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EXPERTS' OPINION

Neurophysiological models of phantom limb pain: what can be learnt

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ABSTRACT

Phantom Limb Pain (PLP) is a dysesthesic painful sensations perceived in the lost limb, resulting from complex interactions between structural and functional nervous systems changes. We analyze its main pathogenetic models and speculate on candidate therapeutic targets. The neuroma model considers PLP to arise from spontaneous activity of residual limb injured axons. Other peripheral-origin models attribute PLP to damage of somatosensory receptors or vascular changes. According to the cortical remapping model, the loss of bidirectional nervous flow and the need to enhance alternative functions trigger reorganization and arm and face skin afferents "invade" the hand territory. On the contrary, the persistent representation model suggests that continued inputs preserve the lost limb representation and that, instead to a shrinkage, PLP is associated with larger representation and stronger cortical activity. In the neuromatrix model, the mismatch between body representation, which remains intact despite limb amputation, and real body appearance generates pain. Another hypothesis is that proprioceptive memories associate specific limb positions with pre-amputation pain and may be recalled by those positions. Finally, the stochastic entanglement model offers a direct relationship between sensorimotor neural reorganization and pain. Amputation disrupts motor and somatosensory circuits, allowing for maladaptive wiring with pain circuits and causing pain without nociception. Relief of PLP depends solely on motor and somatosensory circuitry engagement, making anthropomorphic visual feedback dispensable. Existing and apparently contradicting theories might not be mutually exclusive. All of them involve several intertwined potential mechanisms by which replacing the amputated limb by an artificial one could counteract PLP.

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Sixty percent to 80%[1] of subjects that suffered limb amputation have often their quality of life worsened by phantom limb pain (PLP).[2] Phantom sensation or awareness is the non-painful feeling that the lost limb is still present and kinesthetically perceived, whereas PLP is a dysesthesic and painful sensations perceived in the lost limb. Phantom limbs can be experienced in the form of kinetic sensations (perception of movement), proprioceptive components (size, shape, position) and exteroceptive perceptions (touch, pressure, temperature, itch, vibration).[3] The phantom can be perceived as having a normal limb size, or shorter than the original limb (telescoping) with hands, fingers, or toes perceived at the level of the stump.[4]

The majority of amputees experience PLP as burning (13.6%), cramps (15.3%), prick-

ling (23.4%), electrification (21%) and tingling (20.4%).[1] In 35% of cases, PLP is associated with the reason of amputation or with stump pain originating after amputation.[5]

PLP pharmacological management employs CNS-acting drugs and local anesthetics. Antidepressants, especially amitriptyline, are first-line therapies.[6] Gabapentin is safer than other anticonvulsants,[7] but its efficacy for PLP is low.[8] Strong Opioids are effective,[9, 10] while tramadol – a weak opioid μ-receptor agonist – is rapid but less effective.[8] Memantine, an NMDA glutamate receptor antagonist, is effective in acute pain,[11] yet less effective on chronic one.[12, 13] Local anaesthetics, (e.g. lidocaine – a sodium channel blocker) injected into the dorsal root ganglion transiently relieve PLP.[14]

Interestingly, there are no proofs that combination of medications is superior to single drug.[8] Other treatments include mirror and cognitive behavioral therapy, neuromodulation, and surgery.[15] Also, transcutaneous electrical nerve stimulation (TENS) has been proved to be helpful.[16, 17]

Despite such wide choice of possible treatments, PLP remains often not completely resolved, and sufferers exhibit high psychological and emotional distress,[18] anxiety and mood disturbance.[19]

The origin of PLP has intrigued scientists for long.[20, 21] Initially, PLP was believed to have no organic roots and its psychological consequence were misinterpreted as its cause.[3] Today, PLP is believed to be the result of complex interactions between structural and functional changes of the central and peripheral nervous systems.

In this article we analyze the main pathogenetic models of PLP and speculate on candidate therapeutic targets. Here, we consider a "model" as a theoretical abstraction useful to circumscribe the object of investigation and examine the variables at play.

Peripheral pathogenesis behind PLP was popular in the past and had recently regaining relevance. The neuroma model considers PLP to arise from the spontaneous activity of ectopic hyperexcitable loci on injured axons within the residual limb.[22] Although the brain might misinterpret impulses generated at the residual limb as originating from the absent limb,[23] it may be more appropriate to refer to such pain as "neuroma pain."[24] Whereas neuromas can result in pain perceived in the missing limb treatable by surgical interventions,[25, 26] maladaptive changes in the central nervous system can maintain PLP without a neuroma. Moreover, stump pain should be resolved as it can be a trigger of PLP.

Other models on the peripheral origin of PLP hypothesize that damaged residual somatosensory receptors may produce unwanted discharge causing allodynia,[27] or that non-neural factors, such as vascular changes in the stump, may contribute to phantom pain.[28]

Alongside peripheral models, others focus on central mechanisms. After injury and loss of bidirectional nervous flow, a topographical and functional reorganization of the nervous system takes place, pushed by the need to enhance alternative functions vicariating for the hand loss.[29] An initial unmasking of existing but functionally silent synaptic connections due to the lack of "surround" inhibition from the "orphan" area is followed by a later arising of new path connecting the areas controlling the lost limb with adjacent regions.[30] Such cortical reorganization sets the stage for the cortical remapping model, which is one of the most popular explanations for the PLP.

Afferents from skin in the upper arm and face "invade" the hand territory, in line with the hand cortical representation setting, which is in between the face area on one side and the upper arm on the other.[31]

Built upon an older hypothesis,[32] a keystone study shifted the focus to the CNS by showing that the amount of somatosensory cortical reorganization correlates with the magnitude of PLP, not with non-painful phantom phenomena,[33] suggesting PLP as directly correlated with plastic changes occurring in this cortex. Along this line, PLP patients showed a shift of the lip representation toward the deafferented primary motor and somatosensory hand areas.[34]

The remapping model could explain telescoping; since the cortical representation of the hand is wider and "stronger" compared to that of the forearm, and thus transradial amputations are less likely to develop a phantom forearm.[35, 36]

However, recent experiments found no clear correlation between cortical reorganization and

PLP challenging the orthodoxy of this relationship. In the persistent representation model, maintained representation and continued inputs are supposed to preserve local structures and their functions in an experience-dependent manner.[37, 38] Instead to a shrinkage of the lost limb representation, this model associates greater PLP with stronger cortical activity and larger representation of the phantom. In support of this model, it was found that the amount of PLP reduction experienced by patients undergoing transcranial direct current stimulation, while producing phantom motor execution, inversely correlates with the level of activity in the affected sensorimotor areas.[39] Prior studies have found a reduction of PLP by transcranial direct current stimulation alone,[40] but the combination with phantom motor execution has been theorized as more effective in other models.[24] In addition, similar cortical activity has been observed between able-bodied and subjects with amputations, but latter showed a disruption of inter-regional functional connectivity between homologous cortices governing the intact and the lost limb, which reflects a repeated lack of their coactivation.[37]

Looking at the topic from a different perspective, the concept of body image and schema, the brain dynamic representation of the spatial and biomechanical properties of one's body, derived from sensory inputs and from the copy of the motor commands during the interaction with the external world,[41] could provide a template for understanding phantom limb syndrome after interruption of sensory feedback.[42, 43]

During an anesthetic block of the brachial plexus, patients report their limb to be in one or two predominant postures, which do not vary among patients and ignore the actual position of the limb, as if the posture was coded in a static physical-self.[44] This possibility disrupts the traditional view of the body representation as being only a continuously updating projection of sensory feedback. Melzack hypothesizes that this representation relies on a genetically determined network connecting the cortex with the thalamus and the limbic system, named neuromatrix (Figure 1).[45, 46]

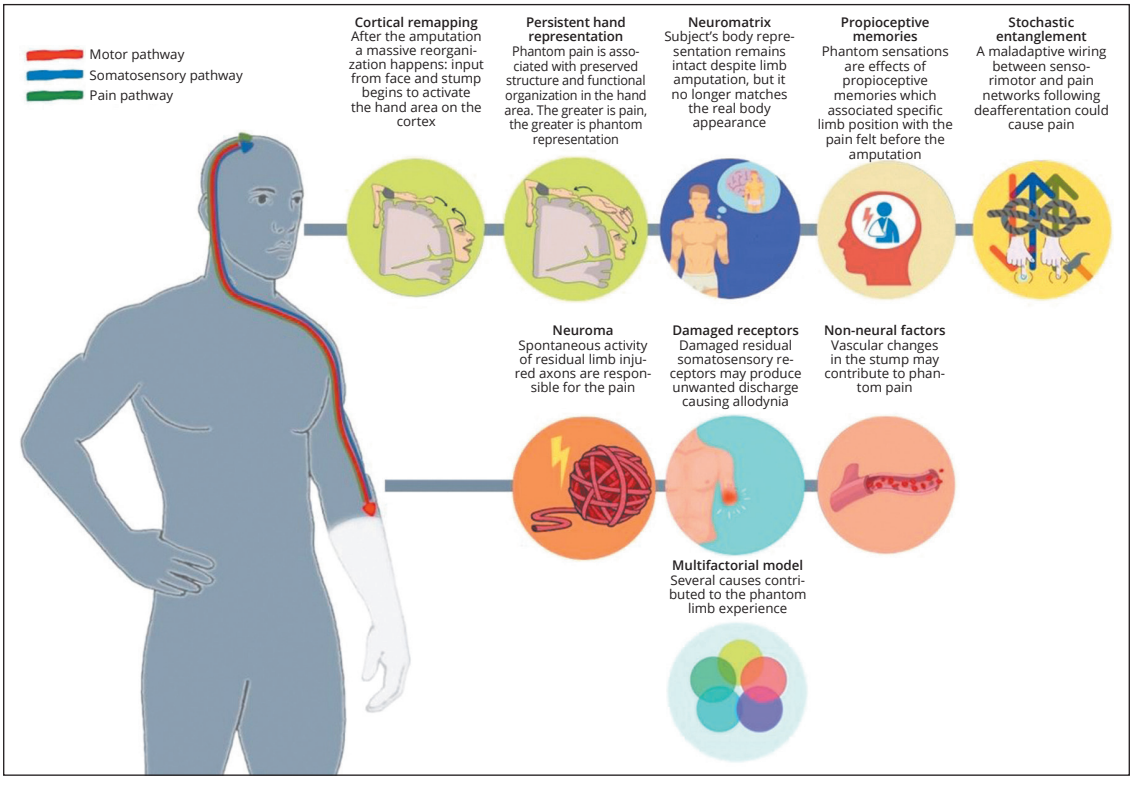

Figure 1.—Brief description of phantom limb pain models.

Neuromatrix is the base for a further PLP model suggesting that subject's body representation remains intact despite limb amputation, but it no longer matches the real body appearance. This mismatch generates pain without nociception and is responsible for PLP.

Accordingly, with a static representation hypothesis, both the quality and location of the phantom pain are the same of the pre-amputation pain in 60% of subjects who reported pain around the time of amputation.[47]

However, the predictive value of pre-operative pain for postamputation pain has been debated[3] and recent studies found no correlation between pre-amputation pain and PLP.[48]

Nonetheless, memory seems to play a crucial role in the perception of PLP. It has been suggested that pain is encoded prior to the amputation and can later be triggered by external stimuli,[47] and that phantom sensations are effect of proprioceptive memories which associated specific limb positions with the pain felt before the amputation.[49] Following the amputation, memories of motor and sensory information for a limb may be recalled,[50] as when during regional anesthesia patients refer to perceive limb position different from the actual one.[51, 52] Visuo-proprioceptive incongruence is due to proprioceptive memories of the lost limb and visual awareness that the limb is missing.

Finally, the stochastic entanglement model is a recent attempt to explain PLP.[24] Previous ideas on the genesis of PLP lack of a direct relationship between observed phenomena (e.g., cortical reorganization) and the neural circuitry generating the experience of pain. Amputation drastically disrupts cortical, sub-cortical, and spinal motor and somatosensory circuits, potentially allowing for maladaptive wiring with pain processing circuits. If under ordinary circumstances pain perception network are solely activated because of noxious stimuli, a stochastic entanglement between sensorimotor and pain networks following deafferentation could cause pain without nociception.

However, existing – and apparently contradicting – theories might not be mutually exclusive: the remapping and persistent representation models could coexist in a scenario in which a partial cortical reorganization occurs while a part of the limb representation is still preserved, or in case of overlapping.[53] The persistent representation model shares with Melzack's hypothesis the idea that PLP arises while the representation of the limb remains mostly unchanged.

Another explanation which holds for several models sees maladaptive plasticity not mainly affecting the extension of the cortical representation or its absolute activity, but other functional features, such as the interplay with relevant areas. Peripheral factors such as neuromas and vascular changes might not directly maintain PLP but, they could contribute to the stump pain that, in turn, could exacerbate PLP driving it to chronicity.

One holistic approach to the complexity of the phenomenon was already suggested in the late nineties, where at least five different causes were argued to play a role in PLP: stump neuromas, cortical remapping, monitoring of corollary discharge from motor commands to the limb, one's body image and vivid somatic memories of painful sensations or posture of the original limb translated into the phantom.[54] These components were thought to work together and influence each other; as a result, subjective experience of PLP may vary substantially from one patient to another. However, the necessity of each of these components, and the exclusion of others, remains an open question.

All considering, it emerges clearly that together with the pharmacological management of pain, the complex nature of the phenomenon is better faced by a multilevel care approach designed to achieve physical and psychological recovery.

From this brief overview of the neuropathogenetic hypotheses behind PLP, few suggestions can be gathered. PLP complexity and its tight relation with other types of pain (e.g. stump or dysautonomic pain) can easily lead to a PLP wrong diagnosis. Improving our knowledge of the phenomenon is the first step towards the most accurate therapeutic approach.

For instance, it is interesting to note how using a prosthesis can modulate body-related sensorimotor integration,[55] which is the basis on which the representation of the body is built, and it can also reduce the perceived pain.[35, 56-59] Interestingly, the use of prostheses was reported to

normalize intra and interhemispheric functional activity and connectivity,[60, 61] and it was negatively correlated with cortical reorganization and positively correlated with the reduction of PLP.[62]

There are several intertwined potential mechanisms by which replacing an amputated limb by an artificial one would counteract PLP; such as: 1) re-engaging of motor and somatosensory neural circuitry; 2) normalizing sensory inputs and motor outputs; 3) normalizing primary sensorimotor cortical representation; 4) normalizing body representation in the frontoparietal network; 4) resolving conflicts among sensory modalities or with the motor commands; and 5) embodying the prosthesis into the body representation.[55]

The stochastic entangle model stipulates that relief of PLP depends solely on the engagement of motor and somatosensory circuitry, making anthropomorphic visual feedback desirable but dispensable.[24] In this case, PLP would also be eliminated with a prosthesis that looks nothing like a human limb, so long its control relies on the missing limb's motor and somatosensory neural circuitry. This is in sharp contrast with the most popular views of models relying on the resolution of sensory-motor incongruence and restoration of body representations, where anthropomorphic visual feedback is not only highly valued but necessary. It is worthy of notice that visual feedback alone is not enough, as a realistic, anthropomorphic, but passive prosthesis does not resolve PLP, while therapies without anthropomorphic visual feedback have shown to relieve PLP.[24, 39, 63, 64]

Conclusions

The utility of a model relies on its ability to accurately predict empirical data, while avoiding unnecessary complexity. We are still far from grasping a full understanding of the PLP phenomenon, for instance, there is contradicting reports on congenital and acquired deafferentations,[65-67] which PLP models should be challenge with. Providing testable hypothesis and explicitly stating the expected prediction, while also increasing collaboration between researchers in the field, would help further understanding of the phenomena.

Key messages

- Peripheral-origin models attribute PLP to neuroma, damaged somatosensory receptor, or to vascular deterioration in the stump.
- Alteration of bidirectional nervous flow and substitution of lost functions trigger cortical plasticity, which "invades" the hand territory (cortical remapping model) or enlarges the hand representation and its activity (persistent representation model).
- Mismatch between damaged body and its preserved representation (neuromatrix model) or harmful association of specific limb position with pre-amputation pain (proprioceptive memories) are further possible PLP causes, but maladaptive rewiring of sensorimotor and pain circuits directly links plasticity and pain (stochastic entanglement model).
- All those apparently contradicting theories might not be mutually exclusive and involve intertwined mechanisms by which high-interacting hand prostheses could counteract PLP.

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