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Research report

Increased ventral premotor cortex recruitment after arm training in an fMRI study with subacute stroke patients

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HIGHLIGHTS

- fMRI activation in ventral premotor cortex is increased after arm training in subacute stroke patients.
- Ventral premotor cortex activation after training is more pronounced than in healthy controls.
- No change is present for the representation of unaffected hand movement.
- Premotor areas may still play a role in good recovering stroke patients.

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ABSTRACT

To investigate therapy associated changes in the cerebral representation of movement after stroke, we used functional magnetic resonance imaging (fMRI) during an active and a passive motor task for the affected and unaffected hand before and after a three week comprehensive hand motor training.

Twelve patients in the subacute phase from 2 to 9 weeks after mild to moderate motor stroke were recruited. During fMRI, the active task comprised fist clenching, which was precisely controlled for motor performance by visual feedback of force and frequency. The passive task consisted of wrist flexion-extension of 1 Hz frequency by means of a pneumatic driven splint. Arm Ability Training (AAT) was conducted one hour per day over 3 weeks in addition to inward rehabilitative therapy. Performance gain was tested using movements trained with AAT, but also with conventional hand motor tests (Nine-Hole-Peg Test, Box-and-Block Test).

Rehabilitation therapy and AAT resulted in considerable improvement of performance in trained tasks and other hand motor functions (e.g., Nine-Hole-Peg Test). FMRI activation in the ventral premotor cortex (vPMC) of the lesioned hemisphere increased over time for the active task only for the affected hand. No such change was present for the passive wrist extension task or the active task with the unaffected hand. In addition, only for the post measurement of the active task performed with the affected hand, bilateral vPMC shows a more pronounced activation than in healthy controls. This finding contradicts the simple "near to normal is good recovery" opinion.

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1. Introduction

Functional imaging has been applied to document motor recovery after stroke for more than two decades [1,2]. However, for the subacute state when patients undergo intensive motor rehabilitation and conditions for motor learning are optimal [3,4], longitudinal data of the functional representation of movements are limited. In addition, performance control during imaging is essential since movement parameters such as force, amplitude and frequency are associated with the magnitude of fMRI activation [5–7].

For cross-sectional studies with patients in the acute or subacute stage, higher activation levels compared to healthy subjects have been reported even in the contralesional hemisphere while moving the affected hand [8]. A meta-analysis of 36 studies at different

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stages of stroke confirmed these findings and reported activations above the levels of healthy controls in several motor areas [9].

One consistent result in cross-sectional and longitudinal studies with different motor tasks is that a development to "normal" activation patterns similar to those of healthy subjects seems to be important for recovery [10] with focused recruitment of the ipsilesional primary motor cortex during movement of the affected hand (M1) [6,8,11–13]. However, the focus on the ipsilesional M1 (M1il) does not necessarily imply good recovery [13] and even good recovering patients may show contralesional M1 (M1cl) activation [14–17]. Especially the dorsal premotor cortices (dPMC) in both hemispheres play a role in recovery processes [18–20]. There is also evidence for an enhanced involvement of the ventral premotor cortex (vPMC) after stroke [21]. In addition connectivity studies emphasized the importance of the connection between the ipsilesional vPMC and M1 [22–25].

The character of activations in secondary motor areas resembles those of complex task activations in healthy subjects. It might therefore reflect the difficulties for patients to perform well [26]. Some results pointed towards a stronger need for higher-order processing in patients and a more specific contribution of these areas to motor recovery than in complex tasks [27].

In order to determine changes in hand motor performance and cerebral representation of hand movements during the recovery from stroke, we investigated subacute patients with mild to moderate unilateral hand motor impairments using an active and a passive task. Both tasks were highly controlled for effort and motor performance. We compared their representation maps of unilateral hand movements to those of healthy controls. The aim was to investigate the role of additionally active motor areas especially when motor performance improved well. This improvement was ensured by investigating patients who underwent Arm Ability Training (AAT) over 3 weeks in addition to inward rehabilitative therapy. The AAT has already been shown to be effective in this stage of hand motor recovery [28,29].

We expected differences in stroke patients' representations before and after training reflecting a recovery of hand function. We hypothesized that these changes in brain activity will lead to movement representations similar to those of healthy controls. Based on the literature [18–21] especially the active task may show some additional involvement of motor areas even in good recovering patients.

2. Methods

2.1. Participants

Overall 18 patients were recruited from the BDH Neurorehabilitation Center in Greifswald. All patients had been diagnosed with a first-ever unilateral ischemic stroke. Exclusion criteria were brainstem infarcts, epileptic seizures, additional neurological or psychiatric diseases, ferromagnetic devices, pregnancy and serious cognitive impairments. In order to perform the motor training patients had to be able to grasp smaller objects and to move their arm against gravity (with a score of $\geq$3 at the Medical Research Council (MRC) scale for pinch grip and $\geq$4 for shoulder abduction and elbow flexion respectively [30]). Four patients did not participate in the whole training program. They were not further analyzed due to incomplete data.

Data of 14 patients (11 male; mean age = 59.7 ± 12.1 years; range = 33–73 years; 12 right-handed; average score of handedness 83.8 ± 32.8 according to [31]) were recorded. Patients were included 2–9 weeks after stroke incident (on average 4.6 ± 1.9 weeks). Data of two patients had to be discarded because of severe motion artifacts. The remaining 12 patients who are described in Table 1 contributed to the final group analysis. All patients showed mild to moderate motor impairments (Motricity Index (MI) Upper Extremity Score 72–92 [32]), mostly no spasticity (REsistance to PAssive movement Scale 0–2 (REPAS, arm score) [33]) and overall minor to moderate stroke severity (National Institutes of Health Stroke Scale 0–6 (NIHSS) [34]) before training (see Table I).

Additionally, 14 age-matched healthy controls (HC; 8 male/6 female: mean age = 60.6 ± 11.6 years; range = 33–73 years; all right-handed) without history of neurological or psychiatric disease participated in a onetime fMRI investigation only. They were recruited by an announcement posted at the university and other public places. Participants in both groups provided written informed consent, which was approved by the Ethics Committee of the University Medicine Greifswald. Only the patient group received the following motor training in addition to inward rehabilitative therapy.

2.2. Motor training

Rehabilitative therapy mostly aimed to improve arm and hand functions. Therapy was adjusted to individual needs. Therefore therapy composition and durations differed between patients (on average 9.55 h per week). All of them additionally received Arm Ability Training (AAT).

The AAT is a repetitive and standardized training targeting different sensorimotor abilities such as fast finger movements, arm-hand steadiness, aiming and dexterity of the affected arm and hand [28]. Patients trained for about one hour each workday for 3 weeks. Details of the standard training procedures for AAT, as it has been applied here, are described elsewhere [35,36]. Training comprised eight different tasks for the affected hand, each of which performed twice. After completion of the 8 × 2 task-set, the series was performed a second time, resulting in a total number of four repetitions per task. The following tasks were trained repetitively: Aiming, tapping, crossing circles, turning coins, labyrinth, nuts and bolts, placing small objects, placing large objects (see also Fig. 1 and [28,29]). At the first day of training, the individual number of repetitions within one minute for each task and block was determined for every patient based on the patient's individual motor capacities and kept constant for the following training days. Time needed for the execution of each of the eight trained tasks was recorded daily. Improved performance was indicated by reduced execution time keeping accuracy demands of the tasks constant. Performance feedback was given verbally and visually in order to maintain motivation. The AAT has been shown to be a highly effective training for mild to moderate arm paresis after stroke [29].

2.3. Motor assessment

Motor performance of patients was assessed before and after training in terms of Nine-Hole-Peg Test (NHPT) [37] and Box-and-Block Test (BBT) [38] for both hands.

2.4. MRI data acquisition

We used a 3T MRI-scanner (Verio, Siemens, Erlangen, Germany) with a 32 channel head coil. Functional imaging was performed with a standard gradient-echo EPI sequence of 34 transversal slices oriented along the subjects AC-PC plane. In plane resolution was $3 \times 3\,mm^2$, slice thickness 4 mm and the gap between slices 1 mm. The field of view was $208 \times 208\,mm^2$ corresponding to an acquisition matrix of 104 × 104. Repetition time was 2 s, echo time 23 ms, and the flip angle 90°.

Structural imaging was carried out using a sagittal T1-weighted 3D MPRAGE with 176 slices, a spatial resolution of $1 \times 1 \times 1\,mm^3$ and a gap of 0.5 mm between the slices. The field of view

Table 1
Demographic and clinical data of stroke patients; 2 additional patients were not included in the analyses because of severe motion artifacts.

Subject	Age	Gender (male/female)	MMST[a]	REPAS[b]	Time since stroke (weeks)	Lesion hemis-phere	Lesion location[c] and volume (cc)	NIHSS[d]	MI[e]
1	65	m	30	2	2	Left	sc; putamen; 0.16	2	79
2	57	m	27	1	5	Left	sc; pt; ic; 0.3	1	92
3	45	m	30	0	5	Right	sc; pt; ic; 0.58	2	85
4	73	m	24	1	6	Left	c; haemoragic; M1; S1; parieto-temporal; 57.48	5	85
5	52	f	23	0	4	Left	sc; pt; 1.17	5	84
6	54	m	28	0	2.5	Left	sc; ec; 0.34	1	77
7	73	m	27	2	6	Left	sc; pt; 3.36	0	85
8	52	f	27	0	3	Right	sc; ic; putamen; 10.99	1	84
9	74	m	27	0	4.5	Right	sc; pt; ic; putamen; 14.38	4	77
10	33	m	30	0	9	Left	sc; pt; ic; 0.87	3	77
11	57	m	27	2	3	Left	sc; pt; ic; putamen; 6.1	2	85
12	66	m	27	0	7	Right	sc; pt; ic; ec; putamen; 2.17	3	77

[a] MMST: mini mental status test.
[b] REPAS: resistance to passive movement scale, affected arm.
[c] lesion location: sc: subcortical; c: cortical; ic: internal capsule; pt: pyramidal tract; ec: external capsule; M1: primary motor cortex; S1: primary sensorimotor cortex.
[d] NIHSS: National Institutes of Health Stroke Scale.
[e] MI: Motricity Index.

was $250 \times 250\,mm^2$ corresponding to an acquisition matrix of 256×256. Repetition time was 1690 ms, echo time 2.52 ms, total acquisition time 3:50 min. In both sequences GRAPPA with a PAT factor of 2 was used.

The first two volumes of each session were discarded to allow for equilibration effects. Each condition lasted 3 min, active and resting blocks alternating every 20 s. Thirty-four phase and magnitude images were acquired in the same FOV by a gradient echo sequence (flip angle 60°; FOV 192 × 192; slice thickness 3 mm; TR 488 ms; TE1 4.92 ms; TE2 7.38 ms) to calculate a fieldmap aiming at correcting geometric distortions in the EPI images.

2.5. Motor tasks during fMRI

Active and passive task were trained outside the scanner to ensure stable performance. Patients underwent two measurements, one before (pre) and one after (post) three weeks of motor training. Healthy controls only participated in one measurement session.

Both tasks were performed in a blocked design, consisting of 5 blocks of rest alternating with 4 blocks of task performance providing 90 whole brain volumes. During all conditions task performance and rest were indicated by "off" and "on" visual cues. These signals were presented via video projection controlled by the Presentation software (Neurobehavioral Systems, Albany, NY, USA) and triggered by the scanner. During scanning, participants lay supine and wore hearing protection.

In the active task both patients and controls performed hand grips with a rubber ball. This task was conducted for each hand side separately. Frequency was paced at 1 Hz via a blinking cue. The performance amplitude was monitored online by a pressure detector connected to an electro-optical biosignal recorder (Varioport-b, Becker Meditec, Karlsruhe, Germany). The signals were recorded and stored for further off-line analysis using PhysioMeter software. The force was adjusted to 30% of the maximal force on this day by coupling the monitor with the pressure device showing the currently exerted force as a moving bar. The participants were told to adjust their force according to the 30% line.

To evaluate the accuracy level during the hand grip, we calculated mean force and frequency and corresponding percentage deviations from mean of the subject's recorded fist clenches.

In the passive task, passive wrist flexion–extension were elicited by a nonmagnetic torque motor at 1 Hz to assess possible differences in representation maps without any voluntary movement or effort contribution [39]. For this task we investigated only the affected hand of patients, because we expected no changes over

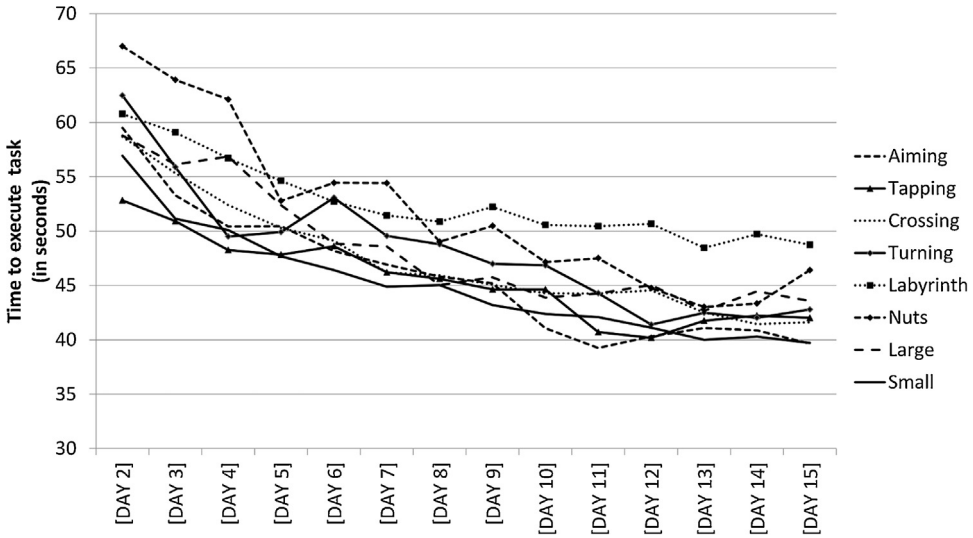

Fig. 1. Development of performance in the AAT for separate tasks (mean of patients, time in s); Tasks comprised aiming, finger tapping, crossing circles, turning coins, labyrinth tracking, bolts and nuts, placing large objects and placing small objects.

time for the unaffected hand. Healthy subjects were matched for the same laterality to control for effects of hand sides.

2.6. Analyses of functional imaging

Preprocessing and statistical parametric mapping was performed with SPM12 (Wellcome Department of Neuroscience, London, UK) and Matlab version 8.5 (MathWorks Inc; Natick, MA). Each time series was realigned and resliced after unwarping in the phase encoding direction (anterior/posterior) to account for movement and susceptibility artifacts and were high-pass filtered (128 s). To correct for the different acquisition times of signals, slice time correction relative to the last slice was used. The T1 image was segmented via the default segmentation in SPM12. The realigned data were spatially normalized to the Montreal Neurological Institute (MNI) template by using the coregistered and segmented T1 image as a reference and resliced to $3 \times 3 \times 3\,mm^3$. The images for the 4 patients with right-hemisphere lesion and the 4 matched HC were flipped in the midsagittal plane before segmentation. All images were smoothed with a Gaussian filter of 8 mm (full width at half maximum). At the first level of analysis, a fixed-effect analysis was performed to obtain contrast images for each condition (active task affected hand, active task unaffected hand, passive task). In patients, we calculated the subtractions of post minus pre and pre minus post measurement to search for changes in activity levels. These contrast images were entered into a second-level random-effects analysis.

The main results of each condition were modeled separately and calculated with significance thresholds for multiple comparison correction in certain regions ($p(FWE) < 0.05$).

In both tasks, we restricted analyses to motor areas of both hemispheres known to be involved [7,9,14,40,41]. This comprised M1, primary somatosensory cortex (S1), supplementary motor area (SMA), dPMC, vPMC and cerebellum.

Many of these regions were reported to play a role in compensatory networks [42] and were therefore included as regions of interest (ROIs).

To evaluate differences between patients and healthy controls, we compared the representation maps of active and passive tasks for each time point to those of the control group. Comparisons between groups were calculated in a 2-sample unpaired *t*-test and were again restricted to the aforementioned areas. For the ROI analysis within these areas, a threshold of $p(FWE) < 0.05$ was used. ROIs were selected using cytoarchitectonic probability masks from the HMAT atlas masks of FSL for M1, S1, SMA, dPMC and vPMC and Automated Anatomical Labeling (AAL) for the cerebellar hemisphere.

2.7. Lesion volumes

Lesion volumes were calculated by manually drawing the border of the lesion in the high-spatial-resolution T1-weighted image for each slice and by calculating the resulting volume (cc) with MRIcron (http://www.sph.sc.edu/comd/rorden/mricron).

3. Results

3.1. Motor performance

All patients showed improvements in the trained tasks. The mean execution time for AAT tasks was reduced on average by 27.7% from day 2 to day 15 ($t(11) = 17.61$, $p < 0.001$; see Fig. 1). Other measurements of the affected hand also exhibited a significant improvement over time. The average time needed to perform the NHPT decreased by 25.2% and the deviation from the age reference value decreased over time ($t(11) = 3.28$, $p < 0.007$). The number of blocks moved in the BBT increased by 20.9% and again the deviation from the age reference value decreased over time ($t(11) = 8.74$, $p < 0.001$) (Fig. 2). The BBT score also showed an improvement for the unaffected hand ($t(11) = 5.04$, $p < 0.001$).

3.2. Functional imaging results: patients at pre and post measurement

In the active task with the unaffected hand, M1, SMA, dPMC, vPMC, S1 and cerebellum in both hemispheres were activated pre and post (Supplementary Table III). In the active task with the affected hand at pre measurement M1, SMA, dPMC, S1 and cerebellum were activated. In the representation map of the post-measurement there was additional vPMC activation in both hemispheres (Supplementary Table II).

For the passive task we detected activity in all aforementioned regions in both hemispheres. In the post-measurement, fewer contralesional regions were activated at group level (Supplementary Table I).

3.3. Longitudinal fMRI changes including differences between groups

The active task with the unaffected hand showed no increases or decreases of fMRI-magnitude in ROIs over time. No differences occurred between groups.

In the active task with the affected hand, the patients showed a significant increase in activation in the ipsilesional vPMC (Fig. 3; $t = 7.25$, $p(FWE) = 0.0059$, MNI-coordinates: −48, 3, 21). No decrease of fMRI-magnitude in ROIs over time was observed.

Patients showed higher activation of vPMC in both hemispheres in the post-measurement compared to that of healthy controls (left: $t = 4.53$, $p(FWE) = 0.017$; MNI-coordinates (x,y,z): −39, −3, 18, and right $t = 4.51$, $p(FWE) = 0.018$; MNI-coordinates: 51, 0, 6).

In the passive task there were no increases of activation over time. The passive task rather showed a decrease of activation of the M1il ($t = 5.43$, $p(FWE) = 0.047$, MNI-coordinates: −33, −12, 69). Patients did not differ from healthy controls neither at pre nor post measurement.

3.4. Association between fMRI changes and recovery

To evaluate the overall importance of the described deactivations and activations in all tasks, we correlated the subtracted representation maps of each patient with the corresponding percental change in AAT, NHPT and BBT. None of the deactivations or activations over time was associated with the AAT, NHPT or BBT change.

3.5. Accuracy during active fMRI task

Mean frequency and amplitude were stable over time. Yet patients showed significant accuracy deficits during active tasks in comparison to healthy controls (Fig. 4). Amplitude error differed between patients' pre measurement and healthy controls (affected hand: $t = 2.27$, $p = 0.033$; unaffected hand: $t = 2.30$, $p = 0.039$). Patients further showed a decrease of amplitude error with the affected hand over time (affected hand: $t = 2.58$, $p = 0.03$; unaffected hand: $t = 1.85$, $p = 0.097$). Frequency error in patients remained significantly higher than in healthy controls over both time points (Fig. 4).

3.6. Correlation between fMRI activation and accuracy gain

To evaluate the relevance of the activation increase in vPMC of both hemispheres during patients' post-measurement in the active

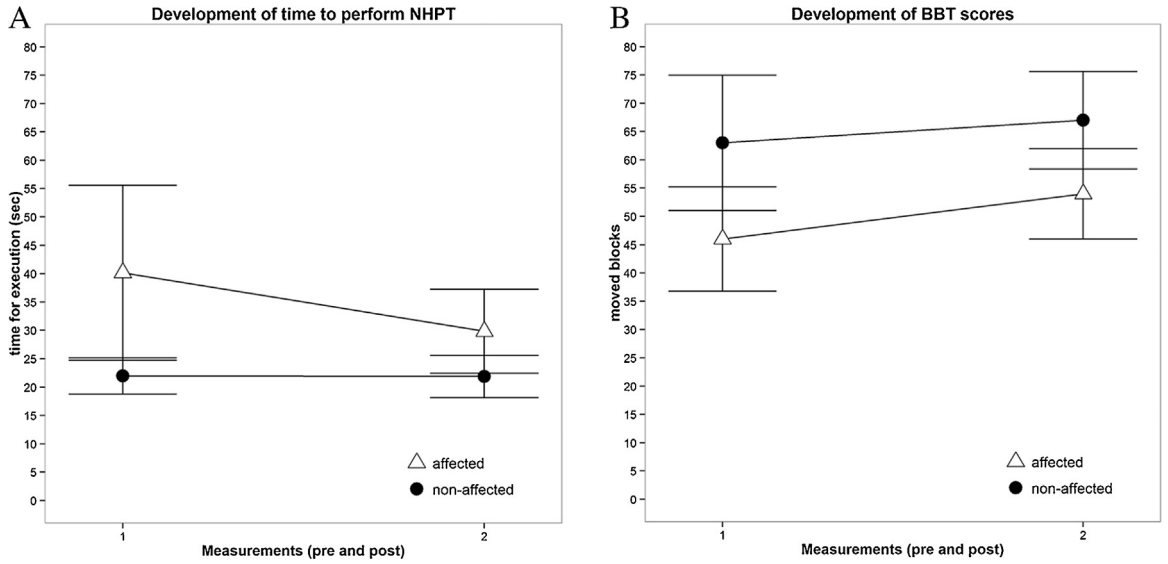

Fig. 2. Performance scores before and after training for the affected and unaffected hand; (A) NHPT time and (B) BBT blocks.

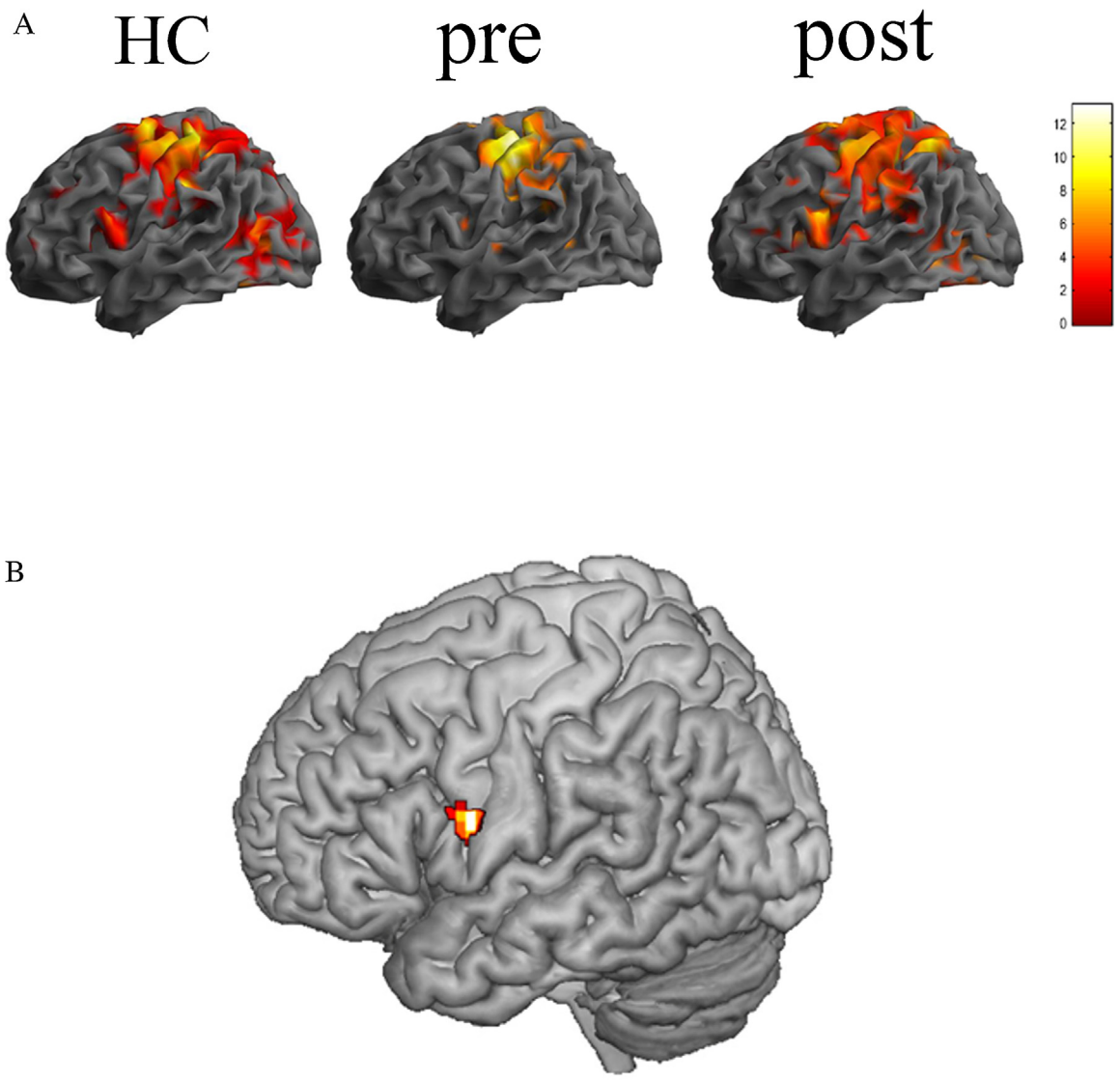

Fig. 3. (A) Main result of active hand grip task with the affected hand in healthy controls (HC) and patients (pre and post), uncorr. ($p < 0.001$); (B) Change in activity over time in vPMC, post minus pre contrast of patient group, displayed on a segmented template (Collins Brain), uncorr. ($p < 0.001$), $x = -48$, $y = 3$, $z = 21$, $T = 7.25$, SVC: $p(FWE) = 0.0059$.

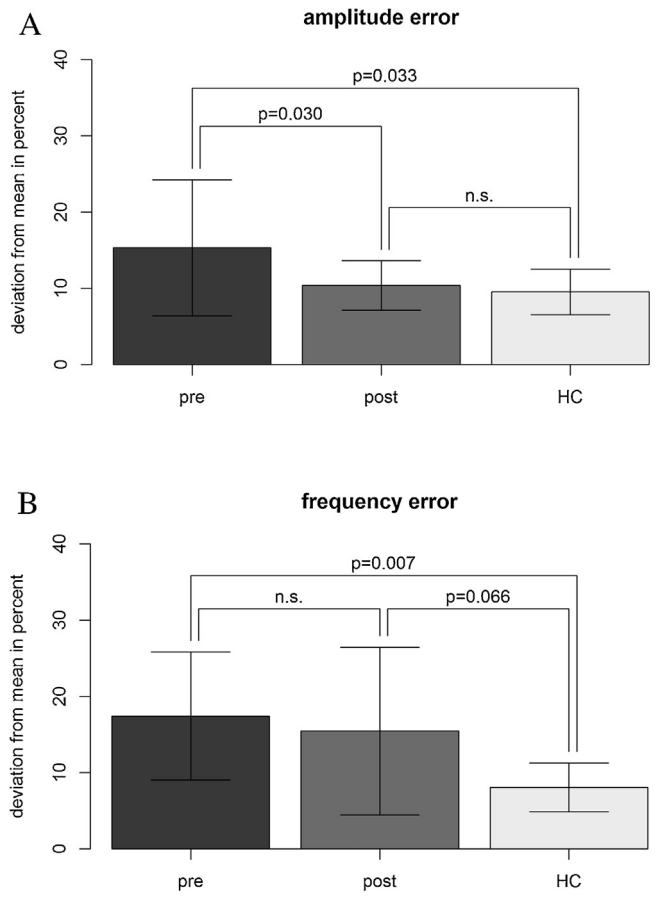

Fig. 4. Differences in accuracy of hand grip task with the affected hand between patients (pre and post) and healthy controls (HC) in terms of (A) amplitude error and (B) frequency error as the deviation from the mean in percent.

task with the affected hand we correlated the representation maps of each patient with the corresponding accuracy levels. Neither the amplitude nor the frequency error was associated with vPMC activity during post-measurement. We also correlated the subtraction maps with these accuracy values. The amplitude error after training was negatively associated with an increase in contralesional vPMC activity ($t = 8.41$, $p(FWE) = 0.013$, MNI-coordinates: 45, −3, 30, $r = -0.69$). This association could not be found in the unaffected hand condition.

4. Discussion

4.1. Discussion of results

We here performed a longitudinal study with patients showing mild to moderate motor impairment in the subacute stage after stroke using precisely controlled performance during the pre and post imaging conditions. In addition, we applied a maximal effective training concept for the impaired hand (AAT and inward neurorehabilitation) over a three week period. Post therapy patients showed improvements in the trained AAT tasks and transferred effects to non-trained tasks (NHPT, BBT).

Investigating representation sites in patients with fMRI, the most prominent change over time was an activation increase in the ipsilesional vPMC when performing an active hand grip task with the affected hand. This alteration was not apparent during passive movement or during the execution of the same task with the unaffected hand. Because the patients' representational maps showed differences compared to healthy controls in ipsilesional and contralesional vPMC only after training, increased vPMC activation contradicted the hypothesis of a recovery pattern towards normal representation maps, as described in previous studies [43]. This result points towards a need for recruitment of additional areas in patients to attain comparable performance levels as shown in [27].

As a consequence of the highly controlled design the effort to perform the active task was comparable over sessions. The differences in accuracy showed that the patients became even better executing the task with both hands respectively. Still the changes in brain representation were limited to the movement of the affected hand. This suggests an effect specific to the paretic limb rather than a general learning effect.

The amplitude error was negatively correlated with a stronger fMRI activation of vPMC. This might be associated with an increased integration of the given visual feedback in the motor network and a more controlled object manipulation. Visual feedback is known to influence task performance [44] and increases brain activation in many visuomotor regions [45]. An interaction between force and feedback seemed to be represented in the contralateral rostral premotor cortex and putamen [45]. We found evidence that this premotor area changes over time in the patient group and is differently activated in patients than in controls. Higher activation in the post-measurement in our study might represent a stronger integration of the visual feedback signal into the motor command. This is in line with TMS studies showing that the vPMC is responsible for predictive scaling of grip force levels [46] and that a key function of vPMC is to process object properties relevant for grasping actions [47]. The vPMC helps to unite multisensory inputs about the body and objects manipulated via an egocentric reference frame [48].

We could not find any association of this activation increase to the overall recovery or training results. This is in line with previous investigations that did not find an association for the whole group due to highly individual patterns of brain changes [7,13]. The lack of associations between brain activations and motor function could also be due to low power or a more complex involvement of the considered regions in hand function [27].

To investigate the relevance of this activation it will be necessary to describe the embedding of the vPMC in the motor network of individual patients and assess the role of these connections in terms of reorganization processes. Interestingly, in a previous fMRI-feedback study the learned self-regulation of the vPMC improved motor performance in chronic stroke patients [49] underlining the role of this area on recovered motor function in the chronic stage after stroke.

4.2. Limitations

Although several research groups found widespread brain activation in early stages after stroke [8,13] we found no differences between healthy controls and stroke patients for the pre-measurement. As depicted in Fig. 3, this might be due to a higher noise level in the patient group and a variable pattern of differences between patients and controls.

We tried to compensate for the variability in age and lesions with an age-matched control group and the inclusion of comparably impaired patients regarding their hand function. For a better understanding of the involved processes studies with more subjects and more frequent measurements have to be performed.

It would be further interesting to distinguish between the effects of conventional rehabilitation training and the additional AAT on hand motor representation, but this aim is beyond the scope of this study. From a study with healthy subjects training their left hand with AAT it is known that there is an increase of fMRI activation

in the putamen and pallidum in the described hand grip task after training, but no increase in vPMC activity as reported here [35].

5. Summary

We found an increase in fMRI activation in vPMC after 3 weeks of intensive hand motor training during active grip movements of the affected hand, controlled precisely for performance. Although the patients' accuracy almost reached the level of healthy controls, additional secondary motor regions were recruited to execute the task. Therefore, the premotor cortex seems to play a role in recovered hand motor function.

Disclosures

None.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbr.2016.04.040.

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