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EFFECTS OF PASSIVE-ACTIVE MOVEMENT TRAINING ON UPPER LIMB MOTOR FUNCTION AND CORTICAL ACTIVATION IN CHRONIC PATIENTS WITH STROKE: A PILOT STUDY

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Objective: **To explore how repetitive passive-active movement training effects upper limb motor function and cortical activation in patients with stroke.**

Design: **Single-group treatment trial with baseline comparisons.**

Patients: **Ten chronic patients with stroke with paresis of the upper limb.**

Methods: **Assessments were performed during a 4-week baseline period before and once after 4 weeks of training using the Motor Assessment Scale of the upper limb, Nine Hole Peg Test, goniometer for range of movement and the modified Ashworth scale for muscle tone. Two patients underwent functional magnetic resonance imaging pre- and post-training. The treatment consisted of daily sessions of repeated functional reaching and grasping movements guided passively and attempted actively during 4 weeks.**

Results: **The group improved in range of motion and Motor Assessment Scale scores. Subjects reported improvements in a variety of daily tasks requiring the use of the affected upper limb. Increases in cortical activation in prefrontal and sensorimotor areas were observed in parallel with improvements of upper limb motor function in the 2 patients scanned.**

Conclusion: **The 4-week training programme improved hand motor function and ability. Cortical activation on functional magnetic resonance imaging changed in parallel suggesting reorganization of areas related to movements of the paretic limb.**

Key words: stroke, upper limb, motor function, movement training, fMRI, cortical reorganization.

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INTRODUCTION

Stroke is a major cause of disability, with up to two-thirds of stroke survivors experiencing impaired function in the paretic arm (1). Impaired upper extremity function limits goal-oriented activities, independence in every day living and work capacity and thus is a major challenge in rehabilitation after stroke.

Most recovery occurs within 3–6 months post-stroke (2). Spontaneous recovery mechanisms, such as resolution of brain oedema and recovery of brain function in areas which were ischaemic but not destroyed, are thought to be the primary cause of recovery in the post-acute phase. However, cortical reorganization is also considered a potential basis for functional recovery both early and late after stroke (3). Proposed mechanisms include the unmasking of existing inactive connections, growth of new connections, long-term potentiation and axonal regeneration (3, 4). Longitudinal neuroimaging studies after brain lesion have demonstrated reorganization of the motor system during recovery (5). Training interventions post-stroke have also been shown to induce changes in cortical sensorimotor maps and improvements in motor function. (6–8).

A variety of therapeutic approaches are used in rehabilitation of patients with stroke, although the evidence basis of these interventions is weak and a physiological model of their effect is often lacking (1). Yet, better outcome has been shown in patients managed in stroke units with a multidisciplinary staff where they are mobilized early (2, 9). Positive effects in the post-acute phase (i.e. from 3 weeks to 6 months) have been reported with intense functional exercises for the arm (10) and training of movement components involved in functional tasks (11). Training regimens with focus on bilateral use of upper limbs seem to be beneficial in both the post-acute and chronic phases (12, 13). Also, improved motor function in patients with chronic stroke after an intensive 2-week constraint-induced movement training (CIMT) programme (14) has been reported. In general, movement training needs to be intense and highly repetitive and the movement patterns trained should be functionally relevant (15). However, the training tasks used in these previous studies require a certain level of intact upper limb motor function. The use of passive movements in patients with lower levels of residual function after stroke has not been previously studied.

Sensory information is regarded as crucial in motor learning and recovery post-stroke (16) and retained sensory function is considered a positive prognostic indicator of motor functional outcome. Conflicting results exist with regards to the effects of superficial sensory stimulation in the rehabilitation post-stroke (17, 18). However, studies in healthy subjects and patients with stroke have demonstrated that proprioceptive inflow can lead to

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Table I. *Demographics and pathology of 10 patients with stroke*

Patient/ sex	Age (years)	Lesion type and topography
1/M	58	Cerebral haemorrhage in left BG region
2/M	63	Cerebral haemorrhage deep in left hemisphere
3/M	57	Multiple small bilateral cerebral infarcts in MCA region
4/M	55	Cerebral infarct in left BG region and IC
5/F	56	Large cerebral infarct in right MCA region
6/M	56	Cerebral haemorrhage in right BG and posterior IC
7/F	54	Cerebral infarct in right MCA region
8/M	61	Cerebral infarct in right MCA region
9/M	58	Multiple small cerebral infarcts in right MCA region
10/M	46	Large cerebral infarct in right MCA region

BG = basal ganglia, MCA = middle cerebral artery, IC = internal capsule.

improvements in motor function and to changes in cortical maps (19–22). Thus, there exists a rationale for the use of passive movements, not only to prevent local tissue complications but also to improve motor function after stroke for those patients who cannot actively achieve functional movements of the paretic arm.

The aims of this study were to explore the effects of repetitive, passive-active movement training on upper limb motor function and ability in patients with chronic stroke with arm paresis and to explore the effects of such a training programme on cortical activation in a pilot functional magnetic resonance imaging (fMRI) study.

MATERIAL AND METHODS

Patients

Patients discharged with a diagnosis of stroke from in-patient hospital care from a city hospital in Stockholm, Sweden in 1999–2001, were considered for inclusion. Details of their medical histories were obtained from computerized medical records. Inclusion criteria included age 40–65 years, at least 12 months post-stroke, arm/hand paresis and intact sensory function (including light touch and proprioception). Exclusion criteria included communication difficulties due to aphasia or impaired cognitive status and a past medical history of stroke or other neurological disorder. A total of 300 medical charts were screened and 42 subjects were found to meet these criteria. Twenty-four subjects responded favourably to an invitation letter. No difference in age, sex, or degree of paresis was apparent between the patients who responded favourably and those who did not. Upon initial testing of arm and hand function, 14 subjects were found to have minimal functional impairment in the affected arm and hand (e.g. were able to play piano, knit, type) and were therefore excluded. This left a total of 10 subjects who were included. Each subject participated in an assessment of upper limb function. Patient information about ambulatory and activities of daily living (ADL) status was obtained from the medical records. Two of these patients (patient 9 and 10), who were right-handed and who both had infarcts in the middle cerebral artery area of the right hemisphere took part in the pilot fMRI part of the study. Each patient's type and location of lesion and demographic details are listed in Table I and the clinical characteristics are listed in Table II.

Written informed consent was obtained for each subject and the study was carried out in accordance with approval of the local ethics committee at the Karolinska Hospital, Stockholm, Sweden.

Upper limb measurements

Assessments included active range of motion (ROM) measurement of the wrist and finger (metacarpophalangeal joints) movements with a goniometer (23), muscle tone assessment of finger and wrist flexors according to the modified Ashworth scale (24), upper limb sections (arm function, hand function, fine motor sections) of Motor Assessment Scale (MAS) (25), and hand and finger dexterity with the Nine Hole Peg Test (NHPT) (26). All patients were measured 3 times over an initial baseline period prior to training 4 weeks and after the 4-week training programme by a physiotherapist who was not involved in the training programme. The patients were also asked to report any changes in activity performance after the training programme.

Training programme

All patients received passive-active movement training of the paretic upper limb 5 days/week × 4 weeks by a physiotherapist (PL). The training was carried out in the subject's home or in a calm hospital setting and the patient was seated at a table. The training consisted of a 5–10 minute warm-up of upper limb active movements (for shoulder, elbow, wrist and hand) which the patient was capable of carrying out independently. Stretching of muscles (hand and finger flexors and forearm pronators) was also performed for up to 5 minutes for subjects with increased muscle tone. Thereafter the patient received passive movement training of the upper limb. The therapist moved the arm or hand in a functional movement pattern repetitively for 20 minutes. The movements chosen for each individual depended on his/her functional capacity defined from the initial assessments. Movements which the patient could not execute him/herself were performed and they consisted of functional reaching, or grasping and letting go movements of wrist

Table II. *Clinical characteristics of the 10 patients at time of inclusion in study. Patients' arm paresis was graded as mild, moderate or severe depending on upper limb Motor Assessment Scale (MAS) score 0–18 (>12, 6–12, <6, respectively)*

Patient	Time of stroke[1]	Clinical characteristics	MAS score	Gait/ADL status	Return to work
1	18	Moderate R paresis, impaired dexterity	12	Ind	50%
2	26	Severe R paresis, aphasia, depression	4	Ind, UC	ER
3	43	Mild L paresis, impaired dexterity, depression	13	Ind	ER
4	33	Severe R paresis, aphasia, depression	2	Ind	ER
5	26	Severe L paresis, impaired memory and concentration, poor balance	1	aADL, UC	ER
6	14	Severe L paresis, poor balance	1	Ind, UC	50%
7	12	Severe L paresis	2	Ind	50%
8	22	Mild L paresis, impaired dexterity	13	Ind	ER
9	47	Severe L paresis	2	Ind	50%
10	12	Moderate L paresis, impaired concentration	10	Ind	50%

[1]Months before study; R = right; L = left; Ind = independent; aADL = assistive activities of daily living; UC = uses cane; ER = early retirement.

and hand or a combination of both. The movement was repeated 200–400 times per session. The patient was encouraged to "feel and observe" the movement. After 20 minutes of passive movement training the patient was encouraged to try to execute the movement with help, assisted active movements, for 5 minutes.

Functional magnetic resonance imaging

Two of the patients (9 and 10) participated in the pilot fMRI study and were scanned before and after the training programme. Patients were scanned in a 1.5T scanner (Signa Horizon Echospeed, General Electric Medical Systems) equipped with a head-coil. We collected gradient-echo, echo-planar T2*-weighted image volumes with blood oxygenation level-dependent contrast (27). The imaging parameters were: echo time = 50 milliseconds; repetition time = 4.0 seconds; field of view = 22 cm; matrix size = 64 × 64; pixel size 3.4 mm; and flip angle = 90°. Thirty contiguous slices of 5.0-mm thickness were collected in each volume. A whole brain high resolution T1-weighted anatomical magnetic resonance imaging (MRI) (3D-SPGR) was also obtained for each subject.

Conditions were alternated in a block design, consisting of rest and active wrist extension of the affected hand from slightly flexed resting position when lying in scanner. Each block was repeated twice in a session and a total of 4 sessions were collected in the scanner. The range of active paretic wrist extension for each patient was such that it could be performed without effort throughout the sessions (i.e. 5° and 30° for patient 9 and 10, respectively). Movement range was controlled by a mechanical stop so that both pre-training and post-training movements were the same. The frequency of the movements was guided by auditory cues. The same sounds were heard during the rest condition to cancel out auditory activations.

Data analysis

All clinical upper limb measurement data collected in this study were analysed using non-parametric statistical methods. Friedman's ANOVA was used to identify whether there was a difference between (i) the 3 baseline measurements and (ii) the baseline measurements and the post-training measurement. Wilcoxon's matched pairs test was then used to determine between which measurements a difference existed. Significance level was chosen at $p < 0.05$. Statistica 6.0 programme was used for the statistical analysis.

For fMRI image processing and statistical analysis SPM-99 software (Wellcome Department of Cognitive Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm) was used. Image processing included spatially realigning and co-registering images to each individual's anatomical T1-weighted image, normalization of images to stereotactic space (28) and finally smoothing of images. Lesion areas were excluded from normalization process by creating a mask of the lesion using MRI-cro software (29). The fMRI data was modelled with a standard linear regression model, as implemented in SPM-99. The significance of the effects was calculated using t statistics for every voxel from the brain resulting in statistical parametric maps (SPM) for each of the defined conditions. These maps showing brain activity in the rest condition were subtracted from activations in the movement condition, giving activations present in the movement condition only. Pre-training activations, for each subject during active paretic wrist extension, were subtracted from post-training activations giving activation images of training effects with active voxels grouped together in clusters ($p < 0.001$, uncorrected).

RESULTS

Motor function

Range of active extension in the affected wrist, during the first pre-training baseline measurement varied in the group (range: 0–64° degrees; median: 30°). The median value for active wrist extension was 30°, 34.5°, and 40.5° at baseline and increased to 50° post-training. Despite the increasing trend between one baseline measurement and the next no difference was found between baseline measurements with application of Friedman's ANOVA (first baseline vs third with Wilcoxon's matched pairs test, $p = 0.32$). A significant difference was found upon applying Friedman's ANOVA between baseline and post-training measurements ($p < 0.001$). Wilcoxon's matched pairs test revealed a significant difference between each baseline measurement and the post-training measurement ($p < 0.05$) (Fig. 1). Patient numbers 2 and 7, with no active wrist extension in the baseline phase, demonstrated 22° and 8° post-training. No other significant group differences in other ROM measurements of wrist or fingers were found.

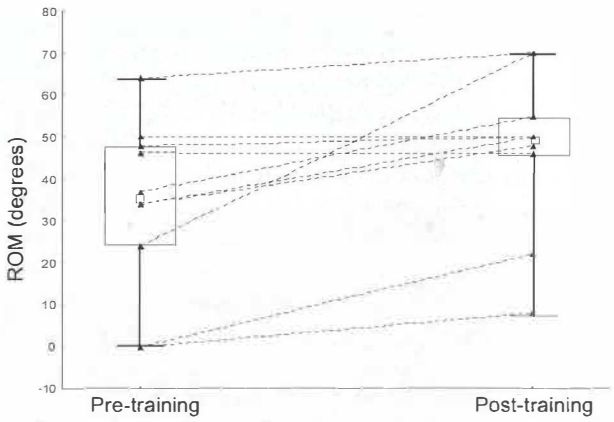

Fig. 1. Individual (broken lines) and group (box-plots) differences in active wrist extension pre and post-training. Pre-training values are the median values of the 3 baseline measurements. ROM = range of motion. Small box: median, large box: 25–75% percentiles; whiskers: min–max.

Muscle tone in forearm and fingers

Seven of the subjects had increased muscle tone upon both the finger and wrist flexion according to the Modified Ashworth scale (range: 1–3 out of a maximum of 4). Three patients had no increase in muscle tone. The values noted in the 7 subjects fluctuated, both up and down by 1 point during the baseline phase. In 2 patients muscle tone decreased post-training. No significant differences were found for the group between baseline and post-treatment sessions.

Arm and hand function

MAS of the upper limb (0–18) were stable during baseline period in 3 patients, fluctuated by 1 point in 7 patients. The median was 3, 3, and 3.5 under baseline measurements and increased to 6 post-training (Fig. 2). No difference was found between baseline measurements but was found between baseline and post-training measurements with application of Friedman's ANOVA ($p < 0.001$). Wilcoxon's matched pairs test revealed a significant difference between each baseline measurement with the post-training measurement ($p < 0.05$). Between baseline measurement 2 and 3 the difference was large but not significant ($p = 0.067$). These results remained statistically significant even if patient 2, who improved 4 points, was left out of the analysis.

Dexterity

NHPT was successfully performed by 4 patients. The others were unable to perform this test. Patient 1 was unable to pick and place any pegs under the baseline tests but was able to pick and place 3 pegs after training. Patient 2 managed 2 pegs at best on 2 baseline measurement trials but only managed 1 post-training. Patient 3 managed all 9 pegs in an average time of 30 seconds under the baseline tests and in 25 seconds after training. Patient 8 also managed to improve his time from 34 seconds under baseline to 27 seconds after treatment. This subgroup was too small for statistical analysis.

Reported activity improvements

After training the patients reported improvements in various upper limb activities not included in the MAS. Patient 4, 6, 7 and 9 reported improvements in arm mobility activities (turning in bed, washing in shower, placing hand on table). Patient 1, 2, 3, 7, 8 and 10 reported improvements in activities requiring paretic hand gripping (talking on telephone, washing dishes, eating fruit, grasping door handle, holding banister, carrying pizza box, pulling golf bag) and patient 1 and 8 reported improvements in dexterous activities (writing and buttoning shirts). Patient 4 reported less discomfort when lying on paretic side. Patient 5 reported no functional improvements.

Individual training effects in subjects with fMRI

In patient 9 muscle tone in wrist flexors was reduced from a baseline rating of 3 to 2 post-training. Active paretic wrist extension improved from baseline level of 37° to 55° post-training. This patient also reported that it was easier to hold arm up when washing in shower and easier to roll over in bed post-training.

In patient 10 MAS scores increased by 1 point to include ability to grasp paper cup, lift and replace it on table (from baseline scores of 10, 10, 11 to 12 post-training). Range of active extension at MCP joint measured at index and middle finger improved from baseline value of 0° to 26° and 44°, respectively. This patient also reported that he can carry a pizza box with both hands, can use his paretic hand to pull up trousers when dressing and can pull a golf bag with his weak hand.

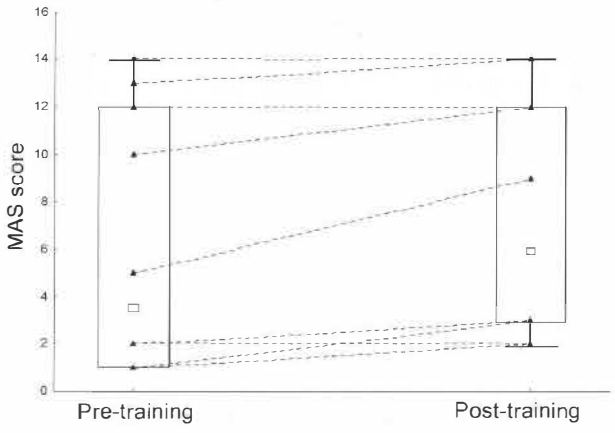

Fig. 2. Individual (broken lines) and group (box-plots) arm and hand function during pre- and post-training. Pre-training values are the median values of the 3 baseline measurements. Two patients are represented by line from 1 to 3. MAS = Motor Assessment Scale. Small box: median, large box: 25–75% percentiles; whiskers: min–max.

Cortical activation

Cortical activation in sensorimotor areas increased post-training (these activations are rendered on the whole brain in Fig. 3). Both patients showed increased activation in primary sensorimotor areas (M1/S1), secondary sensory, premotor, cingulate cortex, and prefrontal areas ($p < 0.001$). Patient 10 also showed activation of ipsilateral cerebellum post-training. The size of the sensorimotor and prefrontal activations (i.e. cluster size) and details of their topography (3D co-ordinates relative to the anterior commisure) are listed in Table III. Both patients also showed an increased activity in contralateral M1 after training (Fig. 4). Patient 9 showed 2 clusters of 9 and 10 active voxels in this region and patient 10 showed 1 large cluster of 391 active voxels in the right precentral gyrus, with $p < 0.001$.

DISCUSSION

Training effects

The training study showed that repetitive, passive-active movement training can improve upper limb motor function and ability in patients with chronic stroke with all degrees of upper extremity paresis. Active wrist extension ROM of the affected hand exhibited a significant group difference post-training as compared with each test during the baseline period. However, fluctuations were observed during the baseline period and ROM even decreased in the final post-training measurement in 3 subjects. These fluctuations were larger than measurement error (5°) and might reflect fluctuations in muscle tone (even though no positive correlation was observed). Arm and hand function according to the MAS also showed a positive group effect post-training. In accordance, 3 out of the 4 subjects who were able to perform the NHPT improved on this test. However, due to the small number of subjects we were unable to analyse this difference statistically. The training effects found are supported by the reported functional improvements. Although only anecdotal, these data were collected as complementary information about tasks perceived as meaningful to the patients.

The passive-active movement training in this study successfully incorporated the use of enhanced somatosensory input which has previously been shown to improve corticomotor output (20–21, 22) and muscle strength post-stroke (19). Such training also enables the inclusion of more severely affected patients with stroke than other training regimens (14) and can therefore be regarded as a useful alternative in rehabilitation.

Cortical reorganization

The fMRI examinations, performed in 2 patients pre- and post-

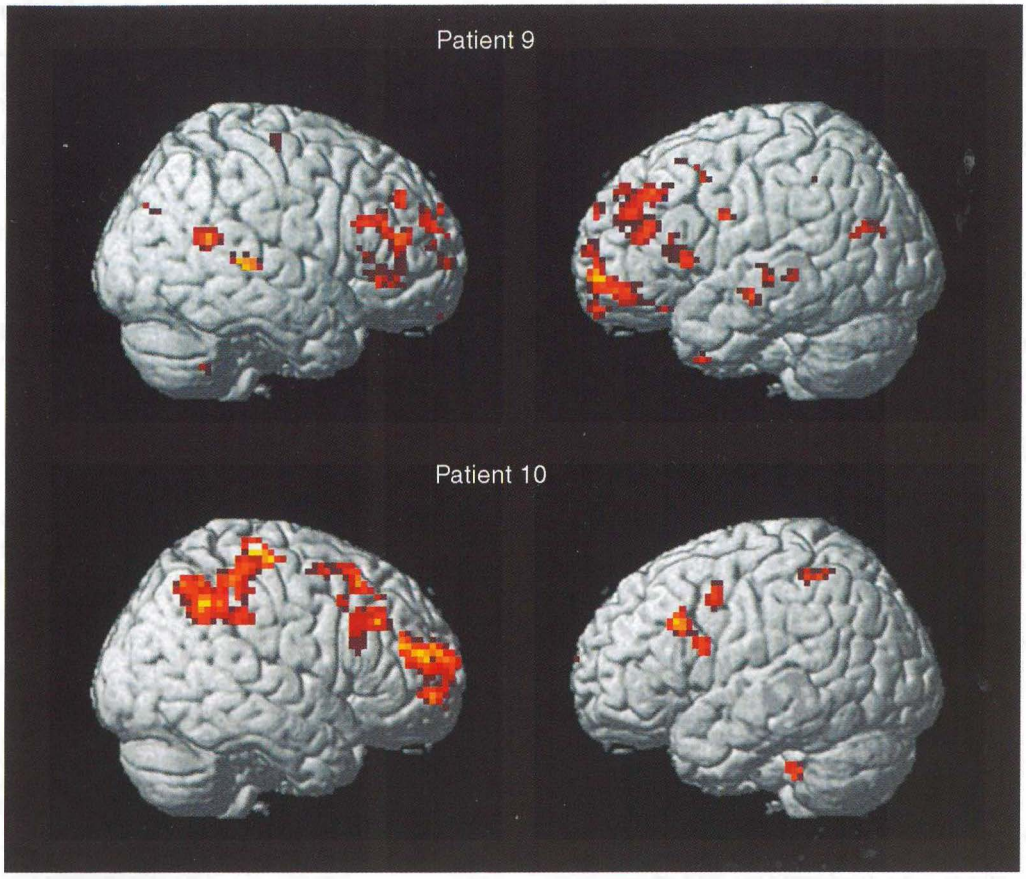

Fig. 3. Post-training activations, with pre-training activations subtracted upon active paretic wrist extension. Images are overlayed onto a template image of the whole brain. Active voxels are significant at $p < 0.001$.

training, indicated cortical reorganization in the sensorimotor areas in parallel with the functional improvements. New cortical areas seem to have been recruited and the total size of cortical activation representing active wrist extension of the affected upper limb increased post-training.

Subtraction of the pre-training scan from the post-training scan demonstrated recruitment of contralateral motor areas. Increased activity in primary motor cortex has been previously reported during recovery from stroke (8, 30). Recruitment of the ipsilateral, dorsal pre-motor cortex has also been reported in

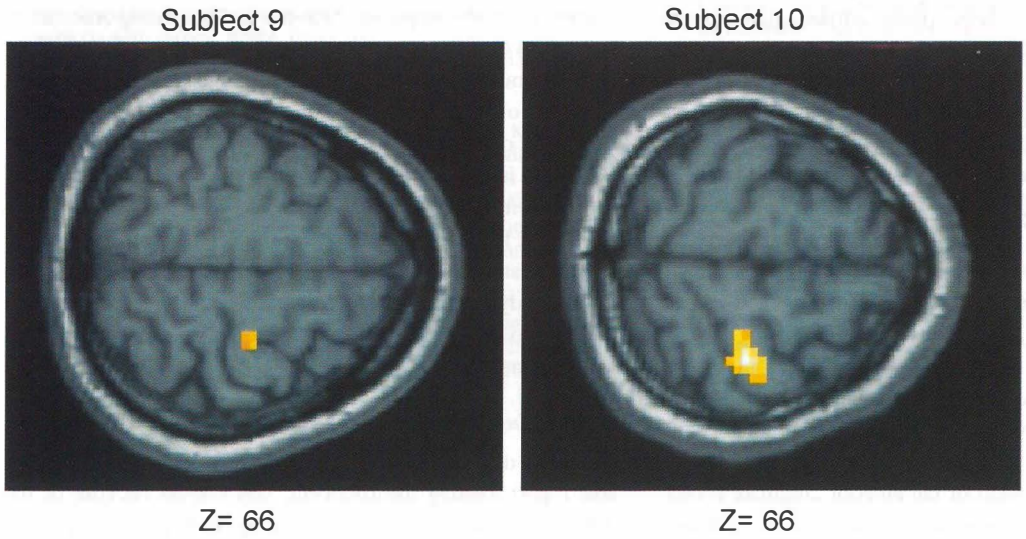

Fig. 4. Axial slices (at 66 mm superior to anterior commisure) showing post-training activation of contralateral M1, in right pre-central sulcus in both subjects. Active voxels are significant at $p < 0.001$.

Table III. *Activations after subtraction of pre-training scan from post-training scan with $p < 0.001$. The t-value represents the significance of the activation at the cluster level*

Side	Anatomical area	BA	Co-ordinates of the centres of gravity			Maximum cluster	
			x	y	z	*t*-value	Size
Patient 9							
Sensorimotor areas							
R	Angular gyrus (S2)	40	63	−54	18	6.02	38
R	Post cingulate cortex	23	6	−51	36	4.74	225
L	Ant cingulate cortex	24	−12	27	27	3.92	28
R	Precentral sulcus (M1)	4	27	−18	66	4.12	9
L	Mid frontal gyrus (PMD)	6/8	−30	9	42	4.1	85
L	Intraparietal sulcus (S2)	39	−33	−45	4	4.02	14
L	Central sulcus (M1/S1)	1–4	−30	−21	33	3.82	28
R	Cerebellum		30	−60	−42	3.67	28
R	Central sulcus (M1/S1)	1–4	36	−36	36	3.62	10
R	Mid frontal gyrus (PMD)	10	12	54	3	4.11	37
Frontal areas							
R	Inf frontal gyrus (PFC)	10/46	33	30	0	5.93	597
L	Sup frontal gyrus (PFC)	9–	33	42	33	5.49	113
L	Inf frontal gyrus (PFC)	10/11	−30	39	−9	5.13	344
L	Supraorbital gyrus (PFC)	9	27	57	24	5.01	27
L	Sup frontal gyrus (PFC)	9	0	60	30	4.46	97
Patient 10							
Sensorimotor areas							
R	Precentral gyrus (M1)	4	33	−27	66	5.45	391
R	Central sulcus (M1/S1)	1–4	54	−51	4		(same cluster)
R	Ant cingulate cortex	24	3	39	24	5.45	121
L	Mid frontal gyrus (PMD)	6	−39	3	45	4.78	22
L	Precentral sulcus (PMD)	6/8	−24	−9	45	4.31	65
R	Mid frontal gyrus (PMD)	8	27	21	51	4.76	107
L	Central sulcus (M1/S1)	1–4	−45	−42	54	3.87	20
L	Cerebellum		−18	−39	−42	5.04	50
Frontal areas							
R	Sup frontal gyrus (PFC)	10/46	24	66	15	5.16	192
L	Mid frontal gyrus (PFC)	46	−18	33	24	4.2	43

BA = Brodmann's area.

recovering patients with stroke (31) and has been correlated to improved hand function in chronic patients after home-based CIMT training (32). The motor task used in these previous fMRI studies consisted of the sequential finger-thumb opposition task (30, 31) and finger tapping (32). The 2 patients with stroke scanned in this study demonstrated similar post-training findings with the wrist extension task. Thus similar patterns of reorganization may mediate recovery in patients with moderate/severe arm paresis.

The patients scanned had moderate/severe degree of paresis of the upper limb and therefore the increased activation observed in primary and in secondary sensorimotor areas could reflect more efficient corticospinal output rather than changes in other more cognitive characteristics of motor control regulated by similar fronto-parietal sensorimotor circuits. It has been shown in monkeys that not only primary but also secondary motor areas have descending corticospinal axons also terminating in the ventral horn (as for M1 efferents) (33, 34). Hence increased sensorimotor activity could represent enhanced corticospinal output resulting in improvements in movement production in these patients.

In both patients, recruitment of the anterior cingulate cortex and distributed frontal areas post-training was observed. These areas are supposed to be involved in attention and motivational aspects of movement production. Evidence for a link between frontal and motor areas exists from both animal and human studies. Also, patients with unilateral prefrontal lesions may have difficulty in learning a motor sequence task (35). Thus, it seems reasonable to assume that the increased frontal activity observed in both our patients was due to the training of attention aspects involved.

The number of neurons and the strength of the neural networks involved in a task are directly related to intensity and frequency of task practise (4). This "use-dependent plasticity" (14) is an important factor to highlight in the rehabilitation of patients with stroke. The intensity and frequency of the functional task being trained should be of such an intensity to drive structural and functional changes in the central nervous system. In this study our training programme seemed to be of sufficient intensity to improve movement production even in patients with severe arm paresis.

Shortcomings of study and guidelines for future

The study design, with 3 baseline measurements before training and 1 post-training measurement, was chosen because of the difficulty in recruiting a patient group with similar degree of

functional impairment in the paretic upper limb. The group was heterogenous with respect to lesion type and location making it difficult to compare patients with a control group, who would also have different symptoms and pathology. Therefore, baseline measurements were used for comparison with post-training results. Thus, the subjects were regarded as their own controls. However, a weakness of this study was that no repeated measures were taken after the training. A 1-month follow-up measurement would have supplied valuable information about how the positive effects of training were maintained or not. For future development of this study a more comprehensive battery of clinical measurements is also recommended.

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