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INVITED REVIEW

The perception of phantom limbs
The D. O. Hebb lecture

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Summary
Almost everyone who has a limb amputated will experience a phantom limb—the vivid impression that the limb is not only still present, but in some cases, painful. There is now a wealth of empirical evidence demonstrating changes in cortical topography in primates following deafferentation or amputation, and this review will attempt to relate these in a systematic way to the clinical phenomenology of phantom limbs. With the advent of non-invasive imaging techniques such as MEG (magnetoencephalogram) and functional MRI, topographical reorganization can also be demonstrated in humans, so that it is now possible to track perceptual changes and changes in cortical topography in individual patients. We suggest, therefore, that these patients provide a valuable opportunity not only for exploring neural plasticity in the adult human brain but also for understanding the relationship between the activity of sensory neurons and conscious experience. We conclude with a theory of phantom limbs, some striking demonstrations of phantoms induced in normal subjects, and some remarks about the relevance of these phenomena to the question of how the brain constructs a 'body image.'

Keywords: phantom pain; neural plasticity; somatosensory cortex; body image; synaesthesia

Abbreviations: fMRI = functional MRI; MEG = magnetoencephalogram

Contents

Introduction

A characteristic feature of the adult primate brain is the existence of a multiplicity of specialized areas, including distinct topographically organized 'maps' concerned with different sense modalities (Adrian and Zotterman, 1926; Mountcastle, 1957; Hubel and Wiesel, 1979; Lin and Kaas, 1979; Sur *et al.*, 1985; Kaas *et al.*, 1990; Garraghty *et al.*, 1991). In the visual domain alone, for example, over 30 distinct areas have been described which contain either partial or complete maps of the visual field. A hundred years of neurology, as well as three decades of single-unit recordings using microelectrodes, have established these basic ideas beyond any reasonable doubt (Allman and Kaas, 1971; Van Essen and Maunsell, 1980; Zeki, 1980). One of the most important early findings was that much of this intricate circuitry, especially in the primary visual cortex, is specified by the genome and remains largely stable throughout life, under ordinary circumstances (Wiesel and Hubel, 1963). This finding provided a vindication of what neurology has always believed: that no new neural connections can be formed in the adult mammalian brain. Once connections have been laid down in foetal life, or during certain critical periods in early infancy, it was assumed that they remain fixed throughout life. Indeed, it is this stability of connections in the adult brain that is often used to explain why there is usually very little functional recovery after damage to the nervous system and why neurological diseases are so notoriously difficult to treat.

In the last two decades, however, several experiments on the effects of deafferentation (or amputation) on somatosensory maps in adult primates and other mammals suggest that we may need to revise this conception of the nervous system (Wall, 1977; Kaas *et al*., 1983; Merzenich *et al*., 1984; Wall, 1984; Byrne and Calford, 1991; Calford and Tweedale, 1991*a, b*; Pons *et al*., 1991; Florence and Kaas, 1995; Florence *et al*., 1996; Kaas and Florence, 1997). These animal experiments have shown that sensory maps can indeed change in the adult brain, and they have been largely responsible for the current resurgence of interest in the clinical phenomenon of phantom limbs (Ramachandran, 1993*b*). Taken collectively, the work on animals and human patients provides a valuable experimental opportunity to investigate not only how new connections emerge in the adult human brain, but also how information from different sensory modules, e.g. touch, proprioception and vision, interact. The study of phantom limbs also provides an opportunity to understand exactly how the brain constructs a body image, and how this image is continuously updated in response to changing sensory inputs.

The phrase 'phantom limb' was introduced by Silas Weir Mitchell (1871, 1872), who also provided their first clear clinical description. Patients with this syndrome experience an amputated extremity as still present, and in some cases also experience pain or cramping in the missing limb. The term is sometimes also used to designate a dissociation between the felt position of the limb and its actual position, e.g. as occurs during a spinal or brachial plexus block (Melzack and Bromage, 1973). It is important to note that in all these cases the patient recognizes that the sensations are not veridical, i.e. what he/she experiences is an illusion, not a delusion.

Phantom limbs were probably known since antiquity and, not surprisingly, there is an elaborate folklore surrounding them. After Lord Nelson lost his right arm during an unsuccessful attack on Santa Cruz de Tenerife, he experienced compelling phantom limb pains, including the sensation of fingers digging into his phantom palm. The emergence of these ghostly sensations led the sea lord to proclaim that his phantom was a 'direct proof of the existence of the soul' (Riddoch, 1941). If an arm can survive physical annihilation, why not the entire person?

Since the time of Mitchell's (1872) original description, there have been literally hundreds of fascinating clinical case reports of phantom limbs. However, there has been a tendency to regard the syndrome as a clinical curiosity, and very little experimental work has been done on it. Contrary to this view, we will argue that a study of phantom limbs can provide fundamental insights into the functional organization of the normal human brain and that they can serve as perceptual markers for tracking neural plasticity in the adult brain.

This article is divided into two parts. First, we will discuss the phenomenology of phantom limbs. Secondly, we will describe some new experiments that have been done on animals and on human patients, and we will attempt to link these experiments to the perceptual phenomena of phantoms. The first part will be brief since there are already a number of lucid reviews that deal specifically with the clinical manifestations (e.g. Henderson and Smyth, 1948; Cronholm, 1951; Sunderland, 1978; Melzack, 1992). The elegant work of Melzack (1992) deserves special mention here, since he has emphasized, quite correctly, that although stump neuromas can contribute to phantom sensations, they are merely part of a much more complicated picture. In particular, the occurrence of phantoms in patients born without limbs (La Croix *et al*., 1992; Ramachandran, 1993*b*; Saadah and Melzack, 1994) obviously cannot be due to neuromas, and it suggests that a central representation of the limb survives after amputation and is largely responsible for the illusion of a phantom. The nature and origin of this representation (and its neural basis) and the extent to which it can be modified by sensory experience will be the main concern of Part II.

Patients also frequently complain that the phantom is painful. The incidence of severe pain is such that it poses a major clinical problem; as many as 70% of phantoms remain painful even 25 years after loss of the limb (Sherman *et al.*, 1984). The origin of phantom pain is no less mysterious than the origin of phantoms themselves, although there is certainly no shortage of speculation (see for example, Sunderland,

1978; Postone, 1987; Katz, 1992). Since very little is known about the physiology of pain—especially its central mechanisms—we will touch on this topic only briefly in this review, despite its clinical importance (see Postone, 1987).

Part I: the phenomenology of phantom limbs

When one first encounters a patient with a phantom limb the following questions arise. We shall try to provide answers to them based partly on our own experience and partly on a number of earlier clinical case reports and review articles.

Incidence

Almost immediately after the loss of a limb, between 90 and 98% of all patients experience a vivid phantom. There are hints that the incidence may be higher following a traumatic loss, or if there has been a pre-existing painful condition in the limb, than after a planned surgical amputation of a non-painful limb.

Phantoms are seen far less often in early childhood. Perhaps in young children there has not yet been enough time for the body image to 'consolidate'. In the Simmel (1962) study, phantoms were reported to occur in 20% of child amputees <2 years old, in 25% of children between 2 and 4 years old, in 61% between 4 and 6 years old, in 75% between 6 and 8 years old and in 100% of children >8 years old.

Onset

Phantoms appear immediately in 75% of cases, as soon as the anaesthetic wears off and the patient is conscious, but their appearance may be delayed by a few days or weeks in the remaining 25% of patients (Moser, 1948). Carlen *et al.* (1978) found that among male Israeli soldiers who underwent amputations during the 1973 Yom Kippur War, 33% experienced phantom limb sensations immediately after amputation, 32% within 24 h and 34% within a few weeks. Onset is not affected by the limb amputated or the place where the amputation is made (Sunderland, 1978).

Duration

In many cases the phantom is present initially for a few days or weeks, then gradually fades from consciousness. In others, it may persist for years, even decades (30% of patients, according to Sunderland, 1978). There are case reports of phantoms which persisted for 44 years (Livingston, 1945) and 57 years (Abbatucci, 1894).

Some patients are able to recall a phantom limb at will after its disappearance with intense concentration or sometimes merely by rubbing the stump. Mitchell (1872) was able to resurrect a long-lost phantom by faradic stimulation applied to the stump of an above-knee amputee. It is perhaps findings such as this that have led to the widespread clinical opinion that neuromas are the primary cause of phantom limbs.

Body part

Although phantoms are most commonly reported after amputation of an arm or leg, they have also been reported following amputation of the breast (Scholz, 1993; Aglioti, 1994*a*, *b*), parts of the face (Hoffman, 1955; Sacks, 1992) or, sometimes, even internal viscera, e.g. one can have sensations of bowel movement and flatus after a complete removal of sigmoid colon and rectum (Ovesen *et al*., 1991), and phantom 'ulcer pains' after partial gastrectomy (Szasz, 1949). It has also been noted that phantom erections and ejaculation can occur in paraplegics as well as in patients who have had the penis removed (Sunderland, 1978), and we have personally seen patients with phantom menstrual cramps after hysterectomy, or even the acute pain of appendicitis following removal of the inflamed appendix. These findings suggest that very elaborate sensory memories can re-emerge in the phantom in spite of, or perhaps as a result of, deafferentation (see below under section headed Emergence of 'repressed memories' in phantoms). The vividness of phantoms appears to depend on both cortical magnification (hence the vividness of perception of the phantom hand) as well as the subjective vividness of that part in one's body image prior to amputation (which would explain why phantoms occur more often following a traumatic loss, or after a painful appendage has been removed, than after a planned amputation of a non-painful limb). This might imply that factors such as pre-amputation attention to a body part can modulate the subsequent vividness of the phantom—an observation that would have important clinical implications.

Posture of the phantom

Patients often comment that the phantom occupies a 'habitual' posture, e.g. partially flexed at the elbow, with the forearm pronated. Spontaneous changes in posture are also common, however. For instance, soon after the patient wakes up in the morning it may assume an unusual and sometimes uncomfortable posture, only to return to the habitual posture a few minutes later. Sometimes the phantom will also temporarily assume, or even become more permanently fixed in, an awkward and painful posture (e.g. the arm twisted back behind the head). Intriguingly, 'memories' of the limb's posture and form prior to amputation often survive in the phantom (Jackson, 1889; Katz and Melzack, 1990); there is even an anecdotal report of soldier who had a grenade explode in his hand, leaving behind a phantom hand stuck in a permanently clenched and painful posture. We have seen a patient whose arm was in a vertical wooden splint, flexed at the elbow, with the fingers hooked over the end of the splint, gripping it tightly. Two days later his arm was amputated, and when we saw him several weeks later, his phantom was in exactly the same position that his real arm had occupied, with the fingers hooked over an imaginary

splint. In addition, after a deformed limb is amputated, the deformity is often carried over into the phantom (Browder and Gallagher, 1948; Sunderland, 1978).

What happens to the phantom's perceived position if the position of the stump is altered? This question was raised and answered by Mitchell (1872), who found that the phantom followed both voluntary and involuntary movements of the stump but, surprisingly, in some patients it lay stuck in the habitual position, never leaving its place despite extreme displacements of the stump.

'Telescoping'

When the phantom does fade from consciousness, it usually does so completely, but in ~50% of cases—especially in those involving the upper limbs—the arm becomes progressively shorter until the patient is left with just the phantom hand alone, dangling from the stump (Weiss and Fishman, 1963; Jensen *et al*., 1983). The reason telescoping occurs is unclear, but it may have something to do with cortical magnification: the fact that the hand is very much over-represented in the somatosensory cortex. We have suggested elsewhere (Ramachandran and Rogers-Ramachandran, 1996) that when dealing with an amputated arm, the brain is confronted with a flood of conflicting signals, e.g. frontal areas send motor commands to the phantom that are simultaneously monitored ('reafference') in the cerebellum and parietal lobes. In a normal person, execution of these commands is verified by proprioceptive and visual feedback from the arm, but in an amputee there is no verification, hence the conflict. One way the brain deals with such sensory conflict is to simply gate or inhibit all of the signals. This is probably one reason why the phantom eventually fades, but since the hand is over-represented in the cortex its sensations may survive longer, hence the phenomenon of telescoping.

It has sometimes been suggested that telescoping occurs because the representation of the limb in the primary somatosensory maps (e.g. S1) changes progressively. This is unlikely, however, because it does not explain the frequent cases in which the patient can telescope or extend his or her phantom at will. One of our patients, for example, had his right forearm amputated below the elbow, and his hand was usually telescoped into the stump just below the elbow. However, if he attempted to shake hands or reach out to grab a cup, his phantom would extend to normal length. Indeed, in one instance, when we suddenly pulled the cup away he yelped in pain, claiming that we had wrenched the cup away from his phantom fingers, causing his arm to telescope unexpectedly.

Finally, it is worth noting that telescoping often fails to occur when there has been a pre-existing peripheral nerve lesion in the limb (e.g. due to sciatica, brachial plexus avulsion, etc.). It is as though the brain has had time to get used to the deafferentation slowly before the limb was actually removed. We have seen occasional exceptions to this rule, however. For instance, a patient we saw recently had sustained a brachial plexus avulsion in her left arm and very soon thereafter experienced a supernumerary phantom, felt very vividly as attached to her paralysed arm, but branching out from the elbow (Ramachandran and Rogers-Ramachandran, 1996). The phantom arm was initially experienced as having normal length and size but became progressively telescoped and small until only the palm and fingers remained, dangling from the elbow. The phantom remained unaffected by vision: opening or closing the eyes had no effect.

Congenital phantoms

It was originally claimed by Simmel (1962) that children with congenitally missing limbs do not experience phantoms, but it soon became apparent that this was not always true (Weinstein *et al*., 1964; Poeck, 1969; La Croix *et al*., 1992). Weinstein *et al*. (1964) studied 13 congenital aplasics with phantom limbs, seven of whom were able to move the phantom voluntarily, and four of whom experienced 'telescoped' phantoms. We recently reported the presence of phantom arms in a patient (D.B.), a 20-year-old woman whose arms had both been missing from birth. All she had on each side were the upper ends of the humerus—there were no hand bones, and no radius or ulna. However, she claimed to experience very vivid phantom limbs that often gesticulated during conversation (Ramachandran, 1993*b*). 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 phantom hand did not fit into the prosthesis like a hand in a glove 'the way it was supposed to.') Secondly, her phantom arms did not feel as though 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. We suggest that these vivid sensations arise from the monitoring of reafference signals derived from the motor commands sent to the phantom during gesticulation. What is remarkable, however, is that the neural circuitry generating these gesticulatory movements is 'hardwired' and has actually survived intact for 20 years in the absence of any direct visual or kinaesthetic reinforcement from her own limbs (although watching other people's limbs might have played a role).

Factors enhancing or attenuating the phantom

Preamputation history

Phantoms are more vivid, and persist longer, after traumatic limb loss, or following amputation for a pre-existing painful limb pathology, than after a planned surgical amputation of a non-painful limb. This may be due to the greater attention paid to the mutilated or painful limb before it is lost, or it may represent the survival of pre-amputation 'pain memories'

(Katz and Melzack, 1990) in the phantom. The more prolonged persistence of painful phantoms compared with painless ones may imply that the two phenomena (phantom pains and neutral phantom sensations, i.e. the non-painful sensory 'image' of the limb) are mutually reinforcing. Absence of the one would reduce the intensity of the other (more on this later).

Condition of stump

Stump pathology (e.g. scarring and neuromas) influences both the vividness and duration of the phantom. Mitchell (1872) noted that a phantom fades more rapidly if the stump heals quickly and well, but this has been challenged by Browder and Gallagher (1948). It is, however, a common observation that local anaesthetic and pressure cuff ischaemia can cause the phantom to fade temporarily, whereas hitting the stump can make the phantom more vivid or sometimes even resurrect an occult phantom.

Mechanical or electrical stimulation

It has been claimed that mechanical or electrical stimulation of the stump has no effect on phantom sensations (Livingston, 1945; Henderson and Smythe, 1948), but others have been able to revive a long-lost phantom by such procedures (Souques and Poisot, 1905).

Central effects

There is some evidence that rest and distraction can reduce the severity of phantom pain, whereas emotional shock can aggravate it (Sherman *et al.*, 1984; Jensen *et al.*, 1985). It is also common clinical experience that voluntary movement, intense concentration, contraction of the stump muscles and so on, can enhance the vividness of the phantom. Interestingly, the incidence of phantom limb pain is not affected by the reason for the surgery (Jensen *et al.*, 1985), the location of the amputation (Sherman and Sherman, 1983) or the sex, age, marital or socioeconomic status of the patient (Jensen *et al.*, 1985; Parkes, 1973; Morgenstern, 1970). It is comforting to know that there are at least some variables that have no influence on phantom limbs.

Movement of the phantom

Many patients with phantom limbs claim they can generate voluntary movements in their phantom. They experience sensations of reaching out to grab an object, making a fist or moving their fingers individually. Involuntary or quasi-voluntary movement is also very common; the phantom may wave good-bye, fend off a blow, break a fall or reach for the telephone. Completely involuntary movements, e.g. the hand suddenly moving to occupy a new position or suddenly developing a clenching spasm of the fingers, are also very common.

Emergence of 'repressed memories' in phantoms

Another fascinating but poorly understood aspect of phantom limbs concerns not only the continued existence of 'memories' in the phantom—of sensations that existed in the arm just prior to the amputation—but also the re-emergence of long-lost memories pertaining to that arm. For instance, it is well known that patients sometimes continue to feel a wedding ring or a watch band on the phantom. Also, in the first few weeks after arm amputation many patients report that they experience excruciating clenching spasms in the phantom hand and that these spasms are often accompanied by the unmistakable sensation of nails digging into the palm. It usually takes several minutes, or sometimes even hours, to voluntarily unclench the phantom but when unclenching eventually does take place, the 'nails digging in' sensation vanishes as well. The reason for this is obscure, but one possibility is that when motor commands are sent from the premotor and motor cortex to clench the hand, they are normally damped by error feedback from proprioception. If the limb is missing, however, such damping is not possible, so that the motor output is amplified even further, and this overflow or 'sense of effort' itself may be experienced as pain. But why would the 'nails digging in' sensation also be associated with the spasm? This is even more difficult to explain, but one might suppose that the motor commands to unclench the hand and the sensation of the nails digging in are linked in the brain, even in normal individuals, by a Hebbian learning mechanism. Furthermore, since the motor output is now amplified, it is conceivable that the associated memory of nails digging in is also correspondingly amplified, giving rise to the excruciating pain. The observation that eliminating the spasms (e.g. with intense, prolonged voluntary effort) also abolishes the digging in sensation is consistent with this view. What we are dealing with here, then, might be a primitive form of sensory learning that could conceivably provide a new way of experimentally approaching more complex forms of memory and learning in the adult brain.

The reactivation of pre-amputation memories in the phantom has been noted before (Katz and Melzack, 1990) but there has been very little systematic work done on it and the significance of the findings for understanding normal memory appears to have gone largely unrecognized. For example, one of our patients reported that, before amputation, the arthritic joint pains in her fingers would often flare up when the weather was damp and cold. Remarkably, whenever the air became humid the same pains would recur in her phantom fingers. Also, when her hand went into a clenching spasm in the evening, the thumb was usually abducted and hyper-extended ('sticking out') but on those occasions when it was flexed into the palm, the spasm was accompanied by the distinct feeling of her thumbnail digging into the pad of the fifth digit. The curious implication of this observation is that even fleeting sensory associations may be permanently recorded in the brain; these memory traces may be ordinarily

'repressed', but may become unmasked by the deafferentation. Also, surprisingly, the traces may be 'gated' by the felt position of the phantom thumb, or even be retrieved on the basis of an unconscious inference: 'If my thumb is flexed it must touch my fifth digit'.

Part II: experimental findings

Plasticity in the somatosensory system

There were some early neurosurgical reports of changing cortical and thalamic representations in the human brain following deafferentation (Talairach *et al*., 1960; Obrador and Dierssen, 1966), but the clearest experimental demonstration of plasticity in the adult CNS was provided by the pioneering work of Patrick Wall and his co-workers (Wall, 1977). These authors recorded from single neurons in dorsal column nuclei and showed striking changes in receptive field size shortly after partial denervation. They suggested that the changes might arise as a consequence of unmasking ordinarily silent synapses. Similar effects have been observed recently in the visual system of primates (Pettet and Gilbert, 1992; De Weerd *et al.*, 1995) and may help explain the perceptual 'filling in' of visual scotomas (Ramachandran and Gregory, 1991; Ramachandran, 1992; Ramachandran, 1993*a*, *c*; Safran and Landis, 1996).

It is known that a complete somatotopic map of the body surface exists in the somatosensory cortex of primates (Kaas *et al*., 1979; Merzenich *et al*., 1984), including humans (see Fig. 1) (Penfield and Rasmussen, 1950). In a series of ingenious experiments, Merzenich *et al*. (1984) amputated the middle finger of adult monkeys and found that within two months the area of cortex corresponding to this digit started to respond to touch stimuli delivered to the adjacent digits, i.e. this area is 'taken over' by sensory input from adjacent digits.

Merzenich and his co-workers (1984) also made two other important observations. (i) If a monkey uses one finger excessively (e.g. if that finger is placed on a revolving corrugated drum) for 90 min each day, after 3 months the area of cortex corresponding to that finger expands, but it is at the expense of adjacent fingers, i.e. there is an increase in the cortical magnification factor for the stimulated finger. Also, the receptive fields in the expanded area were found to have shrunk so that they were unusually small. Hence these effects are unlikely to be 'epiphenomenal'; they must be functionally important. (ii) If more than one finger was amputated there was no 'take over' beyond ~1 mm of cortex. Merzenich *et al*. (1984) concluded from this that the expansion is probably mediated by arborizations of thalamocortical axons, which typically do not extend beyond 1 mm. This 1-mm distance was often cited as the fixed upper limit of reorganization of sensory pathways in adult animals (Calford, 1991). A remarkable experiment performed by Pons *et al*. (1991), 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 is 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 over a centimeter in width, we may conclude that sensory reorganization can occur over at least this distance: an order of magnitude greater than the original 1-mm distance. As a matter of historical interest, it is worth noting that the earliest demonstration of such long-range plasticity in the adult cortex was that of Graham Brown and Sherrington (1912), who showed that repeated stimulation of the face region of the motor cortex in intact chimpanzees results in an immediate expansion of this region to encompass the territory which originally represented the hand.

These exciting results from animals raise two new questions. First, can a similar reorganization of the Penfield map be observed in the human somatosensory cortex following deafferentation or amputation of an arm? Secondly, if such reorganization occurred, what would the person actually feel if his face was touched? Since the message now (presumably) goes to the original hand area of the cortex, would he also experience touch sensation in this missing (phantom) hand? We will now attempt to answer these two questions.

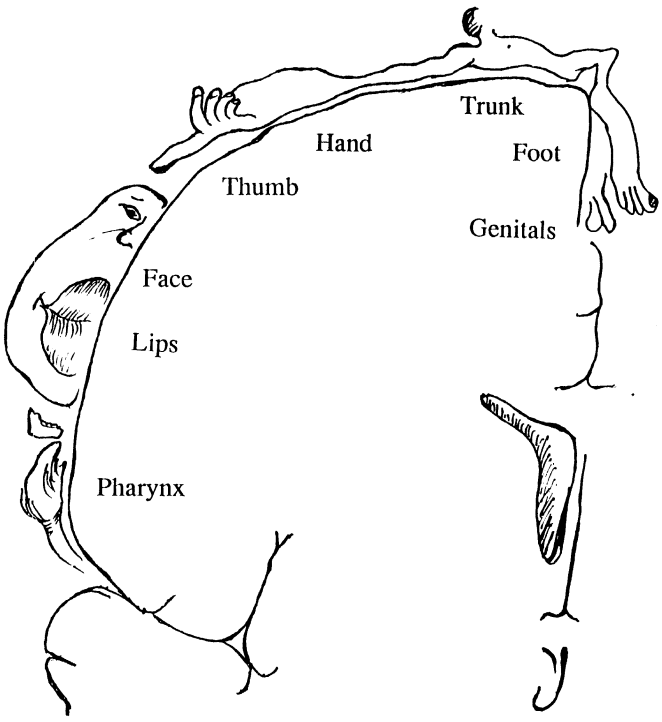


Fig. 1 The Penfield 'homunculus'. Notice that the hand area is bordered below by the face, and above by the upper arm and shoulder: the two regions where reference fields are usually found in arm amputees.

Magnetoencephalogram (MEG) correlates of cortical reorganization

Recent advances in MEG have been made possible with the advent of large array magnetometers and with the understanding of the physics and mathematics of the measurements of cortical electrical activity (Mosher *et al*., 1992). These advances have allowed for fine localizations (>3 mm) of processing (Ilmoniemi *et al*., 1984; Okada *et al*., 1984; Baumgartner *et al*., 1991; Sereno *et al*., 1995). The work of Gallen *et al*. (1993) and Yang *et al*. (1993) is especially relevant, since they have obtained very detailed somatosensory (S1) 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.

We realized that MEG studies could also be useful in determining whether remapping effects of the kind reported in monkeys, would also be seen in human patients following amputation. In collaboration with T. Yang and C. Gallen, one of us (V.S.R.) began such a study in 1992 and found that such reorganization does indeed occur. In all four upper limb amputees whom we studied we found that the sensory input from two regions, i.e. the face and from the upper arm, had invaded the hand territory in S1 (see Fig. 2; recall that in the Penfield map the cortical region corresponding to the hand is flanked on one side by the face and on the other side by the upper arm, chest and shoulder). Thus, it looked as though the famous Penfield map in S1, that every medical student and psychology undergraduate learns about, can be reorganized over a distance of at least 2 or 3 cm even in the adult brain (Ramachandran, 1993*b*; Yang *et al*., 1994*a*, *b*). To our knowledge this is the first demonstration that such large-scale reorganization of topography over several centimeters can occur in the adult human brain.

Perceptual correlates of massive cortical reorganization

From the MEG studies described above, it was clear that remapping occurs in the human brain, just as it does in monkeys. The sensory input from the face now gets sent to two different cortical areas: the original 'face area', and the area that previously only received information from the arm. We wondered what the perceptual correlates of this reorganization might be; for instance, would a sensory stimulus applied to the face be perceptually mislocalized, i.e. would it appear to come from the hand as well as the face? To explore this we had initially studied localization of sensations in two patients (V.Q. and W.K.) after upper limb amputation (Ramachandran *et al*., 1992*a*) and more recently in 16 additional patients. Here we will briefly describe the observations we made on two of these patients (V.Q. and D.S.).

Patient V.Q.

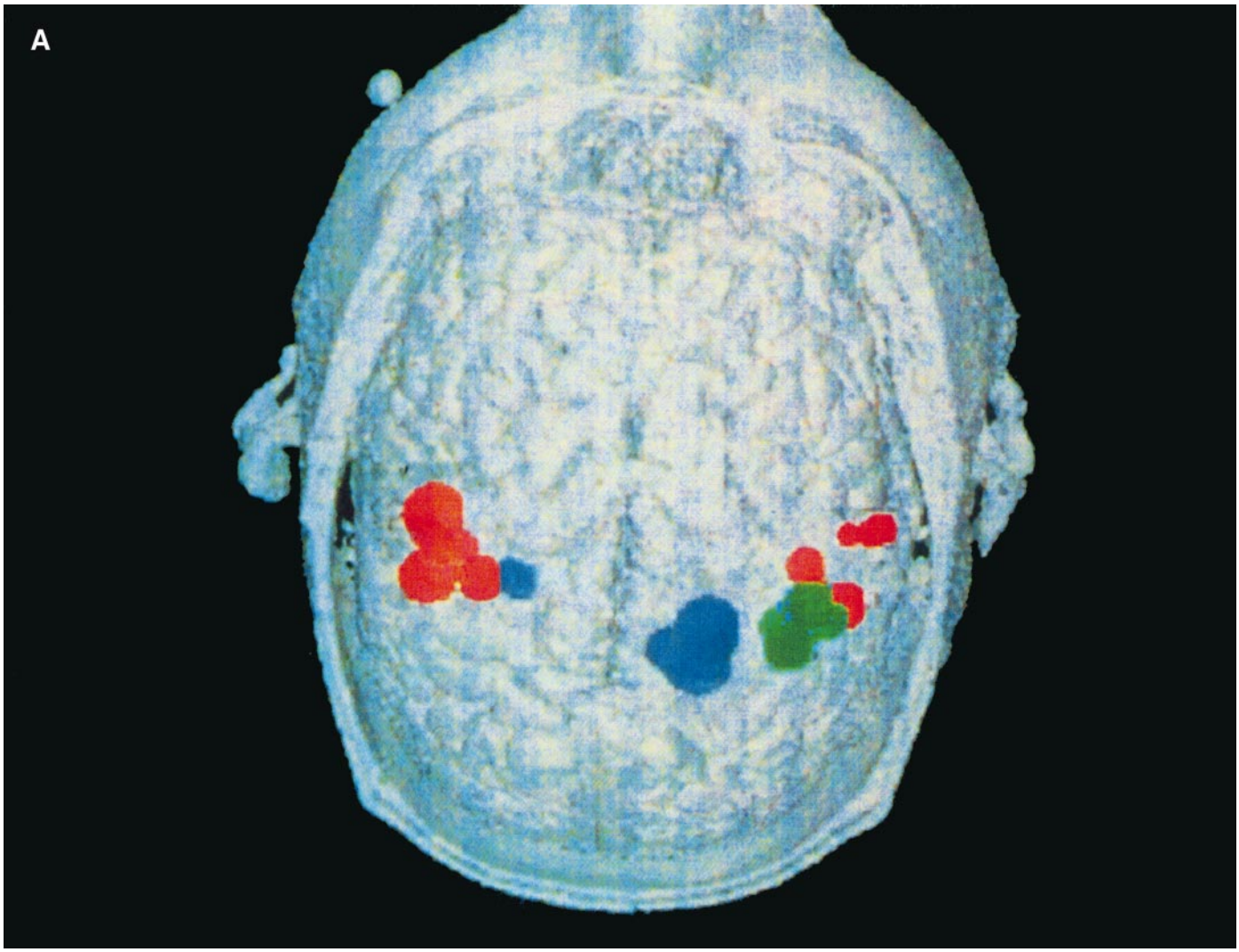
Patient V.Q. was an intelligent, alert 17-year-old who was involved in a car accident. Immediately following the accident, his left arm was amputated 6 cm above the elbow ~4 weeks prior to our testing him. He had also sustained minor head injuries from the accident (including a concussion) but at the time of testing he was mentally lucid, intelligent and fluent in conversation (at least by American standards). He experienced a vivid phantom hand that was 'telescoped', so that it felt as if it were attached just a few centimeters below his stump. We studied localization of touch (and light pressure) in this patient using a cotton swab that was brushed twice in rapid succession at various randomly selected points on his skin surface. His eyes were shut during the entire procedure and he was simply asked to describe any sensations that he felt and to report the perceived location of these sensations. 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. They appeared to be clustered on the lower left side of the face (i.e. ipsilateral to amputation) and 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 upper lip to the index finger and from the chin to the little finger). Typically, the patient reported that he simultaneously felt the cotton swab touching his face and a tingling sensation in an individual digit. By repeatedly brushing the swab 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. 3). 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.

A second cluster of points that evoked referred sensations was found ~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 little finger laterally, as if to mimic the pronated position of the phantom hand. Stimulating points halfway between these two areas elicited referred sensations in the index or ring fingers.

We repeated the whole procedure again after 1 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 1-week period that separated our two testing sessions (Ramachandran *et al*., 1992*a*, *b*).

Patient D.S.

D.S. had a brachial plexus avulsion following a motorcycle accident, and his arm was amputated 1 year after the accident. He experienced a vivid phantom that felt 'paralysed', as if to mimic the paralysis that preceded the amputation. We mapped the distribution of reference fields in this patient extensively on three separate occasions, the first two separated by 24 h and the third after 6 months. The arrangement of reference fields is shown in Fig. 4A. Notice the topographic



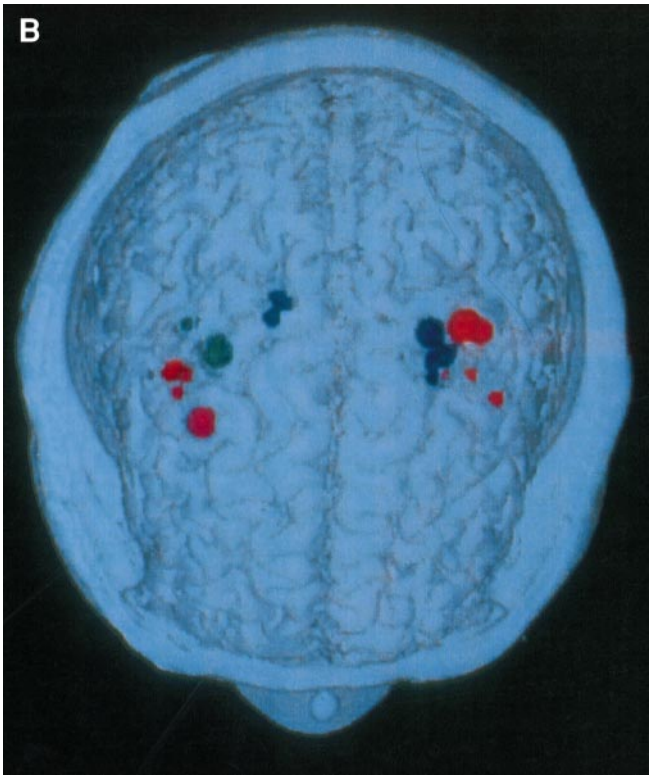


Fig. 2 (**A**) Top view of a combined MEG and 3D surface-rendered MRI of an adult whose right arm was amputated below the elbow at the age of 11 years. The right hemisphere is normal and shows the primary somatosensory face area (red) lateral, anterior and inferior to the hand localizations (green), which are in turn lateral, anterior, and inferior to the upper arm region. The left hemisphere shows the face (red) and upper arm (blue) regions extending into the expected hand territory, reflecting reorganization of the sensory map following amputation. (**B**) Combined MEG and 3D surface-rendered MRI of patient F.A. The unaffected right hemisphere shows three spots corresponding to the left face (red), hand (green) and upper arm region (blue). This patient's right arm was amputated below the elbow 8 years prior to these recordings (for details see Ramachandran, 1993*b*; Yang *et al.*, 1993, 1994*b*).

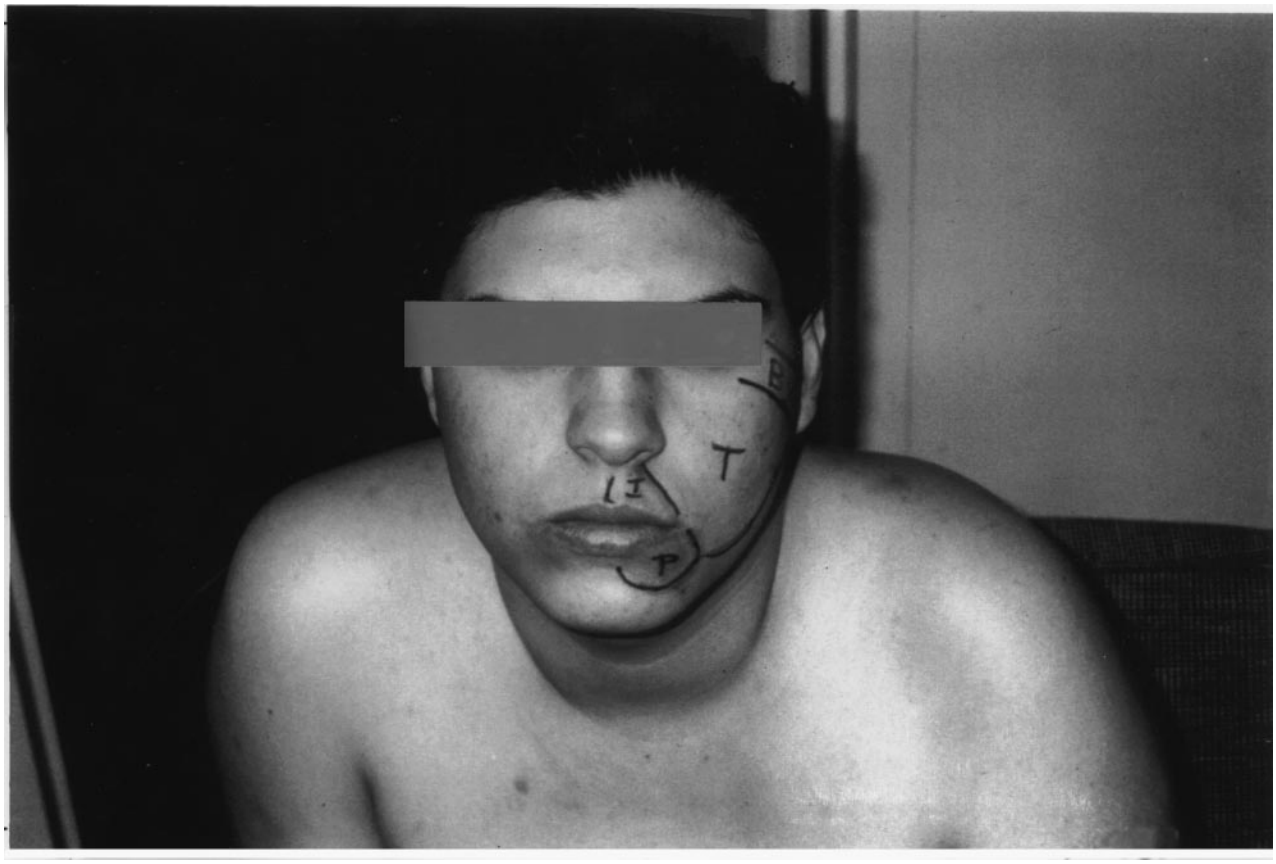


Fig. 3 Regions on the left side of patient V.Q. which elicited precisely localized referred sensations in the phantom digits 4 weeks after amputation. The region labelled 't' always evoked sensations in the phantom thumb, 'P' from the pinkie, 'I' from the index finger, and 'B' from the ball of the thumb.

arrangement of digits on the face (e.g. digits one to four are neatly laid out on the zygoma). The thumb receptive field was especially large, as in some of our other patients.

The map remained stable during the first two testing sessions, but when we saw the patient again after 6 months, there had been some small but noticeable changes (Fig. 4B). In particular, the thumb region appeared to have expanded to stretch across the entire mandible, with the base of the thumb near the ramus and the tip near the symphysis menti. It was unclear why the map had changed in this manner, but it may have occurred as a result of changing patterns of sensory input (and spontaneous activity) from the face and from the stump (see also Halligan *et al.*, 1994). It might be interesting to test this hypothesis by actually stimulating a specific region of the map (e.g. the index finger reference field) for a few days, using a TENS (transcutaneous electrical nerve stimulator) unit or a vibrator, to see whether this increases the size of that reference field. A second map was found in the region of the deltoid muscle and this too was topographically organized. Unlike the face map, however, it remained stable across all three testing sessions (Fig. 4C).

An especially convincing way of demonstrating topography in patient D.S. was as follows. When the cotton swab was moved continuously from the angle of the mandible to the symphysis menti, the referred sensation also felt as if 'it was moving from the ball of the thumb to the tip in an arc-like motion'. This observation was replicated several times. Also, if a short excursion was made on the jaw, the apparent excursion on the hand was correspondingly short. A similar effect could also be evoked by moving the cotton swab across the digit's reference fields on the deltoid muscle, and in this case reversing the direction of the cotton swab also reversed the direction of motion on the phantom hand.

Finally, it was our general impression that in patient D.S., as in other patients, the topography was usually much more precise in the map proximal to the stump than on the face. The reason for this difference is not clear. One possibility is that the frequent co-activation of spatially continuous points may serve to 'stabilize' topography near the stump or on the fingers, whereas the face is rarely involved in such co-activation).

Modality-specific effects

The neural pathways from the skin surface to the brain that mediate the sensations of warmth and cold are quite different

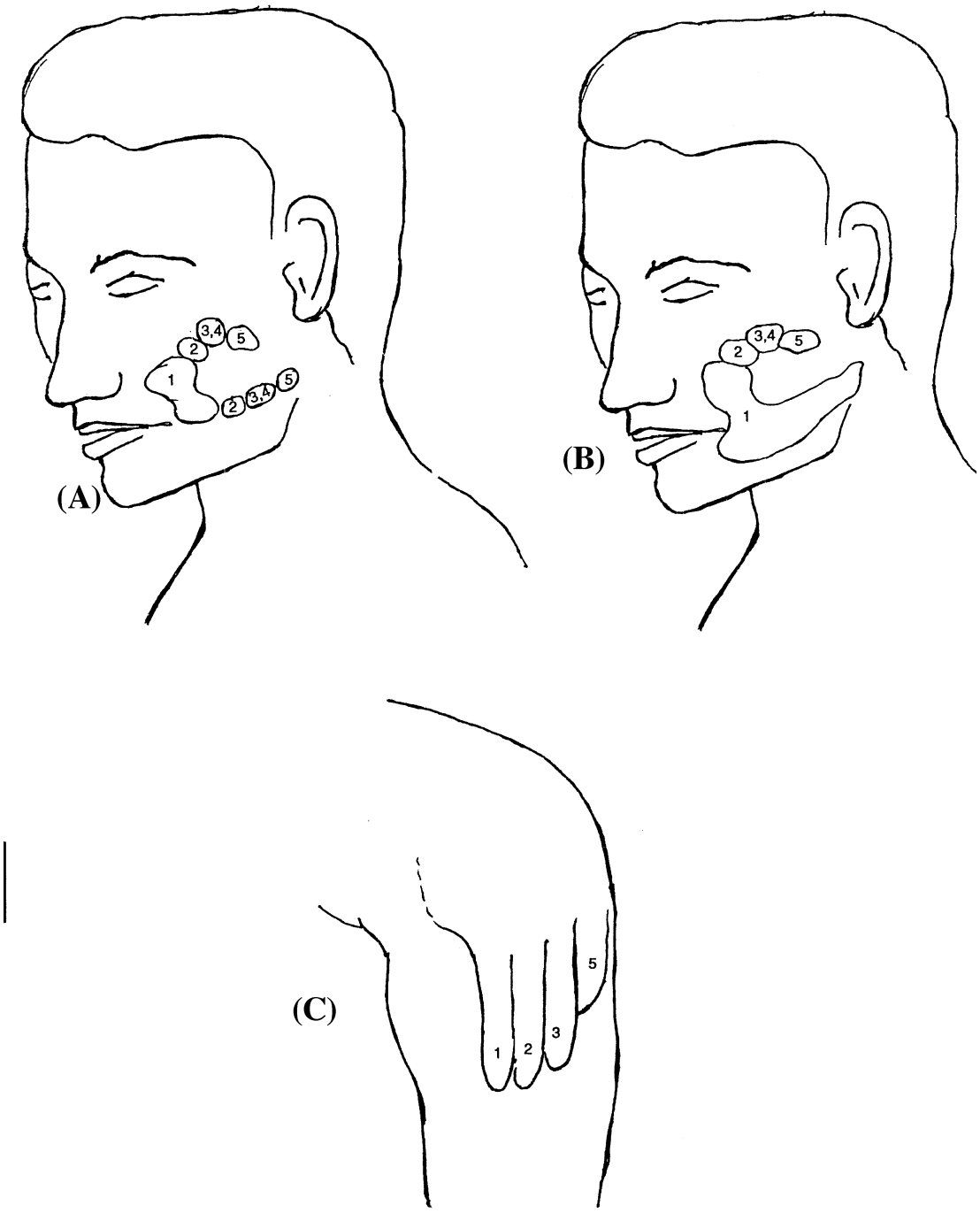


Fig. 4 (**A**) Distribution of reference fields in patient D.S. Notice the prominent representation of the thumb (1), which we have seen in several patients, and the roughly topographic arrangement of digits 2, 3, 4 and 5 on the face. This pattern was nearly identical 24 h later. (**B**) Distribution after 6 months; the representations of some of the digits had changed noticeably. This may occur as a result of sensory input and spontaneous activity from the face (and stump) continuously remodelling neural connections in S1. If this interpretation is correct, then phantom limbs might provide a valuable preparation for studying the manner in which sensory maps emerge and change in the adult nervous system. (**C**) The second map in the region of the deltoid muscle. Patient D.S.'s arm always felt completely extended and paralysed; it was never telescoped into the stump.

from those that carry information about touch (Landgren, 1960; Boyd and Davey, 1968; Kreisman and Zimmerman, 1971). We wondered, therefore, whether the remapping effects reported by Pons *et al*. (1991) occur separately in each of these pathways or only in the touch pathways. To find out, we tried placing a drop of water on V.Q.'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! Finally, in some of these patients, a vibrator placed on the jaw or cheek was felt as vibration of the phantom hand. We have now seen these modality specific effects in five patients, four patients after upper limb amputation and one after an avulsion of the brachial plexus.

These results are important, for they imply that even when the new input is 'heterotypic', i.e. derived from a foreign source, it is still modality-specific and preserves some semblance of topography. The manner in which such new inputs maintain their modality specificity even when innervating a 'foreign' territory remains a challenging question for future research.

How does the point-to-point referral of temperature sensations compare with that of touch? To explore this we tried applying a drop of warm (or cold) water on different parts of the face and found that the heat or cold was usually referred to individual fingers so that there was a sort of crude map of referred temperature that was roughly superimposed on the touch map (e.g. touching the thumb reference field on the face with warm water evoked warmth in the thumb alone, whereas touching the little finger's region of the map evoked a warm sensation confined to the little finger). To ensure that these effects were not simply due to simultaneous activation of touch receptors, we also tried touching the thumb reference field on the face with warm water while simultaneously applying tepid water to the little finger's region of the map. The patient reported that he could feel the touch in both digits, as expected, but that the warmth was felt only in the thumb. We conclude that there are independent modality-specific reference fields for touch, heat and cold on the face and that these reference fields are usually in approximate spatial registration. If we accept the conventional view that perceived location and modality are determined entirely by 'place coding', i.e. by which neuron in a particular sensory map is activated, then it becomes difficult to see how this registration of referred sensations is achieved.

The occurrence of referred sensations in the phantom limb is in itself not new. It has been noticed by many previous researchers (Mitchell, 1872) that stimulating points on the stump often elicits sensations from missing fingers. William James (1887) once wrote 'A breeze on the stump is felt as a breeze on the phantom' (see also an important monograph by Cronholm, 1951). Unfortunately, neither Penfield's map, nor the results of Pons *et al*. (1991) were available at the time, and these early observations were therefore open to several interpretations. For example, the severed nerves in the stump would be expected to reinnervate the stump, which might explain why sensations from this region are referred to the fingers. Even when points remote from the stump elicited referred sensations, the effect is often attributed to 'diffuse' connections in the neuromatrix (Melzack, 1990). What was novel about our observations is that we discovered an actual topographically organized map on the face and that the referral from face to phantom was modality-specific. Indeed, even relatively complex sensations such as 'trickling' were mislocalized from the face to the phantom hand. Obviously, this cannot be attributed to accidental stimulation of nerve endings on the stump, or to 'diffuse' connections. Our observations imply, instead, that highly precise and organized new connections can be formed in the adult brain with extreme rapidity.

Furthermore, we have tried to relate our findings in a systematic way to physiological results, especially the 'remapping' experiments of Pons *et al*. (1991). We have suggested, for example, that the reason we often see two clusters of points—one on the lower face region and a second set near or around the amputation line—is because the map of the hand on the sensory homunculus in the cortex and thalamus is flanked on one side by the face and the other side by the upper arm, shoulder and axilla (Fig. 1). 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 of points (Fig. 2). This principle allows one to dissociate proximity of points on the body surface from proximity of points in brain maps, an idea that we refer to as the remapping hypothesis of referred sensations. If the hypothesis is correct then one would also expect to see referral from the genitals to the foot after leg amputation, since these two body parts are adjacent on the Penfield map, but one would rarely see referral from the face to a phantom foot or from the genitals to a phantom arm (as appears to be generally true; see Ramachandran, 1993*b*; Aglioti *et al*., 1994*a*, *b*).

With regard to our experimental results themselves, what is novel can be summarized as follows.

(i) The extreme rapidity of the observed changes. Patient V.Q. was tested 4 weeks after amputation.

(ii) The strict one-to-one correspondence between individual points on the lower face and points on the phantom limb.

(iii) The non-random distribution of points that evoke referred sensations. In arm amputees the points appeared clustered on the lower ipsilateral face and near or around the line of amputation. This correlates well with the physiological remapping effect described by Pons *et al*. (1991). Recall, especially, that in the Penfield homunculus the hand area is flanked on one side by the face and on the other side by the areas close to the amputation line (shoulder, upper arm). After brachial plexus avulsion, however, the second set tends to be near the chest or scapula, as one might predict (Ramachandran *et al*., 1992*a*; Kew *et al*., 1997)

(iv) The presence of well-defined reference fields with sharp, stable margins.

(v) The disproportionate representation of the hand in general, and the digits in particular, especially the thumb. This may be a consequence of cortical magnification.

(vi) The fact that very specific sensations such as warmth,

'pinpricks', 'trickles' or 'paintbrush' could also be mislocalized (Ramachandran *et al.*, 1992*b*; Borsook *et al.*, 1997). This suggests that referred sensations can be modality-specific.

(vii) The possible existence of topography. The very fact that adjacent points on the normal skin surface (e.g. the cluster of points on the lower face or near the amputation line) map onto adjacent points in the phantom limb (i.e. hand, digits, etc.) is in itself suggestive of topography, of course. Also in patient D.S., when we moved the cotton swab over the jaw he experienced an equivalent movement of referred sensation on his phantom arm.

(viii) The maps of referred sensation were usually stable across testing sessions separated by a few hours or days, but significant changes were seen if testing was done after several months (Ramachandran, 1995).

In addition to these long-term changes, immediate changes in topography were also observed occasionally. In one patient (F.A.), the map proximal to the stump actually shifted medially by 1 cm if the patient voluntarily pronated his phantom hand (Ramachandran, 1993*b*), and then returned to its original position as soon as he supinated it. Hence it would appear that either the cortical map itself, or its subsequent 'read out', can be modulated, in some instances, by central reafference signals derived from motor commands to the phantom. This effect was observed on a single amputee and requires confirmation on additional patients.

Mechanisms of reorganization

What is the actual neural mechanism underlying the perceptual remapping that we have observed? In trying to answer this question we have to bear three facts in mind. (i) The extent of thalamocortical axon arborizations can be quite large—up to 1 cm or more (Jones, 1982). (ii) The distance between the cortical maps for the hand and face is ~1–2 cm in monkeys and even greater in humans. (iii) The changes we observed are quite rapid, whereas Pons *et al*. (1991) recorded from their monkeys nearly 12 years after deafferentation. Taken collectively, these facts suggest that the effects we have shown may arise from the unmasking of 'occult' synapses (i.e. previously subthreshold synaptic activity) rather than actual anatomical changes such as 'sprouting'—a conclusion that would be consistent with the physiological observations of Wall (1977) and Calford and Tweedale (1991*b*). The effect observed by Wall (1977) is presumably based on changes in the equilibrium of an excitatory–inhibitory network brought about by deafferentation or amputation. In addition, reorganization across a larger distance may involve actual axonal growth and reinnervation (Florence and Kaas, 1995). It should be borne in mind, however, that even though the cortical maps had been reorganized, the actual synaptic changes could have occurred anywhere along the somatosensory pathway en route, e.g. in the thalamus or the dorsal column nuclei (e.g. see Florence and Kaas, 1995).

One of the mechanisms of reorganization may be a type of long-term Hebbian potentiation of synapses mediated by *N*-methyl-D-aspartate (NMDA) receptors which detect simultaneous activation of two inputs and then strengthen the connection between the two (Bear *et al.*, 1987; Cramer and Sur, 1995; Kaas and Florence, 1996). Also, it is known that reductions in activity based on sensory deprivation will reduce amounts of the inhibitory neurotransmitter GABA (γ-aminobutyric acid) (Jones, 1990; Garraghty *et al.*, 1991; Rausell *et al.*, 1992), which in turn may allow previously weak synapses to become disinhibited. It has been suggested that these normally suppressed inputs are intracortical, and that they originate from long-range horizontal collaterals of pyramidal neurons located in cortex adjacent to the deafferented area (DeFelipe *et al*., 1986; Jones, 1993; Kew *et al.*, 1997). Consistent with this idea, Jones (1993) has shown that such horizontal collaterals can extend for >6 cm. Conversely, high levels of GABA brought about by persistent intense sensory input can cause weak synapses to become even more strongly inhibited (Welker *et al.*, 1989; Kaas and Florence, 1996).

Whatever the ultimate interpretation of our findings, however, they present a challenge to one of the basic concepts of neuroscience: the stability of connections in the adult brain. The extreme rapidity of the changes that we have observed suggests, instead, that the adult mammalian brain has the latent capacity for a much more rapid functional reorganization and over a much greater spatial extent than previously suspected, a capacity that could conceivably be exploited for therapeutic purposes.

Inter-subject variability

How general are the findings we have reported here? Of the 18 patients we have seen so far, the map on the face was seen in eight. The second cluster of points near the line of amputation, on the other hand, was seen in 12 patients (including the first eight). Six patients showed no referral from any region.

Why do some patients not have a cluster of points on the face? There are at least seven possibilities, that are not mutually exclusive. First, our hypothesis may be wrong; referred sensations may have nothing to do with reorganized sensory pathways in the brain. Secondly, remapping may occur not only in S1 (area 3b) but at multiple stages in the somatosensory pathways, e.g. in the dorsal column nuclei, in the thalamus or in S2, and the disposition of body parts may be different in each area. For instance, in S2 the foot representation is actually close to the hand; consequently one might expect, at least on rare occasions, to see referral from the foot to the ipsilateral phantom hand! Thirdly, some patients have persistent excruciating pain in the phantom and it is possible that the pain overwhelms or 'masks' the more neutral referred sensations. [Consistent with this Borsook *et al*. (1997) have found that some patients who do not initially refer sensations from the face to a phantom that

is painful will do so immediately following intravenous administration of analgesics to relieve the pain.] Fourthly, the brain maps themselves might vary slightly from patient to patient, and this, in turn, might constrain the degree of remapping. Fifthly, some patients may eventually learn to ignore the referred sensations from the face by using visual feedback. Sixthly, even without visual feedback, the plasticity exhibited by the afferent pathways may be propagated further along the pathways to perception, so that the input gets correctly interpreted as originating from the face alone (i.e. the peripheral organ might 'specify' the central connections as suggested by Weiss, 1939). Finally, if the patient uses the stump constantly, the skin corresponding to it may regain the territory that was initially lost to the face. This might explain why (in our experience) the map on the face is seen more often in brachial plexus avulsion patients than in amputees. More extensive testing of a large number of patients is needed before we can distinguish between these possibilities. It is worth noting, in this context, that at least one patient (F.A.) who showed clear evidence of remapping as revealed by MEG (Yang *et al*., 1994*a*) did not refer sensation for his face to his hand, which rules out at least a subset of these seven hypotheses and implies that remapping in the primary sensory areas is not sufficient to guarantee the occurrence of referred sensations, although it may be necessary.

Non-specific responses

In some patients, soon after amputation, intense stimuli applied to other body parts, e.g. the contralateral torso or neck, will also elicit paraesthesiae in the phantom, but usually in a diffuse and unreliable manner. The mechanisms underlying these non-specific effects are obscure but they may have more in common with diffuse 'arousal' than with the remapping that we have considered so far (e.g. the barrage of spontaneous activity from neuromas may normally be gated, but non-specific arousal might make the cortex more sensitive to such impulses). Some support for the arousal interpretation comes from the recent physiological work of Dykes *et al.* (1995), who found two classes of novel responses in the deafferentated hand area of the cortex (S1) of cats. First, there were cells with clearly defined receptive fields of the kind observed by Pons *et al.* (1991) in monkeys. A second class of responses, however, could be obtained by touching almost any part of the animal, i.e. there were no clearly-defined receptive fields. Dykes *et al.* (1995) suggest that these responses are not 'truly sensory in character' and that they may be mediated by brainstem arousal mechanisms. This second category of response usually appeared very soon after deafferentation and may account for some of the non-specific referred sensations that we observed in our patients. (The prediction would be that such sensations should also emerge earlier after amputation than specific, organized reference fields.)

Extinction of referred sensations

A curious fact about the referral of sensations from the face to the phantom is that the patients themselves often fail to notice it. Indeed, even in the clinic, if the patient is asked to touch or stroke her own face, she is often surprised to find that the referred sensations are not felt in the phantom. It is unclear whether this is because the movements are self-initiated so that the tactile sensations are perfectly correlated with the patient's motor commands, or whether the simultaneous stimulation of the contralateral hand somehow causes extinction of the sensations referred from the face.

We were able to study this carefully in only one patient, a 16-year-old girl who had sustained a brachial plexus avulsion and experienced a supernumerary phantom branching off from her paralysed elbow. She had a distinct map on the face, as elicited by the examiner, but felt no referral when she herself touched her face using her normal (right) hand. However, if the examiner touched or stroked her face and the normal hand simultaneously, there was a complete extinction of the referred sensations. Such extinction did not occur if other body parts (e.g. the contralateral shoulder, contralateral chest and contralateral thigh) were touched simultaneously with the face. The effect is probably based on topographically organized inter-hemispheric inhibition mediated by commissural pathways, and it reminded us of the somatosensory extinction (Critchley, 1953) that is commonly seen in parietal lobe syndrome (and the relief of hemianaesthesia during self-directed stimulation, see Weiskrantz and Zhang, 1987). The patient also noticed that the phantom itself became less vivid if her ipsilateral face and contralateral hand were simultaneously stimulated, suggesting that the procedure might have therapeutic potential, e.g. one could try applying TENS units to both of these sites simultaneously to provide relief from phantom pain (Srinivasan et al, 1998).

Related studies by other groups

Our findings on perceptual referral of sensations from the face to the phantom and the accompanying MEG changes were first reported in 1992 (Ramachandran *et al*., 1992*a, b*; Ramachandran, 1993*b*; Yang *et al*., 1994*a*). Although initially considered surprising, during the last 3 years there have been several follow-up studies by other groups that have confirmed and significantly extended these findings. We will now briefly describe some of these studies.

Halligan *et al*. (1993*b*) studied a patient whose arm had been amputated at the shoulder level. They were able to replicate our basic observation, the occurrence of a 'map' on the ipsilateral lower face. Curiously, they found that although the map was nearly complete and was in many ways quite similar to the one we had observed, it lacked an index finger and thumb. Careful questioning of the patient revealed that she had completely lost sensations in her thumb and index finger for >1 year preceding the amputation (she had

suffered from carpal tunnel syndrome). The authors made the ingenious suggestion that this highly specific sensory loss had been 'carried over' into her phantom!

Our own observations, as well as those of Halligan *et al*. (1993*b*) do not resolve the issue of whether what we call 'remapping' arises from the sprouting of new axon terminals that invade the hand territory or from 'unmasking' or disinhibition of previously silent inputs. Since we had seen the face-to-hand referral of sensations 4 weeks after amputation in one patient, we originally suggested that reactivation of previously silent pathways may be involved (Ramachandran *et al*., 1992*a*, *b*), but we had no direct proof.

A recent discovery made by Borsook *et al*. (1997) at the Massachusetts General Hospital suggests that such unmasking may indeed be taking place. They examined two patients (one after amputation and one after brachial plexus avulsion) just 24 h after the deafferentation and found that touch sensations from the lower face were referred to the hand and that the referral was topographically organized. Even more remarkably, if the tactile stimuli were delivered with a paintbrush, finger or a pin, the particular sensation (e.g. 'brushing', 'rubbing' or 'pin') was also carried over into the phantom with exquisite precision. If these preliminary results are confirmed, they would provide compelling evidence that activation of dormant connections can indeed occur at least in some patients. Such rapid activation of latent horizontal connections has recently also been observed in area 17 (striate cortex; Gilbert and Wiesel, 1992) and other extrastriate visual areas (De Weerd *et al.*, 1995) following restriction of visual input, and it may form the basis of perceptual 'filling in' of scotomas (Ramachandran, 1992, 1993*a*, *c*; Ramachandran and Gregory, 1991).

The recent MEG results of Flor *et al*. (1995) are also broadly consistent with what we found. Flor *et al*. (1995) obtained MEG recordings from 20 arm amputees and found that in all of them the input from the face and upper arm could now activate the hand territory. Also, many (but not all) of these patients reported that the tactile stimuli on the face were also felt in the phantom, which is essentially identical to what we had reported. Interestingly, Flor *et al*. (1995) also found that there was a high correlation between the extent of remapping (observed with MEG) and the extent to which the patient reported phantom pain. If these findings hold up, they would have the important implication that cortical remapping not only leads to referral of neutral sensations, it may also contribute to the genesis of phantom pain [but see Borsook *et al*. (1997) for a different view].

Can the referral of neutral (non-painful) touch sensations also be correlated accurately with changes in brain maps? Based on our MEG results (sensory input from the face and upper arm activating the hand region) we had suggested that referred sensations were caused by reorganization of sensory processing in the brain. The most direct proof of this, however, comes from the recent work of Kew *et al*. (1997). These investigators studied two brachial plexus avulsion patients who had 'maps' on the anterior and posterior chest wall. They conducted a PET study of these patients and discovered that there was a very precise correlation between the exact location, e.g. the actual finger, where the referred sensation was felt and the disposition of the cortical maps as revealed by the PET scan. These beautiful results provide striking vindication of what we (Ramachandran, 1993*b*) have dubbed the 'remapping hypothesis' for the origin of referred sensations.

How massive a deafferentation is required for remapping to occur? This has not been investigated in detail but an intriguing report by Aglioti and Berlucci (1998) deserves mention. These authors studied a patient who had lost an index finger and not only reported referral from adjacent fingers (as we had reported in Ramachandran, 1993*b*) but also that there was a topographically organized referral from the ipsilateral face to the finger. Indeed, there appeared to be a map of the finger neatly draped across the cheek and lower jaw. This was seen 5 months after amputation but, when the patient was seen again 3 years later, this map of the finger on the ipsilateral face disappeared and, mysteriously, a scrambled representation of the same finger appeared on a mirror-symmetrical location on the contralateral face (for another example of such scrambling, see Halligan *et al*., 1994)! The referral from the adjacent fingers, however, remained stable and identical to what it had been 3 years earlier. The authors suggest that repeated 'use' of the adjacent fingers helps stabilize topography whereas the map on the cheek disintegrates since it is not used in a systematic manner. This is an important point and is consistent with some of our own speculations (Ramachandran, 1993*b*) as well as the recent findings of Florence *et al*. (1996) in monkeys. Florence *et al*. (1996) found that if the peripheral innervation of the hand is scrambled surgically in an infant monkey, the cortical maps initially show a corresponding scrambling as well (as expected) but very soon afterwards the cortical topography is restored even though the peripheral innervation remains scrambled. Our results suggest that such reorganization of topography can also occur in adults, but this remains to be tested experimentally in animals as well as humans.

The technique of transcranial magnetic stimulation has been elegantly exploited for studying reorganization of the motor cortex (Cohen *et al*., 1991; Liepert *et al*., 1995; Hallett, 1996). Recently, an attempt has been made to track perceptual referral and stimulation-induced referral simultaneously in the same patient (Pascual-Leone *et al*., 1996). No change in the cortical map was observed immediately after amputation, but after 5 weeks, stimulation of the original hand area of the cortex began to evoke dual sensations, one in the hand and one in the lower face. (The resolution of the technique did not allow them to determine whether motor or sensory strips were being stimulated; in all likelihood both were.) Interestingly, touch sensations on the lower ipsilateral face were also referred perceptually to the phantom, as in our patients. Finally, when the experiment was repeated a third time several months later, magnetic stimulation of the face area of the cortex did not evoke sensations in the hand; only

face sensations were felt. (Also consistent with this, touch stimuli on the face were no longer mislocalized to the phantom.) These findings would explain why referral from the face to the phantom may be seen only transiently, e.g. during the first few months, and why the phenomenon may disappear after a few years in many patients (Ramachandran, 1993*b*).

Do phenomena analogous to 'remapping' (or reactivation of normally silent pathways) occur only following amputation or do they also occur after more central deafferentation, e.g. after a stroke? Some years ago Pons *et al.* (1988) showed that lesions in S1 (3b) can lead to massive reorganization in S2 and more recently Nudo *et al.* (1996) have shown that, following small ischaemic infarcts in the hand area of the cortex, repeatedly using the hand prevents loss of additional hand territory to the infarct. Effects such as these might help explain certain odd clinical phenomena that are usually ignored because they do not make sense in terms of the 'static' picture of classical neuroanatomy. We have sometimes received letters from patients who, following a stroke that spares the face but leaves the arm paralysed (possibly due to white matter lesions), claim that they experience face twitches every time they move their arm. Such observations are important, for they suggest that central reorganization may also be relevant for understanding at least some of the symptomatology that occurs after brain injury or disease.

A curious clinical condition called 'gaze-evoked tinnitus' also deserves mention (Cacace *et al.*, 1994). Some patients with bilateral auditory nerve resection (e.g. for acoustic neuroma) hear an annoying sound every time they direct their gaze in one particular direction, but not in any other direction. It has been suggested that this seemingly inexplicable finding can be understood in terms of something like remapping; eye movement commands travel down the brainstem and instead of just activating brainstem nuclei concerned with eye movements, they start activating adjacent deafferented auditory nuclei as well, either from ephaptic conduction or as a result of actual axon sprouting.

What would happen after lower limb amputation? In the Penfield homunculus the genitals are adjacent to the foot and, as one might expect, we found that two patients reported experiencing sensations in their phantom foot during sexual intercourse. One of these patients, a 60-year-old engineer, reported actually feeling erotic sensations in the foot so that his 'orgasm is much bigger than it used to be' (Ramachandran, 1993*b*). Aglioti *et al*. (1994*a*, *b*) undertook a more systematic investigation of several lower limb amputees and found, as expected, that many of them had topographically organized maps proximal to the stump and, often, a second cluster of points on the genitals that yielded referred sensations in the phantom leg. (One wonders whether foot-fetishes in normal individuals may also result from such accidental 'cross wiring'—an idea that is at least more plausible than Freud's view that such fetishes arise because of a purported resemblance between the foot and the penis.)

Finally, the remapping hypothesis also makes the prediction that, following trigeminal nerve or ganglion section, a patient should refer sensations from the hand to the face (Ramachandran, 1995), and an elegant and meticulous study performed recently by Clarke *et al.* (1996) shows that such referral does indeed occur. One week after section of the trigeminal ganglion their patient had topographically organized, modality-specific referral from the hand to the face. This is very strong evidence for the notion that referred sensations are a direct consequence of reorganization in the sensory pathways.

Taken collectively, these studies suggest that the emergence of referred sensations in amputees is a robust perceptual phenomenon that can be related in a systematic way to both animal studies and the results of non-invasive imaging experiments. Given the advent of inexpensive new imaging techniques such as functional MRI (fMRI), the stage is now set for exploring plasticity in the adult human brain by simultaneously tracking perceptual and anatomical changes in individual patients. This, in turn, may allow us to develop conceptual links between conscious experience and the activity of somatosensory maps in the brain.

Inter-manual referral of tactile sensations

In addition to the referral from the ipsilateral face and upper arm (and other regions proximal to the deafferentation), sensations from the contralateral hand are sometimes referred to the phantom hand. The exact incidence of this phenomenon is not known but, in a series of 10 arm amputees, we were able to elicit the effect in four (Ramachandran and Rogers-Ramachandran, 1996). It is possible that the incidence would be much higher in patients examined very soon after amputation.

Several aspects of inter-manual referral deserve emphasis.

(i) In three of the patients the referral is topographically organized, e.g. touching the thumb elicits referred touch in the contralateral phantom thumb and touching the ring finger elicits a corresponding sensation in the phantom ring finger (Ramachandran and Rogers-Ramachandran, 1996).

(ii) The effect seems to occur for touch but not for temperature (cold and heat) and pain, e.g. when the patient dipped his intact hand in a pail of ice water he felt the 'dipping' in the phantom but reported that the cold was not referred ('It feels like the phantom is wearing a glove, doctor'). This was true of all four patients. Similarly, a painful pinprick delivered to the index finger of the intact hand was always felt as a painless 'indentation' of the phantom index finger. The result implies that the newly active inter-manual pathways are probably cortical in origin and 'protopathic' sensations may not be reorganized post-traumatically, either because they are poorly represented in the cortex or because there may be no commissural pathways concerned with these modalities. This effect is also important because it rules out confabulatory responses on the part of the patient; for, if confabulation was involved, why should

touch be referred but not temperature or pain and why the consistency across patients?

(iii) The effect was enhanced if an optical trick was used to convey the illusion that the patient could actually see the phantom being touched (see synaesthesia under Reflecting on phantom limbs).

(iv) In six patients movements of the real hand, both active and passive, were referred to the phantom (Ramachandran and Rogers-Ramachandran, 1996).

(v) Referral was seen from the intact hand and forearm up to a level corresponding to the amputation of the other arm, e.g. for below-elbow amputees referral usually occurred only from below the elbow whereas in above-elbow amputees referral occurred from above the elbow crease to mirror-symmetric locations proximal to the phantom elbow.

(vi) The fact that these effects were topographically precise and modality-specific in three patients rules out any possibility that they are due to non-specific 'arousal' or due to the activation of pain pathways (contrary to the suggestions of Flor *et al*., 1995).

What is the physiological mechanism underlying the emergence of this inter-manual referral? The possibility of new anatomical connections is ruled out by the rapidity of the referral. One would hardly expect sprouting to occur across the corpus callosum in 19 days (although reorganization can also occur in the gracile or cuneate nuclei and it is conceivable that this may 'spill over' across the midline.)

We suggest instead that the effect emerges from reactivation of pre-existing connections linking the two hands. More specifically, we suggest that even in normal individuals, sensory input from say, the left thumb might project not only to the right hemisphere but, via unidentified commissural pathways, to mirror-symmetric points in the other hemisphere (Calford, 1991). This latent input may ordinarily be too weak to express itself, but when the right hand is amputated this input may become either disinhibited or progressively strengthened, so that touching the left hand evokes sensations in the right hand as well. Perhaps there are no commissural pathways concerned with pain and temperature, which might explain why these sensations are not referred. These predictions can be easily tested using MEG or fMRI.

Phantom limb pain

In a study of several thousand amputees, Sherman *et al.* (1984) found that >70% of them continued to experience phantom limb pain as much as 25 years after the amputation. Shooting pains which seem to travel up and down the limb, burning sensations and intense cramping sensations ('It feels like my foot is in a vice') are frequently described. In some amputees the pain is continuous but varying in intensity, while others experience intermittent but high-intensity pain (Sherman and Sherman, 1983). While Sherman *et al*. (1984) found that a small percentage of patients (14%) experienced a reduction in intensity of pain over time, the generally accepted view is that phantom pain persisting >6 months after the operation becomes very difficult to treat.

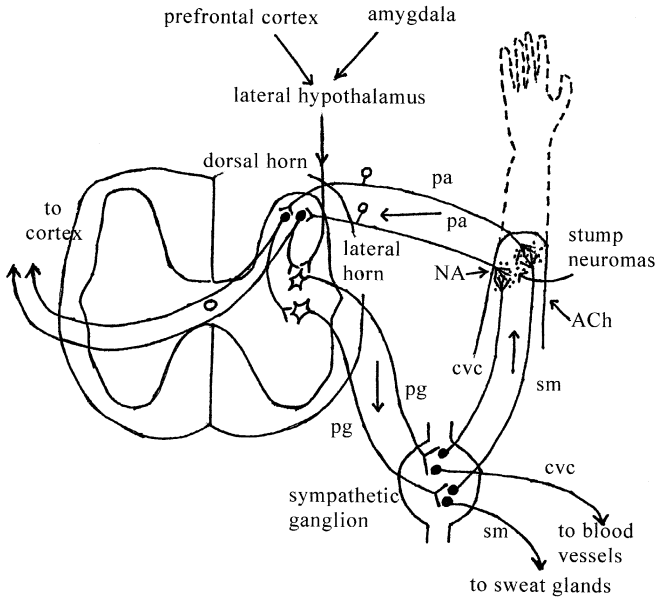


Fig. 5 A possible mechanism for the sympathetic contribution to phantom sensation and pain. Spontaneous activity in the system, or excitatory input from the cortex, begins the cycle by increasing the discharge rate of pre-ganglionic (pg) sympathetic neurons with cell bodies in the lateral horn of the spinal cord and terminals in a sympathetic ganglion. These neurons in turn excite post-ganglionic noradrenergic (NA) cutaneous vasoconstrictor (cvc) and cholinergic (ACh) sudomotor (sm) fibres that impinge on vascular smooth muscle and the sweat glands in the stump; they also excite sprouts from large-diameter primary afferent (pa) fibres trapped in neuromas. The release of acetylcholine and noradrenaline in the neuroma then activates primary afferents to dorsal horn cells in the spinal cord which had enervated the amputated limb. From there the cycle is completed when activity again reaches the sympathetic ganglia, but also, excitation reaches the cortex contributing to paraesthesias. Adapted from Fields (1987) and Katz (1992).

The early finding that blockade or interruption of the sympathetic supply to the stump results in a temporary alleviation of phantom pain (Livingston, 1945; Kallio, 1949) points to a possible connection between phantom pain and activity of the sympathetic nervous system. Based on the work of several researchers (Roberts, 1986; Campbell, *et al.*, 1988), a more detailed hypothesis about the possible sympathetic contribution to phantom pain has been proposed (see Fig. 5 and Katz, 1992). According to this hypothesis, a cycle of sympathetic-efferent somatic-afferent activity may be responsible for the maintenance and amplification of phantom limb pain. The primary cause is the combined effect of cholinergic (sudomotor) and noradrenergic (vasomotor) post-ganglionic sympathetic efferents on primary afferents located in stump neuromas. The release of both acetylcholine and noradrenaline from these efferents may account for the vasoconstriction which has been found in stumps (Sliosberg, 1948), as well as the increased electrodermal activity observed when the phantom is felt more vividly (Katz *et al.*, 1989).

This chemical release may also increase the discharge from sensitized primary afferents located near the stump neuromas. The effect may be intensified by the presence of regenerating sprouts in the neuromas, which have been shown to be hypersensitive, i.e. to discharge more rapidly when acetylcholine and noradrenaline are present (Diamond, 1959; Wall and Gutnik, 1974). Furthermore, the model may also help to explain the frequent finding that emotional distress can trigger phantom limb pain (e.g. Jensen *et al*., 1985; Kroner *et al.*, 1989); the distress may trigger hypothalamic activation of the spinal cord, leading to the release of acetylcholine and noradrenaline by post-ganglionic sympathetic efferents, which in turn excite somatic afferents in the neuromas. Indeed, even the well known influence of weather changes on phantom pain becomes less mysterious when considered in this light (one patient told us that he could use his phantom as a 'barometer' to predict rainfall well ahead of, and more accurately than, the TV weatherman!).

Basbaum's work on 'pain memory' in the spinal cord (Dubner and Basbaum, 1994; Basbaum, 1996) is also pertinent to the issue of phantom limb pain. Woolf (1983) discovered that spinal cord motoneurons increased their discharge rates following a burn injury, and that this 'hyperexcitable' state was not affected by local anaesthetic block of the injured site, indicating that a central sensitization or 'pain memory' had been created. Woolf (1983) and others subsequently found that NMDA antagonists can prevent, and sometimes even reverse, this sensitization process. This sensitization is akin to the opioid tolerance which slowly deprives morphine and its derivatives of its efficacy. Basbaum (1996) has found that these same NMDA antagonists interfere with the development of tolerance. These findings suggest that blocking the spinal cord before and during surgical amputation may reduce the incidence of phantom pain by preventing this sensitization process from affecting the spinal cord.

It has become increasingly clear, however, that neuromas are just the tip of the iceberg and that more central aspects of phantom pain are best explained by the remapping hypothesis discussed in this article. 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 fibres 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, remapping may have two additional consequences that contribute to phantom pain. First, remapping may lead to subtle changes in gain-control (as well as 'gate control') that amplify pain signals along the somatosensory pathways. Secondly, we must bear in mind that remapping is a pathological process and the chaotic or noisy patterns of activity in the remapped zones might be interpreted by the nervous system not only as 'paraesthesiae' but also as pain (assuming that pain does not depend exclusively on labelled lines or place coding, i.e. the pattern of activity might also be critical).

Finally, patients also often complain that the pains that had existed in their limbs prior to amputation persist in the phantom (Katz and Melzack, 1990; Ramachandran, 1993*b*). This persistence of pain is a curious form of sensory memory that certainly deserves further study. It raises the possibility that one could reduce the incidence of post-amputation phantom pain by simply inducing local anaesthesia in the limb prior to a planned surgical amputation (see Schug *et al*., 1995; Basbaum, 1996). Thus, it would appear that one needs to provide the patient with a pain-free period just before amputation in order to erase the pain 'memory', so that it does not linger on in the phantom.

Reflecting on phantom limbs

Some patients with phantom limbs experience vivid movements in their phantom. For example, the phantom might attempt to fend off a blow, wave good-bye, break a fall or even shake hands (Ramachandran, 1993*b*). Many other patients, however, report that the phantom is frozen in a specific position and that they cannot generate voluntary movements in it, even with intense effort. The reason for these differences is obscure and needs careful investigation. In our own experience, however, at least three factors seem to play a role.

(i) If an arm has been paralysed as a result of a peripheral nerve lesion before amputation, the phantom tends to be 'paralysed' as well and tends to occupy the same position the arm did before amputation. Elsewhere we have dubbed this phenomenon 'learned paralysis' (Ramachandran, 1993*b*). The phrase 'learned paralysis' has also been used, however, to denote the paradoxical loss of motor functions (Taub *et al.*, 1993) that occurs very soon following limb deafferentation in primates (Mott and Sherrington, 1895).

(ii) Immediately following a non-traumatic surgical amputation (e.g. for a tumor) subjects usually find they can generate voluntary movement in the phantom. With the passage of time, however, this ability is lost in many (but not all) patients.

(iii) In those instances where a phantom is extremely painful, the patient finds it difficult to move the arm because even an attempt to generate movements can amplify the pain. This may be analogous to the defensive, reflexive immobilization of an intact limb that occurs following any painful injury to the limb (which may also form the basis of reflex sympathetic dystrophy).

It is tempting to assume that the pain that arises from attempts to move the phantom is a simple consequence of neuromas being irritated by muscle activity in and around the stump. This cannot be the whole story, however, because we have sometimes seen such effects when the patient

attempts to move a single digit (e.g. the thumb) following an amputation well above the elbow. We may conclude, therefore, that more interesting central factors must be involved.

Some patients also experience involuntary movements in their phantom, such as a clenching spasm of the hand. ('As though the nails are digging into my palm', one patient told us.) Voluntary unclenching is often effective in relieving the spasm, but the patients usually find this very difficult to do because they have no voluntary control over the phantom.

What exactly does it mean to say that a patient has volitional control of a phantom arm? One possibility is that messages from the motor cortex in the front part of the brain continue to be sent toward the muscles in the hand even though the hand is missing. After all, the part of the brain that controls movement does not 'know' that the hand is missing. It is likely that these movement commands are simultaneously monitored by the parietal lobes which are concerned with body image. In a normal person, messages from the frontal lobe are sent either directly, or via the cerebellum, to the parietal lobes which monitor the commands and simultaneously receive feedback from the arm about its position and velocity of movement. There is, of course, no feedback from a phantom arm, but the monitoring of motor commands might continue to occur in the parietal lobes, and thus the patient vividly feels movements in the phantom.

But how can a phantom (a non-existent limb) be paralysed? One possibility is that during the months preceding the amputation the brain had 'learned' that the arm was paralysed, i.e. every time the message went from the motor cortex to the arm, the brain received visual feedback that the arm was not moving. This contradictory information is somehow stamped into the neural circuitry of the parietal lobes so that the brain 'learns' that the arm is fixed in that position. Therefore, when the arm is amputated, the brain still 'thinks' the arm is fixed in the previous position and the net result is a paralysed phantom limb (Ramachandran, 1993*a*, *b*, 1995).

A similar sequence might occur following a surgical amputation, except that instead of receiving contradictory information (that the arm is immobile), the subject simply receives no feedback confirming that the command has been obeyed. Therefore, immediately after amputation the subject can still generate volitional movements in the phantom, but with the passage of time this ability is lost because of the prolonged absence of confirming sensory feedback.

If the hypothesis of learned paralysis is correct, would it be possible to unlearn the phantom paralysis? To do this, every time the patient sends a message to the phantom arm, he would need to receive a visual feedback message that his arm is indeed moving correctly. But how can this happen when the patient does not even have an arm? To enable the patient to perceive real movement in a non-existent arm, we constructed a 'virtual reality box'. The box is made by placing a vertical mirror inside a cardboard box with the roof of the box removed (Fig. 6). The front of the box has two holes in it, through which the patient inserts his good arm and his phantom arm. The patient is then asked to view the reflection of his normal hand in the mirror, thus creating the illusion of two hands, when in fact the patient is only seeing the mirror reflection of the intact hand. If he now sends motor commands to both arms to make mirror-symmetric movements, he will have the illusion of seeing his phantom hand resurrected and obeying his commands, i.e. he receives positive visual feedback informing his brain that his phantom arm is moving correctly. Would this somehow revive sensations of movement and of voluntary control over the phantom?

We tried this experiment on patient D.S., who had his left arm amputated 9 years before we saw him. He put his hands in the mirror-box and, with his eyes shut, tried to make bilateral mirror-symmetric movements. As expected, the right arm felt as if it were moving but the phantom remained 'frozen as in a cement block'. As soon as he looked in the mirror, however, he exclaimed that he experienced vivid sensations of movement originating from the muscles and joints of his phantom left arm (Ramachandran, 1993*b*). We then removed the mirror and verified that, as before, he could no longer feel his phantom moving even if he tried mirror-symmetric movements ('It feels frozen again', he said). Patient D.S. also tried moving his index finger and thumb alone while looking in the mirror, but this time the phantom thumb and index finger remained paralysed; they were not revived. (This is an important observation for it rules out the possibility that the previous result was simply a confabulation in response to unusual task demands.) Thus, it would appear that there had been a temporary inhibition or 'block' of neural circuits that would ordinarily move the phantom and the visual feedback could overcome the block.

Our second patient, R.T., was an intelligent, 55-year-old engineer who had an infiltrating sarcoma in his left arm that produced a painful ulnar nerve palsy. Six months later his arm was amputated 6 inches above the elbow. When we examined him 7 months after the amputation, he experienced a vivid phantom arm that was of normal length but apparently paralysed, i.e. he could not generate voluntary movements in it except with prolonged, intense effort. His hand frequently went into an involuntary clenching spasm (with 'fingernails digging into the palm') and it took him half an hour or more to voluntarily unclench it. We also verified that R.T. was otherwise completely intact neurologically and that his mental status was normal.

It occurred to us that if one could somehow enable the patient to generate voluntary movements in his phantom he might be able to unclench it during the spasms. To achieve this, we used the mirror-box to convey a visual illusion to the patient that his phantom arm had been resurrected. When he then looked into the right side of the vertical mirror from above the box, he could see the reflection of his right hand and this created a vivid visual illusion that his left arm had been resurrected. We then asked him to simultaneously send motor commands to both hands as if to perform mirror-symmetric movements, e.g. clenching and unclenching of the

Fig. 6 The mirror box. A mirror is placed vertically in the centre of a wooden or cardboard box whose top and front surfaces have been removed. The patient places his normal hand on one side and looks into the mirror. This creates the illusion that the amputated hand has returned.

fist, extension and flexion of the wrist or circular movements as if conducting an orchestra. The very first time he tried this the patient exclaimed with considerable surprise, that all his movements had 'come back': that he now vividly experienced muscle and joint movements in his phantom! He found the return of sensations very enjoyable. For example, at the time of his first visit his phantom fist was clenched and he was unable to unclench it voluntarily with his eyes closed even if he unclenched his other fist. When he looked in the box, however, he was immediately able to unclench his phantom much to his surprise and delight. The procedure was repeated several times with identical results.

We have now tried these procedures on a total of 10 patients (including D.S. and R.T.) with the following results.

(i) In six patients, when the normal hand was moved so that the phantom was perceived to move in the mirror, it was also felt to move, i.e. kinaesthetic sensations emerged in the phantom. In D.S. this effect occurred even though he had never experienced any movements in the phantom during the 10 years before we tested him.

(ii) In four patients, the mirror had no effect whatsoever on the phantom (as one patient said 'I can see my phantom move in the mirror, I want it to move, but it doesn't do anything Doctor').

(iii) Repeated practice (10 min/day for 3 weeks) led to a permanent 'disappearance' of the phantom arm in patient D.S. The hand became telescoped into the stump near the shoulder for the first time in 10 years. As a result of this, the frequent elbow pain he used to experience (prior to the telescoping) also disappeared along with the arm, perhaps because one cannot experience 'disembodied' pain in a non-existent elbow. (This may be the first known case of a successful 'amputation' of a phantom limb!)

(iv) Five patients experienced involuntary painful 'clenching spasms' in the phantom hand, and in four of them the spasms were relieved when the mirror was used to facilitate 'opening' of the phantom hand; opening was not possible without the mirror. Controlled clinical trials are needed, however, in order to determine if this is simply a placebo effect or a specific result of visual feedback with the mirror.

(v) In two patients, visual feedback that the phantom was occupying anatomically impossible positions (such as hyperextension of a finger) resulted in the patient actually experiencing these anomalous positions, much to their surprise.

(vi) In three patients, touching the normal hand evoked precisely localized touch sensations in the phantom. Interestingly, the referral was especially pronounced when the patients actually 'saw' their phantom being touched in the mirror. Indeed, in a fourth patient (R.L.), the referral occurred only if he saw his phantom being touched—a curious form of synaesthesia.

(vii) We also tested a 50-year-old finger amputee with the mirror procedure. The patient had lost his index finger nearly 30 years prior to testing and he had experienced a non-painful phantom of the finger intermittently for 1–2 years before it faded completely. He had never experienced a phantom in the 28 years that elapsed before he came to our laboratory and was amazed to experience movement in it, for the first time, when he looked inside the mirror. This implies that a dormant representation of the faded phantom

must exist somehwhere in his brain. The representation is ordinarily inhibited, but can be revived instantly with visual feedback.

Given that these findings are all examples of visual sensations being experienced as somatic sensations they are, by definition, examples of synaesthesia. It remains to be seen, however, whether similar mechanisms are involved in congenital or 'idiopathic' synaesthesia.

Taken collectively, the experiments suggest that there must be a great deal of back-and-forth interaction between vision and touch, and that the strictly modular/hierarchical model of brain function popularized by artificial intelligence researchers must be replaced with a more dynamic view in which re-entrant signalling (Edelman, 1989) plays an important role. One wonders also whether some formed of 'learned paralysis' may also contribute to other neurological syndromes such as hemiplegia, apraxia and focal dystonias and, if so, whether they might benefit from visual feedback.

Inter-manual interactions between real and phantom movements

The 'reality' of illusory movements in the phantom limb was also demonstrated by us recently using a somewhat different procedure. When normal subjects try to draw two dissimilar figures simultaneously (e.g. a vertical line and a horizontal line) with the two hands, there is considerable inter-manual interference; an interference that is probably central in origin. We found that a similar conflict occurs when a patient tries to 'draw' one figure with his phantom and a different one with his intact hand. (Franz *et al*., 1994), implying that the effect is probably the result of 'corollary discharge' from motor commands sent to the phantom. Such interference did not occur if normal subjects simply 'imagined' performing the dissimilar task with their other hand. It also did not occur when a patient with a 'paralysed' phantom tried the procedure.

Phantoms induced in normal individuals

The question of how the brain constructs a 'body image' has been a topic of considerable interest to neurologists (Head, 1918; Brain, 1941; Critchley, 1953), psychologists (Schilder, 1950) and even philosophers (Merleau-Ponty, 1962; Dennett, 1979; O'Shaughnessy, 1980). Even though this image is constructed from evanescent and fragmentary evidence derived from multiple sensory systems—vision, proprioception, hearing, etc.—we have a stable internal mental construct of a unitary corporeal self that endures in space and time, at least until its eventual annihilation in death.

One key difference between tactile sensations and visual sensations is that the former are localized directly on the sensory surface where the receptors are actually located, whereas the latter are 'projected' onto the external world; e.g. when light from a tree hits your retinal receptors you localize the tree externally, not inside your eyeball. Indeed, vision probably evolved as a 'remote sensing' device that liberates you from the requirement of direct contact with the object you are trying to localize, whether for dodging or grabbing (Dawkins, 1996).

With so ancient a phylogenetic rift between the two systems, it would be very surprising if one could 'project' somatic sensations onto the external world, yet anyone who has used a screwdriver or a razor and a mirror will realize that this must be possible, at least to a limited extent. After extended use of the screwdriver one often begins to 'feel' the tip of the screwdriver. Similarly, when using a shaving mirror one experiences a peculiar mental diplopia—the razor is felt simultaneously on one's own face but to a limited extent also in the mirror image.

Although we ordinarily regard phantoms as pathological, it is relatively easy to generate such illusions, even in otherwise normal individuals. Consider the 'phantom nose' illusion that we recently discovered in our laboratory (Ramachandran and Hirstein, 1997). The subject sits in a chair blindfolded, with an accomplice sitting in front of him, facing the same direction. The experimenter then stands near the subject, and with his left hand takes hold of the subject's left index finger and uses it to repeatedly and randomly to tap and stroke the nose of the accomplice, while at the same time, using his right hand, he taps and strokes the subject's nose in precisely the same manner, and in perfect synchrony. After a few seconds of this procedure, the subject develops the uncanny illusion that his nose has either been dislocated, or has been stretched out several feet forwards, demonstrating the striking plasticity or malleability of our body image. The more random and unpredictable the tapping sequence the more striking the illusion. We suggest that the subject's brain regards it as highly improbable that the tapping sequence on his finger and the one on his nose are identical simply by chance and therefore 'assumes' that the nose has been displaced—applying a universal Bayesian logic that is common to all sensory systems (Ramachandran and Hirstein, 1997). The illusion is a very striking one, and we were able to replicate it on 12 out of 18 naive subjects.

Our 'phantom nose' effect is quite similar to one reported by Lackner (1988) except that the underlying principle is different. In Lackner's experiment, the subject sits blindfolded at a table, with his arm flexed at the elbow, holding the tip of his own nose. If the experimenter now applies a vibrator to the tendon of the biceps, the subject not only feels that his arm is extended, because of spurious signals from muscle stretch receptors, but also that his nose has actually lengthened. Lackner invokes Helmholtzian 'unconscious inference' as an explanation for this effect (I am holding my nose and my arm is extended, therefore my nose must be long). The illusion we have described, on the other hand, does not require a vibrator and seems to depend entirely on a Bayesian principle: the sheer statistical improbability of two tactile sequences being identical. (Indeed, our illusion cannot be produced if the subject simply holds the accomplice's nose.) Not all subjects experience this effect,

but that it happens at all is astonishing: that a lifetime's evidence concerning your nose can be negated by just a few seconds of intermittent tactile input.

Another striking instance of a 'displaced' body part can be demonstrated by using a dummy rubber hand. The dummy hand is placed in front of a vertical partition on a table. The subject places his hand behind the partition so he cannot see it. The experimenter now uses his left hand to stroke the dummy hand while at the same time using his right hand to stroke the subject's real hand (hidden from view) in perfect synchrony. The subject soon begins to experience the sensations as arising from the dummy hand (Botvinick and Cohen, 1998).

Finally, it is even possible to 'project' tactile sensations onto inanimate objects such as tables and shoes that do not resemble body parts. The subject is asked to place his right hand below a table surface (or behind a vertical screen) so that he cannot see it. The experimenter then uses his right hand to randomly stroke and tap the subject's right hand (under the table or behind the screen) and uses his left hand to simultaneously stroke and tap the shoe in perfect synchrony (a table cloth may be used to make sure that the experimenter's right hand and subject's own hand is completely invisible to the subject). After 10–30 s, the subject starts developing the uncanny illusion that the sensations are now coming from the shoe and that the shoe is now part of his body (Ramachandran *et al*., 1998). On some occasions, when the experimenter had accidently made a longer excursion on the shoe than on the hidden hand, the subjects exclaimed that they felt that their hand had become elongated as well!

How can we be sure that the subjects are not simply using a figure of speech when they say 'I feel that the sensations are arising from the shoe'? To rule out this possibility, we waited until the subjects started 'projecting' their sensations onto the table surface and then simply hit the shoe with a giant rubber hammer as they watched. Remarkably, the subjects not only winced visibly but also registered a strong increase in skin conductance when we measured their galvanic skin response [Ramachandran *et al*. (1998); such a change was not seen in a 'control' condition in which the shoe and hand were stroked non-synchronously prior to hitting the shoe]. The surprising implication of these observations is that the shoe was now assimilated into the subject's own body image, i.e. that he or she was not just being metaphorical when asserting that the shoe feels like the hand. Indeed, we may conclude that the shoe is now 'hooked up', in some sense, to the subject's limbic system so that any threat to the shoe produces emotional arousal.

Taken collectively, the three experiments suggest that the so-called body image, despite all its appearance of durability and permanence, is an entirely transitory internal construct that can be profoundly altered by the stimulus contingencies and correlations that one encounters. It is merely a shell, created temporarily for the sole purpose of successfully passing on one's genes to the next generation.

Phantom limbs and sensory codes

According to the 'labelled lines' theory of sensory coding, every neuron in the sensory pathways, e.g. 3b, S2 or area 17, has a specific 'hardwired' signature, i.e. it signals a highly specific percept such as 'light touch on my right elbow'. It is obvious, however, that sensory coding cannot be based exclusively on an endless hierarchy of labelled lines and maps (see, for example, Schieber, 1996). At some stage, 'pattern coding', i.e. the total spatiotemporal pattern of activity, must take over and determine what the subject actually perceives.

The basic presumption of the remapping hypothesis of referred sensations is that the labelled lines have been switched so that the same sensory input now activates a novel set of labelled lines (e.g. the face input activates 'hand neurons' in S1). As we have seen, this is consistent with both the MEG changes in sensory maps that we observed as well as the referred sensations reported by many patients (see also Kew *et al*., 1997), but it is possible that the subsequent changes in pattern-coding somewhere further along in the nervous system eventually leads to the deletion of these anomalous sensations in some patients.

The word 'remapping' carries connotations of actual anatomical change whereas most of the evidence points to unmasking or disinhibition of pre-existing pathways (see, for example, Ramachandran *et al*., 1992*a*, *b*; Ramachandran and Rogers-Ramachandran, 1996; Borsook *et al*., 1997). A more theory-neutral word such as 're-routing' might be preferable in order to indicate that information from a specific location on the sensory surface (e.g. face or shoulder) is now shunted or re-routed either to evoke new patterns of neural activity or to activate new anatomical sites that have different perceptual signatures and therefore lead to novel sensations. In either case, the findings imply that there must have been a relatively permanent or stable change in the processing of sensory signals by the adult brain.

A theory of phantom limbs

Since the time of Mitchell's first description (1871, 1872), innumerable theories have been put forward to account for phantom limbs, ranging from the sublime to the ridiculous. The standard textbook 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 first pointed out by Melzack (1992), this explanation is quite inadequate, since injecting local anaesthetic into the stump or even removing the neuromas surgically often fails to abolish the phantom or to eliminate phantom limb pain. And at the other end of the spectrum is the view that phantom limbs are mainly a form of Freudian 'denial', with the pain being part of the 'mourning' process. It has been suggested, quite seriously, that this might be analogous to the case of a widow who 'unable to believe that her husband is dead, has a strong sense of his presence'

(Parkes, 1972), or to a dream in which unconscious wishes are expressed in a grotesquely deformed manner (Zuk, 1956). Telescoping, according to this view, should be regarded as an attempt to reconcile the denial of loss with the readjustment to reality (Zuk, 1956).

We would like to suggest, instead, that the phantom limb experience arises at least in part because tactile and proprioceptive input from the face and tissues proximal to the stump 'takes over' the brain in area 3b as shown by Pons *et al*. (1991) and possibly also in 'proprioceptive' maps. Consequently, spontaneous discharges from these tissues would get 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' (Melzack, 1992). We would argue, however, that the effect arises, at least in part, from mechanisms of a more specific nature, such as remapping. Partial support for this view comes from the nine reports of acquired focal brain lesion in the contralateral parietal cortex causing a complete disappearance of the phantom limb (Head and Holmes, 1911; Bornstein, 1949; Appenzeller and Bicknell, 1969; Bosch, 1991), observations that would be hard to reconcile with the concept of 'diffuse' representation in a neuromatrix, but that are readily explained by the remapping hypothesis.

Remapping, however, cannot possibly explain all aspects of the phantom limb experience. For example, it does not explain the frequent occurrence of illusory movements, both voluntary and involuntary, in the phantom or the fact that the patient can 'wave good-bye' or 'reach out and grab' a telephone with the phantom. Nor can it account for the observation that phantom limbs are occasionally found in patients who have congenital absence of limbs, which must imply that at least some aspects of one's 'body image' are specified genetically and can survive as a phantom limb (see below and Ramachandran, 1993*b*; Saadah and Melzack, 1994). And last, the remapping hypothesis does not explain why the phantom often occupies the same position that it did prior to the amputation.

Taking these facts into account, we propose a multifactorial model of the origin of phantom limbs—one that can provide a starting point for a more sophisticated future model. To address this, we have to first consider some basic facts about perception. It is clear that to generate any stable percepts (such as one's 'body image') or even a stable belief system (Ramachandran, 1995) the brain must weigh evidence from many different sources and quickly arrive at a decision. Doing this must in turn involve a mechanism for imposing coherence on information from diverse sources and for vetoing discrepancies, a process that can at least partially be accomplished by a using a 'winner-take-all' scheme. The ultimate goal of this, of course, is to confer stability on behaviour, avoid indecisive vacillation and optimize the allocation of one's cognitive and physical resources, given the ever-present need for rapid, effective action. In other words, since the brain's motor output must be coherent, it must have evolved the ability to arrive rapidly at stable sensory representations even if this requires the temporary inhibition of discrepant inputs. In doing this, the organism is making a bet, that if multiple sources of information concur in their verdict, then a single piece of discrepant information can safely be regarded as noise, or as a temporary malfunction of the sensory system which can be ignored (Ramachandran, 1995). The underlying logic is simple; accidental concordance from discrepant sources is extremely rare, whereas accidental discrepancies are common (due to extraneous 'noise', intrinsic noise from circuit malfunction or other reasons), a rule which organisms use to their advantage.

How might this abstract scheme apply to phantom limbs? We suggest that the phantom limb experience depends on integrating experiences from at least five different sources: (i) from the stump neuromas, as taught by the old textbooks; (ii) from remapping, e.g. the spontaneous activity from the face is ascribed to the phantom; (iii) the monitoring of corollary discharge from motor commands to the limb; (iv) a primordial, genetically determined, internal 'image' of one's body; and (v) vivid somatic memories of painful sensations or posture of the original limb being 'carried' over into the phantom. Ordinarily these five factors conspire to reinforce each other but in individual patients there may be discrepancies that modify the clinical picture.

A single discrepancy could simply be vetoed, but consider what would happen if there were two subsets of cues—the cues within each subset being mutually consistent but inconsistent with the other subset. One option, then, would be to 'split' the image into two, resulting in odd phenomena such as supernumerary phantoms (Ramachandran *et al*., 1996).

A similar model can be invoked to account for the occasional emergence of supernumerary phantoms in patients with focal lesions due to stroke. In these patients central reorganizational changes would lead to multiple conflicting cues about limb position, and a 'fusion' or 'splitting' of these cues could explain the emergence of an extra limb. Such an extra limb is usually felt but not actually seen, for the patient recognizes its illusory nature. But if there is additional right frontal damage, the illusion is not 'corrected' and may evolve into a full-blown delusion. Indeed, one patient, D.S. (not the same D.S. mentioned earlier), who lost his left arm in a car accident and also had bilateral frontal lesions, not only felt a phantom arm as expected but actually insisted that he could still see it and that it had not been removed, even though he was mentally quite lucid in other respects (Hirstein and Ramachandran, 1997; see also Halligan and Marshall, 1995).

But even this long list of possibilities, as we shall see, does not completely exhaust all aspects of the complex phenomenology of phantom limbs.

The nature and nurture of phantom limbs

Do phantom limbs arise mainly from epigenetic factors such as remapping and painful stump neuromas or do they represent

the ghostly persistence of a genetically specified body image? The answer seems to be that the phantom emerges from a complex interaction between the two. To illustrate this we provide five examples.

(i) There are a few instances in which the stump of a below-elbow amputee has been refashioned surgically into a lobster claw-like forked appendage. Subjects with this type of surgery often learn to use the pincers to grasp objects, pronate, supinate, etc. Intriguingly the phantom hand also feels split into two with one or more fingers occupying each pincer and it is felt to mimic the movements of the appendage vividly. Remarkably, subsequent amputation of this forked appendage results in a phantom that is also equivalently fork-shaped (Kallio, 1949)!

(ii) We noted earlier that a certain proportion of patients with congenitally missing limbs also experience phantoms (Weinstein *et al*., 1964; Ramachandran, 1993*b*; Saadah and Melzack, 1994) despite earlier claims that they never do (Simmel, 1962). Poeck (1969) described a fascinating case of a child who was born without forearms but experienced distinct phantom hands 13 cm below the stumps. This patient could move her phantom fingers and she actually used them to count and solve arithmetic problems!

La Croix (1992) described a case of a 16-year-old girl who was born with a right leg 10 cm shorter than the left who received a below-knee amputation at the age of 6 years. In addition to the expected phantom foot, corresponding in location to the original, she developed two supernumerary phantom feet, one at the level of amputation and a second one, complete with calf, extending all the way down to the floor where it should have been, had the limb not been congenitally shorter! Although the authors use this example to illustrate the role of genetic factors, one could equally use it to emphasize epigenetic influences, for why would the genome specify three separate images of the leg?

(iii) It has been asserted that patients with leprosy who progressively lose an arm do not experience a phantom (Simmel, 1956) and one of us (V.S.R.) has personally seen cases in India and verified these early claims. It is sometimes suggested that this is because the patient gradually 'learns' to assimilate the stump into his body image, e.g. by using visual feedback, but if this is true, how does one account for the continued presence of the phantom in amputees? It would appear that something about the gradual loss of the limb, or the simultaneous presence of peripheral neuropathy, is critical.

Yet if such a patient develops gangrene in his or her stump, and the stump is amputated, the patient often finds to his amazement that the entire phantom hand is resurrected, not just a 'phantom stump'! The reason for this is obscure, but we would suggest that in these patients' brains there may be two representations: one corresponding to the original 'primordial' body image with an intact arm and a second more recent one in which the arm has been whittled away in response to recent sensory experience. Ordinarily, the recent one inhibits the older one but for some reason amputating the stump disturbs the equilibrium and resurrects the original image.

We are now exploring the possibility that a long-lost phantom that has faded many years ago in an arm amputee, or even one that never existed (e.g. in some patients with a congenitally missing arm) may be lying dormant somewhere in the brain. If so, can it be revived by repeatedly using our mirror box to provide visual feedback apparently 'confirming' its existence? In doing so, one has to be careful not to resurrect the phantom pain, of course! (Ideally, one should do the experiment in patients who have no history of phantom pain.)

We have tried this informally on one patient (P.N.) who had 'lost' her phantom elbow and forearm a few years prior to our testing her, but still had a phantom hand telescoped into the stump. Ordinarily, she could not 'extend' her phantom even with intense voluntary effort, but when looking in the mirror the arm lengthened instantly, much to her surprise and amusement (Ramachandran and Rogers-Ramachandran, 1996).

(iv) Many amputees experience vivid movements, both voluntary and involuntary, in the phantom, but in a majority of them the movements disappear eventually (Sunderland, 1978; Ramachandran, 1993*b*). We have suggested elsewhere that the movements are initially experienced because 'feedforward' or corollary discharge from motor commands to the limb continues to be monitored by the brain even after the amputation. The continued absence of visual and proprioceptive confirmation, however, eventually causes the patient's brain to reject these signals so that the movements are no longer experienced. But if this explanation is correct, how does one explain the continued presence of vivid movements in some patients with congenitally missing arms? Recall that D.B., a 20-year-old woman who was born without arms, continued to feel vivid phantom movement despite absence of feedback for 20 years. One can only surmise that since a normal adult has had a lifetime of visual and kinaesthetic feedback, the brain continues to expect such feedback even after amputation and is 'disappointed' if the expectation is not fulfilled (leading, eventually, to a loss of voluntary movements or even a complete loss of the phantom). The sensory areas of D.B.'s brain, however, have never received such feedback. Consequently, there is no 'learned dependence' on sensory feedback, which would explain why the movements had persisted unchanged for 20 years.

These are speculative conjectures, although at least some of them can be tested using non-invasive image procedures such as MEG and fMRI. We mention them because they suggest that the phantom limbs emerge from an interplay of both genetic and epigenetic variables whose relative contributions can be disentangled only by painstaking and systematic empirical investigations. As with most nature/nurture debates, however, asking which is the more important variable is meaningless. Indeed, the question is no more meaningful than asking whether the wetness of water comes

mainly from the hydrogen molecules or from the oxygen molecules that constitute H_2O.

Concluding remarks

Work on phantom limbs, and their neural basis, has progressd at a rapid pace during the last 5 years. It is now clear that this phenomenon provides a valuable experimental opportunity to investigate how new connections emerge in the adult brain, how information from different sensory modalities, e.g. touch, proprioception and vision, interact, and how the brain continuously updates its model of reality in response to novel sensory inputs.

Referred sensations provide an 'existence proof' for changing cortical maps in the adult human brain, but the question remains: what is the functional significance of remapping? Is it an epiphenomenon—residual plasticity left over from early infancy—or does it continue to have a function in the adult brain? For example, would the larger cortical area devoted to the face after arm amputation lead to an improved sensory discrimination (measured by two-point discrimination or tactile hyperacuity) on the face? Would such improvement, if it occurred at all, co-exist with the referred sensations or would it be seen only after the anomalous sensations (or the phantom itself) have disappeared as a result of subsequent perceptual 'correction'? Such experiments would settle, once and for all, the question of whether remapping is actually useful to the organism or not.

Quite apart from their relevance to neural plasticity and body image, the study of phantom limbs may also enable us to explore the relationship between the activity of neurons and conscious experience. It is an embarrassing fact that despite five decades of single-unit physiology in animals, studied in excruciating detail, we still have no clear idea of how the brain works or why cortical maps exist. [To paraphrase Horace Barlow, the situation in neuroscience today is analogous to a parthenogenetic (asexual) Martian zoologist spending five decades studying the structure and function of the human testicles while not knowing anything about sex.] In patients with phantom limbs, as we have seen, one can simultaneously track perceptual changes and changes in brain maps in the same patients (Ramachandran, 1993*b*) and this strategy may eventually help us determine how the activity of these maps gives rise to perceptual experience. Indeed, these patients provide a unique opportunity for testing some of the most cherished assumptions of sensory physiology—Muller's law of specific nerve energies, 'place coding' (labelled lines) versus 'pattern coding', etc., ideas that are accepted as axiomatic—even though they have never been subjected to rigorous experimental verification. Although they are usually referred to as 'laws', they represent no more than the collective folk wisdom of psychologists and neuroscientists, and there is very little direct evidence for them.

For instance, our upper-limb amputees always experience dual sensations, i.e. when the face is touched, the sensation is felt simultaneously on the face and the phantom hand, presumably because two different points are being simultaneously activated in S1. After trigeminal nerve section, however, tactile sensations on the hand are often felt exclusively on the face (Clarke *et al.*, 1996). This remarkable observation suggests that there may be an initial overshoot during remapping so that the aberrant input from hand skin to the cortical face area is actually stronger than the input to the hand area and therefore comes to dominate perception and masks the sensation on the hand.

You never identify yourself with the shadow cast by your body,

or with its reflection, or with the body you see in a dream or in your imagination.

Therefore you should not identify yourself with this living body either.

Shankara (AD 788–820) *Viveka Chudamani* ('Crown jewel of discrimination'; Vedic scriptures).

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