## 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 contralesional 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.

(Chang Gung Med J 2010;33:628-38)

#### Key words: stroke, rehabilitation, functional magnetic resonance imaging, neuroplasticity

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Received: Dec. 8, 2009; Accepted: May 28, 2010

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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.<sup>(1,2)</sup> Two active rehabilitation approaches, bilateral arm training (BAT) and constraint-induced therapy (CIT), have gained increasing attention in stroke rehabilitation.<sup>(3,4)</sup> 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.<sup>(5,6)</sup>

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.<sup>(5)</sup> 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.<sup>(36,7)</sup>

The relative effects of BAT versus dCIT on motor and functional performance have been studied,<sup>(8)</sup> 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.<sup>(9)</sup> 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.<sup>(10)</sup> 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,<sup>(12-15,17)</sup> whereas others observed increased activation in the contralesional hemisphere or in the bilateral association motor cortices.(15-17)

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,<sup>(18)</sup> lesion location,<sup>(19)</sup> and time since the stroke.<sup>(20)</sup> 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.<sup>(21)</sup> 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.<sup>(22,23)</sup> 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,<sup>(24)</sup> considerable nonuse of the affected UE an amount of (use score < 2.5 on the Motor Activity Log),<sup>(25)</sup> no serious cognitive deficits (score  $\ge 24$  on the Mini-Mental State Examination),<sup>(26)</sup> no excessive spasticity in any joints of the affected UE (Modified Ashworth Scale score  $\leq 2$  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



**Fig. 1** Flow diagram showing the randomization procedure. Abbreviations used: dCIT: distributed constraint-induced therapy; fMRI: functional magnetic resonance imaging; BAT: bilateral arm training.

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.<sup>(27)</sup> 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.<sup>(28,29)</sup> The Action Research Arm Test was designed to evaluate UE function.<sup>(30)</sup> 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.<sup>(31,32)</sup> 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.<sup>(3)</sup> This scale has good reliability and validity.(33,34)

#### **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 orient-ed 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 30second 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<sup>3</sup> (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.<sup>(35)</sup> 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 [(I - I)]C)/(I + C)], where I and C represent the number of activated voxels in the ipsilesional and contralesional ROIs, respectively.<sup>(22,36)</sup> 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 partici-

pants 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 Logquality 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

Patient (group)	Side of lesion	Lesion type	Gender	Age (years)	Time since stroke (months)	MMSE score
1 (BAT)	L	Putaminal and corona radiata infarction	Male	54	11	30
2 (BAT)	L	Corona radiata ischemia	Male	55	57	30
3 (BAT)	R	Lacunar and thalamic infraction	Male	57	14	30
4 (BAT)	R	Thalamus and corona radiata hemorrhage	Male	45	9	30
5 (dCIT)	R	Thalamic hemorrhage	Male	57	10	28
6 (dCIT)	R	Thalamic hemorrhage	Female	68	40	25

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

Abbreviations: BAT: bilateral arm training; dCIT: distributed constraint-induced therapy; MMSE: Mini-Mental State Examination.

Patient (group)	FMA		ARAT		MAL-AOU		MAL-QOM	
ration (group)	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1 (BAT)	53	57	53	54	1.68	1.67	1.64	1.76
2 (BAT)	38	48	35	46	2.31	3.69	2.28	3.72
3 (BAT)	50	57	48	49	0.38	0.96	0.96	1.32
4 (BAT)	52	57	35	42	0.11	0.22	0.26	0.22
5 (dCIT)	48	54	33	50	0.52	1.41	0.76	1.79
6 (dCIT)	39	49	28	29	0.52	1.54	0.70	2.35

 Table 2. Clinical Assessment Scores before and after Intervention

**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).



**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 contralesional hemisphere (blue arrow). (C) During bilateral elbow movement, activation is decreased in both cerebellar hemispheres after treatment (blue arrow).

contralesional 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 contralesional 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 contralesional 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 contralesional hemisphere (Fig. 2B). Patient 3 showed slightly increased activation in the ipsilesional cerebrum and decreased activation in the contralesional cerebrum, and no activation in the bilateral hemispheres of the cerebellum after BAT. Patient 4 exhibited a slight decrease in ipsilesional cerebral activation, an

Group	Test	Cerebral ROIs			(	Cerebellum		Total ROIs (cerebrum + cerebellum)		
		Ι	С	LI	Ι	С	LI	Ι	С	LI
Affected	l hand n	novement								
BAT	Pre	97.0 (100.0)	44.0 (47.7)	0.38	184.2 (243.4)	172.2 (151.3)	0.03	281.2 (232.8)	216.2 (183.2)	0.13
	Post	332.2 (349.0)	124.7 (125.4)	0.45	136.5 (129.1)	153.7 (185.4)	-0.06	468.7 (473.5)	278.5 (280.2)	0.25
dCIT	Pre	256.0 (202.2)	82.0 (116.0)	0.51	140.0 (195.1)	92.0 (130.1)	0.21	396.0 (397.3)	174.0 (246.1)	0.39
	Post	360.9 (360.5)	128.0 (181.0)	0.48	261.5 (365.5)	172.0 (212.1)	0.21	622.4 (726.0)	300.0 (393.1)	0.35
Unaffec	ted han	d movement								
BAT	Pre	19.8 (39.5)	142.0 (186.6)	-0.76	20.3 (40.5)	54.5 (109.0)	-0.46	40.0 (80.0)	196.5 (293.9)	-0.66
	Post	24.5 (27.1)	189.5 (258.2)	-0.77	0 (0)	21.5 (41.0)	-1	24.5 (27.1)	211.0 (297.2)	-0.79
dCIT	Pre	1 (1.41)	43.0 (60.8)	-0.95	0 (0)	6.0 (8.5)	-1	1.0 (1.41)	49.0 (69.3)	-0.96
	Post	116.5 (139.3)	527.9 (503.4)	-0.64	83.5 (109.6)	240.0 (223.4)	-0.48	200.0 (248.9)	767.9 (726.8)	-0.59
Bilatera	ıl arm n	novement								
BAT	Pre	4.3 (8.5)	0.3 (0.5)	0.87	7.0 (14.0)	0 (0)	1	11.3 (22.5)	0.3 (0.5)	0.95
	Post	18.3 (22.1)	9.0 (18.0)	0.34	41.8 (38.5)	40.3 (46.8)	0.02	60.1 (57.8)	49.3 (55.8)	0.10
dCIT	Pre	51.0 (0)	13.0 (18.4)	0.59	112.5 (101.1)	129.0 (171.1)	-0.07	163.5 (101.1)	142.0 (189.5)	0.07
	Post	70.0 (12.7)	44.5 (10.6)	0.22	89.0 (107.5)	22.0 (31.1)	0.60	159.0 (94.8)	66.5 (41.7)	0.41

Table 3. Mean Number of Activation Voxels and Laterality Index of the BAT and dCIT Groups during Hand and Arm Movement

Abbreviations: I: ipsilesional hemisphere; C: contralesional hemisphere; LI: laterality index.

Note: "Cerebral ROIs" activation indicates the sum of the activation values of the 3 cerebral ROIs (i.e., primary sensorimotor cortex, premotor cortex, and supplementary motor area). "Total ROIs" activation indicates the sum of the activation values in the cerebral ROIs and the cerebellum.

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.<sup>(21,37)</sup>

BAT facilitates balanced interhemispheric interaction through transcallosal pathways and reduces intracortical inhibition in both hemispheres,<sup>(5,21)</sup> 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.<sup>(10)</sup> 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.<sup>(15,17)</sup> Increased use of the affected hand in CIT/dCIT may increase ipsilesional activation, enlarge cortical representation of the affected hand,<sup>(38,39)</sup> and facilitate ipsilateral pathways in the contralesional hemisphere.<sup>(16)</sup> CIT/dCIT thereby resulted in use-dependent brain reorganization.<sup>(40)</sup>

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,<sup>(39)</sup> 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.<sup>(41)</sup>

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 UEs 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 neuroplastic 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 activation 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.

#### Acknowledgements

This project was supported in part by the National Science Council (NSC 96-2628-B-002-033-MY2, NSC 96-2320-B-182 -029, NSC 97-2314-B-002-008-MY3, and NSC 98-2811-B-002-015) and the National Health Research Institutes (NHRI-EX98-9742PI) in Taiwan.

#### REFERENCES

- 1. Kwakkel G, Kollen BJ, Krebs HI. Effects of robot-assisted therapy on upper limb recovery after stroke: a systematic review. Neurorehabil Neural Repair 2008;22:111-21.
- 2. Muntner P, Garrett E, Klag MJ, Coresh J. Trends in stroke prevalence between 1973 and 1991 in the US population 25 to 74 years of age. Stroke 2002;33:1209-13.
- Taub E, Miller NE, Novack TA, Cook EW 3rd, Fleming WC, Nepomuceno CS, Connell JS, Crago JE. Technique to improve chronic motor deficit after stroke. Arch Phys Med Rehabil 1993;74:347-54.
- 4. Whitall J, McCombe Waller S, Silver KH, Macko RF. Repetitive bilateral arm training with rhythmic auditory cueing improves motor function in chronic hemiparetic stroke. Stroke 2000;31:2390-5.
- Cauraugh JH, Summers JJ. Neural plasticity and bilateral movements: a rehabilitation approach for chronic stroke. Prog Neurobiol 2005;75:309-20.
- 6. Lin KC, Wu CY, Liu JS, Chen YT, Hsu CJ. Constraintinduced therapy versus dose-matched control intervention to improve motor ability, basic/extended daily functions, and quality of life in stroke. Neurorehabil Neural Repair

2009;23:160-5.

- 7. Taub E, Uswatte G. Constraint-induced movement therapy: bridging from the primate laboratory to the stroke rehabilitation laboratory. J Rehabil Med 2003;41 Suppl:34-40.
- Lin KC, Chang YF, Wu CY, Chen YA. Effects of constraint-induced therapy versus bilateral arm training on motor performance, daily functions, and quality of life in stroke survivors. Neurorehabil Neural Repair 2009;23:441-8.
- 9. Rossini PM, Calautti C, Pauri F, Baron JC. Post-stroke plastic reorganisation in the adult brain. Lancet Neurol 2003;2:493-502.
- Luft AR, McCombe-Waller S, Whitall J, Forrester LW, Macko R, Sorkin JD, Schulz JB, Goldberg AP, Hanley DF. Repetitive bilateral arm training and motor cortex activation in chronic stroke: a randomized controlled trial. JAMA 2004;292:1853-61.
- Dong Y, Dobkin BH, Cen SY, Wu AD, Winstein CJ. Motor cortex activation during treatment may predict therapeutic gains in paretic hand function after stroke. Stroke 2006;37:1552-5.
- 12. Dong Y, Winstein CJ, Albistegui-DuBois R, Dobkin BH. Evolution of fMRI activation in the perilesional primary motor cortex and cerebellum with rehabilitation trainingrelated motor gains after stroke: a pilot study. Neurorehabil Neural Repair 2007;21:412-28.
- Johansen-Berg H, Dawes H, Guy C, Smith SM, Wade DT, Matthews PM. Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. Brain 2002;125:2731-42.
- Kim YH, Park JW, Ko MH, Jang SH, Lee PK. Plastic changes of motor network after constraint-induced movement therapy. Yonsei Med J 2004;45:241-6.
- Levy CE, Nichols DS, Schmalbrock PM, Keller P, Chakeres DW. Functional MRI evidence of cortical reorganization in upper-limb stroke hemiplegia treated with constraint-induced movement therapy. Am J Phys Med Rehabil 2001;80:4-12.
- 16. Schaechter JD, Kraft E, Hilliard TS, Dijkhuizen RM, Benner T, Finklestein SP, Rosen BR, Cramer SC. Motor recovery and cortical reorganization after constraintinduced movement therapy in stroke patients: a preliminary study. Neurorehabil Neural Repair 2002;16:326-38.
- 17. Szaflarski JP, Page SJ, Kissela BM, Lee JH, Levine P, Strakowski SM. Cortical reorganization following modified constraint-induced movement therapy: a study of 4 patients with chronic stroke. Arch Phys Med Rehabil 2006;87:1052-8.
- Ward NS, Brown MM, Thompson AJ, Frackowiak RS. Neural correlates of outcome after stroke: a cross-sectional fMRI study. Brain 2003;126:1430-48.
- Luft AR, Waller S, Forrester L, Smith GV, Whitall J, Macko RF, Schulz JB, Hanley DF. Lesion location alters brain activation in chronically impaired stroke survivors.

Neuroimage 2004;21:924-35.

- 20. Feydy A, Carlier R, Roby-Brami A, Bussel B, Cazalis F, Pierot L, Burnod Y, Maier MA. Longitudinal study of motor recovery after stroke: recruitment and focusing of brain activation. Stroke 2002;33:1610-7.
- 21. McCombe Waller S, Whitall J. Bilateral arm training: why and who benefits? Neuro Rehabilitation 2008;23:29-41.
- 22. Askim T, Indredavik B, Vangberg T, Haberg A. Motor network changes associated with successful motor skill relearning after acute ischemic stroke: a longitudinal functional magnetic resonance imaging study. Neurorehabil Neural Repair 2009;23:295-304.
- 23. Sharma N, Pomeroy VM, Baron JC. Motor imagery: a backdoor to the motor system after stroke? Stroke 2006;37:1941-52.
- 24. Brunnstrom S. Movement therapy in hemiplegia. New York: Harper & Row, 1970.
- 25. Taub E. Constraint-induced movement therapy and massed practice. Stroke 2000;31:986-8.
- 26. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) Examination. J Clin Psychiatry 1987;48:314-8.
- Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. Scand J Rehabil Med 1975;7:13-31.
- Duncan PW, Propst M, Nelson SG. Reliability of the Fugl-Meyer Assessment of sensorimotor recovery following cerebrovascular accident. Phys Ther 1983;63:1606-10.
- 29. Platz T, Pinkowski C, van Wijck F, Kim IH, di Bella P, Johnson G. Reliability and validity of arm function assessment with standardized guidelines for the Fugl-Meyer Test, Action Research Arm Test and Box and Block Test: a multicentre study. Clin Rehabil 2005;19:404-11.
- Lyle RC. A performance test for assessment of upper limb function in physical rehabilitation treatment and research. Int J Rehabil Res 1981;4:483-92.
- Hsieh CL, Hsueh IP, Chiang FM, Lin PH. Inter-rater reliability and validity of the Action Research Arm Test in stroke patients. Age Ageing 1998;27:107-13.
- 32. Lang CE, Wagner JM, Dromerick AW, Edwards DF. Measurement of upper-extremity function early after stroke: properties of the Action Research Arm Test. Arch Phys Med Rehabil 2006;87:1605-10.
- 33. Uswatte G, Taub E, Morris D, Light K, Thompson PA.

The Motor Activity Log-28: assessing daily use of the hemiparetic arm after stroke. Neurology 2006;67:1189-94.

- 34. van der Lee JH, Beckerman H, Knol DL, de Vet HC, Bouter LM. Clinimetric properties of the Motor Activity Log for the assessment of arm use in hemiparetic patients. Stroke 2004;35:1410-4.
- 35. Small SL, Hlustik P, Noll DC, Genovese C, Solodkin A. Cerebellar hemispheric activation ipsilateral to the paretic hand correlates with functional recovery after stroke. Brain. 2002;125:1544-57.
- 36. Cramer SC, Nelles G, Benson RR, Kaplan JD, Parker RA, Kwong KK, Kennedy DN, Finklestein SP, Rosen BR. A functional MRI study of subjects recovered from hemiparetic stroke. Stroke 1997;28:2518-27.
- Ward NS, Brown MM, Thompson AJ, Frackowiak RS. Neural correlates of motor recovery after stroke: a longitudinal fMRI study. Brain 2003;126:2476-96.
- Liepert J, Hamzei F, Weiller C. Lesion-induced and training-induced brain reorganization. Restor Neurol Neurosci 2004;22:269-77.
- 39. Ro T, Noser E, Boake C, Johnson R, Gaber M, Speroni A, Bernstein M, De Joya A, Scott Burgin W, Zhang L, Taub E, Grotta JC, Levin HS. Functional reorganization and recovery after constraint-induced movement therapy in subacute stroke: case reports. Neurocase 2006;12:50-60.
- 40. Taub E, Uswatte G, Pidikiti R. Constraint-induced movement therapy: a new family of techniques with broad application to physical rehabilitation – a clinical review. J Rehabil Res Dev 1999;36:237-51.
- 41. Sheng B, Lin M. A longitudinal study of functional magnetic resonance imaging in upper-limb hemiplegia after stroke treated with constraint-induced movement therapy. Brain Inj 2009;23:65-70.
- 42. Debaere F, Wenderoth N, Sunaert S, Van Hecke P, Swinnen SP. Changes in brain activation during the acquisition of a new bimanual coordination task. Neuropsychologia 2004;42:855-67.
- 43. Serrien DJ, Wiesendanger M. Temporal control of a bimanual task in patients with cerebellar dysfunction. Neuropsychologia 2000;38:558-65.
- 44. Swinnen SP. Intermanual coordination: from behavioural principles to neural-network interactions. Nat Rev Neurosci 2002;3:348-59.
- 45. Jancke L, Peters M, Himmelbach M, Nosselt T, Shah J, Steinmetz H. fMRI study of bimanual coordination. Neuropsychologia 2000;38:164-74.

# 中風病患雙側動作訓練及 侷限誘發治療後腦重組的功能性磁振造影初探

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- 背景: 雙側動作訓練及侷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這兩種療法對中風後腦重組的效應。本文旨在對照雙側動作 訓練與侷限誘發治療對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 與侷限誘發治療組。爲期三週之治療期間,4名雙側動作訓練個案,每週五天、每天 二小時以雙側上肢演練對稱性動作;2名侷限誘發治療組的患者接受每週五天、每天 二小時的患肢迫用訓練,另於治療以外時間接受每日六小時的健側上肢侷限。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(傳格—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者雙側腦活化明顯增加,特別是當患側手執行動作時,腦傷側的腦活化增強;以健側手執行動作時,呈現健側腦的活化增強。當雙側手肘動作時,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;侷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。 (長庚醫誌 2010;33:628-38)
- 關鍵詞:中風,復健,功能性磁振造影,神經塑性

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