IMAGING IN NEURAL REGENERATION

Disappearance of unaffected motor cortex activation by repetitive transcranial magnetic stimulation in a patient with cerebral infarct

The ipsilateral motor pathway from the unaffected motor cortex to the affected extremity is one of the motor recovery mechanisms following stroke (Jang, 2011). Because stroke patients who had shown recovery by this mechanism usually showed poorer motor function, compared with patients who showed recovery by other mechanisms, several researchers have considered this mechanism as a maladaptive plasticity (Jang, 2013).

Change in activity of the ipsilateral motor cortex by various rehabilitative interventions, including repetitive transcranial magnetic stimulation (rTMS), has been reported (Mansur et al., 2005; Takeuchi et al., 2005; Liepert et al., 2007; Kirton et al., 2008; Nowak et al., 2008; Takeuchi et al., 2008; Conchou et al., 2009; Khedr et al., 2009; Takeuchi et al., 2009; Grefkes et al., 2010; Jang, 2011). Many studies have reported that application of rTMS on the unaffected hemisphere could result in improvement of the motor function of the affected hand in stroke patients (Mansur et al., 2005; Takeuchi et al., 2005; Liepert et al., 2007; Kirton et al., 2008; Takeuchi et al., 2008; Khedr et al., 2009; Takeuchi et al., 2009). In addition, a few functional neuroimaging studies have demonstrated the immediate effect of a single session of rTMS on the unaffected motor cortex in stroke patients (Nowak et al., 2008; Conchou et al., 2009; Grefkes et al., 2010). However, no functional neuroimaging study on the effect of application of rTMS on the unaffected motor cortex for several sessions in stroke patients has been reported. In this study, we report on a patient with a cerebral infarct in whom activation of the unaffected motor cortex disappeared after application of rTMS for 2 weeks, as evaluated by fMRI.

A 50-year-old right-handed male patient exhibited severe paralysis of his left upper and lower extremities after coronary artery bypass graft surgery for treatment of coronary artery disease. He was diagnosed as having an infarction in the right middle cerebral artery (MCA) territory, including the precentral knob (Figure 1A). Four weeks after onset, he was transferred to the rehabilitation department of a university hospital in order to undergo rehabilitation. The patient exhibited severe weakness of the left hand (finger flexor: Medical Research Council (MRC)[2^-], finger extensor: MRC[0]) with moderate weakness of other muscles of the left upper and lower extremities (MRC[2^+–4^-])(Table 1).

The patient underwent a comprehensive rehabilitative management program, including movement therapy, medications and neuromuscular electrical stimulation therapy. After 4 weeks of intensive rehabilitation (8 weeks after onset), the patient showed motor recovery of the left hand (finger flexor: MRC[4], finger extensor: MRC[3]) with other muscles as MRC 4–4^+. He was able to perform some fine motor activity, as much as 5 (normal range: 13.8 ± 1.5) on the Purdue pegboard score (Kim et al., 1994). However, grade 3 mirror movements (strong and sustained repetitive movement) on Woods and Teuber's study were observed in the right fingers during movement of the left fingers (Woods and Teuber, 1978). At 10 weeks after onset, the fine motor ability of the left hand showed improvement, with a Purdue pegboard score of 7, and no mirror movements of the right fingers were observed during movements of the left fingers.

Blood oxygen level-dependent (BOLD) fMRI measurements using the echo planar imaging (EPI) technique were performed twice, at 8 weeks and 10 weeks after onset, using a 1.5-T Philips Gyroscan Intera scanner (Hoffman-LaRoche, Ltd., Best, the Netherlands) with a standard head coil. The patient was examined while in a supine position and was firmly immobilized in order to prevent motion in the fMRI scanner. Using a block paradigm (21-second control, 21-second stimulation: 3 cycles), hand grasp-release movements (1 Hz) were performed for stimulation. SPM 8 software (Wellcome Department of Cognitive Neurology, London, UK) running in the MATLAB environment was used for analysis of fMRI data. Statistical parametric maps were obtained, and voxels of cluster level were considered significant at a threshold of uncorrected $P < 0.001$.

On 8-week fMRI, bilateral primary sensori-motor cortices (SM1s) were activated during movement of the left hand (Figure 1B). Activation of the left SM1 had disappeared on 10-week fMRI; instead, activation of the right primary somatosensory cortex (S1) was observed during movements of the left hand. On the contrary, bilateral SM1 were activated during movements of the right hand on both 8-week and 10-week fMRI.

To confirm the exact location of the precentral knob, the hot spot was determined by transcranial magnetic stimulation (TMS). A Magstim Novametrix 200 magnetic stimulator (Novametrix Medical Systems Inc., Wallingford, CT, USA) with a 70 mm butterfly coil was used for performance of TMS. A cloth marked with 1 cm spacing and Cz-referenced to the intersection of the midsagittal and interaural lines was placed on the scalp. Motor evoked potentials (MEPs) were obtained from both abductor pollicis brevis (APB) muscles in a relaxed state. We found that the hot spot for the right APB muscle was located (–5, 1) in the left hemisphere. The patient underwent twelve sessions of rTMS applied to the hot spot (–5, 1) of the left hemisphere, according to the following protocol (MAGPRO, Medtronic Functional Diagnostics, Skovlunde, Denmark): frequency of 1 Hz, intensity of 100% motor threshold, 1,200 stimuli as a single, continuous train lasting 20 minutes, for six sessions per week for a period of 2 weeks (Fregni et al., 2006). During rTMS application for 2 weeks, other rehabilitative interventions including medication and physical therapy did not change. The patient did not report or show any side effect of rTMS.

In the current study, we followed up the motor recovery process in a patient with an MCA infarct. According to our results, it appeared that the motor function of the affected (left) hand had been recovered by bi-hemispherical reorganization evolved from activation of the bilateral motor cortex to activation of the affected motor cortex and peri-lesional reorganization. The patient was diagnosed as having an infarct in the right MCA territory, including the precentral knob, which is known to be the neural center of hand motor function. He had shown complete paralysis of the left hand at the onset of stroke; however, motor function showed a slow recovery over a period of 2 months, to the extent that the patient was able to overcome gravity, strongly suggesting that recovery of motor function of the affected hand had occurred through a process of brain plasticity (Jang, 2010). On 8-week fMRI, bilateral SM1 were activated during movements of the affected (left) hand. However, on 10-week fMRI, activation of the unaffected (left) SM1 had disappeared; instead, activation of the majority of the right S1 was observed during movements of the left hand. As a result, recovery of motor function of the affected hand appeared to have occurred as a result of peri-lesional reorganization into the S1 through bi-hemispherical reorganization.

The disinhibition hypothesis is the most widely accepted hypothesis for activation of the unaffected motor cortex (Liepert et al., 2000). For the past two decades, because the unaffected motor cortex is known to be related to poor motor function, many studies have used rTMS to suppress activation of the unaffected cortex in stroke patients (Mansur et al., 2005; Liepert et al., 2007; Kirton et al., 2008; Khedr et al., 2009; Takeuchi et al., 2005, 2008, 2009). We also applied 12 sessions of rTMS for a period of 2 weeks, and found the disappearance of unaffected motor cortex activation concurrent with motor recovery of the affected hand. The disappearance of mirror movements, which is known to be a phenomenon of the ipsilateral motor pathway in stroke patients, would provide additional evidence for disappearance of activation of the unaffected motor cortex (Lee et al., 2010). However, because this patient underwent rTMS during the critical period (from stroke onset to 3 months) of motor recovery in stroke patients, we cannot confirm that disappearance of activation of the unaffected motor cortex in this patient could be attributed to the rTMS effect or to a process of spontaneous recovery (Jorgensen et al., 1995). However, we believe that the unaffected motor cortex activation was disappeared mainly by the effect of rTMS for the following reasons. First, although the activation of the unaffected motor cortex was much stronger than that of the affected motor cortex on 8-week fMRI, this activation was completely disappeared on 10-week fMRI. Likewise, the strong mirror movement of grade 3 at 8 weeks after onset also completely disappeared at 10 weeks after onset. Second, Takeda et al. (2007) reported that the cortical activation of the unaffected motor cortex decreased to a normal pattern at 35 days after onset in patients with cerebral infarct. However, in our patient, the unaffected motor cortex activation was disappeared between 8 and 10 weeks after onset although other rehabilitative interventions except for rTMS did not change during this

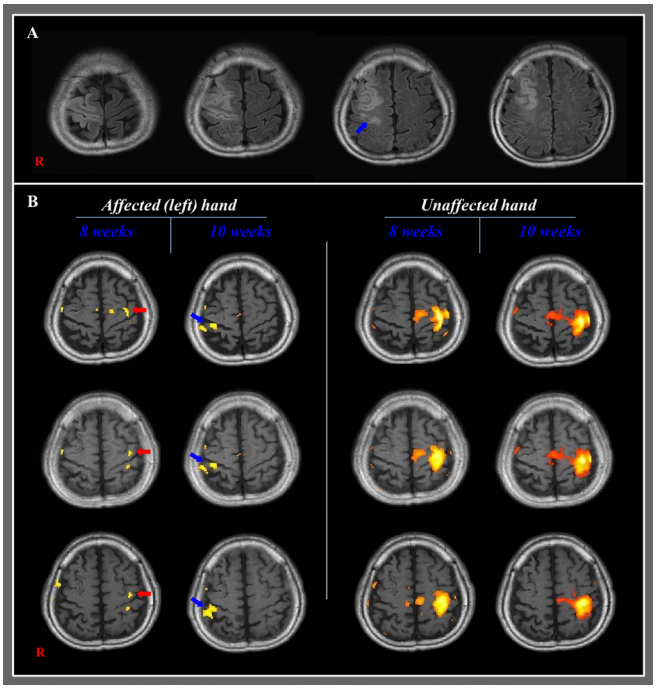

Figure 1 T2-weighted and functional MRI (fMRI) images of a 50-year-old male patient with right middle cerebral artery occlusion (MCAO) exhibiting severe paralysis of his left upper and lower extremities.
(A) T2-FLAIR images showing an infarct in the right middle cerebral artery territory including the precental knob (blue arrow). (B) Bilateral primary sensori-motor cortices (SM1s) were activated during movement of the affected (left) hand on 8-week fMRI images. On 10-week fMRI images, the left SM1 activation (red arrows) had disappeared and activation of the right primary somatosensory cortex (blue arrows) was observed during movements of the left hand. By contrast, bilateral SM1 were activated during movements of the right hand on both 8-week and 10-week fMRI images.

period. In conclusion, we demonstrated the disappearance of activation of the unaffected motor cortex by 12 sessions of rTMS in a stroke patient. Recovery of motor function of the affected hand appeared to have occurred through bi-hemispherical reorganization, and, subsequently, peri-lesional reorganization. Because the methods and results of this study can be applied for rehabilitation in stroke patients who show activity of the unaffected motor cortex, we believe that our results have important implications for stroke rehabilitation. However, because it is a case report, this study is limited. Conduct of further complementary studies involving larger numbers of cases is warranted.

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Table 1 Changes of motor function in the patient with cerebral infarct

			Weeks after onset		
		Onset	4	8	10
MRC	Shoulder abductor	2^-	2^+	4	4^+
	Elbow flexor	2^-	2^+	4	4^+
	Finger flexor	0	2^-	4	4^+
	Finger extensor	0	0	3	4
	Hip flexor	2^-	3^+	4^+	4^+
	Knee extensor	2^-	4^-	4^+	4^+
	Ankle dorsiflexor	2^-	4^-	4^+	4^+
PPT		0	0	5	7
MM		–	–	G3	G0

Medical Research Council (MRC): 0, no contraction; 1, palpable contraction, but no visible movement; 2, movement without gravity; 3, movement against gravity; 4, movement against a resistance lower than the resistance overcome by the healthy side; 5, movement against a resistance equal to the maximum resistance overcome by the healthy side. Mirror movement was assessed with the modified Woods and Teuber scale: grade 0, no clearly imitative movement on contralateral homologous regions; 1, very mild MM or increased tone; 2, a slight but unsustained repetitive movement; 3, a briefer repetitive movement, less than ½ range of motion (ROM) of the metacarpophalangeal joint in the unaffected hand; 4, a stronger repetitive movement, more than ½ ROM of the metacarpophalangeal joint in the unaffected hand; 5, a movement equal to that expected of the intended hand. PPT: Purdue pegboard test; MM: Mirror movement. Mirror movement; –: uncheckable.

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