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Research Article

A Functional MRI Study of Three Motor Tasks in the Evaluation of Stroke Recovery

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Functional brain imaging studies have provided insights into the processes related to motor recovery after stroke. The comparative value of different motor activation tasks for probing these processes has received limited study. We hypothesized that different hand motor tasks would activate the brain differently in controls, and that this would affect control–patient comparisons. Functional magnetic resonance imaging (MRI) was used to evaluate nine control subjects and seven patients with good recovery after a left hemisphere hemiparetic stroke. The volume of activated brain in bilateral sensorimotor cortex and four other motor regions was compared during each of three tasks performed by the right hand: index finger tapping, four-finger tapping, and squeezing. In control subjects, activation in left sensorimotor cortex was found to be significantly larger during squeezing as compared with index-finger tapping. When comparing control subjects with stroke patients, patients showed a larger volume of activation in right sensorimotor cortex during index-finger tapping but not with four-finger tapping or squeezing. In addition, patients also showed a trend toward larger activation volume than controls within left supplementary motor area during index-finger tapping but not during the other tasks. Motion artifact was more common with squeezing than with the tapping tasks. The choice of hand motor tasks used during brain mapping can influence findings in control subjects as well as the differences identified between controls and stroke patients. The results may be useful for future studies of motor recovery after stroke. **Key Words:** Stroke—Motor recovery—Functional MRI.

There is a wide variation in the degree of recovery after stroke (1, 2). The brain events contributing to this recovery remain incompletely understood. Previous motor activation studies in humans using positron emission tomography, functional MRI (fMRI) (5–7), and electrophysiologic methods (4, 8) have provided evidence for a change in brain function within multiple regions, in particular sensorimotor cortex of the nonstroke hemisphere and along the rim of a cortical infarct. An improved understanding of the processes underlying stroke recovery may have directive value in the design of improved treatments targeting this process.

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Functional imaging studies of motor recovery have used a number of different motor tasks to activate the brain (3–11). Not all studies have reached the same findings, for example, regarding activation of sensorimotor cortex of the nonstroke hemisphere during performance of a motor task by the stroke-affected hand. Differences in study findings may have been due to a number of factors, including the choice of motor task used to activate the brain.

These studies have largely focused on motor tasks that can be performed by only a subset of stroke patients, those with good motor function. Early after stroke, or late after stroke when recovery has been limited, patients may have poor motor function. When evaluating such patients, less refined motor tasks may be needed as compared with most of the tasks described earlier. For example, patients with good recovery can perform individual finger movements, being stage 6 of Brunnstrom's six stages of motor recovery (12). Squeezing, however, is stage 3 of 6 and may be seen when there has been only limited recovery from hemiplegic stroke. The comparative utility of less refined movements to study motor recovery has not been evaluated in patients with poor recovery or in patients with good recovery.

The current study aimed to address some of these issues. In control subjects, regional brain activation volumes during performance of three different hand motor tasks were compared. For each of the three tasks, activation volumes in control subjects were compared with findings in patients with a left hemisphere hemiparetic stroke. As a first step toward evaluating different motor tasks, only patients with good recovery were studied. The brain areas of primary focus were sensorimotor cortex of each hemisphere and the rim of intact tissue surrounding a cortical stroke. In addition, because different tasks might induce head motion in dissimilar ways, the number of studies contaminated by excessive head motion was determined for each of the three tasks.

Methods

Subject Selection and Training

Seven right-handed (13) stroke patients with a history of a hemiparetic, ischemic stroke in the left hemisphere were enrolled after review of admitting records to Massachusetts General Hospital and Spaulding Rehabilitation Hospital. Entry criteria were weakness [≤4+ on the MRC scale (14)] in hand interossei and wrist extensor of ≥48 h duration, as well as good motor recovery, defined by improvement in strength by at least one level (to ≥4+ strength) on the MRC scale with resolution of any upper extremity synkinesias. Patients with a history of a prior stroke associated with sensorimotor deficits were excluded. Nine right-handed controls had a normal neurologic examination, no history of a stroke, and no significant active neurologic problems. All subjects gave informed consent. Before scanning, each subject was trained to perform the three motor tasks according to instructions.

MRI Image Acquisition

Echo planar (EPI) and conventional images were obtained using a high-speed whole-body scanner (1.5 Tesla General Electric Signa modified by Advanced NMR Systems) and a quadrature head coil. Velcro restraints were applied to the head and shoulders, and padding was placed around the head. Each scanning session included (a) high-resolution volumetric gradient echo images, 2.8 mm thickness, (b) flow-compensated images in plane with functional images, (c) high-resolution EPI anatomic images in plane with functional images, and (d) blood oxygenation level dependent functional images, consisting of asymmetric spin-echo images for T2* signal change, with TR of 2.5 s, TE of 70 ms, effective field of view of 20 cm^2, and in-plane resolution of 3.1 mm^2. Separate functional imaging data sets were obtained during each of three motor tasks. The whole brain was examined using 20 contiguous horizontal slices of 7 mm thickness. One hundred images were obtained per slice over a 4-min period, during which subjects alternated between 30-s periods of rest and activity.

The three motor tasks were right four-finger tapping, right index-finger tapping, and right hand squeezing. These three were performed during the same fMRI session. Part of the results from this session has been previously reported (5). The first motor task performed was right four-finger tapping at 2 Hz. In this task, the pronated forearm was at the subject's side. The subject tapped the fingertips of digits two to five on the MRI scanner bed in unison while the thumb remained motionless; this involved movement at the wrist and metacarpophalangeal joints. Right index-finger tapping at 2 Hz was performed next, with the forearm in the same position. This involved movement isolated to the second metacarpophalangeal joint. Finally, the forearm was placed in a supinated position. The right hand squeezed a tennis ball at 1 Hz; this involved all hand joints of all five fingers plus some movement at wrist and elbow joints. Subjects were instructed to squeeze with a force sufficient to cause indentation of the tennis ball. Two stroke patients moved *ad lib*, at rates approximating those of other subjects; otherwise all movements were driven by a metronome beep transmitted through plastic headphones (continuously during rest and active periods). The cue to begin and to cease movements was a light tap on the knee. Subjects kept eyes closed at all times. All movements were monitored for accurate performance by one of the experimenters standing in the scanner room at the subject's side.

Image Analysis

Images were motion corrected using image registration software adapted for fMRI by Jiang et al. (15). Statistical parametric maps were generated pixel-by-pixel using the Kolmogorov–Smirnov statistic (16), contrasting movement with rest. A Hanning filter was used to improve signal-to-noise ratio, halving the effective in-plane resolution. Any continuous activation of pixels with $p < 0.001$ around the rim of 1/4 or more of the brain circumference was considered indicative of motion artifact; activation maps with this finding were excluded from further analysis.

For each subject, the activation volume was measured in five motor regions bilaterally. The regions were primary sensorimotor cortex, premotor cortex, supplementary motor area (SMA), cerebellar hemisphere, and basal ganglia. The anatomic landmarks used to define these areas have been described previously (5). Briefly, primary sensorimotor cortex extended from pre-central to postcentral gyrus, brain vertex to sylvian fissure, and lateral brain surface to the depth of the central sulcus. Premotor cortex extended from precentral sulcus to a rostral limit halfway between central sulcus and the anteriormost extent of the brain, brain vertex to sylvian fissure, and lateral brain surface to the SMA. SMA extended rostrocaudally as with premotor cortex, from brain vertex to cingulate sulcus, and midline to the white matter underlying mesial cortex. Infarcted tissue was excluded from analysis of functional images. Significant activation within a pixel was defined using a threshold of $p < 0.001$.

Statistics

For controls, a two-tailed nonparametric paired test was used to compare activation volumes within each brain region across each pair of tasks. A two-tailed Wilcoxon test was used to compare findings between control subjects and stroke patients. Primary analysis examined sensorimotor cortex within each hemisphere. Secondary analyses compared findings within each of the other four brain regions bilaterally. Given the exploratory nature of these studies, no corrections were made for multiple comparisons.

Results

The mean age of the nine controls (65 years; range, 42–76 years) was not significantly different from the mean age of the seven stroke patients (72 years; range, 55–86 years). There was no significant difference in gender distribution between the two groups, with four of nine controls men, compared with five of seven stroke patients. Three patients had a deep infarct in the left internal capsule, whereas four had a left cortical stroke (see Table 1). The time from stroke to fMRI study ranged from 11 days to 14 months. Cerebral arterial anatomy, visible on the flow-compensated images, was normal in all subjects except for an occluded left internal carotid artery in one stroke and in one control subject. One stroke subject was found to have radiologic evidence of a prior stroke during the fMRI study, an asymptomatic small-vessel infarct in the right putamen. For most subjects in this study, activation volumes during index-finger tapping have been previously reported (5).

Several factors reduced the number of studies available for analysis. Data during four-finger tapping were lost because of operator error in one stroke patient, and four-finger tapping was omitted in a second stroke patient, at the patient's request, to shorten the length of the study. Motion artifact resulted in data exclusion for one of 16 index-finger tapping studies (a control), one of 14 four-finger tapping studies (a stroke patient), and five of 16 squeezing studies (two controls and three stroke patients). The frequency with which motion artifact was identified during squeezing was significantly increased as compared with the tapping tasks ($p < 0.05$ using two-tailed Fisher's Exact test).

With few exceptions, tasks were performed precisely as instructed. Examples of brain activation during each of the three tasks are shown in Fig. 1. Additional movements, observed by the examiner during scanning, were much smaller when compared with the intended movements: for controls, one subject had some right-leg adduction during squeezing epochs, and another had some right middle finger movements during index-finger tapping. A third control subject showed a small amount of bilateral leg adduction during squeezing epochs. For stroke patients, during index-finger tapping, one patient had some right middle finger movements, and another patient had some small, intermittent mirror movements in the left hand. One stroke patient had trace thumb movements during both index-finger tapping and squeezing. A fourth stroke patient had small left toe flexions during some squeezes.

The effect of task on regional activation volume was assessed in control subjects. Data from seven control subjects were available to compare activation volumes dur-

Table 1. Patient history

Stroke subject	Age (yr)	Gender	Site of stroke	Hand motor exam acutely after stroke	Time from stroke to fMRI	Hand motor exam on fMRI date
1	86	F	L posterior capsule, medial basal ganglia	0	2 mo	4+
2	70	F	L posterior capsule, medial basal ganglia	0	17 d	4+
3	55	M	L posterior capsule, superior–posterior putamen	2+	11 d	5–
4	75	M	L frontoparietotemporal; dorsally reaches precentral sulcus, ventrally involves precentral gyrus	0	14 mo	5
5	69	M	L frontoparietoinsular, reaches precentral sulcus	4+	9 mo	5
6	75	M	L frontoparietal, involves precentral and postcentral gyri	1+	3 mo	5
7	77	M	L frontoinsular, dorsally reaches precentral sulcus	3+	12 mo	5

fMRI, functional magnetic resonance imaging.

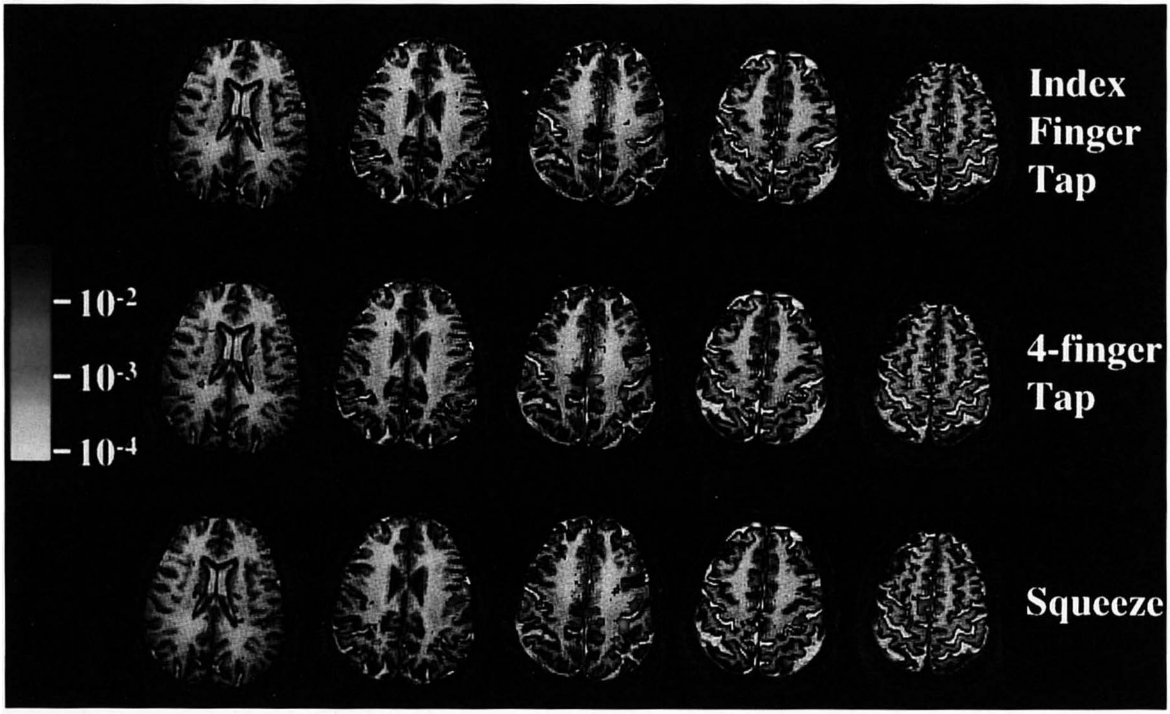

Figure 1. Activation is shown in selected axial brain slices during each right-hand motor task. Functional activation maps have been superimposed on high-resolution anatomic images taken in plane with the functional images. The p value for each 3 × 3 × 7-mm pixel has been encoded in the color strip to the right. The images are in radiologic orientation, with the left hemisphere on the right side. Contiguous slices are shown from a 69-year-old control. The volume activated in left sensorimotor cortex was greater during four-finger tapping as compared with index-finger tapping. The activation volume increased further during squeezing. Right sensorimotor cortex activation was seen only during squeezing.

ing the three tasks. The volume of left sensorimotor cortex activation was significantly larger during right-hand squeezing (17.6 ± 6 pixels; mean ± SEM) as compared with right index-finger tapping (4.0 ± 1.5 pixels, $p < 0.05$). No brain region showed a significant change in activation volume when comparing index-finger tapping with four-finger tapping, or when comparing squeezing with four-finger tapping.

One significant result was found on comparing regional activation volumes between patients and controls. During index-finger tapping, the mean activation volume in right sensorimotor cortex was larger in stroke patients (2.6 ± 1.0) as compared with controls (0.1 ± 0.1, $p < 0.05$) (Fig. 2). During index-finger tapping, the mean activation volume in left SMA showed a trend ($p = 0.053$) toward larger activation in patients (2.1 ± 0.9) as compared with controls (0.1 ± 0.1). No other brain areas showed a difference between patients and controls during index-finger tapping, and no differences between the two groups were identified during four-finger tapping or squeezing.

In two of the four patients with a cortical stroke, motor cortex activation was found in the area associated with hand movements (17), and also was found along the infarct rim. In a patient having index finger and four-finger tapping available for comparison, periinfarct foci of activation were equally apparent. In a patient having all three tasks available, a focus of periinfarct activation was evident during index-finger tapping and squeezing, but not during four-finger tapping.

Discussion

This study used fMRI to evaluate patterns of brain activation during performance of three different motor tasks by the right hand by patients with good recovery after left hemisphere stroke and by control subjects. These tasks represent the spectrum of hand motor abilities present during recovery from stroke (12). Changing the hand motor task influenced patterns of brain activation.

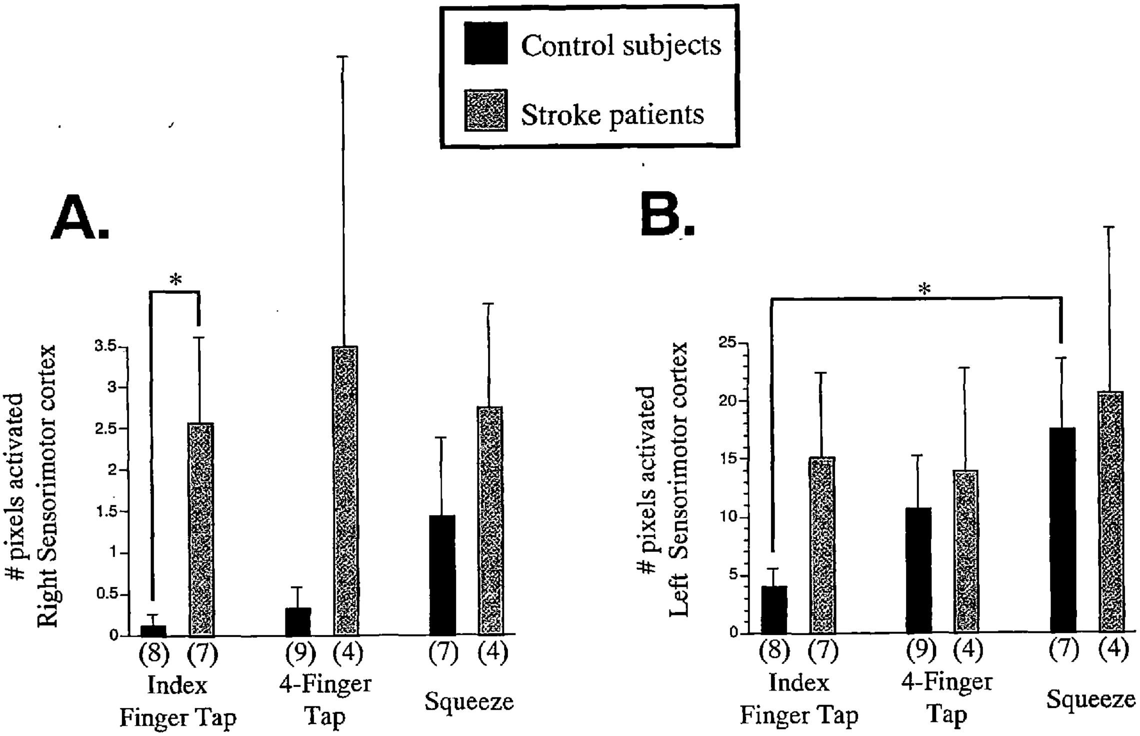

Figure 2. Activation volumes for three tasks performed by the right hand are shown for patients and for controls. For each task, the mean (±SEM) number of activated pixels is shown. The numbers in parentheses indicate the number of studies available for evaluation in each task–subject group. **A:** Right sensorimotor cortex. **B:** Left sensorimotor cortex. $^*p < 0.05$.

In controls, contralateral sensorimotor cortex activation volume was larger with squeezing than with index-finger tapping (Fig. 2B). This is concordant with a previous study in which greater contralateral sensorimotor cortex activation was found with squeezing as compared with a lower-force, fine-motor task (18). This result might be anticipated given that squeezing uses a larger number of upper extremity muscles, activation of which might be expected to occur over a larger segment of motor cortex (19, 20). In addition, squeezing likely involved generation of more force than did tapping, and increasing the level of force output during a hand motor task has been associated with activation of a larger volume of contralateral sensorimotor cortex (21, 22).

Index-finger tapping was best for identifying differences between patients and controls in the volume of activated ipsilateral sensorimotor cortex. Control subjects did show a larger activation volume in right sensorimotor cortex during squeezing as compared with index-finger tapping (Fig. 2A), but this difference was not significant. However, the effect of this increase was that the difference between patients and controls during index-finger tapping was significant, but the difference during squeezing was not. These findings are complicated by the fact that there were fewer observations in stroke patients during four-finger tapping and squeezing as compared with index-finger tapping.

Brain-mapping studies of motor recovery after stroke have used a wide range of motor tasks to activate the brain. Chollet et al. (3) used a five-finger task in which the thumb opposed each of the other four fingers in succession at 1.5 Hz. Cao et al. (6) and Marshall et al. (7) used the same task, but at variable rates. Cramer et al. (5) used 2-Hz index-finger tapping. Honda et al. (4) used 1-Hz wrist extension or fist clenching. Green et al. (8) used middle-finger flexion/extension every 7 s. These studies found evidence for increased activity in sensorimotor cortex of the nonstroke hemisphere. Other functional imaging studies have not found a change in this brain region. For example, Seitz et al. (11) did not find increased activation in sensorimotor cortex of the nonstroke hemisphere during sequential finger movements by the stroke-affected hand. Weiller et al., using the same task as did Chollet et al. (3), did not find increased activation in nonstroke sensorimotor cortex in one study (9), and in a second study, found an increase only in patients exhibiting mirror movements (10). Some, but not all patients in these studies have had increased activation in sensorimotor cortex of the stroke hemisphere during performance of a motor task by the stroke-affected hand. The different results between these studies might have been due in part to the manner in which the control group was defined, the topography of strokes among patients enrolled, or the age of study subjects. The current study suggests that choice of motor task might also have an important influence on brain activation and therefore study results.

The current finding, that a fractionated finger movement (index-finger tapping) activates a smaller volume of ipsilateral sensorimotor cortex compared with a gross movement (squeezing), contrasts with results of a study by Ehrrson et al. (18). These authors compared a low-force, fine-motor task (2-N pinching) with a higher-force, isometric task (20-N squeezing), and found the fine-motor task was associated with greater activation in ipsilateral ventral premotor cortex. Important differences in study design may underlie the divergence of results between the current report and that of Ehrrson et al. (18). The two studies differed in terms of age of the subjects, the motor regions examined in the hemisphere ipsilateral to the active hand (sensorimotor vs. ventral premotor cortex), and the method used to define significant activation. Different motor tasks were used, with Ehrrson et al. (18) comparing a thumb–index-finger pinch with an isometric squeeze, and the current study comparing index-finger tap with a nonisometric squeeze. Perhaps the most important difference is that the current study likely used higher force levels for both tasks, and thus likely the muscles recruited for task performance. Although force was not measured during the fMRI acquisition in the current study, more recent data (Cramer et al., unpublished observations) have found that the index-finger tap in this setting is associated with a force ranging from 2 to 5 N, whereas the squeezing task was associated with a force ranging from 30 to 120 N. These differences further emphasize the vast influence that choice of task can have on probing the motor system.

One limitation of the current study is that human observation was the only method used to describe task performances. It is conceivable that muscle activity was present but not associated with visible movements, and therefore that some of the differences between patients and controls reflect intersubject differences in motor performances rather than differences in motor cortex organization. Differences in site and degree of muscle activity can influence results of brain motor mapping (19–21, 23). Future studies of motor recovery may therefore benefit from obtaining more information regarding individual subject's motor performance. This might be done in two different ways. First, electromyographic data can provide insights into how muscle activity varies between tasks and between subject groups. The utility of this approach was illustrated by Dettmers et al. (21). They found that increased bilateral sensorimotor cortex activation was seen with increased force of unilateral finger flexion. However, increased force was also associated with increased electromyographic activity in bilateral arm muscles, suggesting that some of the force-related changes in brain activation were due to use of different muscles rather than force-related differences in brain organization. A second way in which motor performances can be measured involves recording the force of hand movements with a dynamometer. This approach, commonly used at the bedside (24, 25), has more recently been implemented during acquisition of fMRI data (18, 22).

Activation of foci along the rim of a cortical infarct was apparent in two of the four stroke subjects in this study and has been described previously (5, 6, 11, 26, 27) Surviving tissue along the rim of a stroke may be an important contributor to recovery. The periinfarct zone is the site of expression of a variety of growth-related proteins related to remodeling (28–30). Cellular changes have been described in this zone, such as increased density of dendritic spines (31). In humans, the volume of threatened but surviving tissue along the infarct rim is linearly related to clinical outcome (32, 33). The extent to which these periinfarct activation foci are a biologic marker of events related to recovery remains to be determined. The current results extend the range of motor tasks associated with periinfarct activation.

Although all of the stroke patients in this study had good recovery, the results may be useful in the design of a broader range of stroke-recovery studies. Early after stroke, and in patients with poor recovery, the most refined hand motor task that can be performed may be squeezing (12). However, squeezing may be associated with increased head motion, and so investigations using this task may need to take additional steps to minimize this source of artifact. In controls, left sensorimotor cortex activation volume during squeezing was not identical to that during index-finger tapping (Fig. 2B). This finding may have bearing on interpretation of studies that study stroke patients serially using a different hand motor task at each time point (7), as some of the intrasubject change over time may be attributable to differences in the motor task performed during brain mapping. Squeezing was also less sensitive to patient–control differences. This is based on the current study of patients with good poststroke motor status. If the same is found to be true in patients with poorer motor function after stroke, alternative approaches, such as passive limb movement (34), may prove to be a superior probe of the processes underlying motor recovery after stroke.

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