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CASE STUDY

Music-Supported Therapy induces plasticity in the sensorimotor cortex in chronic stroke: A single-case study using multimodal imaging (fMRI-TMS)

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Abstract

Primary objective: Music-Supported Therapy (MST) has been developed recently in order to improve the use of the affected upper extremity after stroke. This study investigated the neuroplastic mechanisms underlying effectiveness in a patient with chronic stroke.

Methods: MST uses musical instruments, a midi piano and an electronic drum set emitting piano sounds, to retrain fine and gross movements of the paretic upper extremity. Data are presented from a patient with a chronic stroke (20 months post-stroke) with residual right-sided hemiparesis who took part in 20 MST sessions over the course of 4 weeks.

Results: Post-therapy, a marked improvement of movement quality, assessed by 3D movement analysis, was observed. Moreover, functional magnetic resonance imaging (fMRI) of a sequential hand movement revealed distinct therapy-related changes in the form of a reduction of excess contralateral and ipsilateral activations. This was accompanied by changes in cortical excitability evidenced by transcranial magnetic stimulation (TMS). Functional MRI in a music listening task suggests that one of the effects of MST is the task-dependent coupling of auditory and motor cortical areas.

Conclusions: The MST appears to be a useful neurorehabilitation tool in patients with chronic stroke and leads to neural reorganization in the sensorimotor cortex.

Keywords: *Neuroimaging, rehabilitation, stroke, TMS, fMRI*

Introduction

Motor disabilities after stroke have been the target of several recently-developed therapies that have been shown to be more effective than standard physiotherapeutic approaches [1]. For example, inducing the use of the paretic limb over extended periods of time leads to marked clinical improvements which are accompanied by neuroplastic changes [2, 3]. Several basic neuroscience studies have shown that music training produces rapid changes in motor-related brain areas [4, 5]. Against this background, a new motor rehabilitation therapy

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has been recently developed (Musical-Supported Therapy, MST). Musical instruments (a MIDI piano and an electronic drum set geared to produce piano tones) are used to train fine (piano) and gross (drums) motor functions in patients suffering from mild-to-moderate paresis after stroke. In two large samples this therapy showed highly significant and clinically relevant improvements in patients with acute stroke [6, 7]. The current case report not only reports on MST in chronic stroke for the first time but also provides first evidence of neuroplastic changes induced by MST by functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS).

Methods

Case description

The patient was a 43 year-old right-handed woman who had suffered a sub-cortical stroke in the left middle cerebral artery region 20 months before (no previous history of cerebrovascular disease, carotid artery occlusion or other cerebral lesions). MRI showed lesions in the left thalamus, internal capsule and the posterior portion of the putamen (Figure 1). At the time of the study the hand and arm motor functions showed moderate paresis of the right upper extremity (Medical Research Council scale 4-/5). She was able to move the affected arm and the index finger without help from the healthy side (Barthel Index 90). No other severe perceptual or cognitive deficits were revealed and the patient did not report previous musical experience. The study was approved by the Ethics committee of the Hospital. Informed consent was obtained from the patient after she had received a detailed explanation of all procedures.

Music-Supported Therapy (MST)

Over the course of 4 consecutive weeks the patient received 20 individual MST sessions of 30 minutes each. Two different input devices were used to improve motor movements [7]: a MIDI-piano for fine motor movements and an electronic drum set comprising eight pads for gross motor movements. The drum pads (numbered from 1–8) were used to produce piano musical notes (G, A, B, C, D, E, F, G′) rather than drum-sounds. In a similar vein, the MIDI-piano was arranged in such a way that only eight white keys (G, A, B, C, D, E, F, G′) could be played by the patient. Each exercise was shown by the therapist first and then repeated by the patient. MST therapy is manualized and the patient was moved to the next level of difficulty after she was able to complete the current level without errors. Thus, over the course of the therapy the patient proceeded from playing single notes to playing sequences of notes and beginnings of children's songs.

Evaluations

Prior to and at the end of the therapy course the patient was comprehensively evaluated by tests assessing motor functions, 3D-movement analysis, TMS and fMRI. Motor functions were assessed using the following instruments: Action Research Arm Test (ARAT), Arm Paresis Score, the Box and Block Test and the Nine Hole Pegboard Test (9HPT) (see details [7]). 3D movement analysis was performed using an ultrasound-based system (CMS30 P Zebris) and comprised forearm

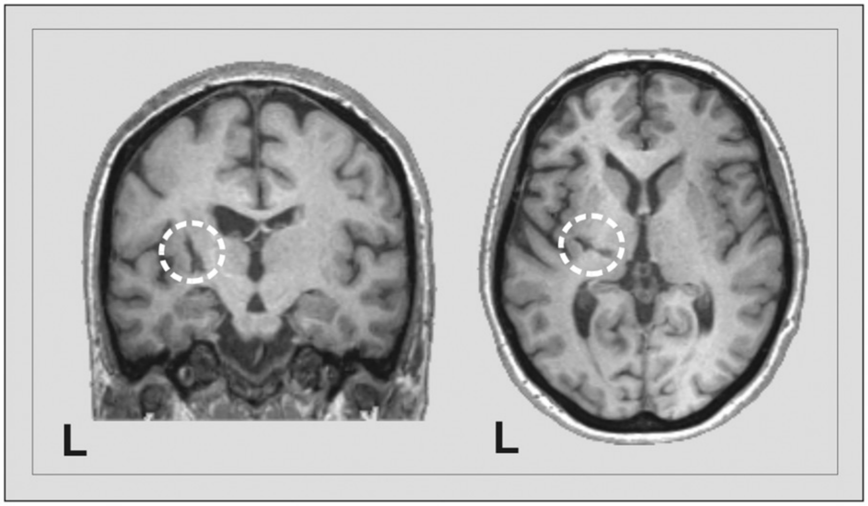

Figure 1. T1-weighted image showing left hemisphere lesion including the left thalamus, internal capsule and the posterior portion of the putamen.

pronation-supination (PS), whole hand tapping (HT) and index finger tapping (FT). For each movement segment the following parameters were computed [8]: frequency, amplitude, maximum angular velocity, symmetry velocities and smoothness of acceleration profiles (NIA).

TMS was performed using a focal figure-8 coil (9 cm diameter each wing) attached to a Magstim Rapid 2 Stimulator. An elastic cap was used in which a 10 × 10 cm grid was drawn to allow identification of stimulation co-ordinates and exact repositioning of the cap for the post-therapy session. Motor-evoked potentials (MEPs) were obtained from the contralateral first dorsal interosseus muscle (both hemispheres were tested). The following parameters were calculated: Co-ordinates of the Hot-spot, Resting Motor Thresholds [9], Silent Period [10], Recruitment Curve [10], Motor Maps [11], Peak-to-Peak amplitude and latency of the maximum MEP and Centre of Gravity (Cog) [12].

The fMRI session comprised two experiments: (i) *Motor task*, the patient was requested to perform sequential movements with her index and middle fingers of each hand during 20 seconds, alternating right and left hand blocks with rest blocks (four blocks per condition in a single run of ~6 minutes) and (ii) *Music task* [4], the patient had to passively listen to short familiar (trained during the rehabilitation therapy) and unfamiliar monophonic piano sequences and songs alternating with no stimulation rest blocks (three blocks per each four conditions, 15 seconds each, in an single run of ~6 minutes). Images were obtained with a 3-T MRI scanner (Siemens Magnetom Trio). Conventional high resolution structural images (magnetization-prepared, rapid-acquired gradient echoes (MPRAGE) sequence, 240 slice sagittal, TR = 2300 ms, TE = 3 ms, 1 mm thickness (isotropic voxels)) were followed by functional images sensitive to blood oxygenation level-dependent contrast (echo planar T2*-weighted gradient echo sequence, TR = 2000 ms, TE = 29 ms, slice thickness = 4 mm).

Data were analysed using standard procedures implemented in the Statistical Parameter Mapping software (SPM2, http://www.fil.ion.ucl.ac.uk/spm). The pre-processing included slice-timing, re-alignment, normalization and smoothing. First, functional volumes were phase shifted in time with reference to the first slice to minimize purely acquisition-dependent signal-variations across slices. Head-movement artifacts were corrected based on an affine rigid body transformation, where the reference volume was the first image of the first run [13]. Functional data were then averaged and the mean functional image was normalized to a standard stereotactic space using the EPI derived MNI template (ICBM 152, Montreal Neurological Institute) provided by SPM2, after an initial 12-parameter affine transformation. Resulting normalization parameters derived for the mean image were applied to the whole functional set. Finally, functional EPI volumes were re-sampled into 4 mm cubic voxels and then spatially smoothed with an 8 mm full-width half-maximum (FWHM) isotropic Gaussian Kernel to minimize effects of inter-subject anatomical differences.

The statistical evaluation was based on a least-square estimation using the general linear model by modelling the different conditions with a box-car regressor waveform convolved with a canonical haemodynamic response function [14]. Thus, a block-related design matrix was created including the conditions of interest (Sequence task: Right sequence, Left sequence and Rest; Listening task: Trained music and Rest).

Six regions of interest (ROIs) were defined on the anatomical images of the patient in order to quantify the numbers of pixels that are activated in response to the sequence task. The toolbox Wfu pickatlas [15] for SPM was applied to generate the ROIs. The following regions were defined for each hemisphere: (1) primary motor cortex (M1); (2) supplementary motor area (SMA) and pre-motor cortex (PMC); (3) anterior cingulate cortex; (4) cerebellum; (5) superior parietal cortex and (6) inferior parietal cortex.

Results

Motor tasks

Some subtests of the ARAT which have been found to be very sensitive to change [7] showed improvement after therapy (Grasp, Grip and Pinch; Figure 2), whereas a clear improvement was absent for the other tests.

3-D movement evaluation

All analysed parameters were statistically contrasted between sessions on the affected hand using a simple paired t-test. Significant improvements were seen for hand tapping frequency ($t(2) = 11.92$, $p < 0.007$) and movement smoothness for finger tapping ($t(2) = 8.69$, $p < 0.05$) (Figure 2). Non-significant improvements were also observed for frequency and smoothness for the other movements.

TMS

Silent period and maximum amplitude of the MEP were statistically contrasted between sessions and hemispheres using a bootstrapping procedure ($p < 0.059$) [16] (Table I). A marked difference was encountered in the MEP amplitude of the

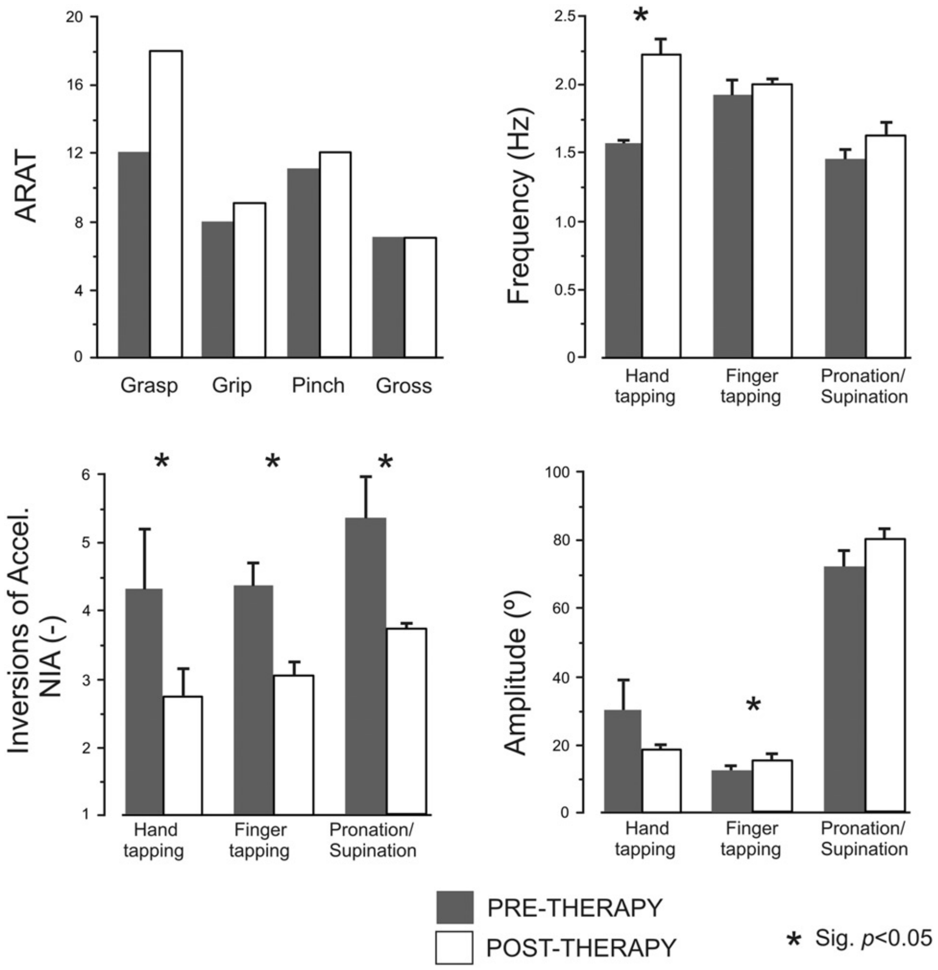

Figure 2. Results for the motor test ARAT and the quantitative movement analysis using the Zebris system (remaining three graphs). NIA = number of inversions of accelerations (=smoothness). Error bars indicate standard error of the mean. Asterisks indicate significant differences between Pre- and Post-Training sessions (*$P < 0.05$).

Table I. Summary of electromyographic parameters obtained in both TMS sessions.

	Affected hemisphere (Left)		Unaffected hemisphere (Right)	
	Pre-therapy	Post-therapy	Pre-therapy	Post-therapy
Resting Motor Threshold (%)	52.00%	54.00%	75.00%	71.00%
Map Area (cm^2)	16	33	19	32
CoG x coordinate	4.79	4.93	5.27	6.19
CoG y coordinate	−0.41	−0.5	−0.3	−0.41
Silent Period (ms)	188 (17.7)	171 (27.1)	243 (7.3)	217 (35.1)
Amplitude MEP_{max} (mV)	1.36 (0.32)	2.14 (0.4)	0.17 (0.08)	0.78 (0.37)
Recruitment curve (Linear peak slope)	35.7	51.7	4.9	13.3

affected and non-affected hand. Also, the amplitude was greater in the second session for both the affected ($p < 0.001$) and non-affected hemisphere ($p < 0.001$). Important differences between affected and unaffected hands were also seen for the Resting Motor Threshold (lower in affected hand), Map Area (smaller in affected hand) and recruitment curve (steeper in affected hand). Silent period was shorter in the affected hand but this difference was not significant (Figure 3).

fMRI motor task

Whole-brain analysis revealed widespread activation of the contralateral primary sensorimotor–pre-motor network as well as some ipsilateral activation for

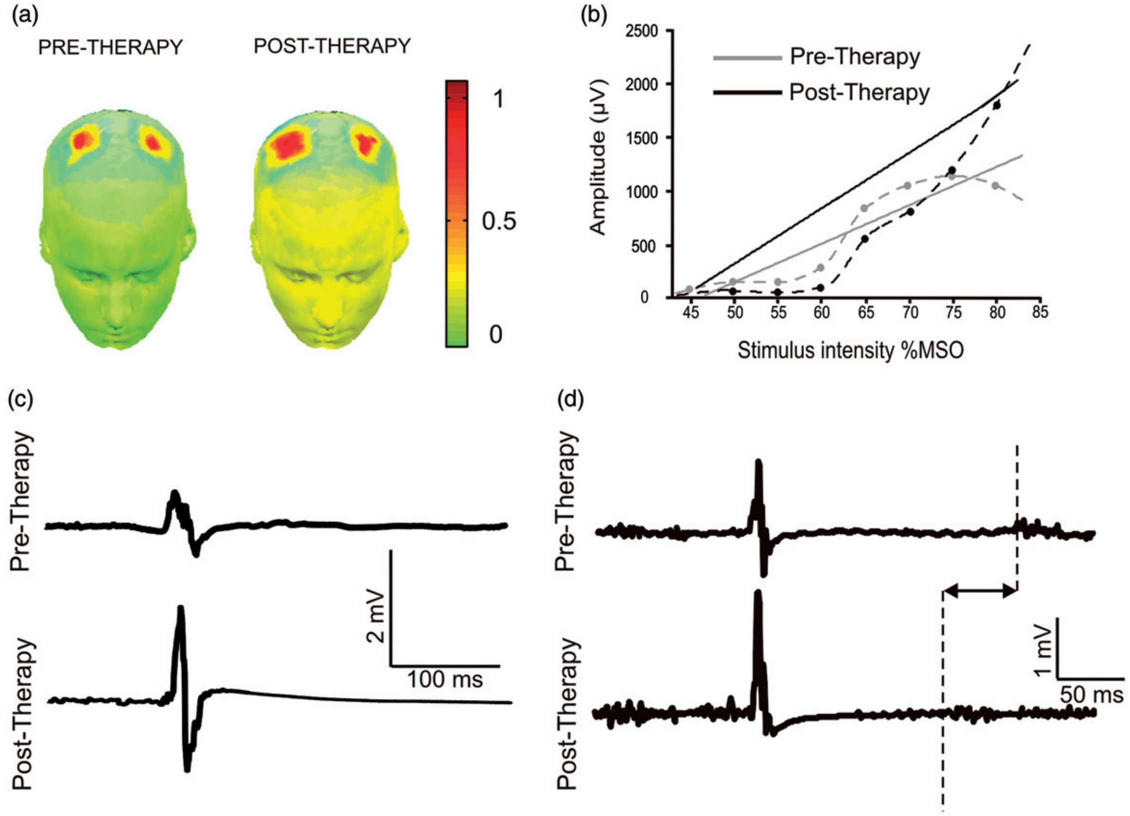

Figure 3. This figure shows the most relevant results from the TMS data analysis. (A) Three dimensional map of the cortical representation of the first dorsal interosseus (FDI) muscle after stimulation of the patient. The map was made either before or after the musical-supported therapy in both hemispheres. After intervention, the active area of the affected (left) and non-affected hemispheres increased. Colors (yellow-red) represent normalized amplitude for each hemisphere. (B) Map of the simulus-response relationship for the lesioned hemisphere, calculated before (gray line) and after the intervention (black line). It is clear an increase of the evoked response in higher stimulation outputs. Continuous lines corresponded to the lineal fit of the stimulus-response relationship. The results also show an increase of the fit slope between sessions. (C) Mean of 5 motor evoked potential (MEP) obtained from contralateral FDI after stimulation of the lesioned (left) hemisphere. Stimulation output was set as which produced maximal response in each session. An increase of the peak-to-peak amplitude of the evoked activity of the muscle from the first to the second session was appreciated and was statistically significant ($p < 0.01$). (D) Mean of 15 motor evoked potential obtained from contralateral FDI after stimulation of the lesioned (left) hemisphere during a voluntary muscle contraction (20% of the maximum voluntary contraction). A reduction of the refractory period on EMG between sessions was appreciated, as indicated by dashed lines.

affected hand movements prior to the treatment course (Figures 4(*a*) and (*b*)). In contrast, after treatment the contralateral activations were reduced in size and ipsilateral activation was greatly diminished. No treatment-related changes were observed for the unaffected hand.

At the ROI level, this study confirmed a general decrease of the size and spread of the activations as a function of therapy (Figure 4(*b*)). Moreover, there was a reduction in the beta parameter estimates in the contralateral and ipsilateral hemisphere for Brodmann area 4 and 6 for movements with the affected right hand (Figure 4(*b*)). To test whether the pre/post difference in the number of voxels significantly activated above a specific threshold (FWE, $p < 0.05$) was reliable, a chi-square test was performed. This was the case for affected hand movements (BA4, $\chi^2(1) = 65.9$, $p < 0.001$; BA6, ($\chi^2(1) = 6.7$, $p < 0.01$) but not for movements with the unaffected hand (BA4, $\chi^2(1) = 2.2$, $p > 0.1$; B6, $\chi^2(1) < 1$). Finally, Laterality index [17] was calculated for the primary motor area to compare cortical activation between the two hemispheres for each ROI. Laterality index was defined as $(C - I)/(C + I)$, where C is the contralateral activation and I the ipsilateral activation of the respective ROI and could range from 1.0 (all activity is contralateral) to -1.0 (all activity is ipsilateral). Laterality increased notably after therapy (pre-MST: 0.37, post-MST: 0.86; an index of 1 would be obtained for purely contralateral activity). For movements with the non-affected hand no differences emerged (pre-MST: 0.98, post-MST: 1).

fMRI music task

Whereas listening to musical pieces elicited only activations in the temporal cortex prior to the course

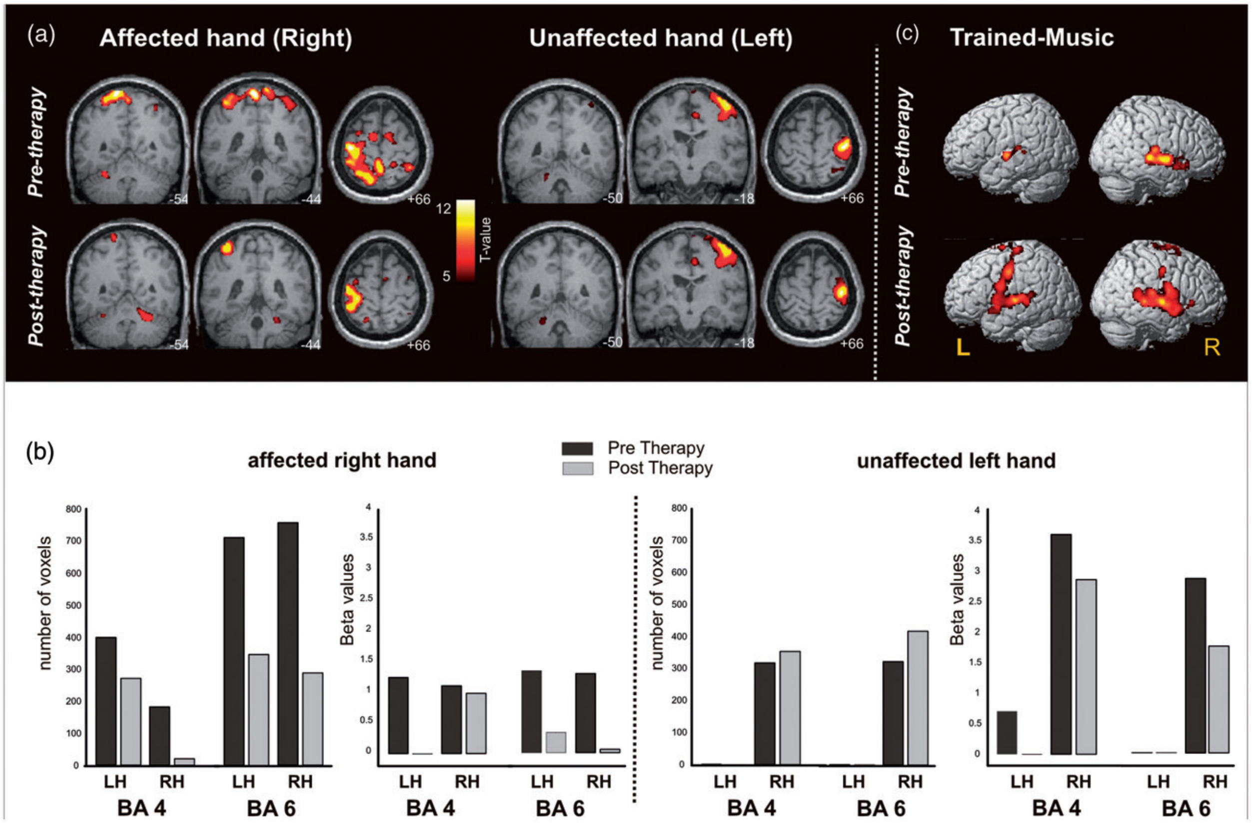

Figure 4. (A) Functional MRI activations in the motor task (superimposed on the patient's T1 image in standard stereotactic space, $P < 0.05$, Family Wise Error corrected). (B) Number of voxels and beta values in primary motor and premotor regions (LH/RH = Left/Right Hemisphere) in the motor task. (C) FMRI activation in the music listening task showing bilateral activation of motor-related brain regions when the patient was listening to trained music after but not before the therapy ($P < 0.05$, FWE corrected).

of therapy, a bilateral but left-lateralized additional activation of the motor areas was observed after these pieces had been extensively trained during the therapy (Figure 4(*c*)). This pattern echoes previous observations in healthy subjects [4, 7, 18] and is consistent with the notion that MST works by audiomotor coupling.

Discussion

Music-supported therapy led to a clinical improvement and to an increased quality of rapidly alternating movements on quantitative movement analysis (Figure 2). These results thus extend previous studies that have demonstrated the clinical efficacy of MST in patients undergoing rehabilitation immediately after a stroke [6, 7]. They suggest that MST, like other recently developed therapies such as CIT [3], is capable to improve motor-functions in patients with chronic stroke. Clinical improvements were accompanied by profound neural changes evidenced by both fMRI and TMS, suggesting plastic changes in the contralateral sensorimotor cortex after therapy.

The TMS results showed a therapy-related increase in the amplitude of the MEP (Table I, Figure 3). These changes are similar to results of previous studies on CIT [9, 19]. Prior to treatment, the silent period on the affected side was shorter than on the unaffected side (as also described previously [10]), demonstrating an increase of excitability on the affected side. The difference in mapping area, increase in the slope of the recruitment curve and resting motor threshold between affected and unaffected hemispheres also suggests increased excitability for the affected side.

Functional MRI of hand movements showed a significant decrease of activation in the contra- and ipsilateral sensorimotor areas and secondary premotor regions after therapy [20]. These findings, as well as the dramatic increase of the lateralization index in M1 post-MST, dovetail nicely with results of previous fMRI longitudinal analysis [21]. The increase of activation observed in the ipsilateral healthy hemisphere prior to treatment is most likely due to loss of inhibition that occurs from the lesional hemisphere to the healthy hemisphere [2]. In healthy persons inhibitory transcallosal conduction occurs between the contralateral and ipsilateral motor cortex during unimanual motor tasks [22], which appears compromised after stroke. The reduced ipsilateral activation after therapy accordingly suggests restored transcallosal inhibition.

Finally, the present fMRI findings in the music task argue in favour of the idea that the mechanism that contributes to the efficacy of MST (besides massed practice of the paretic arm as in the CIT) is audiomotor coupling [6, 7]. Audiomotor coupling has been evidenced in healthy volunteers who were exposed to prolonged piano practice and showed co-activation of motor areas when listening to practiced music in a post-training fMRI-scan [4, 5, 18].

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***Declaration of Interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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