Brain activation reflects smoothness of upper limb movements after stroke

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Submitted
ABSTRACT

Objective: To test the hypothesis that, in patients with stroke, increased recruitment of secondary sensorimotor areas is associated with disturbed quality of motor control.

Methods: In seventeen patients (three females, fourteen males; age: 59.9 ± 12.6 years), cortical activation levels were determined with functional magnetic resonance imaging (fMRI) in 12 regions of interest while they were performing a finger flexion-extension task. Using 3D kinematics, the quality of motor control was assessed by the smoothness of the grasp aperture during a reach-to-grasp task, quantified by normalized jerk.

Results: Ipsilesional premotor cortex, insula and cerebellum, as well as the contralesional supplementary motor area, insula and cerebellum, correlated significantly and positively with the normalized jerk of grasp aperture at week 5 after stroke.

Interpretation: This study suggests that the involvement of secondary motor areas results in less efficient motor strategies, culminating in jerky or unsmooth movements. It is often assumed that increased jerkiness reflects an online correction of movement errors based on the reliance on proprioceptive feedback mechanisms rather than the online feedforward control normally used while reaching. This assumption is supported by the increased activation of the cerebellum, which is known to play a major role in processing proprioceptive feedback information. Recruitment of additional sensorimotor areas therefore seems to reflect the quality of motor control after stroke. These results suggest that therapeutic interventions aimed at maximizing recovery of the primary motor system in the first 5 weeks after stroke might have beneficial effects on the quality of upper limb motor control.
INTRODUCTION

Stroke is a leading cause of disability. However, outcomes of neurorehabilitation after stroke are variable and depend largely on the intensity and task-specificity of the intervention applied.\textsuperscript{1} For the paretic upper limb in particular, meaningful treatment effects are mainly restricted to those patients with some voluntary control of finger extension after stroke.\textsuperscript{1,2} These findings suggest that there is a need for a better understanding of the underlying mechanisms of functional recovery after stroke.

Task-related recruitment of secondary sensorimotor areas in the affected and non-affected hemisphere lasting longer than 3 months after stroke has been associated with poor motor recovery in terms of body functions and activities.\textsuperscript{3-5} In fact, a predominant negative association may exist between the volume of recruited areas in functional magnetic resonance imaging (fMRI) and motor function.\textsuperscript{6,7} It is therefore unlikely that secondary motor areas are able to fully replace the actions of the primary motor system.\textsuperscript{3,7} Recruitment of these additional areas may rather reflect support in the execution of compensatory motor control while performing a motor task with the paretic upper limb.

However, it is still unclear how brain activation patterns may be associated with quality of upper limb motor control after stroke.\textsuperscript{6} Most traditional clinical assessment scales are not suitable for capturing how patients perform functional tasks, and these scales therefore provide little insight into quality of motor control. By contrast, 3D kinematics can assess intralimb coordination as well as smoothness of movement patterns, which are important characteristics of quality of motor control.

A recent study with intensively repeated 3D kinematic measurements in the first 6 months after stroke suggested that patients gradually regain some control over the shoulder and elbow during a functional reaching task as a function of time post stroke.\textsuperscript{8} As a consequence, the ability to plan movements in advance (i.e. feedforward motor control) may improve, thereby decreasing the need for continuous online corrections based on proprioceptive feedback mechanisms.\textsuperscript{9,10} Such corrections based on afferent information have been shown to negatively affect the smoothness of hand and finger movements.\textsuperscript{10}
We have recently shown that jerk decreases (i.e. smoothness increases) substantially in the first 8 weeks after stroke,\textsuperscript{11} suggesting that jerkiness is a sensitive measure to investigate longitudinal change in quality of motor control in patients with stroke. However, due to a lack of studies combining imaging techniques with kinematic analyses, the neurological mechanisms underlying the recovery of smoothness of upper limb movements are still largely unknown.

In the present study we hypothesized that elevated recruitment of secondary sensorimotor areas would be linked to jerky movements. This hypothesis was tested by investigating the association between smoothness of finger movements during a reach-to-grasp task, measured with 3D kinematics, and activation levels in the sensorimotor network during a finger extension motor task, measured with fMRI.\textsuperscript{3} We tested this association at 5 weeks and 26 weeks after stroke, to assess whether the association between brain activation and smoothness changes with time after stroke.\textsuperscript{3,12}

PATIENTS AND METHODS

Patients

Seventeen patients (three females and fourteen males) with acute stroke were included in this study. Patients had a mean age of 59.9 years (SD = 12.6 years) and were included if they (1) had had their first ever ischemic stroke and had suffered from mono- or hemiparesis of the hand at the time of their stroke; (2) were between 18 and 80 years old; (3) were able to understand instructions as indicated by a Mini Mental State Examination (MMSE) score of 23 or higher\textsuperscript{13}; (4) gave written consent to participate in the study. Exclusion criteria were (1) not being able to make flexion-extension movements with the fingers or reach-to-grasp movements with the paretic upper limb; (2) pacemakers or other metallic implants incompatible with the 3T MRI scanner; (3) orthopaedic impairments of the upper extremities; (4) communication restrictions as indicated by a score of 3 or less on the Utrecht Communication Observation (UCO)\textsuperscript{14}; (5) botulinum toxin injections or other medication influencing the function of the upper limb. The seventeen patients were recruited within the EXPLICIT stroke programme from the University Medical Center Utrecht (UMCU),
Brain activation patterns after stroke

Leiden University Medical Center (LUMC), Meander Medical Centre Amersfoort, Diakonessenhuis Utrecht, Diakonessenhuis Zeist and Rijnland Hospital Leiden, all in the Netherlands. All patients followed a rehabilitation programme including practicing the upper limb.

In line with the EXPLICIT-stroke programme, patients were stratified according to the ability to perform some finger extension within 1 week after stroke. Patients with an unfavourable prognosis based on finger extension were stratified into a group that received either electromyography-triggered neuro-muscular stimulation (EMG-NMS) or usual care (N = 5), while patients with a favourable prognosis received modified constraint-induced movement therapy (mCIMT) or usual care (N = 12) in the first 3 weeks after stroke. Handedness was established with the Edinburgh Handedness Inventory. All patients included in the present study participated in two fMRI and two 3D kinematic measurements, performed at weeks 5 and 26 after stroke. To avoid effects of fatigue, measurements were performed on separate days within the same week. Clinical characteristics of the patients included are described in Table 6.1. Informed consent was obtained according to the declaration of Helsinki and the study protocol was approved by the local ethics committee.

Clinical assessments

Motor function of the affected arm of each patient was assessed at 5 and 26 weeks after stroke using the upper limb section of the Fugl-Meyer Motor Assessment (FMA), the Action Research Arm Test (ARAT) and the nine-hole peg test (NHPT). The FMA is based on the concept of sequential stages of motor recovery and it tests reflexes, basic limb synergies of the paretic upper limb and hand function. Each item is scored on an ordinal 3-point scale to obtain a motor score for the affected side, with a total score ranging from 0 to 66. The ARAT is a clinical test of arm motor function. Upper limb movements, in terms of pinch, grasp, grip and gross movements, are performed and scored on a 4-point scale, with a total score ranging from 0 to 57. The NHPT measures dexterity of the hand, focusing on fine motor function. Pegs are inserted and removed from a nine hole peg-board, with scores based on the time (in seconds) taken to complete the test, calculated as a percentage of healthy sample norms.
Chapter 6

Functional MRI

Data acquisition

Images were acquired with two Philips Achieva 3.0 Tesla MR scanners (Philips, Eindhoven, Netherlands), located at UMCU and LUMC. Patients recruited from hospitals near Utrecht (N = 9) were measured with the scanner at UMCU, and patients recruited near Leiden were measured with the LUMC scanner (N = 8). High-resolution whole brain anatomical scans were acquired for all subjects for anatomical reference (3D T1-weighted scan: TR = 9.717 ms; TE = 4.59 ms, flip angle = 8 degrees, 140 slices, 0.875 × 0.857 × 1.2 mm, FOV = 224 × 168 × 177). During the motor task, 384 fMRI PRESTO scans were acquired (flip angle = 10 degrees, FOV = 224 × 256 × 160 mm, voxel size 4 × 4 × 4 mm, TE/TR = 33/23 ms, time per whole-brain volume 0.63 s). To check for mirror movements, EMG was applied to the hand opposite the moving hand, over the musculus extensor digitorum communis and musculus abductor pollicis brevis, with four scanner-compatible surface electrodes (MR Physiology Logging, Philips Medical Systems B.V., Eindhoven, The Netherlands).

Motor paradigm

Patients were asked to perform a motor task in the MRI scanner, consisting of paced flexion and extension of the affected hand at 1 Hz (alternating 30 seconds of movement and 30 seconds of rest for a period of 4 minutes). Before fMRI scanning, subjects were trained to perform active extension movements with their fingers. During scanning, patients used a plastic wrist-hand orthosis, which guaranteed correct movement in the flexion–extension direction, while fixating the wrist and ensuring extension of the fingers. Both arms rested comfortably in a supine position supported by cushions alongside the patient’s hips, with the elbows slightly bent in a comfortable position.

Data pre-processing fMRI

Functional MRI data were analysed with statistical Parametric Mapping (SPM5) software (http://www.fil.ion.ucl.ac.uk/spm/) running on a mathematical platform (Matlab 11.1; The Mathworks Inc, MathWorks, Natick, Massachusetts). All functional images of each participant were realigned to the first functional scan of each session.
After realignment, all images were co-registered to the T1-weighted anatomical scan. Subsequently, images were transformed to standard Montreal Neurologic Institute (MNI) space, and smoothed using a Gaussian kernel with a 8 mm full width at half maximum, while also keeping the non-smoothed data. The task box-car function was convolved with the canonical hemodynamic response function, and the resulting model was estimated in combination with a high-pass filter with a cut-off at 128 seconds to remove low-frequency artefacts. In the first-level analysis, contrast maps were calculated representing periods of motor activity versus rest for each patient and each session separately. Contrast images from twelve patients with right-sided lesions were flipped across the mid-sagittal plane, so that the affected hemisphere corresponded to the left side of the brain for all patients.

ROI data analysis
A region of interest (ROI) based comparison was performed using the unsmoothed data. An automatic segmentation procedure (Freesurfer ASEG) was applied using the individual anatomical images of each subject to delineate the cortical areas. From the automatic segmentation the motor segments were selected which included the bilateral precentral and postcentral gyrus, supplementary motor area, premotor cortex, cerebellum and insula. All the motor segments were visually inspected to ensure correct segmentation for each subject. As shown in Figure 6.1, all selected motor segments were unaffected by the lesions, which were mainly subcortical or in some cases included other cortical areas. The volumes containing the motor segments were normalized to MNI space using the previously estimated normalization parameters. Activation levels within ROIs were established by taking the 15% most active voxels (i.e. the highest mean beta values within a segment) during the motor task in each anatomical motor segment (supplementary motor area, premotor cortex, precentral gyrus and postcentral gyrus, insula and cerebellum). A proportional rather than an absolute threshold was used in the ROI definition to account for between-subject differences in the volume of activation. Blood oxygen level dependent (BOLD) signal changes per ROI were represented by the mean beta value during each task.
Figure 6.1 Axial structural T1-weighted MRI scans at the level of maximum infarct volume for each patient, obtained at the time of the second fMRI session at 6 months after stroke.

**EMG analysis**

The EMG data were analyzed as described by Van Rootselaar and colleagues. During each fMRI session, the EMG signal was recorded using electrodes attached to the extensors and flexors of the hand contralateral to the moving hand. The EMG data were analysed in Matlab (2011a). First, the EMG signal was notch filtered at 45 and 90 Hz to remove fMRI artefacts induced by the gradient magnets, and high-pass filtered at 10 Hz to remove movement artefacts. The signal was rectified to regain low-frequency components. Data were then band-pass filtered between 2 and 130 Hz and a correlation coefficient was calculated for the envelope of the signal time series and the task as a boxcar function. Subjects were asked to perform maximal voluntary contraction (MVC) during extension of the fingers before every task in the scanner. The corresponding EMG signal over that time was averaged and used
as a norm value for average %MVC during movement blocks. Average %MVC was calculated by dividing the average EMG signal during the task by the average MVC and multiplying this by 100%. A score for the presence of mirror movements was calculated from the correlation coefficient of the envelope of the EMG signal and the task boxcar, multiplied by the value for %MVC. This score was correlated with the average beta for each ROI.

**Kinematic data collection**

*Data-acquisition*

3D kinematic data were collected using a portable electromagnetic motion tracking device (Polhemus Liberty, Polhemus, Vermont). The electro-magnetic source was placed at the edge of the table next to the participant at the side of paresis. This source created the magnetic field required for the kinematic tracking of the electromagnetic sensors that were attached to the patient’s paretic upper limb. According to the EXPLICIT-stroke protocol, sensors were attached to the trunk, scapula, upper arm, forearm, hand and fingers of the paretic upper limb. This study focused on the data obtained from the finger sensors. The sampling frequency during the motion recordings was 240 Hz. Before each measurement, a pointer device (ST8, Polhemus Liberty, Polhemus, Vermont) was used to locate the tips of the thumb and index finger relative to their associated finger sensors.

Measurements were conducted at the site where patients resided. A previous study showed that data could be accurately and reliably recorded within a distance of 60 cm from the magnetic source and in a wide range of measurement environments, including a motion laboratory, treatment room or home situation.

**Reaching task**

While seated at a table with a height of 76 cm, participants performed a functional reaching task with the paretic arm. This task consisted of two parts: (1) a reach-to-grasp movement towards a block, followed by (2) a displacement of the block toward a target location. The reach-to-grasp movement started with the hand in front of the shoulder on the edge of the table, keeping the thumb against the index finger. Participants were asked to grasp and displace a 5×5×5 cm cubic block weighing 150
g, after the experimenter gave a verbal ‘GO’ signal. The block was placed in front of the shoulder at each participant’s individual maximum reaching distance of the non-paretic arm.

The reach-to-grasp movement ended successfully when the block had been grasped and had lost contact with the table. Immediately after this block lift, the reach-to-grasp movement was followed by the second part of the task, during which the block had to be displaced toward a target position located at the contralateral side. The displacement of the block served to increase the ecological validity of the paradigm, since we regard grasping a block without a subsequent action as meaningless and therefore non-functional. Participants were instructed to grasp the block between their thumb and index finger and not to slide their hand over the table but to move it through the air. After the ‘GO’ signal, participants were allowed to move their trunk away from the back of the chair if this was more comfortable, but they had to remain seated and were not allowed to slide or twist over the seat of the chair. Seven trials were recorded in each measurement. Details of the kinematic data acquisition and reach-to-grasp paradigm have been published elsewhere.24

Data-analysis
The analysis focused on the first part of the experimental paradigm, the reach-to-grasp movement. The start of reach-to-grasp was defined as the moment at which the forearm sensor exceeded 5% of the maximum speed during the forward reach. The end of reach-to-grasp was defined as the moment at which the displacement of the block started. The end of reach-to-grasp was therefore defined as the moment at which the forearm sensor exceeded 5% of the maximum speed during the displacement of the block. The time-series for grip aperture were calculated from the start to the end of reach-to-grasp, and were filtered with a second-order Butterworth low-pass filter with a cut-off frequency of 20 Hz. All kinematic data processing was performed using custom-made algorithms in Matlab version R2006a.

The smoothness of grasp movement was quantified by the normalized jerk. Normalized jerk of grasp aperture \( \text{NJ}_{\text{grasp}} \) was calculated for each trial. \( \text{NJ}_{\text{grasp}} \) represents the smoothness of the grasp aperture signal and is defined as the amount of jerk \( (i.e. \text{change in acceleration}) \) in the grasp aperture signal, normalized for
movement duration and block size. Details of the kinematic data analysis have been published elsewhere.\textsuperscript{11}

**Statistics**

*Clinical assessments*

The change in the ARAT, FMA and %NHPT between week 5 and week 26 was assessed using two-sided paired-samples t-tests (p < 0.05).

**fMRI**

Differences in the activation in the ROIs between weeks 5 and 26 were tested with a general linear model (repeated measures analysis of variance [ANOVA]), with ROI (12 levels) and time of measurement (2 levels) as within-subject factors. In addition to the ROI-based analysis, a voxelwise analysis was performed to test for possible differences outside the predefined ROIs. Voxelwise differences in the activation maps between weeks 5 and 26 were estimated with a paired samples t-test in SPM5. The resulting statistical maps were thresholded at p < 0.05 (family-wise error (FWE)-corrected).

**Kinematics**

To check whether \(\text{NJ}_{\text{grasp}}\) was normally distributed, we plotted the frequency distribution of the clinical data and \(\text{NJ}_{\text{grasp}}\) and compared these plots visually with a normal distribution. The change in \(\text{NJ}_{\text{grasp}}\) between weeks 5 and 26 after stroke was assessed using a paired t-test (two-sided, p < 0.05).

**Relation between activation in ROIs and Normalized Jerk of grasp aperture**

Repeated measures ANOVAs in SPSS (version 20.0, IBM Corporation, New York) were conducted to investigate how the activation levels in the 12 ROIs at weeks 5 and 26 after stroke interacted with \(\text{NJ}_{\text{grasp}}\) at weeks 5 and 26. In each ANOVA, activation levels in the 12 ROIs at week 5 or 26 were taken as the within-subject factor, whereas \(\text{NJ}_{\text{grasp}}\) at week 5 or 26 was taken as a between-subject covariate. The interaction between activation in the ROIs and \(\text{NJ}_{\text{grasp}}\) specified whether activation in the ROIs was related to \(\text{NJ}_{\text{grasp}}\). Mauchly’s test of sphericity was used to check whether the variances of
the activation levels across the 12 ROIs were equal (i.e. assumption of sphericity). The significance levels were corrected using Greenhouse-Geisser correction when Mauchly’s test of sphericity was significant (p < 0.05). The significance of the interaction between activation in the ROIs and NJgrasp was assessed using a Bonferroni correction to correct for multiple testing. This correction resulted in a significance level of p < 0.05/4 = 0.01. In case of a significant interaction between activation levels and NJgrasp, separate Pearson correlation coefficients were calculated between each ROI and NJgrasp. The significance level for the post-hoc correlation tests was set conservatively at p < 0.01 (two-sided) in order to avoid a type I error as a result of multiple testing.

RESULTS

Clinical data
Seventeen patients were included in this study. Table 6.1 shows their characteristics. Patients improved significantly from week 5 to week 26 as assessed with the FMA (t = -2.911, p = 0.010), ARAT (t = -2.748, p = 0.014) and %NHPT (t = -6.044, p < 0.001). The site of cerebral infarction was determined from the structural MR images, which are shown in Figure 6.1. Thirteen patients had subcortical infarctions in the capsular region, whereas in two patients the infarction extended into the cortex. Two patients had pontine ischemic infarctions. No infarcts included the primary motor cortex (Brodmann area 4). The average (± SD) time post stroke at which the first MRI measurement took place was 6.4 ± 2.1 weeks, and 5.9 ± 1.1 weeks for the kinematic assessment. The second session took place at 29.4 ± 4.7 weeks after stroke for fMRI and 28.8 ± 1.2 weeks for kinematic assessment.
### Table 6.1 Patient characteristics

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**Total/Averages**

|          | **59.9±12.6** | **3 F/14 M** | **1L/16R** | **5L/12R** | **2P/2C/13SC** | **55.0±6.6** | **41.20±14.5** | **51.4±8.7** | **32.5±30.0** | **62.8±21.3** |

Abbreviations: M Male, F Female, Hand Handedness, R right, L left, Hem lesional hemisphere, P pontine, C extending to cortex, SC subcortical.

*NHPT results are given as percentage of norm scores (corrected for age and handedness).*
Imaging results

As shown in Figure 6.2, ROI analysis for cerebellum, supplementary motor area, premotor cortex, precentral cortex, postcentral cortex and insula did not show statistically significant differences in activation levels between week 5 and week 26 (F = 0.699, p = 0.415). We then checked if this lack in significant results could be caused by variations in the quantity of mirror movements between sessions. However, there was no effect of mirror movements as assessed with EMG on brain activity, since all correlations between EMG score and ROI activation were not significant (p > 0.01) for subjects with successful EMG measurements (week 5, N = 13 and week 26, N = 9).

![Activation levels](image)

**Figure 6.2** Mean results for task-related activity for the affected hand at weeks 5 and 26 after stroke. Mean beta values ±1 SE in the cerebellum, premotor area (PM), supplementary motor area (SMA), postcentral gyrus, precentral gyrus and insula for the left (affected) and right (unaffected) hemispheres (LH and RH, respectively). Patients’ T-maps were flipped so the affected hand was always the right hand.

As shown in Figure 6.3, the analysis of the main effect of the flexion-extension task (flexion-extension compared with rest) revealed activation in a broad network of motor areas during both sessions. Voxelwise comparisons between the sessions at 5 and 26 weeks did not reveal any significant increase or decrease in activation.
Brain activation patterns after stroke

Figure 6.3 Group fMRI BOLD activity for flexion-extension motor task with the affected hand (right hand) for week 5 (left) and week 26 (right). T threshold = 6.

Kinematics
Visual inspection of frequency distributions revealed that $\text{NJ}_\text{grasp}$ values were not normally distributed and therefore the data were log-transformed to meet assumptions of normality in subsequent statistical analyses. The mean $\log(\text{NJ}_\text{grasp})$ values were 4.00 (SD = 0.57) and 3.65 (SD = 0.24) in week 5 and week 26, respectively. A paired t-test showed a significant decrease in $\log(\text{NJ}_\text{grasp})$ between weeks 5 and 26 after stroke ($t = 3.3, p = 0.004$, see Figure 6.4 for a typically performing patient).

Figure 6.4 Grasp aperture between the thumb and index finger during the reach-to-grasp movement for one patient with stroke at weeks 5 and 26 after stroke. Each line represents one repetition.
Correlations between brain activation and jerk

Using repeated measures ANOVA, we assessed whether the activity across the 12 ROIs interacted with \( NJ_{\text{grasp}} \). Table 6.2 shows F-values and significance levels of the interaction between task-related activity in the ROIs and \( NJ_{\text{grasp}} \) for each of four analyses (all combinations of the 2 measures and 2 time-points). For none of the ANOVAs could equal variances be assumed (\( p < 0.05 \)) based on Mauchly’s test of sphericity. Therefore, significance levels were corrected using the Greenhouse-Geisser epsilon correction. Table 6.2 shows that task-related activation in the various ROIs at week 5 after stroke significantly interacted with smoothness of grasp aperture at week 5 after stroke. Results from the other three ANOVAs were not significant after Bonferroni correction. Post-hoc Pearson correlations showed that increased activation in the ipsilesional premotor cortex, insula and cerebellum and the contralesional supplementary motor area, insula and cerebellum was significantly (\( p < 0.01 \)) and positively associated with \( NJ_{\text{grasp}} \) at week 5, which is shown in Table 6.3. The significant correlation coefficients between activation in ROIs and \( NJ_{\text{grasp}} \) are also shown by the scatterplots in Figure 6.5. No significant correlations were found between the activation levels in the ROIs and the FMA at week 5.

Table 6.2 F-values and significance levels for each combination of activation levels and \( NJ_{\text{grasp}} \) at weeks 5 and 26 after stroke.

<table>
<thead>
<tr>
<th></th>
<th>Beta week5</th>
<th>Beta week26</th>
</tr>
</thead>
<tbody>
<tr>
<td>( NJ_{\text{grasp}} ) week5</td>
<td>( F = 5.287, p = 0.002 ) *</td>
<td>( F = 1.914, p = 0.099 )</td>
</tr>
<tr>
<td>( NJ_{\text{grasp}} ) week26</td>
<td>( F = 3.209, p = 0.021 )</td>
<td>( F = 2.669, p = 0.029 )</td>
</tr>
</tbody>
</table>

* \( p < 0.01 \)
Figure 6.5 Scatterplots with regression line of significant correlations between beta values of individual ROIs and NJgrasp.
Table 6.3 Post-hoc Pearson correlation coefficients and significance levels between each ROI and $NJ_{\text{grasp}}$ at week 5 after stroke. In italics for illustration purposes the bivariate correlation coefficients with activation levels in each ROI and the FMA.

<table>
<thead>
<tr>
<th>ROI</th>
<th>$NJ_{\text{grasp}}$</th>
<th>FMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsi premotor cortex</td>
<td>$R = 0.776, p &lt; 0.001^{**}$;</td>
<td>$R = -0.336, p = 0.188$</td>
</tr>
<tr>
<td>Ipsi supplementary motor area</td>
<td>$R = 0.316, p = 0.216$;</td>
<td>$R = -0.290, p = 0.259$</td>
</tr>
<tr>
<td>Ipsi postcentral gyrus</td>
<td>$R = -0.106, p = 0.685$;</td>
<td>$R = 0.069, p = 0.793$</td>
</tr>
<tr>
<td>Ipsi precentral gyrus</td>
<td>$R = -0.019, p = 0.943$;</td>
<td>$R = -0.125, p = 0.634$</td>
</tr>
<tr>
<td>Ipsi insula</td>
<td>$R = 0.778, p &lt; 0.001^{**}$;</td>
<td>$R = -0.340, p = 0.182$</td>
</tr>
<tr>
<td>Ipsi cerebellum</td>
<td>$R = 0.832, p &lt; 0.001^{**}$;</td>
<td>$R = -0.310, p = 0.225$</td>
</tr>
<tr>
<td>Contra premotor cortex</td>
<td>$R = 0.380, p = 0.133$;</td>
<td>$R = -0.275, p = 0.285$</td>
</tr>
<tr>
<td>Contra supplementary motor area</td>
<td>$R = 0.665, p = 0.005^{*}$;</td>
<td>$R = -0.458, p = 0.065$</td>
</tr>
<tr>
<td>Contra postcentral gyrus</td>
<td>$R = 0.373, p = 0.140$;</td>
<td>$R = -0.468, p = 0.058$</td>
</tr>
<tr>
<td>Contra precentral gyrus</td>
<td>$R = 0.486, p = 0.048$;</td>
<td>$R = -0.513, p = 0.035$</td>
</tr>
<tr>
<td>Contra insula</td>
<td>$R = 0.617, p = 0.008^{*}$;</td>
<td>$R = -0.439, p = 0.078$</td>
</tr>
<tr>
<td>Contra cerebellum</td>
<td>$R = 0.639, p = 0.006^{*}$;</td>
<td>$R = 0.013, p = 0.962$</td>
</tr>
</tbody>
</table>

* $p < 0.01$ ** $p < 0.001$

DISCUSSION

The present study addressed the hypothesis that jerky movements after stroke are associated with recruitment of non-primary sensorimotor brain regions. To test this hypothesis we assessed the relationship between fMRI brain activation patterns and 3D kinematic measures of quality of motor control. We assessed the impact of time post stroke on this relationship by testing patients at 5 and 26 weeks after stroke. The key finding was that jerkiness correlated highly and positively with levels of brain activity in the ipsilesional premotor cortex, insula and cerebellum and the contralesional supplementary motor area, insula and cerebellum at week 5. Correlation coefficients between activation levels and the FMA were not significant, suggesting that kinematic measures may be a more sensitive measure of motor function than clinical assessment scales.

Regarding effect of time, patients improved significantly on the clinical assessment scales including the ARAT (10 points), FMA (7 points) and %NHPT (30%) from week 5 to week 26. The improvements exceeded the minimal clinically important differences of 5.7 points, 6.6 points and 10% reported for the ARAT, FMA and %NHPT, respectively, reflecting clinically relevant improvements between the two sessions.
In addition, quality of grasping control improved as suggested by a significant decrease of jerkiness of grasp aperture between weeks 5 and 26 after stroke. However, no significant change in brain activation patterns was observed during flexion-extension of the paretic hand, neither with whole-brain analyses nor with ROI analysis. In addition, the significant association between brain activation levels and smoothness was absent in week 26 after stroke. However, this absence could merely be the result of the Bonferroni correction we used to correct for multiple testing. A trend towards an association between brain activation and smoothness was still present at 26 weeks (p = 0.029), and a clear effect of time after stroke could therefore not be discerned.

Previous studies have already shown that activity in the contralesional hemisphere early after stroke is associated with poor performance on clinical assessment scales.\textsuperscript{3,7} The present study extends on this finding suggesting that recruited secondary sensorimotor areas are associated with disrupted quality of motor control as reflected by jerky grasping movements. The mechanisms underlying disruptions of smoothness are, however, poorly understood. One may hypothesize that the reduced selectivity in recruiting the appropriate set of motor units after corticospinal damage causes patients to experience more difficulties in planning and selecting the optimal ballistic movement strategy during the performance of functional tasks.\textsuperscript{9} As a result, patients with stroke might rely more on proprioceptive feedback information to correct for small movement errors during the movement. These error corrections are kinematically reflected as discontinuities in the acceleration signal, i.e. as jerky movements,\textsuperscript{26} which diminish as a function of time early post stroke.\textsuperscript{11} Therefore, the present study suggests that increased activation in secondary motor areas early after stroke is associated with an increase in feedback control, rather than a ‘vicariation of function’ \textsuperscript{27} whereby disrupted feedforward motor control after stroke may be restored.

The role of the cerebellum in feedback motor control is widely acknowledged in the literature. In healthy subjects, ipsilateral and contralateral cerebellar activity have been found to be involved in closed-loop control during goal-directed upper limb movements, based on afferent proprioceptive input and an internal copy of outgoing motor commands, \textit{i.e.} efference-copy.\textsuperscript{28}
The premotor cortex is assumed to be an important brain region during the early stage of motor learning, when motor tasks cannot be automatically controlled.\textsuperscript{29} It has been hypothesized that, early after stroke, the premotor cortex contributes to motor learning processes by which patients learn compensatory motor control strategies.\textsuperscript{29} This hypothesis is supported by the present study, suggesting that the ipsilesional premotor cortex may be involved in feedback motor control to compensate for disrupted feedforward motor control. However, several studies have shown that activity in the premotor cortex increases during reaching movements towards larger targets.\textsuperscript{30,31} Since the reliance on feedback control is assumed to decrease as a function of increasing target size, this finding contradicts our suggestion that the premotor cortex is associated with feedback control. Therefore, the exact role of the premotor cortex in feedback and feedforward motor control remains to be elucidated.

Disrupted activity in the supplementary motor area may underlie hand motor disability after stroke.\textsuperscript{32} In addition, the supplementary motor area is often associated with movement planning, since this area has been shown to be active prior to movement initiation.\textsuperscript{33} Our finding that activity in the supplementary motor area is associated with smoothness of upper limb movements after stroke suggests that the supplementary motor area is recruited to satisfy the higher demands on movement planning during complex tasks after stroke.\textsuperscript{31}

Finally, the insula is associated with a wide range of functions, including motor control,\textsuperscript{34} cognition,\textsuperscript{35} and emotion.\textsuperscript{36} During motor tasks, the activity in the insula seems to depend on the effort with which a task is executed.\textsuperscript{34} Therefore, the observed association between bilateral activity in the insular cortex and smoothness during reach-to-grasp might reflect the increased effort with which the task is executed, especially in more severely affected patients who rely more on feedback motor control.

The apparent inability of secondary sensorimotor areas to restore disrupted feedforward motor control has important implications for neurorehabilitation. The association between jerkiness and brain activation patterns at week 5 after stroke suggests that neurorehabilitation interventions may be more effective if they aim at normalizing the smoothness of upper limb movements, particularly early after...
stroke, to achieve true neurological recovery, i.e. the restoration of activity in the primary motor system in the ipsilesional hemisphere.\textsuperscript{37} Promising findings of rTMS on upper limb 3D kinematics have been found,\textsuperscript{38} however, randomized controlled trials (RCTs) of therapies that are specifically aimed at restoring body functions and quality of motor control early after stroke are currently lacking in the literature. Future RCTs, such as EXPLICIT-stroke, should therefore establish whether impairment-focused therapies starting at an early stage and emphasizing restoration of body functions are indeed able to induce restoration of cortical activation patterns.\textsuperscript{15,39}

While our findings may improve our understanding of neural recovery after stroke, they should be considered in the context of the following limitations. First, the design of the present study required that patients were able to perform flexion-extension movements of the fingers of the paretic upper limb during the fMRI scans and to perform functional reaching tasks during the 3D kinematic measurements. Hence, the present results cannot be generalized to patients with a severe paresis of the upper limb. Second, the flexion-extension task that was administered in the scanner differed from the reaching task during the 3D kinematic measurements. However, we argue that there is still sufficient overlap between both paradigms, since both motor paradigms require flexion-extension of the fingers. For the fMRI measurements the finger flexion-extension task was selected since the ability to extend the fingers is the most important clinical predictor of the outcome of dexterity after stroke.\textsuperscript{2,40} The grasping movement during the 3D kinematic measurements closely resembles this flexion-extension movement in a functional task. However, patients were able to rely on visual feedback during the 3D kinematic measurements, whereas this was not possible during fMRI scanning. Therefore, the present study could not control for the effect of visual feedback on cortical activation patterns. Third, given the high number of patients with a right hemispheric lesion (N = 12) compared to patients with a left-sided lesion (N = 5), possible effects of lesion side on the correlation between brain activation levels and smoothness could not be investigated. Larger studies are needed to investigate the possible effect of hemisphere-specific motor control mechanisms after stroke. Finally, the fMRI scans and 3D kinematic assessments were performed at fixed, somewhat arbitrary moments during the pattern of recovery after stroke (i.e. week 5 and week 26), with less than one week between 3D kinematic and fMRI
measurements. Earlier fMRI scanning was impossible since patients were required to show sufficient finger extension to perform the motor paradigm. However, the moment of 5 weeks after stroke was well within the critical time window of 10 weeks after stroke in which most spontaneous neurological recovery is observed. Ideally, future studies may use more than two measurements, in order to improve our understanding of the brain activation dynamics during the logistic recovery pattern early after stroke.

In conclusion, we have shown that jerkingness of movement after stroke involving the CST is correlated with elevated activity in secondary sensorimotor regions. We argue that the jerky movements, together with overactivated secondary regions, may be the result of an increased reliance on proprioceptive feedback mechanisms instead of relying on feedforward motor control. The finding could be taken to imply that neurorehabilitation interventions would benefit from focusing on normalizing the smoothness of movements of the paretic upper limb. Future studies could further extend the findings by determining correlations between brain activation patterns and quality of motor control, starting at an earlier time point after stroke and following up with intensively repeated measurements to capture the changes in these correlations as a function of time after stroke.
REFERENCES


