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Analysis of fMRI and finger tracking training in subjects with chronic stroke

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Summary

Hand movement recovery and cortical reorganization were studied in 10 subjects with chronic stroke using functional MRI (fMRI) before and after training with an intensive finger movement tracking programme. Subjects were assigned randomly to a treatment or control group. The treatment group received 18–20 sessions of finger tracking training using target waveforms under variable conditions. The control group crossed over to receive the same treatment after the control period. For comparison with a healthy population, nine well elderly females were also studied; however, the well elderly controls did not cross over after the control period. The dependent variables consisted of a Box and Block score to measure prehensile ability (subjects with stroke only), a tracking accuracy score and quantification of active cortical areas using fMRI. For the tracking tests, the subjects tracked a sine wave target on a computer screen with extension and flexion movements of the paretic index finger. Functional brain images were collected from the frontal and parietal lobes of the subject with a 4 tesla magnet. Areas of interest included the sensorimotor cortex (SMC), primary motor area (M1), primary sensory area (S1), premotor cortex (PMC) and supplementary motor area (SMA). Comparison between all subjects with stroke and all well elderly subjects at pre-test was analysed with two-sample *t*-tests. Change from pre-test to post-test within subjects was analysed with paired *t*-tests. Statistical significance was set at $P < 0.05$. Stroke treatment subjects demonstrated significant improvement in tracking accuracy, whereas stroke control subjects did not until after crossover treatment. At pre-test, the cortical activation in the subjects with stroke was predominantly ipsilateral to the performing hand, whereas in the well elderly subjects it was contralateral. Activation for the stroke treatment group following training switched to contralateral in SMC, M1, S1 and PMC. The stroke control group's activation remained ipsilateral after the control period, but switched to contralateral after crossover to receive treatment. All well elderly subjects maintained predominantly contralateral activation throughout. Transfer of skill to functional activity was shown in significantly improved Box and Block scores for the stroke treatment group, with no such improvement in the stroke control group until after crossover. We concluded that individuals with chronic stroke receiving intensive tracking training showed improved tracking accuracy and grasp and release function, and that these improvements were accompanied by brain reorganization.

Keywords: stroke; hand; fMRI; neuroplasticity

Abbreviations: AI = accuracy index; fMRI = functional MRI; ICC = intraclass correlation coefficient; M1 = primary motor area; MP = metacarpophalangeal; PMC = premotor cortex; S1 = primary sensory area; SMA = supplementary motor area; SMC = sensorimotor cortex

Introduction

Constraint-induced movement therapy has been shown to be effective in improving function in individuals with chronic stroke (Liepert *et al*., 1998, 2000*a*, 2001; Levy *et al*., 2001). This therapy involves immobilization of the non-paretic upper extremity to force the subject with stroke to use the paretic upper extremity intensively during functional activities.

As an application of the intensive-use component of constraint-induced movement therapy, but without the

immobilization component, we have developed a training regimen for individuals with stroke that involves tracking a target on a computer screen with reciprocal extension and flexion movements of the index finger. By presenting the subject with a variety of target waveforms under variable conditions, subjects are forced repeatedly to problem solve each situation and execute as accurate a motor plan as possible. The training emphasizes motor learning principles espoused by Schmidt (1991) such that guidance from the therapist is minimized. Instead, the idea is to force the individual to process visual–spatial information while performing repetitive extension and flexion aiming movements of the index finger under different levels of difficulty. The purpose of these repetitive aiming movements is to challenge and thereby develop the subject's own error detection and motor planning capabilities, ideally leading to improved finger movement control.

We elected to focus training on finger movement because paralysis of the hand is one of the most debilitating functional problems associated with stroke (Hummelsheim *et al*., 1997). Furthermore, training of finger movements allows the exploration of whether any improvements in behaviour are supported by a neurological substrate. Functional MRI (fMRI) has been used extensively to investigate neuroplastic changes in the brain following stroke, and study of hand function complies well with the technical requirements of fMRI (Cramer *et al*., 1997, 1999, 2000; Cao *et al*., 1998; Marshall *et al*., 2000). Evidence of neuroplastic changes following treatment would strengthen the validity of the treatment and help to understand the possible mechanism of action. Thus, the purposes of this study were to determine whether finger movement tracking training could improve finger function and produce brain reorganization in subjects with chronic stroke and also to compare these findings with a cohort of well elderly subjects.

Subjects and methods

Subjects

Two groups of subjects were studied, stroke and well elderly. The subjects with stroke included six males and four females with a mean (± standard deviation) age of 65.7 (± 13.3) years. The mean time since onset of stroke was 4.7 (± 6.3) years. Descriptive data for each of the 10 subjects with stroke are summarized in Table 1. The well elderly subjects were nine females with a mean age of 71.8 (10.7) years. The well elderly included females only because it was known from previous work (Carey *et al*., 1994) that well elderly females have more difficulty with the tracking task than males and therefore they might be more likely to show a training effect, whereas males might already be functioning near their maximum potential.

The inclusion criteria for all subjects included satisfactory cognition with a score of at least 24 out of 30 on the Mini-Mental State Examination (Folstein *et al*., 1975) and satisfactory vision, as tested by their ability to detect whether the computer screen cursor positioned by the examiner was slightly above, on or slightly below a target line. For those subjects who normally wore eyeglasses, corrective lenses of the same strength were inserted into plastic frames and worn while performing the tracking task inside the magnet. Additional inclusionary criteria for the subjects with stroke were a single stroke at least 6 months post-onset, finger movement of at least 20° at the metacarpophalangeal (MP) joint of the index finger in the paretic hand, and slowed hand opening from the fisted position of the paretic hand compared with the non-paretic hand. We did not quantify the speed of this hand opening; we ensured that the movement was slower than that of the non-paretic hand or else they were not included. Additional inclusion criteria for the well elderly were that subjects be right-handed, as determined from the Edinburgh Inventory for Handedness (Oldfield, 1971), and that their medical history did not include stroke or any other disorder that could affect finger movement performance. Exclusion criteria for all subjects included metals or implanted medical devices incompatible with fMRI testing, pregnancy and claustrophobia. One of the subjects with stroke was left-handed. We included her because she met all the criteria and, in the final analysis, her results were consistent with those of all the other subjects in her group.

The subjects with stroke were recruited as volunteers responding to announcements at their stroke support group meetings or published in the local newspaper. The well elderly were recruited as volunteers from announcements at an assisted living centre for the well elderly or within the nearby community.

Subjects with stroke were assigned randomly to either a stroke treatment group ($n = 5$) or a stroke control group ($n = 5$). Following the control period, subjects in the stroke control group crossed over and received the treatment. Well elderly subjects also were assigned randomly to a well elderly treatment group ($n = 5$) or a well elderly control group ($n = 4$) with no crossover. This study was approved by the Institution's Committee on the Use of Human Subjects in Research and all subjects signed a statement of informed consent.

Instrumentation and procedure

For the subjects with stroke, the pre-test and post-test consisted of (i) the Box and Block test to quantify performance of finger grasp and release function; (ii) the finger movement tracking test to quantify control of precision movements of the index finger; and (iii) fMRI during the tracking test to quantify cortical activation. The well elderly performed the same pre-test and post-test measures except for the Box and Block test. This test was omitted for the well elderly group because, without any finger impairment in the first place, as determined during the initial screening for arthritis, carpal tunnel syndrome or other medical conditions, we did not believe that this test would be a valid indicator of

Table 1 *Characteristics of subjects with stroke*

Subject	Age (years)	Sex	Dominant hand before stroke	Infarct site	Time since stroke (years)	MM score	Modified Ashworth score at fingers	Active MP motion (°)
1	72	M	Right	Left internal capsule and striatum	2.0	29	1	86
2	76	M	Right	Left pons	4.0	28	1	69
3	74	F	Left	Right posterior limb of internal capsule and posterior putamen	3.5	30	1	55
4	68	M	Right	Left parietal cortex, precentral gyrus, superior and middle temporal gyrus	9.4	24	1+	58
5	68	M	Right	Left posterior limb of internal capsule	0.8	28	1	64
6	30	F	Right	Right posterior limb of internal capsule	2.5	28	1	84
7	61	F	Right	Right frontal and parietal cortex, internal capsule and striatum	21.0	30	1	56
8	73	F	Right	Left posterior limb of internal capsule, striatum and left inferior parietal cortex	1.0	30	0	78
9	68	M	Right	Right internal capsule	1.5	30	1	66
10	67	M	Right	Left thalamus and cerebral peduncle	1.3	27	0	55

M = male; F = female; MM = Mini-Mental; MP = index finger metacarpophalangeal joint.

improved finger function following tracking training. However, because the finger tracking test is a novel task and challenging for all subjects, we believed that this test would be a valid indicator of improved finger movement control following tracking training and allow meaningful comparison between subjects with stroke and well elderly subjects. Furthermore, the finger tracking test would serve as a functional task during which cortical activation could be assessed with fMRI.

Box and Block test

With the subject seated and a divided box positioned waist-high, the subject grasped a 2.54 cm^3 block between the tip of the index finger and tip of the thumb of the paretic hand, lifted the block from one side of the box and released it on the other side. Each subject with stroke performed three 60-s trials of grasping and releasing as many blocks as possible, one at a time (Mathiowetz *et al*., 1985). The validity of this test in discriminating between the performance of healthy and impaired populations has been demonstrated (Cromwell, 1960).

Finger movement tracking test

Control of extension and flexion movement of the index finger was evaluated in all subjects with a finger movement tracking test that occurred simultaneously with fMRI. For this test, the subjects with stroke used their paretic hand and the well elderly subjects used their right hand. The subject was positioned supine inside the bore of the magnet (described below). A computer (Dell Computer Corporation, Round Rock, Tex., USA), connected to a projector, displayed a sine wave at a frequency of 0.4 Hz onto a rear-view projection screen. The subject viewed this image through a small mirror mounted on the head coil apparatus inside the magnet. Head movements were minimized by tightening a stabilization band that surrounded the head inside the head coil.

A potentiometer (Waters Manufacturing and Company, Wayland, Mass., USA) was aligned with the MP joint of the index finger. The voltage signal was directed to the computer through an analogue-to-digital converter (Interactive Structures, Inc., Bala-Cynwyd, Pa., USA) that sampled the signal at a frequency of 60 Hz.

The arm of the test hand was adducted to rest next to the subject's chest. The forearm was flexed ~45° and pronated to rest on the subject's hip. The wrist was supported in the neutral position between flexion and extension by a small bolster. Care was taken to ensure that the bolster did not impede the index finger movement. The thumb and all fingers were allowed to move. Finger extension and flexion movement occurred in the vertical plane during the tracking task. The opposite arm and forearm were positioned in the same way except the wrist was not propped. A non-metallic device was inserted into the palm of the non-performing hand. Squeezing this device was the subject's method of calling the investigator if desired. The subject was instructed carefully not to move the non-performing hand during the test. Headphones and a microphone on the subject allowed the investigators to communicate with the subject prior to the test. No communication occurred during the test.

The upper and lower peaks of the sine wave target were customized to each subject's active range of motion at the MP joint. This range was determined by getting the subject first to flex and then extend all fingers maximally. Upon reaching each maximum, the investigator pressed a key and the maximum active range of motion was recorded. With maximum flexion of the MP joint considered zero degrees, the upper peaks of the sine wave target were set at 85% of the subject's range and the lower peaks were set at 15%. The

subjects received three 10-s trials of tracking practice outside the magnet to familiarize them with the task and for any questions to be answered. One additional practice trial of 15 s duration was provided inside the magnet to familiarize the subject with the task in that environment. This trial also allowed the investigators to observe the non-performing hand during the effort with the tracking hand. The investigators observed that all subjects maintained the resting position of the non-performing hand during this practice.

The tracking experiment then consisted of six consecutive 1-min periods alternating between rest (A) and track (B), creating a sequence of $A_1B_1A_2B_2A_3B_3$. For each period, the subject had a preview of the entire sine wave target. At the start of each period, the investigator pressed a key and the cursor began its 60-s sweep from left to right across the screen. For the three rest periods (A_1, A_2 and A_3), the subject rested and simply watched the cursor without producing any finger movement. For the three track periods (B_1, B_2 and B_3), the subject again watched the cursor sweep but now attempted to track the sine wave target as accurately as possible with careful finger extension and flexion movements.

Just prior to the test, subjects were reminded verbally through the intercom system of this test sequence and also to keep the rest of their body still. During the actual test, there was no auditory input from the investigator to the subject. To assist the subject in remembering when to rest versus when to track, the screen displaying the target also displayed a prompt of either 'rest' or 'track'. At the end of each 1-min period, a brief time (2–3 s) was required to toggle the tracking computer to the next period of either rest or track. This transition time was accounted for by using an electronic MRI counter that allowed synchronization of the MRIs with the functional tracking task.

During the test, the investigators monitored the performance of the tracking hand by viewing the response line on the computer screen. The non-performing hand was not monitored during the test.

MRI

MRIs were obtained in a 4 tesla whole-body magnet (Oxford, UK) equipped with a ^{Unity}INOVA console (Varian, Calif., USA) and a body gradient insert (Siemens, Germany), using a custom TEM head resonator (Vaughan *et al*., 2001).

Anatomical T_1-weighted (inversion recovery) images of the whole brain [multislice turboFLASH, TE (echo time) = 5 ms, TR (repetition time) = 9 ms, TI (inversion time) = 1.2 s, matrix = 128 × 128, FOV (field of view) = 20 × 20 cm, slice thickness = 5 mm, 3 NEX (number of excitations)] were obtained in the transverse, coronal and sagittal planes with a resolution of 1.56 × 1.56 mm to allow identification of the anterior and posterior commissures, and to determine the appropriate volume for the subsequent functional images.

Blood oxygen level-dependent T_2^*-weighted fMRIs in the transverse plane (TE = 25 ms, TR = 111 ms, matrix = 64 × 64, FOV = 20 × 20 cm, slice thickness = 5 mm, 1 NEX) were obtained using blipped echo planar images, with the total imaged volume extending from the superior pole of the cortex to a depth of 135 mm in 27 slices. Functional images had an axial in-plane resolution of 3.125 × 3.125 mm and a 5 mm slice thickness. Functional images were collected every 3 s during the 6-min experiment. Thus, 20 images were collected during each of the 1-min periods alternating between rest and track.

Tracking training

In between the pre-test and the post-test, the five subjects comprising the stroke treatment group and the five subjects comprising the well elderly treatment group received 18–20 tracking training sessions. A given training session lasted 45–60 min. The frequency of training varied between two and five sessions per week, based on subject availability. For each session, the subject sat in a chair and performed three trials at each of 20 tracking protocols, for a total of 60 tracking trials. To create variability within the tracking task, thereby promoting a greater depth of information processing and greater motor learning (Winstein *et al*., 1994), the 20 protocols to be performed at a given session were selected randomly from a host set of 60 protocols assembled in advance.

The host set of 60 protocols was created by varying target parameters and tracking conditions. For example, different waveforms were used including sawtooth, square and triangle. The frequency of the target waveform ranged from 0.13 to 0.8 Hz. The required amplitude of finger movement ranged from 20 to 100% of the subject's full range. The non-paretic hand was used in some protocols to promote intermanual transfer of motor learning (Greenough *et al*., 1985; Imamizu *et al*., 1998). For the subjects with stroke, the tracking hand was the paretic hand for 90% and the non-paretic hand for 10% of the protocols. For the well elderly, the tracking hand was the right (dominant) hand for 90% and the left hand for 10% of the protocols. The hand position was varied between pronated, supinated or mid-position. These positions were used to promote a greater depth of information processing stemming from different levels of stimulus–response compatibility (Carey *et al*., 1998). For 5% of the training protocols, the tracking cursor was invisible to the subject. This added difficulty was included to reduce the external feedback and force further attention to the subject's own internal error detection processes (Schmidt, 1991). Once the 20 tracking protocols for each training session were selected randomly from the host set of 60, all subjects performed the same sequence. To minimize the influence of specificity of training, the specific target waveform, frequency and amplitude used for testing were never used during training.

The three trials of each protocol were performed consecutively with 10–15 s rest between trials. Generally, verbal feedback was given by the investigator to the subject only in a

summary format after completion of the third trial of each protocol to minimize reliance on external sources and instead promote an improved internal error detection system (Winstein *et al*., 1994; Yao *et al*., 1994). Five different investigators directed the training sessions, all of whom were physical therapists experienced with stroke rehabilitation and all were instructed to follow the same training procedure. In addition, two physical therapy graduate students directed the training sessions for the well elderly.

For subjects in the stroke or well elderly treatment groups, the post-test occurred within 1–4 days of the last training session. Between the pre-test and the post-test, subjects in the stroke control group and also the well elderly control group received no training and were instructed to continue with their normal daily routine. These subjects received their post-test within 4–7 weeks of their pre-test. Following the post-test, subjects in the stroke control group underwent 'crossover' and received 20 treatment sessions as described above. This group only then completed a third test (post-crossover). The post-test and post-crossover test followed the same procedures as the pre-test.

Tracking analysis

The computer quantified the tracking performance in each of the three task periods by calculating an accuracy index (AI) (Carey, 1990):

$$AI = 100(P - E)/P$$

E is the root mean square (r.m.s.) error between the target line and the response line, and P is the size of the individual's target pattern, calculated as the r.m.s. difference between the sine wave and the midline separating the upper and lower phases of the sine wave. The magnitude of P is determined by the scale of the vertical axis, which is the subject's range of finger motion. Therefore, the AI is normalized to each subject's own range of motion and takes into account any differences between subjects in the excursion of the tracking target. The maximum possible score is 100%. Negative scores occur when the response line is so distant from the target that it falls on the opposite side of the midline. The validity of the finger movement tracking test in discriminating between the performance of healthy subjects and subjects with stroke has been demonstrated (Carey, 1990; Carey *et al*., 1998).

fMRI analysis

Analysis of the MRIs was done on a Sun Ultra 60 (Sun Microsystems Inc., Palo Alto, Calif., USA) workstation using the interactive image analysis software Stimulate (Strupp, 1996). Anatomical images were acquired in axial, coronal and sagittal planes. The functional image was analysed from the detrended data in which control period data were fit to a line and the slope of the line was subtracted from the data set to remove any linear drifts in baseline. A mask was applied to the functional data such that any voxels with a variation in signal intensity >5% during the control phases were eliminated to remove large vessel contributions (Kim *et al*., 1994).

Our predefined area of investigation included the following five areas bilaterally: (i) sensorimotor cortex (SMC), defined as the combination of primary motor (M1) and primary sensory (S1); (ii) M1 separately; (iii) S1 separately; (iv) premotor cortex (PMC); and (v) supplementary motor area (SMA). PMC was defined as the anterior half of the precentral gyrus and the anterior bank of the precentral sulcus. SMA was defined as the medial wall of the hemisphere from the top of the brain to the depth of the cingulate sulcus with the posterior boundary halfway between the extension of the central and precentral sulci onto the medial surface and the anterior boundary at the vertical line through the anterior commissure (Dassonville *et al*., 1998). Activation was determined using a cross-correlation method (Bandettini *et al*., 1993) between the haemodynamic response to the alternating rest and track periods and our activation model, which defined the MRI scans corresponding to each period and took into account the lag in blood flow change that occurs with activation (Ashe and Ugurbil, 1994). We adjusted the threshold level of correlation between 0.4 and 0.65 and we used a minimum cluster size of either four or five contiguous voxels to produce a map of definitive cortical activation without extraneous activation in such areas as white matter and CSF. Under these conditions, we estimate that the resultant significance value for active voxels was at $P < 0.001$ (Xiong *et al*., 1995). Active voxels were overlaid onto anatomical images and analysed for Talairach location and voxel count. Anatomical landmarks and Talairach locations (Talairach and Tournoux, 1988) were used to assign activation to Brodmann's areas. The investigator performing the analysis, although not blinded to whether the images were from a subject with stroke versus a well elderly subject, was blinded to whether the images were from the pre-test, post-test or post-crossover.

Because of the differences in activation parameters between subjects and because of the variability in the blood oxygen level-dependent signal within subjects (Cramer *et al*., 1997), we used a normalized index, the laterality index (Cramer *et al*., 1997; Marshall *et al*., 2000), to quantify any shift in the balance of cortical activation between the two hemispheres for a specified region as a result of treatment. Thus, we calculated separate laterality indexes for the SMC, M1, S1, PMC and SMA regions. This index is defined as $(C - I) \div (C + I)$, where C = the active voxel count for the specified region in the hemisphere contralateral to the hand performing the tracking task and I = the active voxel count for the corresponding region in the hemisphere ipsilateral to the performing hand.

Statistical analysis

Reliability of the mean accuracy index from pre-test to post-test was examined for the stroke control group combined with the well elderly control group by using a repeated measures analysis of variance to compute the intraclass correlation

coefficient (ICC) (model 3,k). The reliability of the mean Box and Block score was examined using the same procedure for the stroke control group alone because the well elderly group did not receive the Box and Block test. For the laterality indexes, the reliability was computed with the ICC (model 3,1), since the pre-test and post-test data for each subject were single scores rather than means (Portney and Watkins, 2000).

Our between-group analysis for baseline differences between all subjects with stroke and all well elderly subjects on the accuracy index and laterality indexes was done using one-tailed, two-sample *t*-tests. We justified using one-tailed tests based on earlier findings with the accuracy index showing that subjects with stroke tracked with less skill than healthy controls (Carey *et al*., 1998), and findings with the laterality index showing that subjects with stroke used more ipsilateral cortical activity than healthy controls (Cramer *et al*., 1997).

Our within-group analysis for change from pre-test to post-test in the Box and Block score, accuracy index and the laterality indexes was done using one-tailed paired *t*-tests for each group. Also, a further analysis for a training effect in the subjects with stroke was done with greater statistical power by combining comparable data sets of the stroke control group and the stroke treatment group. That is, the post-test scores for the stroke control group were combined with the pre-test scores of the stroke treatment group because both these sets represented the performance immediately prior to treatment for each group. Likewise, the post-crossover scores for the stroke control group, obtained in a third testing session given only to the stroke control subjects, were combined with the post-test scores of the treatment group because both these sets represented the performance immediately following treatment in each group. Statistical significance was set at $P < 0.05$.

Results

ICCs

The ICC for the Box and Block score was 0.98 and for the accuracy index it was 0.78. The ICCs for the laterality indexes were as follows: SMC = 0.81, M1 = 0.92, S1 = 0.78, PMC = 0.69 and SMA = 0.12.

Between-group baseline comparisons

The mean (± standard error) accuracy index for the stroke treatment and stroke control groups combined on the pre-test was –40.2% (± 21.0). The mean accuracy index for the combined well elderly groups was –21.8% (± 9.8). The difference between these combined groups was not significant.

Tables 2 and 3 show the activated voxel counts and the laterality indexes for each cortical area in all subjects with stroke and all well elderly subjects, respectively. Comparison of the pre-test laterality indexes between all subjects with stroke and all well elderly subjects for each neural area is shown in Fig. 1. The negative values for the subjects with stroke indicate that cortical activation was predominantly in the hemisphere ipsilateral to the paretic hand performing the tracking task. In contrast, the positive values, with the exception of the SMA, for the well elderly subjects indicate predominantly contralateral cortical activation while tracking with their dominant (right) hand. The differences in laterality indexes between subjects with stroke and the well elderly subjects were statistically significant for SMC [$t(16) = 2.54$, $P = 0.011$], M1 [$t(16) = 3.37$, $P = 0.002$] and PMC [$t(16) = 3.09$, $P = 0.004$].

The characteristic profile of predominantly ipsilateral activation in subjects with stroke prevailed whether the paretic side was right or left. For the subjects with right hemiparesis, the mean laterality indexes for the SMC, M1, S1, PMC and SMA regions were –0.17 (± 0.30), –0.24 (± 0.32), –0.19 (± 0.40), –0.17 (± 0.22) and –0.04 (± 0.28), respectively. For the subjects with left hemiparesis, the corresponding values were –0.47 (± 0.20), –0.64 (± 0.13), –0.32 (± 0.33), –0.52 (± 0.29) and –0.28 (± 0.10), respectively. None of the comparisons of these corresponding values between the right and left hemiparesis groups were significant.

Within-group comparisons

The mean Box and Block score for the stroke treatment group at pre-test was 27.8 blocks (± 7.68), compared with 34.2 blocks (± 8.1) at post-test, which reflected a significant [$t(4) = 3.37$, $P = 0.014$] improvement in finger grasp and release function. For the stroke control group, the pre-test mean was 30.3 blocks (± 6.0), compared with 32.1 blocks (± 6.0) at post-test (non-significant). However, on the post-crossover test, their mean Box and Block score improved to 38.9 (± 15.6), which was significantly different [$t(4) = 4.18$, $P = 0.007$] from their post-test value.

The mean accuracy index for the stroke treatment group at pre-test was –18.0% (± 12.3), compared with 23.3% (± 5.1) at post-test, which was a significant [$t(4) = 2.92$, $P = 0.022$] improvement in finger movement control. For the stroke control group, the pre-test mean was –62.4% (± 40.0), compared with –31.8% (± 17.8) at post-test (non-significant). However, on the post-crossover test, their mean accuracy index improved to 0.2% (± 20.3), which was significantly different [$t(4) = 4.82$, $P = 0.004$] from their post-test value. The mean accuracy index for the well elderly treatment group at pre-test was –30.1% (± 10.5), compared with 4.9% (± 26.7) at post-test (non-significant). For the well elderly control group, the pre-test mean was –11.4% (± 18.0), compared with –20.5% (± 12.6) at post-test (non-significant). Figure 2 shows the improved tracking performance for one subject in the stroke treatment group (Subject 4) from the first tracking trials of his pre-test and post-test.

Figure 3 shows the change in laterality index for each neural area from pre-test to post-test within each group; plus,

Table 2 *Number of significantly (P < 0.001) active voxels and corresponding laterality index for each neural region during the finger movement tracking task for subjects with stroke*

Stroke subject	Test	SMC			M1			S1			PMC			SMA		
		C	I	LI	C	I	LI	C	I	LI	C	I	LI	C	I	LI
1 (Trt)	Pre	16	15	0.03	16	12	0.14	0	3	–1	40	56	–0.17	6	22	–0.57
	Post	26	8	0.53	25	8	0.52	1	0	1	63	45	0.17	7	4	–0.27
2 (Trt)	Pre	23	4	0.64	20	4	0.67	3	1	0.5	39	49	–11	2	6	–0.5
	Post	60	8	0.76	28	7	0.60	32	1	0.97	154	54	0.48	12	5	0.41
3 (Trt)	Pre	0	52	–1	0	29	–1	0	23	–1	0	6	–1	0	0	NC
	Post	35	85	–0.42	12	33	–0.47	23	52	–0.39	16	10	0.23	8	11	–0.16
4 (Trt)	Pre	5	29	–0.71	1	19	–0.90	4	10	–0.43	6	4	0.20	8	0	1
	Post	38	3	0.85	20	0	1	18	3	0.71	24	13	0.30	0	8	–1
5 (Trt)	Pre	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Post	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
6 (Con)	Pre	20	56	–0.47	8	37	–0.64	12	19	–0.08	49	78	–0.23	6	13	–0.37
	Post	25	26	–0.02	17	18	–0.03	8	8	0	26	60	–0.40	13	20	–0.21
	PC	24	17	0.17	16	5	0.52	8	12	–0.20	10	5	0.33	9	8	0.06
7 (Con)	Pre	20	21	–0.02	6	16	–0.46	14	5	0.47	108	80	0.15	19	34	–0.28
	Post	19	20	–0.03	6	16	–0.46	13	4	0.53	62	50	0.11	16	22	–0.16
	PC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
8 (Con)	Pre	10	7	0.18	6	7	–0.08	4	0	1	10	6	0.25	7	9	–0.12
	Post	14	13	0.04	7	13	–0.30	7	0	1	32	24	0.14	2	4	–0.33
	PC	9	5	0.29	7	3	0.40	2	2	0	12	13	–0.04	5	3	0.25
9 (Con)	Pre	12	28	–0.40	11	23	–0.53	1	5	–0.67	0	7	–1	5	14	–0.47
	Post	9	36	–0.60	6	22	–0.57	3	14	–0.65	5	35	–0.75	1	8	–0.77
	PC	101	28	0.57	82	16	0.67	19	12	0.23	76	104	–0.16	25	9	0.47
10 (Con)	Pre	0	25	–1	0	5	–1	0	20	–1	0	8	–1	4	4	0
	Post	9	36	–0.60	4	13	–0.53	5	23	–0.64	5	6	–0.09	6	3	0.33
	PC	45	8	0.70	26	4	0.73	19	4	0.65	28	5	0.70	3	1	0.50

M1 = primary motor area; PMC = premotor cortex; S1 = primary sensory area; SMA = supplementary motor area; SMC = sensorimotor cortex; C = hemisphere contralateral to tracking hand; I = hemisphere ipsilateral to tracking hand; LI = laterality index; Trt = treatment; Con = control; Pre = pre-test; Post = post-test; PC = post-crossover; NC = not calculable due to division by zero; NA = not available due to head movement. (The number of active voxels can be less than the minimum cluster size when only a portion of the cluster was located in the specified neural region.)

for the stroke control group, it shows the post-test to post-crossover test change. For the stroke treatment group, the laterality index for all neural areas except the SMA inverted from negative to positive. The change was significant for the S1 [$t(4) = 3.05$, $P = 0.028$], whereas the SMC [$t(4) = 2.25$, $P = 0.055$] and PMC [$t(4) = 2.32$, $P = 0.051$] showed trends toward significance. For the stroke control group, the laterality index remained negative for all areas except the S1, which showed only a slight change toward positive. However, for this same group after receiving treatment, the laterality index inverted to positive for each area on the post-crossover test. The changes for the SMC [$t(3) = 2.47$, $P = 0.045$] and M1 [$t(3) = 5.12$, $P = 0.007$] were significant, whereas the SMA showed a trend [$t(3) = 2.34$, $P = 0.051$]. For the well elderly treatment group, the SMC [$t(4) = 2.64$, $P = 0.029$] and the M1 [$t(4) = 3.40$, $P = 0.014$] increased significantly, whereas the SMA showed a trend [$t(4) = 2.13$, $P = 0.050$]. None of the changes were significant for the well elderly control group.

Figure 4 shows the change in laterality index for the stroke subjects only, after combining the pre-test for the stroke treatment group with the post-test for the stroke control group to form a combined pre-treatment group and combining the post-test of the stroke treatment group with the post-crossover of the stroke control group to form a combined post-treatment group. With the added statistical power from more subjects, all areas except the SMA demonstrated significant change in laterality index in the positive direction, indicating a shift from predominantly ipsilateral to predominantly contralateral activation following treatment. Furthermore, the means of the laterality index for all subjects with stroke following treatment now showed close proximity to the corresponding pre-test values of the well elderly subjects (Fig. 1), with two-sample *t*-tests indicating no significant differences in the comparisons of each area.

Figure 5 shows an example of the functional brain images for one subject from the stroke treatment group (Subject 4) while tracking with his paretic right hand before and after treatment. The images show a shift in activation from ipsilateral to contralateral following treatment, including activation in the peri-infarct zone. Figure 6 shows the images for one subject from the stroke control group (Subject 10) using his paretic right hand before and after the control period and also after crossing over to receive treatment. The images show predominantly ipsilateral activity both before and after the control period but predominantly contralateral activity

Table 3 *Number of significantly (P < 0.001) active voxels and corresponding laterality index for each neural region during the finger movement tracking task for well elderly subjects*

Elderly subject	Test	SMC			M1			S1			PMC			SMA		
		C	I	LI	C	I	LI	C	I	LI	C	I	LI	C	I	LI
1 (Trt)	Pre	12	23	–0.31	6	16	–0.45	6	7	–0.08	53	14	0.58	1	8	–0.78
	Post	61	53	0.07	32	38	–0.09	29	15	0.32	67	17	0.60	7	10	–0.18
2 (Trt)	Pre	10	20	–0.33	10	15	–0.20	0	5	–1	14	13	0.04	10	7	0.18
	Post	18	4	0.64	12	4	0.50	6	0	1	20	28	–0.17	13	6	0.37
3 (Trt)	Pre	54	18	0.50	30	7	0.62	24	11	0.37	26	10	0.44	0	0	NC
	Post	25	0	1	15	0	1	10	0	1	18	12	0.20	0	0	NC
4 (Trt)	Pre	18	0	1	10	0	1	8	0	1	16	8	0.33	0	1	–1
	Post	1	0	1	1	0	1	0	0	NC	16	10	0.23	0	0	NC
5 (Trt)	Pre	18	7	0.44	7	7	0	11	0	1	4	3	0.14	5	3	0.25
	Post	28	5	0.70	8	5	0.23	20	0	1	30	0	1	7	3	0.40
6 (Con)	Pre	24	17	0.17	12	5	0.41	12	12	0	25	15	0.25	10	14	–0.17
	Post	9	1	0.80	9	1	0.80	0	0	NC	19	27	–0.17	10	8	0.11
7 (Con)	Pre	29	25	0.07	20	7	0.48	9	18	–0.33	25	17	0.19	0	5	–1
	Post	12	4	0.50	8	2	0.6	4	2	0.33	48	11	0.63	6	4	0.2
8 (Con)	Pre	6	3	0.33	3	0	1	3	3	0	6	3	0.33	7	3	0.40
	Post	27	0	1	13	0	1	14	0	1	12	0	1	4	3	0.14
9 (Con)	Pre	19	0	1	8	0	1	11	0	1	0	0	NC	0	0	NC
	Post	75	9	0.79	43	0	1	32	9	0.56	9	4	0.39	0	0	NC

M1 = primary motor area; PMC = premotor cortex; S1 = primary sensory area; SMA = supplementary motor area; SMC = sensorimotor cortex; C = hemisphere contralateral to tracking hand; I = hemisphere ipsilateral to tracking hand; LI = laterality index; Trt = treatment; Con = control; NC = not calculable due to division by zero. (The number of active voxels can be less than the minimum cluster size when only a portion of the cluster was located in the specified neural region.)

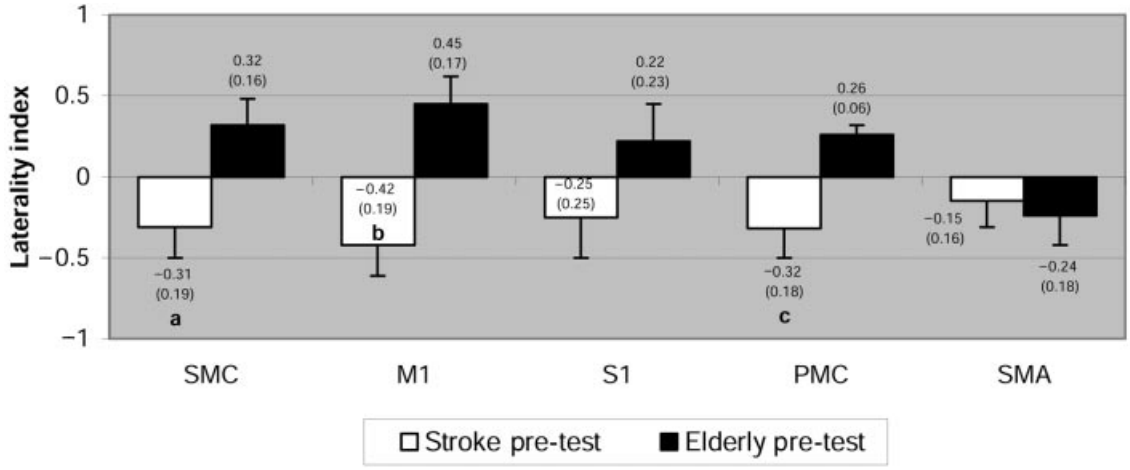


Fig. 1 Mean (± standard error) laterality indexes for the sensorimotor cortex (SMC), primary motor cortex (M1), primary sensory cortex (S1), premotor cortex (PMC) and supplementary motor area (SMA) for all subjects with stroke ($n = 9$) compared with all well elderly subjects ($n = 9$) on the pre-test. [a]Significantly different from well elderly pre-test SMC ($P = 0.011$); [b]significantly different from well elderly pre-test M1 ($P = 0.002$); [c]significantly different from well elderly pre-test PMC ($P = 0.004$)

after treatment. For the well elderly subjects, apart from atrophy, the anatomical images did not show any structural abnormalities.

Discussion

This study shows that individuals with chronic stroke who have impaired finger movement can be trained to improve their finger control through intensive practice at a finger movement tracking task and that the skill learned from such training is transferred to a more functional finger grasp and release task. Furthermore, the fMRI evidence, generated with the high resolution of a 4 tesla magnet (Ashe and Ugurbil, 1994), suggests that the improved finger function is accompanied by brain reorganization.

Evidence of improved finger movement control in the subjects with stroke is seen in the change in the accuracy index from pre-test to post-test. This score improved signifi-

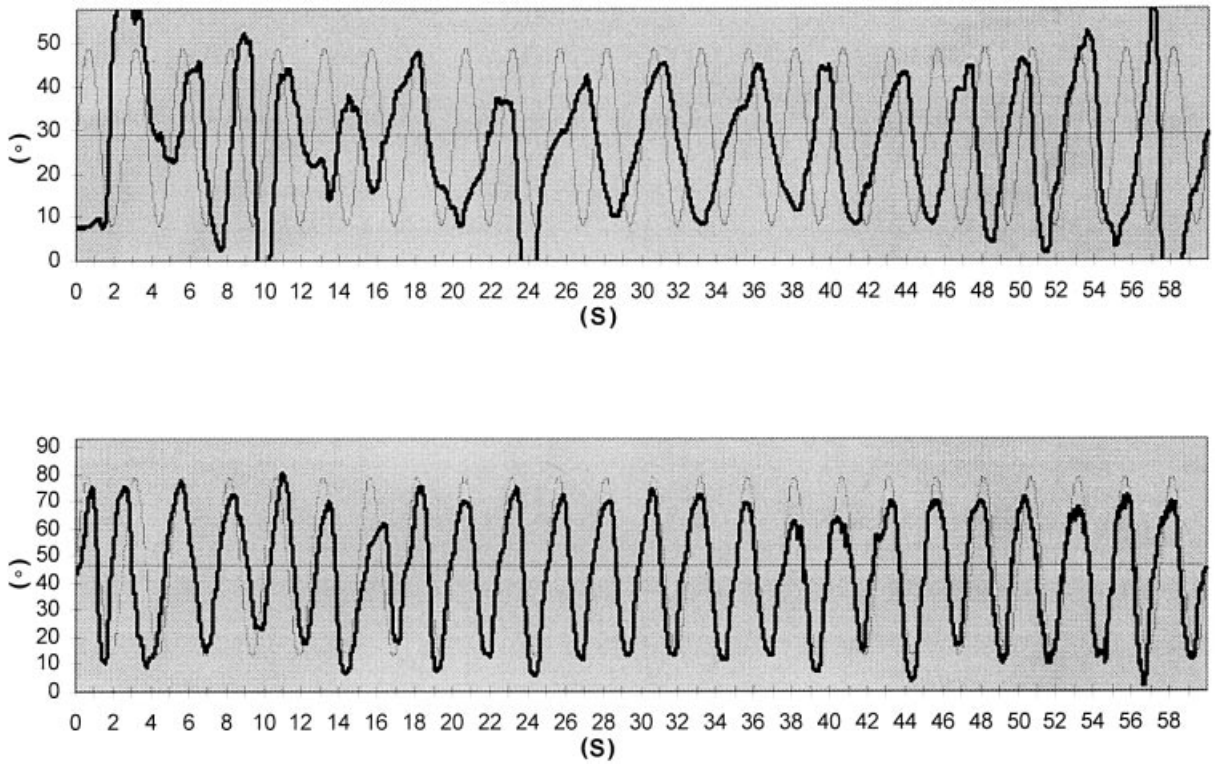
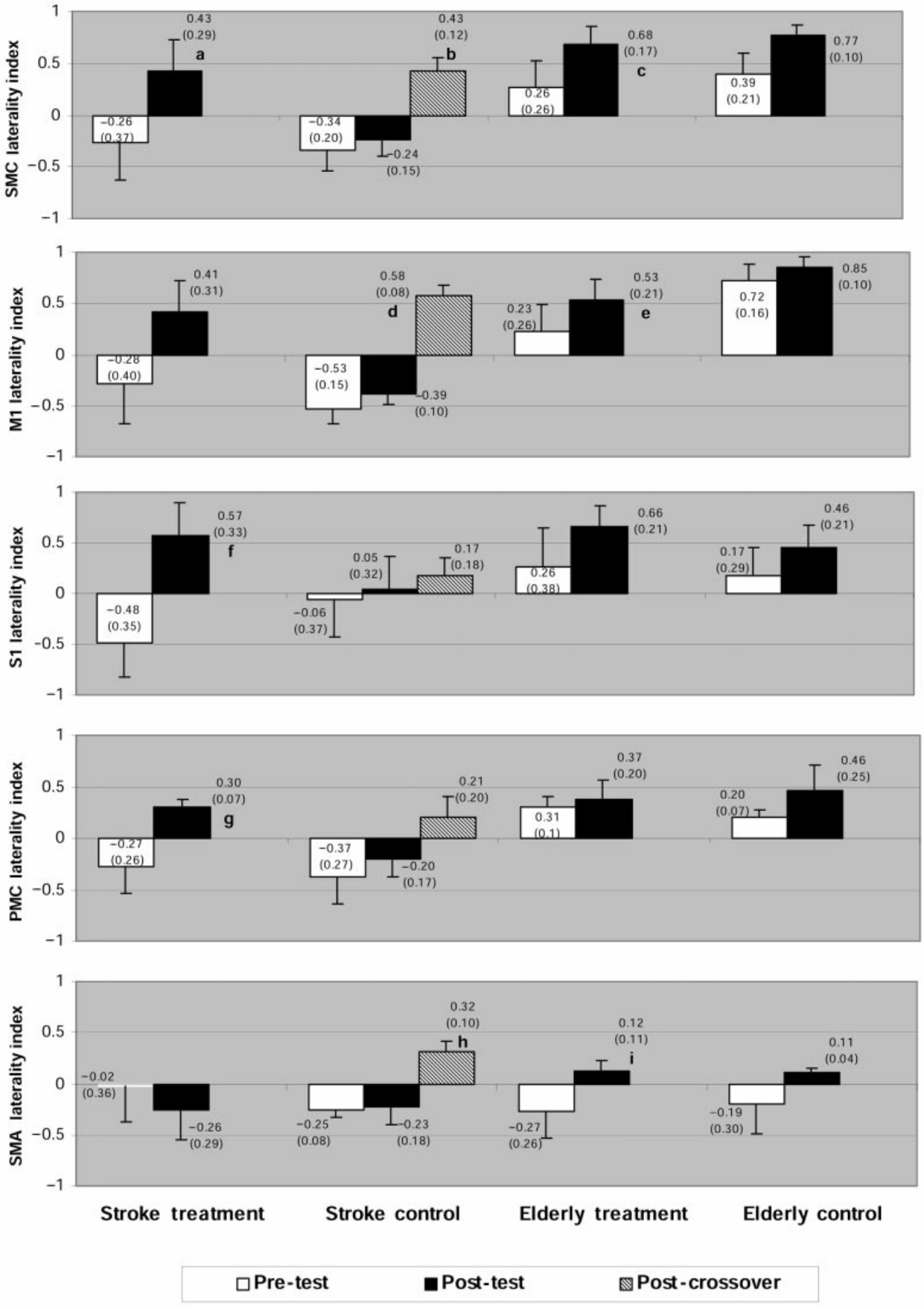


Fig. 2 Finger movement tracking responses from a subject with stroke (Subject 4) performing with his paretic right hand before (*upper*: accuracy index = –56.4%) and after (*lower*: accuracy index = 43.5%) 20 sessions of finger tracking training. Finger extension is upward and finger flexion is downward.

cantly for the stroke treatment group, with no such change for the stroke control group, although this group did improve significantly following crossover treatment. Although the tracking training and the tracking tests had similarities, there were also marked differences so that it could not be presumed that performance on the tracking tests would improve automatically. None of the tracking parameters (waveforms, frequencies and amplitudes) used during the tracking training matched those that were used in the tracking tests. Also, subject position, the visual presentation and extraneous noise inside the magnet were largely different between training and testing. We believe that it is because of these factors creating less than optimum conditions for skilful performance that the accuracy index values were generally negative and lower than earlier findings for both subjects with stroke and well elderly (Carey *et al*., 1998). Nonetheless, by transferring skill acquired during training to a set of conditions entirely different from those used during training, subjects with stroke demonstrated evidence of motor learning (Schmidt, 1988).

Moreover, the stroke treatment group also showed significant improvement on the Box and Block test, whereas the stroke control group did not from pre-test to post-test but they did following crossover treatment. This result is important because the ability to grasp and release small objects repeatedly using the index finger and thumb represents an objective functional corollary to the finger flexion and extension movements required for tracking. Still, the Box and Block scores demonstrated by our subjects with stroke following treatment remained below normal. We did not measure the Box and Block scores for the well elderly, but Mathiowetz *et al*. (1985) reported that the mean (± standard error) for well elderly females of similar age to our group was 68.6 blocks (± 1.3). Thus, with considerable room for improvement still remaining, more work is needed to determine whether extended treatment can produce further improvements beyond these initial findings. Three subjects with stroke volunteered information on how they were pleased with functional improvements (handwriting, keyboarding, sewing) beyond the tracking and Box and Block scores. Others may have experienced the same but did not offer the information. We acknowledge the limitation of anecdotal reports; future studies will employ appropriate tests to examine whether such skill transfers to other real-world functions such as dressing, feeding, etc.

We believe that the laterality index is a reasonable indicator of brain reorganization due to treatment. With the instability of the absolute voxel count that we have observed on repeated testing, we are not confident that a change in voxel count is a direct reflection of the treatment. However, we have recognized that the laterality index remains stable when different cross-correlation coefficients have been used in analysing a single subject's data. Furthermore, the ICCs for


SMC laterality index
M1 laterality index
S1 laterality index
PMC laterality index
SMA laterality index
1
0.5
0
−0.5
−1
0.43 (0.29)
a
−0.26 (0.37)
0.43 (0.12)
b
−0.34 (0.20)
−0.24 (0.15)
0.68 (0.17)
c
0.26 (0.26)
0.77 (0.10)
0.39 (0.21)
0.41 (0.31)
−0.28 (0.40)
0.58 (0.08)
d
−0.53 (0.15)
−0.39 (0.10)
0.53 (0.21)
e
0.23 (0.26)
0.85 (0.10)
0.72 (0.16)
0.57 (0.33)
f
−0.48 (0.35)
0.05 (0.32)
0.17 (0.18)
−0.06 (0.37)
0.66 (0.21)
0.26 (0.38)
0.46 (0.21)
0.17 (0.29)
0.30 (0.07)
g
−0.27 (0.26)
0.21 (0.20)
−0.37 (0.27)
−0.20 (0.17)
0.37 (0.20)
0.31 (0.1)
0.46 (0.25)
0.20 (0.07)
0.32 (0.10)
h
−0.02 (0.36)
−0.26 (0.29)
−0.25 (0.08)
−0.23 (0.18)
0.12 (0.11)
i
−0.27 (0.26)
0.11 (0.04)
−0.19 (0.30)
Stroke treatment
Stroke control
Elderly treatment
Elderly control
Pre-test
Post-test
Post-crossover

the laterality indexes of all neural areas except the SMA were within a range that indicates moderate to good reliability (Portney and Watkins, 2000). The low ICC for the SMA we believe is explained by the combination of the low active voxel count (e.g. 4) in the midline location. Thus, if from the first test to the second test the active voxel count changed by even just one or two voxels and it shifted even the slightest amount right or left from midline, the ipsilateral index could change dramatically, yielding low agreement of values between the two tests when, qualitatively, the activation appeared to be consistent.

We studied the SMC, M1, S1, PMC and SMA based on their reported neuroplastic recovery potential (Aizawa *et al*., 1991; Cramer *et al*., 1997; Seitz *et al*., 1998; Liu and Rouiller, 1999; Cramer *et al*., 2000). Our finding of negative laterality indexes in the subjects with stroke for all of these neural areas at pre-test contrasts sharply with the positive values for the corresponding areas in the well elderly subjects, except the SMA (Fig. 1). This finding is consistent with numerous other studies suggesting that activation of cortical areas ipsilateral to the paretic hand is important in the motor recovery process following stroke (Chollet *et al*., 1991; Weiller *et al*., 1993; Cramer *et al*., 1997, 1999; Cao *et al*., 1998). Furthermore, this finding is consistent with the view of Rossini and Pauri (2000) that multiple and diffuse neural colonies exist that subserve a vast repertoire of movement strategies for a given muscle. Following neural injury then, and under as yet unspecified conditions, spared members of the neuronal circuitry, including the intact hemisphere, may adapt vicariously to substitute a semblance of the desired movement strategy. Studies are needed to uncover both the favourable conditions that promote such adaptation and the unfavourable conditions that may impede it. Furthermore, additional studies are needed to examine the plasticity of other neural areas important in movement control, such as visual cortex, basal ganglia and cerebellum, which were not studied here.

More importantly, however, this study shows an inversion of the laterality index from negative to positive following training of the subjects with stroke, indicating a shift in neural activation of the paretic hand from ipsilateral centres to contralateral centres. In fact, the laterality indexes for the subjects with stroke following treatment (Fig. 4) were in close proximity to the baseline values for the well elderly (Fig. 1). Our results are consistent with results from studies using transcranial magnetic stimulation showing decreased ipsilateral cortical excitability and increased contralateral excit-

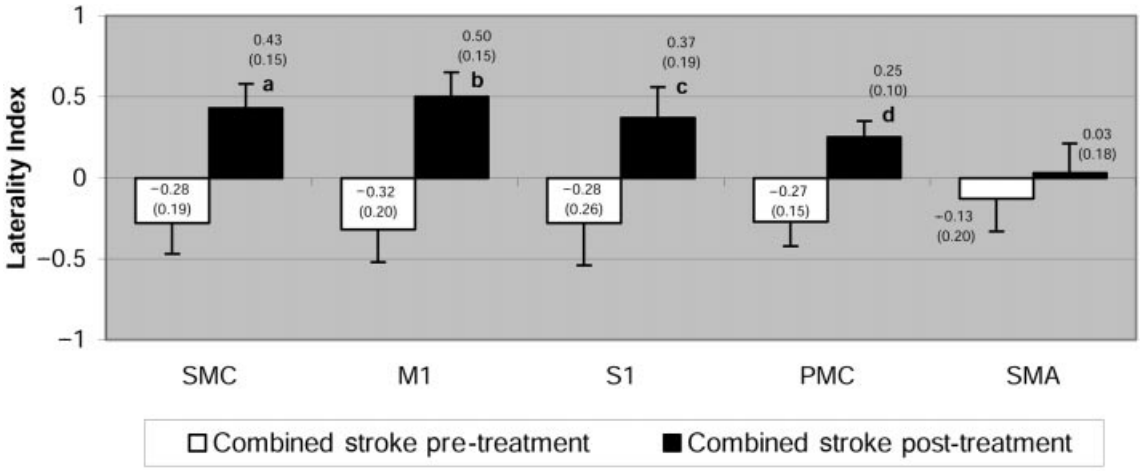


Fig. 4 Mean (± standard error) laterality indexes for the sensorimotor cortex (SMC), primary motor cortex (M1), primary sensory cortex (S1), premotor cortex (PMC) and supplementary motor area (SMA) for the stroke subjects only (n = 8), after combining the pre-test for the stroke treatment group with the post-test for the stroke control group (combined stroke pre-treatment) and combining the post-test for the stroke treatment group with the post-crossover for the stroke control group (combined stroke post-treatment). [a]Significantly different from pre-treatment (P = 0.004); [b]significantly different from pre-treatment (P = 0.004); [c]significantly different from pre-treatment (P = 0.044); [d]significantly different from pre-treatment (P = 0.006).

Fig. 3 Mean (± standard error) laterality indexes for the sensorimotor cortex (SMC), primary motor cortex (M1), primary sensory cortex (S1), premotor cortex (PMC) and supplementary motor area (SMA) for each group on pre-test, post-test and post-crossover test. For stroke treatment pre-test–post-test comparison n = 4. For stroke control pre-test–post-test comparison n = 5 but for stroke control post-test–post-crossover comparison n = 4 (loss of one subject at post-crossover due to head movement). For elderly treatment pre-test–post-test comparison n = 5. For elderly control pre-test–post-test comparison n = 4. [a]Trend toward significant difference from pre-test (P = 0.055); [b]significantly different from post-test (P = 0.045); [c]significantly different from pre-test (P = 0.029); [d]significantly different from post-test (P = 0.007); [e]significantly different from pre-test (P = 0.014); [f]significantly different from pre-test (P = 0.028); [g]trend toward significant difference from pre-test (P = 0.051); [h]trend toward significant difference from post-test (P = 0.051); [i]trend toward significant difference from pre-test (P = 0.050).

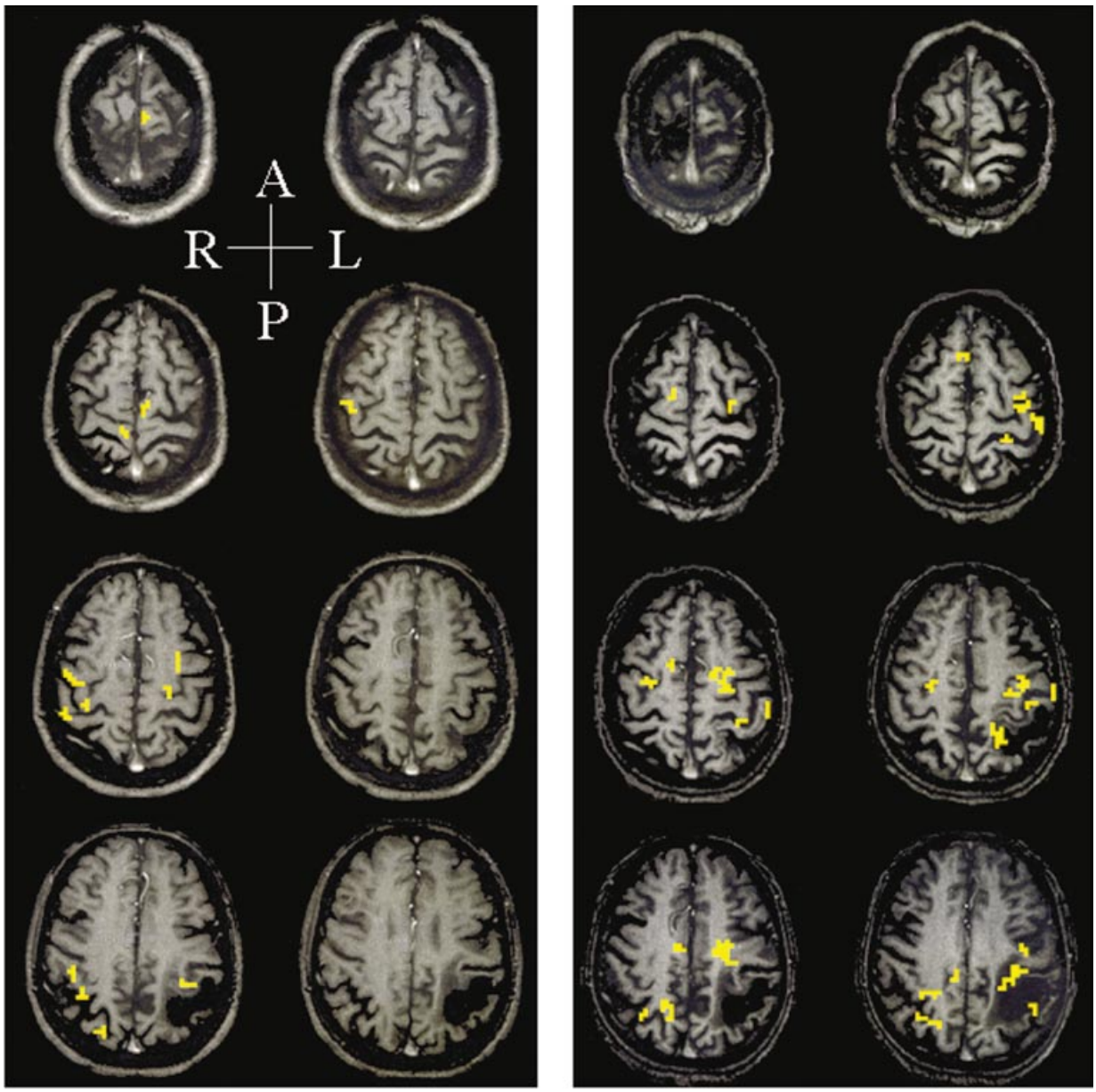


Fig. 5 fMRIs (rostral eight slices) for one subject (Subject 4) in the stroke treatment group (9.4 years post-stroke) performing the finger movement tracking test with his paretic right hand before (pre-test) and after (post-test) 20 sessions of finger tracking training. An infarct in the left parietal cortex is evident in the lower three images of each set. Cortical activation is predominantly ipsilateral before training and predominantly contralateral after training. Cortical activation at the peri-infarct zone is evident after training. Laterality indexes for the sensorimotor cortex, primary motor cortex, primary sensory cortex, premotor cortex and supplementary motor area at pre-test were –0.71, –0.90, –0.43, 0.20 and 1, respectively. At post-test, they were 0.85, 1, 0.71, 0.30 and –1, respectively.

ability following forced use with constraint-induced movement therapy in subjects with stroke (Liepert *et al*., 1998, 2000*a*, 2001). Thus, evidence from two different experimental methods (fMRI and transcranial magnetic stimulation) indicates that neural centres in the stroke hemisphere appear to be responsive to intensive use of the contralateral paretic limb. We do acknowledge, however, that there is a fundamental difference between constraint-induced movement therapy and the tracking training used in this study in that the former employs an additional component (immobilization), which may provide a further stimulus for neuroplastic change.

We also found evidence of increased cortical activity in the 'peri-infarct zone' in one of the two subjects who had parietal lesions (Fig. 5). This observation is consistent with other reports suggesting that the peri-infarct zone in cortical areas

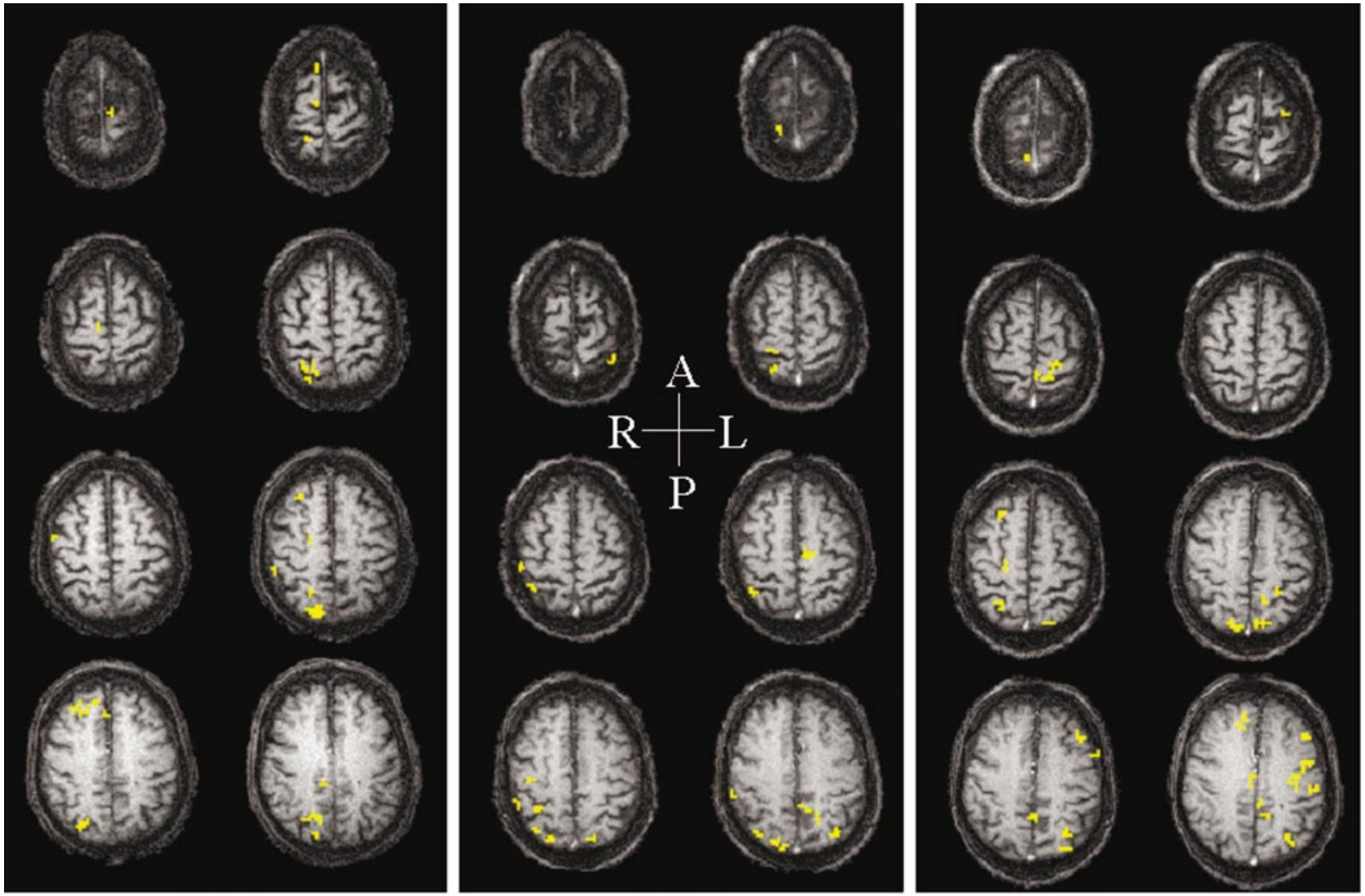


Fig. 6 Functional MRIs (rostral eight slices) for one subject (Subject 10) in the stroke control group (1.3 years post-stroke) performing the finger movement tracking test with his paretic right hand before (pre-test) and after (post-test) the control period and again after 20 sessions of finger tracking training (post-crossover). Cortical activation is predominantly ipsilateral both before and after the control period and predominantly contralateral after training. Laterality indexes for the sensorimotor cortex, primary motor cortex, primary sensory cortex, premotor cortex and supplementary motor area at pre-test were –1, –1, –1, –1 and 0, respectively. At post-test, they were –0.60, 0.53, –0.64, –0.09 and 0.33, respectively. At post-crossover, they were 0.70, 0.73, 0.65, 0.70 and 0.50, respectively.

with partial preservation of function is rich in its capacity to recover and serve the paretic limb, if only stimulated to do so (Furlan *et al*., 1996; Cramer *et al*., 1997; Liu and Rouiller, 1999).

To summarize, from our observations, there may be two different forms of neuroplasticity associated with stroke recovery in the paretic hand. The first is a migration of cortical activation from the infarcted (contralateral) hemisphere to neural colonies in the ipsilateral hemisphere. Certainly, there may also be migration to intact neurones within the infarcted hemisphere but the distinctly different laterality index between subjects with stroke and healthy controls draws much attention to the idea of ipsilateral control. The second appears to be a reversion back to contralateral control. The two may have different, as yet unidentified mechanisms. The former may be associated more with the neural insult and spontaneous recovery (Jones and Schallert, 1994) and not so dependent on intensive use. This, however, is speculative because we do not know in sufficient detail the intensity of the early rehabilitation effort in our subjects with stroke or in those from previous studies that showed increased ipsilateral activation (Chollet *et al*., 1991; Weiller *et al*., 1993; Cramer *et al*, 1997, 1999; Cao *et al*., 1998). The second does appear to depend on intensive use though, as demonstrated by the stroke treatment group of this study coupled with the stroke control group changing only after crossover.

This study also indicates that the time since stroke onset does not appear to be a firm limiting factor to treatment effectiveness. The mean time since stroke onset for subjects in this study was 4.7 ($\pm$ 6.3) years. As a specific example, Subject 4, who showed improved finger movement control (Fig. 2) and brain reorganization (Fig. 5) following training, was 9 years post-stroke. These results refute the time-honoured but evidence-lacking adage that rehabilitation potential is exhausted after 1 year post-stroke.

We acknowledge the concern that the ipsilateral brain activation in subjects with stroke could perhaps not be ipsilateral activation but rather contralateral activation associated with simultaneous activation (mirroring) of the non-paretic hand (Cramer *et al*., 1999). However, we do not believe mirroring occurred in our subjects. We observed the non-paretic hand during the practice trials with the paretic hand prior to the actual test and did not observe mirroring. Furthermore, if mirroring were a characteristic behaviour in some subjects, it seems unlikely that they would show mirroring only before treatment, when the laterality index was negative, and not after treatment, when it was positive.

We questioned whether well elderly subjects, with no known neurological lesion, could also show evidence of brain reorganization following treatment. Jones and Schallert (1994) showed with a forced-use paradigm in rats that two concurrent conditions were required to demonstrate evidence of neuroplasticity, a neurological lesion and forced behaviour. In their study, the presence of a neurological lesion without forced behaviour was ineffective and, furthermore, forced behaviour without a neurological lesion was also ineffective. Conversely, Karni *et al*. (1995) showed with fMRI that healthy adults 24–44 years of age did demonstrate brain reorganization following practice at a complex motor task, evidenced by an expansion of activation into a previously inactive subpopulation of M1 voxels. Our results concur with the latter study and show that brain reorganization in the SMC and M1 areas can occur following training at a visual–spatial task in healthy females considerably older than the subjects used by Karni *et al*. (1995). Thus, although brain neuroplasticity may be optimized under conditions in which forced use is combined with a neurological lesion (Jones and Schallert, 1994), our findings suggest that training-induced brain changes are still possible in humans without overt brain lesions. Still, the brain changes were not as precipitous as in those with an overt brain lesion (Fig. 3) and perhaps this explains why the subjects with stroke showed improved tracking scores with training and the well elderly did not.

We do acknowledge, however, that occult pathology could have been present in our supposedly 'well' elderly group, particularly since their tracking scores were not significantly higher than those of the subjects with stroke. Therefore, it is possible that the well elderly subjects did meet the two requisites for neuroplastic change emphasized by Jones and Schallert (1994). The possible influence of neural lesions, subtle or overt, on neuroplasticity following treatment remains intriguing. This invites further research comparing the elderly with young adults on the same motor learning task to examine whether younger adults, with a mature nervous system but prior to subtle ageing-related neurological lesions (Brewer, 2000), might actually demonstrate a lesser capacity for brain reorganization compared with the elderly.

Overall, our results suggest that certain cortical centres in subjects with chronic stroke, and to a lesser extent in well elderly females, have the potential to change from a quiescent state to an active state when challenged repeatedly with a spatial motor training task. As stated above, the mechanism by which such use-induced brain reorganization occurs is not clear; however, Rossini and Pauri (2000) reviewed three possibilities: changes in neuronal membrane excitability, removal of local inhibition and changes in synaptic effectiveness. Liepert *et al*. (1998) suggested that activity-dependent strengthening of synaptic effectiveness occurs through long-term potentiation to cause increased excitability. Additionally, Liepert *et al*. (2000*b*) theorized that modulations of GABA transmission may be important for use-dependent enlargement of cortical activation. Finally, it is inviting to consider studies with animals showing that repeated physical activity increases production of neurotrophins, which in turn have a beneficial effect on neurone survival and synaptic effectiveness (Neeper *et al*., 1996; Gómez-Pinilla *et al*., 1997).

We conclude that tracking training, with its emphasis on repeated challenging of the error detection, motor planning and motor execution systems, has the potential to promote

further recovery and brain reorganization in subjects with chronic stroke. More studies are needed to examine for effects on real-world functions and determine whether benefits are retained over time.

Acknowledgements

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