

Robot-based hand motor therapy after stroke

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Robots can improve motor status after stroke with certain advantages, but there has been less emphasis to date on robotic developments for the hand. The goal of this study was to determine whether a hand-wrist robot would improve motor function, and to evaluate the specificity of therapy effects on brain reorganization. Subjects with chronic stroke producing moderate right arm/hand weakness received 3 weeks therapy that emphasized intense active movement repetition as well as attention, speed, force, precision and timing, and included virtual reality games. Subjects initiated hand movements. If necessary, the robot completed movements, a feature available at all visits for seven of the subjects and at the latter half of visits for six of the subjects. Significant behavioural gains were found at end of treatment, for example, in Action Research Arm Test (34 ± 20 to 38 ± 19 , $P < 0.0005$) and arm motor Fugl-Meyer score (45 ± 10 to 52 ± 10 , $P < 0.0001$). Results suggest greater gains for subjects receiving robotic assistance in all sessions as compared to those receiving robotic assistance in half of sessions. The grasp task practiced during robotic therapy, when performed during functional MRI, showed increased sensorimotor cortex activation across the period of therapy, while a non-practiced task, supination/pronation, did not. A robot-based therapy showed improvements in hand motor function after chronic stroke. Reorganization of motor maps during the current therapy was task-specific, a finding useful when considering generalization of rehabilitation therapy.

Keywords: stroke; motor therapy; functional MRI; generalization

Abbreviations: IP = interphalangeal; MCP = metacarpophalangeal

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Stroke remains a leading cause of adult disability in the United States and many other countries. Though stroke can cause deficits in a number of neurological domains, the most commonly affected is the motor system (Gresham *et al.*, 1995; Rathore *et al.*, 2002). Disability due to motor deficits has therefore been a topic of considerable research. Furthermore, given the central role that hand movements normally play in human existence (Porter and Lemon, 1993; Wilson, 1998; Wing *et al.*, 1998; Connolly, 1999; Mountcastle, 2005), much attention in rehabilitation research has been focused on understanding and restoring hand motor function after stroke (Baron *et al.*, 2004; Luft *et al.*, 2004; Nudo, 2007).

A major issue in hand motor therapy has been how to best restore function. A recurring theme is that interventions emphasizing intense, active repetitive movement are of high value in this regard. These increase strength, accuracy and functional use when applied to subjects with paresis due to stroke (Taub *et al.*, 1993; Butefisch *et al.*,

1995; Carey *et al.*, 2002b; Wolf *et al.*, 2006). One approach to providing such therapy is robotic technology.

Robots hold promise for enhancing traditional post-stroke therapy. Specifically, robots can provide therapy for long time periods, in a consistent and precise manner, without fatigue; can be programmed to perform in different functional modes with a single click; can be automated for many functions; can measure and record a range of behaviours in parallel with therapeutic applications; and can be enabled to do the above with only remote human control (Burgar *et al.*, 2000; Dobkin, 2004; Fasoli *et al.*, 2004; Reinkensmeyer *et al.*, 2004; Volpe *et al.*, 2005). The latter extends the promise of telerehabilitation, which might improve access by underserved populations (Reinkensmeyer *et al.*, 2002; Lai *et al.*, 2004; Winters, 2004). In addition, robots can be used to gain insights into the stroke recovery process (Takahashi and Reinkensmeyer, 2003; Krakauer, 2006), for example through their ability to apply novel force assistance patterns (Patton and Mussa-Ivaldi, 2004).

Though robot-assisted therapy has been shown to significantly improve arm motor function after stroke (Aisen *et al.*, 1997; Volpe *et al.*, 1999; Krebs *et al.*, 2002; Lum *et al.*, 2002; Fasoli *et al.*, 2003; Ferraro *et al.*, 2003; Kahn *et al.*, 2006b), with few exceptions (Jack *et al.*, 2001; Hesse *et al.*, 2003b), these efforts have been primarily focused on the proximal arm (Krebs *et al.*, 1999; Reinkensmeyer *et al.*, 2000; Lum *et al.*, 2002).

The current study aimed to develop, then assess clinical effects of, a robotic therapy targeting the distal arm. The main hypothesis was that robotic therapy would improve arm motor function in patients with chronic motor deficits after stroke. The content of therapy was built upon several principles of motor learning: (i) intense, active repetitive movement; (ii) sensorimotor integration, given the key influence that sensory events have on motor learning in the normal and post-stroke states (Kaelin-Lang *et al.*, 2002; Lewis and Byblow, 2004; Walker-Batson *et al.*, 2004) and (iii) high attentional valence and complexity of the experience given the effects that these have in normal and neurologically impaired brains (Will *et al.*, 1977; Kolb and Gibb, 1991; Langhorne *et al.*, 1993; Ottenbacher and Jannell, 1993; Kempermann *et al.*, 1997; van Praag *et al.*, 2000). Some studies suggest utility of a virtual reality interface in this regard (Holden *et al.*, 2001; Jack *et al.*, 2001; Ku *et al.*, 2003; Merians *et al.*, 2006; Fischer *et al.*, 2007), and so this too was incorporated. The use of real objects in a natural or purposeful context enhances motor performance of individuals with hemiparesis (Hsieh *et al.*, 1996; Wu *et al.*, 1998, 2000) and might also be useful to maximize attention to the task, and was therefore also incorporated.

Study subjects were divided into two groups that differed according to the dose of active robotic assistance. Robotic systems are capable of assisting movement in a number of different modes (Prange *et al.*, 2006), including *active non-assist* mode, in which the subject does all work and the robot provides no help; and *active assist* mode, in which the subject attempts to move and the robot supplements this effort. These two active modes, which differ in amount of robotic assistance, were directly compared during the first half of the current therapeutic program. These two modes were chosen, and a passive assist mode in which the subjects relaxes while the robot performs all limb movements excluded, because interventional studies suggest greater gains are achieved when the subject actively exerts an effort (Lotze *et al.*, 2003; Perez *et al.*, 2004). In these two active modes, the subject's effort, i.e. devotion of attention and energy to movement generation, is likely similar, though active assist mode might at times require less effort than non-assist mode because a portion of movements can be passive. Active assist mode might have advantages. For example, active assist mode in subjects with hand paresis is likely to produce a larger range of motion, with superior multijoint coordination, than is non-assist mode. As such, active assist mode likely generates greater proprioceptive

sensory signals to the brain than does the active non-assist mode. Proprioceptive sensory signals from these movements reach motor cortex (Vogt and Pandya, 1978; Brodal, 1981; Jones, 1986). The quantity and character of such sensory signals are known to modulate motor cortex function and excitability (Ridding *et al.*, 2000; Kaelin-Lang *et al.*, 2002), and increased afferent feedback has been considered useful for improving motor learning (Poon, 2004; Rossini and Dal Forno, 2004). A sub-hypothesis of this study, therefore, addressed during the first half of therapy, was that a higher dose of active assist mode would be associated with greater behavioural gains.

The current study also attempted to gain insight into the issue of generalization of therapeutic gains. A concern sometimes raised in relation to stroke rehabilitation is that gains achieved during therapy incompletely generalize to the range of demands faced in real-world tasks (Stokes and Baer, 1977; Page, 2003; Huxlin and Pasternak, 2004; Krakauer, 2006; Van Peppen *et al.*, 2006). Given that therapy-related gains are achieved on the basis of brain plasticity (Hodics *et al.*, 2006), this suggests the hypothesis that a highly standardized therapy such as the current robotic intervention will induce motor cortex plasticity for the task employed in therapy but, in the absence of generalization, not for a separate motor task that was not part of therapy.

The approach employed by Nudo *et al.* in non-human primates was used to address this hypothesis (Nudo *et al.*, 1996). These authors used electrophysiological methods to map motor cortex representations before and after monkeys trained for 2–7 weeks at either a finger grasping task, or a forearm supination/pronation task. The authors found that training in a specific behavioural task differentially altered movement representations, with flexion task training specifically associated with expansion of finger movement representations, and supination/pronation task training specifically associated with expansion of forearm movement representations. Studies in healthy human subjects have been concordant with this (Pascual-Leone *et al.*, 1995; Karni *et al.*, 1996; Muellbacher *et al.*, 2001; Floyer-Lea and Matthews, 2005). However, this issue has not been examined in relation to post-stroke therapeutics, where a non-practiced task has not been simultaneously evaluated. Thus, the specificity of training on cortical plasticity has not been previously examined in the post-stroke setting (Hodics *et al.*, 2006). In the current study, functional MRI (fMRI) brain mapping was performed twice, once before and once after therapy, each time examining both the task practiced (grasping), and a task not practiced (supination/pronation), during therapy. The hypothesis was that a movement performed by the stroke-affected distal upper extremity during therapy would show increased representation area over time in stroke-affected primary sensorimotor cortex, while a movement not performed during therapy would not.

Table 1 Demographic and baseline measures

Measure	All subjects	A-A group	ANA-A group	P
n	13	7	6	
Age (year)	63 ± 16 (range 37–86)	58.6 ± 16	67.3 ± 15	0.35
Gender	7F/6M	4F/3M	3F/3M	1.0
Time post-stroke (year)	2.9 ± 5.1 (range 4–19.6)	1.2 ± 1.1	4.8 ± 7.3	0.22
Baseline characteristics				
Geriatric Depression Scale score (>10 indicates depression)	3.1 ± 2.3	3.9 ± 2.2	2.2 ± 2.3	0.20
NIH Stroke Scale score (normal = 0)	4 ± 2	5 ± 3	4 ± 1	0.16
Right (affected) side				
Action Research Arm Test (normal = 57)	34 ± 20	28 ± 20	41 ± 19	0.26
Box and Blocks test # blocks in 60 s	20 ± 19	15 ± 19	25 ± 19	0.36
Arm Motor Fugl-Meyer score (normal = 66)	44.6 ± 10.4	40.4 ± 10.5	49.5 ± 8.6	0.12
Subportion related to hand/wrist (normal = 24)	16 ± 4	14 ± 5	17 ± 3	0.29
Subportion related to proximal arm (normal = 42)	29 ± 7	26 ± 7	33 ± 6	0.09
Ashworth Spasticity Scale, wrist (normal = 0)	0.7 ± 0.9	0.9 ± 1.2	0.3 ± 0.5	0.28
Ashworth Spasticity Scale, elbow (normal = 0)	0.8 ± 1.1	1.2 ± 1.3	0.4 ± 0.8	0.22
Active ROM, wrist extension (deg)	40 ± 25	35 ± 26	45 ± 24	0.49
Nine Hole Pegboard (seconds to complete)	43 ± 31	47 ± 38	39 ± 22	0.67
Stroke Impact Scale, hand motor (normal = 5)	2.4 ± 1.2	1.9 ± 0.9	3.1 ± 1.1	0.06
Grasp force in Newtons	290 ± 215	198 ± 148	396 ± 244	0.10
Pinch force in Newtons	89 ± 55	71 ± 52	111 ± 55	0.21
Left (unaffected) side				
Box and Blocks test # 60 blocks in 60 s	55 ± 10	52 ± 8	59 ± 10	0.16
Nine Hole Pegboard (seconds to complete)	25 ± 5	27 ± 6	22 ± 3	0.08

Results are mean ± SD. The A-A group had the robot in active assist mode for all 15 days, while the ANA-A group had the robot in active non-assist mode for the first 7.5 days of treatment and then active assist mode for the latter 7.5 days of treatment. *P* values reflect A-A and ANA-A group comparisons via Student's *t*-test or Fisher's exact test. The time post-stroke for the ANA-A group was skewed by a single patient who was 20 years post-stroke.

Materials and Methods

Subjects and overall study design

Thirteen subjects with chronic stroke (Table 1), ages 37–86 years, 6 males and 7 females, participated. Each subject provided informed consent in accordance with the U.C. Irvine Institutional Review Board.

Entry criteria included age >18 years, right-handed (Oldfield, 1971), stroke at least 3 months prior that caused right-hand weakness, at least 10 degrees range of motion in the right index finger metacarpophalangeal (MCP) joint, score of 2–20 on the 24 points of the Fugl-Meyer score related to hand motor function, and the time to complete the 9-hole pegboard test had to be at least 25% longer than that measured with the left (non-affected) hand. Exclusion criteria included apraxia [score >2.5 on Alexander's scale (Alexander *et al.*, 1992)], reduced attention [score >0 on NIH Stroke Scale questions 1a–c], substantial sensory loss [right hand Nottingham sensory score (Lincoln *et al.*, 1998a) <75% of normal], severe increase in tone (Ashworth spasticity score ≥4 at right elbow, wrist or MCP), severe aphasia (score ≥2 on NIH Stroke Scale question 9), major depression (Geriatric Depression scale score >8) or another diagnosis having a major effect on hand function.

Prior to treatment, stroke subjects underwent two assessments of hand motor function ability separated by ~2 weeks, to establish motor function stability (Fig. 1A). The latter baseline assessment included an MRI scan and was performed ~1 week prior to treatment initiation. Subjects then underwent 15 consecutive weekdays of treatment. A third set of assessments was performed halfway

through treatment. A fourth immediately followed completion of therapy and was accompanied by repeat MRI scanning. Subjects returned for a fifth assessment 1 month after completing treatment. The two study primary endpoints were change from baseline to end of therapy in the Action Research Arm Test (ARAT) and the Box and Blocks test scores, and the main secondary endpoint was change in the arm motor Fugl-Meyer score.

Subjects were assigned to one of two therapy groups. In the first group, the robot was in active non-assist mode for the first 7.5 days of treatment and then was switched to active assist mode for the latter 7.5 days of treatment ('ANA-A group'). For the second group of patients, the robot was in active assist mode for all 15 days ('A-A group'). The first eight patients were randomly assigned; an interval assessment found differences in baseline measures, and so for the last five patients, treatment group assignment attempted to balance this.

Description of the robot

The Hand Wrist Assistive Rehabilitation Device ('HWARD') is a 3 degrees-of-freedom, pneumatically actuated device that assists the hand in grasp and in release movements. The three degrees are flexion/extension of the four fingers together about the MCP joint, flexion/extension of the thumb at the MCP joint and flexion/extension of the wrist (Fig. 1B–D).

The subject is seated, facing a computer monitor. The hand is secured to the robot mechanism via three soft straps, and the forearm is secured inside of a padded splint that is mounted to the surface of a platform (Fig. 1C). The palmar hand is left

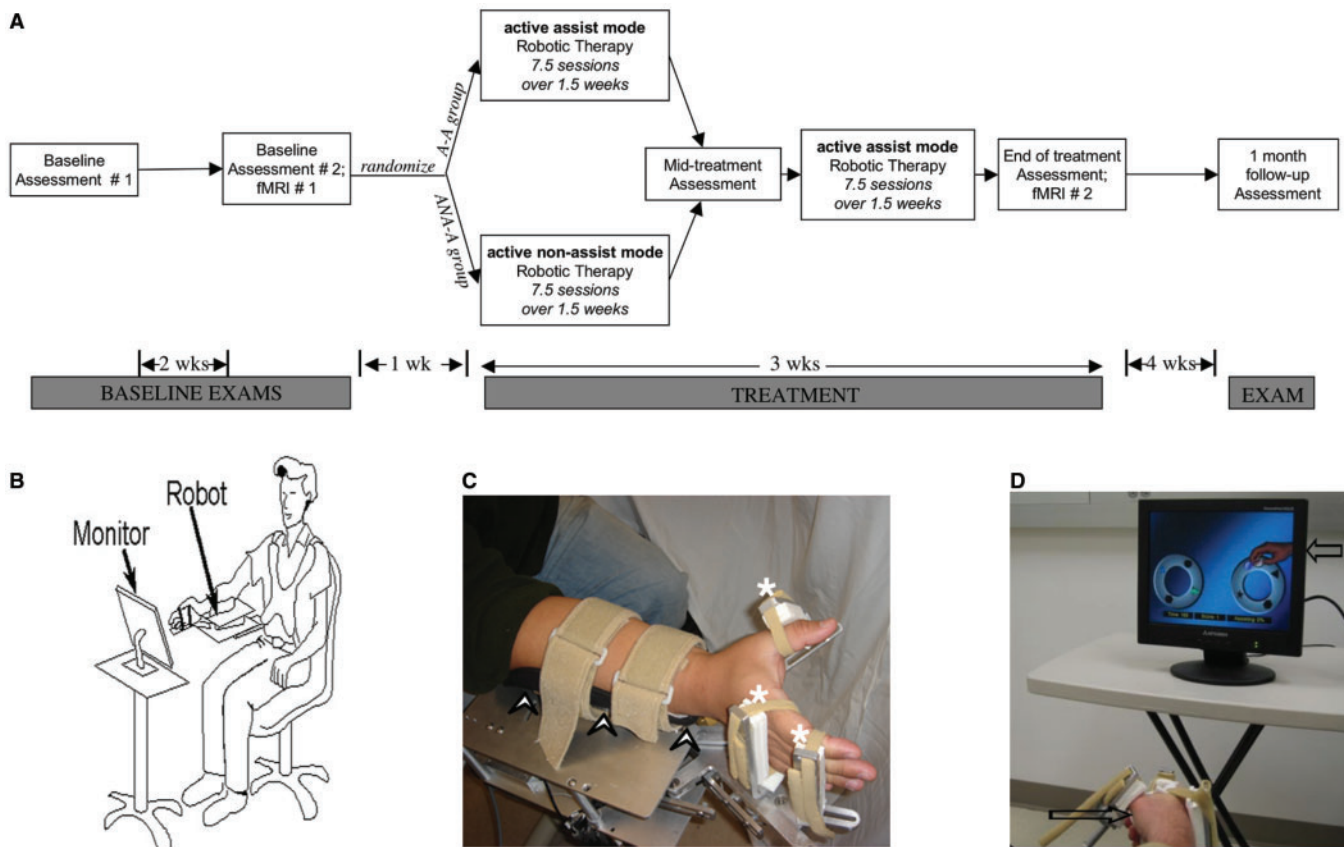


Fig. 1 (A) Study design. (B) Subject's posture, relationship to robot and relationship to computer monitor. (C) A subject's hand in the robot. Arrowheads indicate the splint upon which the ulnar forearm rested. White asterisks indicate the three straps connecting the hand to the robot. (D) Example of virtual reality game, the 'jewel match' game, which required a subject to transfer different-shaped jewels from one rotating wheel to another. As the subject's hand moved (long arrow), the virtual hand on the computer screen (short arrow) moved, in real time.

unobstructed, permitting the placement of real objects into a grasping hand.

A Windows-based software interface facilitates the use and control of the robot via a second computer monitor that is only visible to the examiner. Joint angle sensors in the robot are used to measure the movement of the robot's joints, and hence, movement of the subject's limbs when attached to the robot. This feature enabled real-time virtual reality hand movements, whereby the subject's hand controlled a computer screen virtual hand. The robot is backdriveable, enabling subjects to freely drive movements when the robot is not engaged in active assistance. A more detailed description of this device has been published previously (Takahashi *et al.*, 2005).

Treatment protocol

Each subject received 15 daily sessions, on weekdays, over 3 weeks. Each session was ~1.5 h long, with a brief break in the middle.

Several adjustments were made for each subject. Prior to placing the subject's hand into the robot, the subject's right hand was positioned into HWARD so that both the MCP joint and the wrist centre of rotation were aligned with the robot's finger and wrist joint axes, respectively. To do this, the examiner measured the distance between the centre of wrist rotation to finger MCP joints,

the distance between wrist centre of rotation to thumb interphalangeal (IP) joint, and the distance between the MCP joints to the midpoint of finger IP joints, and then adjusted the robot interface to accommodate. These measures were restored for each subject at the start of each session. Every day, the experimenter determined a subject's comfortable passive range of motion for each degree-of-freedom and adjusted the robot's hard stops accordingly. When in active assist mode, airflow limiters were adjusted at the beginning of each session to insure robot-generated movements were brisk but not excessively forceful. To avoid ceiling and floor effects, the duration of each grasp-release repetition was adjusted, based on hand function, to be shorter for those with better hand function and longer for those with poorer hand function. Note that subjects completed the same number of cycles regardless of hand function of robot mode.

During treatment, subjects sat in an upright position, with the knees flexed at about 90°, trunk supported and maintained against the back of the chair with a shoulder harness, shoulder abducted about 30°, and elbow flexed about 90°. To avoid pain or discomfort during robot treatment, the position of the shoulder was intermittently changed via small movements of the robot platform. The subject's arm was secured to the robotic device.

In the first half of each day's session, subjects performed 9 cycles of 10 repetitions of simple grasp-release exercises.

Each grasp-release exercise was 11–15 s long and involved grasping and releasing while the patient viewed an LCD monitor (Fig. 1B) that provided instructions for each step: ‘Get Ready,’ ‘Close,’ ‘Open’ or ‘Rest’.

When performing the ‘Close’ and the ‘Open’ steps in active assist mode, the subjects were provided 1–3 s to attempt to open or close their hand, after which the robot provided assistance for 1–3 s. In this way, if the patient did not complete the hand movement, the robot moved the hand to complete the range of motion; if the patient did complete the movement, the robot merely applied pressure against the hard stops with no effect on the hand. The 3 degrees-of-freedom were yoked such that active assistance by the robot was done in a power grip pattern, with flexion of fingers and thumb accompanied by wrist extension. Assisted opening therefore extended fingers and thumb and flexed wrist. When performing the ‘Close’ and the ‘Open’ steps in active non-assist mode, the subjects were provided 3–5 s to attempt to open or close their hand, with no subsequent robotic assistance.

Other efforts further increased a subject’s attention to movements. During 75% of the cycles, an examiner placed into the area in front of the subject’s palm one of several objects, each having rich and varied sensory characteristics. Subjects were asked to look at the hand and to answer questions about the object asked by the experimenter regarding object temperature, texture, stiffness, shape, familiarity and functionality.

The second half of each day’s session followed a 15 min break and focused on playing a set of interactive virtual reality computer games (Fig. 1D). Whichever form of robotic assistance was assigned to the exercises was subsequently maintained during these games. Information on joint angle at each of the three degrees of freedom was passed to the computer game program so that a subject’s hand controlled a virtual hand in real time. Nine different computer games were played, each requiring a subject to perform the same hand opening and closing movements as during the first half of the session. Game rules emphasized control of hand movement range, speed and timing. The therapist adjusted game difficulty to avoid ceiling and floor performances.

Assessments

Subjects underwent functional motor testing five times as earlier (Fig. 1A). All assessments were done by a single person (LD) and included the Action Research Arm Test (ARAT) (Lyle, 1981), Box and Blocks test (Mathiowetz *et al.*, 1985), Fugl-Meyer arm motor scale (Fugl-Meyer *et al.*, 1975), the NIH Stroke Scale (Brott *et al.*, 1989), Geriatric Depression Scale (short version) (Burke *et al.*, 1991), Nottingham Sensory Assessment (Lincoln *et al.*, 1998b), an assessment of apraxia (Alexander *et al.*, 1992), dynamometer recording of grip and pinch strength, a goniometer measure of wrist active range of motion, the 9-hole Peg test (Oxford Grice *et al.*, 2003), Stroke Impact Scale hand motor subscale (Duncan *et al.*, 1999) and the modified Ashworth scale (Katz *et al.*, 1992). During assessments, the subject was seated with a standardized posture, using a chair with a firm back but no armrests and a table that approximated the subject’s mid-abdomen.

Electromyography

Immediately prior to each of the two MRI visits, in a room outside of the MRI scanner, surface electromyography (EMG) was acquired while subjects rehearsed the motor tasks to be performed

during fMRI. This rehearsal employed equipment, guidance video and posture that closely mimicked those subsequently employed during fMRI scanning. EMG lead pairs were placed over three muscles (right and left wrist extensor, plus right biceps), signals were amplified (2000×) and bandpass filtered (30–1000 Hz) (ICP511, Grass Technologies), digitally converted (Powerlab 8SP, ADInstruments) and stored for offline analysis.

MRI acquisition

Scanning was all on the same 1.5 Tesla Philips scanner and included acquisition of high-resolution anatomical images, followed by fMRI of two right-sided motor tasks. The first task, ‘grasp’, contrasted rest with opening/closing of the right hand, using a plastic non-actuated exoskeleton identical to the robotic interface. The second task, ‘supination’, contrasted rest with supinating/pronating the right forearm. The range of motion for each task was not controlled, but instead was self-determined. Two fMRI series were acquired for each task. Each series contained 30 s epochs that alternated rest with 0.125 Hz movement. Scanning parameters included 25 axial 5 mm thick slices with no gap, 50 volumes/series, TR = 2500 ms and TE = 40 ms. During the fMRI scan, subjects viewed a guidance video that displayed the desired movement in the form of a stick-figure hand. The video ran continuously with 0.125 Hz movement cycle, being red during rest epochs and green during movement epochs. An investigator observed subject movements during scanning to verify task compliance.

Data analysis

Using SPM2 (www.fil.ion.ucl.ac.uk/spm/), the fMRI images were realigned, normalized to MNI space and then spatially smoothed (FWHM = 8 mm). The first two volumes from each series were discarded due to tissue non-saturation, and then images at rest were contrasted with images during task performance, with the two fMRI series for each task combined, using the standard hemodynamic response function. The fMRI data were analysed in two ways: voxelwise using group maps, and also using region of interest methods in individual maps. For the voxelwise analysis, images were analysed at $P < 0.001$ without correction for multiple comparisons. A one-sample *t*-test was performed on scans for each of the two fMRI tasks, at each of the two visits, from each of which the activation volume was determined for the largest cluster within left (stroke-affected) primary sensorimotor cortex. A paired *t*-test was used to evaluate within subject changes in left primary sensorimotor cortex activation over time, for each task. In individual maps, task-related fMRI signal change was calculated (Brett *et al.*, 2002) within a left sensorimotor cortex region of interest derived from prior hand motor imaging studies (‘hand area’ from <http://hendrix.imm.dtu.dk/services/jerne/ninf/voi.html>).

For EMG data, the root mean square (RMS) was extracted from each muscle’s EMG trace for the first representative 1 s period, for each of task performance and of rest. Results were expressed, for each muscle, as a ratio of (RMS during task)/(RMS at rest).

Statistical analyses were done using JMP (SAS, Cary, NC) and two-tailed, parametric methods, at $\alpha < 0.05$. Data within subject over time were analysed using a paired *t*-test. When comparing the two patient subgroups at any one time-point, Student’s *t*-test (for continuous data) and Fisher’s exact test (for categorical data) were used. When comparing the two patient subgroups over time, a repeated measures ANOVA was performed

Table 2 Effects of therapy on behavioral measures

Test	Change at end of therapy in		
	All Subjects (n = 13)	A-A group (n = 7)	ANA-A group (n = 6)
Action Research Arm Test (normal = 57)	4.2 ± 2.3*** (12%)	5.3 ± 2.1**^ (19%)	2.8 ± 1.8* (7%)
Box and Blocks test # blocks in 60 s	4.2 ± 3.5** (21%)	5.0 ± 4.2* (33%)	3.3 ± 2.4* (13%)
Arm Motor Fugl-Meyer Scale (normal = 66)	7.6 ± 2.5*** (17%)	9.1 ± 2.1***^ (23%)	5.8 ± 1.6** (12%)
subportion related to hand/wrist (normal = 24)	4.0 ± 1.7*** (25%)	3.8 ± 1.5** (27%)	4.2 ± 2.1* (25%)
subportion related to proximal arm (normal = 42)	3.7 ± 3.0** (13%)	5.4 ± 1.3***^ (21%)	1.7 ± 3.2 (5%)
Ashworth Spasticity Scale, wrist (normal = 0)	−0.5 ± 0.8* (−71%)	−0.8 ± 1.0 (−89%)	−0.2 ± 0.4 (67%)
Ashworth Spasticity Scale, elbow (normal = 0)	−0.4 ± 0.5* (−50%)	−0.6 ± 0.6* (−50%)	−0.1 ± 0.2 (−25%)
Active ROM, wrist extension (deg)	4.2 ± 5.5* (11%)	3.9 ± 4.0* (11%)	4.6 ± 7.3 (10%)
Nine Hole Pegboard seconds to complete	−6.6 ± 12.5 (−15%)	−9.6 ± 16.6 (20%)	−3.0 ± 3.8 (8%)
Stroke Impact Scale, hand motor (normal = 5)	0.6 ± 0.5** (25%)	0.9 ± 0.4**^ (47%)	0.3 ± 0.3 (10%)
Grasp force in Newtons	45 ± 56* (16%)	68 ± 67* (34%)	19 ± 23 (5%)
Pinch force in Newtons	16 ± 24* (18%)	28 ± 22*^ (39%)	1 ± 11 (1%)

Values are mean ± SD (and percent) change from baseline to end of therapy for the right (affected) side. *** $P < 0.0001$, ** $P < 0.001$, * $P < 0.05$ change within each group from baseline to end of therapy as assessed using a two-tailed paired t -test. ^ $P < 0.05$, comparing change from baseline to end of therapy between the A-A versus ANA-A groups via Student's t -test. ROM = range of motion.

to examine the time × treatment group interaction, with time as the within-group variable and treatment group as the between-group variable.

Results

Subjects

There were 13 subjects enrolled. Of these, 11 were right-handed and 2 were ambidextrous, 8 were diagnosed with hypertension, 3 were diabetic, 7 were hyperlipidemic and 5 had a history of coronary artery disease. Other baseline measures are presented in the Table 1. Baseline assessments were stable, as paired t -tests of the two baseline measurements demonstrated no significant differences for any behavioural measure ($P = 0.67$ – 1.0). No baseline measure or demographic differed significantly between the two treatment groups. One subject, in the ANA-A group, was not available for the exam at 1 month post-treatment. There were no safety issues or adverse events related to study participation. Among the 10/13 subjects able to undergo MRI, stroke location was pons in two, cortical in two and subcortical in six.

Clinical findings

At baseline, subjects had substantial deficits, for example, the Box and Blocks score on the affected side averaged less than half of the score on the non-affected side (Table 1). Across all subjects, significant gains were found from the mean baseline to end of treatment for the main study endpoints (Table 2). The ARAT showed a 4.2 ± 2.3 (mean ± SD) point increase from baseline to end of treatment ($P < 0.0001$, paired t -test). The Box and Blocks test overall showed a 4.2 ± 3.5 gain in the number of blocks over 60 s from baseline to end of treatment ($P = 0.0009$). The main secondary endpoint, arm motor Fugl-Meyer score, showed a 7.6 ± 2.5 point increase from baseline to

end of treatment ($P < 0.0001$). All subjects showed a gain, for example, 13/13 subjects had an increase in Fugl-Meyer score to end of treatment, and note that in 11/13 subjects this gain was >5 points. Gains were relatively stable over the month following end of therapy: for each scale, change from baseline to 1 month post-therapy remained significant, and in no instance was a significant change present found from end of therapy to exam 1 month later (Fig. 2).

Most other clinical measures also showed significant improvement with robotic therapy, including modest gains in spasticity (Ashworth scale at wrist and elbow), wrist active range of motion, difficulty of hand usage (SIS score) and force of hand grasping as well as of finger pinching (Table 2). Changes in the 9-hole pegboard test did not reach significance. Note that significant change over time was present for both the proximal arm and the hand/wrist subportions of the arm motor Fugl-Meyer scale.

Subjects in the A-A group received active assist mode for both halves of the study and had significantly greater gains than subjects in the ANA-A group, who received active assist mode for only the latter half of the study. This suggests two points. First, this suggests a dose-dependent benefit for the active assist robotic therapy mode, based on results at end of treatment and at 1 month after treatment: A-A group subjects had greater gains than ANA-A group subjects for ARAT score [repeated measures ANOVA, time × treatment group interaction, $F(2,10) = 5.2$, $P < 0.03$ to end of treatment and $F(3,8) = 5.0$, $P < 0.04$ to 1 month post-treatment, using exact F -values, see Fig. 2] and for the arm motor Fugl-Meyer score [$F(2,10) = 4.8$, $P < 0.04$ and $F(3,8) = 8.4$, $P < 0.008$, respectively]. Second, this suggests greater benefit with active assist, as compared to active non-assist, robotic therapy mode, based on results from baseline to mid-treatment, i.e. based on the time when robot mode differed: during this period, subjects in the A-A group showed greater gains as compared to subjects in the

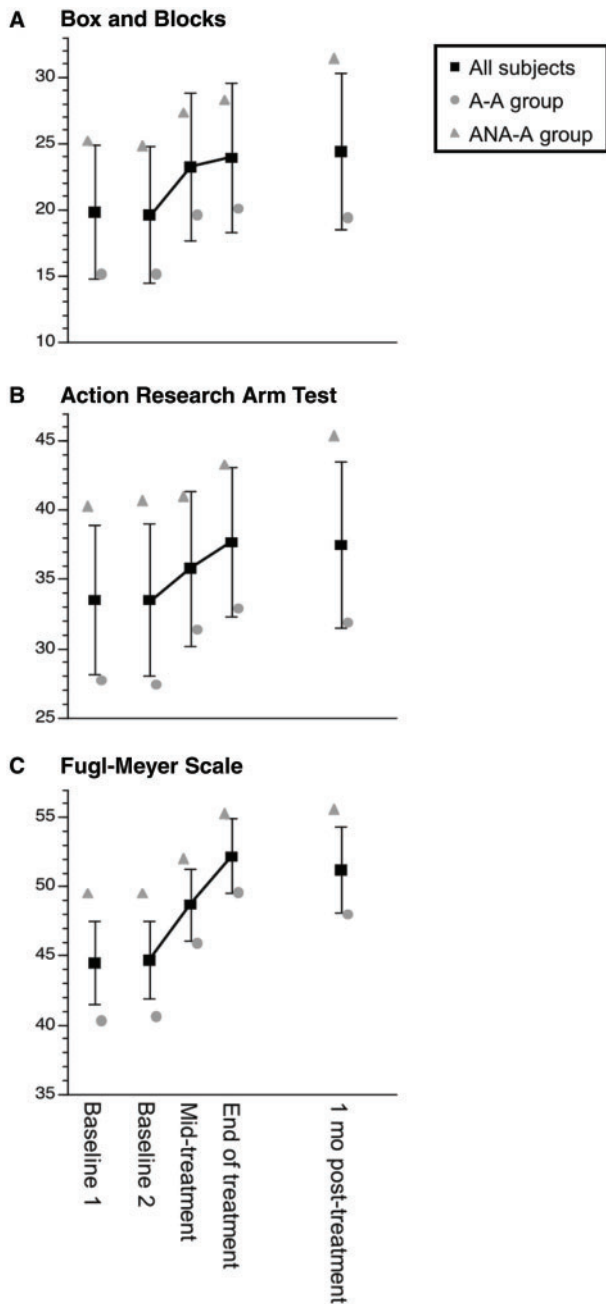


Fig. 2 Results are presented for the two primary endpoints (A and B) and the main secondary endpoint (C), with scores on the y-axis presented in relation to the five testing times. Values displayed for all subjects (mean \pm SEM) are shown in black. Values for the A-A (active assist mode throughout the study) and ANA-A (active non-assist mode for initial study visits, followed by active assist mode for latter study visits) subject groups are shown in gray. Note that baseline differences between these two groups in these endpoints were not significant ($P > 0.1$). Across all subjects, for all three endpoints, significant gains were found across the period of time from baseline to end of treatment. These gains were stable, as no significant changes from end of treatment to 1 month later were present. Results from baseline to end of treatment suggest a dose-dependent benefit for active assist mode of robotic therapy. During this interval, the A-A group had twice the dose of active assist therapy and showed greater gains in ARAT and Fugl-Meyer scores, as compared to the ANA-A group.

ANA-A group for ARAT score [$F(1,11) = 10.9$, $P < 0.008$] and arm motor Fugl-Meyer score [$F(1,11) = 5.1$, $P < 0.05$]. Inspection of Fig. 2 provides a graphic demonstration of the latter point, with the A-A group having a steeper slope than the ANA-A group for the ARAT and Fugl-Meyer scores from baseline to mid-treatment. *Post-hoc* analysis comparison of the two groups at each separate time point found that, for ARAT and Fugl-Meyer score, change in score from baseline was significantly different between the two treatment groups at mid-treatment and at end of treatment but not at 1 month-post treatment; when the respective baseline score was added as a covariate to these *post-hoc* analyses, it was not significant in any instance, ARAT findings and end of treatment Fugl-Meyer findings were unchanged, and Fugl-Meyer findings at mid-treatment became a trend. Also, note too that, while the above analyses of change from baseline to mid-treatment for these two scales used *actual score values*, findings remained significantly different between groups when expressed as *percentage change* (for ARAT, $22 \pm 19\%$ versus $0.9 \pm 1.9\%$, A-A versus ANA-A group, $P < 0.02$; for arm motor Fugl-Meyer, $14 \pm 8\%$ versus $6 \pm 6\%$, $P < 0.05$). Furthermore, the ANA-A group did derive some benefit from baseline to mid-treatment: while lesser gains were present for this group during this interval in comparison to the A-A group, paired testing from baseline to mid-treatment for the ANA-A group was nevertheless significant ($P < 0.05$), for the Fugl-Meyer score (Fig. 2c). The Box and Blocks test was not significant in any of these analyses.

EMG findings

EMG could not be obtained in one subject at the second pre-fMRI session due to technical reasons. Motor task performance was stable over time for each task, as from the first pre-fMRI EMG to the second pre-fMRI EMG, for each of the three muscles, there was no significant within subject EMG change over time (Fig. 3). Furthermore, the two motor tasks had a similar pattern of muscle recruitment, as there was no significant EMG difference between the two tasks for any of the three muscles, at either time point.

Functional MRI findings

MRI scanning could not be attempted in three subjects due to presence of ferrous metal or claustrophobia. One subject showed excess head movement during the supination/pronation task at each fMRI visit, leaving 10 interpretable scans for the grasp task and 9 interpretable scans for the supination/pronation task, at each of the two fMRI sessions. During the pre-therapy fMRI scan, one subject

Also, results from baseline to mid-treatment suggest greater benefit with active assist mode of robotic therapy as compared to active non-assist. During this interval, the A-A group had active assist therapy and showed greater gains in ARAT and Fugl-Meyer scores. On the other hand, the ANA-A group had active non-assist therapy during this period and showed lesser behavioural gains.

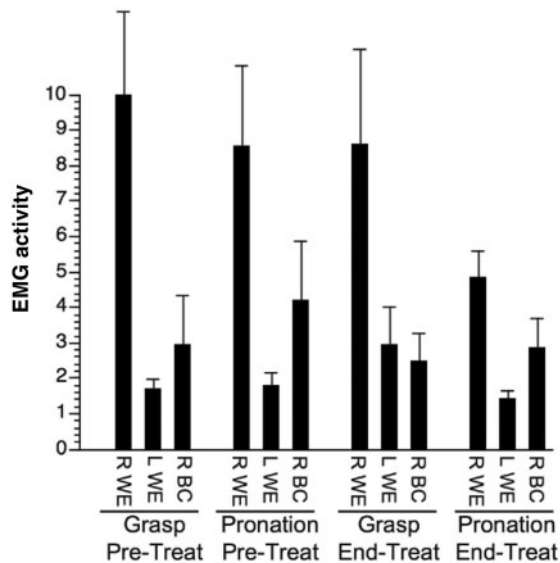


Fig. 3 EMG data (mean \pm SEM) were acquired immediately prior to fMRI scanning at two time points, prior to treatment and at end of treatment, in three different muscles, during each of the two forearm motor tasks that were subsequently performed during fMRI. Data are ratio of (EMG activity during task performance)/(EMG activity at rest). For each muscle and each task, there was no significant change over time. Also, at each time point, there was no significant EMG difference between the two tasks for any of the three muscles. R = right, L = left, WE = wrist extensor, BC = biceps brachii.

had incomplete movements of the right hand, one had small visible mirror movements in the left hand and six had visible movement in the right foot or elbow at least one time. During the post-therapy scan, one subject had incomplete movement of the right hand, three had small visible mirror movements in the left hand and the same six subjects had visible movement in the foot or elbow at least one time.

The task that was part of therapy (grasp) showed significantly increased activation volume over time within the left (stroke-affected) primary sensorimotor cortex, while the task that was not part of therapy (supination/pronation) did not. For the grasp task, left sensorimotor cortex activation volume *increased* from 176 mm³ prior to therapy to 9520 mm³ after therapy (Fig. 4). Paired testing found this activation difference to be significant over time ($P < 0.05$). However, supination/pronation showed *decreased* activation volume, from 4968 mm³ prior to therapy to 1688 mm³ after therapy; this change over time did not reach significance on paired testing (Fig. 4). The interaction of time by task did not disclose significant activation in this brain region. Other changes were measured across the brain over time. For grasp, these include increased activation over time in right cerebellum, right sensorimotor cortex and supplementary motor area plus decreased activation in right inferior parietal lobule; for supination/pronation, these included increased activation in right inferior parietal lobule plus decreased activation in

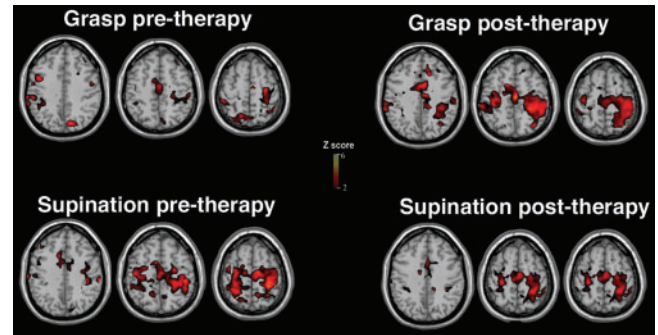


Fig. 4 The grasp task that was central to therapy showed significantly increased activation volume over time within the left (stroke-affected) primary sensorimotor cortex, while the non-practiced supination task did not. This change in grasp task activation volume was not accompanied by a change in task-related EMG, suggesting that its basis was altered brain organization rather than altered subject performances.

supplementary motor area and right sensorimotor cortex. These changes did not reach significance on paired testing. The sensorimotor cortex laterality index (Cramer *et al.*, 1997) as determined from group maps changed from -0.40 to $+0.84$ for grasp, indicating a shift in interhemispheric balance over time from the unaffected to the stroke-affected side, while it showed little change (0.40 became 0.41) for supination/pronation.

The change in activation volume over time for the grasp task was not accompanied by a change in the activation magnitude, measured via task-related signal change. Thus, the percent signal change in the left primary sensorimotor cortex region of interest remained stable for the grasp task, being $0.67\% \pm 0.64$ pre-therapy and $0.63\% \pm 0.51$ after therapy ($P > 0.3$). Signal change was also stable for the supination/pronation task ($0.30\% \pm 0.69$ versus $0.34\% \pm 0.49$, $P > 0.8$).

Discussion

Goals of the current study were to develop a robotic system and therapy program to retrain hand grasping/releasing after stroke based on motor learning theories, to assess safety and effectiveness of this intervention, to examine how dose of robotic assistance influences behavioural gains, and to evaluate the degree to which therapy effects on motor cortex organization are task-specific. The main study result is that patients with chronic stroke showed significant gains in many distal arm behavioural measures, based on both impairment- and functional-based assessments, in a manner that was safe and persistent for at least 1 month after end of intervention. The fMRI findings suggest that this robotic therapy changed sensorimotor cortex function in a task-specific manner.

The data highlight the importance of sensorimotor integration to motor learning after stroke, based on the suggested dose–response relationship between amount of

active assist mode robot therapy and resultant behavioural gains. The dose of active robot assistance was experimentally manipulated by varying robot assist mode during the initial 7.5 of the 15 therapy sessions. Two sets of findings suggest greater behavioural gains associated with the active assist mode. First, active assist mode appeared to be more effective than active non-assist mode: subjects who received the active assist mode of robotic therapy for completing hand/wrist movements from baseline to mid-treatment (A-A group) showed significantly greater gains than those subjects who were in active non-assist mode (ANA-A group) during this interval. Second, a larger dose of active assist mode appeared to be associated with greater behavioural gains: subjects who received active assist mode for both halves of the study (A-A group) had significantly greater gains at end of treatment than subjects who received active assist mode for only the latter half of the study (ANA-A group). The comparison of results between treatment groups must be interpreted with some caution given the small sample sizes as well as the trend for baseline imbalances in clinical status (Fig. 2). Regarding the latter concern, however, note that some (Feys *et al.*, 2000; Shelton *et al.*, 2001; Lin *et al.*, 2003; Cramer *et al.*, 2007; Stinear *et al.*, 2007), though not all (Stinear *et al.*, 2007), prior analyses of stroke patient cohorts mitigate this issue because they suggest that the direction of the current trend (towards *better* baseline motor scores in the ANA-A group) would predict *greater*, not the observed *lesser*, gains among subjects in the ANA-A group.

One key effect that active assist mode likely has, as compared to active non-assist mode, is to produce a wider range of motion for hand/wrist joints, that is more normally coordinated, and thus a larger and more organized afferent signal to brain sensorimotor areas (Humphrey *et al.*, 1970; Brooks and Stoney, 1971; Miles and Evarts, 1979; Waldvogel *et al.*, 1999). Though active assist mode might also generate clinical benefit via other mechanisms, such as by increasing strength or by decreasing spasticity, these findings regarding dose of active robot assistance substantiate the assertion that proprioceptive feedback and sensorimotor integration are important to the effectiveness of motor-based therapies (Ridding *et al.*, 2000; Kaelin-Lang *et al.*, 2002; Poon, 2004; Rossini and Dal Forno, 2004), a conclusion that is underscored by the rich structural and functional connections between primary sensory and motor cortices (Vogt and Pandya, 1978; Brodal, 1981; Jones, 1986). Future designs might vary any of several aspects of this proprioceptive feedback, for example, by changing the timing at which it is provided in relation to active subject movements, such as to a time much closer to the point of movement onset.

The current findings, suggesting that active robotic assistance provides greater benefits than dose-matched but unassisted practice, contrast with those of Kahn *et al.* (2006b), who found that in subjects with chronic stroke, reaching exercises supported by an active assist mode robot

provided the same, rather than greater, behavioural gains as compared to matched unassisted reaching. There are several possible reasons for their observations, discussed in their report. Most notably was that for subjects in the active assist group of Kahn *et al.* (2006b), the robotic device was programmed to assist the moving arm in real time in order to specifically minimize errors of movement trajectory, an approach that might have diminished the motor system's own learning processes related to correcting these errors. Given the potential importance of sensorimotor processing to achieving behavioural gains from active assist mode robotic therapy, therefore, a key factor to consider when implementing active assistance is how sensorimotor processing and learning are affected.

Some gains in the ANA-A group did achieve significance during the period when the robot was in the active non-assist mode. This emphasizes that active robotic assistance (i.e. active assist mode) *per se* is not a requirement for motor gains in this setting (Kahn *et al.*, 2006a). Indeed, by increasing the dose of active non-assist therapy beyond that provided herein, it might be possible to achieve outcomes similar to those obtained in the current study with 3 weeks of active assist therapy. If equally effective, such an approach would vastly reduce the complexity and cost of a robotic therapy device.

Robot-assisted therapy has been shown to significantly improve arm motor function after stroke (Aisen *et al.*, 1997; Volpe *et al.*, 1999; Krebs *et al.*, 2002; Lum *et al.*, 2002; Fasoli *et al.*, 2003; Ferraro *et al.*, 2003; Reinkensmeyer *et al.*, 2004; Kahn *et al.*, 2006b). With few exceptions, however, these efforts have been primarily focused on the proximal rather than distal upper extremity (Hesse *et al.*, 2003a). HWARD represents only one of a number of new robotic devices designed for distal upper extremity stroke rehabilitation. Other recently introduced examples that focus on the hand and/or wrist include a recent extension of the MIT-MANUS (Charles *et al.*, 2005), a pneumatically or cable-controlled glove (Kline *et al.*, 2005; Merians *et al.*, 2006; Fischer *et al.*, 2007), an EMG-controlled hand exoskeleton (Mulas *et al.*, 2005), an augmented-reality body-powered finger orthosis (Luo *et al.*, 2005), an MR-compatible exerciser (Khanicheh *et al.*, 2005), the 3By6 Finger Device (Kurillo *et al.*, 2005) and the electrical muscle stimulation-based Bi-Manu-Trak robot arm trainer (Hesse *et al.*, 2005). Each of these devices has its own unique approach to stroke treatment, but it is not yet clear how each design will improve function after stroke, and ultimately a combination of approaches might prove best.

Functional MRI brain mapping performed before and after therapy provided insights of possible importance to this therapy as well as to stroke rehabilitation in general. The primary sensorimotor cortex representational map for the grasp task that was the content of therapy increased substantially over time. However, the size of the map for supination/pronation, a task not practiced over time, did not change. These results therefore characterize specificity

of treatment-induced cortical reorganization, particularly given that muscle activity was similar across the two tasks at both time points. Furthermore, the fMRI changes for the grasp task reflect altered brain organization rather than altered task performance given the stability of grasp task EMG measures over time. The finding of increased activation volume but not signal change over time suggests that behavioural gains were more supported by recruitment of cortical areas neighboring the original ipsilesional sensorimotor cortex activation site rather than by a change in cortical function at this original site. As with all motor fMRI studies in stroke patients with significant deficits, the results need to be interpreted with caution given the occurrence of occasional and small adventitious movements. The fMRI findings over time raise the question as to whether gains from the robot therapy, which was focused on hand/wrist, generalized to the proximal arm.

Generalization can be said to be present when therapy-induced changes ‘occur over time, persons and settings, and the effects of the change sometimes should spread to a variety of related behaviours’ (Stokes and Baer, 1977). This is a potentially important topic in post-stroke rehabilitation, as the intent of therapy is to improve function across real-world demands, beyond the tasks rehearsed during therapy. Reduced generalization might therefore limit the impact of certain rehabilitation interventions (Stokes and Baer, 1977; Page, 2003; Huxlin and Pasternak, 2004; Krakauer, 2006; Van Peppen *et al.*, 2006). The current intervention repeated a very highly stereotyped, single hand/wrist motor task but was associated with significant motor gains in both proximal arm and hand/wrist (Table 2). This is similar to the findings of Butefisch *et al.* and others (Taub *et al.*, 1993; Butefisch *et al.*, 1995; Carey *et al.*, 2002b; Wolf *et al.*, 2006), who found that patients undergoing repetitive hand flexion/extension training showed gains not only in hand movements, but also in overall arm function. Such results might be interpreted as demonstrating presence or absence of generalization.

Interpreting the current behavioural results as demonstrating generalization suggests that a 3-week program of highly controlled exercises restricted to the distal arm directly produced motor gains in the proximal arm. An extension of this interpretation would be that behavioural changes are dissociated from fMRI changes over time; that is, while all tasks showed behavioural gains over time, the rehearsed task showed expanded cortical representation but a non-rehearsed arm task did not.

Interpreting the current behavioural results as demonstrating lack of generalization suggests that, while measured motor gains in proximal arm are real, they are not directly due to generalization. Instead, other processes must have contributed to these findings, secondarily, such as reduced tone throughout the arm (suggested by change in elbow tone, Table 2), increased social activity (such as provided across the 15 study visits to the university), and/or increased proximal arm use secondary to therapy-induced

gains in distal arm function. In this interpretation, the effects of treatment do correspond to the change in fMRI maps over time, with the change in fMRI maps representing experience-driven alterations in cortical representations. This interpretation is directly concordant with the primate intracortical microstimulation mapping results of Nudo *et al.* (1996), though the cortical infarct model employed by these authors varied from the subcortical stroke location present in the majority of the current subjects. The results are also consistent with prior fMRI (Karni *et al.*, 1996; Floyer-Lea and Matthews, 2005) and transcranial magnetic stimulation (Pascual-Leone *et al.*, 1995; Muellbacher *et al.*, 2001) studies in healthy human subjects, which found tasks practiced over weeks show increased size of representational maps in primary sensorimotor cortex, while non-practiced tasks do not. The results for the laterality index, i.e. an increase indicating a shift in interhemispheric balance over time towards sensorimotor cortex in the stroke-affected hemisphere, are also consistent with prior fMRI studies on the effects of therapy in chronic stroke (Pariente *et al.*, 2001; Carey *et al.*, 2002a; You *et al.*, 2005). This view would suggest that the issue of behavioural result generalization was more untested than disproved, and that highly precise measures, such as multijoint kinematics (Cirstea and Levin, 2007), would have identified greater gains in distal than proximal arm. In retrospect, the current study would have been improved by serially collecting careful measures of a supination/pronation behaviour.

Two points arise from this consideration of generalization of behavioural gains with rehabilitation therapy. First, precise behavioural measures might be needed to most accurately address the issue of generalization. Second, for long-term multi-visit interventional studies, the activities in which research subjects engage outside of the laboratory might impact results. Indeed, the current cohort of subjects described numerous gains during study intervention, such as with dressing or meal preparation, and such non-study activities likely contributed to the final behavioural scores.

The current therapy, like other activity-based approaches, significantly improved upper extremity motor function in subjects with chronic stroke and mild-moderate hand motor deficits. The extent to which such gains differ from those achieved by traditional physiotherapy remains to be clarified (Dromerick *et al.*, 2006). Robotic therapy, however, offers certain potential advantages over traditional therapies, such as consistency, precision, non-fatigability, programmability and ability to measure and record in parallel with therapy delivery. Robotic approaches, capable of functioning at sites remote from human therapists, also enable telerehabilitation (Burgar *et al.*, 2000; Reinkensmeyer *et al.*, 2002, 2004; Dobkin, 2004; Fasoli *et al.*, 2004; Lai *et al.*, 2004; Winters, 2004; Volpe *et al.*, 2005). In some cases, these properties might allow patients to achieve access to rehabilitation therapy, and in other cases robot-based

therapy might be used to enhance traditional post-stroke therapies.

The results of this study suggest that the current robot-based therapy produced significant behavioural gains in patients with moderate motor deficits chronically after stroke. The therapy emphasized several motor learning theories: active repetitive movement practice, maximum sensory input via tactile (grasping sensory-rich objects) and proprioceptive pathways, maximum attention via multiple study features, plus use of interactive virtual reality computer games. The specific factors that contributed most to the measured gains remain unclear, but the results of this feasibility study are promising. Future directions might include adapting the approach to patients with a wider range of motor deficits after stroke, and implementation of technology for home use given increasing emphasis on telerehabilitation (Reinkensmeyer *et al.*, 2002; Lai *et al.*, 2004; Lum *et al.*, 2006).

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