A prospective study of motor recovery following multiple subpial transections

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Received 31 January 2002; accepted 31 January 2002

A prospective study of motor recovery was undertaken in a patient scheduled to undergo multiple subpial transections (MST) of right sensorimotor cortex. Pre-transection, functional MRI (fMRI) and cortical stimulation mapping confirmed left hand motor control within right primary motor cortex. Immediately post-transection, behavioral testing demonstrated preserved strength bilaterally but decreased dexterity in the left hand. Seven weeks post-transection, dexterity returned to normal and left hand finger tapping corresponded with multiple bilateral foci of fMRI activation. At 16 weeks, fMRI activation returned to pre-transection levels. These data indicate that cortical injury due to MST resulted in the temporary recruitment of distant cortical sites which presumably subserved normal motor function during recovery. *NeuroReport* 13:665–669 © 2002 Lippincott Williams & Wilkins.

Key words: Cortex; Cortical stimulation; Epilepsy; fMRI; Human; Motor; Plasticity; Recovery; Reorganization; Surgery

INTRODUCTION

Motor recovery has been investigated using a variety of techniques in patients with acute motor system injuries due to cortical stroke [1–3], subcortical stroke [4–6], spinal cord injury [7,8], and limb amputation [9–11]. These studies have shown that the cerebral cortex is not fixed in its organization. Indeed, loci of cortical activation can shift many centimeters away from their expected locations, relative to anatomical landmarks, both within and across hemispheres [12,13].

Studies of motor system responses to cortical injury in humans have been almost exclusively retrospective, relying on normal participants as controls. In contrast, studies in non-human animals are often prospective, with the advantage that each animal can serve as its own control, thereby allowing for a detailed study of motor recovery on a case-by-case basis [14]. Prospective studies in humans would be advantageous as between subject variability in motor system localization, relative to anatomical landmarks, can be large. However, there is typically no way to determine when a focal lesion will occur in humans, thus precluding determination of pre-lesion localization.

Retrospective studies in humans have yielded insight into the reorganization and recruitment patterns of the motor system due to cortical insult with two common themes emerging: (1) recruitment of contralesional motor pathways and (2) expanded or shifted regions in ipsilesional cortex [15]. Such disparate results may relate to the timecourse of recovery, as increased motor cortex activation during finger opposition tasks has been shown contralesionally early in recovery and ipsilesionally later in recovery [16]. In a monozygotic twin study, in which one twin of each pair suffered from an early focal brain lesion, the pattern of cortical activation in the lesioned twin during a motor task involving the contralesional hand was in perilesional and contralesional cortex while the pattern of cortical activation in the healthy twin was exclusively in contralateral cortex [17]. This study had the advantage in that the healthy twin presumably had the same gyral anatomy and cortical functional organization as the effected twin and thus served as a very similar control. Still, as is done in nonhuman animals, an ideal study of human motor recovery would be prospective, using prelesioned cortical activity as a baseline for comparison with post-lesion cortical activity.

In the present study, we prospectively assessed cortical motor recovery following multiple subpial transections (MST) of motor cortex using a combination of behavioral measures and fMRI. Through knowledge of pre-lesion activation patterns, the mechanisms underlying functional recovery of motor systems following cortical injury have been refined.

MATERIALS AND METHODS

Patient history: A 30-year-old right-handed man had a history of seizures since age 5 involving stiffening and twisting of the left hand and arm. Seizures occurred multiple times per day despite optimal medical manage-

ment. At age 22, a subdural electrode grid was implanted, and the seizure focus localized within his right motor cortex [18]. Surgery was deferred at that time due to the possibility of a disabling motor deficit. However, his seizure frequency gradually increased and at age 30 he was scheduled for readmission for another subdural electrode grid and possible MST surgery. Prior to planned readmission, he underwent quantitative behavioral testing and fMRI. He understood and consented to all of the testing performed before and after his clinically indicated surgery.

Behavioral testing: Motor strength was assessed using a dynamometer (Chatillon, Lexington, KY) whereby the patient's maximum force was recorded for flexion of the biceps, triceps, and wrist, extension of the wrist and fingers, and grip (both right and left hands/arms measured serially). Finger tapping speed was measured using a lever connected to an accumulator which counted the number of complete taps executed with the index finger as quickly as possible in a 10 s period. The average of three 10 s trials is reported. Dexterity was assessed in each hand using the grooved pegboard task. In addition to pre-transection testing, the patient underwent testing on post-transection day 3, week 7, and week 16.

Subdural electrode array: Following initial behavioral assessments and fMRI, the patient was admitted for surgical implantation of a subdural electrode array. The array consisted of 84 electrodes placed on the pial surface of the right hemisphere (see Fig. 1). The electrodes were used to record seizure activity for localization of ictal onset. Using the same electrode array, cortical stimulation mapping of motor function was performed by systematically stimulating pairs of electrodes within the grid to produce a temporary electrical lesion and observing motor function [18]. Skull x-rays were co-registered with a high resolution MRI reconstruction of the cortical surface to confirm localization of the electrodes (see fMRI section for additional details).

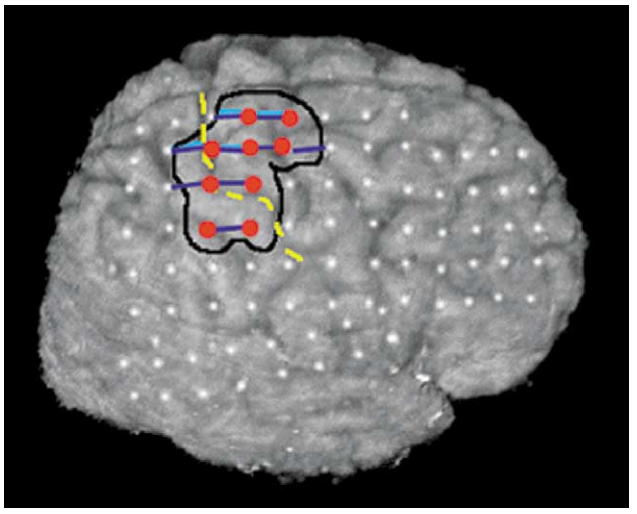

Fig. 1. Surface reconstruction of right hemisphere, using high-resolution MRI, co-registered with subdural electrode grid. White circles indicate electrodes tested. Dark blue lines indicate left hand motor stimulation mapping. Light blue lines indicate left arm motor stimulation mapping. Red electrodes indicate seizure focus. Yellow dashes indicate central sulcus. Black line surrounds transected area.

MST: An extensive portion (shown in Fig. 1) of the right pre- and post-central gyri corresponding to the epileptic focus, identified using the pre-transection subdural electrode grid, was transected perpendicular to the sulcal axis using linear cuts spaced 5 mm apart [19].

fMRI: During each of the three sessions, the patient was instructed to repeat a complex finger tapping sequence with his right (control) hand for 30 s blocks interleaved with 30 s rest. The patient also completed this tapping/rest sequence with his left hand.

A 1.5 T GE Signa scanner with a head coil was used to acquire whole brain functional and anatomic data. T2*-weighted functional images were acquired using an echo planar imaging sequence (TE = 40 ms, flip angle = 90°, TR = 3000 ms, 64 × 64 matrix, 240 mm FOV, 11 slices, 7 mm slice thickness, 1 mm gap). High-resolution T1-weighted anatomical images were acquired using an SPGR sequence for overlay of functional results (TE = 5 ms, flip angle = 45°, TR = 35 ms, 256 × 128 matrix, 124 slices, 1.5 mm slice thickness, no gap). Surface reconstruction was conducted using Curry (Neuroscan, Sterling, VA, see Fig. 1).

Functional analysis was conducted using BrainVoyager (Maastricht, The Netherlands). Pre-processing of functional images included slice-time correction, motion correction, and spatial/temporal filtering between 1–16 Hz and 2–12 Hz, respectively (where spatial Hz refers to cycles per matrix size and temporal Hz refers to cycles per run length). A cross-correlation analysis was conducted using a gamma function to estimate the hemodynamic response [20]. In addition to pre-transection testing, fMRI was repeated at weeks 7 and 16.

For the correlation analysis, motor cortex was considered the region-of-interest. During analysis of right hand finger tapping data (which corresponds to the non-lesioned left hemisphere), the correlation threshold was selected such that activation was significant to $p < 0.05$, Bonferroni corrected for multiple voxel comparisons, and the extent of activation in primary motor cortex was approximately equal across all sessions. Equating extent of activation was necessary to account for day-to-day variability in fMRI signal strength and noise level. Given that right hand function was normal, it was assumed that left hemisphere primary motor cortex activation was also representative of normal. As such, for each recording session, cortical activation thresholds of the lesioned right hemisphere were set equal to that determined from the non-lesioned left hemisphere (i.e. using the non-lesioned hemisphere as a within subject control). By using the threshold from the non-lesioned hemisphere, we reduced the potential confound of changes in signal and/or noise levels between recording sessions.

RESULTS

Following MST, formal testing of gross motor function revealed no loss of strength in major muscle groups of the

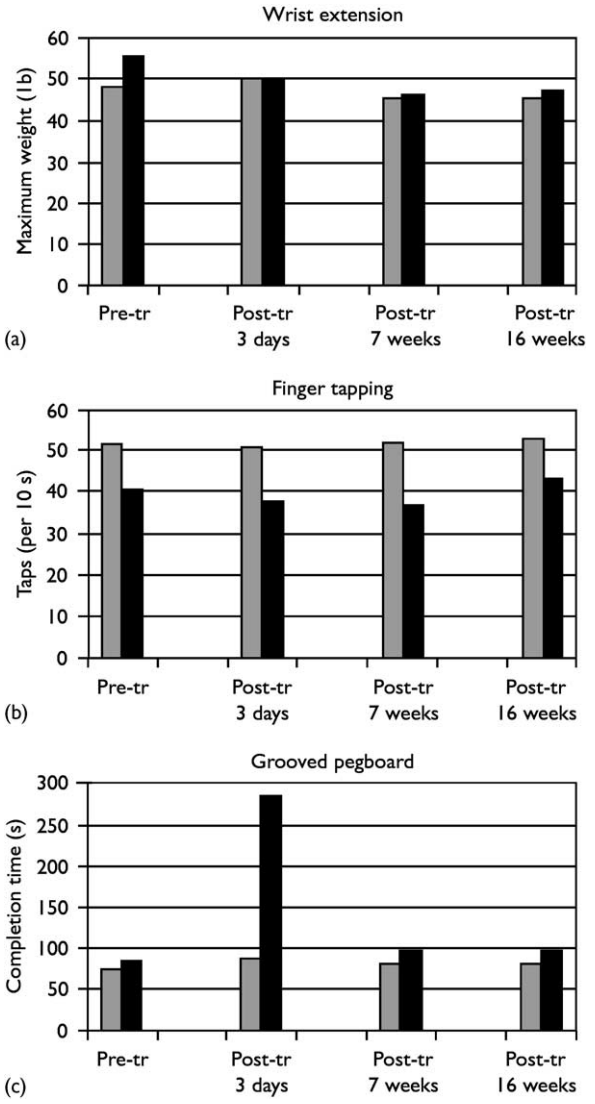

Fig. 2. Pre-transection (pre-tr) and post-transection (post-tr) behavioral measures. Right hand performance shown in gray; left hand performance shown in black. (**a**) Maximum wrist extension strength as measured by dynamometry. (**b**) Index finger tapping speed. (**c**) Grooved pegboard time.

upper extremities including biceps, triceps, wrist flexion, and wrist extension (Fig. 2a). Dexterity, as measured by finger tapping speed also remained unchanged post-transection (Fig. 2b). However, the grooved pegboard task, which requires fine motor skills, showed a dramatic slowing of the left hand immediately post-transection with subsequent recovery by 7 weeks (Fig. 2c; z score $= -20.8$ for grooved pegboard with left hand at 3 days post-transection; all other grooved pegboard performances within 3 s.d. of mean for age). This was consistent with the patient's subjective report as he complained of left hand clumsiness immediately post-transection, especially in his 4th and 5th digits. The patient was maintained on his preoperative medications and was free of all seizures from 12 weeks until at least 6 months post-transection.

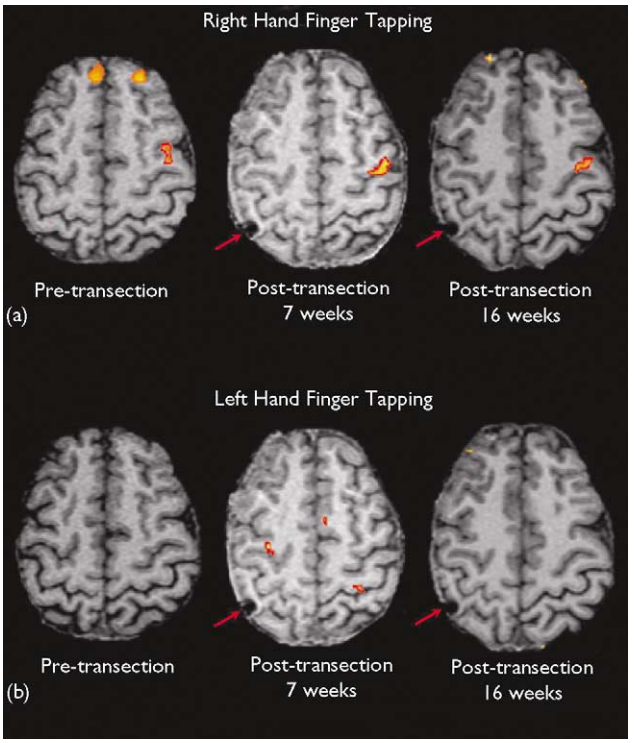

Fig. 3. (**a**) Pre- and post-transection fMRI activation, outlined in red, corresponding to right hand complex finger tapping sequence (radiological convention, i.e. right hemisphere on left). Activity located in pre-motor cortex (BA6) just anterior to primary motor cortex in pre-central gyrus (BA4). Red arrows indicate locus of surgical craniotomy. (**b**) fMRI activations corresponding to left hand complex finger tapping sequence.

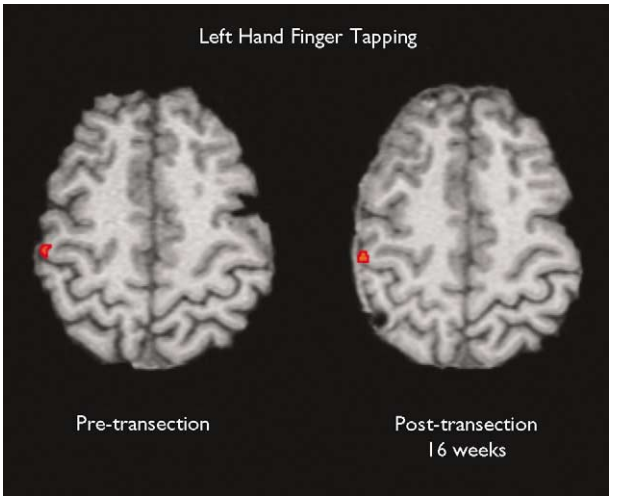

Fig. 4. Pre- and 16 week post-transection fMRI activation at reduced threshold, outlined in red, corresponding to left hand complex finger tapping.

Figure 3a shows fMRI activations corresponding to right hand complex finger tapping measured pre-transection, at 7 weeks post-transection, and 16 weeks post-transection (using correlation thresholds of $r = 0.58$, $r = 0.84$, and $r = 0.68$, respectively). Left hemisphere pre-motor activa-

tions were associated with right hand complex finger tapping and were quite stable across all three scanning sessions (center of activation in Talairach coordinates for session 1: −39, −3, 42, session 2: −39, −8, 47, and session 3: −38, −5, 46 following Talairach transformation; not illustrated). Of note, as shown in the leftmost illustration of Fig. 3a, there were activations in superior frontal sulcus bilaterally (i.e. BA 9). Activation in this area has been attributed to working memory [21] and, as this was the first in the series of complex finger tapping sessions, may reflect the patient holding the tapping sequence in mind.

The left side of Fig. 3b shows, at the same threshold as Fig. 3a, that there was no pre-transection fMRI activation during left hand complex finger tapping, indicating there was more signal change corresponding to right hand movement than left hand movement. Although fMRI showed no activation, pre-transection cortical stimulation over right paracentral cortex consistently produced dysfunction in the left hand (Fig. 1). In other words, the pre-transection cortical map of the left hand was largely normal and overlapped the seizure foci/transected region; thus, we hypothesized that the absence of significant fMRI activation was due to a lack of sensitivity (at the threshold used). At 7 weeks post-transection, multiple areas of activation corresponded to left hand finger tapping (Fig. 3b middle) in ipsilesional premotor cortex (right lateral BA 6), contralesional primary motor cortex (left BA 4), and contralesional supplementary motor cortex (left medial BA 6; Talairach coordinates 28, −11, 47; −31, −31, 48; and −4, 5, 48). At 16 weeks, similar to pre-transection results, there was no significant fMRI activation corresponding to left hand finger tapping; again, we hypothesized this was due to the *a priori* selected threshold.

To test our hypothesis, i.e. that the absence of significant pre-transection and 16 week post-transection fMRI activation was due to threshold selection, the pre-transection left hand finger tapping correlation threshold was lowered until activity was detected in right hemisphere motor cortex (the region-of-interest). At a correlation threshold of $r = 0.20$, pre-transection fMRI activity in right hemisphere primary motor cortex (right BA 4, Talairach coordinates 51, −13, 48) was revealed (Fig. 4, left). The same threshold was applied to the 16 week post-transection left hand finger tapping analysis and resulted in remarkably similar right primary motor cortex (right BA 4) fMRI activation (Fig. 4 right; Talairach coordinates 48, −15, 48).

DISCUSSION

As expected, right hand finger tapping resulted in similar pre- and post-transection fMRI activation in the non-lesioned left hemisphere motor cortex. In contrast, left hand finger tapping resulted in the same pre- and 16-week post-transection levels of fMRI activation, but multiple additional foci of activation, both contralesional and ipsilesional, were evident 7 weeks post-transection. These prospective data indicate that at 7 weeks, both ipsilesional and contralesional cortical loci were recruited consistent with both patterns of recovery previously reported in retrospective studies [15]. Specifically, pre-motor cortex (associated with motor programs) ipsilesionally (BA 6) and primary motor cortex (associated with motor execution) contralesionally (BA 4) were demonstrated during performance of the complex finger tapping sequence. Contralesional primary motor cortex activity has also been associated with poor functional recovery from motor stroke [15]. Indeed, full recovery of grooved pegboard behavioral performance at 7 weeks (Fig. 2c) indicates that such cortical compensation resulted in normal dexterity. These results favor mechanisms of cortical recruitment which include disinhibition of preexisting but functionally inactive motor systems [22] or neighboring pluripotential regions, and are less consistent with sprouting of new fibers from surviving neurons, considering the time scale, distances from primary motor cortex, and reversibility of the observed activation pattern [23]. At 16 weeks, the return to pre-transection activation may be indicative of cortical recovery, local remapping within the transected area, and/or large-scale cortical remapping. Furthermore, the lack of pre-motor activation at this stage of recovery may reflect the successful relearning of the motor sequence, as achievement of expertise for a given motor program is increasingly associated with primary motor cortex activation.

CONCLUSION

In this prospective study of motor recovery in a human, MST of right hemisphere motor cortex resulted in the temporary recruitment of ipsilesional and contralesional pathways. Moreover, the cortical foci recruited due to injury were capable of subserving behaviorally normal motor function. Such data are illustrative of the flexibility in cortical reorganization following acute injury and are most consistent with pre-existing parallel or redundant motor pathways that become disinhibited during recovery from cortical injury.

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Acknowledgements: We would like to thank Michael Kraut for assistance with analysis, Sarah Kremen for technical assistance, and Nathan Crone and Hao Lei for assistance with cortical reconstruction.