Author:
Matteo Galea

Reviewer:
Dr. Christian Zammit

Phantom Limb Syndrome: A Review

Introduction

Phantom limb syndrome is a condition whereby patients experience painful or non-painful, kinaesthetic sensory sensations in a non-existing limb. French surgeon Ambroise Paré was the first to observe this phenomenon in 1551, after critically wounded soldiers had to undergo subsequent limb amputation.1,2 An approximate 98% and up to 80% of amputees experience phantom limb sensations (PLS) and phantom limb pain (PLP) respectively.3,4 This literature review will primarily focus on the pathophysiology of phantom limb syndrome, its clinical manifestation and PLP management. Despite its prevalence, phantom limb syndrome is still regarded as a poorly understood phenomenon making it a chronic syndrome particularly difficult to treat.

Pathophysiology

The "body schema" provides a general framework and serves as a basis for its underlying pathophysiological mechanism. It can be broadly defined as an ongoing dynamic and evolving bodily experience whereby combined 'visual', 'motor' and 'proprioceptive' feedback information generate a single, integrated perception of oneself. Pathological states may potentially influence this combined self-perception leading to disorders of spatial perception as may occur as a result of limb nerve deafferentation and amputation.5,6 With an amputated limb, the brain receives solely proprioceptive information regarding its location rather than combined visual-proprioception feedback.

This dissociation might cause the brain to conjure up a phantom limb (PL).7 The perception of PL movement may in turn occur due to mirror neurons which potentially play a pivotal role both in the 'body schema' and hence in PLS. These mirror neurons allow one to mimic other people's bodily movement through simple observation by activating the observer's own muscles involved in the perceived action.8 Melzack's neuromatrix theory further explores this notion of the "body schema" and hypothesizes that pain is a

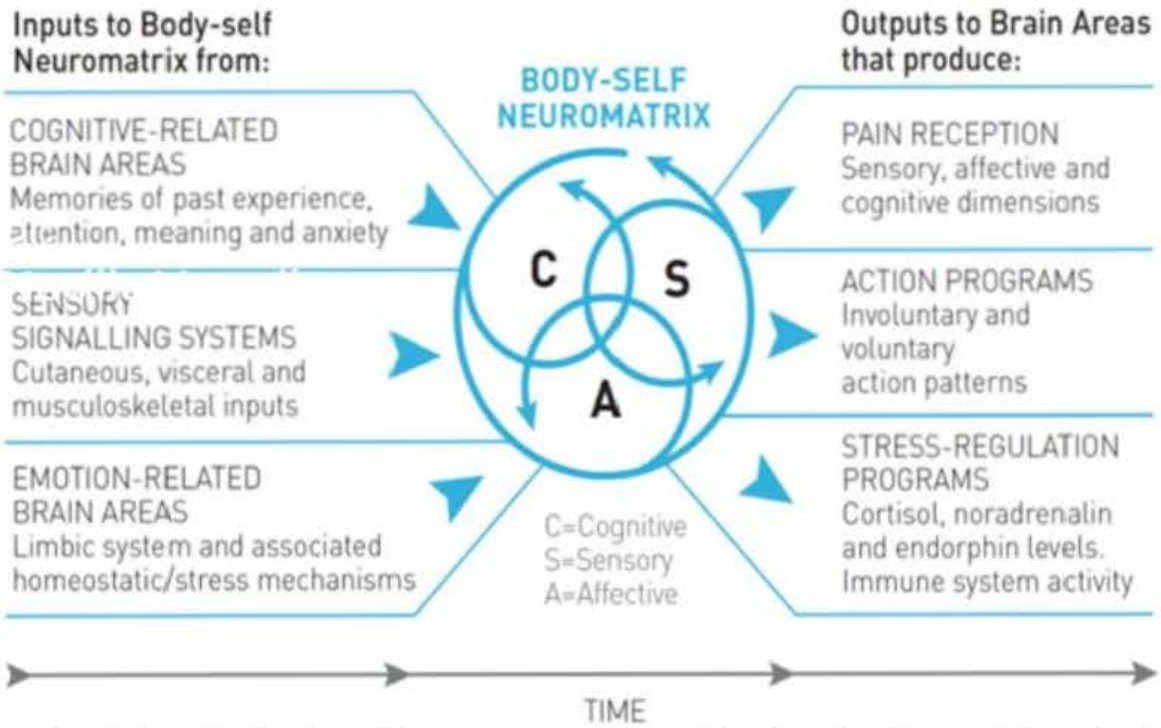

Figure 1: Melzack's body-self neuromatrix model of pain. Several input signals to the brain may trigger a pain neurosignature including cognitive, sensory and limbic feedback information. Pain is ultimately an output of the brain brought about by the activation of neurosignatures and regardless of any sensory input.11

complex experience brought about by the modulation and triggering of 'neurosignatures'(Figure 1).9,10

Neurosignatures are pattern characteristics in the neuromatrix which are generated through repeated "cyclical processing and synthesis of nerve impulses". Apart from being triggered through perceptual inputs affecting the thalamocorticol, somatosensory and limbic systems, they can also be self-generating in the absence of any input signals from the body.11,12 This correlates with the pain memory hypothesis which states that pain experienced by patients prior to subsequent amputation is stored in one's memory, thus being an important trigger for eliciting phantom pain even in the absence of any peripheral stimulation.13

Similarly, these pain memories play a fundamental role in 'empathic pain' which may elicit PLP by simply acknowledging, thinking or inferring an observed person in pain.10

Despite these theories suggesting a common etiology for both PLS and PLP, several studies have observed that phantom pain relief does not alter phantom sensations and vice versa.14 This suggests that there may be more underlying pathophysiological mechanisms for eliciting PLP.

Patients suffering from anxiety, stress, depression and poor coping mechanisms are more likely to experience PLP. However, the psyche should not be regarded as a primary elicitor.15 In fact, the peripheral system

is undoubtedly involved as it has been observed that the frequency of PLP is higher amongst patients suffering from stump pain. This most likely arises from neuromas at the nerve transection site due to increased ectopic firing of the A and C fibers. Despite this, patients may still experience PLP even in the absence of stump pain.16

The central nervous system also plays a prominent role in PLP. Unregulated activity of peripheral nociceptors at amputation site induces plasticity of dorsal horn neurons resulting in central sensitization. These neurons eventually become damaged generating pain impulses.17 Similarly, peripheral nerve damage may trigger central hyperexcitability resulting in spinal cord reorganization (Figure 2).18 Moreover, Flor et al. observed that cortical reorganization and PLP development were found to be directly proportional, suggesting that supraspinal changes may play a prominent role in PLP.19 Cortical remapping has also been attributed to telescoping of the limb, whereby the cortex remaps the distal limb portion onto adjacent areas e.g. shoulder. This causes amputee patients to perceive the phantom limb as being shortened such that the distal portion of the missing limb is closer to the stump and appears to be magnified. 3,10,15

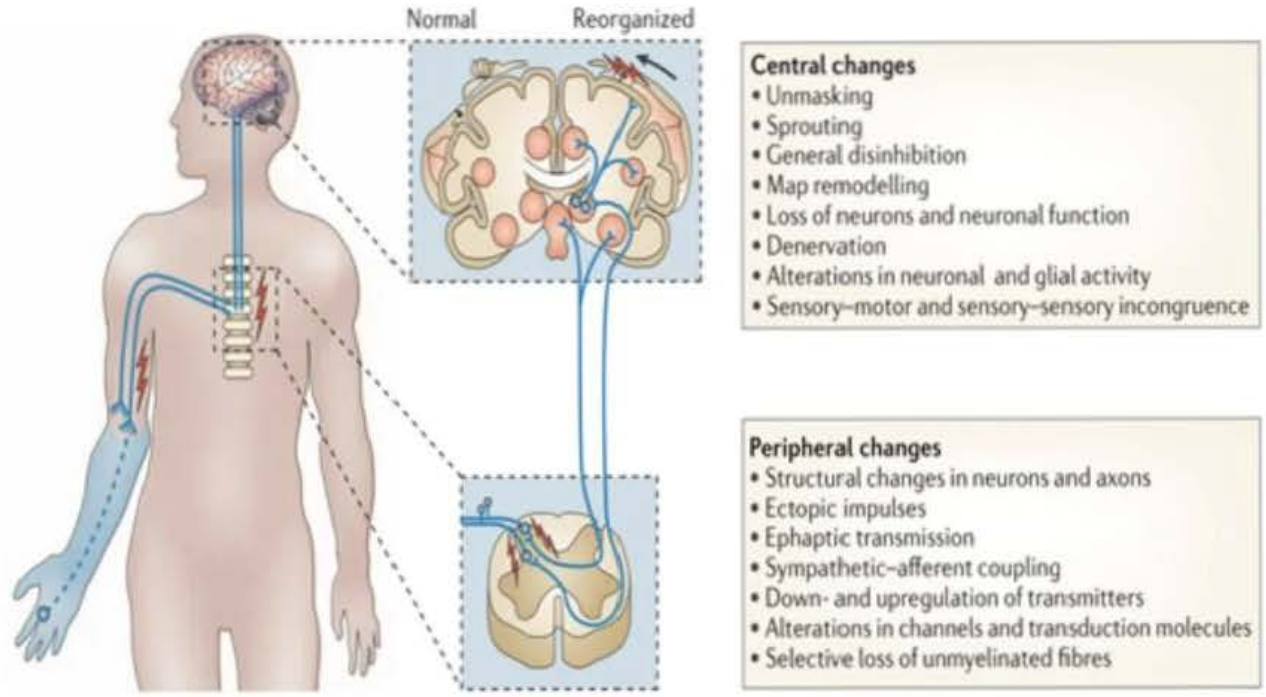

Figure 2: Central and peripheral changes occurring in PLP. Peripheral areas include the residual limb and dorsal root ganglion whilst the central areas include the spinal cord and the supraspinal centres namely the cortex, thalamus, brainstem and limbic system.18

Evaluation

Diagnosing PLP is somewhat difficult. Care must be taken to try and differentiate PLP from residual limb pain (RLP) as these are treated differently. Careful examination is required, both of skin tissue at amputation site so as to exclude infection/wounds as well as the joint above, to check for any signs of joint dysfunction. Sensations tests are also carried out and pain intensity is assessed. RLP is usually mild compared to PLP, the latter of which is often described as being intermittent with burning, throbbing/tingling, cramping or shooting sensations. Indeed, PLP diagnosis is often a 'diagnosis of exclusion' and heavily reliant on the patient's history.20

Treatment

The complexity of PLP combined with the fact that much of its pathophysiology stills remains uncertain, makes it a chronic syndrome which is arduous to treat. Various treatment options exist including pharmacological, non-pharmacological and invasive treatments. However, the treatment plan offered to the patient is mainly based upon the severity of pain being experienced (Table 1).21

Table 1: Overview of Treatment Modalities for PLP.21

PHARMACOLOGICAL	NONINVASIVE	INVASIVE
NSAIDS	**Mirror Therapy**	**Neurectomy**
Acetaminophen	**Transcutaneous Electrical Nerve Stimulation (TENS)**	**Dorsal Root End Zone (DREZ) lesion**
Opioids: Morphine Tramadol Methodone	**Biofeedback**	**Cordotomy**
	Relaxation Technique	**Thalamotomy**
Antidepressants: TCAs SNRIs	**Hypnosis**	**Sympathectomy**
	Acupuncture	**Spinal cord stimulation**
Anticonvulsants: Gabapentin Carbamazepine Topiramate		**Deep brain stimulation**
NMDA receptor antagonists: Ketamine Memantine		
Calcitonin		

Pharmacological Treatment

Pharmacotherapy is generally regarded as the first-line treatment modality. The most commonly prescribed drugs for providing moderate pain relief include non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen.22 Anticonvulsant drugs such as gabapentin may also prove useful to tone down neuropathic pain intensity and frequency.

However, similar to antidepressants as well as calcitonin, their effect on PLP has still been not confirmed as reports from various clinical trials have been inconsistent in their findings.21 Opioids and opiates may prove to be a suitable alternative and are often prescribed for neuropathic pain relief.

These perhaps represent the most effective type of pharmacological treatment for short-term relief, despite their negative connotation with drug dependence and the commonly reported side-effects such as constipation, sedation and nausea. Indeed, studies have reported a significant reduction in PLP both with oral and intravenous administration of morphine.23,24 It has been hypothesized that a contributing factor for opioid efficacy lies in their ability to disrupt cortisol reorganization, considered to be one of the main contributing factors for the pathophysiology of PLP. Despite this, available studies have not assessed whether morphine is effective in providing long term pain relief.24,25 On the other hand, intravenous administration N-methy-D-Aspartate (NMDA) receptor antagonist, namely ketamine, proved to be highly effective in reducing PLP incidence and potentially complete resolution.26 Nevertheless, these observations were mainly reported when such drugs were given intravenously. In fact, Maier et al. reported no significant clinical benefits in alleviating chronic PLP through oral administration of memantine.27

These perhaps represent the most effective type of pharmacological treatment for short-term relief, despite their negative connotation with drug dependence and the commonly reported side-effects such as constipation, sedation and nausea. Indeed, studies have reported a significant reduction in PLP both with oral and intravenous administration of morphine.23,24 It has been hypothesized that a contributing factor for opioid efficacy lies in their ability to disrupt cortisol reorganization, considered to be one of the main contributing factors for the pathophysiology of PLP. Despite this, available studies have not assessed whether morphine is effective in providing long term pain relief.24,25 On the other hand, intravenous administration N-methy-D-Aspartate (NMDA) receptor antagonist, namely ketamine, proved to be highly effective in reducing PLP incidence and potentially complete resolution.26

Nevertheless, these observations were mainly reported when such drugs were given intravenously. In fact, Maier et al. reported no significant clinical benefits in alleviating chronic PLP through oral administration of memantine.27

Non-Invasive treatment

Mirror therapy (MT) is proving to be a pioneer in providing PLP relief both in terms of cost and efficacy, with one study even reporting a 93% decrease in pain intensity.28 It consists of a parasagittally placed mirror between the upper/lower limb. The patient then moves the unaffected limb whilst observing its reflection in the mirror.

At the same time, they try to mimic the perceived movement in the reflection using their phantom limb. Thus, the virtual limb takes the role of the amputated limb. It has been hypothesized that the basis of MT lies in the dampening of the distorted perception between visual and proprioceptive feedback. This concept of MT has also recently taken a step forward via virtual reality proving a more avant-garde perspective in alleviating PLP.16 Another form of non-invasive procedure is transcutaneous electrical nerve stimulation (TENS) which is also proving to be a promising treatment modality. TENS employs the use of skin electrodes to transmit a mild electric current to cutaneous nerve fibers. A reported average decrease of 66% in PLP has been reported and may provide a temporary relief of PLP for up to one year.29

Invasive treatment

Invasive treatment is generally avoided and is associated with high recurrence rates and high risks for permanent nerve damage apart, apart from providing only short-term relief. Such procedures may include neuroablative neuroma resection, anterolateral cordotomy and sympathectomy amongst others. These are regarded as the last resort and before patients are referred to surgical intervention, it is ensured that conservative treatment modalities have been thoroughly exhausted without any clinical success.21

Conclusion

The exact underlying pathophysiology of phantom limb syndrome together with the potential manifestation of PLP, are complex mechanisms which despite their prevalence, remain elusive. Some promising therapies have been proposed throughout the years, most notably the use of MT and virtual reality. However, further research is required. Most of the current treatment options offered are rather of low quality. Indeed, the best treatment modality for management ultimately lies in unlocking the underlying pathophysiological mechanisms for their clinical manifestation.

References

1.Chahine L, Kanazi G. Phantom limb syndrome: a review. Middle East J Anaesthesiol. 2007;19(2):345-355.

2.Keil G. Sogenannte Erstbeschreibung des Phantomschmerzes von Ambroise Paré. "Chose digne d'admiration et quasi incredible": die "douleur ès parties mortes et amputées" [So-called initial description of phantom pain by Ambroise Paré. "Chose digne d'admiration et quasi incredible": the "douleur ès parties mortes et amputées"]. Fortschr Med. 1990;108(4):62-66.

3.Ramachandran VS, Hirstein W. The perception of phantom limbs. The D. O. Hebb lecture. Brain. 1998;121 (Pt 9):1603-1630.

4.Kooijman CM, Dijkstra PU, Geertzen JH, Elzinga A, van der Schans CP. Phantom pain and phantom sensations in upper limb amputees: an epidemiological study. Pain. 2000;87(1):33-41.

5.McGonigle DJ, Hänninen R, Salenius S, Hari R, Frackowiak RS, Frith CD. Whose arm is it anyway? An fMRI case study of supernumerary phantom limb. Brain. 2002;125 (Pt 6):1265-1274.

6.Vallar G. Spatial frames of reference and somatosensory processing: a neuropsychological perspective. Philos Trans R Soc Lond B Biol Sci. 1997;352(1360):1401-1409.

7.Collins KL, Russell HG, Schumacher PJ, et al. A review of current theories and treatments for phantom limb pain. J Clin Invest. 2018;128(6):2168-2176.

8.Fadiga L, Craighero L, Olivier E. Human motor cortex excitability during the perception of others' action. Curr Opin Neurobiol. 2005;15(2):213-218.

9.Melzack R. From the gate to the neuromatrix. Pain. 1999;Suppl 6:S121-S126.

10.Giummarra MJ, Gibson SJ, Georgiou-Karistianis N, Bradshaw JL. Central mechanisms in phantom limb perception: the past, present and future. Brain Res Rev. 2007;54(1):219-232.

11.Melzack R. Pain and the neuromatrix in the brain. J Dent Educ. 2001;65(12):1378-1382.

12.Melzack R. The gate control theory 25 years later: new perspectives on phantom limb pain. In: Bond MR, Charlton JE, Woolf CJ. Pain research and therapy: Proceedings of the VIth World Congress on Pain. Amsterdam: Elsevier, 1991:9-26.

13.Flor H. Phantom-limb pain: characteristics, causes, and treatment. Lancet Neurol. 2002;1(3):182-189.

14.Davis RW. Phantom sensation, phantom pain, and stump pain. Arch Phys Med Rehabil. 1993;74(1):79-91.

15.Flor H, Nikolajsen L, Staehelin Jensen T. Phantom limb pain: a case of maladaptive CNS plasticity?. Nat Rev Neurosci. 2006;7(11):873-881.

16.Weeks SR, Anderson-Barnes VC, Tsao JW. Phantom limb pain: theories and therapies. Neurologist. 2010;16(5):277-286.

17.Woolf, C. J. & Salter, M. W. in Wall and Melzack's Textbook of Pain (eds Koltzenburg, M. & McMahon, S. B.) 91–105 (Elsevier, Amsterdam, 2005).

18.Woolf CJ. Dissecting out mechanisms responsible for peripheral neuropathic pain: implications for diagnosis and therapy. Life Sci. 2004;74(21):2605-2610.

19.Flor H, Elbert T, Mühlnickel W, Pantev C, Wienbruch C, Taub E. Cortical reorganization and phantom phenomena in congenital and traumatic upper-extremity amputees. Exp Brain Res. 1998;119(2):205-212.

20.Hanyu-Deutmeyer AA, Cascella M, Varacallo M. Phantom Limb Pain. In: StatPearls. Treasure Island (FL): StatPearls Publishing; July 4, 2020.

21.Luo Y, Anderson TA. Phantom Limb Pain: A Review. Int Anesthesiol Clin. 2016;54(2):121-139.

22.Hanley MA, Ehde DM, Campbell KM, Osborn B, Smith DG. Self-reported treatments used for lower-limb phantom pain: descriptive findings. Arch Phys Med Rehabil. 2006;87(2):270-277.

23.Wu CL, Tella P, Staats PS, et al. Analgesic effects of intravenous lidocaine and morphine on postamputation pain: a randomized double-blind, active placebo-controlled, crossover trial. Anesthesiology. 2002;96(4):841-848.

24.Wu CL, Agarwal S, Tella PK, et al. Morphine versus mexiletine for treatment of postamputation pain: a randomized, placebo-controlled, crossover trial. Anesthesiology. 2008;109(2):289-296.

25.Huse E, Larbig W, Flor H, Birbaumer N. The effect of opioids on phantom limb pain and cortical reorganization. Pain. 2001;90(1-2):47-55.

26.Nikolajsen L, Hansen CL, Nielsen J, Keller J, Arendt-Nielsen L, Jensen TS. The effect of ketamine on phantom pain: a central neuropathic disorder maintained by peripheral input. Pain. 1996;67(1):69-77.

27.Maier C, Dertwinkel R, Mansourian N, et al. Efficacy of the NMDA-receptor antagonist memantine in patients with chronic phantom limb pain--results of a randomized double-blinded, placebo-controlled trial. Pain. 2003;103(3):277-283.

28.Chan BL, Witt R, Charrow AP, et al. Mirror therapy for phantom limb pain. N Engl J Med. 2007;357(21):2206-2207.

29.Melzack R. Prolonged relief of pain by brief, intense transcutaneous somatic stimulation. Pain. 1975;1(4):357-373.