Action observation has a positive impact on rehabilitation of motor deficits after stroke

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Evidence exists that the observation of actions activates the same cortical motor areas that are involved in the performance of the observed actions. The neural substrate for this is the mirror neuron system. We harness this neuronal system and its ability to re-enact stored motor representations as a means for rehabilitating motor control.

We combined observation of daily actions with concomitant physical training of the observed actions in a new neurorehabilitative program (action observation therapy). Eight stroke patients with moderate, chronic motor deficit of the upper limb as a consequence of medial artery infarction participated. A significant improvement of motor functions in the course of a 4-week treatment, as compared to the stable pre-treatment baseline, and compared with a control group have been found. The improvement lasted for at least 8 weeks after the end of the intervention.

Additionally, the effects of action observation therapy on the reorganization of the motor system were investigated by functional magnetic resonance imaging (fMRI), using an independent sensor-motor task consisting of object manipulation. The direct comparison of neural activations between experimental and control groups after training with those elicited by the same task before training yielded a significant rise in activity in the bilateral ventral premotor cortex, bilateral superior temporal gyrus, the supplementary motor area (SMA) and the contralateral supramarginal gyrus. Our results provide pieces of evidence that action observation has a positive additional impact on recovery of motor functions after stroke by reactivation of motor areas, which contain the action observation/action execution matching system.

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Introduction

Motor deficiency is the leading cause of disability following stroke (Duncan et al., 1992). The mechanisms underlying recovery are multifold including active relearning strategies and passive processes of lesion adaptation (Seitz et al., 2002). The traditional neurorehabilitative approach to treat motor deficits after stroke is mainly based on techniques aiming at stimulating the use of the paretic limb during supervised training sessions (Rossetti et al., 2005). The main tenet is that practice of repetitive, active movements by a paretic limb leads to effects induced by positive neuronal plasticity. The effects of repetitive training are empirically well proven (Shepherd, 2001; Aichner et al., 2002; Jang et al., 2003; Byl et al., 2003; Dombovy, 2004); this approach was demonstrated to be more effective than conventional physiotherapeutic approaches (Beer, 2000; Hesse et al., 2002), with a smaller learning time of manual arm movements (Beer, 2000), a faster recovery and smaller therapy lasts (Kwakkel et al., 1999). Examples include the “constraint-induced movement therapy” (Taub et al., 1993; Duncan, 1997; Elbert et al., 2003), the motor relearning program (Langhammer and Stanghell, 2003), and repetitive arm training (Buetefisch et al., 1995). These neurorehabilitative trainings are supposed to have attained the best rehabilitative outcomes so far.

There is increasing experimental evidence that motor areas are recruited not only when actions are actually executed, but also when they are mentally rehearsed or simply observed (for a review...
Dementia, depression, severe to moderate aphasia, anosognosia or neglect, amnesia or impaired level of consciousness (confusion, stupor, coma), ischemic lesions in the territory of posterior or Anterior Cerebral Artery, has not yet been tested as a potential tool in neurorehabilitation.

The major aim of this study was to assess whether action observation therapy may lead to clinical improvement of motor impairment in chronic stroke patients, as measured by standard functional scales. Based on the findings of previous studies concerning the use of mental techniques in neurorehabilitation (Page et al., 2001), we combined action observation with the direct effects of action execution. Our hypothesis was that the activation of motor areas by action observation becomes reinforced by the concomitant active execution of the observed actions (Binkofski et al., 2004; Buccino et al., 2004a). Additionally, by means of fMRI we studied the reorganization within the motor areas following this treatment, using an independent sensorimotor task consisting of object manipulation.

Materials and methods

Patients

Patients were recruited from the local Rehabilitation Centre. We excluded patients older than 76 years, with hemorrhagic stroke or ischemic lesions in the territory of posterior or Anterior Cerebral Artery, impaired level of consciousness (confusion, stupor, coma), severe to moderate aphasia, anosognosia or neglect, amnesia or dementia, depression.

After giving their informed consent fifteen patients (4 females) with a confirmed diagnosis of a first ever ischemic stroke in the territory of the medial cerebral artery (MCA) sustained more than 6 months prior to study entered the study (see Table 1 for demographic details). All patients had a moderate paresis of the contralateral arm, as assessed by standard functional scales (see below; Table 1). Patients were randomly assigned to either the experimental or the control group. All patients had undergone intensive classical physiotherapy before entering our study (mean treatment duration for both groups: 111.3 days; range: 44–238 days; mean lesion occurrence before pre-measurement: 1098.813 days with 990.74 days standard deviation; see Table 1 for descriptive statistics for each group). All patients did not undergo any other treatment or therapeutic intervention during the course of the present study. The study was approved by the local ethics committee.

Treatment

During the rehabilitation sessions, patients entering the experimental group (“action observation therapy”) sat relaxed on a chair with their arms placed on a table them. They had a free view of a large TV screen (25 in.) that was positioned ca. 2-m distance in front of them. They were asked to watch carefully video sequences containing daily life hand and arm actions that were followed by repetitive practice of the observed actions. After the observation of the video sequence for 6 min, the patients were asked to perform the observed action at the best convenience for 6 min with their paretic upper limb using the same objects as shown in the video film. Each action was presented twice during the training. During the treatment patients were assisted by a psychologist who kept them attentive to the video sequences, they were not allowed to move their hands/arms while watching the videos. As a whole each rehabilitation session lasted 90 min. Patients underwent eighteen rehabilitation sessions on 18 consecutive working days.

Fifty-four different video sequences were shown over the course of the study. Every day a ‘unit’ of three hand and/or arm movements of increasing complexity were presented. Each unit showed manipulation of the same objects in a more and more complex manner. In each 6-min video sequence the presented action was shown from three different perspectives. The actor used both his hands. The treatment started with observing and practicing of simple translation movements such as using a piece of tissue. The complexity was then consecutively staggered both during each rehabilitation session and during the course of the training (starting with the use of a ball or a cup, and then performing more complex actions such as turning a water tap on and off, etc.)

Patients entering the control group (labeled as “control”) matched the experimental treatment with the exception that the patients watched sequences of geometric symbols and letters instead of action sequences. We used geometric symbols as control stimuli because non-object pictures like letters and symbols very unlikely elicit significant activity in motor areas or areas belonging to the mirror neuron system and therefore did not cause any interference with the goal of the study. Videos showing any movements, even those not specifically trained, could possibly activate the mirror neuron system to unknown extent as it was planned only for the experimental treatment and could have therefore a rehabilitative effect not controlled by the experiment. The practiced hand and arm actions were performed by instruction of the assisting therapist in the exact order as they were practiced under the experimental condition. Great care was taken to ensure that the intervention was equal across groups.

Clinical examination

For the evaluation of the clinical status of patients standard functional scales (Frenchay Arm Test—FAT; DeSouza et al., 1980; Wolf Motor Function Test—WMFT; Wolf et al., 1989) as well as subjective scales (Stroke Impact Scale—SIS; Duncan et al., 1999) were used. All tests were delivered by the same therapist, who was trained in the application of the used inventories in order to keep the experimental conditions constant.

The average times for performing the different tasks of the WMFT, the sum scores of the FAT and the sum scores of the SIS were used as measurements for further analysis. Patients were assessed at three different times: 14 days before the onset of the action observation therapy (“baseline”), the second on the day preceding the onset of the treatment (“pre-test”), and the third at the end of the rehabilitation treatment (“post-test”). A further
Table 1
Demographic details and results of the statistical comparison of the two patient groups, labeled as “Control” and “Experimental”

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient</th>
<th>Gender</th>
<th>Age</th>
<th>Stroke onset before pre-measurement</th>
<th>Time of former therapies</th>
<th>Localization of lesion</th>
<th>Increased tone, reflexes</th>
<th>Dexterity</th>
<th>FAT</th>
<th>WMFT</th>
<th>SIS</th>
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<tr>
<td>Experimental</td>
<td>MK</td>
<td>m</td>
<td>61</td>
<td>May 1992</td>
<td>84</td>
<td>Left large fronto-parieto-temporal (media territory)</td>
<td>Tone: ++</td>
<td>Reflexes: +</td>
<td>2</td>
<td>13.14</td>
<td>241</td>
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<td></td>
<td>HC</td>
<td>m</td>
<td>66</td>
<td>August 2000</td>
<td>112</td>
<td>Right basal ganglia, capsule</td>
<td>Tone: +</td>
<td>Reflexes: +</td>
<td>–</td>
<td>4</td>
<td>2.41</td>
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<tr>
<td></td>
<td>AK</td>
<td>f</td>
<td>38</td>
<td>August 2003</td>
<td>140</td>
<td>Right parieto-temporo-occipital, up to intraparietal sulcus</td>
<td>Tone: (+)</td>
<td>Reflexes: (+)</td>
<td>–</td>
<td>5</td>
<td>4.05</td>
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<tr>
<td></td>
<td>RW</td>
<td>f</td>
<td>64</td>
<td>June 2000</td>
<td>142</td>
<td>Right basal ganglia, capsule</td>
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<td>Reflexes: +</td>
<td>–</td>
<td>2</td>
<td>5.52</td>
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<tr>
<td></td>
<td>HF</td>
<td>m</td>
<td>55</td>
<td>January 2000</td>
<td>113</td>
<td>Right frontal operculum</td>
<td>Tone: (+)</td>
<td>Reflexes: (+)</td>
<td>(−)</td>
<td>3</td>
<td>20.17</td>
</tr>
<tr>
<td></td>
<td>GB</td>
<td>m</td>
<td>54</td>
<td>July 2002</td>
<td>238</td>
<td>Left basal ganglia</td>
<td>Tone: (+)</td>
<td>Reflexes: (+)</td>
<td>–</td>
<td>1</td>
<td>7.31</td>
</tr>
<tr>
<td></td>
<td>RB</td>
<td>m</td>
<td>60</td>
<td>March 2002</td>
<td>50</td>
<td>Right primary sensorimotor cortex</td>
<td>Tone: (+)</td>
<td>Reflexes: (+)</td>
<td>–</td>
<td>2</td>
<td>12.62</td>
</tr>
<tr>
<td></td>
<td>PH</td>
<td>f</td>
<td>63</td>
<td>August 1999</td>
<td>74</td>
<td>Right parietal (media territory)</td>
<td>Tone: +</td>
<td>Reflexes: +</td>
<td>–</td>
<td>2</td>
<td>15.37</td>
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<td></td>
<td></td>
<td>57.16</td>
<td>1472.9 (1258.8)</td>
<td>119.13 (57.60)</td>
<td>2 × Left hemispheric</td>
<td>–</td>
<td>–</td>
<td>2.63</td>
<td>10.07</td>
<td>261.25</td>
</tr>
<tr>
<td>Control</td>
<td>HT</td>
<td>m</td>
<td>69</td>
<td>June 2001</td>
<td>44</td>
<td>Right parietal (media territory)</td>
<td>Tone: (+)</td>
<td>Reflexes: (+)</td>
<td>–</td>
<td>0</td>
<td>26.91</td>
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<tr>
<td></td>
<td>IO</td>
<td>m</td>
<td>60</td>
<td>June 2003</td>
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<td>Right parietal (media territory)</td>
<td>Tone: +</td>
<td>Reflexes: +</td>
<td>–</td>
<td>3</td>
<td>15.36</td>
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<tr>
<td></td>
<td>KG</td>
<td>m</td>
<td>69</td>
<td>April 2004</td>
<td>58</td>
<td>Right parietal (media territory)</td>
<td>Tone: +</td>
<td>Reflexes: +</td>
<td>(−)</td>
<td>0</td>
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<tr>
<td></td>
<td>GB</td>
<td>m</td>
<td>62</td>
<td>June 2004</td>
<td>122</td>
<td>Left lentiform nucleus</td>
<td>Tone: +</td>
<td>Reflexes: +</td>
<td>(n)</td>
<td>3</td>
<td>4.17</td>
</tr>
<tr>
<td></td>
<td>KV</td>
<td>m</td>
<td>49</td>
<td>August 2003</td>
<td>63</td>
<td>Media and posterior territory, multiple lacunar lesions</td>
<td>Tone: (+)</td>
<td>Reflexes: (+)</td>
<td>–</td>
<td>3</td>
<td>5.32</td>
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<tr>
<td></td>
<td>ML</td>
<td>m</td>
<td>44</td>
<td>April 2004</td>
<td>194</td>
<td>Right basal ganglia</td>
<td>Tone: +</td>
<td>Reflexes: +</td>
<td>n</td>
<td>3</td>
<td>7.07</td>
</tr>
<tr>
<td></td>
<td>SP</td>
<td>f</td>
<td>39</td>
<td>February 2005</td>
<td>77</td>
<td>Left parietal (media territory)</td>
<td>Tone: (+)</td>
<td>Reflexes: +</td>
<td>n</td>
<td>3</td>
<td>4.46</td>
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<tr>
<td></td>
<td>EW</td>
<td>f</td>
<td>56</td>
<td>November 2003</td>
<td>103</td>
<td>Right parietal (media territory)</td>
<td>Tone: +</td>
<td>Reflexes: +</td>
<td>–</td>
<td>1</td>
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<td>Descriptive</td>
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<td>55.40</td>
<td>724.8 (360.9)</td>
<td>103.63 (54.31)</td>
<td>2 × Left hemispheric</td>
<td>–</td>
<td>–</td>
<td>2.00</td>
<td>16.88</td>
<td>253.38</td>
</tr>
</tbody>
</table>

The cells show the patient gender with f=female and m=male, age in years, the duration of former therapies in days (the descriptive section shows the results of the mean lesion occurrence before pre-measurement in days), lesions locations and sensorimotor and motor deficits defining parameters, assessed 14 days before onset of the respective intervention for every patient of the groups. Listed are the dexterity of the affected hand and the muscle tone and reflexes (according to Kunesch et al., 1995) using the following assessment markers: [−−]—markedly affected, [−]—moderately affected, [−(−)]—slightly affected, [n]—normal, [(n)]—almost normal, [(+)][−]—marginally increased, [+][−]—slightly increased, [++]—moderately increased, [++++]—markedly increased. The severity of motor deficit was assessed using the Frenchay Arm Test (FAT, the Wolf Motor Function Test (WMFT) and the Stroke Impact Scale (SIS). The “descriptive” labeled line lists the mean test values and modus test values reached per group, respectively, the numbers in parenthesis show the standard deviation. The information regarding corresponding Z (standardized sum of ranks) and asymptotic significance levels (two-tailed) error probability for the applying of the statement, that the compared values of the two treatment groups using the Wilcoxon signed rank test originate from different distributions (see text).
evaluation (“follow-up”) was carried out 8 weeks after the end of the rehabilitation treatment only in the treated patients. We asked the participants to carry on with their basis physiotherapy during the follow-up period, but not to begin any new therapy schemas.

The results of WMFT, FAT and SIS at the baseline assessment were statistically compared to the results of the “pre-test” measurement (Wilcoxon signed rank test) in order to ascertain the stability of the motor deficit at the beginning of treatment.

In 7 members of the experimental group an additional follow-up measurement was performed 8 weeks after the end of the intervention.

fMRI measurements

fMRI measurements were performed before (pre-test) and soon after the end of the treatment (post-test) by seven patients of the experimental group and six patients of the control group. One patient of the experimental and two patients of the control group were not able to participate in the scanning procedures due to technical reasons. Subjects lay prone in the scanner, with their eyes opened and the head fixed. The task consisted of manual exploration of objects (Binkofski et al., 1999). A total of 16 objects of a size fitting well into the palm (small flask, syringe, etc.) and a neutral object (sphere) were used. Objects were passed to the patient by the experimenter who was cued by a visual stimulus (not visible to patient) as to the next condition. An auditory countdown to the beginning of each epoch via head phones was also delivered to the experimenter so that the touching of the participants’ hand and the delivery of the object into the hand were kept tightly regulated. Objects were randomly selected but not re-used during a session and each object was presented for one full epoch. Two sessions were conducted, one for each hand. Patients were able to maintain the object in their affected hand, although all patients sought means to improve grip with the affected hand by using their lower body to wedge the object before attempting to manipulate/explore. The importance of continual manipulation of the objects was particularly stressed to the subjects and all patients included in fMRI analysis were observed to fully comply. Scanning was conducted on a 3-T system (Siemens Trio) with gradient echo EPI T2*-sensitive sequence, using a standard head coil. Contiguous gradient echo, echo-planar images in thirty-four 3-mm thin slices, 1-mm gap, interleaved acquisition, TR 2 s, TE 25 ms, with a flip angle of 80°. Slices covered the entire brain positioned parallel to the plane intersecting the anterior and posterior commissure. The matrix acquired was 64*64 with a FOV 192 * 192 mm. Additionally a FLASH 3D sequence was acquired for each patient.

fMRI data analysis

fMRI data were analyzed using SPM2 (Welcome Dept. of Cognitive Neurology, London, UK) and MATLAB 7 (The Mathworks Inc). 10 of 13 subjects had right hemisphere lesions, the other three subjects brains were therefore flipped along the x-axis prior to pre-processing so that right represents ‘lesioned hemisphere’. The first four images of each subject were discarded to remove out of phase measurements. The subsequent data series was first realigned to the first volume. Normalization to MINI (Montreal Neurological Institute) standard space was conducted so that group analysis could be undertaken. Masks of the lesions were applied to exclude lesion affected regions from being included in assessing normalization parameters. Those masks were created by manually outlining the regions affected by the lesion on the subject’s high-resolution structural image, which was than used to cover the lesion site in the normalized EPI images. Normalized images were then spatially smoothed using a Gaussian filter of 10-mm FWHM prior to conducting statistical analysis. The four sessions (2 hands, pre and post) were included in each individual’s design matrix with two conditions ‘explore an object’ and ‘manipulate a sphere’ per session. Epochs were modeled using a canonical hemodynamic response function convolved with a box car function. Data were high pass filtered at 128 s so as to remove low-frequency artefacts. First level analysis of each participant was conducted with two regressors, for each of the four sessions. Thereafter, contrast maps (i.e., estimates of the raw-score differences of the beta coefficients between the pre and post training regressors for each condition), were generated for each subject and the differences between sessions for each condition were calculated using the t-statistic. The ensuing contrast images of the first level were taken to the second level and compared either within or between groups using a random effects analysis (one- or two-sample t-test respectively). Subsequently, t-values were transformed into Z-scores. Unless otherwise stated only clusters with more than 20 contiguous voxels with a peak threshold of p<0.05 corrected for the expected False Discovery Rate (FDR) of whole brain analysis are reported. Automated anatomical labeling (AAL) (Tzourio-Mazoyer et al., 2002) was used as it not only consistently labels clusters with reference to a standard atlas but also indicates what proportion (superscripted values in tables) of the cluster lies within a particular region.

Results

Clinical results

Each of the analyses was performed using the Wilcoxon signed ranks test. Age and duration of former therapies as the two most important demographic details revealed no significant difference between the treatment and the control groups (Wilcoxon signed rank test; see Table 1). In all patients the neurological impairment was stable as demonstrated by the lack of any significant difference between the results of the standard functional scales (WMFT, FAT) and the subjective self-assessment (SIS) at the baseline measurement and at the pre-test measurement (Wilcoxon signed rank test; p<0.4; Table 1). The main analysis of the clinical data consisted of two parts: the first level analysis contained the comparison of the test scores before and after the treatment (Table 2) and the second level analysis contained the comparison of the rehabilitative gain between the two groups—the treatment and the control group (Table 3).

The results of the first level analysis are shown in Table 2. Significant differences occurred only in the experimental group at a level far below p<0.05. This result could be found for the subjective self-assessment of the own functional abilities within the scales of the SIS (p<0.0125). There were no significant changes in the objective and subjective clinical scales within the control group (Table 2).

The second level analysis containing the calculation of the differences between post-test and pre-test measurements between the experimental and the control group showed a significant difference at a significance level below 0.001, except for the result of the WMFT comparison, which just reached the lowest level of significance (p<0.05) (Table 3).

An additional analysis was carried out using the clinical results of the post-test and follow-up time points. Seven members of the experimental group agreed in the evaluation of the WMFT and FAT,
and all members of the experimental group agreed in the evaluation of the SIS at the last evaluation time point. The comparison between the results of the assessment of all three clinical scales (WMFT, FAT and SIS) at the end of the treatment and at the follow-up measurement in the subgroup of 7 patients showed that in all scales no statistically significant worsening of the clinical status during this time period (Wilcoxon signed rank test; \(p < 0.7\)) (see Table 2).

**fMRI results**

**Network for exploratory finger movements**

Pre training data for the main effect of exploring complex objects with the unaffected arm in the control group is listed in Table 4 (\(p < 0.05\) FDR corrected, cluster size >20). Similarly to a previous study (Binkofski et al., 1999), activity is seen in a frontoparietal circuit including the parietal inferior lobule, inferior frontal gyrus (IFG), supplementary motor area (SMA), and post central gyrus. Activity in the ventral premotor cortex was identified in the operculum as well as at the intersection of the IFG pars triangularis with the inferior frontal orbital gyrus.

### Treatment-related changes in activation

The fMRI examination of the control group revealed almost no change in cerebral activity between the time points pre and post control treatment at the low level of significance of \(p < 0.001\), cluster size >20. The only change identified was when using the unaffected hand to manipulate objects. Two clusters indicate a trend to greater activity pre treatment than post treatment. The first in the anterior cingulate (\(xyz=8 40 -2, Z=3.89\)) and the second in the superior part of the calcarine fissure (\(xyz=22 -56 18, Z=3.86\)).

In contrast with the control group, the experimental group showed large and numerous differences when contrasting brain pre-treatment and post-treatment brain activations. A post-treatment increase in activation was observed in large parts of the sensorimotor network including the supplementary motor area,
bilateral ventral premotor cortex, bilateral superior and inferior parietal areas and bilateral cerebellum (see Table 5a).

Increases, of activity post training were also seen when manipulating complex items with the unaffected hand (see Table 5b). Although these only appeared at a lower threshold ($p < 0.001$ uncorrected), they occurred both at the ipsi- and contralesional hemispheres. Contralesional activations included inferior and superior parietal lobule and cerebellum, whereas ipsilesional activations were found in the ventral premotor cortex and cerebellum.

Table 5a

<table>
<thead>
<tr>
<th>Regions</th>
<th>BA</th>
<th># Voxels</th>
<th>Z score</th>
<th>MNI coordinates</th>
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<tr>
<td>Normal hemisphere</td>
<td>Lingual gyrus $^{46}$/cerebellum $^{45}$.6</td>
<td>27</td>
<td>457</td>
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<td></td>
<td>PCG $^{30}$/rolandic Operc $^{26}$/IFG Operc $^{17}$</td>
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<td>1027</td>
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<td>542</td>
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<td>73</td>
<td>3.98</td>
</tr>
<tr>
<td></td>
<td>Cerebellum $^{9100}$</td>
<td>$-41$</td>
<td>3.89</td>
<td>$14$</td>
</tr>
<tr>
<td></td>
<td>Middle temporal gyrus $^{43}$/superior temporal gyrus $^{46}$</td>
<td>21</td>
<td>100</td>
<td>3.82</td>
</tr>
<tr>
<td></td>
<td>Cerebellum $^{45}$.6/Cerebellum Crus I $^{240}$</td>
<td>$-172$</td>
<td>3.81</td>
<td>$30$</td>
</tr>
<tr>
<td></td>
<td>IFG Operc $^{39}$ Orb $^{39}$/rolandic Operc $^{20}$</td>
<td>38</td>
<td>171</td>
<td>3.6</td>
</tr>
</tbody>
</table>

(b) Main effect explore complex objects post training (control group, affected hand)

Normal hemisphere

<table>
<thead>
<tr>
<th>Regions</th>
<th>BA</th>
<th># Voxels</th>
<th>Z score</th>
<th>MNI coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lingual gyrus $^{46}$/cerebellum $^{45}$.6</td>
<td>77</td>
<td>30</td>
<td>457</td>
<td>4.84</td>
</tr>
</tbody>
</table>

Lesioned hemisphere

<table>
<thead>
<tr>
<th>Regions</th>
<th>BA</th>
<th># Voxels</th>
<th>Z score</th>
<th>MNI coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supramarginal gyrus $^{54}$/STG $^{36}$</td>
<td>48</td>
<td>431</td>
<td>4.88</td>
<td>$54$</td>
</tr>
</tbody>
</table>

Increases in activity post training in the experimental group. Contrast taken when exploring complex objects with the affected hand. Thresholds and abbreviations identical to those described for Table 4.
The most important measure of the effects of therapy was the comparison of treatment-related changes in activation between the experimental and the control groups. The increases in activity when manipulating complex objects with the affected hand were tested to see if they were due to training effects by applying a two-sample $t$-test. First level contrasts of post training $>$ pre training for manipulation of complex objects were entered into a two-sample $t$-test. Table 6 lists the clusters where increase between time points is greater for the experimental group than the control group. Significant increase of activation could be identified in the non-affected hemisphere in the ventral premotor cortex, the SMA, insula and the superior temporal gyrus, and in the affected hemisphere in ventral premotor cortex, the supramarginal gyrus and the superior temporal gyrus (see also Fig. 1).

Discussion

There are two important findings in the present study. First, we could demonstrate that the new rehabilitation program combining action observation with intensive repetitive practice of the observed actions provides a significant improvement of motor functions, and this in chronic stroke patients with a well-established motor impairment of the upper limb. This improvement could be quantified in standard functional motor scales (WMFT, FAT) as well as in the subjective self-assessment of the patients (SIS). Such an improvement could not be observed in the control group of patients, who were similarly engaged in actually executing actions, but were not involved in the action observation treatment. Therefore, action observation in combination with previous training schemes has a significant neurorehabilitative impact beyond that of these schemes alone.

Second, in the same patients a functional activation study using a task containing manual exploration of objects revealed an increase of activation following the rehabilitation treatment in a network of areas (bilateral ventral premotor cortex, bilateral superior temporal gyrus, supplementary motor area (SMA) and contralateral supramarginal gyrus) which build up the action observation/action execution matching system (mirror neuron system). This finding suggests that the improved motor skills in our patients were associated with reactivation of a physiological network of motor areas, where motor representations of trained actions are known to be present.

Basis of the action observation therapy

The major novelty of our rehabilitation program was the combination of the recruitment of motor areas by means of action observation with actual execution of the observed actions (Binkofski et al., 2004; Buccino et al., 2006). This approach has a strong physiological basis in the discovery of the mirror neuron system (Rizzolatti et al., 1996; Gallese et al., 1996; Fadiga et al., 1995; Buccino et al., 2001). It is well known that action observation recruits areas within the mirror neuron system as a function of motor experience and competence of the observed actions. For example, in a recent paper Buccino et al. (2004b) showed that the mirror neuron system is active during the observation of actions (e.g., biting) which are part of the motor repertoire of the observer, but not when the observed actions (e.g., barking) are not motorically represented in the observer's brain. In keeping with this Calvo-Merino et al. (2005) found that capoeira dancers showed stronger activation in the premotor and parietal areas plus in the superior temporal sulcus (STS) region, when observing capoeira movements than when observing classical
ballet movements, while classical ballet dancers showed a stronger activation of the same areas during the observation of classical ballet movements than during the observation of capoeira movements.

Similarly, Haslinger et al. (2005) found that during the observation of piano playing there is a stronger activation of the mirror neuron system in professional pianists than in musically naive controls. Complementary to these findings are those that demonstrate a role of action observation and the mirror neuron system in acquiring new motor skills. For example, observational simple thumb movement can induce a new sensorimotor memory trace (Stefan et al., 2005), even in elderly individuals who appear to have reduced abilities to acquire new motor memory traces (Celnik et al., 2006). Furthermore, the mirror neuron system has been shown to be involved in imitation learning. In an event-related fMRI study, Buccino et al. (2004c) found that in musically naive participants, required to learn some guitar accords following a model, the mirror neuron system was active from the observation of the model till the actual execution of the observed accord. These findings clearly support the notion of a specific role of the mirror neuron system in the acquisition of new motor skills.

In the present study chronic stroke patients were asked to observe everyday life actions (and therefore of high ecological value), of which they had motor competence and experience, but that had to be trained or relearned because of the vascular accident. Both these aspects of the observed actions possibly highly triggered brain areas belonging to the mirror neuron system. The results of the study clearly support a positive effect of action observation therapy, especially because we could a significant additional effect of the present treatment to conventional physiotherapy, since all of our patients were in the chronic stage after stroke and had previously received, on average, more than 100 days of standard physiotherapy. More importantly, in a randomized control group, which performed the same amount of action exercise, but without the action observation component, the therapy effects were much weaker. The direct statistical comparison between the treatment and the control group showed a significant improvement in the treatment group.

The successful implementation of combined observation and imitation of actions into our rehabilitation schema have confirmed previous experiences with motor imagery, where the combination with execution showed additional positive effects (Page et al., 2001).

One might argue that at least part of the improvement in our patients was due to the daily therapeutic intervention and the care given by the therapist. We can clearly discard this argument because the matched control group of patients, which performed the same amount of motor exercise, but without the action observation component, did not show a comparable improvement to the treatment group. The direct statistical comparison between the two groups showed a significant improvement in the treatment group over the control group.

Interestingly, the positive effect of the treatment seems to be sustained over time. This is suggested by the persisting level of improvement measured at the follow-up assessment 8 weeks after the end of the therapy in a subgroup of seven patients. Unfortunately, due to the temporary lack of follow-up results in the control group, this result can only be regarded as a trend. However, due to the fact that the participating patients did not undergo any new neurorehabilitative treatment during this phase, the results can be seen as an evidence for a lasting effect of the present therapy. Further investigations are needed to identify the long term effects of the video-therapy.

Brain plasticity following the action observation therapy

The second major part of the current study was an fMRI-based investigation of reorganization of the motor system related to the treatment. There were three reasons led us to choose object manipulation as independent task: (1) the task was not related to the stimuli and the exercises used in the present rehabilitation schema. (2) The continuous object manipulation has been proven to cause only few movement-related artifacts. (3) The task elicits a robust activation of the sensorimotor system (Binkofski et al., 2004c).
1999; Binkofski and Seitz, 2004). While using this task we could confirm our own previous results that manipulation of complex objects activates a bilateral parieto-premotor network of areas that control for different aspects of this task (Binkofski et al., 1999).

But, far more important was the investigation of the effects of the action observation therapy on brain activations. These effects were found by comparing in the experimental group activations related to object manipulation with the affected hand before entering the study and soon after its end. This contrast showed that the motor improvement in the patients of the experimental group was related to an increased activation in a network of areas consisting of bilateral ventral premotor and inferior parietal areas (supposedly containing the mirror neuron system) plus bilateral superior temporal gyrus, supplementary motor area (SMA) and contralateral supramarginal gyrus (Buccino et al., 2004a; Rizzolatti and Craighero, 2004; Binkofski and Buccino, 2004, 2006). As described above the mirror neuron system (or the human homologue of it) may play an important part in motor learning and recovery of motor function related to action observation.

Previous neuroimaging studies found already an increased activation of the parietal and premotor areas in the course of rehabilitation treatment of motor functions after stroke (Nelles et al., 1999, 2001; Johansen-Berg et al., 2002). Substantial evidence indicates that the premotor cortex plays a crucial role for the recovery of the motor functions in this network (Seitz et al., 1998; Johansen-Berg et al., 2002). Although the task that was used for the current fMRI study was not related to the action observation and action execution stimuli used during the video-therapy, it was suitable to reveal increased activation in the parieto-premotor areas containing the human homologue of the mirror neuron system due to the effect of the therapy. Our data thus support the notion that activation of central representations of actions in the parieto-premotor network might constitute a powerful mechanism for recovery of motor deficits after stroke.

In conclusion, we provide evidence that action observation has a positive effect on rehabilitation of motor deficits after stroke. This effect appears to be superior to standard neurorehabilitative programs and it is lasting for at least 8 weeks after treatment. The positive effect of the therapy is achieved by a combination of observation of everyday purposeful actions and a matched physical practice. The additional component of action observation is leading to a significantly higher impact on rehabilitation than physical training alone. The increased activation of the mirror neuron system as a specialized physiological motor network in the course of this new treatment suggests that this improvement relies on reactivation of motor representations related to the observed actions. We suggest that the application of this observational component of daily activities to current post stroke rehabilitative training therapies should ameliorate the therapeutic effects.

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References


