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BRIEF REPORT

Chronic stroke recovery after combined BCI training and physiotherapy: A case report

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Abstract

A case of partial recovery after stroke and its associated brain reorganization in a chronic patient after combined brain computer interface (BCI) training and physiotherapy is presented. A multimodal neuroimaging approach based on fMRI and diffusion tensor imaging was used to investigate plasticity of the brain motor system in parallel with longitudinal clinical assessments. A convergent association between functional and structural data in the ipsilesional premotor areas was observed. As a proof of concept investigation, these results encourage further research on a specific role of BCI on brain plasticity and recovery after stroke.

Descriptors: BCI, Chronic stroke, fMRI, DTI

Spontaneous recovery of motor function in chronic stroke patients is reduced and often negligible. Functional recovery mainly occurs in response to intensive therapeutic intervention and rehabilitation such as constrained induced movement therapy, bilateral arm training, or robot-assisted training (Wolf et al., 2006; Prange et al., 2006; Page & Levine, 2007). However, the success of rehabilitation programs in chronic patients with severe hemiparesis is limited. Moreover, most of these treatments rely on the existence of residual hand/arm functionality; hence, patients with no or minimal motor function are excluded. New technologies such as the development of brain computer interfaces (BCI) that utilize neurophysiologic or metabolic brain activity to drive external devices offer promising strategies to modulate neuroplasticity and motor behavior in stroke survivors (Birbaumer & Cohen, 2007; Buch et al., 2008). Recently, a non-invasive BCI based on neurophysiological signals has been proposed to apply in patients with severe motor disability resulting from stroke. Using BCI, chronic stroke patients learned to control a mechanical orthosis affixed to the paralyzed hand, which moves in a hand-grasping or hand-opening fashion, depending upon sensorimotor rhythm activity (Buch et al., 2008). BCI training is hypothesized to induce brain reorganization by contingently linking motor commands to hand movements and thus providing afferent feedback to sensorimotor cortex. Here we report, as a proof of concept study, a case of partial recovery after stroke and its associated brain reorganization in a chronic patient after combined BCI training and physiotherapy. A multimodal neuroimaging approach was used to study functional and structural plasticity. In parallel with the longitudinal clinical assessments, we applied fMRI and psycho-physiological interaction (PPI) analysis to assess functional connectivity and diffusion tensor imaging (DTI) to evaluate the structural integrity of the cortico-spinal tract (CST).

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Methods

Patient

The patient—aged 67 years, right handed—suffered from severe hand paresis as a result of a single unilateral cerebrovascular incident of the right thalamus and the adjacent corticospinal tract of the internal capsule 14 months prior to study entry (Figure 1a). Neglect and motor extinction was excluded by extensive neurological exams and neuropsychological tests. He was not able to extend his fingers or to use his hand/arm for any relevant daily life activity. His paretic arm blocked him from standing up

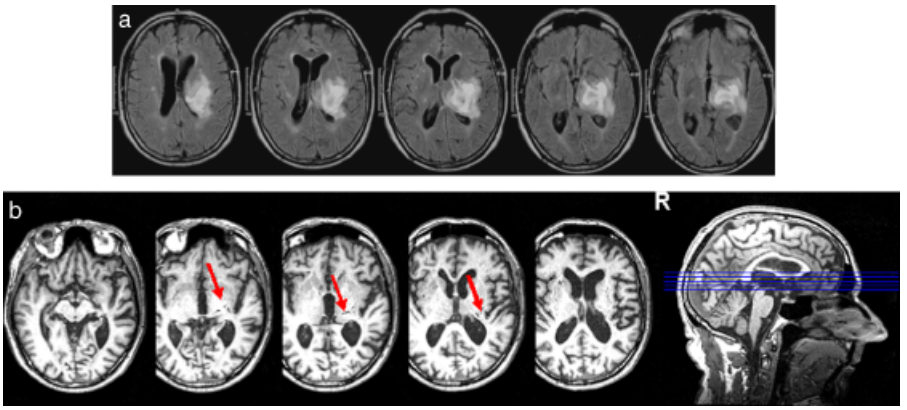

Figure 1. a. T2 fluid-attenuated inversion recovery (FLAIR) axial slices. b. Lesion location. The patient had a single unilateral cerebrovascular incident of the right thalamus and the adjacent corticospinal tract of the internal capsule 14 months prior to study entry.

and walking. Physiotherapy was applied to the patient immediately after the stroke, but no substantial improvement of the hand functionality was observed after 14 months. Patient provided written informed consent, and the study was approved by the Ethical Committee of the Faculty of Medicine of the University of Tübingen.

BCI Training

The patient underwent two main rehabilitation trainings using magnetoencephalography [4 weeks MEG-BCI between month 14 (S1) and 18 (S2) after stroke] and electroencephalography based BCI [4 weeks EEG-BCI between month 18 and 22 (S3) after stroke] in combination with physiotherapy. MEG-BCI training consisted of 20 sessions, during which the patient learned, using hand/arm motor imagery, to modulate the μ rhythm (synchronization and desynchronization) over the ipsilesional sensorimotor area by means of an online visual feedback representing the recorded signal. Depending on the signal amplitude, a mechanical orthosis attached to the paretic hand flexed and extended the patient's fingers in a hand-grasping or hand-opening fashion (for a detailed description see Buch et al., 2008). Similarly, during EEG-BCI sessions (20), the patient was trained to modulate the μ rhythm over the same region, but the learned control drove forward and backward movements of an arm robot (Motorika, Caesarea, Israel). BCI performance was assessed by measuring the proportion of trials in which the patient was successful in producing the requested μ rhythm amplitude modulation. MEG-BCI based training increased over sessions from 53.50% to 86.85% ($t = 23.20$, $p < 0.001$) whereas during EEG-BCI based training the performance remained stable around 76.96% ± 5.78 (mean ± *SD*).

After each session, the patient underwent 1 h of active and passive physiotherapy. Hand and arm motor functions were assessed during S1, S2, and S3, by using Fugl-Meyer Assessment for the arm (FMA), Wolf Motor Function Test (WMFT) functional ability, Modified Ashworth Scale, and Goal Attainment Score (GAS). The GAS task consisted in taking the cane with him in the paretic hand while grabbing a banister during climbing stairs. Clinical scores indicated a paretic hand/arm motor performance improvement of between 10.8–85.7% (Table 1).

Magnetic Resonance Imaging

Three fMRI and DTI datasets were collected during S1, S2, and S3, respectively. Neuroimaging data were acquired using a 1.5 Tesla Siemens MRI system. Functional MR images were acquired using a gradient-echo planar imaging (EPI) aligned in axial orientation: TR (repetition time) = 2000 ms; TE (echo time) = 46 ms; flip angle = 90°; FOV (field of view) = 320 mm; matrix size = 64; interslice gap = 1 mm; slices = 22; slice thickness = 4 mm. A T1-weighted anatomical MR image was acquired using a 1 mm isotropic MPRAGE sequence with the following parameters: TR = 1300 ms; TE = 3.19 ms; TI = 660 ms; flip angle = 15°; FOV = 256 × 256; matrix size = 256 × 256; number of slices = 176; slice thickness = 1 mm, bandwidth = 190 Hz/Px (Figure 1B). Diffusion tensor images were acquired using 2 mm isotropic EPI sequence: number of slices = 65; orientation = transversal; phase-encoding direction A > P; slice thickness = 2 mm; TR = 7500 ms; TE = 71 ms; averages = 3; *b*-value = 800 s/mm2; dimensions = 256 mm × 256 mm × 130 mm; EPI factor = 128; bandwidth = 1502 Hz/Px; noise level = 40; number of diffusion directions = 6. In order to reduce movements, two foam cushions immobilized the participant's head.

Table 1. *Clinical Assessment*

Motor	FMA passive	FMA sensory	FMA motor	WMFT functional ability	MAS	GAS
S1 (baseline)	37	5	13	7	8	− 2
S2	39	5	19	9	4	+2
S3	41	6	24	13	4	− 1
% change from baseline	10.8	20	84.6	85.7	50	

Note: FMA (passive movement and pain: 0 = maximum disability, 48 = normal; sensory loss: 0 = maximum disability, 12 = normal; motor function: 0 = maximum disability, 66 = normal), WMFT (0 = maximum disability; 80 = normal), MAS (spasticity, 0 = normal; 36 = maximum disability), GAS (− 2 = outcome much less than expected, 0 = program goal/expected outcome; 2 = outcome much better than expected; as the patient scored +2 in S2, the S3 baseline was reset to allow detection of a further improvement).

fMRI Design and Analysis

Each fMRI session consisted of four runs (190 volumes) of visually and auditorily cued, executed and imagined flexion–extension of the fingers (12 s), with either the affected (left) or the unaffected (right) hand, alternating with rest (12 s). fMRI data analysis was performed using SPM5.

EPI volumes of the three fMRI sessions were realigned, slice-time corrected, anatomically coregistered, spatially normalized to the Montreal Neurological Institute (MNI) reference space, and smoothed (9-mm). Hemodynamic response amplitudes were estimated using standard regressors, constructed by convolving a boxcar function, for each of the three different conditions (actual movement, imagined movement, and rest), with a canonical hemodynamic response function using standard SPM5 parameters. The time series in each voxel were high-pass filtered at 1/128 Khz to remove low frequency drifts. Movement parameters were also included into the general linear model (GLM) as covariates to take into account head motion artefacts. Voxels were identified as significant if they surpassed a threshold of $P < .001$ family-wise error (FWE) corrected for multiple comparisons.

Small volume correction analysis based on anatomically selected regions, MI, PMC, SMA SI, SII, and the cerebellum, allowed us to calculate, for each region of interest (ROI), a lateralization index (LI) during left and right hand movements. LI, expressed as the normalized difference between the number of active voxels in the left and the right hemisphere, approaches a value of 1 or -1 when the activity was either purely contralesional or ipsilesional.

PPI Analysis

Motor network reorganization was assessed using PPI analysis as implemented in SPM5. PPI is a simple fMRI-based brain connectivity method that determines whether a given region, the seed/source, 'predicts' the activity in other brain regions as a function of a task/context specific factor with no need of anatomical pathways to be specified. In particular, it calculates the change in the inter-regional covariance using the difference in regression coefficients between the neuroimaging signals from two brain regions. Recently, Kim and colleagues demonstrated that fMRI based PPI analysis produces reliable results reflecting the underlying changes in neural interactions (Kim & Horwitz, 2008).

The first eigenvector of a sphere of 6 mm radius centered on the right dorsal PMC was selected as a 'seed' region. This area was identified based on the peak maxima measured when the executed movement condition of the paretic hand in S3 was compared to S1. The ipsilesional PMC's modulatory effect on the remaining brain areas was assessed over time. In order to consider contextual connectivity changes, PPI analysis ($P < .05$ FWE) was conducted comparing actual to imagined movement condition. PPI analysis was also conducted using a size/coordinates matched volume of interest in the healthy hemisphere corresponding to the left PMC for the task being performed with the healthy hand. We expected to observe no significant changes of the interregional covariance over sessions.

DTI Analysis

Diffusion-weighted raw data were first corrected for eddy current distortions and motion artifacts using the FMRIB Diffusion Toolbox (FSL). Diffusion images from multiple sessions were then realigned and co-registered to the skull-stripped TL-image. The diffusion tensor and fractional anisotropy (FA) maps were calculated using MedINRIA software. Tractography was carried out using Diffusion Toolkit and TrackVis. Fiber tracking was performed using the Interpolated Streamline algorithm with a step-length of 0.5 mm and was terminated if FA was less than 0.15 or the tract angle between successive steps was greater than 35°.

Results

fMRI

Whole brain analysis revealed primarily contralateral activity in the primary sensorimotor areas (SMI) and in the secondary motor areas when the task was performed with the healthy hand (MNI peak maxima S1, S2, S3: (BA3, x, y, z = -42, -27, 60, $t(708) = 31.35$; 35.60; 27.72; Table 2). These results were consistent over sessions, and no significant difference was measured over sessions. Highly distributed and bilateral brain activity was observed during the affected hand task (MNI peak maxima S1: BA40, x, y, z = 45, -39, 60, $t(708) = 16.89$; S2: BA40, x, y, z = 45, -39, 60, $t(708) = 17.13$; S3: BA6, x, y, z = 30, -15, 68, $t(708) = 15.94$; Table 2). A significant difference in the secondary motor areas, specifically in the bilateral SMA (BA6, x, y, z = -9, 27, 44, $t(3540) = 8.66$; BA6, x, y, z = 6, -12, 52, $t(3540) = 7.23$) and in the ipsilesional PMC (BA6, x, y, z = 36, -12, 60, $t(3540) = 6.85$), was observed when the executed movement condition in S3 was compared to S1 (Figure 2a). The activity during motor imagery performed either with the healthy or the paretic hand was bilateral with a bias toward the contralateral regions, and no statistical difference emerged over sessions. Healthy and paretic hand movements were controlled during each condition: visually during S1 and S2 and in addition by parallel electromyographic (EMG) signal acquisition during S3. No movements were observed and recorded with EMG in S3 during motor imagery and rest condition, and no mirror movements or involuntary co-contraction were observed or measured during the actual movement condition.

ROI analysis indicated contralateral activity over all sessions during the healthy hand task. The paretic hand task was associated with bilateral SMI activity shifted to the contralesional hemisphere during S1 and to the ipsilesional hemisphere during S2 and S3. The PMC showed a noteworthy reallocation to the ipsilesional side from S1 (LI = 0.76) to S3 (LI = -0.10) (Figure 2c).

Both whole brain and ROI analyses showed increased activity in the ipsilesional and contralesional SMI and an extensive bilateral recruitment of the PMC and SMA during S1 when the task was instructed to be performed with the paretic hand. During S3 a more focal bilateral activity was found, probably the result of less effort involved as a consequence of automatization and improved mastery of the skill, or both. Additionally, a shift to the ipsilesional hemisphere, quite considerable for the PMC, was observed.

Functional Connectivity

During left paretic hand movements, the right PMC activity positively co-varied with the ipsilesional primary and secondary sensorimotor regions across all sessions, with visual areas in S1 and S2 and with the contralesional secondary sensorimotor cortex during S3 (MNI peaks maxima S1: BA17, x, y, z = -3, -87, -12, $t(708) = 7.40$; S2: BA18, x, y, z = 9, -84, -16, $t(708) = 4.97$; S3: BA40, x, y, z = -48, -39, 60, $t(708) = 8.93$); Table 2 (see also Figure 2B). Left PMC showed a stable positive covariation with the left sensory and motor areas over all sessions when the task was performed with the right non-paretic hand (MNI peak maximum S1: BA3, x, y, z = -42, -30, 60, $t(708) = 11.02$; S2: BA3, x, y, z = -42, -27, 60, $t(708) = 8.04$; S3: BA3, x, y, z = -42, -30, 60, $t(708) = 9.79$; Table 2).

Table 2. *fMRI and PPI Results During S1 and S3*

Activated areas	MNI coordinates (x, y, z)	*t*-value
fMRI results		
Healthy		
S1		
Contralesional		
SI (BA3)	−42, −27, 60	31.35
MI (BA4)	−36, −24, 64	22.31
PMC (BA6	−30, −12, 60	11.21
SMA	−3, −12, 48	12.47
Ipsilesional		
SII (BA40)	46, −36, 60	12.00
PMC (BA6	30, −12, 64	7.49
Cerebellum	15, −54, −16	16.53
Vermis	0, −63, −12	11.18
S3		
Contralesional		
SI (BA3)	−42, −27, 60	27.72
MI (BA4)	−36, −24, 64	22.65
PMC (BA6	−30, −12, 60	7.95
SM	−3, −9, 52	10.23
Ipsilesional		
SII (BA40)	42, −39, 60	10.55
MI (BA4)	36, −24, 64	6.88
PMC (BA6)	33, −15, 68	8.34
Cerebellum	12, −54, −12	14.62
Paretic		
S1		
Contralesional		
SII (BA40)	−45, −42, 56	11.06
MI (BA4)	−36, −24, 64	8.35
PMC (BA6)	−39, −9, 56	6.15
Cerebellum	−30, −63, −20	5.81
SMA	−3, −15, 64	15.16
Ipsilesional		
SII (BA40)	45, −39, 60	16.89
MI (BA4)	39, −24, 64	10.58
PMC (BA6)	39, −9, 56	8.59
Cerebellum	30, −57, −24	4.86
V2 (BA18)	3, −102, 4	15.28
S3		
Contralesional		
SII (BA40)	−45, −45, 60	12.19
MI (BA4)	−36, −27, 60	7.08
PMC (BA6)	−27, −15, 64	7.22
Cerebellum	−30, −63, −20	5.30
Ipsilesional		
SII (BA40)	42, −42, 60	15.09
MI (BA4)	39, −24, 64	15.64
PMC (BA6)	30, −15, 68	15.94
Cerebellum	30, −57, −24	5.96
SMA	0, −15, 56	14.97
PPI results		
Healthy		
S1		
Contralesional		
SMI (BA3)	−42, −30, 60	11.02
V2 (BA17)	0, −84, −16	6.02
S3		
Contralesional		
SMI (BA3)	−42, −30, 60	9.79
Paretic		
S1		
Contralesional		
V2 (BA17)	−3, −87, −12	7.40
Mid front (BA8)	−33, 18, 48	7.13
Ipsilesional		
Thalamus	0, −15, 12	6.99
SMA (BA8,6)	3, 15, 56	5.37
Sup par gyrus (BA7)	33, −63, 60	6.51
SMI (BA3)	39, −36, 68	5.78
S3		
Contralesional		
SII (BA40)	−48, −39, 60	8.93
Ipsilesional		
SMA (BA6)	0, −12, 64	7.23
SMI (BA1,2)	54, −27, 48	6.92
SMI (BA1,2)	39, −42, 64	6.59

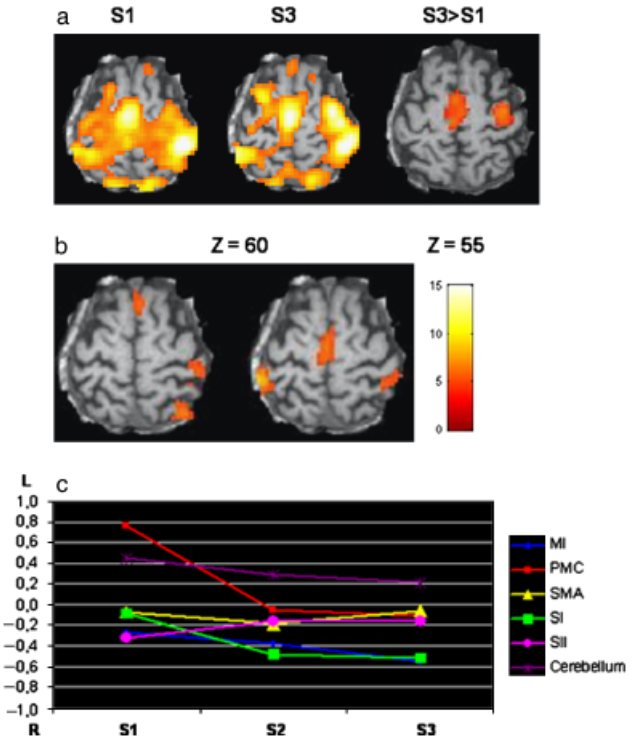

Figure 2. fMRI and PPI results during the paretic hand motor task execution. a. Activated areas during S1, S3, and comparing S3 to S1. b. Areas covarying with the right ipsilesional premotor cortex. c. Lateralization index (LI).

DTI

DTI analysis and tractography were applied to assess the CST integrity and to localize potential preserved descending pathways. Using S1 data, a smaller number of fibers was reconstructed in the ipsilesional hemisphere ($n = 8$) compared to the contralesional side ($n = 667$). CST reconstruction overlaid on the MRI structural image disclosed fibers descending from the ipsilesional premotor region (Figure 3). FA index of a perilesional portion of the CST and of a corresponding area in the contralesional hemisphere was calculated over the three sessions. FA, representing on a scale from 0 to 1 the extent to which myelin sheets constrain diffusion of water molecules along a specific direction, provides an index of the tissue microstucture's integrity. Fa, being influenced by several factors, such as axonal myelination, fibers' diameter, density, and orientation, decreases when the CST is disrupted, and it indicates the degree of axonal loss and Wallerian degeneration (Møller et al., 2007). A number of studies emphasized the CST integrity as a predictor of cortical reorganization and motor recovery in chronic stroke (Stinear et al., 2007). Voxelwise analysis ($n = 97$) showed increased FA values in the perilesional region of the CST from 0.20 ± 0.12 (mean $\pm$ *SD*, S1) to 0.24 ± 0.12 (S3) (S3 vs S1 $t = 9.51$ $p < .001$) but not in the contralesional side: 0.75 ± 0.16 (S1), 0.74 ± 0.16 (S3) (S3 vs S1 ns). Recent studies on animal models demonstrated that FA is a good measure of white matter reorganization (Chen et al., 2002). Increased FA values in the perilesional area, as index of augmented density and directionality of myelinated fiber tracts, indicate a better outcome of neurological function after stroke (Schaechter et al., 2009).

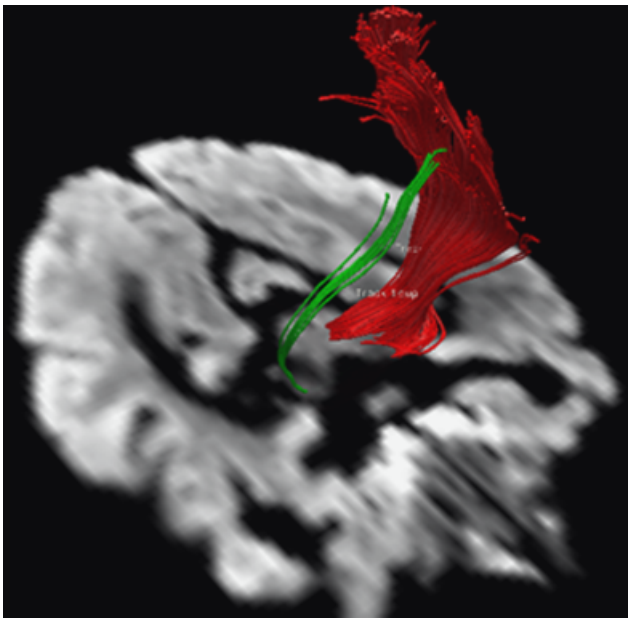

Figure 3. DTI based reconstruction of the ipsilesional (green) and contralesional (red) CST fibers superimposed on the T1 MPRAGE.

Discussion

Although specific and individual effects of the different rehabilitative methods applied are not possible to discern, a significant and clinically substantial recovery of the hand motor function was observed over time. We believe this finding to have relevant implications for rehabilitation of chronic patients with no or minimal residual hand movements, who generally do not show significant improvements after rehabilitation programs and often are not eligible for physical therapies. The clinical outcome, as assessed by the Fugl-Meyer test, was higher than that obtained by chronic stroke patients with moderate and severe upper limb impairment after robot-aided therapy (Prange et al., 2006), and it was twice the effect of 10 weeks of modified constraint-induced therapy in chronic stroke patients with minimal movement ability in the affected arm (Page & Levine, 2007). A similar improvement was reported after 4 weeks of computerized arm training in subacute stroke patients with severe upper limb paresis (Hesse et al., 2005).

Therefore, the results of the proposed approach based on a combination of BCI training and physiotherapy, which applies to chronic patients with severe hand paresis, seem promising and call for a more structured and controlled clinical trial.

Overall fMRI data reveal an increased lateralization toward the ipsilesional sensorimotor regions, specifically, an enhanced activity in the dorsal premotor region and supplementary motor area after the training. These results are in line with previous studies indicating the adaptive and compensatory role of the ipsilesional PMC in hand movement after stroke and its participation as a substrate mediating functional recovery of executive motor function (Fridman et al., 2004).

The evidence of preserved anterior fibers of the CST in the anterior part of the internal capsule originating either from anterior parts of MI or from the PMC may constitute the anatomical prerequisite for the observed cortical reorganization and behavioral improvement over time. Furthermore, structural analysis of the motor pathways indicated a small but significant increase of the fractional anisotropy in the ipsilesional CST, potentially indicating white matter reorganization. This finding would be in line with the postulated mechanisms involved in long-term plasticity (Chen, Cohen, & Hallett, 2002) and results in animal models and humans (Chen et al., 2002; Schaechter et al., 2009). However, further group studies on patients and controls are necessary to test these hypotheses.

As a proof of concept investigation, these results encourage further research on a specific role of BCI on brain plasticity and recovery after stroke. Finally, our findings suggest the importance of fMRI and DTI investigations for tailoring specific rehabilitation programs in chronic stroke patients based on preserved functionality of the motor system.

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