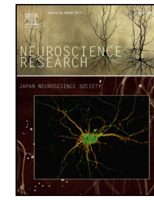
Neuroscience Research 92 (2015) 29–38

Contents lists available at ScienceDirect

Neuroscience Research

journal homepage: www.elsevier.com/locate/neures



Task-specific brain reorganization in motor recovery induced by a hybrid-rehabilitation combining training with brain stimulation after stroke

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ARTICLE INFO

Article history:
Received 15 May 2014
Received in revised form 3 October 2014
Accepted 6 October 2014
Available online 18 October 2014

Keywords:
Stroke
Transcranial magnetic stimulation
Hemiparesis
Neuroplasticity
Task specificity
Rehabilitation

ABSTRACT

Recently, we have developed a new hybrid-rehabilitation combining 5 Hz repetitive transcranial magnetic stimulation and extensor motor training of the paretic upper-limb for stroke patients with flexor hypertonia. We previously showed that the extensor-specific plastic change in M1 was associated with beneficial effects of our protocol (Koganemaru et al., 2010). Here, we investigated whether extensor-specific multiregional brain reorganization occurred after the hybrid-rehabilitation using functional magnetic resonance imaging. Eleven chronic stroke patients were scanned while performing upper-limb extensor movements. Untrained flexor movements were used as a control condition. The scanning and clinical assessments were done before, immediately and 2 weeks after the hybrid-rehabilitation. As a result, during the trained extensor movements, the imaging analysis showed a significant reduction of brain activity in the ipsilesional sensorimotor cortex, the contralesional cingulate motor cortex and the contralesional premotor cortex in association with functional improvements of the paretic hands. The activation change was not found for the control condition. Our results suggested that use-dependent plasticity induced by repetitive motor training with brain stimulation might be related to task-specific multi-regional brain reorganization. It provides a key to understand why repetitive training of the target action is one of the most powerful rehabilitation strategies to help patients.

1. Introduction

Use-dependent plasticity is a neurophysiological basis of functional recovery in neuro-rehabilitation (Butefisch et al., 1995; Dimyan and Cohen, 2011; Hummelsheim, 1999; Masiero and Carraro, 2008; Nudo and Milliken, 1996; Nudo et al., 1996a,b; Richards et al., 2008). Repeating a specific motor training induces use-dependent plasticity in the primary motor cortex (M1) through long-term potentiation (LTP)-like changes of specific corticospinal motoneurons for the trained task (Butefisch et al., 2000; Classen et al., 1998; Rossini and Pauri, 2000).

Patients with chronic stroke, with moderate-to-severe hemiparesis, often suffer from motor deficits associated with flexor hypertonia, as well as motor weakness. In order to facilitate use-dependent plasticity for extensor function which counteracts flexor hypertonia, we have developed a new hybrid-rehabilitation combining 5 Hz repetitive transcranial magnetic stimulation (rTMS)

Abbreviations: ANOVA, analysis of variance; AOU, Amount of Use; CMC, cingulate motor cortex; EDC, extensor digiti communis; FCR, flexor carpi radialis; FMA, Fugl-Meyer Assessment; fMRI, functional MRI; LTP, long-term potentiation; M1, primary motor cortex; MAL, Motor Activity Log; mAS, Modified Ashworth Scale; MEP, motor evoked potentials; MCP, metacarpophalangeal; MNI, Montreal Neurological Institute; MT, motor threshold; PMC, premotor cortex; QOM, Quality of Movement; ROI, region of interest; ROM, range of movement; rTMS, repetitive transcranial magnetic stimulation; %SC, percentage signal change; SIAS, Stroke Impairment Assessment Set; SMC, sensorimotor cortex; SPM, Statistical Parametric Mapping; TMS, transcranial magnetic stimulation.

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http://dx.doi.org/10.1016/j.neures.2014.10.004
0168-0102/

Table 1
Characteristics of the patients.

Patient	Age (years)	Gender	Months after stroke	SIAS (shoulder, arm-fingers)	Hemorrahge (H)/infarct (I)	Hemiparetic side	Lesioned site	Sensory disturbance
1	57	M	6	3_1c	I	Right	Posterior limb of internal capsule, corona radiata	None
2	64	M	12	5_1c	H	Right	Thalamus, Posterior limb of internal capsule	None
3	54	M	16	3_1c	H	Left	Posterior limb of internal capsule	None
4	68	M	7	5_3	I	Right	Posterior limb of internal capsule	None
5	68	M	6	1_0	I	Left	Posterior limb of internal capsule	Mild
6	60	F	16	3_1c	I	Left	Posterior limb of internal capsule, corona radiata	None
7	58	F	20	4_2	I	Left	Posterior limb of internal capsule	None
8	56	M	64	2_1a	H	Left	Posterior limb of internal capsule	None
9	62	M	66	3_1c	I	Right	Posterior limb of internal capsule	None
10	67	F	96	2_1c	H	Left	Putamen, Posterior limb of internal capsule	Moderate
11	55	M	33	2_1c	I	Right	Posterior limb of internal capsule, corona radiata	None

In the Stroke Impairment Assessment Scale (SIAS), proximal sites of paretic upper-extremities, such as a shoulder and an arm, are evaluated by Knee-Mouth test and distal sites such as fingers are evaluated by the Finger-function test. The lower the value is, the more severe the impairment is. A score of 0 = total paralysis, score of 1–2 = incompletion of a task, score of 3–4 = completion of a task with clumsiness and the maximum score of 5 = normal status.

given over the ipsilesional M1 area and extensor motor training aided by electrical neuromuscular stimulation for the paretic upper-limb. It led to a functional recovery with reduction of flexor hypertonia, attributable to the extensor-specific change in M1 (Koganemaru et al., 2010). In our previous study, neuromuscular stimulation of our protocol had little influence on hypertonia (Koganemaru et al., 2010). In previous reports, its effects are still controversial on reduction of hypertonia of paretic upper limbs (Dewald et al., 1996; Fujiwara et al., 2009; Hines et al., 1993; Hummelsheim et al., 1997).

Neuroimaging studies demonstrated that multi-regional brain reorganization occurred in several motor-related regions including bilateral M1, premotor cortices (PMC), cingulate motor cortex (CMC), basal ganglia and cerebellum in process of recovery after stroke insults (Carey et al., 2002; Jang et al., 2003, 2005; Johansen-berg et al., 2002a; Luft et al., 2004; Nelles et al., 2001; Ward et al., 2003a,b, 2004; Ward and Cohen, 2004). Over-activity of non-M1 regions in an acute stage was progressively decreased with an improvement of motor performance of the hemiparetic limbs (Calautti et al., 2001; Small et al., 2002; Ward et al., 2003a,b). In a chronic stage, the magnitude of brain activity in the non-M1 regions was negatively correlated with the clinical outcome (Ward et al., 2003a,b) and positively correlated with the extent of damage in corticospinal function (Ward et al., 2006) probably due to the compensatory mechanism of secondary motor areas (Feydy et al., 2002; Ward et al., 2003a,b). However, if any repetitive motor training could induce task-specific enhancement of the ipsilesional M1 function, a compensatory drive from secondary motor areas would be reduced when the trained task was performed.

In order to investigate whether extensor-specific multi-regional brain reorganization was induced by the hybrid-rehabilitation, we performed the fMRI scanning in chronic subcortical stroke patients. We hypothesized that the hybrid-rehabilitation would reduce brain activity of non-M1 regions specific for an extension-related task if it could recover residual corticospinal function from the ipsilesional M1 involved in paretic extensor function. Furthermore, we expected that extensor-specific activity change would be related to functional improvement of the paretic upper-limbs.

2. Subjects and methods

2.1. Subjects

We investigated 11 post-stroke patients (eight men and three women) aged 54–68 years (mean ± standard deviation, 60.8 ± 5.3), who were all right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971), and had experienced their first-ever subcortical stroke (seven with infarction and four with hemorrhage) >6 months ago (31.0 ± 30.5). The lesions were documented by MRI (T_1- and T_2-weighted images). All of the patients had no pharmacological treatment of spasticity, epilepsy, depression and other drugs which could interfere with cortical excitability. They were hemiparetic, six in the left and five in the right hand. The paretic state of the affected upper limb was evaluated by the upper-extremity motor scores of the Stroke Impairment Assessment Set (SIAS) (Chino et al., 1994; Sonoda et al., 1997; Tsuji et al., 2000) (Table 1).

2.2. Ethics statement

The study protocol was approved by the Committee of Medical Ethics of the Graduate School of Medicine, Kyoto University, Japan (E-1065), and written informed consent was obtained from all subjects.

2.3. EMG recording

Subjects were seated in an armchair with their forearms pronated on an armrest and with the shoulder joint in resting position and the elbow joint flexed at a right angle, in order to prevent synchronized movements of extensors of the paretic upper limb. Surface EMGs were recorded from the right and left flexor carpi radialis (FCR) muscles, and the right and left extensor digiti communis (EDC) muscle, using a pair of silver electrodes in belly-tendon montage. The EMG was amplified, filtered (bandpass, 5–1000 Hz) and digitized at a sampling rate of 10 kHz using the Map1496 system (Nihon-Santeku Co., Osaka, Japan).

2.4. Intervention: hybrid-rehabilitation

Patients participated in the hybrid-rehabilitation protocol of 6 weeks at the outpatient clinic, which consisted of a motor task for extensors of the paretic upper limb and 5 Hz high-frequency rTMS given over the ipsilesional M1 based on our previous study (Koganemaru et al., 2010) (Fig. 1). They performed 15 cycles of exercises for the extensors of the wrist and fingers. Each cycle consisted of exercises for the extensors for 50 s followed by a train of 5 Hz repetitive TMS for 8 s, which was both preceded and followed by a resting period of 1 s (total time = 1 min). The motor task comprised of 50-time repeats of 1 Hz rhythmic voluntary