EFFECTS OF HAND TRANSPLANTATION ON CORTICAL ORGANIZATION

by

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DISSERTATION ABSTRACT

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Amputation induces substantial reorganization of the body part somatotopy in primary sensory cortex (S1), and these effects of deafferentation increase with time. Determining whether these changes are reversible is critical for understanding the potential to recover from deafferenting injuries. Here, we report evidence that the representation of a transplanted hand and digits can actually recapture the pre-amputation S1 hand territory in two transplant patients. With limited sensation 4 months post operation, one of the patient's (D.S.) palmar tactile stimulation evoked contralateral S1 responses that were indistinguishable in location and amplitude from those detected in healthy matched controls. The other patient (M.S.) demonstrated not only much improved sensation but also recovered ability to localize tactile stimuli 120+ months after the operation. The results described suggest that even decades after complete deafferentation, restoring afferent input to S1 leads to re-establishment of the gross hand and digits representations within their original territory.

Stimulation of the deafferented cortical maps may play an important role in maintaining their viability until the afferent input is restored. Motor imagery and creation of virtual visual feedback of the absent hand with a mirror have been proposed as stimuli.

We used fMRI to record neural activity while 11 unilateral hand amputees and matched controls performed aurally-paced thumb-finger sequencing movements with their intact hand (matching hand in case of controls) under visual guidance during four conditions: 1) intact hand (ME), 2) ME with motor imagery of the amputated hand, 3) ME with virtual visual feedback of the amputated hand, and 4) ME with motor imagery and the virtual visual feedback of the amputated hand. In contrast to controls, amputees showed increases in activity during all four conditions within the former functionally-defined sensorimotor hand territory. Movements of the intact hand likely increase activity in the former hand territory as a result of decreased interhemispheric inhibition. This stimulation may maintain deafferented hand representations that can recover soon after the afferent input is restored by hand transplantation.

This dissertation includes both my previously published and unpublished co-authored materials.

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This work is dedicated to my family.

TABLE OF CONTENTS

APPENDICES

Chapter Page

LIST OF FIGURES

Figure Page

Chapter II

Chapter III

Chapter IV

LIST OF TABLES

Table Page

CHAPTER I

INTRODUCTION

This thesis is broadly concerned with a human sensory system mediating touch, especially its cortical organization and reorganization after hand amputation and subsequent transplantation. In the introduction, we will first briefly review the normal organization of the human sensory system, then its reorganization due to peripheral nerve injury and regeneration, and finally introduce three papers that constitute the three chapters of this thesis.

TYPICAL ORGANIZATION OF TACTILE SYSTEM IN PRIMATES, INCLUDING HUMANS

The human hand is an organ of remarkable capacity and versatility in motor and sensory tasks as well as in combinations of the two. Its complex functions are dependent upon a number of neural factors, peripheral as well as central. In the periphery, two types of mechanoreceptors embedded in skin of the hand, slowly adapting (SA) and rapidly adapting (RA), detect pressure and touch, respectively (Kandel, Schwartz, and Jessell 2000). From the mechanoreceptors, RA and SA tactile afferents course independently via dorsal root ganglia and dorsal column of the spinal cord to the dorsal column complex in the brain stem where they terminate in separate locations, also segregated from the termination point of the proprioceptive information originating from the muscle spindle and joint receptors. From the dorsal column nucleus, the afferents decussate and ascend to the contralateral somatosensory thalamus via medial lemniscus. RA and SA cutaneous axons project to the ventral posterior lateral (VPL) nucleus where they form a systematic representation of the body. The relayed inputs from muscle spindles terminate dorsally to the cutaneous inputs in the ventral posterior superior (VPS) nucleus. VPL projects densely to area 3b, less densely to area 1, and sparsely to area 2 of the sensory cortex (S1). VPS projects to areas 3a and 2. Each area forms a distinct somatotopic map of the receptor surfaces (Kaas 1997; Jain, Catania, and Kaas 1998). A somatotopic map is an ordered projection of a sensory surface to one or more structures of the CNS (Dykes and Ruest 1984) in such a way that adjacent neurons are sensitive to adjacent areas on the skin that are called receptive fields (RF). Area 3b projects to area 1, secondary somatosensory cortex (S2) in the parietal operculum, and other associative areas. The representational order in area 3b proceeds from low extremities to tongue in a mediolateral sequence. This body part somatotopy is called homunculus (Penfield 2006) in the context of the human sensory cortex. Within the homunculus, hand, also lips and tongue, are overrepresented in terms of cortical real estate relative to their skin area. This is called cortical magnification and is a reflection of extremely dense peripheral innervation. Most of the hand representations are occupied by the fingertips where the innervation density is the highest. One of the behavioral consequences of cortical magnification is its inverse relationship with localization error. For example, in the hand the error of localization decreases in a proximodistal direction, being smallest at the fingertip (1 mm to 1.5 mm) compared with the palm (5 mm to 6 mm) (Nakada 1993). Because the primary map of the hand is the most reliably activated and most detailed in area 3b, this representation has been the focus of studies of somatosensory plasticity (Kaas and Florence 2001).

REORGANIZATION OF THE SOMATOSENSORY CORTEX DUE TO NERVE INJURY

Loss of afferents due to a minor peripheral nerve injury, a nerve crush or transection or digit loss, induces the corresponding somatosensory representation in area 3b to become transiently unresponsive (Merzenich, Kaas, Wall, Nelson, et al. 1983; Merzenich, Kaas, Wall, Sur, et al. 1983). Soon, however, the neurons in the deafferented cortex become sensitive to new receptive fields adjacent on the still innervated skin (Calford and Tweedale 1988) via “unmasking” of previously existing inhibited connections. In the short term, the amount of reorganization appeared limited to a cortical zone 500–700 µm on either side of the initial boundaries of the deafferented representation (Merzenich et al. 1984). This distance limit on reorganization was challenged, however, by studies of longer recovery periods and more drastic peripheral injuries.

Cortical reorganization after major deafferentations that follow, for instance, upper limb amputation, may dwarf the distance limit and take years to achieve its full extent. More than 12 years after the total loss of sensory input from the arm in macaques, the neurons in the deprived cortex that spanned 10-14 mm in area 3b became highly responsive to intact, remaining inputs, mostly from the chin {Pons 1991ui}. Such dramatic cortical remapping is likely a result of subcortical axonal sprouting into the deafferented area from its neighbors (Florence and Kaas 1995).

Similar to monkeys, humans with long-term limb amputations might have an extensively reorganized cortex. A possible perceptual corollary of such reorganization are reports of “phantom” limbs (Flor et al. 1995) and so-called referred sensations felt by amputees on the missing hand when touched on the face (Ramachandran, Rogers-Ramachandran, and Stewart 1992), presumably because face stimulation activated the deafferented hand representation. The somatosensory reorganization in amputees is extensive enough to be detected with non-invasive imaging techniques, such as magnetoencephalography (MEG) or functional magnetic resonance imaging (fMRI). In long-term amputees, the face and the stump representations appear to expand to occupy the former hand territory (Halligan et al. 1993; Elbert et al. 1994; Yang et al. 1994; Florence and Kaas 1995; Flor et al. 1998). Degree of cortical reorganization has been reported to correlate with levels of phantom limb pain (Flor 2003; Harris 1999).

REORGANIZATION OF THE SOMATOSENSORY CORTEX DUE TO NERVE REPAIR

The best evidence that reafferentation following peripheral nerve repair and regeneration facilitates recovery of the former representation comes from studies of peripheral nerve transection and repair in monkeys (Wall et al. 2003). After nerve injury and repair, peripheral nerves regenerate at about 1 mm a day in monkeys (Wall, Felleman, and Kaas 1983; Wall et al. 2003). Initial silencing followed by reactivations take their course in the deafferented cortex, as described in the previous section, until peripheral reinnervation restores afferent input. Peripheral reinnervation after nerve crush proceeds completely and accurately, mediated by surviving Schwann cells, so that after several month long recovery the deafferented cortex completely reverses its organization (Wall, Felleman, and Kaas 1983). Peripheral reinnervation after nerve transection, however, is far from perfect (Wall et al. 2003). Regenerating afferents, lacking the guiding support of the Schwann cells, reach their original destination but terminate randomly within it (Horch 1979; Dykes and Terzis 1979; Dykes, Terzis, and Strauch 1979). The cortical consequence of the peripheral disorder is degraded somatotopy (Paul, Goodman, and Merzenich 1972; Florence et al. 1994; Wall and Kaas 1986) such that many neurons have more than one RFs on the reinnervated skin. The loss of somatotopic order in the case of nerve transection appears to be permanent and for many years after nerve repair patients complain about sensory abnormalities. They do not confuse classes of sensation (temperature, pain, pressure, vibration) but mislocalize touch stimuli and cannot make use of patterns of spatial relationships (Moberg 1958; Dellon 1981). The central brain structures appear to have limited abilities to compensate for peripheral reinnervation errors (Wall and Kaas 1986; Hallin, Wiesenfeld, and Lungnegård 1981; Hawkins 1948; Mackel 1985) but sometimes more complete recovery is possible and cortical reorganization presumed important there.

STATEMENT OF THE PROBLEM

Normal hand sensory abilities, such as locognosia or touch localization, an aspect of tactile spatial discrimination, relies on the density and integrity of peripheral end-organs in the skin, as well as an intact somatotopic representation of the surface of the hand and digits in the primary sensory cortex (area 3b) (Jerosch-Herold, Rosén, and Shepstone 2006). The somatotopic representations are competitively maintained by afferent input and local inhibitory connections. Long-term removal of afferent input due to upper limb amputation causes the deafferented cortex to reorganize extensively. This reorganization may be associated with sensory dysfunctions and phantom limb pain. Restoring afferent input due to nerve repair and regeneration can reactivate the deprived cortex but might not restore its normal topography with consequent sensory dysfunctions, like touch mislocalization. The outlook for successful recovery from extensive peripheral nerve damage seems grim (Lundborg and Rosen 2007), yet here we report results from three studies that paint somewhat more optimistic picture of human ability to recapture normal cortical topography. First we report two cases of long-term adult amputees who received an allogeneic hand transplant. Allogeneic hand transplantation involves attaching multiple tissues (skin, muscle, tendon, bone, cartilage, fat, nerves and blood vessels) of a hand from a donor to a stump of an amputee. The two studies aimed to answer the question whether chronically deafferented hand and digits representations would recover their typical organization after hand transplantation? The third study was motivated by the conjecture that if normal somatosensory representations are maintained by afferent input, then providing it by cognitive-behavioral means to amputees might slow down or reverse the deafferentation-induced reorganization. Next we briefly describe the studies.

CHRONICALLY DEAFFERENTED CORTEX RECOVERS TYPICAL HAND ORGANIZATION

Here, we report the first evidence that the representation of a transplanted hand can actually recapture the pre-amputation S1 hand territory. Despite limited sensation, palmar tactile stimulation delivered 4 months post-transplant evoked contralateral S1 responses that were indistinguishable in location and amplitude from those detected in healthy matched controls. Our results suggest that even decades after complete deafferentation, restoring afferent input to S1 leads to re-establishment of the gross hand representation within its original territory. Unexpectedly, large ipsilateral S1 responses accompanied sensory stimulation of the patient's intact hand. These may reflect a change in interhemispheric inhibition that could contribute to maintaining latent hand representations during the period of amputation.

TYPICAL DIGITAL REPRESENTATIONS EMERGE AFTER LONG-TERM RECOVERY

High resolution fMRI combined with a rapid event-related tactile stimulation protocol non-invasively produced high-resolution somatosensory maps of separate digits for a allogeneic hand transplant recipient in late stages of recovery. The individual digit representations within the primary sensory cortex returned to their grossly normal organization in parallel with recovered sense of locognosia. At the gross level of body-part somatotopy, these changes seem reversible even in the mature brain, a fact that may have broad implications for our understanding of the brain's response to deafferenting injuries.

INTACT HAND MOVEMENTS STIMULATE DEAFFERENTED HAND AREA

That normal hand and digit representations can be recovered after restoring afferent input via hand transplantation seems remarkable in the context of dramatic reorganization of the sensory cortex caused by hand amputation. However, recovery of normal sensory organization seems less surprising if the deafferented representations do not disappear but lie dormant, maintained by afferent input from a source other than the amputated hand. Another piece of evidence for persisting maintenance of the former hand representation is provided by the fact that chronic unilateral upper extremity amputees can reactivate the former sensorimotor hand territory behaviorally. If this is true and the former sensorimotor hand representations persist post hand deafferentation, how can they be activated? We tested two cognitive-behavioral manipulations, i.e., mirror and imagery tasks, that garnered tentative and mixed support as effective stimuli for the deafferented hand area. We found that imagining or simply observing movements of the intact hand reflected in a mirror had no effect. However, the intact hand movements engaged the former hand territory, thus providing a possible source for maintaining latent hand representation in unilateral hand amputees.

POSSIBLE CLINICAL RELEVANCE

In 2005 nearly 1.9 million people in the US were living with the loss of a limb and each year approximately 185,000 more undergo amputation of a limb as a result of a trauma, complications of diabetes or vascular disease. While most amputees report independence, they do experience limitations in daily life activities, 27.9% reported being retired due to a disability. Almost 70% of all those surveyed said that they had residual limb pain, 80% reported phantom pain (pain in the part of the limb that is missing). In 2009, hospital costs associated with amputation totaled more than $8.3 billion (Ephraim et al. 2005).

Chapters II, III and IV include both my previously published and unpublished co-authored materials.

CHAPTER II

CHRONICALLY DEAFFERENTED SENSORY CORTEX RECOVERS A GROSSLY TYPICAL ORGANIZATION AFTER ALLOGENIC HAND TRANSPLANTATION

This work was previously published in Volume 18 of the journal Current Biology in 14 October 2008. I am a second author. I took part in the experiments and performed fMRI data analysis. Scott Frey assisted with the data analysis. Scott Frey, Jolinda Smith and Scott Watrous designed experimental protocol and collected most data. The manuscript was written and edited by Scott Frey, Jolinda Smith and me.

RESULTS

Behavioral

Semmes-Weinstein filament testing revealed that the patient could both detect and localize touch within two areas on the transplanted hand in the absence of vision. One area was located on the thenar eminence in the distribution of the median nerve (threshold = 8g), and the second was on the lateral base of the thumb in the radial nerve distribution (threshold = 1.4g). The rest of the hand remained insensitive at this stage of recovery. No sensory disturbances, such as mislocalization, were detected during examination of D.S.'s intact hand.

fMRI Sensory Mapping in Controls

Stimulation of either palm in the control group resulted in increased activation of the contralateral hemisphere within S1 (Figure 1A). Peaks within these S1 clusters were located symmetrically in the central sulci of the two cerebral hemispheres (see Table S1 in the Supplemental Data), and activity extended rostrally into the precentral gyrus (preCG) and caudally into the postcentral gyrus (postCG). Additionally, stimulation of the left hand increased activity significantly in the contralateral parietal operculum (including putative S2 [7]), whereas stimulation of the right hand evoked bilateral operculum responses.

fMRI Sensory Mapping in D.S.

Similar to controls, stimulation of D.S.'s transplanted right palm produced a focal increase in contralateral S1 and bilateral operculum (Figure 1B; see Table S1). In addition, significant increases were detected in, the caudal cingulate zone (CCZ) (Kwan et al. 2000) and caudal insula (Gelnar et al. 1998), two other areas previously implicated in somatosensation. Stimulation of D.S.'s healthy left hand was also associated with focal activation of the contralateral S1, bilateral operculum, CCZ, and insula. Unexpectedly, a large region of increased activity was detected along the length of the ipsilateral postCG (Figure 1B). The peak of this activation was located on the caudal bank of the postCG (-62, -18, 44), which corresponds to cortical areas 1 (Geyer et al. 2000) and/ or 2 (Grefkes et al. 2001) of the S1 complex defined probabilistically. This contrasts with previous findings of small ipsilateral S1 responses to tactile hand stimulation in healthy adults (Hansson and Brismar 1999). The coordinates of this peak are located in lateral, anterior, and inferior positions with respect to those associated with stimulation of either D.S.'s (-40, -20, 54) or the control group's (-38, -28, 58) right palms. Significant increases in ipsilateral activation of the lateral postCG were not observed during stimulation of the transplanted right hand or during stimulation of either hand in the control group. Transformation of D.S.'s data into a flattened standard space map illustrates the high degree of overlap with the contralateral activations detected in the

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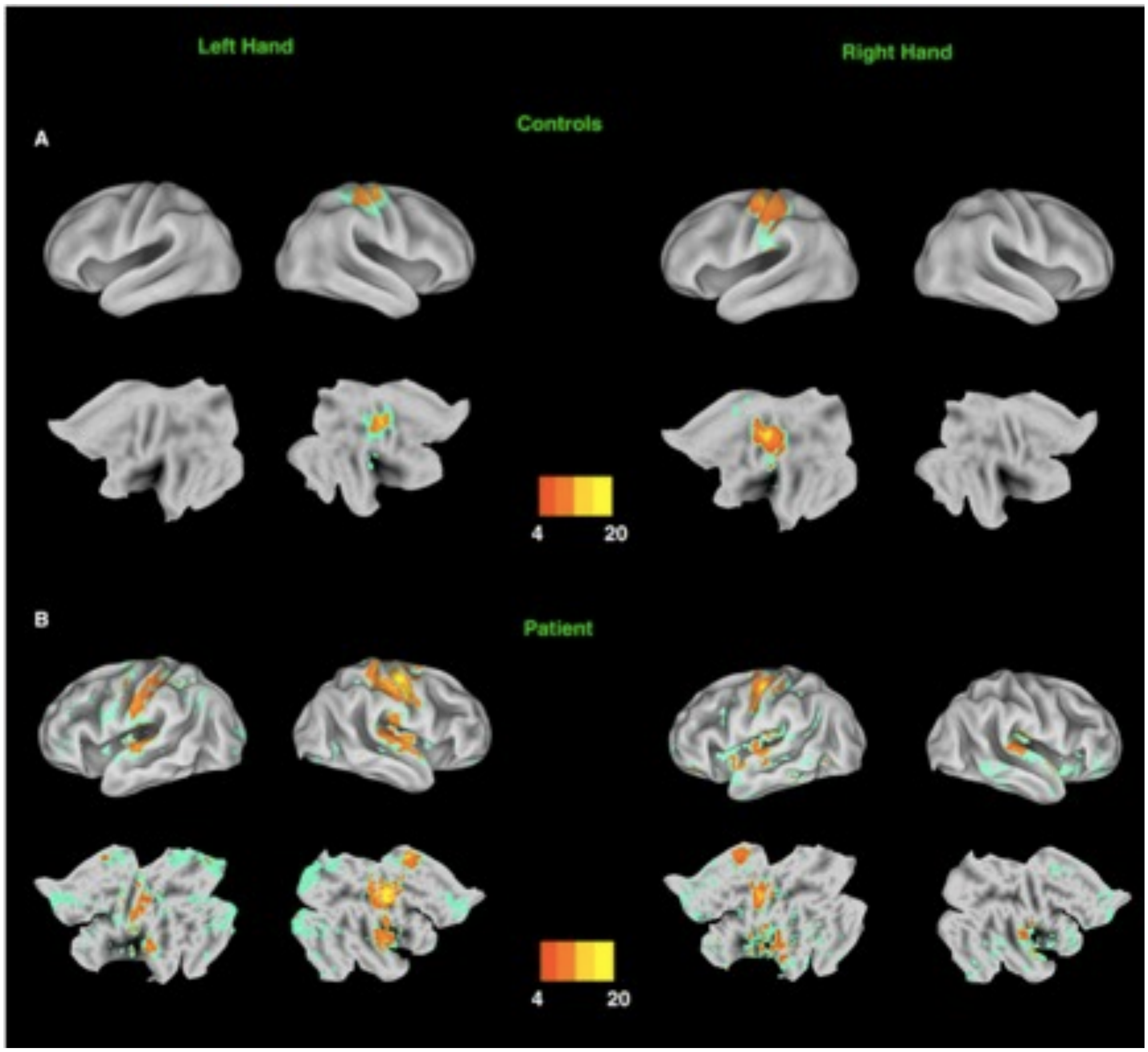
Figure 1 (next page). Statistical parametric maps representing areas of increased activity associated with tactile stimulation versus rest. All areas in color showed significant increases in activity during movement ($z > 2.3$, $p < 0.05$, cluster-based correction for multiple comparisons). Areas of peak activation (i.e., $z > 4.0$) are represented in warm colors corresponding to values indicated in the color bar. Nonpeak areas of significantly increases activity ($2.3 < z < 3.99$) are represented in green. Mean control data are displayed on the PALs template brain (see Supplemental Data) that has been partially inflated (upper rows) or flattened (lower rows) so that activations located in sulcal folds may be visualized. Patient D.S.'s data are displayed on inflated and flattened surface renderings created from high-resolution anatomical images of his own brain.

(A) Stimulation of the left or right palms of control subjects increased activity in contralateral S1. The peak was located in the CS, and activity extended rostrally on the preCG and caudally into the postCG. Contralateral activation is also detected in the parietal operculum (including putative S2). During stimulation of the right hand, left parietal operculum also showed a small but significant increase in activity (Table S1). However, because of individual variation in cortical topography, this ipsilateral cluster did not survive the multi-fiducial adjustment for individual differences in cortical topography and therefore is not visible in these surface renderings (See Experimental Procedures). **(B)** Similarly, stimulation of the D.S.'s transplanted (right) or intact (left) palms evoked peak responses within contralateral S1 (see text). In addition, stimulation of the intact left palm was associated with a large region of increased activity along the ipsilateral postcentral gyrus. Bilateral responses were also observed in putative S2, CCZ and insula (see text).



control group during sensory stimulation of either hand (Figure 2). It can also be seen that relative to controls, substantially larger regions of the parietal operculum were engaged bilaterally during stimulation of either of D.S.'s palms.

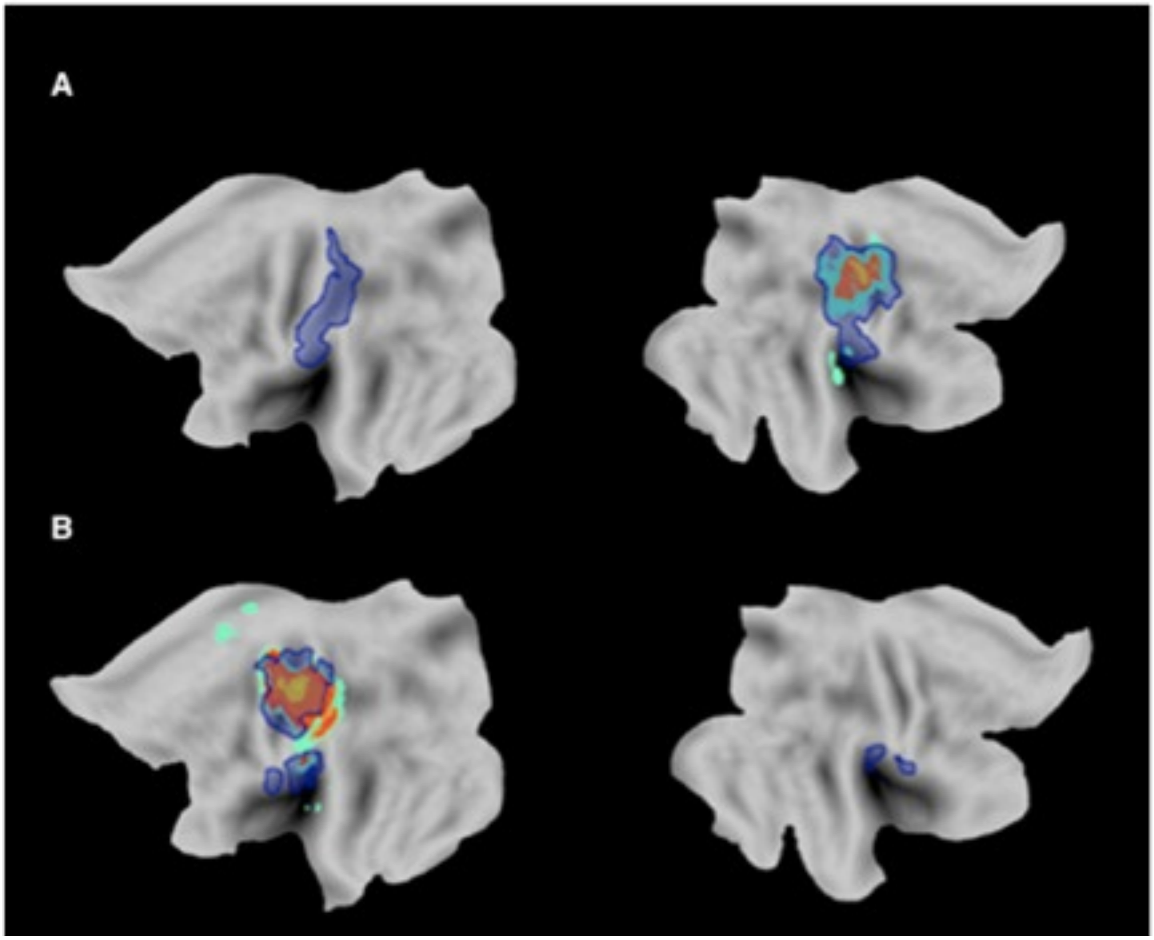


Figure 2. Activations associated with hand stimulation in D.S. and controls are represented in standard space. The multi-fiducial mapping procedure [29] was used for transforming data from patient D.S. (blue overlay) into standard space for direct visual comparison with mean activations of the control group (see Supplemental Data). For D.S., all significant activations within preCG, postCG, parietal operculum, and insula are included (See Figure 1). These flattened illustrations illustrate the high degree of overlap between D.S.'s contralateral S1 responses and those of the control group.
(A) Responses associated with stimulation of the left palm. In contrast to results for controls, stimulation of D.S.'s left palm elicited a strong ipsilateral response along the length of the postCG and into the operculum. **(B)** Responses associated with stimulation of the right palm. Note the high degree of overlap between data from D.S. and control participants.

Activity within the Normal S1 Hand Representation

As described in the Experimental Procedures, activation foci in the control-group sensory-mapping data were used for functionally defining the normative (i.e., pre-amputation) S1 hand representations. Stimulation of D.S.'s transplanted right hand evoked a response that is comparable to that of the control group within the territory of the right hand (Figure 3A). Stimulation of his left hand caused a modest ipsilateral increase in activity within this region, and this increase exceeded that of the controls. Stimulation of D.S.'s left hand likewise produced a response comparable to that of controls within the left-hand representation (Figure 3B). Stimulation of the cheeks, however, did not evoke a strong response in either hand representation for D.S. or the control group.

DISCUSSION

These experiments yielded two major findings. First, we found that even 35 years after an amputation, the gross S1 hand representation in the mature brain has a remarkable capacity to return to a state of organization that is indistinguishable from what would be expected prior to hand loss. This is extraordinary when one considers the well-established reorganizational changes that occur after deafferentation (Jones 2000; Kaas 1991), and the fact that these effects increase with time (Pons et al. 1991). Second, in addition to these apparently normal contralateral S1 responses, we found unexpectedly large responses in the ipsilateral postCG during stimulation of D.S.'s intact hand (Figures 1 and 2). Both findings greatly extend our understanding of the ability of the cerebral cortex to respond adaptively to dramatic changes in stimulation even when it is fully mature. We discuss these two points in detail below.

Grossly Typical Sensory Cortical Organization

Previously, it was demonstrated that stimulation of a transplanted hand 2 years after amputation evoked a strong contralateral S1 response (Neugroschl et al. 2005). Control data were not used for functionally defining the territory of the normative (i.e., pre-amputation) hand representation. However, the center of gravity (COG) of the S1 activation reportedly became increasingly disparate from that of healthy controls during the 4 months immediately after the transplant ((Neugroschl et al. 2005); their Table 2). This may indicate recruitment of sensory regions other than those formerly devoted to the patient's birth hand. Unfortunately, the interpretation of this finding is complicated because the COG was computed across a large activation cluster that included not only S1 but also the parietal operculum and insula. By contrast, we used data from matched controls to functionally define the normative S1 hand territory. Four months after the procedure, we found that stimulation of the transplanted palm evoked responses that were comparable in peak location, spatial extent, and amplitude to those detected in control participants (Figures 1–3; see Table S1).

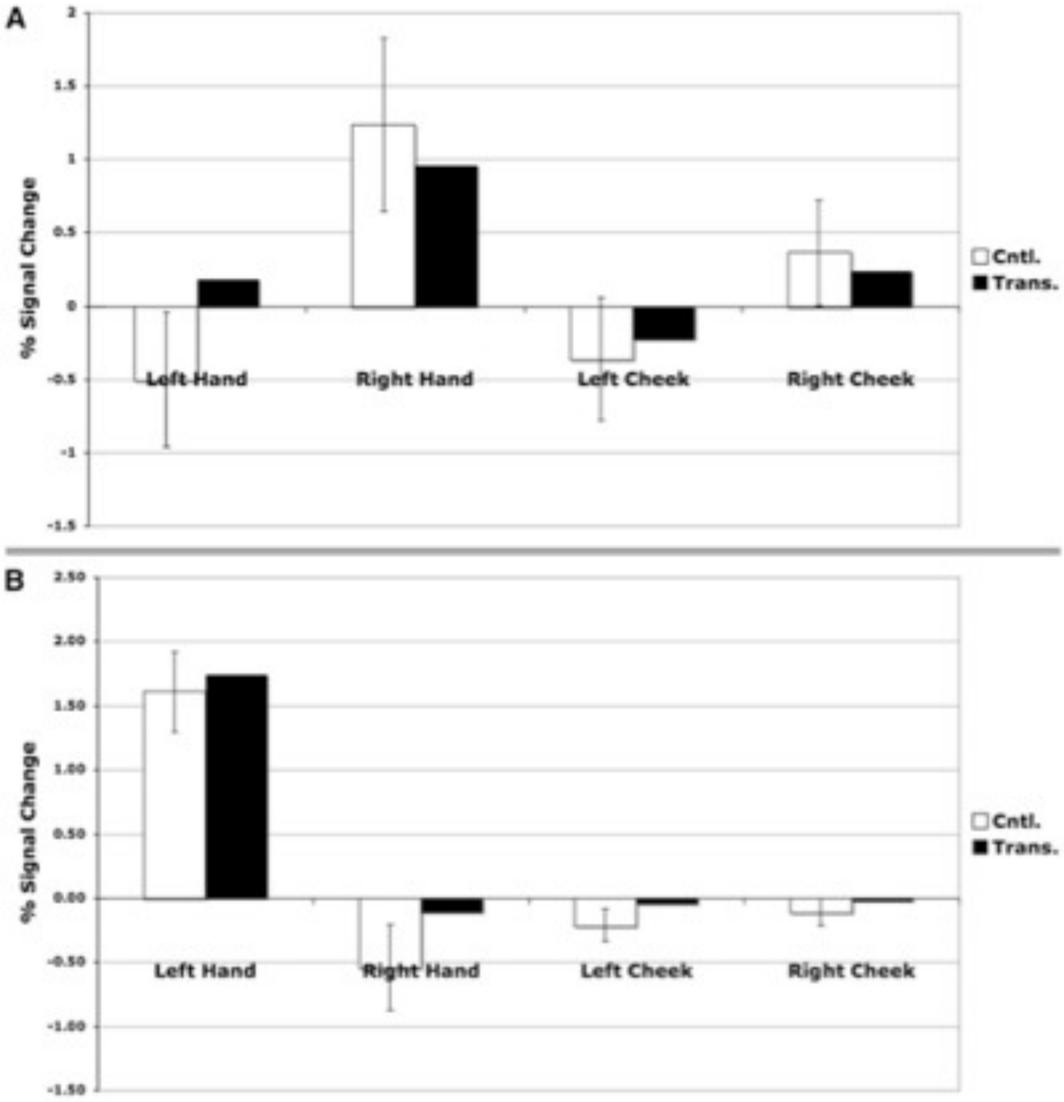


Figure 3. Percent BOLD signal change associated with sensory stimulation of the palms or cheeks within normal S1 hand representations defined functionally on the basis of control data. Error bars represent 95% confidence intervals around group means. **(A)** Left hemisphere: S1 hand representation. Within the right hand S1 representation, D.S. and controls showed a strong increase during stimulation of the right hand. D.S. also showed a modest increase in activity during stimulation of the left hand (see text). **(B)** Right hemisphere: S1 hand representation. In the left hand S1 representation, both D.S. and controls showed comparable increases in activity during stimulation of the contralateral left hand. D.S. showed no greater response to stimulation of the cheeks than controls in either hemisphere.

At the time of testing, D.S.'s sensitivity was limited to a relatively small portion of the grafted hand. This suggests that the recovery of the S1 hand territory might precede increasing sensitivity in the grafted hand. It is important to note that at this stage of recovery we cannot rule out the possibility that the individual digit representations within the S1 hand map remain disorganized. In fact, this seems quite likely on the basis of studies of nonhuman primates. The loss of topographical order in the peripheral nerves, caused by median nerve transection and surgical repair, leads the recovered cortical representation of the reinnervated hand in adult monkeys to be intrinsically disordered (Florence et al. 1994). Additional work is underway to evaluate these predictions. Within the normative S1 hand territory, responses to stimulation of patient D.S.'s cheeks were minimal and did not differ from those of controls (Figure 3). This has not been previously studied in transplant patients. However, chronically deafferented monkeys (Pons et al. 1991) and human amputees (Yang et al. 1994; Elbert et al. 1994) do show evidence of encroachment of the face representation into the former hand territory. It is widely held that the somatotopic organization of S1 is maintained through competitive interactions (Jones 2000; Kaas 1991). During the 4 postoperative months, increasing afferent input from the transplanted hand might therefore have effectively reclaimed the hand territory from the face. Due to the absence of pre-transplant data, however, we cannot rule out the possibility that for unknown reasons D.S.'s face representation simply did not shift into the hand territory after amputation. Reorganizational changes in S1 somatotopy appear to be more pronounced in amputees with significant phantom pain (Flor et al. 1995), and D.S. suffered minimally from this syndrome.

The mechanisms responsible for the recovery of a grossly normal S1 hand representation remain uncertain, and changes occurring subcortically in the thalamus and/or brainstem might play an important role (Jones 2000). One possibility is that, despite the dynamic functional rebalancing that occurs for inhibitory and excitatory synapses after deafferentation (Kaas 2000), a latent representation of the gross organization of the hand is retained in the pattern of S1 neuronal connectivity. When afferent input is re-established after the transplant, this latent representation could be actively recovered. A parallel might be drawn here with the rodent sensory cortex, where adult whisker amputation alters the receptive-field properties of barrel cells but appears to leave the architecture of the cortical map intact (Fox, Glazewski, and Schulze 2000; Yang et al. 1994; Petersen 2007; Elbert et al. 1994). Yet, peripheral injuries in primates are accompanied by growth of intracortical (but not thalamocortical) connections, which might play a role in map reorganization (Jones 2000; Florence, Taub, and Kaas 1998; Kaas 1991). The impact of hand allotransplantation on these changes remains unknown.

Ipsilateral Sensory Responses

We found that sensory stimulation (Figures 1 and 2) of D.S.'s intact hand evoked, in addition to the normal contralateral responses, strong responses in the ipsilateral postCG. These activations were not, however, located predominantly within the region that would have represented the right hand prior to amputation (Figure 3A). This ipsilateral response was much larger than that reported previously in healthy adults (Hansson and Brismar 1999) and was not apparent for D.S.'s transplanted hand or for either hand in the control group.

It is possible that this reflects a functional adaptation to the chronic imbalance created in the somatosensory system by unilateral S1 deafferentation. Some neurons in the S1 complex (area 2) have strong bilateral receptive fields and fire in response to stimulation of the ipsilateral hand via transcallosal connections (Iwamura, Iriki, and Tanaka 1994). Left and right S1 areas are also known to be connected via inhibitory transcallosal pathways (Hlushchuk and Hari 2006). Previous results show that acute deafferentation induces bilateral reorganizational changes in S1 (Calford and Tweedale 1990; Werhahn, Mortensen, Van Boven, et al. 2002). Long-standing amputation could decrease the normal level of interhemispheric inhibition and thereby facilitate transcallosal neural activity coming from the primary representation of the intact hand. If so, then we predict that these ipsilateral responses will decrease as D.S.'s sensory recovery progresses.

In conclusion, allogenic hand transplantation provides an unprecedented opportunity to investigate the reversibility of changes in cortical organization after amputation. Our findings suggest that, at the gross level of body-part somatotopy, these changes are indeed highly reversible even in the mature brain, a fact that may have broad implications for our understanding of the brain's response to deafferenting injuries. A future objective will be to evaluate the internal organization of digit representations within the S1 maps of transplanted hands once a more advanced stage of sensory recovery has been achieved.

EXPERIMENTAL PROCEDURES

Subjects

D.S. is a male who suffered a wrist-level traumatic amputation of his dominant right hand at age 19 years, 7 months. Early in his recovery he experienced phantom sensations and pain, but these dissipated with time. He regularly wore a mechanical prosthesis for work. Thirty-five years after this accident, at age 54 years, he underwent a successful allogenic transplantation. D.S. underwent testing four months after the procedure. Data were also acquired from four age- (M = 54 years, SD = 4.9), sex-, and handedness-matched control participants. All subjects gave informed consent prior to their participation.

fMRI Sensory Mapping Task

Subjects each completed two 12:48 blocks with their eyes closed. Blocks were divided into four 3:12 cycles. Within each cycle, four body parts (left hand, right hand, left cheek, or right cheek) were stimulated in pseudo-randomized order. Each period of stimulation lasted for 24 s and was followed by a rest interval of equal duration. The palmar surface of each hand was stroked with a coarse sponge at a rate of 1 Hz. Movements were unidirectional and swept from proximal (heel of hand) to distal (fingertips). Previous work shows that moving stimuli are an effective means of mapping human S1 (Bodegård et al. 2000), and this sponging technique has been used previously with healthy adults (Disbrow, Roberts, and Krubitzer 2000) and a hand-transplant patient (Neugroschl et al. 2005), and it has been shown to stimulate S1 (Werner 1968) and S2

(Whitsel, Petrucelli, and Werner 1969) neurons in monkeys effectively. Unilateral cheek stimulation was delivered separately to each cheek at a rate of 1 Hz.

Prior to each block, the body part to be stimulated next was cued on a monitor visible only to the experimenter. An aural cue then signaled the beginning of the stimulation block, and stimulus delivery to was paced by an auditory 1Hz tone. The final tone in each stimulation block was at a higher frequency, enabling the experimenter to prepare to stop. Stimulation of the cheeks was accomplished by briefly tugging on 1m long cotton strings attached to the perioral regions of each cheek with medical tape to induce an approximately 1cm displacement. To control force, a section of each string was replaced with a calibrated (130.41g/25.4mm) MRI-compatible spring. Preliminary testing verified that this technique did not create image artifacts.

fMRI Data Acquisition

A Siemens' 3-Tesla Allegra MRI scanner was used for collecting BOLD echoplanar images (EPI) with a T2*-weighted gradient echo sequence with prospective acquisition correction (PACE) (Thesen et al. 2000). The initial 4 scans in each BOLD fMRI run were discarded to allow steady-state magnetization to be approached. Whole brain EPI images were collected using a standard birdcage radio-frequency coil and the following parameters: : TR = 2000ms, TE = 30ms, flip angle = 800, 64 x 64 voxel matrix, FoV = 200mm, 33 contiguous axial slices, thickness = 3.0mm. A double gradient echo sequence was used to acquire a field map that was used to correct for EPI distortions. Two high resolution T1-weighted structural images were acquired using the 3-D MP-RAGE pulse sequence: TR = 2500ms, TE = 4.38ms, TI = 1100ms, flip angle = 8.00, 256 x 176 voxel matrix, FoV = 256mm, 176 contiguous axial slices, thickness = 1.0mm. Siemens' Auto Align Scout and True FISP sequences were executed prior to the start of each functional run to ensure that slices were prescribed in exactly the same positions across runs. DICOM image files were converted to NIfTI format using MRIConvert software (http://lcni.uoregon.edu/~jolinda/MRIConvert/).

fMRI Data Analysis

All data preprocessing (EPI dewarping, motion correction, brain extraction, spatial smoothing, registration, and normalization) and modeling were conducted with FEAT (FMRI Expert Analysis Tool) Version 5.91 in the FSL image-processing tools (http://www.fmrib.ox.ac.uk/fsl/). Surface reconstruction and visualization were accomplished with version 5.5 of the CARET software (http://brainmap.wustl.edu/caret/) (Van Essen et al. 2001).

Each fMRI run for a given subject was modeled separately at the first level. Prior to statistical estimation, the following pre-processing steps were undertaken: EPI dewarping using Fugue, motion correction using MCFLIRT (Jenkinson et al. 2002); non-brain removal using BET (Smith 2002); spatial smoothing using a Gaussian kernel of 5 mm (FWHM); mean-based intensity normalization of all volumes by the same factor; high pass temporal filtering (sigma=50.0s). Estimates of the degrees of freedom in the statistical model were corrected for autocorrelation in the data by using the FSL pre-whitening technique (Woolrich et al. 2001). Time-series statistical analysis was carried out using FILM with local autocorrelation correction (Jones 2000; Woolrich et al. 2001). Delays and undershoots in the hemodynamic response were accounted for by convolving the model with a double-gamma basis function. Registration to high resolution and standard images (MNI-template) was implemented using FLIRT (Jenkinson and Smith 2001; Jenkinson et al. 2002). Inter-session (Level 2), and inter-subject (Level 3, for control participants only) levels of analysis were carried out using a fixed effects model, by forcing the random effects variance to zero in FLAME (FMRIB's Local Analysis of Mixed Effects) (Worsley et al. 1992; Kaas 2000; Beckmann, Jenkinson, and Smith 2003). Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 2.3$ unless otherwise indicated and a (corrected) cluster significance threshold of $p < 0.05$ (Worsley et al. 1992).

D.S.'s statistical parametric maps were overlaid on a 3-D rendering of the cortical surface of his brain created with version 5.5 of the CARET software http://brainmap.wustl.edu/caret/ (Van Essen et al. 2001). To account for individual variation in cortical topography, control group average data were mapped onto the population, landmark and surface-based atlas (PALs B12) of Van Essen using the multi-fiducial procedure (Van Essen 2005). To account for individual variation in cortical topography, control group average data were mapped onto the population, landmark and surface-based atlas (PALs B12) of Van Essen using the multi-fiducial procedure (Van Essen 2005).

Functionally Defining Normative Hand Representations

A multistep procedure was used for defining the spatial extent of normal hand sensory maps conservatively on the basis of mean control-group data. First, the overall maximum z-value was identified within conditions involving the hands. Second, thresholds for statistical parametric maps for both left and right hand conditions were set at 50% of this maximum z-value. All voxels surviving this thresholding procedure were defined as being within the normal left or hand representation.

CHAPTER III

HIGH RESOLUTION DIGIT SOMATOTOPY

This chapter includes both published and unpublished work. The published part previously appeared as posters at the 2009 and 2011 ISMRM conferences, co-authored by Jolinda Smith, Sergei Bogdanov, Scott Watrous and Scott Frey. Jolinda Smith and Bill Troyer designed and built the apparatus. I assisted with data collection and performed the majority of the data analysis. Scott Frey designed the paradigms and assisted with the data analysis. The unpublished text was written by me and edited by Scott Frey.

INTRODUCTION

Cortical Reorganization due to Deafferentation

The hypothesis that somatotopic organization of sensory cortex is maintained through competitive interactions between adjacent maps has received substantial empirical support. One source of evidence comes from demonstrations that local deafferentation by peripheral nerve injury induces reorganizational changes in somatosensory cortical areas 3b and 1 (Merzenich, Kaas, Wall, Nelson, et al. 1983; Merzenich, Kaas, Wall, Sur, et al. 1983). Reorganization involves representational shifts that increase in extent over time (Pons et al. 1991). In the short-term, the initial silencing of the deafferented area is followed by its acquisition of the new receptive fields (Calford and Tweedale 1988) that are sensitive to the adjacent regions of skin within the same body part. In the long term, a major deafferentation that follows dorsal rhizotomy or hand amputation, may result in neurons of the deafferented hand area becoming responsive to inputs from a different body part, i.e. the former hand area starts responding to the input from the face or the stump of the arm (Pons et al. 1991; Florence and Kaas 1995). Such dramatic cortical remapping is likely a result of subcortical axonal sprouting into the deafferented area from its neighbors (Florence and Kaas 1995). A possible perceptual corollary of extensive cortical reorganization after chronic limb amputation in humans are reports of so-called referred sensations when amputees feel touch on the missing hand when touched on the face (Ramachandran, Rogers-Ramachandran, and Stewart 1992) and phantom limb pain (Flor et al. 1995).

Cortical Organization Recovers after Nerve Repair

The best evidence that reafferentation following peripheral nerve repair and regeneration facilitates recovery of the former representation comes from studies of peripheral nerve transection and repair in monkeys (Wall et al. 2003). After nerve is repaired, peripheral reinnervation follows, paralleled by cortical reorganization. After a prolonged recovery process, which is paced by a 1 mm a day peripheral nerve growth limit (Wall et al. 2003), nerve regeneration reestablishes the cortical capacity to process tactile information from the reinnervated skin. The recovery of normal tactile sensitivity appeared incomplete due to imprecise peripheral innervation (Wall and Kaas 1986) and possibly degraded representational topography reflecting this peripheral imprecision (Hallin, Wiesenfeld, and Lungnegård 1981; Hawkins 1948; Mackel 1985; Wall et al. 2003).

Effects of Hand Allotransplantation on Cortical Organization

Earlier BOLD fMRI data demonstrated increased S1 activity, although not specific to the former hand territory, in response to stimulation of an allogeneically transplanted hand (Neugroschl et al. 2005). In our study of another transplant patient (D.S.) 4 months post operation, we first functionally defined the normative S1 hand territory using data from matched controls. Then we stimulated D.S.'s transplanted right palm while recording fMRI activity in his somatosensory cortex. The tactile stimulation produced a focal increase in contralateral S1, bilateral operculum, the caudal cingulate zone, and caudal insula. Peak locations and spatial extent of the evoked responses and fMRI signal amplitude in the normative S1 hand territory were comparable to those detected in control participants. At the time of testing, D.S.'s sensitivity was limited to a relatively small portion of the grafted hand. This suggested that the recovery of the S1 hand territory might precede increasing sensitivity in the grafted hand. More support for cortical renormalization could be provided by evidence of normal somatotopy of digital representations in area 3b which requires separable digital representations in mediolateral order. In fact, the hand tactile stimulation did evoke activity in area 3b but digital mapping was impossible at that early stage in the recovery as the individual digits were yet to regain sensitivity. At the time of the tests, D.S.'s hand still remained insensitive except for the two areas, the thenar eminence in the distribution of the median nerve and the lateral base of the thumb in the radial nerve distribution, where the patient could detect and localize light touch in the absence of vision. Therefore, there was no way to test whether the individual digit representations within the S1 hand map remained disorganized, as the results from studies of nonhuman primates would suggest (Wall and Kaas 1986). Here we address this question by reporting the results of another case study, this time characterized by long-term post operation recovery of hand sensory function. A 36 year-old male (M.S.) received a left hand graft 23 years after the amputation and was tested more than 10 years after the transplantation. Despite reduced hand sensitivity, M.S. could detect and localize tactile stimuli delivered to his transplanted hand accurately within 8 mm without vision. We hypothesized that this became possible due to recovery of normal organization of S1 and, specifically, recovery of individual digit representations in his contralateral primary sensory cortex (Brodmann Area 3b, BA3b) believed to be necessary for digit-specific touch localization (Almquist and Eeg-Olofsson 1970).

To map out the finer structure of M.S. somatosensory cortex, we built an MRI compatible pneumatic stimulation system (Huang and Sereno 2007) to deliver tactile air puffs to finger tips inside a magnet. Previous work shows that moving stimuli are an effective means of mapping human S1 (Bodegård et al. 2000), and this air puffing technique has been used previously with healthy adults (Huang and Sereno 2007; Stringer et al. 2011). We combined this system with a high-resolution (1.5 x 1.5 x 2.0 mm) rapid event-related scanning fMRI protocol designed to produce detailed maps of the somatosensory representations of the digits in individual human subjects at 3T with an acquisition time totaling approximately 14 minutes (Gelnar et al. 1998; Maldjian et al. 1999; Schweisfurth, Schweizer, and Frahm 2011; Schweizer, Voit, and Frahm 2008;

Stippich et al. 1999; Disbrow et al. 1999; Harrington and Hunter Downs 2001; Kurth et al. 1998; McGlone et al. 2002).

This study aims to provide evidence that M.S. somatosensory digital representations have recovered their normal organization in area 3b. Normal organization is defined as the expected somatosensory response in area 3b of the control group to tactile stimulation of individual digits described by (1) statistical parametric map and BOLD signal magnitude (2) separable digital representations, (3) thumb-to-ring lateral-medial digital somatotopy. Given the definition of the normal digital organization, we hypothesize that if restoration of afferent input due to hand transplantation has resulted in the recovery of the digital somatotopy in M.S., then tactile stimulation of his individual digits will evoke in area 3b (1) statistical parametric map and BOLD signal magnitude, comparable to those in the control group, (2) separable digital representations, comparable to those in the control group, and (3) thumb-to-ring lateral-medial somatotopy, comparable to the one in the control group.

EXPERIMENTAL METHODS

Subjects

A 46 year old male (M.S.) received a left hand transplant 11 years prior to the study, 23 years after he lost his dominant hand in a fireworks accident. A group of 8 age- (average 43 yrs, range 39 to 50 yrs) and sex- matched participants were recruited to serve as a control group. All subjects gave informed consent prior to their participation.

Apparatus for Tactile Stimulation

The system (Figure 1) consists of 16 lengths of flexible tubing (¼” ID, 1/16” wall) connected to a bank of high-speed solenoids (NVKF334, SMC Pneumatics, Indianapolis, IN). A compressor provides pressurized air to the solenoids, which are computer controlled by a multifunction DAQ with clocked IO (PCI-6229, National Instruments, Austin, TX) and LabView™ software. The solenoids can be operated at frequencies of up to 10 Hz. Each of the 16 lines is connected to an adjustable-flow valve in order to regulate the air flow at each nozzle. The lines are brought into the magnet room through a wave guide and terminated with different nozzles, depending on the stimulation target.

Figure 1. Pneumatic digit stimulator.
For digit stimulation, ten lengths of flexible tubing are connected to ¼” Loc-Line™ adjustable modular hose via a custom-built manifold. The manifold is attached to a ¼” sheet of plastic to which the subject’s hand is secured with Velcro straps. The Loc-Line™ hose is adjusted for each subject so that the 1/16” terminating nozzles are directed at the pads of the thumb and fingertips. The manifold may be attached to different bases for different stimulation targets or special subject populations, such as amputees. Loc-Line™ adjustable modular hose with a custom-built manifold for hand stimulation. This Figure was presented as part of a poster at ISMRM in 2009.

Digit Stimulation Paradigm

MS completed two and each control subject completed one 14-min session with eyes closed. Within each session, four digits of the left hand (D1-4 or thumb, index, middle, ring) were individually stimulated. Stimuli consist of pulsed air puffs delivered during a single run to four targets, alternating with rest. The air puffs are pulsed at 8 Hz with a 50% duty cycle. To ensure subject attention, between 7 – 10% of the pulse trains occur at lower frequency (2 or 4 Hz) and subjects are asked to count the number of these oddball stimuli delivered throughout the run. The inter-trial interval varies between 3 and 6 seconds in duration. Each target is stimulated in pseudo-random order a total of 32 times, for a total run duration of approximately 14 minutes. An additional 2 minutes of rest is included at the beginning of the trial in order to establish a quiet baseline.

fMRI Data Collection

All scanning is performed in a Siemens' Allegra 3T scanner, using a four-channel phased-array head coil. An EPI-BOLD sequence is used with a 144 × 216 mm field of view and a 96 × 144 matrix size for an in-plane resolution of 1.5 × 1.5 mm. Fifteen 2 mm thick coronal slices with a 0.5 mm inter-slice gap are obtained with a TR of 1030 ms and a TE of 30 ms.

The initial 4 scans in each BOLD fMRI run were discarded to allow steady-state magnetization to be approached. A double gradient echo sequence was used to acquire a field map that was used to correct for EPI distortions. A high resolution T1-weighted structural image was acquired using the 3-D MP-RAGE pulse sequence: TR = 2500ms, TE = 4.38ms, TI = 1100ms, flip angle = 8.00, 256 x 176 voxel matrix, FoV = 256mm, 176 contiguous axial slices, thickness = 1.0mm. Another high-resolution T2-weighted structural image was acquired to assist registration with the following sequence. Siemens' Auto Align Scout and True FISP sequences were executed prior to the start of each functional run to ensure that slices were prescribed in exactly the same positions across runs. DICOM image files were converted to NIfTI format using MRIConvert software (http://lcni.uoregon.edu/~jolinda/MRIConvert/).

Functional localizer. A functional localizer was used to identify sensorimotor areas of the brain to determine slice placement for the high-resolution EPI (Figure 2). This localizer comprised five minutes of aurally paced movements of the hands or lips in a block design. A t-test was performed on the console contrasting hand and lip movements. These results are then used to determine the position of the rostral-most slice of the high-resolution scan, enabling full bilateral coverage of primary (S1) and secondary (S2) somatosensory cortices.

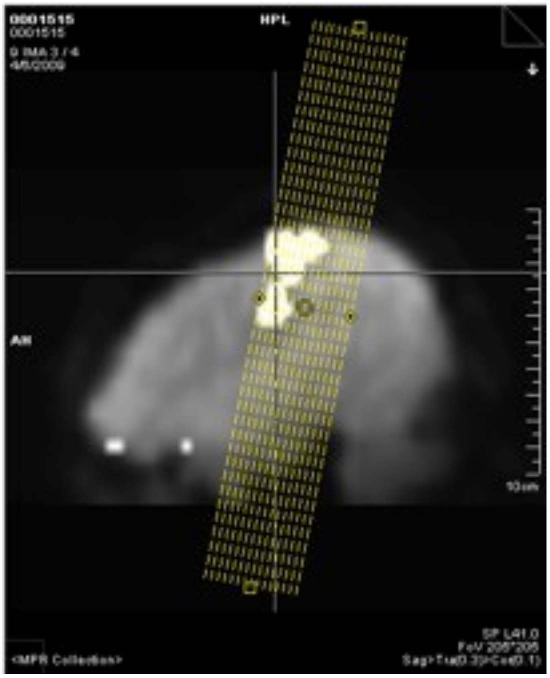


Figure 2. EPI slice placement covers sensorimotor cortex, localized by a yellow cluster, activated by a 2-min motor task. Precise slice placement guided by the functional localizer allowed us to collect more data from the region of interest. More collected data allowed for grater averaging with subsequent improvement in the SNR.

fMRI Data Analysis

FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.98, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The following pre-statistics processing was applied; motion correction using MCFLIRT (Jenkinson et al. 2002); fieldmap-based EPI unwarping using PRELUDE+FUGUE (Jenkinson 2003; Jenkinson 2004); slice-timing correction using Fourier-space time-series phase-shifting; spatial smoothing using a Gaussian kernel of FWHM 3.0 mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; high pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=50.0s).

Inter-session (Level 2), and inter-subject (Level 3, for control participants only) levels of analysis were carried out using a fixed effects model, by forcing the random effects variance to zero in FLAME (FMRIB's Local Analysis of Mixed Effects) (Worsley 2001; Woolrich et al. 2004). Estimates of the degrees of freedom in the statistical model were corrected for autocorrelation in the data by using the FSL pre-whitening technique (Woolrich et al. 2001). Time-series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich et al. 2001). Delays and undershoots in the hemodynamic response were accounted for by convolving the model with a double-gamma basis function. Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 2.3$ unless otherwise indicated and a (corrected) cluster significance threshold of $p < 0.05$ (Woolrich et al. 2004). Time-series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich et al. 2001). Motion parameters and time series extracted from a location in the ventricles and white matter region were entered as nuisance covariates. Within-modality (T2-weighted) registration of unwarped middle volume from the EPI time series to low resolution structural (whole-head EPI image) was accomplished with FLIRT set to use correlation ratio as a similarity function with a subset of linear transformation allowed (rigid body translations and rotations, dof = 6). Between-modality (T2-weighted to T1-weighted) registration of the low resolution structural (whole-head EPI image, T2-weighted) to the high resolution structural (MPRAGE, T1-weighted) was accomplished with FLIRT set to use mutual information as a similarity function with all linear transformations allowed (rigid body rotations/translation, non-uniform inflation and shearing, dof = 12). Initial registration from the high resolution structural to the standard space images was carried out also using FLIRT (Jenkinson et al. 2002). Registration from high resolution structural to standard space was then further refined using FNIRT nonlinear registration (Andersson, Jenkinson, and Smith 2007b).

Control participants' and M.S.'s average statistical parametric maps were overlaid on a 3-D rendering of the cortical surface of a template (Conte69 fs_LR) atlas created with version 5.5 of the CARET software http://brainmap.wustl.edu/caret/ (Van Essen et al. 2001; Keller et al. 2004; Van Essen et al. 2011). Such probabilistic atlas-based representations account for individual variation in cortical topography, as the average data were mapped onto the population, landmark and surface-based atlas (fs_LR) using the multi-fiducial procedure (Van Essen 2005).

Functionally Defining Normative Hand Representations

The hand representation typically occupies a large portion of S1 cortex on the anterior bank of the postcentral gyrus. Individual variability makes it difficult to define normative maps of a population of subjects. A multistep procedure was used for defining the spatial extent of normal hand sensory maps conservatively on the basis of mean control-group data. We used a motor rather than sensory functional localizer for two reasons: (1) motor activity produces sensory feedback that is probably more common in everyday life, and thus more ecologically valid, compared to the sensory feedback evoked by passive stimulation, and (2) this motor localizer data were also used in another experiment that required a motor localizer task.

First, we obtained a functional localizer of somatosensory hand representation from a separate group of healthy participants. Specifically, 17 healthy adults were recruited as controls for a study of sensorimotor representations in amputees. Magnetic resonance imaging was performed in a Siemens Allegra 3T head-only scanner. The imaging protocol included a high-resolution T1 structural scan, a field map, and a fourteen-minute BOLD EPI scan (TR = 2 sec, FOV = 200 x 200 mm, resolution 64 x 64, slice thickness = 4 mm) during which the subject performed paced movements. The EPI scans utilized prospective motion correction via Siemens' PACE option. Subjects were asked to move the toes on each foot, open and close each hand, and purse their lips. All movements were cued in pseudorandom order by audio instructions and paced by a 1 Hz tone. Each body part was moved for 16 seconds, followed by a 12 second rest. Because a subset of participants' data were left-right flipped for comparison with matched amputees, we refer to the cerebral and cerebellar hemispheres as "contralateral" or "ipsilateral" to the moving hand or foot rather than to "left" or "right" (Smith et al. 2004).

Second, Tensor ICA (Beckmann and Smith 2005) was performed on the data to identify components corresponding to lip, hand, and foot movement. The time course of each component was compared with the time courses of each movement type after convolution with the hemodynamic response function in a post-hoc regression. The component maps were thresholded using a mixture model fit and a probability for being in the “active” class of 0.5. The largest contiguous sets of thresholded voxels in the cortex and in the cerebellum were used to define ROIs.

Third, the ROI functionally defining sensorimotor hand representations, obtained during the previous step, was further refined into hand specific BA1, 2, 3a and 3b areas by intersected this functional localizer separately with the Brodmann Areas 1, 2 and 3 provided by Juelich probabilistic cytoarchitectonic atlas (Geyer, Schleicher, and Zilles 1999). All voxels surviving this intersection procedure were defined as being within one of the four normal left hand representations: BA1, 2, 3ab (see Figure 3).

Measure of Interdigit Distance

Distance between two activations peaks A (x_1, y_1, z_1) and B (x_2, y_2, z_2) was computed according to the Euclidian metric with the standard (MNI) space coordinates (Kurth et al. 2000):

$$d = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2 + (z_2 - z_1)^2} \, .$$

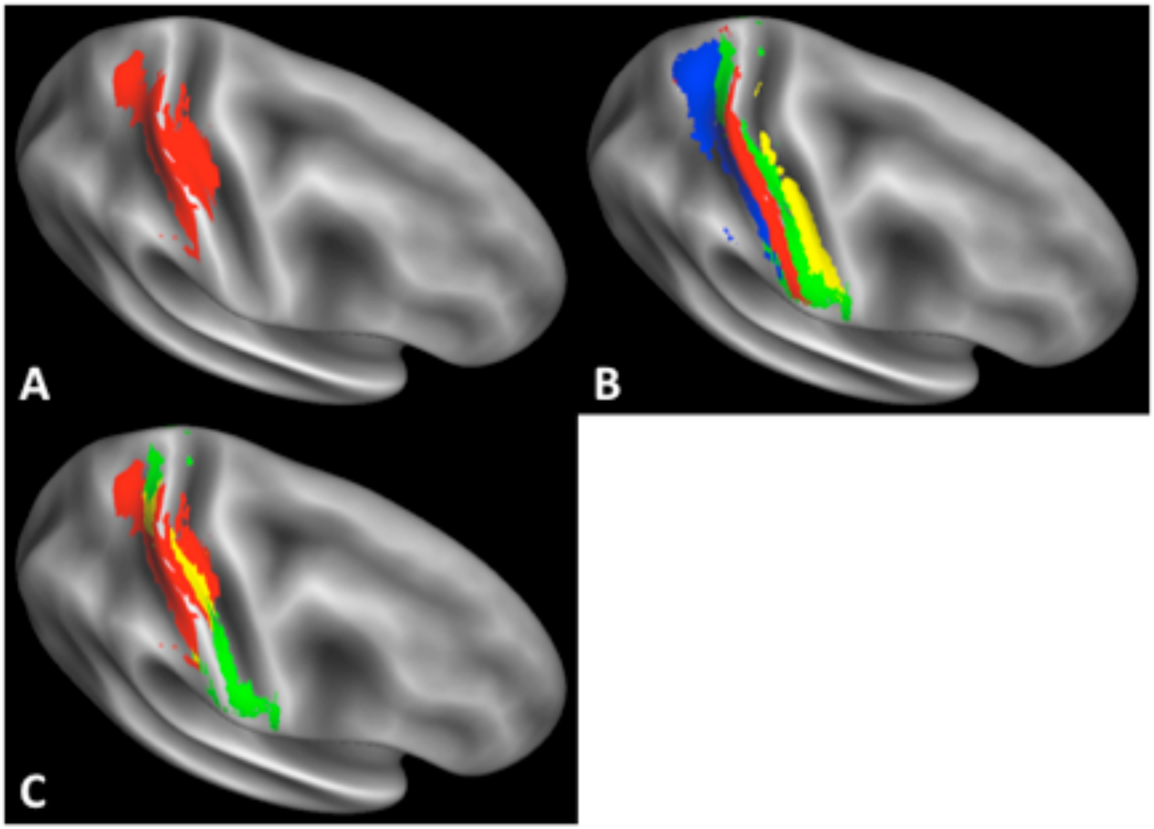


Figure 3. Normative maps of the sensory hand and digit representations. **(A)** A normative sensory hand map derived functionally from a separate group of healthy controls executing open–close hand movement with right hand without visual feedback. In this Figure, group average data are overlaid onto the inflated fs_LR atlas in Caret 5.65 using the multifiducial mapping procedure (Van Essen et al. 2011). **(B)** A parcellation of S1 in Brodmann areas (BA) 1, 2, and 3 according to the Juelich atlas (Geyer, Schleicher, and Zilles 1999). BA3a primarily in the fundus of the CS shown in yellow, BA3b on the anterior wall of the postCG is shown in green; BA1 on the crest of the postCG is shown in red; and BA2 on the posterior wall of the postCG is shown in blue. **(C)** An intersection of the functional hand map (in red) with the Juelich BA 3b map (in green), shown in yellow, defines the BA3b area that is most likely to be processing afferent information from the left hand and digits.

RESULTS

Behavioral

Ten years after the surgery, M.S.'s overall sensory function of his transplanted hand was remarkably good and improved since the last examination a year prior. Protective sensation (hot, cold, pain) was normal with cold hypersensitivity. Semmes-Weinstein filament testing of the transplanted hand revealed tactile sensation in the normal range in the median nerve distribution (0.08 gms), diminished in the ulnar nerve distribution (0.217 gms), localization error of 12.1 ± 7.8 mm (2.8 ± 1.6 mm on the intact hand) in the absence of vision. Touch localization was present and accurate except for the radial ring. Static and movement two point discrimination improved from the year before, but M.S. reported that sensation, especially 2 point discrimination, was difficult because of lots of tingling in the hand overall. Interestingly, M.S. reported no sweating in the transplanted hand.

Motor function and praxis were still recovering as M.S. displayed full passive flexion and extension of fingers, no tendency to claw but lacked the ability to move the fingers individually. M.S. possessed weak grip and pinch. With eyes closed he was unable to perform Moberg test (Moberg 1958) that involves picking up and manipulating small everyday objects (coins, pins, etc.) and object identification (Hodges 2009).

fMRI Mapping

Similar S1-Complex Responses to Cutaneous Stimulation in M.S. and Controls. Consistent with the hypothesis that restoration of afferent signals is associated with responses within the former hand territory, M.S.'s statistical parametric map is comparable to that of the controls. Peaks within the S1 clusters were located in the anterior bank, crest and posterior bank of in the postcentral gyrus in areas 3b, 1 and 2, respectively (see Table S1 in the Supplemental Data), and activity extended inferiorly into the parietal operculum (S2) and caudally into the parietal cortex. Activity in BA2, BA5 and parietal operculum (including putative S2) were symmetrically bilateral. Similarly bilateral S2 responses to vibrotactile activations has been reported before (Gelnar et al. 1999; McGlone et al. 2002). Additionally, stimulation of the left hand digits significantly increased activity in the right insula, thalamus and cingulate gyrus, areas known to be involved in somatosensation.

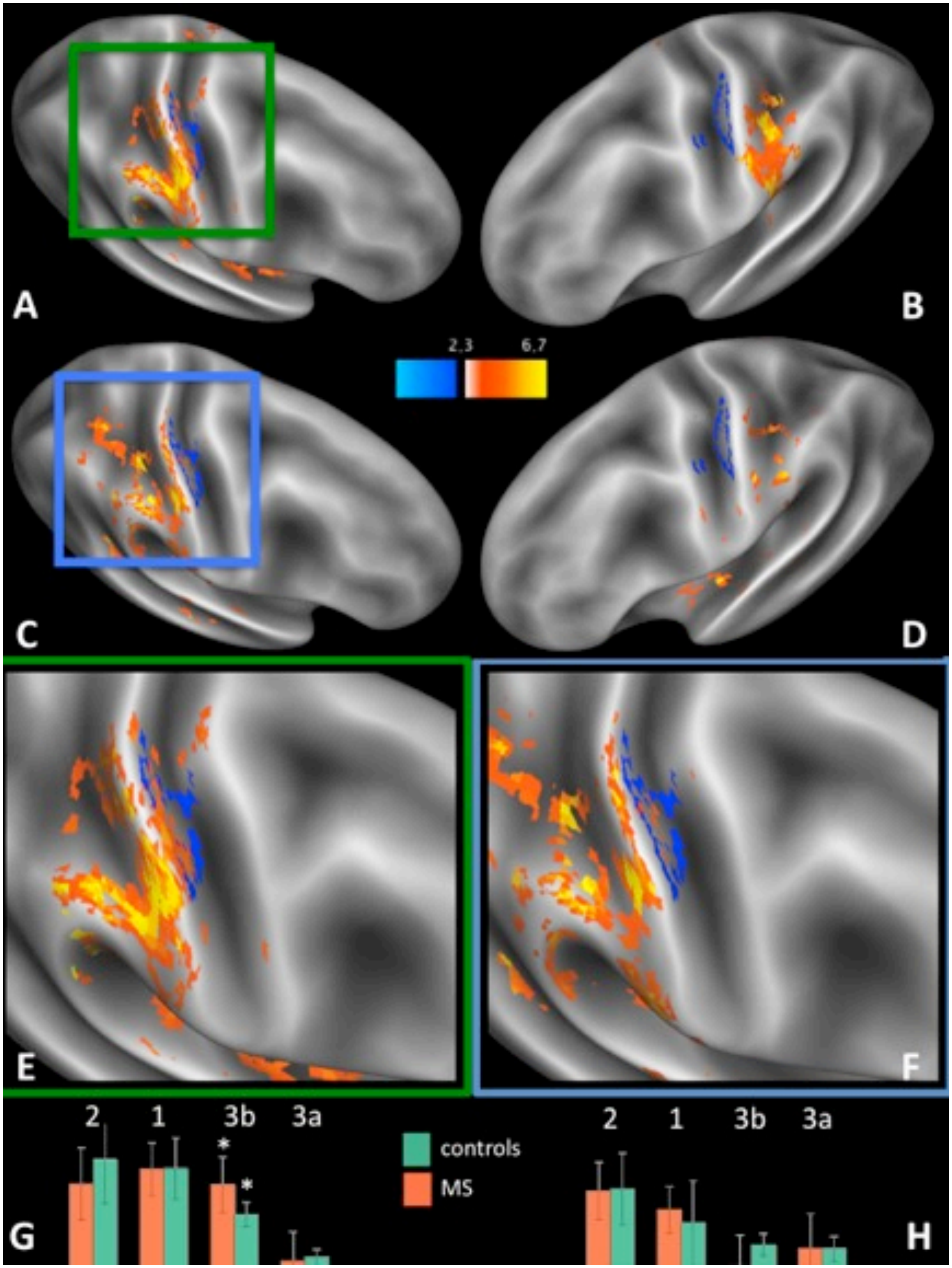
As described in the Experimental Procedures, a functional localizer combined with Juelich cytoarchitectonic probabilistic atlas (Caspers et al. 2007) were used for functionally defining the normative area 3b, 3a, 1, and 2 hand representations. The normative area 3b (Figure 1C) is delineated with the blue contour in Figure 4A-F.

Similar area 3b Responses to Cutaneous Stimulation in M.S. and Controls.

Consistent with the hypothesis that M.S.'s primary somatosensory cortex was recruited by tactile digit stimulation, visual inspection of Figure 4 reveals the presence of statistically significant clusters of activity inside the blue contour that is delineating normative hand area 3b, for both M.S. (Figure 4F) and the control group (Figure 4E). The magnitude of BOLD signal, extracted from the normative area 3b, was significantly elevated above baseline for both the control group, $t(31) = 3.38$ $p < 0.001$, and M.S., $t(3) = 9.2$, p-value < 0.01, without significant difference between them $p > 0.05$ (see Figure 4G).

Tactile stimulation evoked preferentially contralateral activity in areas 3b and 1, bilateral activity in area 2 and no activity in area 3a in both the control group and M.S.

Figure 4 (next page). Statistical parametric Maps (A-F) and Signal magnitude graphs (G-H) representing areas of increased activity associated with tactile stimulation of left hand digits. In Panels A-F, all areas in color showed significant increases in activity during tactile digit stimulation (F-test with $z > 2.3$, $p < 0.05$, cluster-based correction for multiple comparisons) corresponding to values indicated in the color bar. Both mean control (A, B, E) and M.S. (C, D, F) data are displayed on the Conte69 fs_LR midthickness surface (Van Essen et al. 2011) that has been partially inflated so that activations located in sulcal folds may be visualized. **(A)** Stimulation of the left hand digits of control subjects increased activity in contralateral S1, specifically BA3b indicated by the blue contour (also see E). The peaks were located in the CS, and activity extended rostrally on the preCG and caudally into the postCG. Contralateral activation was also detected in the parietal operculum, including putative S2. **(B)** Ipsilateral response to the left hand digit stimulation in the controls was confined to BA2 and parietal operculum (S2). Both areas are known to process bilateral sensory information. **(C)** Stimulation of the M.S.'s transplanted (left) hand digits, similar to controls, evoked peak responses within contralateral S1, specifically areas 3b, 1 and 2 and putative S2 (see text). Digit stimulation evoked activity in contralateral area 3B specifically, which is indicated by the blue contour (C, F). (**D)** M.S.'s ipsilateral response to the left hand digit stimulation was also similar to that of the controls but weaker: areas BA2 and parietal operculum (S2) were active. Both areas are known to process bilateral sensory information. (**E)** Close up of Panel A (**F)** Close up of Panel C. **(G, H)** Graphs represent mean percent BOLD signal change associated with sensory stimulation of the left hand digits within normative subareas (areas 1, 2, 3a, 3b) of S1 hand representation defined functionally on the basis of control data intersected with probabilistic map of S1. Each bar represents an average across left hand digits responses. Error bars represent 95% confidence intervals around group means. Within all normative areas M.S. and controls showed comparable increases during stimulation of the left hand digits. In the S1 hand representation contralateral to the stimulated digits mean BOLD response significantly exceed that from the ipsilateral S1 normative area. With the exception of the area 3a, the mean BOLD response for both control group and M.S. was significantly above baseline. The mean BOLD response evoked by digits stimulation within contralateral area 3b was significantly greater that that in the ipsilateral 3b for both M.S. and control participants.


A
B
2.3
6.7
C
D
E
F
2
1
3b
3a
*
*
controls
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G
2
1
3b
3a
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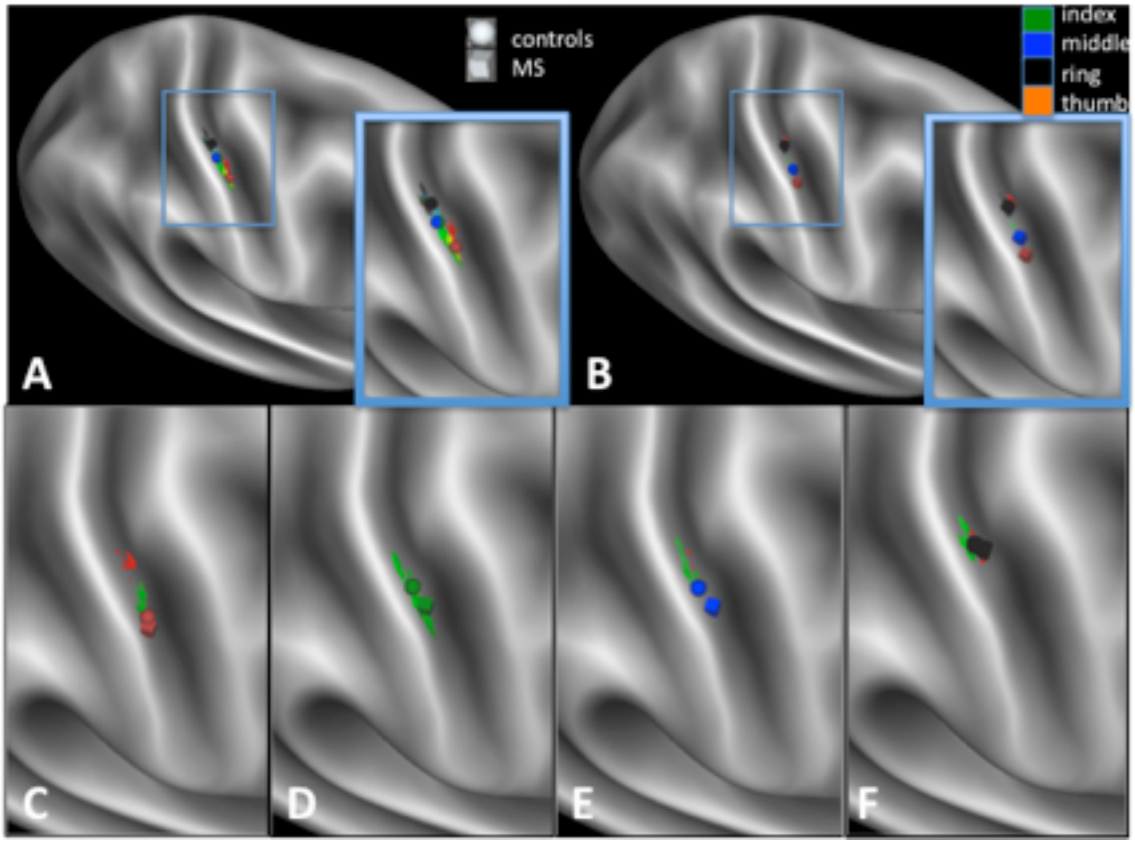
Separable and Mediolateral Digit Somatotopy in area 3b. Consistent with the hypothesis that restoration of afferent signals is associated with normalization of responses within the former hand territory, individual digit tactile stimulation evoked separable digit representations, except for the index and middle digit representations, and typical thumb-to-ring lateral-medial somatotopy for the control group (Figure 5A) and M.S. (Figure 5B). The zoomed-in images in Figure 5A,B illustrate similar patterns for both controls and M.S. with the thumb (red) located most laterally, the ring digit (black) located most medially, and the index (green)/middle (blue) digits cluster located in between. The finding of the mediolateral digital somatotopy in the healthy control group confirms several studies in primates and humans (Stoeckel et al. 2007; Stringer et al. 2011). The co-location of the peak activations for the index and middle digits was unexpected and is discussed further in the discussion section. Consistent with the known RF properties of these areas, no separable digit somatotopy was observed in areas 1 and 2 for either the control group or M.S.

Comparison of interdigit distances between the control group and M.S. reveals that (Figure 5, Table S3), (1) peak activations for the index and middle digits overlap for the control group and M.S., (2) the thumb-index/middle distance for the control group (8.2 mm) was double that for M.S. (4 mm), (3) the thumb-ring distance for the control group (12 mm) exceeded that for M.S. (7.5 mm), (4) from the pattern of distances described above, we can conclude that the index/middle digit representation is located between the thumb and the ring digit representations.

Figure 5 (next page). Peak activations foci representing locations of peak activity associated with tactile stimulation of left hand digits. Areas in color underlying foci showed significant increases in activity during tactile stimulation of each digit versus rest (with $z > 2.3$, $p < 0.05$, cluster-based correction for multiple comparisons). The area evoked by the stimulation of thumb is in red, index digit in green, middle digit in blue, and ring digit in dark-gray. Overlaps of activations are shown in mixed colors. Color and symbol coding for digits' peak activations are represented in the legend located in the top right-hand corner. Both mean control (Panel A) and M.S. (Panel B) activation foci are displayed on the Conte69 fs_LR template brain (see Supplemental Data) that has been partially inflated so that activations located in sulcal folds may be visualized (Panel A). **(A)** Independent stimulation of the controls' left hand digits, ring to thumb, increased activity in contralateral BA3b in successively mediolateral locations. The index and middle digit representations overlapped but the representations of the thumb, index/ middle and ring digits were separated (see Table S1). **(B)** Similarly, stimulation of the M.S.'s transplanted (left) hand digits, from ring to thumb, evoked peak responses within contralateral BA3b (see text), also laid out along the mediolateral axis. The coordinates for the index and middle digits peak voxels were identical. **(C)** panel represents the almost overlapping peak activations of the thumb stimulation condition of the control group (indicated by a sphere symbol) and M.S. (indicated by a box symbol). The peak foci are shown on top of the overlay of the statistical maps indicating the areas of increased activity when thumb was stimulated versus rest. The significantly activated areas are shown here, and in the rest of the panels, in green for the controls and in red for M.S. **(D)** illustrates the close locations of the peak activity for the index digit in the controls and M.S. **(E)** shows inter-digit separation for the middle digits of the control group and M.S., and, finally, **(F)** depicts virtually identical peak locations for the peak activations of ring digit versus rest in the control group and M.S. All areas in color, controls in green and M.S. in red, underlying foci show significant increases in activity during tactile digit stimulation versus rest (with $z > 2.3$, $p < 0.05$, cluster-based correction for multiple comparisons). Overlaps of activations are shown in yellow. Color and symbol coding for digits' peak activations are represented in the legend located in the top right-hand corner. All panels show data on the Conte69 fs_LR template brain (see Supplemental Data) that has been partially inflated so that activations located in sulcal folds may be visualized.



Finally, we compared the peak activation coordinates for all digits between the control group and M.S (also see Figure 5C-F and Table S5). The peak activation for the thumb representation (red in Figure 5C) was located at (44, -16, 44) for the control group and (48, -18, 46) for M.S. The peak activations for the index/middle cluster were as follows: index (44, -18, 52)/middle (46, -20, 52) for the control group and index (44, -18, 46)/ middle (44, -18, 46) for M.S. The peak activations for the ring digit were located at (40, -24, 52) for the control group and (42, -22, 48) for M.S. The peak activations for the digit representations appear similar between the control group and M.S. and to some of the coordinates reported previously (see Table S5).

DISCUSSION

The results of this experiment demonstrate that, despite extensive cortical reorganization due to deafferentation (Jones 2000; Kaas 1991), the mature brain has a remarkable capacity to return to a state of digit somatosensory organization that is indistinguishable, given our method, from what would be expected prior to hand loss. The following three findings, applicable to both the control group and M.S., support this conclusion: (1) Tactile digit stimulation evoked BOLD responses in hand territory of areas 3a, 3b, 1, and 2 indistinguishable from those of the control group in location, extent and signal magnitude, (2) furthermore, area 3b showed evidence of digit-specificity, and (3) these digit-specific representations exhibited typical thumb-to-ring lateral-medial somatotopy. To our knowledge, this result is the first evidence of successful recovery of separable digit representations after allogeneic hand transplantation. We hasten to add that a necessary and expected limitation of the study is its correlational character that provides no means to evaluate the putative causal relationship between somatosensory maps and sensory hand function. With this caveat, these findings extend our understanding of the long-term ability of the cerebral cortex to respond adaptively to dramatic changes in stimulation even when it is fully mature. We discuss these results and some limitations of the study in detail below.

Typical Sensory Activity Within S1

Consistent with the hypothesis that the restoration of afferent input by hand transplantation facilitates recovery of normal organization of the digital somatotopy in S1, M.S. exhibited typical response profiles, indistinguishable from those in the normal group, to tactile stimulation in areas 3a, 3b, 1 and 2. Typical somatosensory response to cutaneous stimuli delivered to a hand involves recruitment of contralateral areas 3b and 1 that are primary targets of thalamocortical cutaneous afferents, no response in area 3a that receives proprioceptive inputs ultimately from deep muscle and joint receptors, and bilateral recruitment of area 2 that receives inputs from area 3a, 3b, and 1 and is populated with neurons sensitive to multi-digit, often bilateral, receptive fields (Basbaum 2007; Gelnar et al. 1999; Kurth et al. 1998; McGlone et al. 2002). The integrity of the test described above depends critically on a careful and accurate definitions of the normative areas 3a, 3b, 1 and 2. Human somatosensory cortex is notoriously variable architectonically (Geyer, Schleicher, and Zilles 1999; Roland et al. 1997), anatomically (Schoenemann 2006) and functionally (Bandettini 2009). We designed a careful objective procedure, described in the Experimental Procedures section, that combined a functional localizer of hand area in S1 obtained from a separate group of healthy adults (Poldrack 2007), our best guess at functional localization in the face of considerable individual anatomical differences, with probabilistic normative areas 3a, 3b, 1 and 2 obtained on the basis of integration of microstructural and fMRI data from ten postmortem brains (Geyer et al. 2001). Finally, having described a typical physiological response within areas 3a, 3b, 1 and 2 of human somatosensory cortex to cutaneous digit stimulation, and having objectively constructed the normative regions of interests (ROIs) covering the somatosensory areas, we actually obtained maps of BOLD signal with fMRI from a group of healthy matched participants by stimulating their digits individually with air puffs, verified that they showed expected pattern of BOLD response, and used them as a norm or template to compare against M.S. pattern of BOLD activity. To reiterate, the end result of the procedure described above is two-fold, (1) in the control group, the BOLD somatosensory response to tactile stimulation is normal, as described above, and (2) M.S. somatosensory response is not different from normal.

Separable Digital Representations In Area 3b

Restoration of afferent input to M.S. area 3b, as hypothesized, facilitated recovery of the normal digital somatotopy in area 3b. Specifically, with the exception of the fused digital representations for the index and middle digits, separable digital representations in M.S., evoked by cutaneous stimulation of individual digits, were comparable to those in the control group in location and interdigit distance. Below we evaluate this result in the context of (1) comparative functional neuroanatomy of other species with advanced hand function, (2) an adequate sensitivity and specificity provided by our experimental protocol to detect such representations.

Comparative functional neuroanatomy of other species with advanced hand function. Existence of separable digital fields has been established in several species with advanced hand function, like Old and New World monkeys (Kaas, Jain, and Qi 2002), primates and humans (Kaas and Collins 2001), more recently using non-invasive methods (i.e., fMRI), especially with humans (Stringer et al. 2011) (van Westen et al. 2004; Gelnar et al. 1998). These separate digital maps have been associated with digit-specific somatosensory processing as indicated by classical mapping results (Jain, Catania, and Kaas 1998; Penfield 2006), by fused digit maps due to congenital (syndactyly) (Mogilner et al. 1993) or surgical (Lundborg 2000) fusing of digits, disappearing digit maps following digit transient or permanent deafferentation (Kaas and Florence 2001), and scrambled digit maps after hand reinnervation following peripheral nerve injury (Wall et al. 2003).

Sensitivity and specificity of the experimental protocol. Our experimental apparatus and protocol were optimized to resolve individual digit representations in area 3b (Weibull et al. 2008). Individual digits were stimulated with simultaneous recording of the evoked activity in the primary sensory cortex at the resolution (1.5 x 1.5 x 2 mm) high enough to resolve individual digital representations that presumable extend several millimeters (Burton 2002). A summary description of BOLD activation patterns by activation peaks or peak voxels, rather than voxel cluster ROIs or cluster center of gravity, is an established and, arguably, more objective and neurophysiologically grounded practice in fMRI analysis (Arthurs and Boniface 2002). Distinct digital representations described by single or multiple activation foci that were clearly separable have been reported previously (Gelnar et al. 1999; Krause et al. 2001; Kurth et al. 2000; Schweizer, Voit, and Frahm 2008), and sometimes associated with within-digit somatotopy, especially at higher spatial resolution achieved with high MRI field (Sanchez-Panchuelo et al. 2010; Schweisfurth, Schweizer, and Frahm 2011; Stringer et al. 2011). Thus the evidence for the existence of distinct digital representations provided by the 3D separability of activations peaks evoked by tactile stimulation of individual fingers in the rigorous experimental context, bolstered by similar findings in other species, comparable findings in several human fMRI experiments, appears convincing. One exception to this conclusion, as we alluded before, is the fusion of the index and middle representations. On the one hand, fused digital representations have been reported before (Francis et al.

2000; van Westen et al. 2004; Hlustík et al. 2001). These results are difficult to compare directly due to differences in experimental procedures between studies. The locations of peak activations associated with stimulations of index and middle digits were almost identical for both the control group and M.S. which was low compared to previously reported average of 7.25 ± 0.96 mm (Francis et al. 2000; Gelnar et al. 1999; Stringer et al. 2011). Two reasons suggested that this result may be an isolated artifact. First, the peak activations and interdigit distances for other digits agree much better with the previous reports. Second, the index and middle digit representational overlap was present both in the control group and M.S. The two digits might have been stimulated simultaneously either due to their physical proximity and/or due to the pneumatic stimulator's failure to deliver focal stimulus on the fingertips. The interdigit distances differ somewhat from the ones reported previously in healthy adults, perhaps unsurprisingly given large differences in experimental procedures: 6 mm thumb-index and 12 mm thumb-ring (Maldjian et al. 1999), 12 mm index-pinky (McGlone et al. 2002).

Typical Mediolateral Digital Organization In Area 3b

Consistent with the hypothesis that the restoration of afferent input by hand transplantation facilitates recovery of normal organization of the digital somatotopy in area 3b, M.S. exhibited typical digital mediolateral somatotopy there, indistinguishable from that in the normal group. Specifically, peak activation of the thumb representation was lateral and anterior to that activated the ring digit, and the index/middle cluster was in between (Penfield 2006; Geyer, Schleicher, and Zilles 1999; Stringer et al. 2011).

The average interdigit distance for M.S. was shorter than that for the controls. This finding must be tempered with the original observations that the regularity of the mapping of the human hand attaches primarily to the mediolateral ordering, and not to the absolute locations, of the digit representations (Penfield 2006). On the other hand, reports describing dystonia (Bara-Jimenez et al. 1998; Bara-Jimenez et al. 2000) and other hand-related neurological conditions (Napadow et al. 2006; Tinazzi et al. 1998) indicate that cortical separation between affected digits representations becomes reduced in affected individuals. May be reduced localization acuity in M.S. can be explained by a similar mechanism.

Representational Plasticity In Area 3b

This return to normal somatosensory organization, accomplished by M.S. over 11 years of recovery, is remarkable in at least following three ways. First, long-term upper limb amputation is associated with dramatic somatotopic reorganization (Pons et al. 1991; Florence and Kaas 1995; Ramachandran, Rogers-Ramachandran, and Stewart 1992) that is due to not just physiological competitive rebalancing (Lundborg and Rosen 2007) that reacts to changing patterns of afferent input almost immediately but also structural mechanisms, such as axonal sprouting, that take much longer to produce results cortically and subcortically and, presumably, take just as long to return to normal. Second, peripheral reinnervation is known to be imprecise (Lundborg and Rosen 2007) and, resulting afferent input, reflecting this imprecision, may degrade cortical topography and limit sensory function (Stoll, Jander, and Myers 2002). Third, cortical maps are shaped by peripheral input and M.S. has lacked individuated finger movements to provide digit-specific afferent input. The cortical representation of a body part is dynamically modulated based on the pattern of afferent input (Chen, Cohen, and Hallett 2002). Correlated input as in syndactyly or dystonia fuses cortical digit fields (Allard et al. 1991; Mogilner et al. 1993). The factors facilitating recovery of typical cortical reorganization after hand transplantation are unclear. How can we explain such a surprising result?

One possibility is that the somatosensory cortex did not reorganize, or reorganized minimally, after hand amputation for M.S. We cannot rule this possibility out as we have no direct experimental evidence of the cortical reorganization due to the long term amputation pertaining to M.S. specifically, because we have no data collected prior to M.S. transplantation. In our assumption of M.S.'s extensive cortical reorganization post deafferentation, we relied on a circumstantial but considerable and mostly consistent body of evidence, pertaining to animal (Garraghty and Kaas 1991; Garraghty and Kaas 1992; Jenkins et al. 1990; Pons et al. 1991; Kaas and Merzenich 1983) and human (Borsook et al. 1998; Moore, Stern, and Dunbar 2000; Ramachandran, Rogers-Ramachandran, and Stewart 1992) effects, but see (Lund, Sun, and Lamarre 1994) for an alternative more parsimonious point of view describing so-called dual sensitivity cells that are sensitive to more than one peripheral location. Another speculative piece of evidence against extensive cortical reorganization in M.S. is that he suffered minimally either from phantom limb or phantom limb pain syndrome that had been linked to the extent of cortical reorganization (Flor 2003; Harris 1999).

Moore & Schady (2000) argue the cortical reorganization might have no functional correlates. When the individual nerve fibers were microneurographically stimulates in the stump of a group of amputees with presumably reorganized sensory cortex, they reported sensations comparable to the ones reported by the normal subjects. (Davis et al. 1998) reported more evidence that the former hand territory for the missing limb continues to signal the missing limb. The authors recorded from the thalamus of patients being treated for pain after limb amputation. The recordings indicated the region of the stump as activating parts of VPL that would normally be responsive to the missing limb. When subsequently reactivated neurons with receptive fields in the stump were electrically stimulated, the patients fell sensations in the missing limb rather than the stump.

Another possibility is that, despite putative extensive reorganization in the primary sensory cortex, extensive recovery can happen, even in an adult brain. Evidence for extensive recovery is accumulating. Previously, it was demonstrated rapid recovery tactile sensitivity in transplanted hands and typical contralateral S1 response to stimulation 2 years after amputation (Dubernard et al. 2003; Farnè et al. 2002; Neugroschl et al. 2005). We reported that even 4 months post-operation, tactile stimulation of the transplanted hand evoked BOLD activity specifically within the functionally defined normative (i.e., pre-amputation) hand area of the somatosensory cortex hand representation (Frey et al. 2008). Based on relatively few studies of long-term recovery after peripheral reinnervation with animals (Paul, Goodman, and

Merzenich 1972; Wall et al. 2003), and humans (Schuind et al., 2006; Breidenbach et al. 2008), recovery time-line is still unclear.

Limitations of the Study

The following methodological limitations impose some constraints on the interpretations of the results of this study. We will cover a few but not all in this section.

We present probabilistic representations of activations and cortical areas because precision with which borders can be identified using cytoarchitecture, surface anatomical criteria or functional localizers is limited. Activations clusters can extend across several area or areal boundaries, loci of peak activity can be at least equally well interpreted. Besides smoothing and statistical modeling, basic neurophysiological mechanisms underlie formation of clusters. The BOLD responses occupy large territories due to hyperoxic vascular response beyond the region of elevated neuronal activity (Malonek and Grinvald 1996). Due to diffuse projections of thalamocortical fibers, even a focal stimulus will engage a sizeable cortical territory (Jones, 1998) and hemodynamic response overshoots the increased metabolic demand in volume and spatial extent (Menon and Goodyear 1999). The spatial spread is alleviated if short duration stimuli are applied, as in our case.

To increase sensitivity, we created group-averaged maps since averaging of multiple subjects increases signal to noise ratio in approximate proportion to the square root of the number of samples. Typically this method allows inferences about populations to be made at the expense of richness of individual subject data. We, however, constrained the between-subject variability in our group model to be nil, thus exchanging the possibility of population inference for further increase in SNR. Inter-individual variability in the data is extreme but not random and probably represents individual differences in brain organization or cognitive strategy.

fMRI data interpretation can be confounded on several levels (Logothetis and Wandell 2004; Logothetis 2008). First, the fMRI signal is based on the complex interaction of neuronal activity, neuronal metabolism, blood flow and blood volume on a spatial scale that lumps together hundreds of thousands of neurons in each MRI voxel. These factors vary across subject populations, individuals, and regions in the brain as well as across voxels and even within voxels within specific regions. This hemodynamic variability poses a severe limit on how fMRI can be used. The limits in our knowledge of precisely what neuronal activity (excitation, inhibition, sub-threshold activity, top-down or bottom-up modulation) is manifested by the hemodynamic response (Bandettini 2009).

Increasing field strength compensates for loss in SNR due to reduction in voxel size but introduces stronger image distortions due to macroscopic field inhomogeneity. Even though fMRI seems to be perfectly suited for such goals (Harel et al. 2006), the realities of working with older, less fit, and less accessible participants, dictate shorter time frame for experiments and simpler experimental designs. Shorter scans coupled with higher chances of data corruption by participants' movements inside the scanner make collecting high quality data a challenge (Harel et al. 2006). Some of these limitations can be alleviated but not overcome by judicious data processing (Gelnar et al. 1999; Nelson and Chen 2008).

CONCLUSIONS

High resolution fMRI combined with a rapid event-related tactile stimulation protocol non-invasively produced high-resolution somatosensory maps of separate digits for a allogeneic hand transplant recipient in late stages of recovery. The individual digit representations within the primary sensory cortex returned to their grossly normal organization in parallel with recovered sense of locognosia. Allogeneic hand transplantation provides an unprecedented opportunity to investigate the reversibility of changes in cortical organization after amputation. At the gross level of body-part somatotopy, these changes are indeed highly reversible even in the mature brain, a fact that may have broad implications for our understanding of the brain's response to deafferenting injuries.

An interesting question to explore in the future is the effects of limb deafferentation higher order somatosensory areas, area 5 and 7. Would area 5 still respond to tactile input after deafferentation? Would it undergo a reorganization of its own? Would this reorganization have a multisensory compensatory character?

BRIDGE

In this and the previous chapters we provided evidence that normal hand and digit representations can be recovered after restoring afferent input via hand transplantation. These findings seem remarkable in the context of dramatic reorganization of the sensory cortex caused by hand amputation. However, recovery of normal sensory organization may seem less surprising if the deafferented representations do not disappear but lie dormant, maintained by afferent input from a source other than the amputated hand.

Another piece of evidence for persisting maintenance of the former hand representation is provided by the fact that chronic unilateral upper extremity amputees can reactivate the former sensorimotor hand territory behaviorally. If this is true and the former sensorimotor hand representations persist post hand deafferentation, how can they be activated? We tested two cognitive-behavioral manipulations, i.e., mirror and imagery tasks, that garnered tentative and mixed support as effective stimuli for the deafferented hand area. We found that imagining or simply observing movements of the intact hand reflected in a mirror had no effect. However, the intact hand movements engaged the former hand territory, thus providing a possible source for maintaining latent hand representation in unilateral hand amputees.

CHAPTER IV

FORMER HAND TERRITORY ACTIVITY INCREASES AFTER AMPUTATION DURING INTACT HAND MOVEMENTS, BUT IS UNAFFECTED BY ILLUSORY VISUAL FEEDBACK

This chapter includes both published and unpublished work. The published part previously appeared online, ahead of print, in the journal "Neurorehabilitation and Neural Repair" on 18 January 2012, co-authored by myself, Jolinda Smith and Scott H. Frey. I performed the majority of the experiments and analysis. Scott Frey performed some of the analysis. Jolinda Smith and Scott Watrous designed and built apparatus and Jolinda Smith ran some of the experiments. The manuscript was written and edited by Scott Frey and me.

INTRODUCTION

There is considerable evidence that the functional organization of cortical sensory and motor representations is activity dependent (Kaas 1991; Sanes and Donoghue 2000). Studies of nonhuman primates reveal training-related expansions in primary sensory (Jenkins et al. 1990) and motor (Nudo and Milliken 1996) maps located contralateral to the involved effector. Conversely, lesions of the peripheral nervous system that disrupt the flow of afferent and efferent signals, including those accompanying limb amputation, lead to extensive reorganizational changes in the contralateral sensory (Merzenich et al. 1984; Pons et al. 1991) and motor cortex (Qi, Stepniewska, and Kaas 2000; Wu and Kaas

1999). The result is that some primary sensory neurons in the now deafferented territory become responsive to tactile stimuli applied to somatotopically adjacent regions of the residual forelimb or face (Florence and Kaas 1995). Years after amputation, microstimulation of motor neurons in areas that formerly targeted amputated hand muscles evoke movements of the residual forelimb or shoulder but not the face (Wu and Kaas 1999; Qi, Stepniewska, and Kaas 2000). Evidence from noninvasive functional neuroimaging studies suggests that similar reorganizational changes occur in humans following hand amputation. Post-injury, the sensory representation of body surfaces proximal to the injury (Kew et al. 1997), and/or the face (Yang et al. 1994), may intrude into the former sensory hand territory. Likewise, evidence suggests that amputees show an expanded motor representation of muscles of the residual limb (Kew et al. 1994) and a medial shift in the representation of facial muscles (Karl et al. 2001). The interpretation of this evidence has, however, recently been questioned (Gagné et al. 2011). Amputees also exhibit a larger contralateral sensory representation of the intact hand that may result from increased use (Elbert et al. 1997).

Amputation also affects the ipsilateral hemisphere. Whereas healthy adults sometimes show small increases in ipsilateral premotor cortex activity during hand movements (Cramer et al. 1999), amputees manifest large ipsilateral increases in sensorimotor cortex activity when using the intact hand (Kew et al. 1994; Cruz et al. 2003; MacIver et al. 2008). These changes may reflect an immediate reduction in normal levels of interhemispheric inhibition (IHI) following unilateral deafferentation (Werhahn, Mortensen, Kaelin-Lang, et al. 2002) and/or experience-dependent changes in the representation of the intact hand associated with increased use (Frey et al. 2008). It is important to note that it remains unknown whether these increases are localized to the portion of the sensorimotor cortex formerly devoted to the now absent hand (i.e., the former hand territory).

Despite considerable evidence for activity dependence, other findings suggest persistence of a cortical representation of the amputated hand (Reilly and Sirigu 2008). Attempts to move amputated segments of the limb volitionally are associated with selective increases in activity of severed nerves previously targeting those specific muscles of the missing hand (G. Dhillon, Krüger, and Sandhu 2005; G. S. Dhillon et al. 2004) and are accompanied by distinct patterns of electromyographic activity (Reilly et al. 2006). Transcranial magnetic stimulation of the motor cortex contralateral to the amputation is known to evoke "phantom" sensations of movement in the absent limb (Reilly et al. 2006; Cohen et al. 1991) (Malouin et al. 2009; Mercier et al. 2006; Pascual-Leone et al. 1996). Phantom sensations can also be elicited in some patients by exposing them to an illusion of the missing limb (Lotze and Halsband 2006; Mercier and Sirigu 2009; Lotze and Halsband 2006; Roux et al. 2001) created by reflecting movements of the intact hand in a mirror (Ramachandran and Rogers-Ramachandran 1996). This illusory visual feedback (VF) (Diers et al. 2010) and motor imagery (MI) of the amputated hand(Lotze and Halsband 2006; Mercier and Sirigu 2009; Roux et al. 2001) are reported to increase contralateral sensorimotor activity. However, it remains unknown whether these effects occur precisely within the former sensorimotor hand territory. This is relevant because a growing number of reports indicate that mirror therapy reduces pain in unilateral amputees (Chan et al. 2007) and complex regional pain syndrome patients (Cacchio et al. 2009) and increases function after stroke (Dohle et al. 2009; Sathian, Greenspan, and Wolf 2000; Stevens and Stoykov 2003), hand (Rosén and Lundborg 2005), or brain surgery (Shinoura et al. 2008). Yet an understanding of the neural mechanisms underlying these effects is presently lacking (Moseley, Gallace, and Spencec 2008).

We tested whether former hand territory (defined functionally on the basis of independent control data) activity is modulated by movements of the intact hand performed alone or with accompanying MI and/or illusory VF of the absent hand. A positive result would indicate a means of effectively stimulating cortical representations even in the absence of contralateral hand movements. Furthermore, it would suggest that experience-dependent changes in primary sensorimotor representations might account for the reported therapeutic benefits of mirror therapy.

EXPERIMENTAL METHODS

Participants

A total of 11 adult unilateral upper-limb amputees (3 women), averaging 50 years of age (range, 25 to 70 years), and 11 healthy yoked controls consented to participate in the approved protocol (Table 1). Amputations occurred at an average of 25 years before testing (range, 5 to 42 years). Each control performed movements with the same hand (left, right) as his or her yoked patient. Amputees' hand dominance, documented in Table 1 and based on their self-reports, refers to each participant's hand dominance prior to amputation.

Table 1. Selected demographic and medical information for traumatic amputees and yoked controls. Abbreviations: AE above elbow, BE below elbow amputation.

Subject	Sex	Age	Amputated Hand	Location of Amputation	Years of Amputation	Hand Dominance	Yoked Controls		
							Sex	Age	Hand Dominance
789	M	58	Left	BE	37	Right	M	62	Right
791	M	48	Right	BE	28	Right	M	47	Right
805	M	54	Right	AE	31	Right	M	50	Right
806	F	45	Right	AE	23	Right	F	44	Right
809	M	64	Right	BE	42	Right	M	65	Right
810	M	70	Right	AE	5	Right	M	52	Right
819	F	25	Left	AE	15	Right	F	24	Right
820	M	60	Right	AE	23	Right	M	61	Right
825	F	55	Right	AE	36	Right	F	57	Right
826	M	38	Right	AE	5	Right	M	38	Right
835	M	40	Left	BE	35	Right	M	41	Right

Apparatus

A midsagittal mirror was placed on the participant's torso so that it reflected movements of 1 hand, creating an illusion of bimanual coupled movements (see Figure 1). Stiff black boxboard was used to cover the mirror in conditions without mirror feedback. Dark cloth covered the area surrounding a participant's moving hand to create a homogeneous background. Participants removed any rings prior to the experiment.

A lateral free-standing mirror, placed on either the left or the right side of the MRI bed, reflected the image of the participant's moving hand from the midsagittal mirror. A remotely controlled, MRI-compatible camera captured the image from this lateral mirror. The camera was aligned with the magnet table and located approximately 1 m above the end of the bed. Live video stimuli were projected through a waveguide and onto a back-projection screen located at the rear of the magnet's bore. Participants viewed this image in a small mirror attached to the birdcage head coil. Prior to testing, adjustments were made to create a compelling and uniformly sized bimanual illusion.

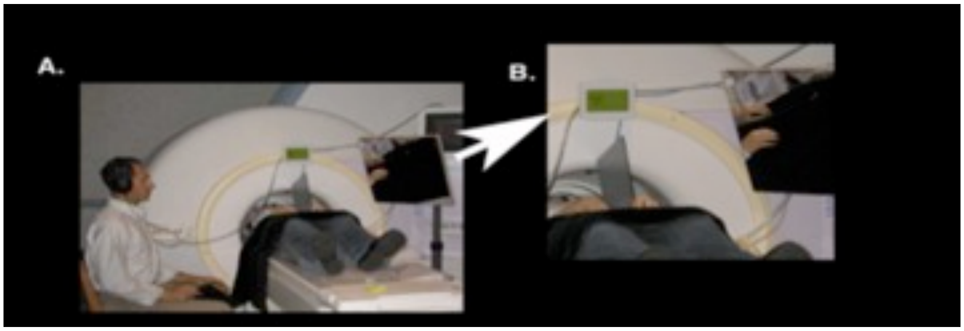


Figure 1. Experimental setup with mirrors and an experimenter present. The two mirrors present and a camera (not shown) provide an illusion of both hands moving when the subject executes TSFT unimanually. The experimenter covers and uncovers the parasagittal mirror on cue.

An experimenter was present in the room and controlled the illusion by manually covering or uncovering the mid- sagittal mirror during rest periods when the participant's eyes were closed. The experimenter was cued by instructions on a video monitor.

Functional Magnetic Resonance Imaging (fMRI) Task

Every participant completed 2 functional runs, each lasting 720 s. A run consisted of 4 experimental conditions (detailed below), each presented 5 times. All the 20 experimental blocks were presented in a pseudorandomized order. Each block was cued by a 3-s auditory command that signaled participants to prepare for the upcoming task. Immediately following the auditory cue, a tone signaled the beginning of a trial and was repeated at 1 Hz for the trial's 21-s duration. Participants were required to open their eyes and perform a unimanual thumb–finger sequencing task (TFST) in synchrony with this pacing tone. The TFST involved sequentially touching the index, middle, ring, and little finger to the thumb. The word "stop" cued participants to end their movements and close their eyes for the 12-s rest period. Each block thus lasted for a total of 36 s.

Although all 4 experimental conditions involved per- forming the TFST task, they differed in the following ways:

Motor execution (ME). The mirror was covered, and participants saw only their moving hand. "Move right" or "Move left" instructed the participants to start TFST with the intact (amputees) or matched (controls) hand.

Motor execution with motor imagery (ME+MI). The mirror was covered and participants saw only their moving hand. "Move right, imagine left" or "Move left, imagine right" instructed them to imagine moving their amputated hand (or the matched hand in the case of controls) in synchrony.

Motor execution with visual feedback (ME+VF). This was identical to the ME condition except that the mirror was uncovered.

Motor execution with motor imagery and visual feedback (ME+MI+VF). This was identical to the ME+MI condition, except that the mirror was uncovered.

fMRI Data Acquisition

All scans were performed on a Siemens 3-T Allegra MRI system. Whole-brain BOLD echoplanar images (EPIs) were collected using a standard birdcage radio-frequency coil and the following parameters: Repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; flip angle = 80°; 64 × 64 voxel matrix; field of view (FoV) = 200 mm; 33 contiguous axial slices; slice thickness = 3.0 mm. A double echo gradient echo sequence was used to acquire a field map that was used to correct for EPI distortions. A high-resolution T1-weighted structural image was acquired using the 3D MP-RAGE pulse sequence: TR = 2500 ms; TE = 4.38 ms; TI = 1100 ms; flip angle = 8.0°; 512 × 512 × 176 voxel matrix; FoV = 256 × 256 mm2; slab thickness = 176 mm. Siemens' Auto Align Scout and True FISP sequences were executed prior to the start of each functional run to ensure that slices were pre- scribed in exactly the same positions across runs. DICOM image files were converted to NIfTI format using MRIConvert software (http://lcni.uoregon.edu/~jolinda/ MRIConvert/).

fMRI Data Analysis

Data were analyzed using the FSL software tools version 4.1(Smith et al. 2004): http://www.fmrib.ox.ac.uk/fsl/. Each fMRI run for a given participant was modeled separately at the first level. Prior to statistical estimation, the following preprocessing steps were undertaken: EPI dewarping using FUGUE (unwarps geometric distortion in EPI images using B0 field maps), motion correction using MCFLIRT (corrects intra-modal motion), non-brain removal using BET (segments the brain from non-brain structures), spatial smoothing using a Gaussian kernel of 5 mm (full width at half maximum), mean-based intensity normalization of all volumes by the same factor, and high-pass temporal filtering (σ = 100 s). Estimates of the degrees of freedom in the statistical model were corrected for autocorrelation in the data by using the FSL pre-whitening technique. Time-series statistical analysis was carried out using FILM (robustly estimates first-level general linear model using pre-whitening) with local auto-correlation correction. Delays and undershoots in the hemodynamic response were accounted for by convolving the model with a double-gamma basis function. Registration to high resolution and standard images (MNI template) was implemented using FLIRT (linear registration) and FNIRT (nonlinear registration) (Andersson, Jenkinson, and Smith 2007a). Intersession (level 2) and inter- participant (level 3) levels of analysis were carried out using a fixed-effects and mixed-effects model in FLAME (models and estimates the random-effects component of the measured intersession mixed-effects variance for group statistics), respectively (Beckmann, Jenkinson, and Smith 2003; Woolrich et al. 2004). Z (Gaussianised t) statistic images were thresholded using clusters determined by $z > 2.3$ unless otherwise indicated and a corrected cluster significance threshold of $P < .05$.

To enable group analysis, data from the 3 left-hand amputees and their yoked controls were left–right flipped prior to image preprocessing. As a consequence, the left hemisphere was always contralateral to the amputated hand and ipsilateral to the intact moving hand. Participants’ group statistical parametric maps were overlaid on a 3D flattened rendering of the cortical surface of the standard brain created with version 5.61 of the CARET software (http://brainvis.wustl.edu/wiki/index.php/Caret:About). To account for individual variation in cortical topography, average data of the amputee and control groups were registered to the population, landmark, and surface-based atlas (PALS B12) using the multifiducial mapping procedure (Van Essen 2005).

Functionally Defined Normative Sensorimotor Hand Representation

Data from a separate group of 17 participants (10 female) were used to functionally define the normative sensorimotor hand representations. This approach allows us to establish the boundaries of the normative hand representation probabilistically and is well suited for population-level inference (Poldrack 2007). The group's mean age was 28.2 ± 7.7 years; 8 participants were right- and 9 left-handed as verified by the Edinburgh handedness inventory (Oldfield 1971). Data from 1 left-handed female participant were discarded from this sample prior to analysis because of her noncompliance with the experimental instructions.

Participants performed the TFST paced by 1-Hz auditory tones with their eyes closed. Each participant completed 2 functional runs composed of 3 conditions presented in counterbalanced order: (1) right hand moving, (2) left hand moving, and (3) both hands moving. Each 24-s movement condition was separated by a 12-s period of rest. Because our objective in the main study was to determine whether sensorimotor activity during unimanual movements performed under various manipulations would approximate activity detected during bimanual movements, data from condition 3 were used to define the normative sensorimotor maps.

Because no cortical areas showed a significant effect of hand dominance, the group statistical parametric maps were obtained by pooling the data from both left- and right- handed participants. All voxels located within the neuroanatomically restricted primary sensorimotor cortices contralateral to the moving hands, and surviving a statistical threshold of $z > 2.3$ with clusterwise correction of $P < .05$, were defined as being within the normal left or right sensorimotor hand territory (Figure 2).

Region of Interest Analyses

Mean percentage signal change relative to resting baseline was computed separately for every participant and each condition of the main experiment within the respective normative hand representations contralateral and ipsilateral to the moving hand. Mean percentage signal change values were then submitted to a 2 (Group: amputee, control) × 4 (Condition: ME, ME+MI, ME+VF, ME+MI+VF) repeated- measures ANOVA.

RESULTS

Equivalent Contralateral Hand Area Responses for Both Groups

Relative to resting baseline, increased activity was detected within a widely distributed network of cortical regions during the performance of all 4 experimental conditions for both amputees and healthy controls (Figure 2). In addition to regions within and along the central sulcus (CS) contra- lateral to the moving hand (visualized here as the right hemisphere), these cortical areas included the supplementary motor area (SMA), ventral and dorsal premotor areas, posterior parietal area, rostral middle frontal gyrus, and occipital and temporal cortices. Subcortical increases were also detected in both groups within the thalamus, basal ganglia, and lateral cerebellum. Critically, as elaborated below, only amputees showed evidence of significant increases along the CS in the hemisphere ipsilateral to the moving hand (visualized here as the left hemisphere).

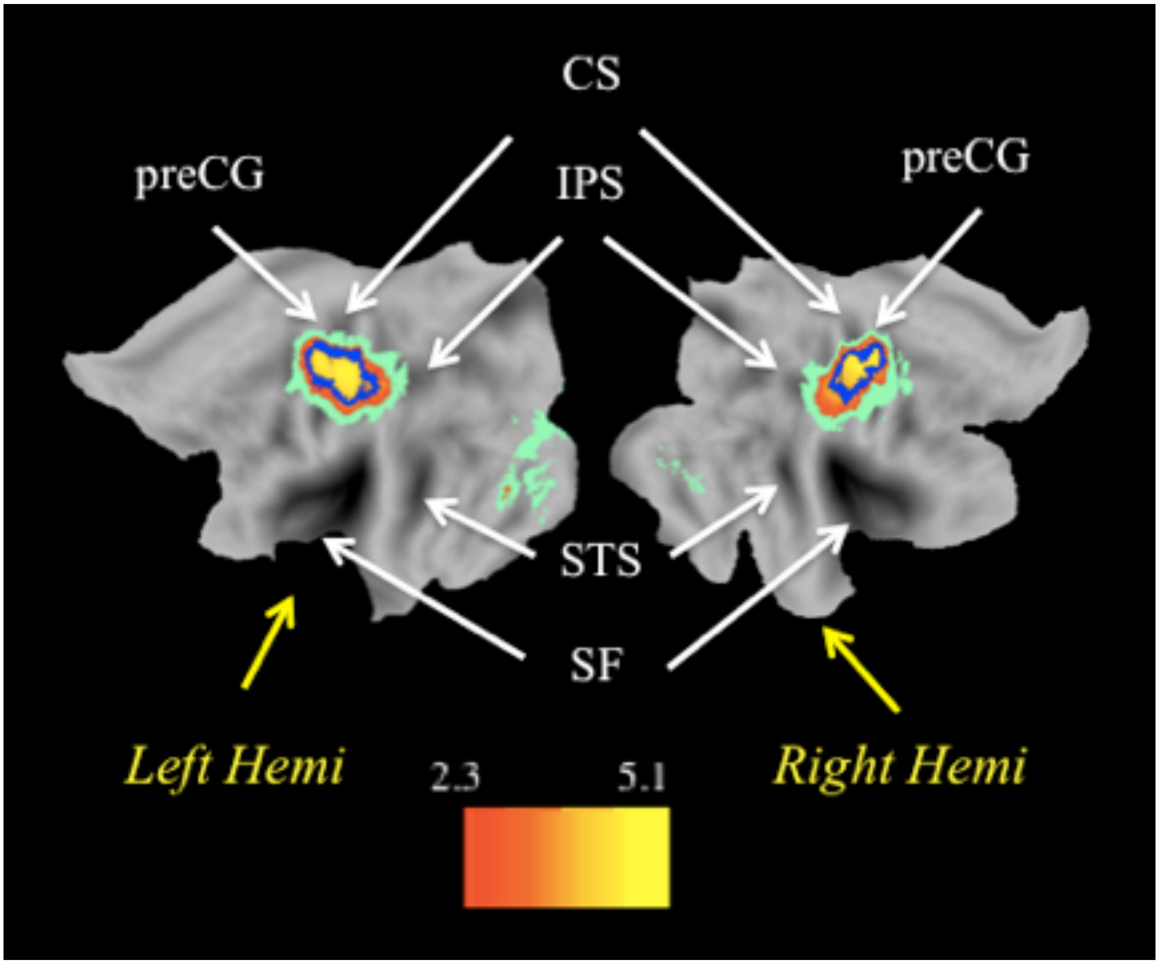
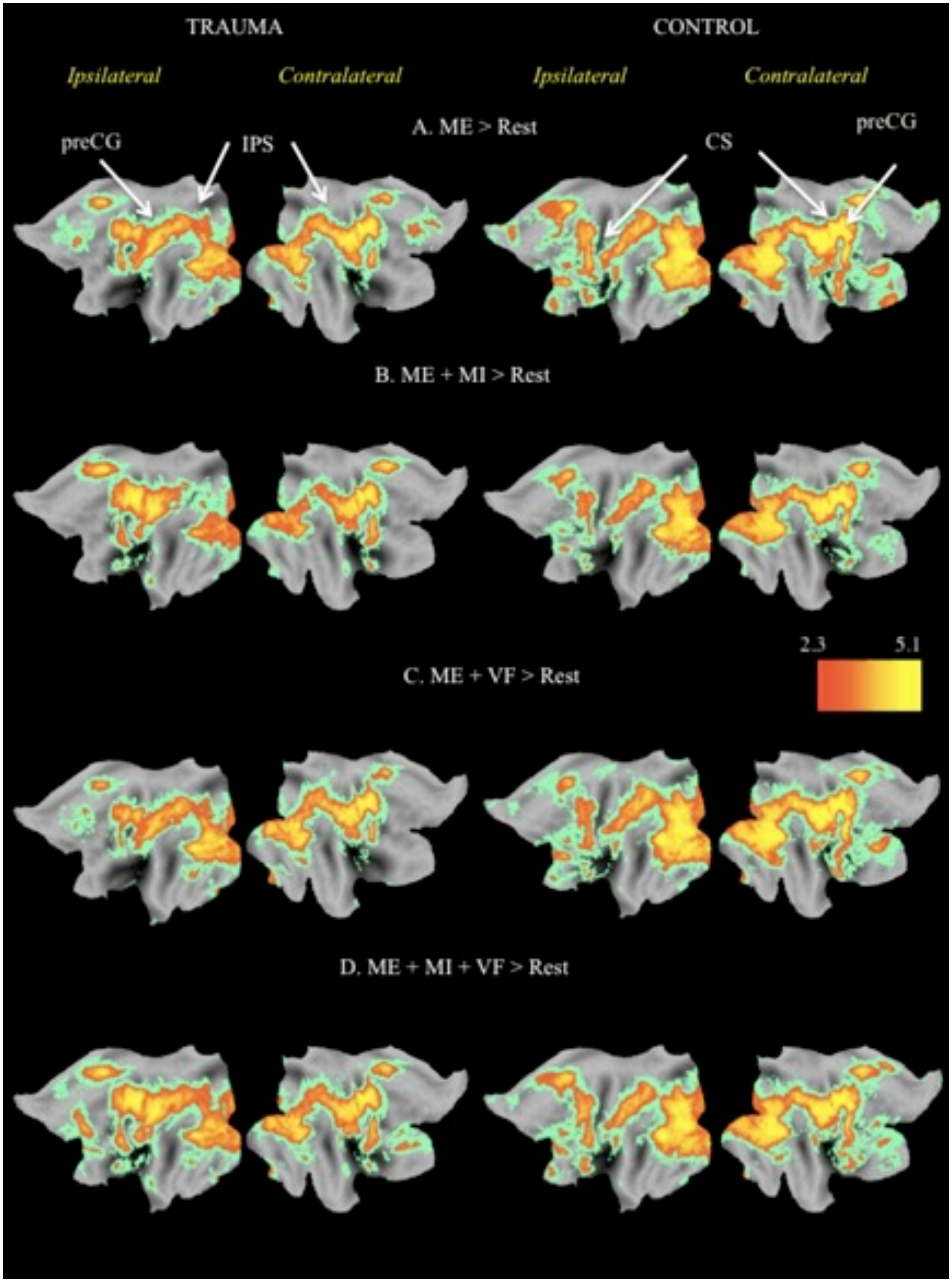


Figure 2. Normative maps of the sensorimotor hand representations derived functionally from a separate group of healthy controls executing thumb–finger sequencing task movements with both hands simultaneously, without visual feedback. Here and in subsequent figures, group average data are overlaid onto the flattened PALs atlas in Caret 5.61 using the multifiducial mapping procedure.47 Areas showing significant activation after multifiducial mapping are represented in warm hues. Pale green areas were significantly activated in the group analysis but did not survive the multifiducial correction for inter-participant anatomic variability. The blue outline represents the boundaries resulting from thresholding at $z > 4.0$, clusterwise corrected $P < .05$.The left hemisphere primary sensorimotor activation spans the central sulcus (CS) and extends into precentral gyri (preCG) and postcentral gyri. It includes 1092 voxels with peak activation at (−38 mm, −22 mm, 54 mm). The right hemisphere primary sensorimotor activation includes 769 voxels, with peak at (38 mm, −22 mm, 52 mm).

Increased Ipsilateral Hand Area Responses for Amputees

When compared directly with controls, amputees showed focal increases in activity during all 4 conditions along the CS, extending rostrally into the precentral gyrus and caudally into the postcentral gyrus (Figure 3). The high degree of overlap between this cluster and the functionally defined normative hand representation (blue outline) indicates that it likely includes the former hand territory, a point to which we will return shortly. It is also worth noting that the spatial extent of this cluster (at a fixed statistical threshold of $z > 4$, with cluster-wise correction of $P < .05$) was similar for both the ME and ME+VF conditions (see panels E and G, Figure 3). Relative to these conditions, however, the addition of MI in both the ME+MI and ME+MI+VF conditions was associated with an expansion of this cluster in the medial direction (see panels E and G vs F and H in Figure 3). The similarity of clusters for the ME+MI and ME+MI+VF conditions suggests that combining MI and mirror feedback did not further influence the spatial extent of this activation (see panels F and H, Figure 3).

Figure 3 (next page). Statistical parametric maps representing areas of significantly increased activity ($z > 2.3$, clusterwise corrected $P < .05$) associated with comparison of experimental conditions versus rest for both amputee and control groups. Here and in the subsequent figures, contralateral refers to the hemisphere opposite to the moving hand, whereas ipsilateral denotes the hemisphere located on the same side as the moving hand (i.e., contralateral to the amputated hand in patients). Motor execution (ME; panel A) activates the ipsilateral sensorimotor cortex in amputees but not in controls. Both groups do show increased activity in bilateral dorsal and ventral premotor cortices and posterior parietal areas within and along the intraparietal sulcus (IPS) and contralateral to the moving hand along the precentral gyrus (preCG), central sulcus (CS), and postcentral gyrus. This same network of areas is engaged when undertaking motor imagery (ME+MI) (panel B), visual feedback (ME+VF; panel C), or both (ME+MI+VF; panel D).


TRAUMA
CONTROL
Ipsilateral
Contralateral
Ipsilateral
Contralateral
A. ME > Rest
preCG
IPS
CS
preCG
B. ME + MI > Rest
2.3
5.1
C. ME + VF > Rest
D. ME + MI + VF > Rest

Effects of MI and Mirror VF Relative to ME With the Intact Hand

Whole-brain contrasts were run to identify regions modulated by either MI or VF when activity associated with ME of the intact hand was subtracted. For amputees, but not controls, MI was associated with significantly increased activity in the former hand territory (blue outline, left hemisphere), extending into more medial regions of the precentral and postcentral gyri and rostrally into the premotor area and the pre-SMA (Figure 4A). In contrast, in the VF condition, both amputees and controls exhibited increased activity within areas of the occipital, posterior temporal, and parietal cortices but not in sensorimotor hand representations or other regions of the frontal cortex implicated in motor representation (Figure 4B). This is consistent with recent findings with controls where only effects of VF in visual areas were detected (Matthys et al. 2010).

Region-of-Interest Analyses: Activity in the Normative Sensorimotor Hand Area Contralateral to the Moving Hand

Increased activity relative to baseline was detected in the functionally defined primary sensorimotor hand representation contralateral to the moving hand during all experimental conditions for both groups; $P < .001$ in all cases. Differences between groups or conditions were non-significant; $P > .10$ in both cases (Figure 5).

Region-of-Interest Analyses: Activity in the Normative Sensorimotor Hand Area Ipsilateral to the Moving Hand

All conditions were associated with increased ipsilateral activity above what was detected during resting baseline for the amputees; $P < .001$ in all cases (Figure 5). In contrast, none of the conditions was associated with significant increases in activity for controls; $P > .05$ in all cases. The magnitude of the signal change differed significantly between amputee and control groups: $F(1, 20) = 14.8$, $P = .001$. The main effect of Condition was not significant: $F(3, 60) = 2.12$, $P = .11$. The interaction effect between Group and Condition was significant, with amputees showing a greater response than controls particularly in conditions involving MI: $F(3, 60) = 3.23$; $P = .03$.

For amputees, imagining moving the absent hand in sync with moving the intact hand (ME+MI) compared with moving the intact hand alone (ME) was associated with a

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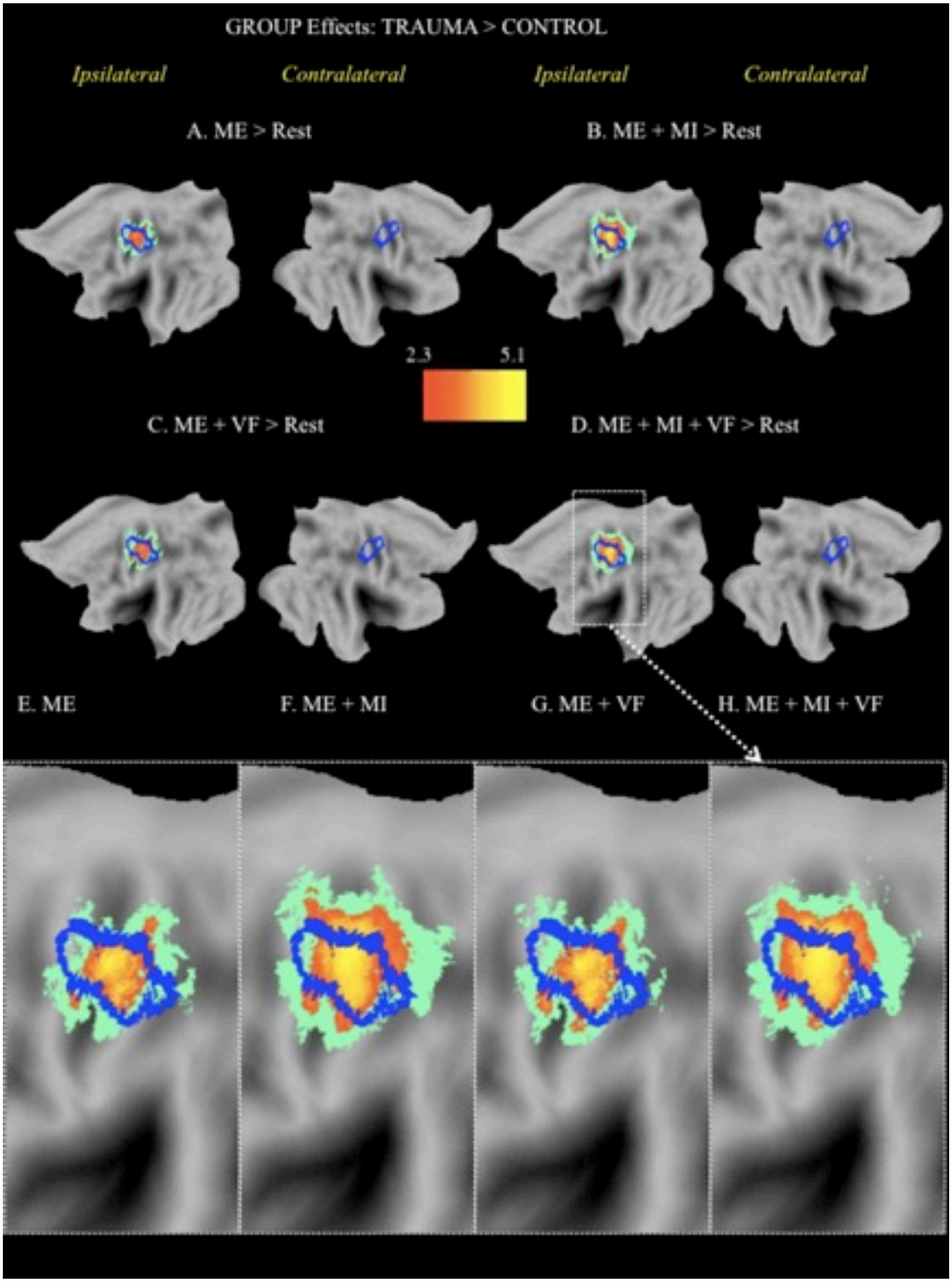
Figure 4 (next page). Amputees show significant increases in the ipsilateral sensorimotor cortex in all conditions relative to controls. Increased activations in the ipsilateral sensorimotor cortex were present only in the amputee group. The normative hand representations from the localizer are overlaid as blue contours on the group results (A-D).The zoomed views of the ipsilateral sensorimotor data from panels A to D (E-H).The cluster size associated with the motor execution (ME) task alone (630 voxels in panel E) slightly increases with the addition of visual feedback (ME+VF; 682 voxels, panel G).The addition of motor imagery (MI) is associated with substantial medial expansion of the ipsilateral sensorimotor cluster (ME+MI: 1522 voxels, panel F; ME+MI+VF: 1372 voxels, panel H).


GROUP Effects: TRAUMA > CONTROL
Ipsilateral
Contralateral
Ipsilateral
Contralateral
A. ME > Rest
B. ME + MI > Rest
2.3
5.1
C. ME + VF > Rest
D. ME + MI + VF > Rest
E. ME
F. ME + MI
G. ME + VF
H. ME + MI + VF

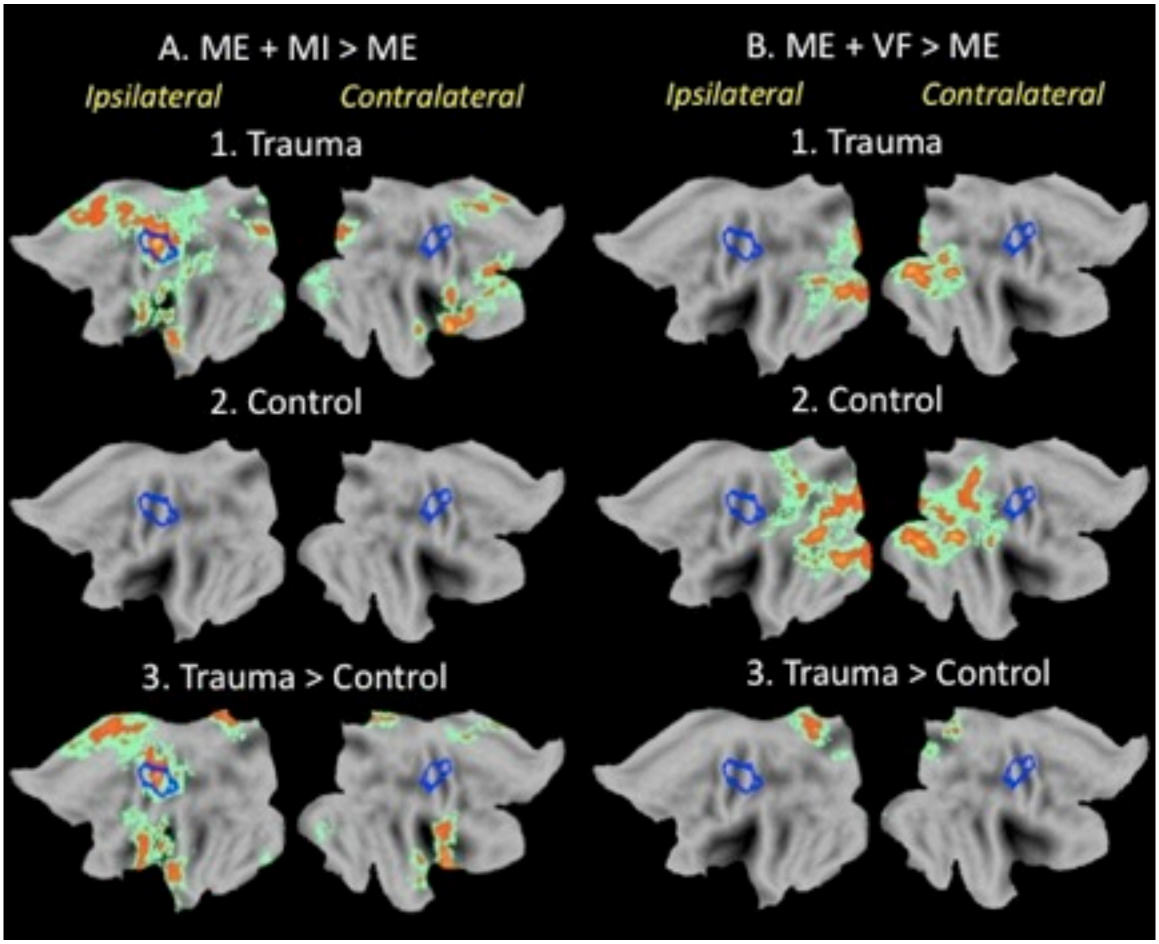


Figure 5. Effects of motor imagery (MI) on activity in the distributed sensorimotor network exceed those associated with intact hand movements in amputees. **A.** Relative to motor execution (ME) alone, the addition of MI (i.e., ME + MI) resulted in increased activity in the former sensorimotor hand territory (blue outline, left hemisphere). Increases were also detected in more medial precentral and postcentral gyri and in the premotor and pre–supplementary motor area (SMA) of amputees (1) but not controls (2).These effects were significantly greater than those detected in controls (3). **B.** In contrast, the addition of mirror visual feedback (ME + VF) resulted in increased activity in occipital, posterior temporal, and parietal areas in both groups (1 and 2), most likely because of increased visual stimulation. For reasons that are uncertain, amputees showed larger increases in the medial parietal cortex (3).

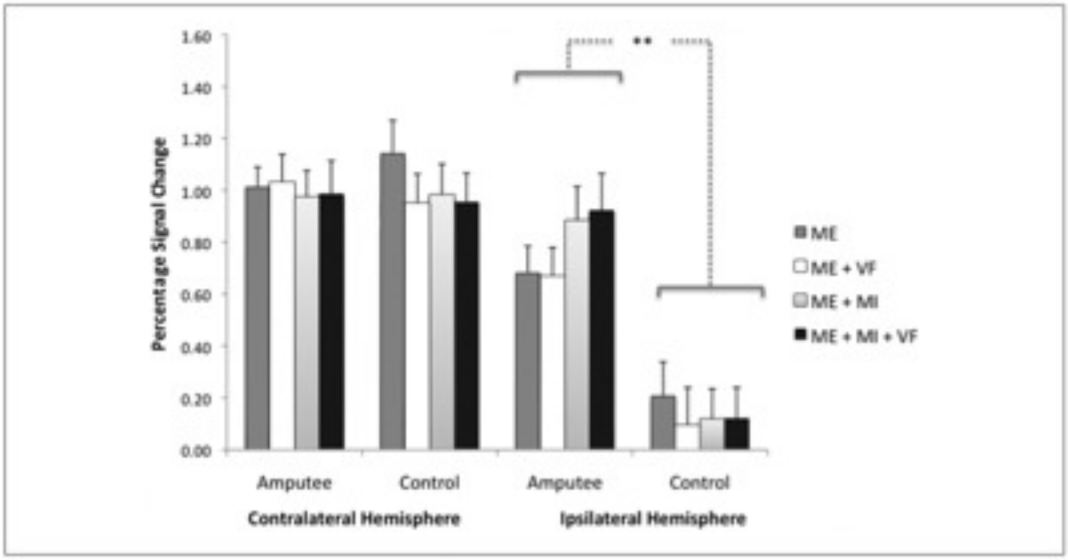


Figure 6. Group mean percentage signal change (PSC) within functionally defined normative sensorimotor hand representations during the 4 experimental conditions. Error bars represent standard errors; **P < .001. Hemisphere contralateral to the moving hand: the magnitude of mean group PSC did not differ significantly between amputee and control groups. Hemisphere ipsilateral to the moving hand: controls showed no increases above baseline. For amputees, imagining moving the absent hand while moving the intact hand (motor execution + motor imagery [ME+MI]) was associated with a non-significant trend toward increased activity relative to moving the intact hand alone (ME).The addition of illusory visual feedback (VF) to motor execution (ME+VF) failed to increase activity beyond what was observed in the ME condition. The MI and VF condition (ME +MI+VF) also resulted in a non-significant trend toward increased activity relative to the ME condition. See text for details.

non-significant trend toward increased activity within the former hand territory: t(10) = 1.83; Bonferroni corrected P > .05. The addition of illusory VF to ME (ME+VF) failed to increase activity beyond what was observed in the ME condition: t(10) < 1.0. Combined MI and VF (ME+MI+VF) also resulted in a non-significant trend toward increased activity relative to the ME condition: 1-tailed paired t(10) = 2.0; Bonferroni corrected P > .05.

This was no greater than what was observed in the ME+MI condition: t(10) < 1.0. The difference between conditions involving (ME+MI and ME+MI+VF) versus those not involving MI (ME and ME+VF) approached, but failed to achieve, significance: t(10) = 2.04; Bonferroni corrected P > .05.

DISCUSSION

The results of this experiment demonstrate that chronic amputees reactivate the former sensorimotor hand territory when moving their intact hands. There is a non-significant tendency for these effects to be enhanced when simultaneously imagining movements of the missing hand but not when viewing illusory VF created with a mirror. We now consider each of these findings, and their implications, in detail.

Increased Former Hand Area Activity Evoked by Movements of the Intact Hand

Compared with matched controls, unilateral amputees showed significantly increased activity in the sensorimotor cortex ipsilateral to the moving intact hand (i.e., contralateral to the amputated hand). This was true for all conditions, including simply moving the intact hand under visual guidance (Figure 3). Whereas increased ipsilateral sensorimotor activity has been reported in previous functional neuroimaging studies of unilateral amputees (Cruz et al. 2003; MacIver et al. 2008; Dettmers et al. 2001; Hamzei et al. 2001), we show that these effects are located specifically within the former hand territory as defined functionally on the basis of data from matched controls. This is an important difference from the modest ipsilateral increases reported in healthy adults during hand movements, which are located rostrally in the precentral cortex(Cramer et al. 1999) (Figure 5).

Increases in the former hand territory associated with use of the intact hand may be attributable to a reduction in IHI following unilateral deafferentation (Perez and Cohen 2009). In healthy adults, transcranial magnetic stimulation of the ipsilateral primary motor cortex exerts a time-dependent inhibitory influence on the contralateral motor cortex (Ferbert et al. 1992). Acute deafferentation reduces IHI, leading to increased excitability in the primary motor cortex ipsilateral to the affected limb (Ziemann, Corwell, and Cohen 1998). These changes are likely mediated by GABAergic transcallosal pathways and are specific to primary motor areas representing muscles homotopic to those that underwent deafferentation (Werhahn, Mortensen, Kaelin-Lang, et al. 2002). It is interesting to note that these inhibitory effects are reported to be moderate in unilateral amputees, suggesting a possible rebalancing of interhemispheric interactions following chronic deafferentation (Werhahn, Mortensen, Kaelin-Lang, et al. 2002). Our fMRI findings, however, indicate persistence of these ipsilateral increases in patients tested an average of 25 years post-amputation (range, 5-42 years). This raises the interesting question of whether long- term increased use of the intact hand contributes to the ipsilateral effects found here.

MI and Activity in the Former Hand Territory

Recent behavioral findings suggest that chronic amputees maintain the ability to imagine certain movements of their missing limbs accurately (Philip and Frey 2011). MI was associated with greater activity in the hand territory ipsilateral to the moving hand (former hand territory) for amputees versus controls. However, when the effects of intact hand movement were controlled, trends toward increased activity during MI for amputees did not survive corrections for multiple comparisons (Figure 5). For amputees, MI was associated with significant increases in activity that extended beyond the former hand territory into more medial portions of the pre- central and postcentral gyri and rostrally into premotor areas and the pre-SMA (Figure 4). Increased activity in these latter 2 regions is commonly detected in studies of MI. In short, activity associated with imagining movements of an amputated hand differs substantially from what is observed during MI of an intact hand by controls, with the most pronounced effects occurring in regions outside the former hand territory. As a result of extended training, these responses could come to affect experience-dependent changes in the former hand territory.

Failure to Detect Effects of Mirror VF on Sensorimotor Activity

In the absence of MI, illusory VF (ME+VF) failed to increase activity in the sensorimotor cortex beyond what was observed during movements of the intact hand alone (ME; Figures 4 and 5). Consistent with earlier results in healthy adults (Matthys et al. 2010), effects of the mirror in both groups were detected exclusively in occipital, posterior temporal, and parietal cortices and are most likely associated with increased visual stimulation (i.e., observing movements of both hands vs. one). A recent article reports increases in the primary sensorimotor cortex ipsilateral to the moving hand when healthy adults or amputees without phantom limb pain perform visually guided unilateral hand movements but not when performed by patients with pain (Diers et al. 2010). These ipsilateral movement-related effects increased in the presence of the mirror illusion (i.e., our ME+VF condition) and were also detected when these 2 groups imagined movements of the affected side while the intact hand remained still. Because of the absence of a functional localizer, however, it is unclear that these responses are specific to the former hand territory. Compared with the normative hand representations used in the current study (left primary motor cortex: −38 mm, −22 mm, 54 mm; see Figure 2), peaks of these ipsilateral responses are quite rostral (refer to Table 2 of (Diers et al. 2010), right primary motor cortex: 39 mm, −9 mm, 54 mm in healthy controls and 42 mm, −6 mm, 57 mm in amputees without phantom pain). According to an established histological atlas (Eickhoff et al. 2005), these loci have a high probability of being in the premotor cortex (Brodmann area 6) and a relatively low likelihood of falling in the primary motor cortex (Brodmann areas 4/4a). We too find strong bilateral increases in the premotor cortex for both patients and controls in all experimental conditions relative to resting baseline (Figure 2) but not in the ipsilateral hand area for controls (Figures 3 and 5). When the effects of intact hand movement are controlled, these ipsilateral premotor activations are increased only for the amputees and in conditions involving MI but not for mirror feedback alone (Figure 4). This is true despite the fact that only 4 out of 11 participants in the current work indicated no current or recent pain.

CONCLUSIONS

It is possible that the effects of the mirror feedback on activity in the former hand territory may evolve with practice or that responses may differ in acute amputees. That said, our failure to detect increases in association with the addition of mirror feedback may explain why reductions in pain for amputees assigned to such an intervention failed to exceed those experienced in a control condition where the same exercises were performed with the intact limb while the mirror was covered (Brodie, Whyte, and Niven 2007). At first glance, our findings appear less easily reconciled with those of another trial demonstrating a substantial reduction in pain in all 6 lower-extremity amputees who undertook a month-long course of 15 minutes of daily mirror training. None of the 6 individuals assigned to the MI control group experienced a significant reduction in phantom limb pain until crossing over to the mirror intervention (Chan et al. 2007). However, participants only performed simultaneous movements of the intact limb during the mirror treatment and not the imagery condition. At least for upper-extremity amputees, movements of the intact limb are a highly effective stimulus for the portion of the sensorimotor cortex that would have previously represented the amputated limb. With practice, the effects of MI on the adjacent cortex might enhance these responses.

APPENDIX A

LOCATIONS OF MEAN PEAK ACTIVATIONS IN PRIMARY AND SECONDARY SENSORY CORTICES DURING THE CONDITIONS OF THE SENSORY MAPPING TASKS FOR THE CONTROL GROUP AND PATIENT D.S.

Coordinates are defined in the space of the Montreal Neurological Institute's standard template brain (MNI-152; see Experimental Procedures).

	X	Y	Z
Primary Sensory	**CONTROLS**		
Left Hand	40	-24	58
Right Hand	-38	-28	58
Left Cheek	56	-4	44
Right Cheek	-62	-16	40
Secondary Sensory			
Left Hand	46	-24	16
Right Hand	-50	-22	16
	50	-32	22
Primary Sensory	**PATIENT D.S.**		
Left Hand	38	-22	46
	-62	-18	44
Right Hand	-40	-20	54
Left Cheek	62	0	42
Right Cheek	-50	-32	18
Secondary Sensory			
Left Hand	-60	-20	6
	52	-14	10
Right Hand	-54	-30	16
	52	-30	22

APPENDIX B

LOCATIONS OF MEAN PEAK ACTIVATIONS IN PRIMARY SENSORY CORTICES (BA1, 2, 3) DURING THE CONDITIONS OF THE SENSORY MAPPING TASKS FOR THE CONTROL GROUP AND PATIENT M.S.

Coordinates are defined in the space of the Montreal Neurological Institute's standard template brain (MNI-152; see Experimental Procedures).

	X	**Y**	**Z**
BA3b	**CONTROLS**		
Left Thumb	44	-16	44
Left Index	44	-18	52
Left Middle	46	-20	52
Left Ring	40	-24	52
BA1			
Left Thumb	58	-18	46
Left Index	58	-18	48
Left Middle	58	-18	48
Left Ring	58	-18	46
BA2			
Left Thumb	56	-20	46
Left Index	58	-20	48
Left Middle	56	-20	46
Left Ring	50	-28	56
	50	-20	46
BA3b	**PATIENT M.S.**		
Left Thumb	48	-18	46
Left Index	44	-18	46
Left Middle	44	-18	46
Left Ring	42	-22	48
BA1			
Left Thumb	44	-24	64
	34	-36	66
Left Index	56	-18	52

	46	-24	64
Left Middle	44	-26	64
Left Ring	44	-24	64
	54	-18	50
BA2			
Left Thumb	54	-22	46
	42	-32	46
Left Index	52	-22	46
	42	-38	58
Left Middle	58	-22	46
	38	-32	42
Left Ring	52	-22	46
	40	-32	44

APPENDIX C

EUCLIDEAN DISTANCES BETWEEN LOCATIONS OF MEAN PEAK ACTIVATIONS IN PRIMARY SENSORY CORTEX BA3B DURING THE CONDITIONS OF THE SENSORY MAPPING TASKS FOR THE CONTROL GROUP AND PATIENT M.S.

		M.S.				**CONTROLS**			
		Thumb	index	middle	ring	thumb	index	middle	ring
M. S.	thumb	0.00							
	index	4.00	0.00						
	middle	4.00	0.00	0.00					
	ring	7.48	4.90	4.90	0.00				
CN TR L	thumb	4.90	2.83	2.83	7.48	0.00			
	index	7.21	6.00	6.00	6.00	8.23	0.00		
	middle	6.63	6.63	6.63	6.00	9.17	2.83	0.00	
	ring	11.7	9.38	9.38	4.90	12	7.21	7.21	0.00

APPENDIX D

EUCLIDEAN DISTANCES BETWEEN LOCATIONS OF MEAN PEAK ACTIVATIONS IN PRIMARY SENSORY CORTEX BA1 DURING THE CONDITIONS OF THE SENSORY MAPPING TASKS FOR THE CONTROL GROUP AND PATIENT M.S.

		M.S.				**CONTROLS**			
		Thumb	index	middle	ring	thumb	index	middle	Ring
M. S.	thumb	0.00							
	index	18.00	0.00						
	middle	2.00	18.76	0.00					
	ring	0.00	18.00	2.00	0.00				
CN TR L	thumb	23.58	6.32	24.17	23.58	0.00			
	index	22.09	4.47	22.72	22.09	2.00	0.00		
	middle	22.09	4.47	22.72	22.09	2.00	0.00	0.00	
	ring	22.45	6.00	23.07	22.45	2.00	2.83	2.83	0.00

APPENDIX E

EUCLIDEAN DISTANCES BETWEEN LOCATIONS OF MEAN PEAK ACTIVATIONS IN PRIMARY SENSORY CORTEX BA2 DURING THE CONDITIONS OF THE SENSORY MAPPING TASKS FOR THE CONTROL GROUP AND PATIENT M.S.

		M.S.				**CONTROLS**			
		Thumb	index	middle	ring	thumb	index	middle	Ring
M. S.	thumb	0.00							
	index	2.00	0.00						
	middle	4.00	6.00	0.00					
	ring	2.00	0.00	6.00	0.00				
CN TR L	thumb	2.83	4.47	2.83	4.47	0.00			
	index	4.90	6.63	2.83	6.63	2.83	0.00		
	middle	2.83	4.47	2.83	4.47	0.00	2.83	0.00	
	ring	2.83	4.47	2.83	4.47	0.00	2.83	0.00	0.00

APPENDIX F

DETECTION OF CHANGES IN THE FREQUENCY OF THE SENSORY STIMULATION (ODD BALLS) INTRODUCED TO ENSURE ATTENTION TO THE AIR PUFFS DELIVERED TO THE FINGER TIPS IN THE SENSORY MAPPING TASKS FOR THE CONTROL GROUP AND PATIENT M.S.

Subject	M.S.	0087	0330	0454	0560	1115	1374	1380	1382
left hand	11/11	9/10	10/10	5/11	5/11	7/10	10/10	4/10	8/11
right hand	10/11	8/11	10/11	10/13	2/11	11/10	15/13	10/13	11/13

APPENDIX G

LOCATIONS OF MEAN PEAK ACTIVATIONS IN PRIMARY SENSORY CORTEX BA3B DURING THE CONDITIONS OF THE SENSORY MAPPING TASKS FROM PREVIOUS STUDIES.

Coordinates are defined in the space of the Montreal Neurological Institute's standard template brain (MNI-152; see Experimental Procedures).

	BA3b	**Bogdanov**	**Maldjian**	**Others**	
Thumb	**X**	44	54		
	Y	-16	-16		
	Z	44	38		
Index	**X**	44	50/40	48[1]	
	Y	-18	-20/-27	-19[1]	
	Z	52	44/41	44[1]	
Middle	**X**	46	44	41[2]	
	Y	-20	-29	-26[2]	
	Z	52	47	55[2]	
Ring	**X**	40	30		
	Y	-24	-43		
	Z	52	49		

[1] (McGlone et al., 2002)

[2] (Blankenburg, Ruben, Meyer, Schwiemann, & Villringer, 2003) both right digit.

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