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Phantom limb pain in the primary motor cortex: topical review

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Introduction: what is a phantom limb and phantom limb pain?

Following limb amputation, 80% or more of patients perceive the existence of their lost limb, or sensations such as hot–cold or tingling, in the space where their lost limb once existed. The experience of the existence of this lost limb and sensations is known as "phantom limb". Even without limb amputation, phantom limb can develop as a result of motor palsy or sensory deafferentation by cerebral stroke, spinal cord injury, or peripheral nerve injury; in these cases, such a condition is called supernumerary phantom limb. The perception of phantom body parts has also been reported to occur after breast, penis, or eyeball excision. In patients who have had a limb amputated, the incidence rate of phantom limb complicated by pathological pain (phantom limb pain) is 50–80%. According to some reports, a majority of patients continue to suffer from phantom limb pain for several years after onset [1].

In animal experiments, it has been shown that the mechanisms underlying phantom limb pain are induced by various factors, such as neuroma-derived abnormal impulses resulting from peripheral nerve injury, hyperexcitability of neurons on the spinal dorsal horn, and hyperexcitability of neurons in the supraspinal central nervous system. Functional brain imaging studies suggest, however, that functional reorganization of the supraspinal central nervous system plays an important role in the onset of phantom limb pain. Brain regions within the primary somatosensory cortex (S1) correspond to a specific part of the body, constituting a somatotopic map (somatotopy). After amputation of an upper limb, for example, reorganization is observed in S1: the brain region corresponding to the affected upper limb shrinks, and the adjacent area in

S1 corresponding to the mouth/facial surface area expands [2]. Furthermore, a somatotopic map also exists in the primary motor cortex (M1). After amputation of an upper limb in patients with phantom limb pain, both shrinkage of the upper-limb area and expansion of the mouth/facial surface area are observed in M1, and the excitability of neurons in the upper-limb area increases excessively. Because the reorganization of the somatotopic map observed in S1/M1 (the sensorimotor cortex) is observed not only in cases of phantom limb pain but also in cases of pain following spinal cord injury [3] or complex regional pain syndrome [4], it seems to be a common underlying mechanism of neuropathic pain.

Motor control of phantom limbs: involuntary and voluntary movements of phantom limbs

Patients who have phantom limb pain complain of various kinds of pain. In a study involving 1,250 patients with phantom limb pain who lost a limb during the civil war in Bosnia and Herzegovina [5], approximately 58% of patients complained of pain associated with sensations on the skin surface, such as being cut with a knife, receiving an electrical shock, or feeling a stinging sensation. Approximately 42% of patients complained of pain associated with a sensation of movement (i.e., proprioceptive sensation), such as spasms or cramps in the phantom limb, or feeling that the phantom limb was twisted. Thus, almost half of patients with phantom limb pain perceived unpleasant involuntary movements of their phantom limb. Which neural substrates could underlie movement sensations of phantom limbs? Among phantom-limb patients, there are persons who can voluntarily "move" the phantom limb; that is, they can clearly perceive that the phantom limb is moving voluntarily. Functional brain imaging studies on phantom limb movements show activation of M1/S1 and the supplementary motor area (SMA) similar to that which occurs during voluntary movements of healthy limbs [6]. In the case of involuntary "movements" accompanied by an unpleasant feeling in the phantom limb, in addition to activation of S1/M1 and SMA, activation of the cerebellum, anterior cingulated cortex (ACC), and posterior parietal cortex (PPC) are observed [7]. Both ACC and PPC are known to relate with limb-movement control and the perception of this movement [8]. In one phantom limb study, however, ACC and PPC activations were correlated linearly with the degree of pain and discomfort arising from phantom-limb involuntary movements [9]. The patterns of brain activations (including ACC and PCC activations) accompanying phantom limb movements and healthy limb movements appear to be similar, regardless of whether the phantom limb movements are voluntarily or involuntarily. In terms of the perception of limb movements in the brain, there may be no discrimination between phantom and healthy limbs.

It has recently been revealed that motor commands to the phantom limb are generated from the hand area in M1, which is invaded and submerged by the mouth/facial surface area through M1 reorganization following the limb amputation [10]. It has also been reported that a combination of somatosensory feedback of muscle contractures in the residual limb and motor commands to the phantom limb can produce movement sensations in the phantom limb [11].

Up to this point in this review, we have described movement sensations of phantom limbs. The perception of phantom limb movements, posture (position), and size can fluctuate from moment to moment [12]. The phantom limb is often perceived to be intact, resembling a normal limb, or telescoped and shrunken so that the proximal portion of the limb is perceived to be missing or shortened, with the more distal portion floating near the stump. Occasionally, patients with phantom limbs perceive that the missing limb is swollen or enlarged compared with the intact limb. These phenomena are known as "telescoping". The degree to which telescoping is perceived (how short the phantom limb is felt to be) correlates with the degree of reorganization. As such, phantom hand movements of a completely telescoped phantom limb create activity in the S1/M1 cortical region that normally manifests the shoulder somatotopy, indicating enlargement of the hand region in S1/M1, while phantom hand movements of partially telescoped phantom limbs create activity in the S1/M1 region of the arm under normal circumstances, and those of a non-telescoped phantom limb activate the hand region [2]. Thus, the neural substrates for moving the phantom limb seem to be closely related with those for producing phantom limb sensations.

Phantom limb pain and the primary motor cortex

Movement sensations of phantom limbs are closely related with activity in M1, but what is the relationship between M1 and pathologic pain occurring in the phantom limb? As described in the Introduction, reorganization in the S1/M1 cortices is one of the underlying mechanisms of phantom limb pain, and the reorganization in M1 is not observed in patients who do not suffer from phantom limb pain following amputation of an upper limb [13]. It has been reported that repeated transcutaneous magnetic stimulation of M1 and electrical motor cortex stimulation (MCS) are effective in cases of neuropathic pain, such as phantom limb pain [14, 15]. Further, in order to produce such analgesic effects, the M1 somatotopic map area related to

the phantom limb must be stimulated [16]. In addition to MCS, electrical spinal cord stimulation (SCS) has been used to treat phantom limb pain, but the analgesic mechanism of this treatment has not yet been shown in detail. In functional brain imaging studies, various brain regions are activated during SCS. In a majority of these studies, M1 activation was specifically observed [17, 18]. One proposal is that SCS stimulates the dorsal column of the spinal cord and its electric impulses ascend through the dorsal column–medial lemniscal pathway to the brain. In physiological conditions, the dorsal column–medial lemniscal pathway conveys proprioception, vibratory sense, and discriminative touch sense, and these types of somatosensory information are thought to terminate at S1. However, recent studies clearly show that proprioceptive information is directly transmitted to both S1 and M1 [19], and proprioceptive information is mainly perceived at M1 [20]. On the basis of these notions, electric impulses generated by SCS would ascend the dorsal column–medial lemniscal pathway and terminate in M1, and the impulses may then be perceived at M1. Finally, SCS may produce an analgesic effect through the stimulation of M1. Interestingly, no analgesic effect is observed when patients treated with SCS cannot perceive the electrically stimulated sense in their phantom limb, suggesting that SCS must stimulate the phantom limb's somatotopic area in M1 in order to be effective. Although the somatotopic area of the phantom limb is invaded and submerged after amputation by the reorganization of M1 (i.e., expansion of mouth/facial surface area), electrical impulses by SCS (or MCS) toward the somatotopic area of the phantom limb may induce further reorganization of M1 (i.e., expansion of the phantom limb area and shrinkage of the mouth/facial surface area). This could theoretically result in the alleviation of phantom limb pain, but future studies would be needed to confirm such a viewpoint.

Reconstruction of the somatotopic map of phantom limbs: future perspectives on neuropathic pain therapy

In order to improve activities of daily living, patients with an upper limb amputation sometimes wear an electrical hand prosthesis connected to the stump of the amputated limb. Hand movements are produced by the contraction and relaxation of muscles at the stump. The prosthesis can become functional through training, and this training can also be useful for treating phantom limb pain [21]. Since the somatotopic map in S1/M1 corresponding to the prosthesis forms after motor learning of the functional limb [22, 23], it seems likely that the acquisition and expansion of the somatotopic area in S1/M1 that corresponds to the residual limb and phantom limb is linked to the analgesic effects of the prosthesis training. In fact, the somatotopic area in S1/M1 is reported to expand through the training of repeated somatosensory stimulations, and this seems to alleviate neuropathic pain in the affected limb [24, 25]. There are many reports on neurorehabilitation for neuropathic pain using visuomotor feedback of the affected limb. Following visuomotor feedback, the generation of voluntary movement perceptions of the affected limb can induce expansion of the somatotopic area in S1/M1 and then alleviate neuropathic pain, such as phantom limb pain [26–28], post-spinal cord injury pain [29], post-brachial plexus injury pain [30], and complex regional pain syndrome (CRPS) [31].

We have conducted neurorehabilitation using visuomotor feedback treatments (namely, mirror visual feedback and prism adaptation to optical deviation [32, 33]), but the treatments are still not effective for alleviating pain in many patients. We believe that, in addition to visuomotor feedback from the affected limb, a more powerful neurorehabilitation strategy using motor control of and somatosensory feedback from the affected limb should be developed. To accomplish this, we are now cooperatively developing a rehabilitation robot suit system (Fig. 1) [34, 35]. The system detects movements from a sensor attached to the healthy limb (for example, elbow joint flexion), and then artificial muscles and wires of the actuator (attached to the affected limb) create passive movements of the affected limb resembling those of the healthy limb. Thus, the affected limb, which may have been paralyzed following nerve injury, can be exercised voluntarily when patients intend to exercise the affected and healthy limbs simultaneously in similar manners.

Under the condition in which motor commands to the limb are successively generated from motor intention and then somatosensory feedback of the limb movement reaches S1, the activation of S1 is stronger than the condition in which the limb is exercised passively without any motor intentions or commands [36]. Furthermore, M1 activation is observed much more strongly when exercising the limb voluntarily than during passive movements of the limb. In particular, activation of the somatotopic area of the limb was observed in M1. By intending to command and actually commanding the affected and healthy limbs to exercise simultaneously, therefore, the rehabilitation system enables voluntary movements of the affected limb, and then (1) visuomotor feedback regarding the affected limb movements is acquired, as in a mirror visual feedback treatment, (2) somatosensory feedback of the affected limb movements are derived through the residual limb, and finally (3) the somatotopic area corresponding to the affected limb would expand, and this would result in alleviating neuropathic pain. With this rehabilitation system, the coordinative linkage of visuomotor and

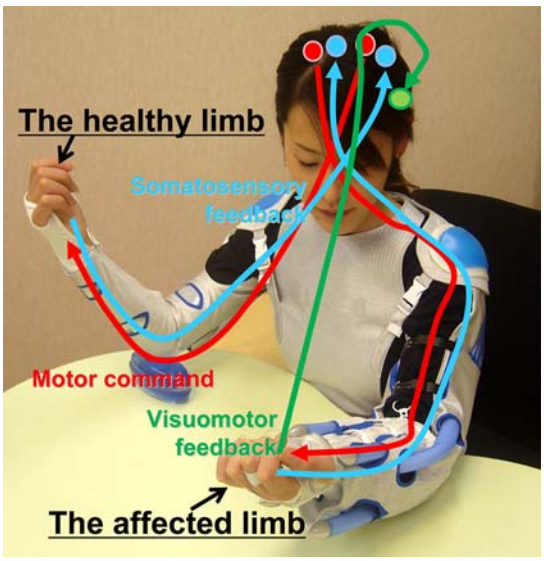

Fig. 1 Rehabilitation robot suit system for an upper limb with motor paralysis and neuropathic pain. A sensor suit is worn on the *right* upper limb (the healthy limb). On the *left* upper limb (the affected limb), an actuator consisting of artificial muscles and wires is fitted. Intending and forwarding the same motor commands from bilateral motor cortices toward both upper limbs (*red circles* and *arrows*), the sensor suit detects movements of the right limb, and the actuator carries out movements of the left limb resembling the movements of the healthy right limb. Thus, using this system, patients can passively but voluntarily exercise their affected limb, even in cases of motor paralysis and neuropathic pain resulting from nerve injury. Even though voluntary-like movements of the left limb are performed passively, patients perceive visuomotor (*green circle* and *arrow*) and somatosensory (*blue circle* and *arrow*) feedback in accord with their motor intention and commands of the left limb. Thus, the system can help a patient reconcile the coordinative sensorimotor integration of the left limb, secondarily expand the somatotopic area in the primary motor and somatosensory cortices, and finally provide relief from neuropathic pain (Co-development with Active-link Inc)

somatosensory feedback in accordance with motor intentions and commands of the affected limb could become a more effective strategy than current conventional neurorehabilitation treatments. In fact, in a psychophysical study involving healthy individuals, performance of the discriminant somatosensory function of the limb improved after exposure to the rehabilitation system (personal communications and unpublished data). In addition to determining the future clinical utility of the rehabilitation system for motor paralysis and neuropathic pain, we aim to gain supporting evidence through functional brain imaging studies.

Conclusion

Phantom limb sensation and phantom limb pain are often discussed as one phenomenon, but some patients who have a phantom limb do not perceive pain. The neuromatrix theory (i.e., a hypothesis that neural substrates for recognizing one's own body in the central nervous system underlie phantom limb sensation and phantom limb pain) [37] is a convenient and attractive thesis for explaining phantom limb phenomena, but it does not provide a satisfactory explanation for why phantom limbs are accompanied by pathologic pain.

Since pathological pain and coordinative linkage of sensorimotor integration are intimately related [32, 33], we anticipate that therapeutic mechanisms which affect the reorganization in M1/S1 may lead to a clarification of the underlying mechanisms of phantom limb sensations as well as of phantom limb pain.

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