The labelled-lines principle of the somatosensory physiology might explain the phantom limb phenomenon

José Carlos Pereira Jr. a,*, Rosana Cardoso Alves b

a Faculdade Medica Jundiaí, Rua Francisco Telles, 250, ZC: 13 202 550 Jundiaí, São Paulo, Brazil
b Department of Neurology, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

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A B S T R A C T

In the somatosensory system, various different sensory receptors capture different stimuli and convey them to the sensory cortex. Each type of receptor is specialised, that is, receives the stimulus to which it is predetermined to receive. Immediately as it is stimulated, the receptor sends a signal to the somatosensory cortex, via nerve fibres, and the area of the cortex that receives the signal determines the mode of the consequent perception. This mechanism is called principle of the “labelled” lines. The somatic receptors are the structures designated to receive stimuli, however, if their afferent fibres are stimulated at any point when approaching the cortex, the mode of perception by the cortex is the same as when the somatic receptor is stimulated directly. This occurs after the amputation of a limb, wherein the remaining fibres transmit to the cortex the mode of sensation for which they were specialised, despite the lack of somatic receptors at the beginning of the afferent pathway. However, the afferent pathway ends at the same cortex area as before the deafferentation. Since the somatic receptors and the integrity of afferent pathways are important to the regulation and modulation of the received stimuli, after the deafferentation the afferent pathway becomes anatomically and functionally abnormal. We believe these factors, involved in the pathophysiology of phantom limb (PHL), might be the explanation for this intriguing phenomenon.

Introduction

The term phantom limb (PHL) has been used to define the illusory sensation that an amputated limb is still present. PHL pain (PHLP) is reported as originating from a non-existent limb. PHL sensation (PHL-S) is defined as any perception that is interpreted as coming from an amputated limb [1]. PHL restless legs syndrome (PHL-RLS) describes sensations that are similar to those reported by patients with restless legs syndrome (RLS) [2–6].

When deafferentation occurs, the remaining afferent proximal fibres are deprived of their receptors but continue to send impulses to the sensory cortex as they did before amputation [7]; however, the stimuli now are directly received by the fibres and not indirectly by the sensory receptors. The regulator/modulator role of the sensory receptor is lost and, therefore, the specific adaptability of each receptor is also lost. After deafferentation, there are anatomical changes in the sensory axons that lead them to a greater exposition to environmental stimuli, turning them more susceptible to nonspecific stimuli. The remaining afferent fibres at the proximal end send to sensory cortex no specific stimuli, as now there is not the filtering activity of the sensory receptors, more than they did before amputation. These facts, inferred when one studies the normal somatosensory physiology [8], allow for the assessment of PHL-S as a peripheral, rather than central, neuropathy.

Signalling mechanism for the sensory cortex after deafferentation

The amputation of a limb is traumatic for the tissues of the affected region, and the peripheral innervations also suffer the consequences of that trauma. The inflammatory process that is triggered by amputation and the subsequent healing affects the peripheral innervations. The affected nerve pathways exhibit injuries on their protective structures, epineurium, perineurium, endoneurium, and Schwann cells. In addition to the injury, the myelin of the axons that is present surrounding the axons also suffers inflammatory damage and much of it is lost. Nevertheless, a large number of free nerve endings remain viable at the ends of the remaining nerves in the stump of the amputated limb [7]. These histologically anomalous fibres retain their sensory capabilities and are able to trigger action potentials. However, it is obvious that they do not detect specific stimuli anymore, as specialised sensory receptors are lacking after amputation. They detect nonspecific stimuli that stem from the region in which they are exposed. At the other end of the sensory pathway, the histology and anatomy are not
changed, that is, the afferents end at the exact same location in the sensory cortex as they did before the amputation [7]. The nonspecific signals of anomalous innervations, then, result in specific perceptions according to the location of the cortex where the neural impulse arrives. In other words, the afferent pathway is actually "labelled" by the location of the cortex in which it ends [8].

The extent to which the surgical trauma affects the tissues of the amputated region, the way healing occurs, and formation of neuromas determine the extent and manner in which the afferent pathway will constitute a new (but anomalous) grouping of "sensory receptors". These "improvised" peripheral sensors are easily excitable and lack the "adaptability" that characterise real sensory receptors. It is reasonable to claim that the type and extent of the healing that occurs in the peripheral innervations determine the "intensity" and "type" of PHL-S that the patient experiences. We could argue that "deafferentation" is not the most appropriate denomination for what actually happens; perhaps misafferentation could be a better term.

The idea that a sensory pathway is destroyed after amputation [9] is not entirely correct. For example, when a traumatic interruption of nerves occurs, occurring or not a neuroma, pain is felt by the patient in the territory that were nourished by the nerves. This is a practical proof that the remaining fibres are able to signalise to sensory cortex [10]. Evidence that the free nerve endings remain functional in the region of the nerve sectioned by amputation comes from a study by Grube et al. (2008). By gradually treating the stump neuroma with phenol, they substantially reduced both stump and phantom pain [11]. This result indicates that the neural sclerosis of the free nerve endings induced in their patients caused these nerve endings to become functionally inert and unable to generate action potentials. Schady et al. (1994) studied the responsiveness of the somatosensory system after nerve injury and amputation in the human hand. They concluded that the somatosensory system remains able to process information from a nervous fascicle that has lost its cutaneous territory. Furthermore, they verified that the somatosensory localisation remains accurate despite the presumed central reorganization that takes place after nerve division or amputation [7].

However, severe secondary damage does occur after amputation. Furthermore, it is logical to conceive that loss of the structures that constitute the distal sensory receptors of the pathway limits its ability to function normally after trauma. The physical presence of a limb is not what informs the conscious mind that the limb exists. The conscious mind recognises the limb as present as long as there is an area that represents the physical limb in the sensory cortex. As long as this area continues to receive signals, the conscious mind will perceive the presence of the limb, even though it is physically absent. Phantom patients usually describe that they feel the missing limb as in movement [12]. To this movement sensation, we suppose that can be applied the same reasoning: as the motor cortex commands the movement, the conscious mind "perceives" the phantom limb in movement as it always did.

Ropper and Samuels (2009) describe the various histopathological changes that follow injuries to the peripheral nervous system (PNS) [10]. Although the PNS retains the ability to send stimuli to the sensory cortex following histopathological damage (due to various diseases), these impulses are not properly regulated and modulated. Despite the differences between amputation and specific diseases of the PNS, it is important to recognise that amputation trauma is able to trigger changes in the PNS that are similar to those triggered by diseases. Several paraesthesias and dyesthesias are commonly experienced by patients with peripheral neuropathy, such as "pins and needles, falling asleep, stabbing, tingling, prickling, and electrical". Peripheral neuropathies cause pain that can be described as burning, aching, sharp/cutting, or crushing [10]. The unpleasant sensations felt by these patients are quite similar to symptoms felt by PHL patients. The physical presence or absence of the limb distinguishes paraesthesia-dysesthesia and pain in a patient with peripheral neuropathy from a patient with PHL-S. Nevertheless, whether the limb is physically present, or not, is irrelevant to the conscious mind, because the limb is always "present" as long as it is represented by the area of the sensory cortex that defines it. Therefore, it follows that there are few differences between the pathophysiology of symptoms in a patient with PN in comparison to one with PHL, except by physical presence, or not, of the limb.

However, to the sense of sight the lost limb is obviously not seen and, then, for the conscious mind the fact remains a paradox: a limb can be perceived but cannot be seen. Humans rely on the sense of vision to believe that a physical form indeed exists, and thus, to feel a limb that is impossible to see gives the patient an impression that a phantom is tied to his body. But, as long the neural map of the lost limb continues to receive information from nerves that were connected to the lost limb, as it indeed does, to conscious perceptive mind the limb still exists although cannot be seen.

**Considerations about some theories on the phantom limb phenomena and clinical correlates**

Immediate phantom pain (72%) and sensations (84%) after the amputation are felt by the majority of patients [13]. The rapid initiation of PHL-S after amputation implies that PHL, most possibly, is not secondary to any neuroplasticity: it is generally understood that neuroplasticity is a slow acting phenomenon. This fact is a clear inference that the afferent axons are not entirely destroyed when deafferentation occurs, i.e., the nerve fibres that were connected to the lost limb continue to signal from the stump to sensory cortex. That a true deafferentation does not happen has to be taken into consideration, as a premise, whenever one studies PHL-P and PHL-S, and also PHL-RLS phenomena.

The neuromatrix theory on PHL is based on the assumption that the afferent pathway is entirely destroyed [14], what might make of it an incorrect explanation of the PHL phenomena, moreover, only 7.4% of children born without a limb feel the missing part [15]. And to this small number of children that feel a phantom we can consider that it is present, not destroyed, the nerve fibres that were connected to the missing part of the limb, and thus, once these afferents are stimulated, the neural map that represents the congenitally missing part is also being stimulated.

When a peripheral nerve is cut, the fascicles of its proximal part remain without their sensory receptors, specialised "devices" able to filtrate and modulate stimuli that are to be sent to sensory cortex. Of course, then, a dramatic drop of normal inputs occurs [16] and a dramatic increase in abnormal inputs sent to sensory cortex ensues, as the loss of the sensory receptors makes the remaining afferent free nerves more exposed to the stump tissue environment. The plethora of inputs to dorsal root ganglia consequently is also followed by a dramatic surge of an abnormal activity in the dorsal root ganglia [16]. After the amputation, so rapidly is the abnormal activity surge of the dorsal root ganglia that it can be considered a natural after-effect of cutting the nerves, and secondary to the accentuated volume of inputs sent upstream by the free nerves endings. The phenomenon is a normal physiological mechanism of neurotransmission: no neuroplasticity is necessary for its occurrence. Also the neural map that represents the territory that has been amputated starts to receive an overwhelming body of chaotic, purposeless, information from periphery of tissues surrounding the cut nerves. The entire remaining line of afferents is overwhelmed by electrochemical activity, so a maladaptive neuroplasticity as the inputs are meaningless probably occurs, and certainly the whole clinical picture of the patient might be modified
according to pre-existing pathologies that have motivated the amputation [1], and to the intensity of the maladaptive neuroplasticity that occurs. The neural map of the lost limb has to accommodate a huge amount of not filtered and not modulated inputs, so that as the same here is expected to occur a maladaptive neuroplasticity. As the PHL-S commonly are a long time enduring condition [1], it can be inferred that the neural map of the phantom receives stimulation for a long time yet after the amputation. We assume that it is not necessary for the PHL, for being felt, that it receives “auxiliary functioning” from neighbourhood neural maps [17]. Most possibly, the phantom neural map increments and “in-vades” adjacent neural maps: the phantom map collides with its vicinity and not the contrary.

Theories that invoke neuroplasticity to explain the phantom phenomena (see review by Casale et al. [1]) might be devoid of physiological foundations. However, on the balance of probabilities, maladaptive neuroplasticity – that most certainly occurs – in the cortex that represents the amputated limb can be an important modifier of PHL clinical presentation.

Paraesthesia and pain resulting from a pathological process of peripheral nerves are, as a rule, localised distally (EKBOM 1961) to the fingers, toes, hands or feet, what is considered as a consequence of the longer fibres being the most vulnerable. This clinical fact could explain why the immediately post amputation pain is more localised in the distal parts of the phantom [18]. The so called telescoping phenomenon, the fading over time of the proximal part of the phantom sensations [19], could be explained in the same manner: the long nerves that transmit electrical impulses from distal parts of the limb could be the latest ones to heal.

Many chemicals have a crucial role in nociception: some directly stimulate nociceptors, like for example bradikinin, among many; others, like prostaglandins and P substance increment the threshold of nociceptors to firing pain signals. All these chemicals are liberated secondarily to tissue damage caused by the amputation trauma. Nociceptors do not have an easy adaptation nature, what can be physiologically understood by the necessity of awareness that tissue damage continues [8]. As the damaged tissues of the amputated limb take a long time to heal the chemical substances that incite pain might also take a long time to stop their release: so, pain tends to be chronic. There is no evidence that failure of the pain modulating systems, like opioidergic system, have a direct role in PHL-P. However, some individuals might have less effective pain modulating systems than others, what might also cause differences in the individual clinical presentation of the PHL-P condition.

The importance of the thyroid hormone for phantom limb pathophysiology

The importance of thyroid hormone (TH) to sensory systems [20] must be considered when studying somatosensory disturbances, such as pain syndromes because pain is only a specific kind of sensitivity. For instance, in RLS an increase in the tone of the hypothalamic–pituitary–thyroid (HPT) plays a central role in the onset of typical symptoms [21]. In hyperthyroidism, alertness and excitability of the individual are generally high, whereas, in hypothyroidism, they are low [8]. TH increases the active transport of ions across cell membranes, and NA⁺-K⁺-ATPase [8] is an enzyme that increases in concentration in response to TH, which is fundamental to the development of action potentials and signalling to somatosensory cortex. In patients with hypothyroidism, a decrease in the nerve conduction velocity is common, and this effect has been observed in both the sensory and motor systems [8].

TH has an excitatory effect on synapses [8] and increases their consumption of glucose [20]; these results indicate that the transmission of nerve impulses is increased in situations where the hypothalamic–pituitary–thyroid axis is not sufficiently modulated, as occurs in RLS [21]. Anything that stimulates or inhibits the HPT axis can increase or decrease the symptoms of pathological conditions that are secondary to PN [21]. This result occurs because all electrochemical neural impulses, including the impulses that are ‘labelled’ as pain, are more strongly transmitted when the HPT axis is enhanced. For example, dopamine and dopamine agonists (inhibitors of the HPT axis) are effective for both patients with RLS and patients with PHL-RLS [3,4]. Similarly, any drug that might influence the metabolism of TH could potentially be important. Thus, cytochrome P450 enzymes inhibitors (which participate in the degeneration of TH) increase the symptoms of a patient with PHL, whereas inducers decrease these symptoms. Moreover, a shortage of iron, which triggers an imbalance between TH and the dopaminergic system that modulates TH [21], may increase the symptoms in patients with PHL pain.

Many chronic pain conditions (including PHL pain) show variation in the intensity of pain throughout the day, with a greater intensity at night and particularly during the evening [2,22,23]. In the early evening, the levels of thyroid-stimulating hormone (TSH) elevate, which is called TSH surge. There is a rapid elevation of TSH levels at night in comparison to daytime levels [24]. The fact that the TSH surge and the worsening of painful conditions both occur in the early evening is not merely a coincidence. Because TH is critical to somatosensory system [20] and acts to increase the speed of synaptic transmission [8], it can be assumed that the worsening of nocturnal pain syndromes is secondary to the TSH surge [21]. Applying a cold pack onto an injury reduces pain by slowing the speed of nerve transmission [25]. This popular treatment of pain allows one to consider how important might be for painful conditions methods that decrement the intensity of the hypothalamic–pituitary–thyroid axis.

Final comments

After the amputation, as the proximal part of the free nerve endings continue to send inputs to cortex, that will turn to be unpleasant perceptions, it is possible that refinements in surgical techniques prevent the free nerves of being able of firing action potentials, what probably would relieve the PHL-S.

Regarding PHL-P and other pain syndromes, it is important to consider the evidence that defines the HPT axis as central to the regulation of pain intensity. Agents that block the activation of the HPT axis might be able to non-specifically reduce the symptoms intensity of pain syndromes in general. In patients with chronic pain, iron deficiency should be actively investigated and treated when present because it decrements the dopaminergic system, which is (an inference from the clinical features and pathophysiology of RLS) an important modulator of the HPT axis. RLS should be considered to be a paradigm for other peripheral neuropathies (including PHL-S) that involve modulation deficits in impulses to the sensory cortex.

A most appropriate explanation of the physiological causes of their sensations and pain may not cure the disease experienced by PHL patients; however, it could have the power to relieve the anxieties that might arise from the belief that a missing limb causes pain.

Conflict of interest

The authors declare that there are no conflicts of interest.

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