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Cortical reorganization following intradigital tendon transfer

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We distinguish between two models of adult cortical reorganization, adaptive and constant somatotopy, using functional magnetic resonance imaging maps corresponding to individual thumb and fourth finger digits in a patient with a right-hand fourth digit tendon transfer that salvaged impaired function of the right thumb. Comparison of motor and sensory maps for both digits and both hands was consistent with a model of 'adaptive somatotopy' in which thumb control was taken over by regions adjacent to the fourth finger control cluster rather than at the presurgical lateral region as predicted by a model of 'constant somatotopy'. These findings are the first to demonstrate that rerouting of peripheral input, in the absence of brain injury, is sufficient to drive cortical reorganization resulting in recovery of lost motor function, and further suggest an adaptive mechanism associated with brain tissue engaged in intact motor functions. *NeuroReport* 00:000–000

Keywords: brain mapping, functional magnetic resonance imaging, motor cortex, neuroplasticity, somatotopy

Introduction

Somatotopic organization of the primary motor cortex (M1) illustrates the fundamental organizational principle of functional specificity in the brain [1,2]. Recent evidence on the basis of intracortical electrical stimulation, pharmacological studies, and imaging modalities that detect blood flow (i.e. positron emission tomography) [3], however, suggests that somatotopy is reorganizable [4–7], although mechanisms of cortical reorganization remain active areas of investigation. The advent of technologies such as functional neuroimaging provides increasingly accessible and noninvasive techniques to interrogate the reorganization of M1 cortex and to elucidate the mechanism of cerebral plasticity.

Plasticity within the M1 cortex has been described for recovery from stroke [8], and, in the case of normal subjects, learning simple or complex motor tasks such as playing a piano, Braille reading, and athletic training [1,4,9]. In these examples, motor function is either regained, acquired, or preserved, respectively. Hemodynamic impairment is also sufficient to stimulate neuroplasticity even in patients without a stroke or a prior transient ischemic attack by modification of the cortical substrate that drives the performance [10]. In this study, we distinguish between two models of neural plasticity, adaptive and constant somatotopy, in a case when the peripheral input to the hand is altered by a tendon-transfer procedure.

In this study, we applied functional magnetic resonance imaging (MRI) brain mapping techniques to evaluate the cortical reorganization that accompanied regained motor function of a thumb following peripheral reorganization of motor pathways that surgically merged thumb and fourth finger pathways. We reasoned that restoration of motor control of the thumb was due either to reorganization of the fourth finger motor cortical area or to reactivation of the original thumb sensitive motor control area. In the case of the former, the observations would support a model of 'adaptive somatotopy' in which the nonimpaired digit region that post-operatively received information from two digits 'adopted' the motor control of thumb; or in the case of the latter, the observation would support a model of 'constant somatotopy' in which the pathways for the impaired digit would be cortically re-routed to the original thumb-control region of cortex.

Materials and methods

Case history

A healthy 84-year-old retired male airline pilot with a prior medical history of hypertension, hypercholesterolemia, Factor V Leiden deficiency, and median neuropathy at the wrist presented for routine evaluation. Fifteen years before presentation, he had developed severe paresis of the right thumb for which he underwent a partial fourth digit-to-thumb tendon transfer. Motor function to the thumb was restored acutely in the postoperative course. The patient was, however, initially unable to segregate movements of the thumb and fourth digit. After a 6-month course of mental and physical rehabilitation, discrete motor control to each digit was restored, closely approximating normal function. Thus, functional imaging of the reorganized motor cortex occurred 15 years after the restorative surgery.

Informed consent for the imaging procedure was obtained according to institutional guidelines.

Functional magnetic resonance imaging

Images were acquired with a GE Signa (General electric, Milwaukee, Wisconsin, USA) 1.5 T MRI scanner with a standard head coil. Conventional high-resolution T1 images were obtained in axial and sagittal projections. Functional images were acquired in the same axial plane locations as the structural T1 data in 25 contiguous slices with a T2*-weighted echoplanar imaging sequence (TR=4000 ms, TE=60 ms, flip angle=60°, FoV=190 mm, Nex=1) of 4.5-mm slice thickness, cubic size of each volume element (voxel) of 10 mm^3, and 1.5×1.5 mm in-plane resolution. This sequence is known to be sensitive to signal variations that reflect alterations in deoxyhemoglobin levels in the local vasculature coupled to neuronal activation. Images were acquired parallel to a standard reference line that intersected the superior edge of the anterior commissure and the inferior edge of the posterior commissure, allowing direct comparison of acquired images with the Human Brain Atlas [11] for confirmation of the location of the primary motor and somatosensory cortex. Images were, however, not normalized to either the acquired T1 images or to a standard atlas to preserve the acquired resolution. This spatial grid enabled high-resolution observations of activity centroids associated with each finger. These experimental parameters follow standard paradigms established for neurosurgical planning and single-subject studies that require high-resolution mapping techniques [12–21].

Prior studies performed at the same or at lower resolution have been able to resolve discrete activation in M1 corresponding to individual digits in the hand [22,23]. Three-dimensional distances between centroids for the second and fourth finger movements have been reported to be within 2.46 mm [24], well within the limits of resolution for these scans.

Seventy-two images of the brain were acquired for each condition, lasting 4 min and 48 s. A standard block design was utilized, by which 10 images (40 s) were acquired during baseline epochs, interspaced by task epochs of the same duration, which consisted of either single-finger tapping or tactile stimulation of the targeted finger. The two performance epochs were interspersed between baseline epochs. A fixation crosshair was used to minimize patient head movement [12].

Image analysis

Before statistical analysis, all images were aligned, and corrected in the x and y dimensions for movement artifacts. A two-dimensional Gaussian filter (approximately two to three voxels at half-height) was applied to enhance signal-to-noise characteristics for each voxel. Signal changes during cortical brain activity were identified using a block design that compared average signal amplitude acquired during the activity epochs with average signals acquired during baseline epochs according to the assumptions of a general linear model. An 'active' voxel was defined as one in which the average MRI signal acquired during the stimulation periods was significantly greater than the average baseline levels computationally corrected for multiple comparisons, $P < 0.0005$, and confirmed by empirically validated false positive rates obtained using both resting brain and copper sulfate phantoms [12]. This particular voxel-by-voxel analysis procedure is used routinely to map sensorimotor, language, and visual functions for individual patients for neurosurgical planning that aimed to reduce potential morbidity owing to therapeutic neurosurgical interventions, and has been validated by conventional mapping techniques such as direct cortical stimulation, somatosensory-evoked potentials, and surgical outcome studies [12].

The motor cortex was identified as the gyrus anterior to the central sulcus, and the somatosensory cortex was defined as the gyrus posterior to the central sulcus. These regions were confirmed anatomically on the basis of T1-weighted images acquired at the same locations as the T2* images for functional studies. For each statistical contrast, centers-of-mass (COMs) of the significantly activated voxels in the putative primary motor cortex (M1) and primary somatosensory cortex (S1) were determined on the basis of the original acquisition grid in which each voxel in every slice was identified on the original (scanner-based) acquisition coordinate system representing spatial distance (millimeter) in the brain [12,15,17]. This technique provided a measure of actual distances between cluster centroids (COM) without error because of the registration of T2* and T1 images [15].

Results

We confirmed the known parallel correspondence between sensory and motor mapping along the precentral and postcentral gyri, associated with the fourth digit during tactile (sensory) stimulation. The sensory map of the thumb served as an indicator of the somatotopic preoperative motor (precentral gyrus) organization. In addition, the motor and sensory somatotopy of the unaffected left thumb and fourth digit served as a second indicator of the preoperative somatotopic organization.

Motor and sensory stimulation of the individual digits elicited blood oxygen level-dependent signals in the contralateral M1 and S1 cortex as expected for each hand. Figure 1 shows the slice of brain that represents activity in all four conditions: right hand motor and sensory stimulation (rows), and thumb and fourth finger digits (columns). The grid indicates the acquisition resolution in which each square represents a 5×5 array of voxels each approximately 1.5 mm in the x and y dimensions. Activated voxels were elicited by the tactile and motor stimulations (Fig. 1a–d), and are indicated by the yellow ($P \leq 0.0001$) and orange ($P \leq 0.0005$) colors. The COM for each activation is shown in figure: right thumb motor function (upper left) at x, y coordinate (83,72), right thumb sensory function (lower left) at (99,72), right fourth finger motor function (upper right) at (87,69), and right fourth finger sensory function (lower right) at (89,77). These coordinates provide a measure of distances between centroids and are indicated in Table 1.

Distances (millimeter) from the vertical midline of the slice (x dimension) observed for both right and left thumbs and both fourth fingers allows a comparison of the left and right hand somatotopic organizations. The COM-to-midline distance of the right thumb sensory function (58.5 mm) is similar to that of the left thumb sensory function (58.5 mm), and the left fourth finger motor function (40.5 mm) is similar to the right fourth finger motor function (40.5 mm) consistent with expectations of symmetry between the two

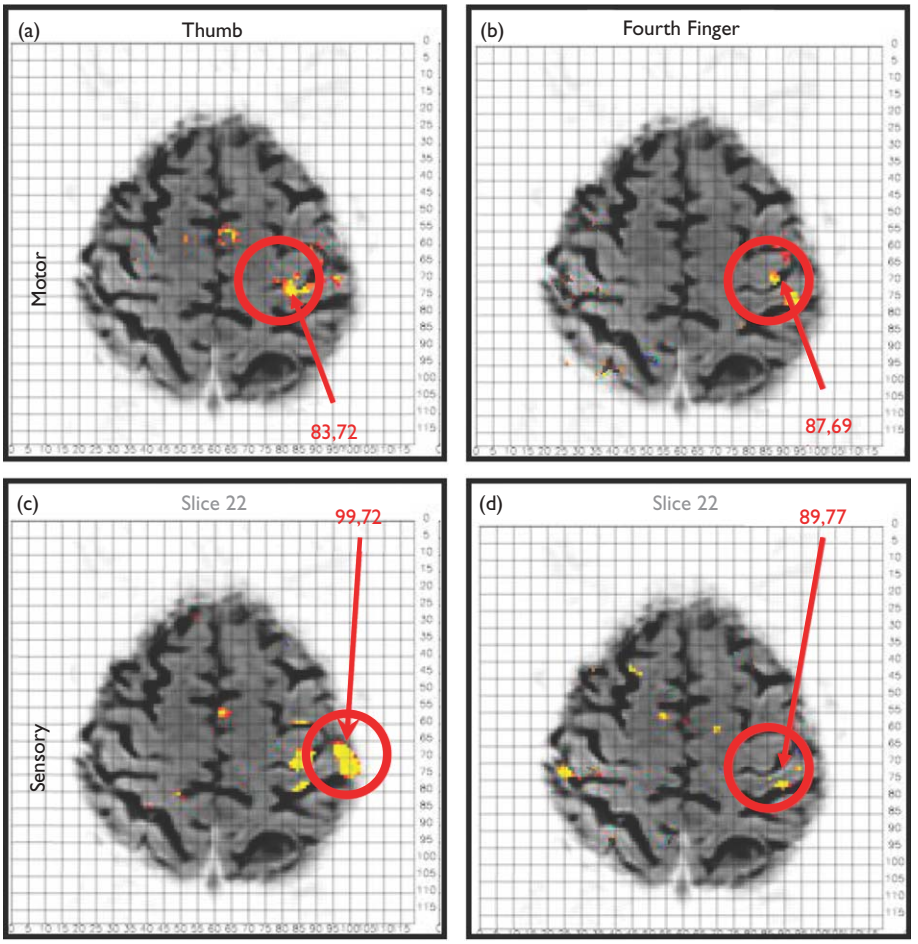

Fig. 1 Activated regions of the postoperative motor and sensory functions (rows) of the right thumb and fourth finger (columns) are indicated by colored voxels enclosed in circles. Center-of-mass (COM) coordinates are indicated for the right thumb motor (a), right thumb sensory (c), fourth finger motor (b), and fourth finger sensory (d) activity. Plasticity of the right thumb motor function (change in position of the COM) within the MI cortex (a) is documented by a shift of the right thumb motor COM (83,72) medially (along the *x*-axis) from the expected position of the right thumb (estimated by the sensory activity) (99,72) (c) to territory near the right fourth finger motor activity (87,69) (b).

Table 1 Center-of-mass distances (millimeter) from the vertical midline

Digit	Sensory	Motor	Difference
Right thumb	58.5	34.5	24
Right fourth finger	43.5	40.5	3
Left thumb	58.5	58.5	0
Left fourth finger	40.5	40.5	0

hemispheres with respect to somatotopy. In addition, the COM distance of the right fourth finger sensory function (43.5 mm) is similar to that of the right fourth finger motor function (40.5 mm). Further, the COM for the left thumb motor function was also 58.5 mm from the midline and the COM for the left thumb sensory was 58.5 mm from the midline confirming the expected left hand somatotopy for thumb. Likewise, the COM for the left fourth finger motor was 40.5 mm from the midline and the sensory was also 40.5 mm from the midline, also confirming the expected somatotopy. The difference between the sensory and motor distance for the surgically repaired right thumb is, however, 24 mm (Table 1, top row), which is clearly outside the bounds of expected somatotopic organization, and consistent with postsurgical reorganization of the motor cortex.

We assume that the right thumb sensory COM coordinates (99,72) estimate the expected position of the presurgical motor representation of the right thumb. Nonetheless, the observed right thumb motor coordinates (83,72) are shifted in the medial, *x*, direction by 16 voxels or approximately 24 mm from the expected location (Table 1). In comparison, the COM of the right thumb motor function (83,72) is displaced only by four voxels or approximately 6.0 mm in the lateral dimension, and three voxels or 4.5 mm in the rostral/caudal dimension from the COM of the right fourth finger motor function (87,69). Thus, right thumb motor performance is now post-operatively associated with activation of medial M1 cortex, in a region generally corresponding to motor activity of the right fourth digit.

Discussion

These activity maps corresponding to thumb and fourth finger digits suggest that right thumb motor recovery is associated with a shift of somatotopic organization from the

original lateral representation to a medial region near the right fourth finger motor representation. Evidence includes the displacement of the right thumb motor centroid in relation to the right thumb sensory centroid. This organization is in distinction to the left thumb motor and sensory representations in the respective S1 and M1 cortices when sensory and motor functions are mapped at nearly the same lateral location (Table 1).

Here, we document a novel condition that induces cortical reorganization following surgical transfer of the right thumb tendon. The circumstances that promoted this reorganization are distinct from previously reported recovery from stroke or brain injury or the effects of learning a motor skill such as piano playing [1,4,9]. In this case, the peripheral input was reorganized by the tendon transfer procedure that initially linked the control of thumb to the fourth finger. Thus, functional segregation of the two digits required the generation of a new neural pathway corresponding to the rerouted peripheral input.

Our research question aimed to determine the neural strategy that led to the recovery of independent motor control of thumb. Findings are consistent with an 'adaptive somatotopy' model, whereby a new motor control region emerged at an atypical location (Fig. 1). Specifically, the observations are consistent with the interpretation that the active right 'ring' finger control area (that post-surgically controlled both fourth finger and thumb) became functionally partitioned to independently control the 'ring' finger as well as the thumb. Of equal significance is the observation that the original thumb motor control area apparently did not reconnect with the thumb following the peripheral reorganization as would have been predicted by the model of 'constant somatotopy.' Of interest is the observation that the sensory-related thumb activation (Fig. 1c) also includes a medial component, suggesting that the 'original' lateral sensory-related COM (99,72) is also accompanied by a second COM more consistent with the medial location of the motor COM (83,72). This may represent a 'joint' reorganization between the motor and sensory functions, although the possibility of activity owing to undetected additional simultaneous movement of the thumb cannot be ruled out.

These data extend our understanding of the mechanisms of cerebral plasticity. It has been postulated that M1 contains a unique substrate to implement mechanisms [9] for plasticity [3]. Motor cortex slice preparations reveal the existence of horizontal connections between superficial layers II and III and the deeper layer V within the M1 cortex [3]. An expanding body of evidence from tissue analysis using stereological measures and synaptophysin immunoreactivity also suggests that plasticity involves an increase in cortical thickness and a corresponding increase in the number of synapses in the intact cortex. [4,5]. Thus, the mechanism of plasticity likely occurs macroscopically, in relation to cortical regions of the brain, as well microscopically, involving synaptic neurotransmitter exchanges and cerebral recruitment of motor units.

Previously proposed mechanisms for the recovery of cortical function following a cortical insult include 'diaschisis,' 'behavioral compensation,' and 'functional plasticity'. Although these explanations involve a reparative response to cortical injury, our study is the first to demonstrate plasticity within uninjured cortex in response to a peripheral injury; in this case, injury to the thumb tendon, and subsequent corrective tendon transfer of the thumb which reconstituted motor function. This is consistent with the notion that M1 is capable of rapid and long-lasting reorganization [3].

In the case of our patient, initial peripheral loss of motor function was followed by surgical intervention to redirect motor function to pathways previously dedicated to another digit. This peripheral reorganization was assumed to catalyze reorganization within the neural axis. The mechanism of this recovery is likely related to the 6 months of rehabilitation before the functional recovery and supports the notion that synapse formation in the neighborhood of active brain tissue may play a role in learning-dependent cortical organization [5]. Understanding this mechanism of plasticity within the M1 cortex may be invaluable in a host of clinical settings including musculoskeletal tendon or ligament repair, as a means for developing corrective surgical procedures, and for clinical follow-up of musculoskeletal congenital malformations. Other potential applications include measuring functional cerebral reserve in a preoperative setting before neurosurgery for resection of masses, and as a prognostic index of plastic recovery following cerebral insult.

Conclusion

This study is the first to demonstrate cortical plasticity in the adult brain in response to a peripherally driven digit transfer, and suggests that restitution of function from a peripheral focal point within the neuraxis can effect a cortical mutation in the form of adaptive somatotopy. This demonstration of neural plasticity in undamaged motor cortex is the first documented genesis of new regional specificity and suggests a potential new role for surgical interventions to redirect peripheral input destinations to uninjured regions of the motor strip as a strategy to recover lost motor functions.

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