有關，未來需
透過更大樣本與較複雜的功能性磁振造影任務來進行後續研究。

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關鍵詞：中風，復健，功能性磁振造影，神經塑性

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