Training-Induced Brain Plastic Changes in Stroke Patients

脑中风病人进行训练后所诱发之脑塑性改变

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Brain plasticity

- Brain plasticity:
  - Kolb (1995) described the life of a woman (Donna).
  - One of the most intriguing and important properties of the human brain.
  - Allows the brain to response to environment changes or changes within the organism itself.
  - Behavior (experience) ⟷ Brain
- Stroke recovery depends on functional and structural neuroplasticity.

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Patterns of reorganization

- New synaptic pathways
- Unmasking of silent synapses
- Improved functional connectivity
- Enlargement of cortical representation
- Shifts from primary to secondary areas and to the homologous areas of the non-affected hemisphere.
- ……
- A dynamic process in cortical reorganization during recovery.

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Constraint-induced therapy

- CIT:
  - From basic research with monkeys and behavioral psychology
  - To overcome the learned nonuse phenomenon
  - Positive effectiveness of CIT and dCIT:
    - Most studies used clinical scales to evaluate effects
- CIT mechanisms ?
  - Liepert et al (1998), TMS
  - Use-dependent cortical reorganization

Dr. Taub

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Neuroimaging Techniques ~

Permit studies of training-induced plasticity and unravel the mystery of recovery

fMRI PET TMS

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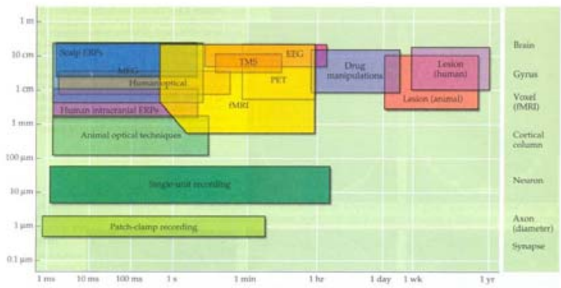
Spatial and temporal resolution



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(Levy et al., 2001)

Functional MRI Evidence of Cortical Reorganization in Upper-Limb Stroke Hemiplegia Treated with Constraint-Induced Movement Therapy

ABSTRACT

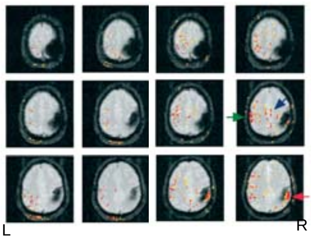
Levy CE, Nichols DS, Schmalbrock PM, Keller P, Chakeres DW: Functional MRI evidence of cortical reorganization in upper-limb stroke hemiparesis treated with constraint-induced movement therapy. *Am J Phys Med Rehabil* 2001;80:4–12.

Objective: The purpose of this pilot study was to test constraint-induced movement therapy for chronic upper-limb stroke hemiparesis and to investigate the neural correlates of recovery with functional magnetic resonance imaging (MRI) in two subjects. Both subjects had been discharged from traditional therapy because no further improvement was anticipated.

Design: Constraint-induced movement therapy consisted of 6 hr of daily upper-limb training for 2 wk; a restrictive mitt was worn on the nonparetic limb during waking hours. Functional MRI was performed on a 1.5-T MRI with echo-planar imaging; at the same time, the subjects attempted sequential finger-tapping.

Results: Compared with baseline, performance time improved an average of 24% immediately after training and also continued to improve up to 33% 3 mo after training. Lift, grip strength, and Motor Activity Log scores likewise improved. Initially, on functional MRI, subject 1 activated scattered regions in the ipsilateral posterior parietal and occipital cortices. Subject 2 showed almost no areas of significant activation. After training, subject 1 showed activity bordering the lesion, bilateral activation in the association motor cortices, and ipsilateral activation in the primary motor cortex. Subject 2 showed activation near the lesion site.

Conclusion: Constraint-induced movement therapy produced significant functional improvement and resulted in plasticity as demonstrated by functional MRI.



Red: activation bordering the lesion

Green: S1, M1, PMC activation in non-lesioned cortex

Blue: bilateral activation in SMA

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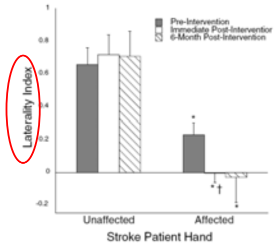
(Schaechter et al., 2002)

Motor Recovery and Cortical Reorganization after Constraint-Induced Movement Therapy in Stroke Patients: A Preliminary Study

Judith D. Schaechter, Eduard Kraft, Timothy S. Hilliard, Rick M. Dijkhuizen, Thomas Benner, Seth P. Finklestein, Bruce R. Rosen, and Steven C. Cramer



A shift of motor cortical activation toward the undamaged hemisphere

Lower LI indicate relatively greater activation in ipsilateral motor cortices

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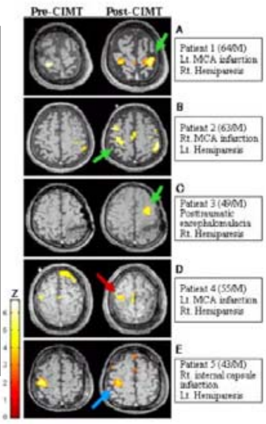
(Kim et al., 2004)

Plastic Changes of Motor Network after Constraint-Induced Movement Therapy

Yun-Hee Kim, Ji-Won Park, Myoung-Hwan Ko, Sung-Ho Jang, and Peter K. W. Lee

The effects of short-term constraint-induced movement (CIM) therapy on the activation of the motor network were investigated with functional magnetic resonance imaging (fMRI). Movement of the less-affected arms of five patients was restricted and intensive training of the affected upper limb was performed. Functional MRI was acquired before and after two-weeks of CIM therapy. All patients showed significant improvement of motor function in their paretic limbs after CIM therapy. For three patients, new activation in the contralateral motor/premotor cortices was observed after CIM therapy. Increased activation of the ipsilateral motor cortex and SMA was observed in the other patient. Our results demonstrated that plastic changes of the motor network occurred as a neural basis of the improvement subsequent to CIM therapy following brain injury.



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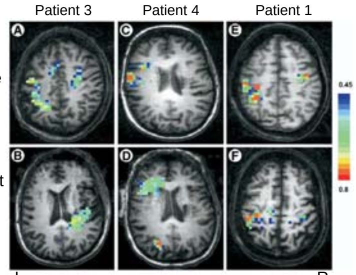
(Szaflarski et al., 2006)

Cortical Reorganization Following Modified Constraint-Induced Movement Therapy: A Study of 4 Patients With Chronic Stroke

Jerzy P. Szaflarski, MD, PhD, Stephen J. Page, PhD, Brett M. Kissela, MD, Jing-Huei Lee, PhD, Peter Levine, BA, PTA, Stephen M. Strakowski, MD



In patients who responded to mCIMT, cortical reorganization was positively related to degree of increase in affected arm use and ability.

Patient 3: (A) signal changes in the left pre- and postcentral gyrus and right precentral gyrus to (B) the post-mCIMT BOLD signal changes in the subcortical and cortical structures in the right hemisphere.
Patient 4: shows change in BOLD signal from (C) the left inferior frontal gyrus to (D) the left middle frontal gyrus.
Patient 1: shows no substantial change between (E) the pre-mCIMT and (F) post-mCIMT scans

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Issues

- Provocative but equivocal findings on cortical reorganization pattern in patients after CIT
- Case study or small sample size
- Lack of a controlled therapy
  - E.g. customary rehabilitation

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Our study

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Purposes

- To assess therapy-induced plasticity in stroke patients undergoing dCIT compared with customary rehabilitation (CR) using fMRI.
- To examine the benefits of dCIT in functional outcomes:
  - The FMA: evaluating motor function
  - The MAL: subjectively representing daily function

(FMA=Fugl-Meyer Assessment, MAL=Motor Activity Log)

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Research Questions

- Do patients receiving 3-week dCIT exhibit better motor and daily function compared to the CR group ?
- Does dCIT give rise to plastic changes in the motor areas that is both specific and different from the patterns of reorganization after CR ?

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Participants

- Study inclusion criteria:
  (1) A single stroke that caused unilateral hemiplegia or hemiparesis
  (2) Sufficient cognitive ability (MMSE score≧24)
  (3) The ability to extend metacarpophalangeal joint 10 and interphalangeal joints 20 degrees on last 4 fingers of the affected hand
  (4) No excessive spasticity in any of the joints of the affected UE
- Additional criteria for functional MRI:
  (1) No seizure attacked in 6 months recently
  (2) No metal implant or fixed partial denture inside
  (3) No claustrophobia
  (4) Able to perform repetitive finger flexion-extension motor task

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Demographic & clinical characteristics of the participants

	dCIT group (N=12)	CR group (N=14)
Age, year	44.6 (14.9)	55.1 (11.8)
Gender (male/female)	10/2	12/2
Side of lesion (right/left)	4/8	5/9
Time post onset, month	8.6 (10.0)	11.9 (13.0)
MMSE, mean (SD)	27.7 (2.5)	26.5 (3.4)

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Interventions

Distributed CIT group

Training:
- Shaping techniques
- Intensive training
- Functional tasks
- 2h/d, 5d/wk for 3 wks

Restraint:
- Restraint of the less affected limb 6h/d

Customary rehabilitation group

Training:
- Neurodevelopmental treatment
- 2h/d, 5d/wk for 3 wks

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Functional MRI measures

- 1.5-T scanner (Siemens, Erlangen, Germany)
- Blood oxygenation level-dependent (BOLD) functional images
- Motor task:
  - Flexion and extension of 4 fingers at 2/3 Hz.
  - Block design: 6 x21 second rest and 6 x21 second movement epochs

- Minimized head motion and avoid mirror or associated movement.

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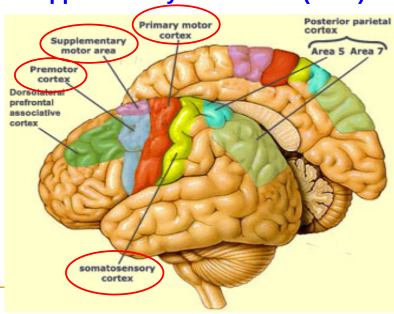
Regions of interest (ROIs) ~

Primary sensorimotor cortex (SMC)
Premotor cortex (PMC)
Supplementary motor area (SMA)



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Laterality index (LI)

$$LI = \frac{[(cSMC + cPMC + cSMA) - (iSMC + iPMC + iSMA)]}{[(cSMC + cPMC + cSMA) + (iSMC + iPMC + iSMA)]}$$

where c = contralateral and i = ipsilateral

- +1: indicating that all sensory and motor cortical activation occurred in the hemisphere contralateral to the moving hand
- -1: indicating that all sensory and motor cortical activation occurred in the hemisphere ipsilateral to the moving hand.

(Dong, Dobkin, Cen, Wu, & Winstein, 2006)

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Results

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Results of motor & daily function

- After treatment, the EIs of the dCIT group showed significant higher than those of the CR group:
  - the FMA (p= 0.0045, and effect size r= 0.50)
  - the MAL-AOU (p= 0.014, and effect size r= 0.43)
  - the MAL-QOM (p< 0.001, and effect size r= 0.68)

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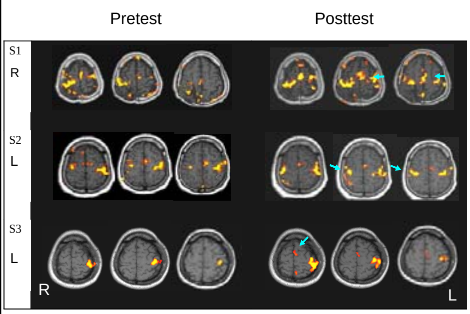
Cortical activation patterns of the dCIT group (S1～S3)



S1 & S2 showed brain activation increased not only in contralateral hemisphere but also in ipsilateral hemisphere

S3 showed new activation in contralateral SMA

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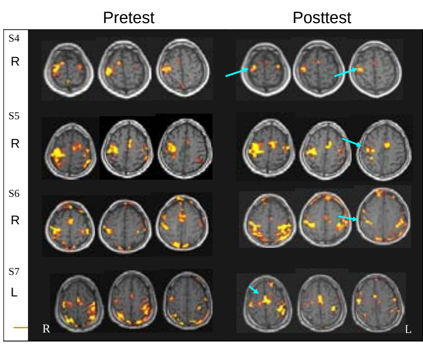
Cortical activation patterns of the CR group (S4～S7)



S4~S6 showed decreased activation in contralateral SMC

S7 exhibited increased bilateral SMA activation

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Number of activation voxels in dCIT group

ROI	More-affected hand		Less-affected hand	
	Pre	Post	Pre	Post
C-				
SMC	106.67 (63.7)	120.67 (77.5)	154.67 (11.6)	189.00 (35.8)†
PMC	15.67 (11.8)	22.33 (21.1)	45.33 (20.6)	34.33 (30.1)
SMA	24.67 (22.8)	35.67 (28.5)	36.67 (32.7)	39.00 (40.4)
Total	147.00 (97.3)	178.67 (120.1)	236.67 (61.7)	262.33 (104.1)
I-				
SMC	27.67 (44.5)	51.00 (56.7)	8.33 (14.4)	4.33 (7.5)
PMC	16.33 (15.2)	27.67 (26.2)	7.00 (8.2)	11.33 (19.6)
SMA	16.00 (16.5)	36.33 (46.6)	22.67 (22.0)	12.33 (12.5)
Total	60.00 (62.1)	115.00 (95.4)†	38.00 (33.9)	28.00 (29.6)

* $p < 0.05$, †$p < 0.06$

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Number of activation voxels in CR group

ROI	More-affected hand		Less-affected hand	
	Pre	Post	Pre	Post
C-				
SMC	139.00 (60.8)	98.25 (45.9)*	118.75 (62.8)	118.00 (46.6)
PMC	33.5 (15.3)	19.75 (14.7)	15.5 (13.0)	28.00 (30.0)
SMA	7.50 (3.8)	17.00 (20.1)	13.75 (12.5)	26.5 (27.8)
Total	180.00 (71.0)	135.00 (49.6)*	148.00 (82.7)	172.50 (80.2)
I-				
SMC	35.75 (28.3)	47.50 (61.4)	13.25 (10.7)	20.00 (19.1)
PMC	16.50 (9.5)	21.25 (19.0)	13.5 (11.6)	12.00 (9.9)
SMA	17.50 (12.4)	23.75 (25.4)	7.00 (9.2)	11.00 (14.0)
Total	69.75 (39.0)	92.50 (72.7)	33.75 (25.7)	43.00 (40.0)

* $p < 0.05$, †$p < 0.06$

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Laterality index in dCIT group

	dCIT			
	More-affected hand		Less-affected hand	
ROI	Pre	Post	Pre	Post
SMC	0.76 (0.4)	0.57 (0.5)	0.91 (0.2)	0.96 (0.06)
PMC	0.32 (0.6)	-0.07 (0.3)	0.80 (0.2)	0.78 (0.39)
SMA	0.15 (0.3)	0.13 (0.32)	0.45 (0.6)	0.57 (0.5)
Total	0.60 (0.4)	0.38 (0.4)*	0.76 (0.2)	0.83 (0.2)

* $p < 0.06$

Ipsilateral (unaffected) hemisphere activation increased

$$LI = \frac{c - i}{c + i}$$

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Laterality index in CR group

	CR			
	More-affected hand		Less-affected hand	
ROI	Pre	Post	Pre	Post
SMC	0.62 (0.2)	0.48 (0.4)	0.84 (0.1)	0.76 (0.2)
PMC	0.33 (0.2)	0.04 (0.4)	0.05 (0.2)	0.44 (0.4)
SMA	-0.10 (0.8)	-0.09 (0.4)	0.35 (0.3)	0.42 (0.5)
Total	0.47 (0.3)	0.29 (0.4)	0.71 (0.2)	0.68 (0.2)

Contralateral (affected) hemisphere activation decreased

$$LI = \frac{c - i}{c + i}$$

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Discussion

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Main findings

Functional recovery → Improvements on motor and daily function: dCIT > CR

Brain plastic changes →

dCIT group: Increased activation in the bilateral hemispheres after intervention, especially in the unaffected hemisphere

CR group: Decreased activation in the affected hemisphere

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Plastic changes after CIT

Activations shift toward the unaffected hemisphere (ipsilateral)

- Increased activation of the ipsilateral motor cortices in adults when they performed challenging and difficult motor tasks. (Kim et al., 1993; Roland et al., 1980)
- Participants in the dCIT group:
  - Practice on tasks that were challenging and graded in the level of difficulty (shaping).
  - Achieving functional use of the affected arm by problem solving, motor planning and learning.

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Plastic changes after CR

Decreased activations in the affected hemisphere

- Decreased activations in the affected hemisphere together with less motor improvement after CR might be associated with the learned nonuse phenomenon that was not successfully overcome by this intervention.

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Limitations & further suggestions

- Limited sample size:
  - Further research based on a larger sample to establish the robustness of the plastic changes observed in this study.
- To elucidate the mechanisms associated with spontaneous or treatment-facilitated recovery:
  - Further research may recruit an additional control group who are not undergoing rehabilitation intervention during the study period.

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Conclusion

- This is the first functional neuroimaging study that has used a control group for comparison with CIT.
- Our results showed that dCIT gave rise to brain plastic changes and motor gains.
- The findings indicate that brain adaptation may be modulated by specific rehabilitation practices.

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