

## Phantom limbs and the concept of a neuromatrix

Ronald Melzack

Ronald Melzack is at the Department of Psychology, McGill University, 1205 Dr Penfield Avenue, Montreal, Quebec, Canada H3A 1B1.

The phenomenon of a phantom limb is a common experience after a limb has been amputated or its sensory roots have been destroyed. A complete break of the spinal cord also often leads to a phantom body below the level of the break. Furthermore, a phantom of the breast, the penis, or of other innervated body parts is reported after surgical removal of the structure. A substantial number of children who are born without a limb feel a phantom of the missing part, suggesting that the neural network, or 'neuromatrix', that subserves body sensation has a genetically determined substrate that is modified by sensory experience.

Phantom limbs occur in 95–100% of amputees who lose an arm or leg<sup>1</sup>. The phantom is usually described as having a tingling feeling and a definite shape that resembles the somatosensory experience of the real limb before amputation. It is reported to move through space in much the same way as the normal limb would move when the person walks, sits down, or stretches out on a bed. At first, the phantom limb feels perfectly normal in size and shape, so much so that the amputee may reach out for objects with the phantom hand, or try to step onto the floor with the phantom leg. However, as

time passes, the phantom limb begins to change shape. The arm or leg becomes less distinct and may fade away altogether, so that the phantom hand or foot seems to be hanging in mid-air (Fig. 1). Sometimes, the limb is slowly 'telescoped' into the stump until only the hand or foot remains at the stump tip<sup>2</sup>. However, the neural basis of the phantom does not disappear. Injury of the stump years or decades after fading or telescoping may suddenly produce a phantom as vivid and full-sized as that felt immediately after amputation<sup>3,4</sup>.

Amputation is not essential for the occurrence of a phantom. After avulsion of the brachial plexus of the arm, without injury to the arm itself, most patients report a phantom arm (the 'third arm'), which is usually extremely painful<sup>5</sup>. Even nerve destruction is not necessary. About 95% of patients who receive an anesthetic block of the brachial plexus for surgery of the arm report a vivid phantom, usually at the side or over the chest, which is unrelated to the position of the real arm when the eyes are closed but 'jumps' into it when the patient looks at the arm<sup>6</sup> (Fig. 2). Similarly, a

**Fig. 1.** Drawings of phantom arms and legs based on patients' reports. The phantom is indicated by a dotted line, with solid lines to show the most vividly experienced parts. Note that some of the phantoms are telescoped into the stump. (Taken, with permission, from Ref. 2.)



spinal anesthetic block of the lower body produces reports of phantom legs in most patients<sup>7</sup>, and total section of the spinal cord at thoracic levels leads to reports of a phantom body including genitalia and many other body parts in virtually all patients<sup>8-10</sup>. This review describes phantom limb phenomena, draws inferences regarding possible underlying neural mechanisms and proposes a new hypothesis for the neural basis of phantom limb phenomena.

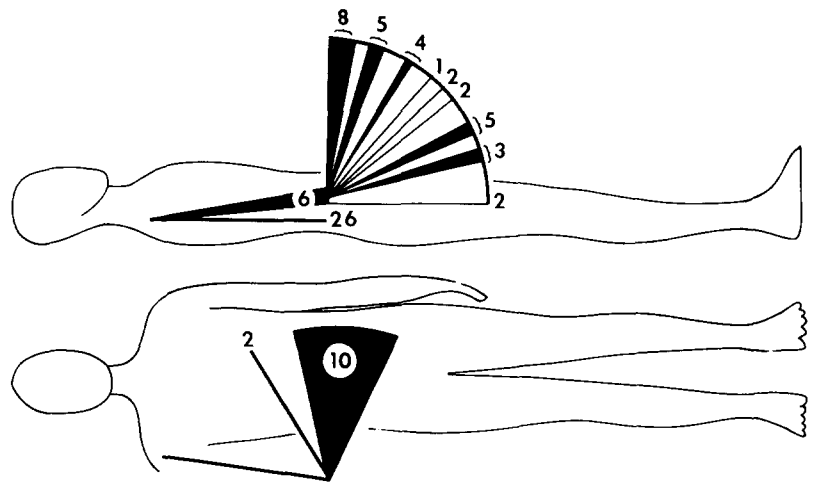
### Phantom limb phenomena

The most astonishing feature of the phantom limb is its 'reality' to the amputee<sup>1</sup>, which is enhanced by wearing an artificial arm or leg; the prosthesis feels real, 'fleshed out'. Amputees in whom the phantom leg has begun to 'telescope' into the stump, so that the foot is felt to be above floor level, report that the phantom fills the artificial leg when it is strapped on and the phantom foot now occupies the space of the artificial foot in its shoe<sup>11</sup>. Patients who have undergone a cleavage of the forearm stump muscles to permit them to hold objects report that the phantom hand also has a cleavage and lies appropriately in the stump<sup>12</sup> (Fig. 3).

The remarkable reality of the phantom is reinforced by the experience of details of the limb before amputation, particularly at sites of earlier painful injuries<sup>4,11,13</sup>. In addition, some people may feel a painful bunion that had been on the foot or even a tight ring on a phantom finger. Some amputees, who receive drugs that produce the tremor of tardive dyskinesia, even report a tremor in the phantom<sup>14</sup>.

Phantoms of other body parts feel just as real as phantom limbs. Heusner<sup>15</sup> describes two men who underwent amputation of the penis. One of them, during a 4-year period, was intermittently aware of a painless but always erect phantom penis. The other man felt severe pain from the phantom penis. Phantom bladders and rectums have the same quality of reality<sup>8,16</sup>. The bladder may feel so real that patients, after a bladder removal, sometimes complain of a full bladder and even report that they are urinating. Patients with a phantom rectum may actually feel that they are passing gas or feces. Menstrual cramps may continue to be felt after a hysterectomy. A painless phantom breast, in which the nipple is the most vivid part, is reported by about 25% of women after a mastectomy and 13% feel pain in the phantom<sup>17</sup>.

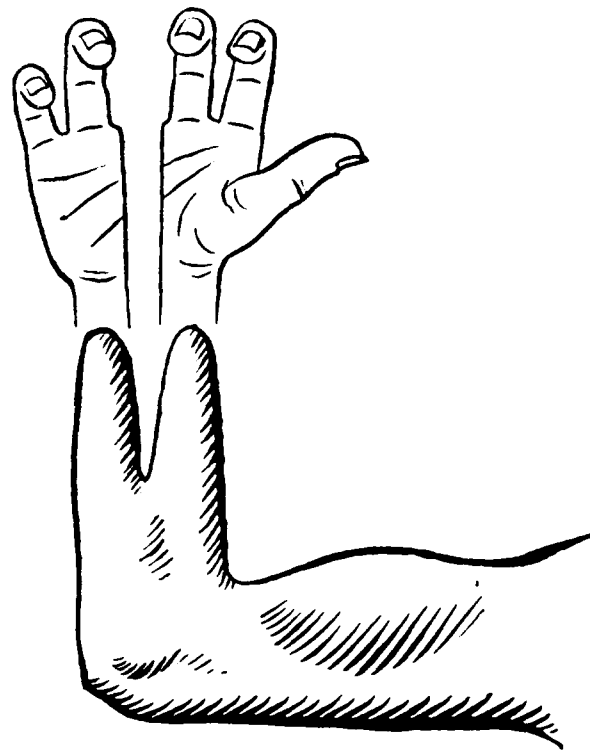
The reality of the phantom body is evident in paraplegics who suffer a complete break of the spinal cord. Even though they have no somatic sensation or voluntary movement below the level of the break, they often report that they still feel their legs and lower body<sup>8,18</sup>. The phantom appears to inhabit the body when the person's eyes are open and usually moves in a manner that is coordinated with the visually perceived movements of the body. Initially, after an accident, the patient may realize the dissociation between the phantom and his real body when he sees his legs stretched out on the road and yet feels them to be over his chest or head



**Fig. 2.** Schematic representation of the positions of the phantom arm first described after anesthetic block of the brachial plexus. The subjects who reported that the phantom arm was at the side are shown at the top; those who reported it above the abdomen or chest are shown below. The number of subjects who reported the phantom arm in each position, or within a given angle range, is indicated on the drawings. Subsequent changes in position are from the side to the abdomen and back again, or changes in the angle of the elbow. One subject, who reported that the phantom arm was straight up from the shoulder and bent in over his face, is not shown. (Taken, with permission, from Ref. 6.)

(Fig. 4). Later, the phantom becomes coordinated with the body, and dissociation is rare.

Descriptions given by amputees and paraplegics indicate the range of the qualities of experience of phantom body parts<sup>1,8,11</sup>. Touch, pressure, warmth, cold and many kinds of pain are common. There are also feelings of itch, tickle, wetness, sweatiness, and tactile texture. Even the experience of fatigue due to movement of the phantom limb is reported<sup>9</sup>. Furthermore, male paraplegics with a total spinal section report feeling erections, and paraplegic



**Fig. 3.** Cleavage of the phantom hand after a cleavage of the muscles of the forearm to allow the patient to pick up objects. (Taken, with permission, from Ref. 12.)

women describe sexual sensations in the perineal area. Both describe feelings of pleasure, including orgasms<sup>8,19,20</sup>.

One of the most striking features of the phantom of a limb or any other body part, including half of the body in many paraplegics, is that it is perceived as an integral part of one's self. Even when a phantom foot dangles 'in mid-air' (without a connecting leg) a few inches below the stump, it still moves appropriately with the other limbs and is unmistakably felt to be part of one's body. The fact that the experience of 'self' is subserved by specific brain mechanisms is demonstrated by the converse of a phantom limb, the feeling that a part of one's body does not belong to one. Typically, people who

have suffered a lesion of the right parietal lobe or any of several other brain areas<sup>21</sup> deny that a side of the body is part of themselves and even ignore the space on that side<sup>21,22</sup>. From these cases, it is evident that the brain processes that underlie the experience of our bodies must impart a special signal that provides the basis for experience of self. When individuals lose these brain areas, they deny that a part of the body belongs to them. Even when a hand, for example, is pinched hard so that the patient winces or cries out, they still deny that the hand is theirs.

There is convincing evidence that a substantial number of children who are born without all or part of a limb feel a vivid phantom of the missing part. The long-held belief that phantoms are experienced only when an amputation has occurred after the age of 6 or 7 is not true. Weinstein and his colleagues<sup>23</sup> and Poeck<sup>24</sup> have reviewed evidence that phantoms are experienced by children who are born without a limb (congenital aplasia). In one patient, for example, the left arm was deformed so that the hand was attached to the shoulder, but the phantom arm felt as though it was half the length of the right arm, which was normal in all respects. Similarly, a 6-year-old child born without a leg reported that her phantom leg consisted of the upper calf and two toes. Another child felt the palm and middle finger of a phantom hand. These descriptions of partial or deformed phantom limbs make it unlikely that the children were simply describing a fantasy of a normal limb.

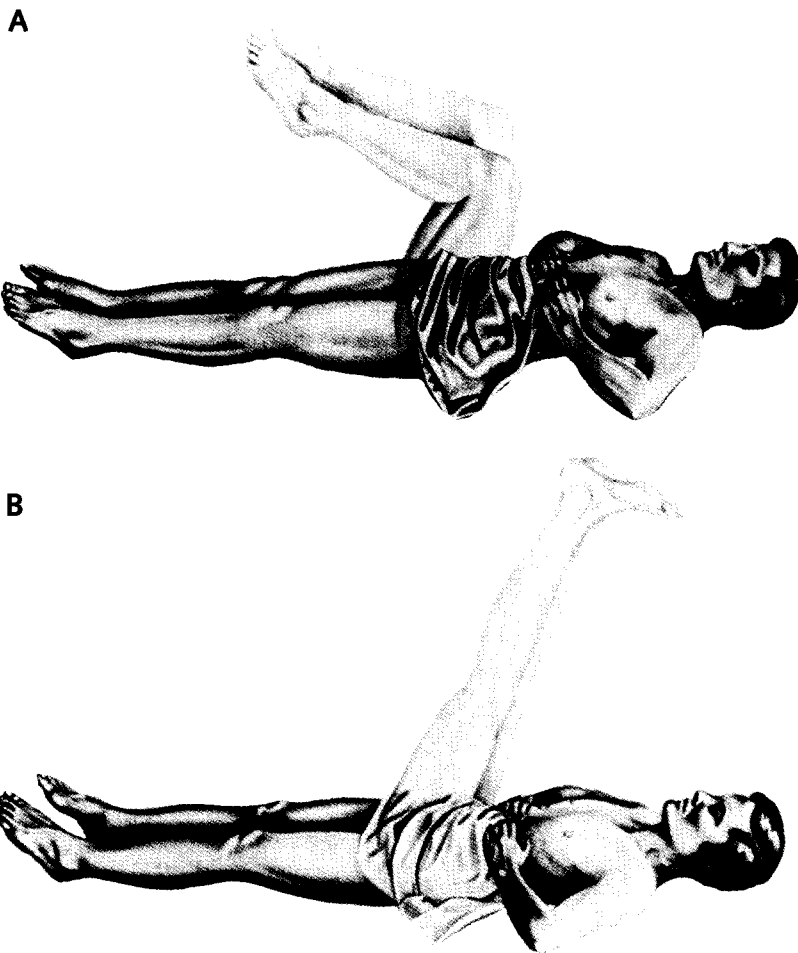
The innate neural substrate implied by these data does not mean that learning experience is irrelevant. Learning obviously underlies the fact that people's phantoms often assume the shape of a prosthesis<sup>12</sup>, and that people with a deformed leg or a painful corn often report, after amputation, that the phantom is deformed or has a corn. That is, sensory inputs play an important role in the experience of the phantom limb. Heredity and environment clearly act together to produce the phenomena of phantom limbs.

The observations on phantom limb phenomena can be summarized in four points<sup>25</sup>.

- (1) The experience of a phantom limb has the quality of reality because it is produced by the same brain processes that underlie the experience of the body when it is intact.
- (2) Neural networks in the brain generate all the qualities of experience that are felt to originate in the body; inputs from the body may trigger or modulate the output of the networks but are not essential for any of the qualities of experience.
- (3) The experience of the body has a unitary, integrated quality which includes the quality of the 'self', the feeling that all the parts of the body are uniquely one's own.
- (4) The neural network that underlies the experience of one's physical self is genetically determined but can be modified by sensory experience.

#### A hypothesis for phantom limbs: the neuromatrix

The explanation of phantom limb phenomena is a



**Fig. 4.** Perception of phantom legs dissociated from the body in two men with spinal cord injury. **(A)** This patient was thrown from a motorcycle and made paraplegic, with motor and sensory impairment up to the seventh thoracic (T-7) level, with mild sacral sparing on the right side. He stated that as soon as he gained awareness he felt as if he was still on his motorcycle, and the sense of flexion or being seated (shown in figure) persisted up to 15 h after the accident, in spite of conscious voluntary efforts to 'get the legs back down to where they really were'. He reported an intermittent recurrence of this sensation for several weeks afterwards. (Taken, with permission, from Ref. 9.) **(B)** This patient fell about 10 m from scaffolding and developed a quadriplegia at the fifth cervical (C-5) level. Over a period of seven months he showed no functional neurological recovery. Within minutes of the fall, he felt that his legs, which were lying on the ground, had become extended at the hips (shown in figure). This sensation lasted about 15 min and recurred intermittently over the next seven months. (Taken, with permission, from Ref. 9.)

major challenge. It is now generally agreed that they cannot be explained in terms of peripheral mechanisms such as neuromas or other pathological activities in the stump. Loeser and Melzack<sup>10</sup> described several patients who underwent complete surgical transection of the spinal cord and yet continued to suffer severe pain in the phantom body (even after bilateral sympathetic block), although there was no possible spinal route for events in the periphery to reach the brain. Explanations for phantom limb phenomena must, I believe, be sought in the brain. However, the identification of phantom limb phenomena with the post-central somatosensory cortex<sup>1</sup> is erroneous. Excisions of the somatosensory cortex for phantom limb pain show that, with time, the phantom limb and the pain both return<sup>26</sup>.

The four-point summary given above suggests a new concept of the nervous system. It is generally assumed that the neural mechanism that underlies the experience of the physical self is learned. Henry Head<sup>27</sup>, for example, proposed the traditional view of the existence of a 'body schema', which is continually changing and represents all possible positions of the limbs. I find this idea improbable. Patients with an anesthetic block of the brachial plexus do not report that the limbs are in random positions but, rather, that they are predominantly in one of two positions<sup>6</sup>. At any instant, millions of nerve impulses arrive at the brain from the cutaneous and proprioceptive systems, as well as from the visual and vestibular systems, which are known to contribute to our experience of the body<sup>11,27</sup>. How can all these inputs be integrated into a unity of experience of the body?

It seems more likely that a genetically built-in matrix of neurons for the whole body produces characteristic nerve-impulse patterns for the body and the myriad somatosensory qualities we feel. The inadequacy of the traditional view becomes especially evident when we consider paraplegics with high-level complete spinal breaks. In spite of the absence of inputs from the body, virtually every quality of sensation and affect is experienced, from excruciating pain to orgasm. It is known that the absence of input produces hyperactivity in spinal cells above the level of the break. But how, from this jumble of ascending activity, do we get the meaningful experience of movement, the coordination of the phantom limb with other limbs, cramping of specific (non-existent) muscle groups, pain from a bunion or injury that was felt years or decades earlier<sup>13</sup>? These processes must occur in the brain.

I propose that the anatomical substratum of the physical self is a network of neurons that extends throughout widespread areas of the brain<sup>25</sup>. I have termed the network, whose spatial distribution and synaptic links are initially determined genetically, and are later sculpted by sensory inputs, a 'neuromatrix'. Thalamocortical and limbic loops that comprise the neuromatrix diverge to permit parallel processing in different components of the neuromatrix and converge repeatedly to permit interactions between the output products of processing. The repeated cyclical processing and synthesis of

nerve impulses in the neuromatrix imparts a characteristic pattern or 'neurosignature'.

The neurosignature of the neuromatrix is imparted on all nerve impulse patterns that flow through it; the neurosignature is produced by the patterns of synaptic connections, which are initially innate and then modified by experience, in the entire neuromatrix. All inputs from the body undergo cyclical processing and synthesis so that characteristic patterns are impressed on them in the neuromatrix. Portions of the neuromatrix are assumed to be specialized to process information related to major sensory events (such as injury) and may be termed neuromodules, which impress sub-signatures on the larger neurosignature.

The concept of a neuromatrix may seem radical, but it may be visualized as a Hebbian 'cell assembly' whose synaptic connections are genetically laid down rather than built up neuron by neuron, and in which synaptic competition due to inputs results in neural and synaptic death and survival and, therefore, the eventual neural-synaptic architecture unique for the individual's body<sup>28,29</sup>. I believe this concept to be consistent with recent discoveries of the astonishing precision of neural migration to predetermined destinations<sup>30,31</sup>, the parallel distributed processing systems that incorporate widespread areas of the brain<sup>32</sup>, and the simultaneous development of brain areas<sup>33</sup> that would permit the growth-as-a-whole of a neuropsychological unit such as the neuromatrix for the physical self.

#### Phantom limb pain

About 70% of amputees suffer burning, cramping, or other sensations of pain in the first few weeks after amputation. Even seven years after amputation, 50% still continue to suffer phantom limb pain<sup>34</sup>. Why is there so much pain in phantom limbs? I propose that the active neuromatrix, when deprived of modulating inputs from the limbs or body, produces an abnormal signature pattern that subserves the psychological qualities of heat or burning, the most common qualities of phantom limb pain. Cramping pain, however, may be due to messages from the neuromatrix to produce movement. In the absence of the limbs, the messages to move the muscles may become more frequent and 'stronger' in the attempt to move a part of the limb. The end result of the output message may be felt as cramping muscle pain. Shooting pains may have a similar origin, in which the neuromatrix attempts to move the whole limb and sends out abnormal patterns that are felt as pain shooting down from the groin to the foot. The origins of these pains, then, lie in the brain.

Surgical removal of the somatosensory areas of the cortex or thalamus<sup>26</sup> fails to relieve phantom limb pain. However, the new theory conceives of a neuromatrix that extends throughout selective areas of the whole brain, including the somatic, visual and limbic systems. Thus, to destroy the neuromatrix for the physical self which generates the neurosignature pattern for pain is impossible. However, if the pattern for pain is generated by cyclical processing

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and synthesis, then it should be possible to block it by injection of a local anesthetic into appropriate discrete areas that are hypothesized to comprise the widespread neuromatrix. Data obtained in rats have shown that localized injections of lidocaine into diverse areas, such as the lateral hypothalamus<sup>35</sup> and the cingulum<sup>36</sup>, produce striking decreases in experimentally produced pain. It is hoped that experiments such as these, carried out to test the neuromatrix theory, will one day lead to new approaches to the relief of phantom limb pain. If so, the theory will have served a valuable function.

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## letters to the editor

### Identification of nicotinic receptor ACh-binding subunits

SIR:

The review by Steinbach and Ifune in *TINS*, and the primary studies referenced therein, suggest that the  $\alpha$ -subunits of nicotinic acetylcholine receptors (nAChRs) can be identified on the basis of overall amino acid sequence homology with known  $\alpha$ -subunits and by the presence of specific amino acids such as the adjacent cysteines at positions homologous to Cys<sup>192</sup> and Cys<sup>193</sup> of the *Torpedo*  $\alpha$ -subunit<sup>1</sup>. The disulfide-linked cysteines at positions 192 and 193 are uniquely conserved in the  $\alpha$ -subunits and they can be selectively labeled by the active-site directed affinity reagent [<sup>3</sup>H]-MBTA<sup>2,3</sup>. In addition, reduction of these cysteines *in situ* or replacement of either cysteine with serine alters receptor function<sup>4–6</sup>. Although the exact role of these cysteines in receptor function is unclear, they remain a useful diagnostic criterion for identification of the  $\alpha$ -subunits of nAChRs.

It is possible, however, that consideration of overall amino

acid sequence homology and the presence of Cys<sup>192</sup> and Cys<sup>193</sup> is not sufficient for identification of functional  $\alpha$ -subunits. The presence of additional amino acids that are uniquely conserved in all  $\alpha$ -subunits and are known to be in close proximity to the acetylcholine-binding site should also be considered. Tyr<sup>190</sup> fulfills these criteria, since it is uniquely conserved in the  $\alpha$ -subunits and has recently been shown to react covalently with two very different active-site directed affinity reagents. The lophotoxin family of coral toxins are irreversible inhibitors of both muscle and neuronal nAChRs, and these toxins have been shown to react covalently with Tyr<sup>190</sup> (Refs 7, 8). The photoaffinity reagent [<sup>3</sup>H]DDF represents a different type of active-site directed affinity reagent that reacts primarily with Trp<sup>149</sup>, Tyr<sup>190</sup>, Cys<sup>192</sup> and Cys<sup>193</sup> (Ref. 9). While the functional role of Tyr<sup>190</sup> is somewhat uncertain, the charge distribution of [<sup>3</sup>H]DDF and the ability of positively charged ligands to prevent reaction of the receptor with the coral toxins, suggest that Tyr<sup>190</sup> may be involved in binding the quaternary ammonium group of acetylcholine<sup>7,9</sup>. On the other

hand, the structure and reactivity of active-site directed affinity reagents such as MBTA and bromoacetylcholine suggest that Cys<sup>192</sup> and Cys<sup>193</sup> are positioned somewhere near the acyl methyl group of acetylcholine<sup>4</sup>.

Based upon the above considerations, we suggest that Tyr<sup>190</sup> may be a useful frame of reference for identification of the ligand-binding subunits ( $\alpha$ -subunits) of nAChRs.

**Stewart N. Abramson  
Palmer Taylor**

Department of Pharmacology, University of California at San Diego, La Jolla, CA 92093, USA.

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