Exploratory Study on the Effects of a Robotic Hand Rehabilitation Device on Changes in Grip Strength and Brain Activity after Stroke

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Background: The brain mechanisms underlying successful recovery of hand function after stroke are still not fully understood, although functional MRI (fMRI) studies underline the importance of neuronal plasticity. **Methods:** We explored potential changes in brain activity in 7 patients with subacute to chronic stroke (69 ± 8 years) with moderate- to high-grade distal paresis of the upper limb (Motricity Index: 59.4) after standardized robotic finger-hand rehabilitation training, in addition to conventional rehabilitation therapy for 3 weeks. Behavioral and fMRI assessments were carried out before and after training to characterize changes in brain activity and behavior. **Results:** The Motricity Index (pre: 59.4, post: 67.2, $P < .05$) and grip force (pre: 7.26, post: 11.87, $P < .05$) of the paretic hand increased significantly after rehabilitation. On fMRI, active movement of the affected (left) hand resulted in contralesional (ie, ipsilateral) activation of the primary sensorimotor cortex prior to rehabilitation. After rehabilitation, activation appeared "normalized," including the ipsilesional primary sensorimotor cortex and supplementary motor area (SMA). No changes and no abnormalities of activation maps were seen during movement of the unaffected hand. Subsequent region-of-interest analyses showed no significant ipsilesional activation increases after rehabilitation. **Conclusion:** Despite behavioral improvements, we failed to identify consistent patterns of functional reorganization in our sample. This warrants caution in the use of fMRI as a tool to explore neural plasticity in heterogeneous samples lacking sufficient statistical power. **Key words:** *functional MRI, motor recovery, robotic devices, stroke*

Stroke represents one of the main causes of disability in adults, with the most widely recognized impairment being motor impairment.[1] Intensive rehabilitation is necessary to optimize the process of healing, decrease long-term disability,[2] and enable affected individuals to regain independence in daily activities. However, evaluation of rehabilitation effects is challenging on clinical grounds,[3] and thus the mechanisms of successful rehabilitation after stroke are still unclear. In this context, functional MRI (fMRI) has been proposed as an objective approach for identifying changes in brain activity potentially underlying rehabilitation-mediated recovery of function.[2] Insights obtained from the use of fMRI have potential implications for optimal timing and efficacy of interventions, patient selection, and development of new rehabilitation strategies. This proposed approach is based on the concept that recovery is linked to reorganization of cortical networks and that rehabilitative methods may accelerate this process to reduce long-term disability.

Early after stroke, increased activation of the contralesional primary sensorimotor cortex (SMC) has been observed with movement of the impaired upper limb.[4,5] Cross-sectional studies revealed a relationship between motor recovery of hand function and a reduction in contralesional activity and an increase in ipsilesional activity of the SMC,[6–10] suggesting that successful rehabilitation is associated with normalization of activation patterns in moderately impaired patients.[9] Moreover, in longitudinal studies investigators

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found that behavioral improvements correlated with increased ipsilesional activation (premotor cortex and somatosensory cortex), presumably reflecting functional reorganization in the motor cortex adjacent to the lesion.[11]

Disturbed hand function is one of the greatest functional deficits after stroke.[12] Conventional rehabilitation methods for hand function, such as bilateral training, constraint-induced movement therapy, high-intensity therapy, repetitive task training, and splinting,[1] are challenging and time consuming and often have unsatisfactory results. In contrast, robotic devices allow for the delivery of well-characterized, highly frequent, repetitive movement sequences to practice and improve impaired finger movements. Consequently, robotic therapy may complement standard rehabilitation.[13] Significant improvements in motor function and strength of the paretic arm have been attributed to robot-assisted arm training in a meta-analysis including 11 studies and 328 patients.[14] To date, several robotic devices are available to promote hand recovery after stroke (eg, haptic knob,[15] HEXORR,[16] MIT-Manus[17]); so far, these methods have been evaluated only at the behavioral level.

We aimed to assess the effects of a robotic finger-hand rehabilitation device on changes in grip strength and functional reorganization using fMRI. Conceptually, this robotic-assisted therapy offers a promising approach to augment training-induced plasticity after stroke by increasing motor input and output in a standardized manner. It promises to enable specific, directed, and automatized training of finger movements, imitating natural grasping movement. We therefore hypothesized that recovery of hand function after a 3-week period of training would be associated with consistent changes in brain activation in patients with subacute to early chronic stroke (33 to 94 days post stroke).

Methods

Patients

We included 7 patients between the ages of 59 and 80 years, satisfying the primary criterion of inclusion, that is, impaired motor function of the upper limb (Motricity Index: 59.4[18]) caused by an imaging-confirmed first ischemic or hemorrhagic infarct irrespective of size and location, which had occurred at a minimum of 4 weeks before. None of the patients showed severe spasticity of the affected hand (Ashworth Scale <3). Patients were excluded from participation if there was any contraindication for MRI or robotic-assisted hand rehabilitation (orthopedic or rheumatic disease); if there was any cognitive (Mini-Mental State Examination score of <27), psychological, or sensory impairment that could have affected engagement in the study (eg, major depression, dementia, neglect); or if there was synkinesia, severe leukoaraiosis, or other neurologic disorders. Additionally, we did not accept subjects who began receiving or had a change in neuroleptic, anticonvulsant, or antidepressant medication less than 4 weeks before study entry or during the study. The study was approved by the local ethics committee, and all patients gave informed written consent.

Outcome assessment

Before and after the training, patients underwent clinical examination, including 5 clinical scales and scores (Motricity Index [MI], Rivermead Mobility Index[19] [RMI], modified Rankin Scale [mRS], National Institutes of Health Stroke Scale [NIHSS], Barthel Index [BI]), and the grip force of the affected hand was measured using the robotic device.

The MI ranges from 0 to 99 and evaluates motor impairment (eg, pinch grip, elbow flexion, shoulder abduction); higher scores indicate better function. The RMI consists of 15 items to test body mobility (such as gait, balance, and transfers), with higher scores indicating better mobility. The mRS ranges from 0 to 5, with higher scores indicating higher degree of disability and more dependence in daily activities. The NIHSS ranges from 0 to 42 and is used to assess severity of stroke in 12 items (eg, level of consciousness; language; visual, motor, and sensory function), with higher scores indicating more severe impairment after a stroke. The BI (0-100) is used to measure performance in activities of daily living (ADLs; eg, toilet use, dressing, and bathing), with higher scores indicating greater autonomy.

The upper limb section of the MI (in particular, the pinch grip: 0-33) served to monitor therapy-related changes in motor function. The mRS, NIHSS, BI, and RMI were used to assess disability and autonomy. Furthermore, we assessed potential changes in brain function by means of fMRI before and after the training.

Training and physical therapy

During 3 weeks of neurorehabilitation, attendants obtained 15 units each lasting 20 minutes (resulting in an average of 3,600 grip movements) using the robotic hand rehabilitation device (Amadeo; Tyromotion, Graz, Austria), in addition to the conventional training program (on average, 18 units of occupational therapy, 20 units of training of ADLs, 29 units of physical therapy in 30 minutes, 12 units of strength training, 6 units of lymph drainage, 8 units of partial massage, and 6 units of cognitive training). For this sample, very small variations in training intensity exist, because this was a dedicated study. The study design is presented in **Figure 1**.

Robotic hand rehabilitation device

The specific robot provides task-related training, using successive or simultaneous automated extension and flexion movements of fingers. The linear (2-dimensional) forward and backward motion allows continuous and ergonomic simulation of the grasping movement. Strength and pace were individually adjusted for each patient. Total number of grasping movements, pace, strength, and range of motion were recorded (Amadeo).

MRI

MRI data were acquired on a 3 Tesla MRI system (Siemens, Erlangen, Germany) using a multi-slice gradient-echo echo planar imaging (EPI) sequence (TR = 3000 ms; TE = 30 ms). Care was taken to cover all critical brain regions, including the vertex and the cerebellum. A conventional high-resolution T1-weighted structural image was acquired at baseline to allow functional image registration, precise localization of activation, and location of brain damage caused by infarcts. Functional runs were acquired on 2 occasions, at the beginning and the end of the rehabilitation program, using identical scanning parameters and the same paradigm.

Paradigm design

An fMRI block design, comprising 2 conditions (active vs passive flexion and extension of digits

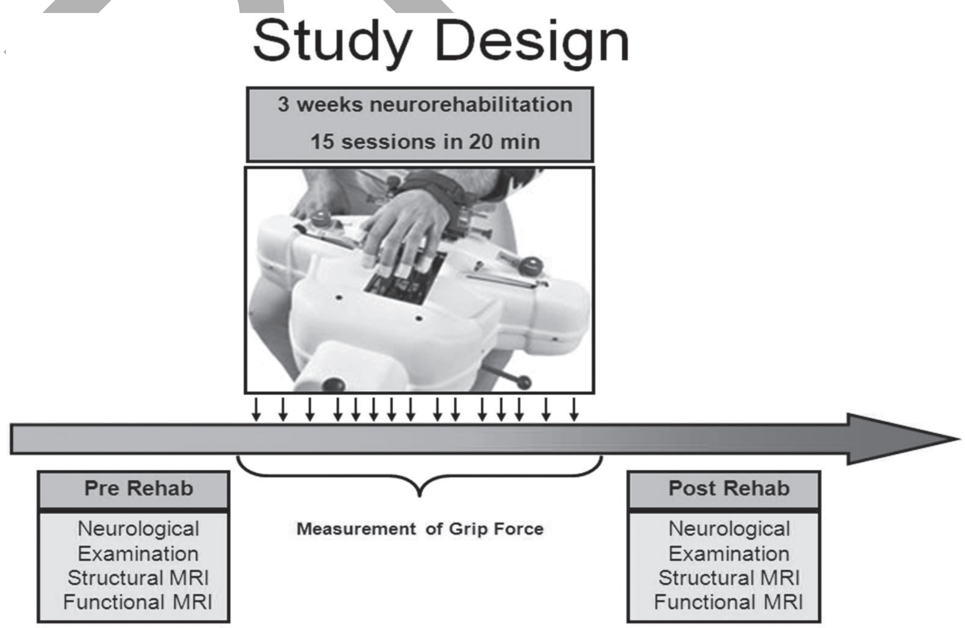

Figure 1. Study design.

2 through 5) was used.[20] Active movement was paced by a visual cue and passive movement by the experimenter (who paced the movements in accordance with a visual cue [LED bar] readily visible, where lights flashed in an ascending and descending order at the determined pace and frequency), both at a rate of approximately 1 Hz.[20] Vision was corrected with prism lenses if necessary. Active and passive movement periods (blocks) of 30 seconds alternated with periods of rest (24 seconds). Each session included 5 active movement blocks and 5 passive movement blocks, separated by 10 blocks of rest. Total scanning time for unilateral movement of 1 hand was approximately 7.5 minutes. In each session, 1 run was performed moving fingers 2 to 5 of the unaffected hand supported by a movable splint, and another run was performed moving the paretic hand (as effectively as possible). For the baseline and follow-up sessions, the sequence of movements was pseudo-randomized across subjects.

Before entering the scanner, subjects practiced the paradigm. Visual cues for hand movement were presented on a screen, and the experimenter explained the 2 conditions, conducting an active and a passive run outside the scanner. After initial training, none of the patients exhibited a clinically detectable radiation of movement (synkinesia) to the unaffected side or upper limbs with the experimental task.

Data processing

Functional imaging analysis was carried out using FEAT (FMRI Expert Analysis Tool, Version 5.98, part of FMRIB's Software Library [www.fmrib.ox.ac.uk/fsl]). Functional and structural images from the only patient with a left hemisphere stroke were mirrored across the midline, so that in all of the patients, virtually, the affected hemisphere was the right hemisphere. The following prestatistical processing was applied: high-pass filter cutoff of 100 seconds, motion correction using MCFLIRT, nonbrain removal using BET, spatial smoothing using a Gaussian kernel of 5 mm full width at half maximum (FWHM), and high-pass temporal filtering. Time-series statistical analysis was carried out using FILM. To further minimize the impact of differences, motion parameters were included as a covariate of no interest in the general linear model. Registration to high-resolution and/or standard images was carried out using FLIRT. In a first-level analysis, the effects of the active and passive movement blocks versus rest were determined for each subject, session (pre or post), and limb (affected or unaffected). Head motion was assessed by controlling the displacement of the functional images in any direction, as derived from the FEAT motion correction report. Higher level analysis was done using FLAME (FMRIB's Local Analysis of Mixed Effects). Z statistic images were thresholded using clusters determined by $Z > 2.3$ ($Z > 2.7$, for better visualization) for mean activation of active and passive movement and by $Z > 2.3$ for post versus pre comparison with a corrected cluster significance threshold of $P > .05$. All analyses were run for both active and passive movement with inclusion of age as covariate.

According to the functional findings and theoretical background,[5] we computed 8 functional region-of-interest (ROI) analyses for 2 subdivisions of the cerebellum (V and VI), the precentral gyrus and supplementary motor area (SMA) for both hemispheres, using FEATQUERY (part of FSL). In addition, we explored changes in the laterality index [LI = 1 × Q left hemisphere (LH) - Q right hemisphere (RH)/QLH + QRH] in the cerebellum, precentral gyrus, and SMA over time, applying a threshold of 0.2 (<0.2 = bilateral[21]), using the extent of significant voxels (Q) or the magnitude (Z statistic; Q) to define changes in LI.

Data analysis

The results of the scores and scales were analyzed with the Statistical Package of Social Science (PASW Statistics 18; SPSS Inc., Chicago, IL). The level of significance was set at .05.

To detect parameters with effect on grip force, we conducted correlation analyses to assess whether the extent of focal brain damage, the total amount of grasping movements during training, or the interval between the stroke and training onset would show any influence on grip force.

Table 1. Patient characteristics

Patient: Lesion description	Side of paresis	Lesion volume, cm^2	Interval to stroke, days	Age, years	AS affected upper limb (0-5)
1: Thalamic bleeding	L	3.28	90	63	1
2: Cortical infarct in MCA territory affecting SMC	L	1.61	54	79	1
3: Infarct in MCA territory	L	1.23	41	59	1
4: Corticosubcortical infarct in MCA territory	L	90.64	49	67	1
5: Basal ganglia infarct	L	8.14	94	70	0
6: Periventricular infarct in MCA territory	R	0.93	66	80	1
7: Pons infarct	L	0.29	33	68	2
Mean ± SD		15.16 ± 33.4	61 ± 24	69 ± 8	1 ± 0.7

Note: AS = Ashworth Scale; MCA = middle cerebral artery; L = left; R = right; SMC = sensorimotor cortex.

Results

Clinical features of the cohort

Patients were moderately impaired and differed regarding lesion location and size (see **Table 1**). All patients were right handed; 6 had left-sided paresis and 1 had right-sided paresis. Six patients had an ischemic stroke, and one had an intracerebral bleeding (see **Table 1** and **Figure 2**).

Therapy-associated effects on motor function

On average, hand function across the group improved after therapy. The MI score of the affected arm (pre: mean 59.4 ± 23; post: 67.2 ± 23; P = .02) and the subcategory pinch grip (pre: 22 ± 7.8; post: 26 ± 5; P = .03) improved. The MI of the unaffected arm did not change significantly. The mean grip strength of the affected hand also increased significantly (pre: mean 7.26 ± 2.95; post: 11.87 ± 5.8; P = .004) (**Table 2**). Disability tended to decrease and autonomy tended to increase according to the BI, NIHSS, and RMI, but these changes were not significant (**Table 2**).

Correlational analyses showed that the extent of focal brain damage, the total amount of grasping movements, and the interval between the stroke and training onset had no influence on grip force.

fMRI findings

At baseline with active movement of the paretic (left) hand, we observed ipsilesional activation in the primary SMC and SMA and diffuse bilateral activation in the cerebellum, frontal pole, and posterior parietal cortex. After training, bilateral (frontal pole and posterior parietal cortex) and ipsilesional activation of the motor network decreased, and significant activation clusters emerged in the contralesional (right) SMC and SMA (Z > 2.7) (**Figure 3**).

In contrast, active movement of the unaffected (right) hand showed constant activation in key motor areas before and after the rehabilitation (contralateral in the SMC and SMA and ipsilateral in the cerebellum; Z > 2.7) (**Figure 3**).

Also, during passive movement of the unaffected (right) hand, consistent activation in the expected motor network (primary SMC and contralateral and ipsilateral cerebellum) was found before and after rehabilitation. No significant activation clusters for passive movement were observed during movement of the paretic hand with a threshold of Z > 2.7, but expected activation clusters in the SMC and SMA were observed at a threshold of Z > 2.3.

The statistical whole-brain posttraining versus pretraining comparison revealed no significant differences (Z > 2.3) for active and passive movement versus rest for the paretic and nonparetic hands.

No subject had to be excluded because of excessive head motion (>3 mm in any direction as assessed from displacement in the head images). The mean absolute displacement at the pretest was 0.69 ± 0.47 and 0.51 ± 0.30 mm for movement

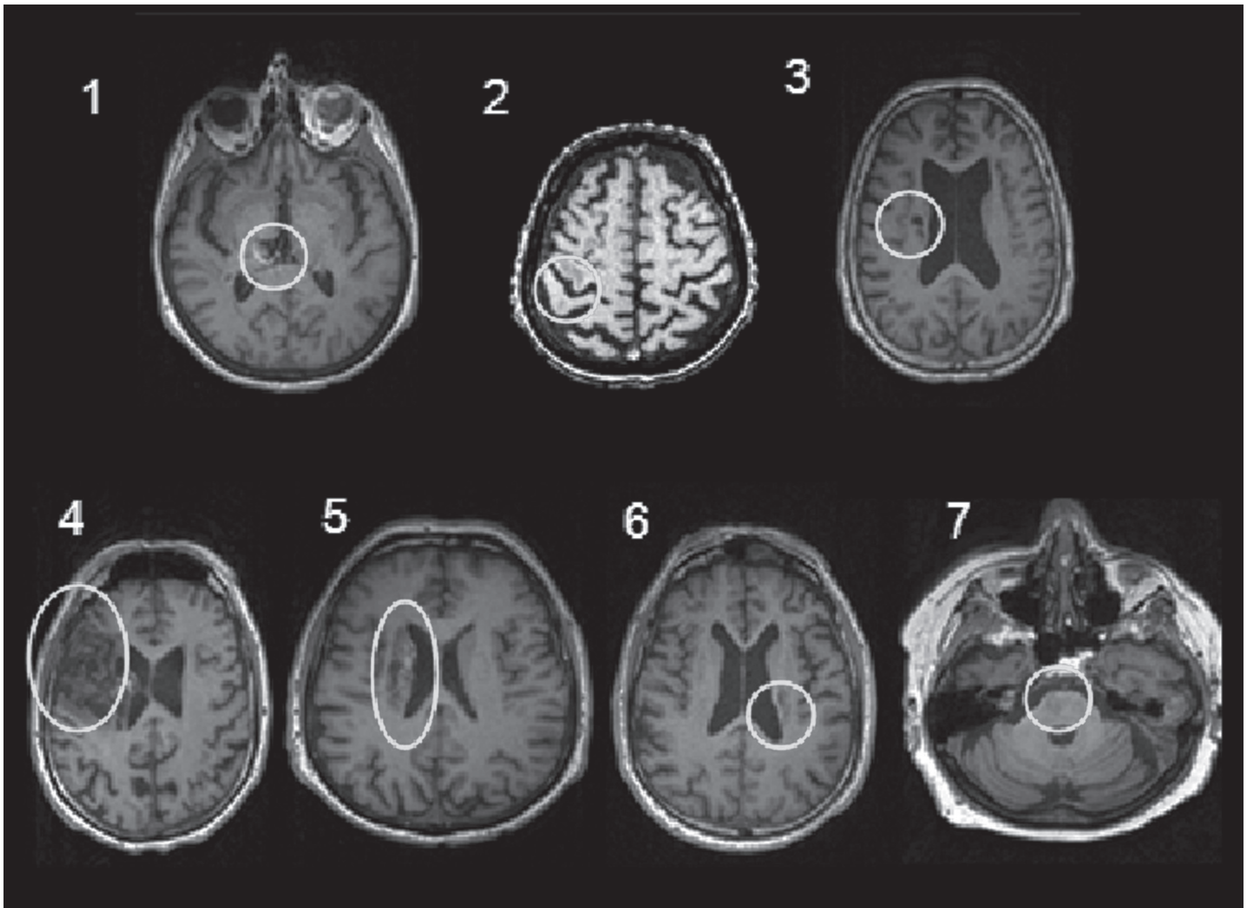

Figure 2. Lesion location.

Table 2. Changes in clinical scales, scores, and behavioral measures after 3 weeks of robot-assisted training of hand function

Outcome measures	Pre	Post	*P* value	η_p^2
Rivermead Mobility Index (0-15)	5.8 ± 5	8.6 ± 4.9	.206	.36
Barthel Index (0-100)	60 ± 23.2	76 ± 21.6	.094	.55
NIHSS (0-42)	4.5 ± 1.9	3.2 ± 2.1	.080	.69
Modified Rankin Scale (0-5)	3.6 ± 0.5	3.4 ± 0.6	.374	.20
Motricity Index – affected arm (0-99)	59.4 ± 23	67.2 ± 23	.024	.76
Motricity Index – pinch grip affected arm	22 ± 7.8	26 ± 5	.034	.71
Mean grip force over 3 sessions, N	7.2 ± 2.95	11.8 ± 5.83	.004	.69

Note: N = newton; η_p^2 = partial eta-square indicating effect size; NIHSS = National Institutes of Health Stroke Scale.

of the affected (left) and unaffected (right) hand, respectively. Respective values at the posttest were 0.47 ± 0.17 and 0.51 ± 0.28 mm.

ROI analyses and LI

There were no significant increases or decreases of activation in the 8 regions of interest (cerebellum, SMC, and SMA; see **Table 3**). Furthermore, we found no significant changes in LI within our sample.

Discussion

In this exploratory study, we aimed to assess the effects of a robotic-assisted finger-hand training program in addition to conventional rehabilitation therapy in 7 patients with stroke and impaired hand function by focusing on fMRI changes. In general,

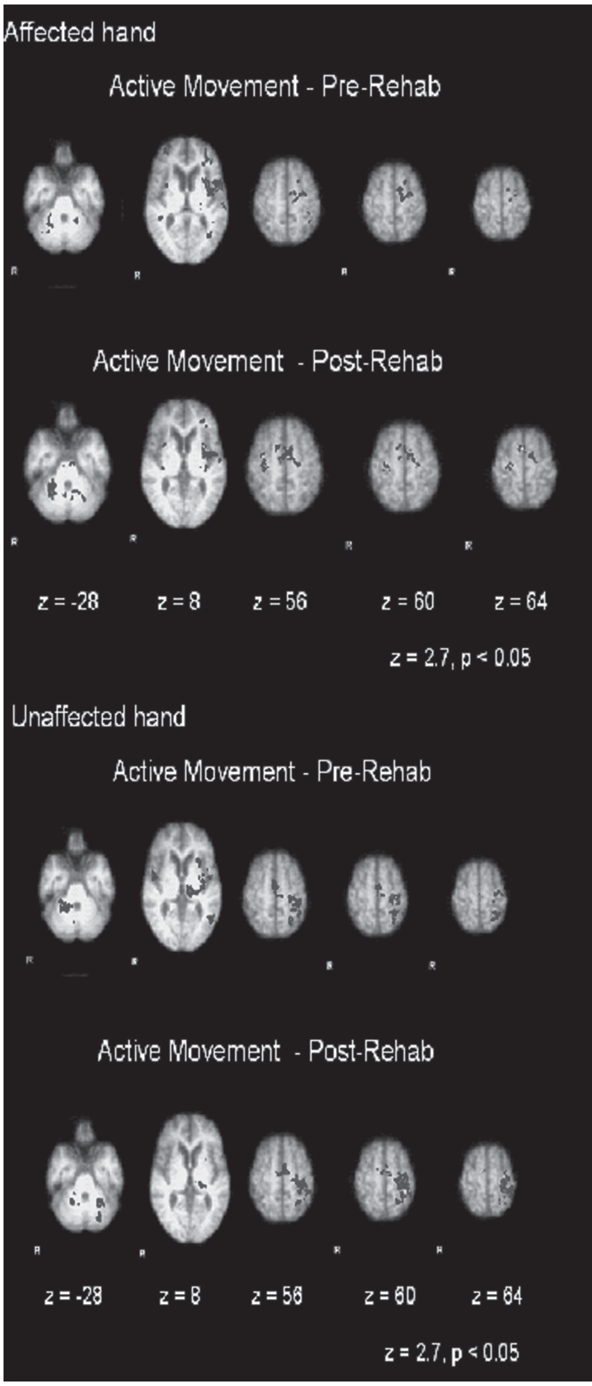

Figure 3. Functional MRI results at the group level: active movement affected left hand versus rest and unaffected right hand.

Table 3. Mean contrast of parameter estimate for regions of interest (ROI) during active movement

ROI	Pre	Post	*P* value	η_p^2
Movement unaffected hand				
↓ Left precentral gyrus	0.76	0.74	.88	.004
↑ Left SMA	0.81	0.91	.75	.018
↑ Right precentral gyrus	0.44	0.56	.32	.166
↑ Right SMA	0.71	0.87	.45	.099
↓ Right cerebellum (V, VI)	0.70 0.57	0.68 0.54	.93 .89	.001 .003
Left cerebellum (V, VI)	0.29 0.34	0.31 0.33	.88 .91	.004 .002
Movement affected (left) hand				
↓ Left precentral gyrus	0.68	0.62	.82	.010
↓ Left SMA	1.10	1.09	.96	.000
↑ Right precentral gyrus	0.84	0.85	.96	.000
↑ Right SMA	1.17	1.25	.48	.086
Right cerebellum (V, VI)	0.73 0.69	0.72 0.79	.95 .66	.001 .034
Left cerebellum (V, VI)	0.87 0.82	0.78 0.86	0.74 .91	.020 .002

Note: η_p^2 = partial eta-square indicating effect size; SMA = supplementary motor area.

the robotic training was safe and well tolerated. Functional gains after training were determined by clinical scales and by force measurements in our study, but a case-control design would have been needed to address this point more precisely. These findings appear to be consistent with results of prior studies in which significant improvements in motor function and strength of the paretic arm were reported in relation to robot-assisted arm training.[14]

On the other hand, although clinical improvement was noticeable and treatment was safe, we failed to identify consistent patterns of activation changes with the use of fMRI.

According to findings from previous studies, we expected to see increased activation in the ipsilesional SMC and pre-SMA, as well as contralesional SMC and cerebellum parallel to hand motor recovery.[2,5,9] In this study, thresholded mean activation maps revealed that active movement of the affected (left) hand resulted in activation of the left (contralesional) SMC before the intervention, whereas additional activation clusters were found in the right (ipsilesional) SMC and SMA after rehabilitation. This would be consistent with results of prior studies in which better motor recovery was reported to be related to a reduction in contralesional activity and an increase in ipsilesional activity of the SMC.[9]

However, this observation was not confirmed through statistical testing; significant differences in fMRI contrasts in areas of activation changes between the time points were not found. This could be due to a lack of statistical power, given the low patient numbers and considerable heterogeneity regarding lesion size, location, and interval since stroke.

The importance of the interval since stroke is demonstrated by Johansen-Berg et al,[2] who longitudinally investigated 7 patients with chronic stroke and found that increases of brain activity in the ipsilesional premotor cortex and secondary somatosensory cortex and in both sides of the cerebellum were related to improvement in hand function. Even though the sample size and variation of lesion extent were the same, all patients were assessed at least 6 months post stroke, and 6 patients with an infarct in the middle cerebral artery (MCA) territory were included, which probably led to a more consistent and stable change in brain activation patterns within the group.

In addition, the interval from stroke to initiation of rehabilitation could have influenced reorganization mechanisms of the brain. A faster initial recovery of body function in the first days to weeks after stroke onset (influenced by mechanisms of spontaneous recovery and rehabilitation), followed by a slower asymptotic pattern, is typically observed.[1,22] Different (probably more widespread) reorganization processes in patients 1 month after stroke might have occurred during the 3 weeks of rehabilitation, as compared with patients 3 months after stroke.

Unlike Calautti et al,[6] we did not include only patients with subcortical strokes who had an intact or largely preserved hand area on structural imaging. Thus, it is likely that differences in lesion topography may have introduced variation caused by different mechanisms of recovery and plasticity, as indicated by Luft et al.[23] Nonetheless, increases in sample size and randomization might overcome this.[24]

In subsequent ROI analyses, we focused on key regions involved in recovery of motor function. However, these analyses revealed no significant ipsilesional activation increases (or contralesional decreases) after the rehabilitation. It is crucial to further investigate these findings in a larger sample.

Moreover, the inclusion of a control group would have facilitated interpretation. In our study, movement of the unaffected hand served as a control condition. Consistent activation patterns during movement of the unaffected hand in key motor areas were found. However, we do not know if and how stroke influences the observed activation patterns of the unaffected hand observed by fMRI.

Conclusion

Functional MRI has great potential to extend our understanding of reorganization of brain activity related to recovery of motor function.[22,25–29] Although our exploratory study showed behavioral improvements after robotic-assisted rehabilitation, no consistent pattern of functional reorganization could be observed in our heterogeneous study sample. This underscores the need for a larger number of patients, a homogeneous sample, and a control arm.

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