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Review

Behavioral and magnetoencephalographic correlates of plasticity in the adult human brain

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ABSTRACT **Recent behavioral and physiological evidence suggests that even brief sensory deprivation can lead to the rapid emergence of new and functionally effective neural connections in the adult human brain.**

Until about 10 years ago, it was widely believed by neurologists that no new neural connections can be formed in the adult mammalian brain. It was assumed that, once connections had been laid down in fetal life, or in early infancy, they hardly changed later in life. It is this stability of connections in the adult brain, in fact, that is often used to explain why there is usually very little functional recovery after damage to the nervous system.

Everyone recognizes, of course, that *some* changes are possible even in the adult brain for otherwise one could not account for phenomena such as memory and learning (1, 2). Yet it is often assumed that, except in invertebrates (1), these phenomena are probably based on rather subtle changes at the synaptic level and do not necessarily involve alterations in the basic circuitry of the brain.

During the last four decades, the use of the microelectrode has completely transformed our understanding of the brain and has resulted in two major new insights: (*i*) the concept of the "receptive field"—a set of receptors funneling in information from the sensory surface on to single neurons in the brain [e.g., the somatosensory receptive fields studied extensively by Mountcastle (3) and his colleagues in primate S1 and the visual receptive fields described in detail by Hubel and Wiesel (4) in area 17 of the cat and monkey] and (*ii*) topography—fixed sensory maps (e.g., the somatotopic representation of the body surface in S1 and the retinotopic arrangement of the visual field in area 17).

Recordings from newborn animals revealed that many of the basic features of visual receptive fields and visual topography were present at birth and were probably specified by genes (5). (And although there was no direct evidence, it was tacitly assumed that the same was also probably true for the somatosensory system.) Moreover it was found that, although profound alterations in the receptive fields could be produced by procedures such as monocular deprivation, such changes could occur only within a well-defined critical period in early infancy. In the adult, on the other hand, both receptive field structure and topography were assumed to be stable and resistant to selective sensory deprivation or enrichment.

This picture has changed radically since the 1980s. It has become evident that the neural pathways of adult animals are capable of a surprising degree of reorganization following peripheral nerve injury (6, 7). There is now a wealth of empirical evidence demonstrating that procedures such as denervation or amputation can lead to massive reorganization in the primary somatosensory cortex of even adult primates (8).

Although the physiological evidence for such changes in animals is considerable, there have been remarkably few attempts to look for such effects in human subjects and to demonstrate the *behavioral* consequences of these effects. The magnetoencephalographic (MEG) studies reported recently (9) and behavioral experiments on human patients following amputation and brachial plexus avulsion (10–12) suggest that such correlates do exist. Using MEG, Mogilner *et al.* (9) were able to demonstrate highly precise somatotopic organization of the digits in normal human subjects. To explore somatosensory plasticity, they obtained MEG recordings from two adult human subjects before and after surgical separation of congenitally webbed fingers (syndactyly). The presurgical recordings revealed a shrunken cortical hand representation that lacked topography. A few weeks after surgery, however, a striking cortical reorganization occurred, spanning distances of 3–9 mm and the representation of the digits became clearly somatotopic.

My purpose in this essay is to review the evidence for somatosensory plasticity in the adult mammalian brain. Some excellent reviews are already available on the physiological work (13–16) and I will therefore mention these experiments only briefly. I will focus, instead, on our own behavioral work and on the MEG correlates of somatosensory reorganization in humans.

Plasticity in the Visual Cortex

Striking parallels exist between the reorganization effects observed in the somatosensory domain and the "filling in" of scotomas caused by damage to the retina (17–20) or cortex (12, 21). My own interest in these filling-in phenomena began more than a decade ago when I first encountered patients with focal lesions in the visual cortex. Usually such patients have what is described as a scotoma (1)—a region in the visual field within which nothing can be consciously perceived. Remarkably, the patients themselves are often unaware of this gaping hole in the visual field. When they look at a colored wall or a regular pattern of any kind (e.g., a carpet or a tile floor), the scotoma is "filled in" by the surrounding color or pattern. Or if they gaze at a companion seen against a background of wallpaper, the companion's head may vanish and be "replaced" by the wallpaper pattern.

We know surprisingly little about the nature of the neural representation that corresponds to the filling in of scotomas and blind spots. Unfortunately, observations on the natural blind spot are difficult to make because it is so far from the center of gaze, and patients with small, well-circumscribed scotomas of cortical origin are not easy to come by. In an effort to overcome these difficulties, Richard Gregory and I recently developed a technique (22, 23) for creating an artificial blind spot or scotoma that is closer to the center of gaze. The filling in of such an artificial scotoma, we found, was just as vivid as the filling in of the natural blind spot, and the technique has the additional advantage of facilitating careful observations.

Artificial Scotomas. To create an artificial scotoma, we used a twinkling pattern of dots that resembles the "snow" seen on a detuned television set. You can repeat our experiment by using your own television set at home. Pick a channel on which you can see only "snow"—no picture. In the middle of the screen, stick on a small, circular gummed label with a

Abbreviation: MEG, magnetoencephalography(ic).

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tiny black dot on its center. (The purpose of the black dot is to ensure steady fixation.) About 7–8 cm from this black dot, stick on a 1-cm^2 piece of gray paper (pick a gray that has roughly the same mean luminance as the twinkle on the television screen). If you view the display from a distance of about 1 m and fixate the central dot very steadily for 5–10 s, you will find that the square vanishes completely and is replaced by the twinkle invading from the surround. This filling in with the twinkle is obviously analogous to the filling in of scotomas and blind spots and may be based on similar neural mechanisms.

But what causes the square to fade in the first place? The effect is vaguely reminiscent of *Troxler fading*, the tendency for small, stationary objects in the peripheral visual field to disappear completely on steady, prolonged fixation. However, unlike Troxler fading, the effect that we have observed cannot be due to local adaptation (e.g., in the retina) to the luminance edges that define the square because these edges are being refreshed constantly on the screen. Indeed, the fading is actually enhanced if a dynamic noise background is used instead of static, two-dimensional noise. We would argue, therefore, that the fading is caused by adaptation or fatigue of neural detectors that are specialized for extracting texture borders and kinetic edges. Such neurons have been described in both area 17 and the middle temporal area.

We noticed that the fading of the square was especially pronounced with eccentric viewing. This finding may simply reflect the progressive increase in receptive field size with retinal eccentricity. If the fading occurs as a result of fatigue of neurons that extract the border of the gray square, then even a tiny eye movement will restore the square by stimulating a new set of neurons. Because the receptive fields are smaller near the fovea, a smaller eye movement will be sufficient to restore the square near the center of gaze, and this might explain why the square does not fade as easily in central vision. Gregory and I tested this hypothesis directly by waiting until the square disappeared and then moving it to see how large a displacement would be needed to make it reappear (Fig. 1). We found, as expected, that much greater displacements were required in peripheral vision than near the center of gaze.

The Physiological Basis of Filling In. What are the physiological mechanisms underlying the described filling-in process? A partial answer comes from a series of physiological experiments performed recently by Gilbert and Wiesel (20). They destroyed a small patch of retina and recorded from the area of visual cortex to which this patch would normally project. These cells were silent initially, of course, as one would expect, but the researchers found that within a few minutes, the same cells had receptive fields outside the zone of lesion; they could be excited by visual stimuli that lay outside the scotoma! More recently, Pettet and Gilbert (24) tried repeating these experiments using an artificial scotoma instead of a real one. Instead of destroying retinal receptors, they used a display similar to ours. (The display they used had small line segments moving around randomly outside the area occupied by the gray square.) They found that cells that initially had receptive fields within the gray square developed much larger receptive fields within just a few minutes, so that they could be excited by stimuli outside the square. These rapid changes in receptive field organization may provide an explanation for some of the perceptual filling-in effects that we had observed. Since these cells were originally responding to stimuli inside the scotoma (i.e., the grey square), perhaps higher brain centers are "fooled" into thinking that stimuli immediately outside the scotoma are now inside it. This would correspond roughly to what I am calling filling in.

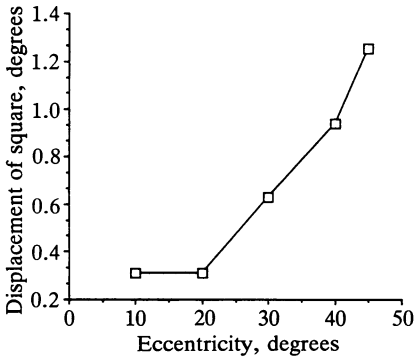

FIG. 1. Displacement thresholds for restoring visibility of the square (3.5° × 3.5°) as a function of eccentricity. Note that smaller displacements will restore visibility near the center of gaze but not in peripheral vision. (Each datum point represents the mean of 24 trials: four subjects × 6 trials each.)

An even more striking physiological correlate of our filling in effect was observed recently by De Weerd *et al.* (25), who recorded from neurons in V2/V3 of alert behaving monkeys that had been trained to fixate steadily. The classical receptive field of a single neuron was first mapped out and a grey occluder that was much larger than the receptive field was then displayed on the screen so that it covered the receptive field and extended well beyond its margins. Dynamic noise was then introduced in the surround and it was found that after a latency of about ≈10 s—the same latency we had observed for the perceptual filling in of artificial scotomas—the cell started firing again, as though it was responding to the filled-in noise.

Plasticity in Adult Somatosensory Pathways

Are there similar effects in other sense modalities such as touch and hearing? It is known that a complete somatotopic map of the entire body surface exists in the somatosensory cortex of primates (26–28). In a series of pioneering experiments, Merzenich *et al.* (29) amputated the middle finger (see *iii* below) of adult primates and found that within two months the area in the cortex corresponding to this digit began to respond to touch stimuli delivered to the adjacent digits; i.e., this area is "taken over" by sensory input from adjacent digits.

Merzenich *et al.* (29) also made three other important observations. (*i*) If a monkey "used" one finger excessively (e.g., if that finger was placed on a revolving corrugated drum) for an hour and a half each day, then after 3 months the area of cortex corresponding to that finger "expanded" at the expense of adjacent fingers (30). Also, the receptive fields of neurons in this area were found to have shrunk so that they were unusually small. (*ii*) If a monkey was forced to always use two fingers *jointly* by suturing two of its fingers together, then after several weeks it was found that single neurons in area 3b had receptive fields that spanned the border separating the two digits (31). In normal animals, receptive fields never cross the borders between digits. (*iii*) If more than one finger was amputated there was no "take over" beyond about 1 mm of cortex. Merzenich *et al.* (29) concluded from this that the expansion is probably mediated by arborizations of thalamo-cortical axons that typically do not extend beyond one mm.

This figure—1 mm—has often been cited as the fixed upper limit of reorganization of sensory pathways in adult animals (32). A remarkable experiment performed by Pons *et al.* (33), however, suggests that this view might be incorrect. They found that after long-term (12 years) deafferentation of one upper limb the cortical area originally corresponding to the hand was taken over by sensory input from the face. The cells in the "hand area" now start responding to stimuli applied to the lower face region! Since this patch of cortex is >1 cm wide, we may conclude that sensory reorganization can occur over at least this distance—an order of magnitude greater than the original 1-mm "limit."

Immediate Unmasking. In addition to these long-term changes that are typically seen several weeks after deprivation or stimulation, Calford and Tweedale (34)

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recently reported short-term changes that are based, presumably, on the unmasking of preexisting connections rather than on anatomical "sprouting." They anesthetized the digital nerve supplying the middle finger of a flying fox and found that within 20 min the cortical neurons in S1 that originally subserved that digit could then be activated by touching the adjacent digits as well; i.e., the receptive fields had expanded to include adjacent digits. This short-term expansion of receptive fields is analogous to the artificial scotomas of Pettet and Gilbert (24) and should be contrasted with the *shrinkage* of receptive fields and changes in topography observed by Merzenich *et al.* (29). We must bear in mind, however, that although such effects have often been lumped together under the heading "plasticity," they may, in fact, be based on very different underlying mechanisms.

Curiously, Calford and Tweedale (34) also found that this short-term receptive field expansion is seen for neurons in the mirror symmetric locations on the other hemisphere. Following digital nerve block of the middle finger in the left hand, for example, the neurons of the left hemisphere—corresponding to the *right* middle finger—also showed an expansion of receptive fields. Such effects were observed in flying foxes as well as in primates.

Perceptual Correlates of Somatosensory Plasticity in Humans. Despite the wealth of physiological experiments demonstrating striking plasticity in the primary sensory areas of primates, there have been few attempts to directly look for the behavioral consequences of this reorganization. Pons *et al.*'s observation (33), for example, makes the curious prediction that if one were to touch a monkey's face after long-term deafferentation, the monkey should experience the sensations as arising from the *hand* as well as from the face. To test this prediction, we recently studied the localization of sensations in several adult human subjects who had undergone either an amputation of one upper limb or a brachial plexus avulsion. Two of these (VA and WK) have been described in detail elsewhere (10–12). In this essay, I will briefly summarize our findings for these two patients and will also describe some preliminary results from a third patient (FA).

Patients. *VQ.* Patient VQ was an intelligent alert 17-year-old male whose left arm had been amputated 6 cm above the elbow about 4 weeks prior to testing. We studied localization of touch in this patient by brushing a Q-tip at various randomly selected points on his skin surface. His eyes were shut during the entire procedure and he was simply asked to report the perceived location of these sensations. Using this procedure, we found that even stimuli applied to points remote from the amputation line were often systematically mislocalized to the phantom arm. Furthermore, the distribution of these points was not random (10). There appeared to be two clusters of points with one cluster being represented on the lower part of the face ipsilateral to the amputation. There was a systematic one-to-one mapping between specific regions on the face and individual digits (e.g., from the cheek to the thumb, from the philtrum to the index finger, and from the chin to the fifth finger or pinkie). Typically, the patient reported that he simultaneously felt the Q-tip touching his face and a "tingling" sensation in an individual digit. By repeatedly brushing the Q-tip on his face we were even able to plot "receptive fields" (or "reference fields") for individual digits of the (phantom) left hand on his face surface (Fig. 2). The margins of these fields were remarkably sharp and stable over successive trials. Stimuli applied to other parts of the body such as the tongue, neck, shoulders, trunk, axilla, and contralateral arm were never mislocalized to the phantom hand. There was, however, one specific point on the contralateral cheek that always elicited a tingling sensation in the phantom elbow.

The second cluster of points that evoked referred sensations was found about 7 cm above the amputation line. Again there was a systematic one-to-one mapping with the thumb being represented medially on the anterior surface of the arm and the pinkie laterally.

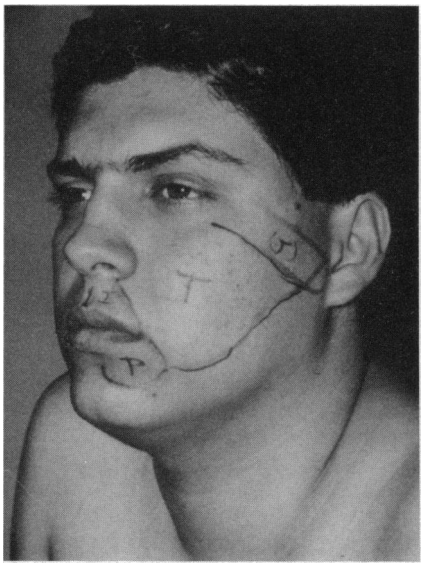

FIG. 2. Regions on the left side of the face of patient VQ that elicited precisely localized referred sensations in the phantom digits. "Reference fields," regions that evoke referred sensations, were plotted by brushing a Q-tip repeatedly on the face. The region labeled T always evoked sensation in the phantom thumb; P, from the pinkie; I, from the index finger; and B, from the ball of the thumb. This patient was tested 4 weeks after amputation.

We repeated the whole procedure again after one week and found an identical distribution of points. We conclude, therefore, that these one-to-one correspondences are stable over time—at least over the one-week period that separated our two testing sessions.

WK. In testing the second patient (WK) we found a similar pattern of results although there were some interesting differences. Following a carcinomatous infiltration of the brachial plexus, this patient had a right "forequarter" disarticulation, i.e., his entire right arm and right scapula were removed. He experienced a vivid phantom that was "paralyzed"—as if to mimic the paralysis of the original limb. We tested him exactly 1 year after amputation.

We had WK close his eyes and firmly rubbed the skin of his right lower jaw and cheek with a finger or the tip of a ballpoint pen. A representation of the entire phantom arm was found on the ipsilateral face with the hand being represented on the anterior lower jaw, the elbow on the angle of the jaw, and the shoulder on the temporamandibular joint. Again, as in patient VQ, there appeared to be a precise and stable point-to-point correspondence between points on the lower jaw and individual digits.

A second cluster of reference fields representing the hand was found just below the axilla—analogous, perhaps, to the cluster of points we found on VQ's upper arm. In this region even a Q-tip was effective in eliciting referred sensations in the thumb, forefinger, pinkie, or palm. And lastly, there was a third cluster of points near the right nipple and the arrangement of these points also showed some hint of topography. Thus it would appear that there is a tendency toward the spontaneous emergence of multiple somatotopically organized maps even in regions remote from the line of amputation. The exact mechanism by which such maps are formed remains an interesting question.

We have now studied seven patients after upper limb amputation and found that sensations were referred from the face to the phantom arm in only three of them. The cluster(s) of points just proximal to the line of amputation, on the other hand, was seen in all seven patients.

FA. This patient lost his right arm as a result of an accident on a fishing boat in 1982. (His arm has been amputated ≈8 cm below the elbow crease.) He experienced a very vivid phantom hand that was usually "telescoped," i.e., the hand felt as if it were directly attached to the stump with no intervening forearm. FA was one of the subjects we examined who did have a map on his face. As in the

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other patients, he also had several points near the amputation line that elicited referred sensations. After carefully mapping these points, we established that there were *two* distinct somatotopic representations that were almost completely identical to each other (Fig. 3). One of these extended from the amputation line to about 3 cm below the elbow, while the second one extended from about 6 cm above the crease to ≈14 cm. Stimuli applied to points between these two maps were completely ineffective in producing referred sensations even though skin sensitivity was normal in this region.

Modality-Specific Effects. The neural pathways that mediate the sensations of pain, warmth, and cold are quite different from those that carry information about touch from the skin surface to the brain (35–37). We wondered whether the remapping effects reported by Pons and his collaborators occur separately in each of these pathways or only in the touch pathways. To find out, we tried placing a drop of warm water on VQ's face. He felt the warm water on his face, of course, but remarkably he reported (without any prompting) that his phantom hand also felt distinctly warm. On one occasion when the water accidentally trickled down his face, he exclaimed, with surprise, that he could actually feel the warm water trickling down the length of his phantom arm! We have now seen this effect in three patients, two after upper-limb amputation and one after an avulsion of the brachial plexus. The latter patient was able to use his normal hand to trace out the exact path of the illusory "trickle" along his paralyzed arm as a drop of cold water flowed down his face. (The distance traversed by this illusory trickle was about 5 times the distance on the face as one might expect from the obvious differences in cortical magnification for the face and arm representations.) And finally, in one patient we found that a vibrator placed on the ipsilateral lower jaw elicited a sensation of "vibration" in the phantom hand.

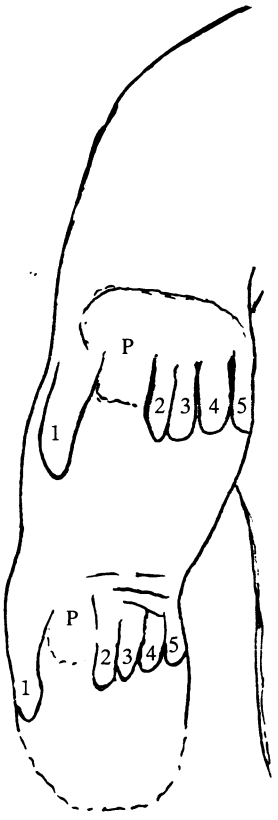

FIG. 3. Somatotopic maps of referred sensations in patient FA. Note that there are two distinct maps—one close to the line of amputation and a second 6 cm above the elbow crease. The maps are almost identical except for the absence of fingertips in the upper map. When patient FA imagined he was pronating his phantom, the entire upper map shifted in the same direction by about 1.5 cm. 1, Thumb; 2, index finger; 3, middle finger; 4, ring finger; 5, pinkie. These reference fields usually elicited sensation in the glabrous portions of these digits. The dorsal surface of the hand is represented on the dorsolateral part of the upper arm lateral to the palm (P) and thumb (1) representations. No referred sensations in the phantom could be elicited by stimulating the skin region between these two maps.

Digit Amputation. We also examined a 45-year-old patient whose middle (third) finger had been amputated at the base when she was 16. Using a Q-tip, we found that touching either digit two or digit four on various points on the side adjacent to the amputated digit evoked referred sensations in roughly the corresponding locations on the phantom finger. Drops of warm or cold water at these sites evoked warmth or cold in the phantom finger and, when we tightly gripped and released her index finger, she felt her phantom finger being tightly gripped. (Interestingly, a "memory" of the gripping sensation persisted for 7 or 9 s in the phantom but not in the normal digit.) These findings may be a direct perceptual correlate of the observations of Merzenich *et al.* (29), who found that after deafferentation of one digit in an adult monkey, the area in SI corresponding to that digit gets taken over by sensory input from adjacent digits.

What would happen if *two* dissimilar sensations were referred simultaneously to the same location on the phantom? How would the two referred sensations interact with each other? To find out, we applied a drop of warm water on digit two and one of cold water on digit four and asked the patient what she felt. After a delay of 2 or 3 s the patient reported that she experienced the two sensations clearly alternating in time—a wave of cold was followed by a wave of warmth and that by a wave of cold. (We have also elicited this curious effect in upper-limb amputees by placing warm water on the face and cold water on the second "map" near the amputation line.) This alternation continued until the sensations eventually died out. When the drop of hot water and the drop of cold water were both placed on a single digit, however, she volunteered that an unusual sensation was experienced—a kind of paradoxical "heat–cold"—as though the phantom was simultaneously warm and cold.

We then repeated these experiments on an additional seven patients with digit amputation. Systematic mislocalizations of sensations were seen in only three of the seven. It is possible that in some patients the weak referred sensations in the phantom are masked or inhibited by the stronger "real" sensations arising from the normal digit.

Another curious observation that we made on the finger amputees also deserves mention. These patients experienced vivid phantom fingers, as one might expect, but only when they flexed their normal fingers as when making a fist or grabbing a real or an imaginary cup. There was usually a latency of 2–3 s before the phantom finger emerged "in place," grabbing the cup and then, when the normal fingers were suddenly extended again, the phantom took several seconds to disappear. Interestingly, two of the patients reported that the phantom finger also felt as if it were gradually extending as if to "follow" the other fingers with a slight delay before it eventually faded. These observations would be compatible with the view that the phantom finger arises from an interaction between two sources of information: (*i*) from "remapping" occurring in cortical and thalamic maps (10) that are concerned with proprioception rather than touch and (*ii*) from reafference signals originating from the motor command centers that control the fingers. As we shall see below, information from these two sources might be combined in the parietal cortex to generate a vivid image of the moving fingers—including the moving phantom finger.

Memory-Like Effects. The upper-limb amputees as well as the digit amputees spontaneously volunteered the following intriguing observation. When stimuli were applied to the face (or an adjacent digit), there was often a 2- to 3-s latency before the sensation was referred to the phantom and, when the stimulus was removed, the sensation usually persisted for 8–10 s in the phantom but not in the site where the stimulus had been delivered (10). These effects were especially pronounced for referral of temperature but they also occurred for simple touch sensations.

The delay in experiencing the referred sensations suggests that the receptive field properties of neurons in the remapped cortical areas may not be entirely normal—a

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conjecture that can be verified experimentally. The reason for the echo-like persistence of the referred hand is far from clear, but the effect certainly deserves further study since it may be related to what psychologists call "short-term memory."* One possibility is that the persistence is mediated by the numerous reciprocal pathways that are known to connect the different sensory maps in the thalamus and cortex—a process similar, perhaps, to the "reverberations" postulated by Hebb (39).

Discussion: The Remapping Hypothesis

The occurrence of "referred sensations" in the phantom limb is in itself not new. It has been noticed by many researchers (40, 41) that stimulating points on a stump often elicits sensations from missing fingers, and the great American psychologist William James (42) once wrote "A breeze on the stump is felt as a breeze on the phantom." Such findings have often been attributed to direct reinnervation of the stump by the severed axons. Even when points remote from the stump were found to be effective in producing referred sensations, the phenomenon was often attributed to "diffuse" connections in the nervous system. I would argue, instead, that the effects I have observed are a direct consequence of the remapping observed by Merzenich *et al.* (26) and by Pons *et al.* (33), which in turn is constrained by proximity of maps in the brain. The reason that there are two clusters of points, for example—one on the face and one near the upper arm—is that the hand area in the Penfield homunculus is flanked on one side by the face and on the other side by the upper arm, shoulder, and axilla (Fig. 4). If the sensory input from the face and from around the stump were to "invade" the cortical territory of the hand, one would expect precisely this sort of clustering (10) of points.† In the remainder of this essay I shall refer to this view as the "remapping hypothesis" of referred sensations (10).

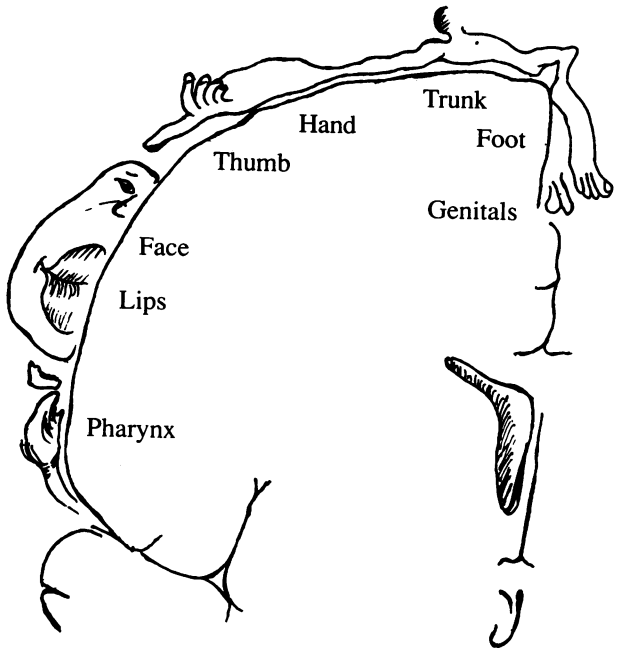

FIG. 4. The Penfield homunculus. Note that the sensory hand area is flanked below by the face and above by the upper arm and shoulder—the two regions where we usually find reference fields in arm amputees.

With regard to our empirical results, what is novel may be summarized as follows: (*a*) There was a precise one-to-one correspondence between points on the face and individual digits. Also, the points were not distributed randomly; there were two clusters of points—one on the lower face region and one near the amputation. (*b*) The effect is topographical; e.g., in two patients, when we moved the Q-tip over the mandible, they experienced movement of equivalent direction, distance, and speed across their phantom hand. (*c*) Even complex sensations may be referred from regions remote from the line of amputation; e.g., warm water trickling down the face was felt as a sensation of warm water trickling down the phantom hand. (*d*) Reorganization is relatively rapid; the study was carried out after 4 weeks rather than 12 years. This rapidity might suggest that the reorganization is based on the unmasking of silent synapses (e.g., through disinhibition) rather than on anatomical sprouting. Whatever the interpretation, however, these findings represent a clear demonstration that highly organized, modality-specific "rewiring" of the adult mammalian brain can occur in as little as 4 weeks and that this rewiring can be functionally effective. It remains to be seen, of course, whether this latent capacity can be exploited for therapeutic purposes.

Sprouting or Unmasking? What is the actual neural mechanism underlying the "expanded" hand representation in the Silver Spring monkeys and in our patients? We need to consider two theories: (*i*) When a patch of sensory neurons (e.g., in the "hand area") is deprived of sensory input, it may begin to secrete neurotrophic factors that provoke sprouting of new axon terminals from neurons supplying anatomically adjacent cortical areas. These same trophic factors might subsequently "attract" these terminals to the denervated zone. (*ii*) Perhaps even in normal individuals any given point on the skin projects simultaneously to several locations; e.g., the sensory input from the face projects simultaneously to both the face and the hand neurons in the cortex (or thalamus). The unwanted input to the hand area, however, might be subject to tonic presynaptic inhibition (e.g., via an inhibitory interneuron) by the "correct" axons that arrive there from the hand. If the arm is amputated, on the other hand, this occult input is unmasked through disinhibition and this would lead to mislocalized sensations. What this model does not explain, of course, is why only one of several "occult" inputs is unmasked and why you find a topographic arrangement. The manner in which maps might arise in the brain is now a topic of great theoretical interest (43).

There is at present no strong reason for favoring one hypothesis over the other. There are some hints that rapid "unmasking" of synapses can occur in the

*These short-term memory effects should be distinguished from the vivid long-term memory (38), in the phantom, of very specific sensory experiences such as the pain of arthritis or the sensation of wearing a wedding ring on one of the phantom fingers.

†Note that in Penfield's map the area of S1 representing the genitals is just below the area representing the foot. It has not escaped our notice that this may provide an explanation for foot fetishes. Penfield's claim is based on very few data points but, if confirmed, the remapping hypothesis would also predict that, after leg amputation, touching the genitals should evoke referred sensations in the phantom foot. Two letters we received recently support that such effects do occur. A neurosciences graduate student wrote to us that soon after her left lower leg was amputated she found that sensation in her phantom foot was enhanced in certain situations—especially during sexual intercourse and defecation. Similarly, an engineer in Florida reported a heightening of sensation in his phantom (left) lower limb during orgasm and that his erotic orgasmic experience "actually spread all the way down into the foot instead of remaining confined to the genitals"—so that the orgasm was "much bigger than it used to be. . . ."

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visual system (24) as well as in the somatosensory system (7, 34). Such short-term changes, however, usually result in an enlargement of receptive field size and there is no strong evidence that topography can be altered. Furthermore, the unmasking idea is rendered somewhat unlikely by the fact that neither the arborization of thalamocortical axon terminals nor corticocortical connections have been found spanning more than a few millimeters of the cortex (32, 44). Finally, we also examined two patients following anesthetic block of the brachial plexus and one patient immediately after amputation and found no evidence of a "map" on the face.

Even if the sprouting hypothesis is correct, however, one would still have to account for the emergence of topography and modality specificity; i.e., the sprouting would have to be *organized* and the new axon terminals would have to find their appropriate targets. The guidance of such new terminals to appropriate targets would, if it occurred at all, have to depend on poorly understood mechanisms such as "chemoaffinity."

Site of Remapping: Thalamus or Cortex? There is very little evidence from the physiological work on the question of whether the somatosensory remapping occurs in the thalamus or cortex (or indeed, the spinal cord).

One way to answer this question would be to repeat our psychophysical experiments on neurological patients instead of amputees. One could select patients who have damage to the internal capsule causing loss of sensations (and/or movements) in the limbs (or just arm) without a loss of sensation in the lower face. If the remapping effects are cortical in origin then we would expect sensations from the face to be mislocalized or "referred" to the paralyzed arm. To our knowledge, there are no such effects reported in the clinical literature but they would be easy enough to look for.

Phantom Limb Pain. The remapping hypothesis may also help explain phantom limb pain. Keeping in mind that the remapping is ordinarily modality specific—touching the face evokes "touch" in the phantom but cold water is felt as cold and hot water as warmth—we may conclude that the fibers concerned with each of these modalities must "know" where to go. But if there were a slight error in the remapping—a sort of "cross-wiring"—so that some of the touch input was accidentally connected to the pain areas, the patient might experience severe pain every time regions around the stump or face were accidentally touched. (The provoking stimulus might be so trivial that he or she might not notice it at all while being overwhelmed by the pain.) Also, such cross-wiring might lead to subtle changes in gain control that might amplify the pain signals in the somatosensory pathways.

MEG Correlates of Remapping

The work on monkeys by Merzenich *et al.* (29) and by Pons *et al.* (33) was based on direct single-unit recordings from the cortex. Unfortunately, it is difficult to ask a monkey about perceived sensations and, thus, it was not obvious that the observed changes in receptive fields might indeed give rise to referred sensations. Ideally, one would like to be able to use the same subjects in both experiments. Recent advances in MEG have been made possible with the advent of large array magnetometers (>30 detectors) and the understanding of the physics and mathematics of the measurements of cortical electrical activity (45–48). These advances have allowed for fine localizations (<3 mm) of processing. The work of Suk *et al.* (46) and of Yang *et al.* (48) is especially relevant, since they have obtained very detailed somatosensory (SI) maps of the hand, face, and several other body parts. They have been able to resolve the cortical areas representing individual digits and even segments of digits.

An ingenious experiment by Mogilner *et al.* (9) suggests that MEG may provide a powerful new technique for exploring somatosensory plasticity in the human brain. In order to establish a baseline for their study they first obtained cortical somatosensory maps in nine normal subjects. A composite hand map was then obtained by superimposing the finger locations of different subjects. Surprisingly, little variability was observed across subjects. Next, they compared these maps with those obtained from two adult males with congenital syndactyly, who were studied before and after surgical separation of the digits. In both subjects the representation of the digits was scrambled; i.e., there was no topography—and in one of them, the entire hand representation was also shrunken, compared to that of normal subjects. A few weeks after surgery, the MEG recordings were obtained once again and it was found that a somatotopic representation of digits had emerged and that the distances between individual digit representations was nearly normal. The exciting implication of this study is that cortical topography is not fixed; it is maintained dynamically by ongoing activity from the sensory surface—as originally suggested by Merzenich *et al.* (29).

Obviously, MEG studies could also be useful in exploring remapping effects of the kind observed by Pons *et al.* (33) and our group has recently undertaken such a study (49) in collaboration with Christopher Gallen and Tony Yang. Preliminary evidence from a single patient indicates that such remapping does indeed occur. The arm of this patient had been amputated 8 cm below the elbow about 10 years prior to our testing him. We obtained MEG recordings from the left hemisphere (contralateral to the amputation) and compared this with the somatosensory map of the normal limb in the right hemisphere. Although perfect symmetry between the two hemispheres in normal subjects is not guaranteed, the results of Yang *et al.* (48) suggest that this is generally true. In patient FA, on the other hand, the maps showed a striking asymmetry caused, presumably, by the reorganized pathways in the left hemisphere. The "hand" area in the left hemisphere could no longer be discerned and this area could be activated by touching either the lower face or the "map" in his upper arm 10 cm above the line of amputation (49). If this effect is confirmed on additional patients, it would represent the first direct evidence for somatosensory remapping in human subjects spanning such large distances.

Transcranial Magnetic Stimulation. Another promising technique (50) for studying reorganization of maps in humans involves the use of transcranial magnetic stimulation. It has been found, for example, that *motor* areas can also undergo reorganization after amputation (51, 52) in a manner analogous to the sensory effects reported by Pons *et al.* (33). In patients who have lost a limb, muscles proximal to the stump can be activated by focal transcranial magnetic stimulation of a much larger number of scalp positions than for the corresponding muscles on the other side. It seems likely that in these patients the original motor areas subserving the hand are now "taken over" by more proximal muscles. These findings, together with our work on amputees, suggest an obvious behavioral experiment: What would happen if an upper-limb amputee is asked to move his phantom fingers? Would there be electromyographic activity in his proximal muscles or, indeed, even in his facial muscles?

We have recently confirmed some of these predictions in a patient (RW) whose arm had been amputated 2 years prior to our testing. In addition to observing two clusters of points on this patient—one on the face and one on the upper arm—we also noticed another intriguing effect. Whenever we asked RW to imagine voluntarily flexing or extending his phantom fingers, we noticed vigorous involuntary contractions of his proximal shoulder and upper arm musculature (e.g., the pectorals major and deltoid). This motor remapping effect might be analogous to the sensory remapping reported by Pons and Merzenich and their collaborators, but it is not clear where the actual plastic changes take place. One possibility is

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that the changes might be occurring as far down as the anterior horn cells of the spinal cord; i.e., when the anterior horn cells that normally supply the hand degenerate, the pyramidal axons that would normally supply these neurons begin to sprout and supply adjacent neurons that innervate the proximal muscles.

Some Potential Problems. *Intersubject variability.* How general are the findings we have reported here? Of the seven patients we have seen so far, the "map" on the face was seen in three. The second cluster of points near the line of amputation, on the other hand, was seen in all seven patients.

Why do some patients not have a cluster of points on the face? There are at least three possibilities that are not mutually exclusive. First, the brain maps themselves might vary slightly from patient to patient, and this, in turn, might influence the degree of remapping. Second, some patients may eventually "learn" to ignore the referred sensations from the face by using visual feedback. Third, if the patient uses the stump constantly the skin corresponding to it may "regain" the territory that was initially lost to the face.‡

Contralateral effects. Points that elicit referred sensations in the phantom arm are usually clustered around regions proximal to the line of amputation and around the ipsilateral caudal face area as predicted by the remapping hypothesis, although the details of the maps varied considerably from patient to patient. These observations are, on the whole, consistent with the remapping hypothesis but mention must be made of the occasional presence of maps in the *contralateral* limb at locations that were approximately mirror symmetrical with the line of amputation. Touching these points usually elicited sensation in the phantom or, rarely, in the normal hand.§ The origin of these contralateral effects is obscure but one possibility is that they arise from long-term *transcallosal* changes analogous to the short-term effects reported by Calford and Tweedale (34). To our knowledge such long-term plastic changes have not been reported in hemisphere ipsilateral to the deafferentation but they would be easy enough to look for.

Stability of maps over time. In patients WK, VQ, and FA, the overall features of the map were remarkably stable with repeated testing across weekly intervals (for 4 weeks). In patient FA, however, we made an intriguing observation that suggests that the fine details of the map may be dynamically maintained.

Recall that FA had lost his arm 10 years ago when the beam of a sailboat landed on it and crushed it. Upon careful questioning, we discovered that FA's phantom hand usually occupied a position halfway between pronation and supination with the fingers slightly flexed as though he was holding an imaginary vertical staff. We were also struck by the fact that the topography of points on the upper arm seemed to approximately "mimic" the position of the phantom fingers—a tendency that we had previously noticed in other patients. Out of curiosity, we asked him to voluntarily pronate his phantom hand all the way and remapped the points on the upper arm while his hand was still pronated. To our astonishment, we found that the entire map had shifted systematically leftward by ≈1 cm as if to partially "follow" the pronation (12). Since the arm below the elbow was clamped, this shift in the map could not be attributed to accidental upper arm movements. Also, when he returned the phantom to its resting position, the map also shifted rightward and returned to its original location. A particularly convincing way of demonstrating this effect was to place a constant stimulus such as a small drop of water on (say) the pinkie region of the map. When he was then asked to pronate his phantom, he reported that he very distinctly felt the drop of water moving from the pinkie to the ring finger.

These observations are quite remarkable for, although their functional significance is not obvious, they suggest that the fine details of the map may be dynamically maintained and that either the map in S1 itself or in subsequent "readout" can be profoundly modified by reafference signals from motor commands sent to the hand.

A Theory of Phantom Limbs

The remapping hypothesis not only explains referred sensations but may also provide an explanation for the very existence of phantom limbs. The old clinical explanation of phantom limbs is that the illusion arises from irritation of severed axon terminals in the stump by the presence of scar tissue and "neuromas." Unfortunately, as originally pointed out by Melzack (53), this explanation is inadequate since injecting local anesthetic into the stump or even removing the neuromas surgically often fails to abolish the phantom or to eliminate phantom limb pain.

We suggest, instead, that the phantom limb experience arises because tactile and proprioceptive input from the face and tissues proximal to the stump "takes over" not only the brain in area 3B, as shown by Pons *et al.* (33), but possibly also in "proprioceptive" maps. Consequently, spontaneous discharges from these tissues would be misinterpreted as arising from the missing limb and might therefore be felt as a "phantom." This hypothesis is different from, although not incompatible with, the view that phantom limbs arise from the persistence of a "neurosignature" in a "diffuse neural matrix" (53). We would argue, however, that the effect arises from mechanisms of a more specific nature such as remapping.

The remapping hypothesis does not, however, explain all aspects of the phantom limb experience. Consider, for example, the observation that phantom limbs are occasionally seen in patients who have *congenital* absence of limbs. We have recently studied one such patient (DB)—a 20-year-old female whose arms had been missing from birth. All she had on each side was the upper end of the humerus—there were no hand bones and no radius or ulna. Yet she claimed to experience very vivid phantom limbs that often gesticulated during conversation! It is unlikely that these experiences are due to confabulation or wishful thinking for two reasons. First, she claimed that her arms were "shorter" than they should be by about a foot. (She knew this because her hand did not fit into the prosthesis like a hand in a glove "the way it was supposed to.") Second, her phantom arms did not feel as if they were swinging normally as she walked—they felt rigid! These observations suggest that her phantom limbs did not originate simply from her desire to be "normal." It is also difficult to see how the remapping hypothesis, in its simple form, can explain the vivid gesticulation and other spontaneous movements that DB and other patients experience. We suggest, instead, that the sensations arise from *reafference* signals derived from the motor commands sent to the phantom. What is remarkable, however, is that the neural circuitry generating these gesticulatory movements was "hard-wired" and had actually survived intact for 20 years in the absence of any visual or kinesthetic reinforcement.

Based on these observations, we suggest that the phantom limb experience probably depends on integrating information from three different sources: First, from the spontaneous activity of tissues in the face and tissues proximal to the amputation—i.e., the "remapped" zones; second from reafferance signals that accompany motor commands sent to the muscles of the phantom limb; and third, to some extent even from the neuromas—as taught by the old textbooks. Information from these sources is probably combined in the parietal cortex to create a vivid dynamic image of the limb—an image that persists even when the limb is removed.

‡One prediction from this would be that the cluster of points on the face should be seen much more frequently after brachial plexus avulsion than after amputation. We have some evidence that this is indeed true.

§In one patient, vigorous rubbing of the lower face contralateral to the amputation also occasionally evoked referred sensations in the phantom but the sensations were usually weak and very poorly localized.

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Indeed, there is at least one case on record of a patient actually *losing* his phantom (54) as a result of a stroke affecting his right parietal cortex, just as one would predict from our hypothesis.

Conclusions

Taken collectively, the findings on visual and somatosensory filling in considered in this review challenge two of the accepted dogmas in neuroscience: the concept of the receptive field as a set of receptors simply converging onto sensory neurons and the concept of fixed maps or topography. The results suggest, instead, that even in adults, the classical receptive field is just the tip of the iceberg—its profile can be altered by ongoing visual stimulation in the surround (as in artificial scotomas). And it appears that topography, too, can change over surprisingly short periods; shortly after arm amputation, a subject begins to feel sensations in the missing arm when stroked on the face. Although these findings should not force us to go all the way back to the ideas of Lashley (55), they do imply that we need to revise some of our views on the stability and functional significance of maps and receptive fields.

It is at present unclear whether the remapping effect we have seen in our patients (or the ones observed using MEGs) (9, 49) are based on sprouting or unmasking. The fact that anatomical studies have repeatedly failed to reveal any preexisting long-range connections, however, suggests that the sprouting hypothesis is probably correct. If so, perhaps the single most important implication of our work is that the sprouting must be sufficiently fine-grained and precise that it permits the emergence of topography and the elaboration of even such sophisticated compound sensations such as "trickle" or "gripping," although, of course, the sensations are abnormally localized. The rapid occurrence of such precise, functionally effective sprouting has never before been documented in the adult human brain and it provides some grounds for optimism.

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