

# The Pathophysiology of Phantom Limb Pain

Yixuan Liu

*Chengdu No.7 High School, Chengdu, Sichuan, 610000, China*  
*Corresponding author's e-mail: Vivian.wang@cas-harbour.org*

## ABSTRACT

In major cases after amputation, patients are reported to have painful sensation in missing limbs, what is known as phantom limb pain (PLP). Since the first record of PLP hundred years ago, thorough research has been conducted in order to figure out the pathophysiology of this mental disorder. Alterations associated with central nervous system, typically several degrees of plastic changes, are first used to explain PLP. Transformations in residual portion, the effect of peripheral nervous system, are also accounted. However, all the various theories result in controversies rather than provide a united and comprehensive explanation for PLP. By literature analysis, this paper discussed a few theories of PLP pathophysiology, articulating their ground-breaking perspectives and factors that are omitted, and also states that people should attach more importance to the exploration of the correlations of different theories.

**Keywords:** *Phantom limb pain, amputation, neurologic mechanisms*

## 1. INTRODUCTION

Phantom limb pain (PLP), a pervasive chronic neuropathic pain, is generally known as pain perception in body regions that no longer exist after extremity amputation. High in morbidity, intense in pain level, and intractable to treat, PLP significantly plagued 50-80% amputees in their daily activities. Although it has been hundreds of years since the first known record of PLP by a French surgeon Ambrose Pare, people have not yet established a systematic understanding of PLP mechanisms[1]. Dispute around PLP pathophysiology is still continuing today.

For decades of research of the PLP etiology, the most widespread theory is the central nervous system theory, which primarily attributes the occurrence of PLP to maladaptive brain plasticity. Another acclaimed theory raised subsequently is the peripheral nervous system theory, denoting major significance in terminal inputs and structure including neuroma and dorsal root ganglia. Simultaneously, from a more full-scale perspective, some scientists further integrate several claims and form a rather linked explanation [2]. However, no single theory is heretofore informative or comprehensive enough to account for all phenomena of PLP, and each of them manifests different degrees of insufficiency and discrepancy.

Since the mysterious nature of PLP pathophysiology, the treatment for it is highly diverse, from traditional ones of pharmacologic treatment (mainly opioids and anticonvulsants), electropathy, and mirror therapy that employs mirror box previously and VR and AR in more recent decades, to innovational ones of targeted muscle reinnervation, yet few of them set signs on PLP mechanism or demonstrate consist efficacy[3]. Aiming at providing an overview for current progress of PLP

pathophysiology, this article will summarize several associated hypotheses and insert both older and later literature, to make clear the cardinal dispute. Through this article, the author hopes to inspire further research on PLP therapies targeted on its mechanism, which may readily be way more effective.

## 2. THEORIES OF PLP PATHOPHYSIOLOGY

When mentioning phantom limb pain (PLP), many scientists strive to distinguish it from phantom limb sensation (PLS), which is identified as the feelings from amputated limbs, sometimes even accompanied with movement sensation. Compared with PLS, PLP has a much more intense perceptual level, and patients experience extensive pain types including stinging, burning, and throbbing as reported[1, 2]. Since the great majority of amputees are troubled by PLP from a duration of few months to several decades every year, plenty of research has been taken out, which results in various theories about its pathophysiology. In general, all these theories can be roughly classified into central nervous system, peripheral nervous system, or both

### 2.1. Central nervous system

#### 2.1.1. Cortical Reorganization

Cortical reorganization theory is one of the most widespread and acceptable explanations for PLP phenomenon, whose main idea is about the maladaptive plasticity. Literature has indicated that a change of boundary occurs in primary somatosensory cortex (S1)

after amputation, so that areas originally represent the limbs are taken over by neighboring regions[2, 4]. This view is supported by multiple experiments from animal to human accumulatively over years. One of the earliest remarkable evidence for cortical plasticity is the owl monkey experiment. Using microelectrode to trace, researchers found out that previous representation of a finger was replaced by adjacent structure after cutting[5]. Later, human trials were conducted with imaging technologies like positron emission tomography (PET), magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI)[6]. The dimension of topography reorganization is proved to be in direct association with PLP intensity, which can reach a maximum of centimeters in adult brain[2, 7]. A great amount of evidence also showed that facial somatosensory region (mainly lips as some literature suggest) could invade about arm-related somatosensory region and cause patients pain in response to facial stimulation[2, 4]. However, despite the tremendous success achieved by cortical plasticity studies, there are indeed some inherent deficiencies. First of all, due to various experimental restrictions, few studies attempt to record the whole homunculus while studying PLP, but they simply focus on particular structures of arm, leg, and mouth instead, leaving out possible details[6]. Another group of scientists also accuse its ignorance of plausible factors other than PLP that contributes to cortical remapping, since with methodology disparate to past ones, they have found relatively indifferent yet consistent results with respect to pain-remapping causation[8]. Anyhow, the rationale of cortical reorganization theories still needs further confirmation and reassessment. Promisingly, advanced imaging techniques and non-invasive human research may lay a solid foundation for further experimental verification.

### 2.1.2. *Spinal Cord and Thalamus*

From another perspective, cortex may not be the single central nervous structure that sustain ramification after amputation. Spinal cord and thalamus are other two reasonable accounts for PLP. In spinal cord, a constant signal of inflammatory pain can lead to central sensitization, a change of synaptic function in spinal dorsal horn. And after neuron injury during amputation, another similar process called central hyperexcitability frequently occurs along with phantom sensation and pain. Possible causes of this include decreasing inhibitory process in spinal cord, increasing stimulation of the dorsal horn neurons, and the abnormality of Na<sup>+</sup> channel expression in thalamus and spinal cord pathways. Since the independence of thalamic hyperexcitability from spinal cord, thalamus itself can act as pain generator and amplifier. Notably, some animal experiments further propose that reorganization might first start from thalamus and then relays up to the cortex[4, 9, 10]. The putative relationship between these subcortical organizations and PLP is intricate and ambiguous, certainly expects deeper investigation, particularly in regards to their mutual effect

with superior and inferior structures.

### 2.1.3. *Proprioceptive memory*

Another possible attribution to PLP etiology is the proprioceptive memory theory. According to this view, the term proprioceptive memory stands for the internal awareness and memory of limbs and their positions. Such three-dimensional scheme is relatively independent, namely it will not be affected by a visual confirmation of an absent limb. This hypothesis is supported by the regional anesthesia study, in which patients reported that their limbs were remained at the same site after being relocated during anesthesia. Therefore, it is highly possible that only the last input from proprioceptive system will be accounted by the memory and the limb impression for amputees is maintained as before the operation, leading to misrepresentation and continuous activities in nerves. Some symptoms such as muscle cramping can thus be explained by the impact of proprioceptive memory[2, 10]. Remarkably, neuromatrix theory and body image theory, though different appellations, are actually two theories that share similar thought with proprioceptive memory—all three concentrate upon inner representation of body limbs and its further coordination with other systems. In a lot of literature, stark distinction between them is not made.

## 2.2. *Peripheral nervous system*

### 2.2.1. *Residual Limb Pain and Neuroma*

While amputation may give rise to the indirect consequence of reorganization in central nervous system, it does straightly change the morphology of peripheral neurons. The theory of peripheral nervous system occurrence of PLP earns its advocates with time. One potent statement of peripheral origin of PLP is associated with residual limb pain. Several reports indicate that patients with residual limb pain often suffer from PLP stronger in significance and higher in frequency, and when touching residual portion adjacent to amputate section, intensification in PLP sensation is recorded[2, 4]. This may be partially attributed to the neuroma form at the site of amputation, in which unusual activities occur in response to mechanical and chemical stimulation. Ectopic afferent barrage, or retrograde impulse, to the spinal cord, is plausible factor that promotes chronic pain[1]. Notwithstanding all the interrelationships and the efficiency of targeted muscle reinnervation therapy, neuroma theory is not compelling to interpret the entire PLP etiology[3]. Whereas neuroma may not develop immediately, PLP commonly arises within 24 hours after operation[2]. What is more, the cases of inborn amputees afflicted by PLP inspire us that neuroma is never necessarily decisive for PLP[11].

### 2.2.2. *Dorsal Root Ganglia*

In addition, the dorsal root ganglia (DRG) are another site worth discussion. Similar as neuroma, the regions of DRG can generate abnormal inputs likewise and even summate with the effect from neuroma to amplify the perceived pain. Compared to neuroma, the contribution of DRG is discovered much later. However, its importance is widely acknowledged as far beyond description, with numerous essays demonstrating the need for further investigation[4]. DRG is the spot, in which axons of the somatic cell body in peripheral nervous system located. Targeted at the surficial layers of the dorsal horn and the dorsal column nuclei of the brain stem, the axonal terminals in DRG are projected up to the spinal cord. After amputation, DRG axons are cut off from their initial distal portion, driving to inflammation and anomalous sprouting, and in certain cases, triggering the formation of neuroma. Subsequently, the injured portion of axons in the residual limb display hyperexcitability, which is transported by the remaining pathways to the spinal cord, results in chronic pain[4, 10].

### 2.2.3. *Pre-amputation Pain and Protheses*

Furthermore, some studies also reveal that those patients who are exposed to pre-amputation pain formerly are higher in incidence rate of PLP. Nonetheless some scientists propose that this phenomenon should not be overestimated: it has been verified that pre-amputation pain only plays a role in short-run PLP, with few similarities in location and characteristics with before[2, 10]. Besides, prosthetic use is found to be beneficial to alleviate PLP severity. While motor reorganization caused by somatosensory reorganization is positively associated with PLP intensity, it is inversely proportional to the usage of protheses. Therefore, persistent employment of functional protheses can contribute to the reduction of PLP severity. The reasoning underlying this effect is not fully understood yet. However, according to some claims, the protheses may compensate one's inner body image.

### 2.3. *Linked theories and others*

Except for the above theories that are particularly lean to central or peripheral nervous system, there are also some theories that are rather linked, which are more inclined to be some sort of integration and compilation. Ramachandran and Hirstein, for instance, have prompted a compositive statement in 1998, attributing PLP to multiple sources: (1) neuromas located in residual portion; (2) reorganization of cortex; (3) monitor of corollary discharge from central to peripheral; (4) one's internal awareness limb arrangement; (5) continuous recalls of painful sensation memories in the original limb[2, 12]. The advantage of such ascription is evident, because it emphasizes collaborative effects of both central and peripheral passages, indicating their mutual influences and

reinforcement. Such reciprocity is also in consistency with the diversified PLP symptoms depending on patients' individual circumstances and the dynamic outcomes of some focused treatment.

Nevertheless, detailed exemplification in determining respective contribution level of each factor is still in dearth, since such linked theories are a lot less prevalent than specific central or peripheral one solely nowadays. Recent studies mostly work on exploring deeper into one view separately, instead of examining holistic relationships between. In addition, research on PLP treatment typically investigate one therapy at a time, regardless of potential joint effectiveness. As a matter of fact, this corporate realm is actually promising, holding the prospective of developing theories of higher comprehension and therapies of greater precision, and thus should be paid more attention to.

## 3. CONCLUSION

It is undeniable that the recent centuries have witnessed a dramatic cumulation of human's understanding of PLP, including its many aspects such as incidence, characteristics, and mechanisms. But with numerous essays coming out every year debating on its dominant pathophysiology, heated discussion is not assuaged. With the help of new technologies in imaging and monitor, old and new theories begin to thrive. The latest studies have risen questions in regards to both traditional (such as cortical reorganization) and innovational theories, implying that the controversy about PLP pathophysiology is far from being explicitly addressed.

Till today, there is still a lack of factual backup and unequivocal justification to explain why PLP symptoms are miscellaneous, what exact factors contribute to it, how significant each specific factor is, and how all elements work together to enhance or weaken each other. To answer these questions requires researchers not only to explore sub-theories separately, but also to bear in mind constructing correlative bond between different theories by combining conformities and eliminating discrepancies. Apart from directing treatment and mitigating patients' mental and physical sufferings, the profound impact of figuring out PLP pathophysiology may lie in providing a novel vision about how somatic motion is realized, both through ascending and descending processes.

## ACKNOWLEDGMENT

I would like to express my most sincere gratitude to my research supervisors Professor Chiang-shan Ray Li, Yale University; Ms. Yuanyuan Dong; and Ms. Yi Li, for their constant encouragement, profound suggestions, and valuable facilities. I also wish to thank my parents and friends, for they are always my firm

backups.

This paper would never be fruited without their support.

## REFERENCES

- [1] S.M. Weinstein. Phantom limb pain and related disorders. *Neurol Clin* 1998, 16(4):919-936.
- [2] S.R. Weeks, V.C. Anderson-Barnes, J.W. Tsao. Phantom limb pain: theories and therapies. *Neurologist* 2010, 16(5):277-286.
- [3] A. Aternali, J. Katz. Recent advances in understanding and managing phantom limb pain. *F1000Res* 2019, 8.
- [4] H. Flor, L. Nikolajsen, T. Staehelin Jensen. Phantom limb pain: a case of maladaptive CNS plasticity? *NatRev Neurosci* 2006, 7(11):873-881.
- [5] M.M. Merzenich, R.J. Nelson, M.P. Stryker, M.S. Cynader, A. Schoppmann, J.M. Zook. Somatosensory cortical map changes following digit amputation in adult monkeys. *J Comp Neurol* 1984, 224(4):591-605.
- [6] T.R. Makin, H. Flor. Brain (re)organisation following amputation: implications for phantom limb pain. *Neuroimage* 2020:116943.
- [7] H. Flor, T. Elbert, S. Knecht, C. Wienbruch, C. Pantev, N. Birbaumer, W. Larbig, E. Taub. Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature* 1995, 375(6531):482-484.
- [8] T.R. Makin, J. Scholz, D. Henderson Slater, H. Johansen-Berg, I. Tracey. Reassessing cortical reorganization in the primary sensorimotor cortex following arm amputation. *Brain* 2015, 138(8):2140-2146.
- [9] S.G. Waxman, B.C. Hains. Fire and phantoms after spinal cord injury: Na<sup>+</sup> channels and central pain. *Trends Neurosci* 2006, 29(4):207-215.
- [10] K.L. Collins, H.G. Russell, P.J. Schumacher, K.E. Robinson-Freeman, E.C. O'Connor, K.D. Gibney, O. Yambem, R.W. Dykes, R.S. Waters, J.W. Tsao. A review of current theories and treatments for phantom limb pain. *J Clin Invest* 2018, 128(6):2168-2176.
- [11] R. Melzack, R. Israel, R. Lacroix, G. Schultz. Phantom limbs in people with congenital limb deficiency or amputation in early childhood. *Brain* 1997, 120 ( Pt 9):1603-1620.
- [12] V.S. Ramachandran, W. Hirstein. The perception of phantom limbs. The D. O. Hebb lecture. *Brain* 1998, 121 (Pt 9):1603-1630.