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Somatosensory cortical plasticity in adult humans revealed by magnetoencephalography

(somatosensory cortex/brain mapping)

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ABSTRACT **Microelectrode recordings in adult mammals have clearly demonstrated that somatosensory cortical maps reorganize following peripheral nerve injuries and functional modifications; however, such reorganization has never been directly demonstrated in humans. Using magnetoencephalography, we have been able to demonstrate the somatotopic organization of the hand area in normal humans with high spatial precision. Somatosensory cortical plasticity was detected in two adults who were studied before and after surgical separation of webbed fingers (syndactyly). The presurgical maps displayed shrunken and nonsomatotopic hand representations. Within weeks following surgery, cortical reorganization occurring over distances of 3–9 mm was evident, correlating with the new functional status of their separated digits. In contrast, no modification of the somatosensory map was observed months following transfer of a neurovascular skin island flap for sensory reconstruction of the thumb in two subjects in whom sensory transfer failed to occur.**

Understanding the presence, degree, and functional correlations for human cortical plasticity is of major significance for fundamental neuroscience as well as a potential aid in the diagnosis and rehabilitation of patients with peripheral and central nervous system injuries. That cortical maps can undergo reorganization in adult mammals has been demonstrated following a variety of peripheral sensory alterations including nerve transection (1–3), digital amputation (4, 5) and syndactyly (6), and behavioral modification (7, 8). Direct neurophysiological evidence for human somatosensory cortical plasticity, however, has never been demonstrated (9).

Magnetoencephalography (MEG) is a noninvasive functional brain imaging technique that provides information regarding neuronal activity with high temporal and spatial resolution (10–14). Initial studies using MEG (10, 12, 14) demonstrated the somatotopy of the human somatosensory cortex, and present-day technology allows such functional maps to be defined with millimeter precision (14). We have been investigating the detailed functional organization of the hand area in normal adult humans and in patients with a variety of congenital and traumatic hand abnormalities. We report here evidence of adult human cortical plasticity, occurring over a time period of weeks to months following surgical correction of congenital syndactyly in two adult males.

METHODS

A 14- and a 37-channel biomagnetic recording system (Biomagnetic Technologies, San Diego) were used. The orientation of the subject's head in relation to the MEG recording probes was calculated using the sensor position indicator (SPI), a system of transmitters located on the dewars and receivers affixed to a headband on the patient's head. Sensor locations were expressed using a head-based coordinate system whose origin was defined as the point of perpendicular intersection of the line extending from the nasion and the line connecting the periauricular points. The x, y, and z axes were the lines from the origin to the nasion, to the left periauricular point, and orthogonally superior, respectively. The center of the sphere model of the head used for dipole fitting was determined by digitization of the surface of the scalp and calculation of a best-fitting local sphere.

Magnetic fields were recorded from the scalp in the area of parietal somatosensory cortex in response to tactile stimulation of the digits of the contralateral hand, using stimulators designed in our laboratory (15). Approximate area of skin contact was 28 mm^2. Close-up photographs were taken of the hands at each session, such that the stimulators could be placed at the same location for each study. The order of stimuli was randomized among the different fingers during each recording session. The stimulus was triggered at 50 msec after the start of each recording window of 300 msec, for a duration of 100 msec. The randomized interstimulus interval ranged from 350 to 550 msec. Averaged signal data (500 averages per finger for 14-channel system, 250 per finger for 37-channel system) were used to generate equivalent current dipole source locations based on the peak occurring $\approx$50 msec after stimulus onset. Dipole solutions with correlations of <0.97 were discarded from the analysis. For every subject, multiple (mean = 7) acquisitions were performed and the resulting dipole coordinates from each acquisition for each finger were averaged to obtain a source location and error for each finger in each of three dimensions in the head-based coordinate system. Unless otherwise stated, all results are expressed as mean ± SEM.

To compare dipole maps obtained on different occasions, and to compare dipole maps of patients against the normative data, interfinger dipole distances were calculated from the absolute dipole locations and compared using t tests at a $P = 0.05$ significance level.

When magnetic resonance imaging (MRI) scans were obtained, lipid markers were placed on the MEG fiduciary points to define the MEG head-based coordinate system and to allow for superposition of dipole sources onto the MRI images. Three-dimensional volumetric reconstruction of MRI images was performed on a PIXAR image-processing computer.

Abbreviations: MEG, magnetoencephalography; MRI, magnetic resonance imaging; SPI, sensor position indicator.

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RESULTS AND DISCUSSION

To establish the necessary baseline for this study, the cortical somatosensory map was determined using MEG in nine normal adults (eight male, one female; 18–40 years of age). The study included recording and localization of tactile-evoked magnetic fields for all five fingers in four subjects and the thumb, index, and little fingers in the remaining five. Superposition of equivalent current dipole sources onto MRI images has shown that these sources lie in area 3b of sensory cortex, located on the anterior bank of the postcentral gyrus (14). Fig. 1 shows the normal distribution of the hand area in one representative subject (UR) and a composite map obtained from all normal subjects (Fig. 1*E*). The digits of the hand are represented sequentially from thumb to little finger as one ascends the postcentral gyrus. In all subjects studied, the thumb was located most inferiorly, and the little finger was located superiorly to the thumb, index, and middle fingers (all cases) and to the ring finger (three of four cases). The accuracy of the individual finger localizations was 1.5, 1.6, and 1.6 mm (SEM) in the x, y, and z dimensions, corresponding to a sphere of roughly 0.8-mm radius (average of 10 subjects). These results were consistent with those obtained by other researchers using MEG and subdural electrocorticogram recordings combined with single dipole modeling of the hand area of somatosensory cortex (10, 16). A composite hand area (Fig. 1*E*) was obtained by superimposing the finger locations of different subjects. The resulting map clearly demonstrates the remarkable degree of similarity between somatosensory maps in different individuals. The functional thumb–little finger distance, calculated separately for each subject and then averaged, was found to be 1.1 ± 0.16 cm (mean ± SD).

Primate studies following cross-nerve innervation (17) have demonstrated little, if any, central compensation following errors in peripheral innervation, in contrast to the plasticity observed following normal nerve regeneration. We studied two patients with persistent mislocalization errors following transfer of a neurovascular island flap from a digit to the thumb to determine if the cortical topography reflected the sensory findings. The neurovascular island flap is used to provide sensibility following irreparable nerve injury (18). In this surgery, a vascularized and innervated flap of skin is moved from a donor finger to a recipient finger, usually the thumb. Following surgery, sensory stimuli delivered to the flap skin are referred by the patients to the donor finger. Long-term follow-up studies indicate that ≈20% of such patients learn to reorient stimuli to the recipient finger; however, this reorientation occurs years after the surgery (18–22). We have studied two such patients in the months following this surgery. In both subjects, the sensory examination indicated persistent mislocalization of stimuli applied to the thumb flap, with the stimuli referred to the donor (ring) finger. Fig. 2 shows the cortical area for one of the patients studied 6 weeks following transfer of skin from the ring finger to the thumb. The dipole locations of the thumb and of the ring finger were nearly identical; the thumb flap–ring finger interfinger cortical distance, 0.5 ± 0.3 mm, was significantly ($P < 0.005$) less than the normal interfinger distance of 5.2 ± 0.5 mm and the patient's own other interfinger distances (average distance of 5.5 ± 1.9 mm, $P < 0.05$), indicating no cortical reorganization in accordance with the sensory cognitive findings. In addition, this measurement demonstrates that cortical localization is reproducible at a fraction of a millimeter resolution even when the spatial localization of the stimulus has been moved a large distance over the hand.

Somatosensory cortical plasticity was detected in two adult males with congenital syndactyly (webbed fingers), who were studied before and after surgical separation of the

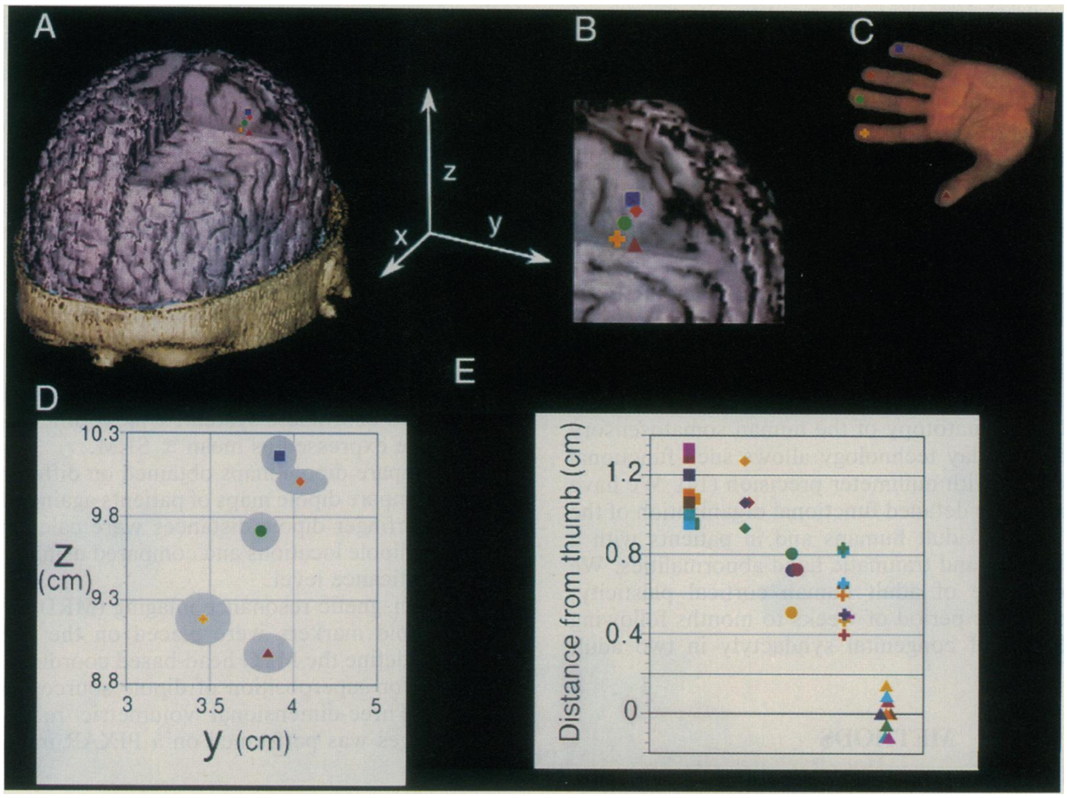

FIG. 1. Hand area of normal adult somatosensory cortex. (*A* and *B*) Subject UR: Dipole locations for the digits of the hand projected onto a three-dimensional MRI reconstruction of the subject's brain, with the color key shown in *C*. (*D*) Subject UR: Two-dimensional plot of the above dipole locations showing the average (symbols) and standard errors (surrounding gray ovals) of localization for each finger in the *yz* (coronal) plane. (*E*) Composite intersubject map of hand area in nine subjects obtained by repetitive least-squares minimization of same-finger distances for all fingers between subjects.

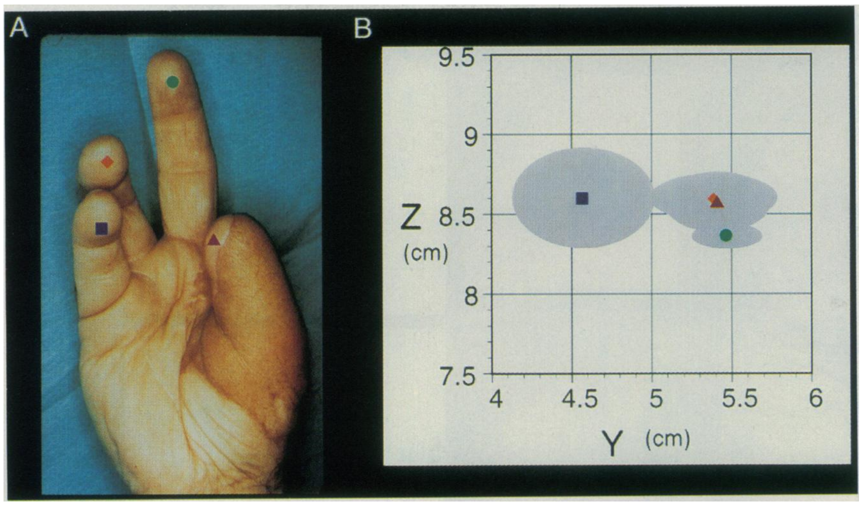

FIG. 2. Patient SL: neurovascular island flap following traumatic amputation of index finger and transfer of innervated skin from ulnar aspect of ring finger to thumb. Map obtained at 6 weeks postsurgery. Dipole source for thumb flap stimulation is clearly in its original (ring finger) location, between the index and the little fingers. Analysis of interfinger distances indicates that the thumb–ring finger distance is significantly ($P < 0.005$) smaller than normal, indicating a nearly identical cortical location for both sources of ring finger skin.

digits. The presurgical maps of both patients were abnormal in several respects. In patient OG, a 32-year-old male with brachysyndactyly secondary to a constriction band syndrome (Fig. 3*A*), the spatial organization of the cortical hand map was nonsomatotopic, with the little finger located between the thumb and index finger, a finding not observed in any of the normal subjects. The cortical thumb–little interfinger distance, 0.2 cm in the *yz* plane, was significantly ($P < 0.05$) smaller than that of normal subjects. The cortical representation of the hand area of patient JM, a 26-year-old male with complex acrosyndactyly secondary to Apert syndrome (Fig. 4*B*), was shrunken, and the digits were nonsomatotopically represented. Thus, in both cases, abnormal hand structure and function are reflected centrally by abnormal cortical topography.

One to 5 weeks after surgery, MEG studies of these two patients revealed significant reorganization of the hand area. In patient OG (Fig. 3*B*), the 26-day postsurgical cortical topography displayed a clear somatotopic organization of the hand area, with the thumb–little finger distance, 1.1 cm, well

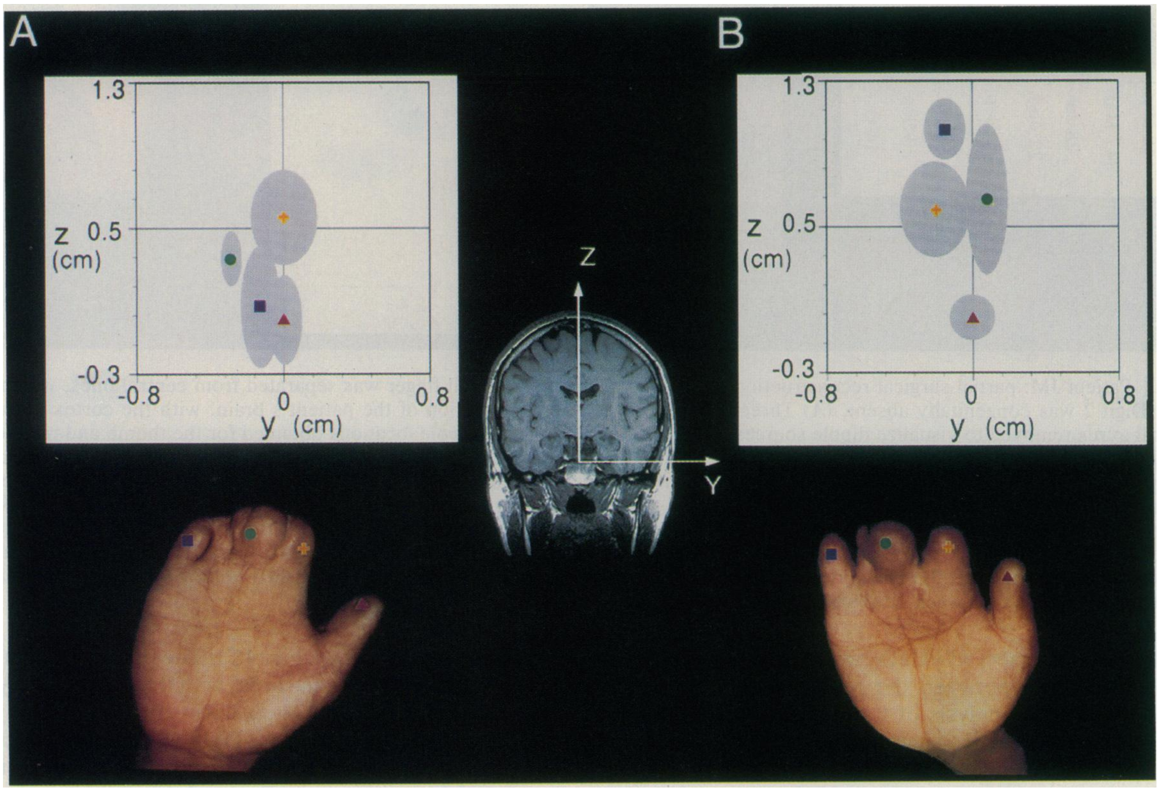

FIG. 3. Patient OG: surgical correction of syndactyly of digits 2–5, coronal sections. (*A*) Preoperative map of dipole source locations for the thumb, index, middle, and little fingers of the hand. Data are shown normalized to the thumb in the *yz* (coronal) plane. Note the abnormal, nonsomatotopic organization of the hand area (thumb–little–middle–index). The thumb–little cortical distance was significantly ($P < 0.05$) smaller than normal. (*B*) Twenty-six days postsurgical separation of the digits. The organization of the hand area is now somatotopic, and the thumb–little distance has increased to 1.06 cm.

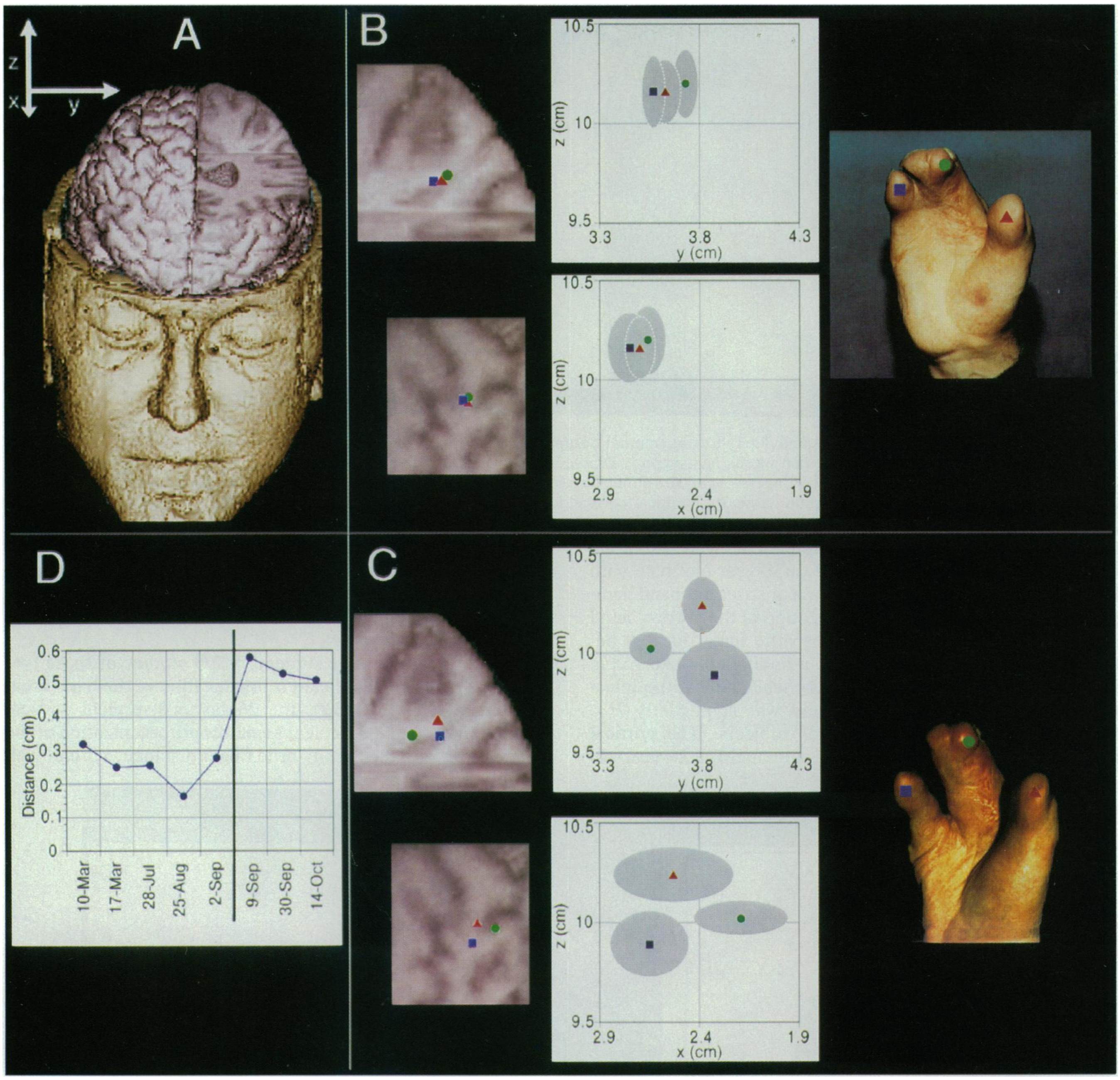

FIG. 4. Patient JM: partial surgical reconstruction of complex syndactyly. Small finger was separated from central ones, which remained together. Digit 2 was congenitally absent. (*A*) Three-dimensional MRI reconstruction of the patient's brain, with the cortex anterior to the postcentral gyrus removed to visualize dipole sources. (*B*) Pre-surgical map with dipole locations obtained for the thumb and middle and little fingers; the hand is shown on the right with the color-coded key. Coronal (top) and sagittal (bottom) graphs of dipole locations (mean ± SEM) are shown for these three digits studied. Maps show significant overlap of digit locations and a reduced inferior–superior extent of the hand area compared to normative data. (*C*) Hand map following surgical separation of digit 5. Data shown were obtained 7 days postsurgery. Coronal (top) and parasagittal (bottom) views illustrate that the fingers have attained distinct cortical locations. (*D*) Plot of middle–little finger distance over time. The patient was studied presurgery five times over a period of 6 months and 1, 4, and 6 weeks postsurgery. The thick vertical bar indicates the date of surgery (September 3). The cortical interfinger distance increased by 2.9 ± 1 mm ($P < 0.001$) following surgery, and this increase was observable as soon as 1 week after surgery.

within the normal observed values, indicating an increase in separation of 9 mm between the respective dipole finger locations. Statistical analysis of the finger locations before and after surgery revealed a significant ($P < 0.05$) shift in the location of the little finger. The cortical topography evident following surgery clearly reflects the new functional status of the hand, in that each digit was now able to function independently, and a different image was generated in the patient, who felt the fingers as individual entities for the first time in his life. In patient JM, 1 week following surgery, cortical changes were evident (Fig. 4*C*). The postsurgical map shows an expansion of the hand area, with the digits occupying more distinct cortical locations. Serial evaluations of this patient 1, 4, and 6 weeks postsurgery (Fig. 4*D*) revealed a significantly maintained increased cortical distance of 2.9 mm (presurgery = 2.5 ± 0.6 mm, postsurgery = 5.4 ± 0.4 mm; mean + SD, $P < 0.001$) between the middle and the "new" little finger.

If we are to assume that the features of cortical maps reflect the function of the associated body part, it is not surprising that these congenitally deformed hands would have abnormal cortical topography. In primate studies following surgically induced syndactyly (6, 23), the resulting cortical maps were clearly abnormal. The distinct borders between individual digits disappeared, resulting in a cortical representational topography of the fused digits that was similar to that of a normal single digit. Receptive fields in area 3b that, prior to syndactyly, were selectively responsive to a single finger became responsive following surgery to stimulation of both syndactylic digits. In our patients, the abnormally shrunken and nonsomatotopic hand areas presumably reflect a similarly abnormal cortical organization, consistent with a lifetime of abnormal hand function.

Invasive animal studies of cortical plasticity have the advantage of reproducibility. An identical injury can be induced in a large number of animals, and high-precision maps (under 1-mm resolution) derived from direct cortical microelectrode recordings can be obtained. The clear advantage of human studies is the correlation of topographical plasticity with higher level sensory function. Following nerve injury and repair in humans, in addition to behavioral information, very sophisticated and subtle information regarding sensory abnormalities such as mislocalization, poor localization, hyperesthesias and dysesthesias (24), and overall subjective imagery regarding hand sensation can be determined as well as changes of the above with training and use (24). Indeed, though there have been attempts to compare the various features of reorganized primate maps with human sensory phenomena and with primate psychophysical phenomena (7, 25), it is clear that a human model of cortical plasticity is far superior in comparing cortical topography and sensory cognition.

In the patients with the neurovascular island flap, it is evident that persistent sensory mislocalization is a reflection of the lack of reorganization of the cortical representation of the hand area. In the syndactyly patients, independent digital function resulting from surgical separation of the digits results in the attainment of distinct cortical digital locations. In one of these patients (OG), the resulting organization was clearly somatotopic and attained a close to normal area of the cortical representations. In the second patient (JM), the reorganization resulted in distinct cortical locations for the digits, although the resulting hand area was smaller than normal and the organization was nonsomatotopic. The degree of reorganization observed in these patients is well-correlated with the severity of their syndactyly—i.e., patient OG had clearly discernible individual digital pads, whereas JM did not. Thus, the larger presurgical extent of the cortical hand area of patient OG correlated with the greater differentiation of the digits of his hand. We believe that further MEG studies of patients with a wide variety of congenital and traumatic peripheral nerve problems will provide new insight as to the mechanisms of cortical plasticity, and MEG may prove useful as an adjunct to the process of sensory reeducation and rehabilitation as well as surgical reconstruction following peripheral nerve injury.

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