

# Phantom Limb Pain

## Theories and Therapies

Sharon R. Weeks, AB,\* Victoria C. Anderson-Barnes, BA,\* and Jack W. Tsao, MD, DPhil†

**Background and Objective:** Since the beginning of the conflicts in Iraq and Afghanistan, there has been a dramatic increase in the number of military service members with single and multiple-limb amputations. Phantom limb pain (PLP) frequently develops in these individuals. As a result, identifying the best methods to treat PLP is critical. The review highlights areas of inquiry related to phantom pain, with a focus on PLP.

**Review Summary:** This review discusses phantom sensations and phantom pain that arise after amputation of a body part, and summarizes the differences between the 2 conditions. Characteristics of PLP are also discussed, including the onset, duration, and location of PLP. Theories explaining the etiology and presence of PLP are reviewed, along with the numerous treatment options reported in the published data for such pain, including the use of mirrors for treating pain. We conclude with a description of one military hospital's experiences with PLP.

**Conclusions:** Although more research has been done in previous years, this review identifies the need for continuing investigations. The etiology of PLP needs to be determined through more vigorous investigation, and a focus must be placed on defining treatment options in addition to mirror therapy that will improve the quality of life of those who suffer from this condition.

**Key Words:** phantom limb pain, amputation, rehabilitation, military medicine, mirror therapy

(*The Neurologist* 2010;16: 277–286)

The concept of phantom pain—pain that is perceived in a region of the body that is no longer present—was first introduced by the French military surgeon Ambrose Pare in the mid-16th century.<sup>1</sup> Years later, Silas Weir Mitchell, the famous Civil War surgeon, provided perhaps the most complete early description of this unique, painful phenomenon, coining the term “phantom pain.”<sup>2</sup> Since then, scientists and researchers alike have been investigating the pathophysiology and etiology of phantom sensations and phantom pain. A wealth of knowledge about the characteristics of phantom pain has been acquired in recent decades, and advances have been made with regard to its etiologies. The present review will focus on the numerous theories that have been formulated by researchers in the field, and a discussion of the potential treatment options for phantom pain will be provided. Finally, we will offer an insight into phantom pain from a military perspective based on our clinical experience with amputee patients from the

ongoing conflicts in Iraq and Afghanistan and will conclude the review with suggestions for future studies.

### PHANTOM SENSATION AND PHANTOM PAIN

The published literature routinely distinguishes between phantom “sensations” and phantom “pains” (see<sup>1,3–5</sup> for a review). Weinstein,<sup>1</sup> for example, has proposed that phantom sensations can be divided into 3 categories: kinetic sensations, kinesthetic components, and exteroceptive perceptions. Kinetic sensations are the perception of movement, taking into consideration perception of both spontaneous and willed movements. In contrast, kinesthetic components refer to the size, shape, and position of the missing body part, whereas exteroceptive perceptions include touch, pressure, temperature, itch, and vibration. Weinstein<sup>1</sup> describes phantom pain as falling under the category of “exteroceptive perceptions,” but distinguishes pain from sensation, stating that phantom pains have a greater intensity than phantom sensations.

Furthermore, several attempts have been made to establish a precise description or definition of “phantom pain.” Sherman and Sherman<sup>5</sup> concluded from a survey effort that the characteristics of phantom pain can be divided into 4 domains: (1) intensity of pain sensations; (2) frequency of episodes; (3) duration of each episode; and (4) description of the pain. Earlier work from Melzack<sup>3</sup> also sought to characterize phantom pain. His work describes phantom pain as consisting of 4 distinct properties: (1) persistent, enduring pain after the injured tissue has healed; (2) comprised of “trigger zones” that potentially spread to other (healthy) areas of the body; (3) often develops in patients who have experienced previous pain in the affected limb (more common in civilian amputees compared with military amputees) and frequently resembles the pain experienced prior to amputation; and (4) both increases and decreases of somatic input seem to have a positive influence on pain, and in some cases may even relieve the patient of phantom pains. However, despite the numerous attempts to classify and define phantom pain, the pathophysiology and etiology of the condition remain a mystery.

Perhaps surprisingly, phantom sensations and phantom pains can occur in many regions of the body. There have been reports of phantom sensations and pain emanating from unique places such as the breast (for a review, see<sup>6</sup>), nose,<sup>1</sup> and rectum,<sup>7</sup> as well as phantom menstrual cramps following hysterectomy<sup>8</sup> and urination or erection following penis removal.<sup>9</sup> For a more complete review of the various regions where phantom pain has been experienced, see Table 1.

Despite the number of body parts associated with phantom sensations and phantom pains, phantom limbs are by far the most commonly reported body part associated with a “phantom.”<sup>8</sup> Limb amputations are typically due to vascular disease, diabetes, or are the result of a traumatic event such as a vehicle accident or war-related trauma, such as blast injury from an improvised explosive device. What follows is a description of the characteristics that have been associated with phantom limb pain (PLP).

### CHARACTERISTICS OF PLP

#### Onset and Duration

The reported incidence of PLP varies widely in the literature (Table 2). These discrepancies likely result from confusion between the

From the \*Department of Orthopedics and Rehabilitation, Walter Reed Army Medical Center, Washington, DC; and †Department of Neurology, Uniformed Services University of the Health Sciences, Bethesda, MD.

Supported by the Military Amputee Research Program and the Dana Foundation. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army, Department of the Navy, or the Department of Defense.

S.R.W. and V.C.A. contributed equally to this work.

Reprints: Jack W. Tsao, MD, DPhil, Department of Neurology, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Rd, Room A1036, Bethesda, MD 20814. E-mail: jtsao@usuhs.mil.

Copyright © 2010 by Lippincott Williams & Wilkins

ISSN: 1074-7931/10/1605-0277

DOI: 10.1097/NRL.0b013e3181edf128

**TABLE 1.** Body Parts That Have Been Associated With Phantom Sensations or Phantom Pain

Body Part	Reference
Appendix	8
Bladder	1, 10, 11, 12
Breast	1, 6, 8, 12
Digit	1
Eye	1, 12, 13
Face (if certain portions of the face have been removed)	8
Menstrual cramps after hysterectomy	1, 8, 12
Nose	1
Penis (including phantom erections and ejaculation in paraplegics and in patients who have had the penis removed; also including the sensation of urination following penis removal)	1, 9, 12
Rectum (including sensations of flatus and feces; and pains including pricking and shooting, as well as hemorrhoids or hard stools that would rupture rectum)	1, 7
Teeth	1, 12, 14
Tongue	1
Ulcer pains after partial gastrectomy	8

**TABLE 2.** Reported Incidence of Phantom Limb Sensation (PLS) and Phantom Limb Pain (PLP) in the Literature

No. Subjects	PLS Incidence (%)	PLP Incidence (%)	Reference
300	98		15
98		4	
73	100	67	16
72	86.1	82 upper limb 54 lower limb	17 18
58	84 after 8 d 90 after 6 mo	72 after 8 d 67 after 6 mo	19
764		85	5
2750		78	20
124		59	21
176	87	78	22
32		50	23
56		75	24
526		55	25
60*	7.4 congenital 69.7 surgical	3.7 congenital 48.5 surgical	26
99	76	51	27
65	53.8	44.6	28

\*Study limited to children and adolescents ages 8 to 18.

definition of “phantom pain” and “phantom sensation” and an inability to distinguish phantom pain from residual limb pain.<sup>5</sup> Nevertheless, most recent studies report PLP at rates of 50% to 85%, significantly higher percentages than seen in the early literature which reported rates under 10%.<sup>15,25</sup> The differences in the reported rates can likely be attributed to the methods of data collection; earlier studies tended to calculate frequencies from medical records based on how many patients sought treatment for PLP, resulting in an underestimation of PLP incidence.<sup>30,31</sup> Incidence rates have been shown to be independent of gender, age (in adults), and location and level of amputation.<sup>5,24,27</sup> In

addition, the literature has not shown that incidence rates are related to the mechanism of amputation, that is, elective surgical versus traumatic.<sup>22</sup>

*Most recent studies report phantom limb pain at rates of 50% to 85%.*

Most prospective studies report correlations between preoperative pain and PLP,<sup>22,24,32</sup> with increased pain before amputation being associated with increased PLP after amputation. However, other studies report no such association.<sup>5,27,33</sup> The relationship is not simply understood because prospective studies, by necessity, include patients scheduled for amputations due to medical illnesses. As a result, they must exclude those patients who suffer traumatic amputations. As traumatic amputees largely do not have pain prior to amputation, it is likely that prospective studies overestimate the association between preamputation pain and PLP. To further confound the relationship between preamputation pain and PLP, Nikolajsen et al, who found a statistically significant correlation between the 2 pain indices, also found that patients are likely to have inaccurate memories of their preoperative pain.<sup>24</sup> Furthermore, Lacoux et al<sup>34</sup> reported that the incidence of PLP is not significantly different in traumatic amputees who lose a limb at the moment of the traumatic event compared with those who suffer an amputation secondary to the injury incident, eg, because of infection or other failed limb salvage.

The correlation between residual limb pain and PLP is likewise ambiguous, as some studies show a positive correlation between pain in the residual limb and PLP<sup>20,24,27</sup> whereas others do not report an association.<sup>5</sup> It is possible that some of this reported correlation results from an inability to differentiate between the 2 types of pain.

Most studies report that the onset of PLP occurs immediately after amputation, within the first 24 hours for about half of all patients and within a week for another 25%.<sup>16</sup> However, there have been case reports of PLP onset years and even decades after amputation.<sup>30</sup> Whether the presence or severity of PLP decreases over time remains an open question. Some studies show significant decreases in PLP over time postamputation,<sup>22,32</sup> whereas others show no significant changes.<sup>5</sup> In one study, Nikolajsen et al found that while the incidence did not decrease over time, the frequency and severity of an individual's PLP episodes did decrease.<sup>24</sup> As previously mentioned, this study also identified the difficulty patients have in reflecting back on previous pain levels.<sup>24</sup> This inability to recall pain severity likely contributes to the inconsistencies of incidence rates in the literature.

*The onset of phantom limb pain occurs immediately following amputation, within the first 24 hours for about half of all patients and within a week for another 25%.*

## Description and Localization

Patients report experiencing a wide range of pain characteristics, including burning, cramping, and tingling, as well as lanci-

nating electrical shocks, itching, stabbing, throbbing, and even a feeling of “pins and needles.”<sup>1,4</sup> Some patients also give very specific descriptions of their phantom limb that mirror preamputation pain, eg, fingernails digging into the palm,<sup>8</sup> or from our clinical experience, cramping resulting from clutching a grenade, firing a rifle, or boots compressing toes too tightly.<sup>3,5</sup> A few amputees are in constant pain, but most experience episodes that can be as short as a few seconds or as long as an hour or 2.<sup>8,35</sup> Although PLP is experienced in both upper and lower limb amputees, it tends to be localized distally regardless of amputation location.<sup>24,32</sup>

---

*Patients report experiencing a wide range of pain characteristics, including burning, cramping, and tingling, as well as lancinating electrical shocks, itching, stabbing, throbbing, and even a feeling of “pins and needles.”*

---

As is evident, the characteristics of PLP are widespread and tend to be unique across individuals. Although discrepancies exist in the reported incidence of PLP, recent studies have indicated a higher prevalence of PLP than ever before (see Table 2). From our experience with wounded soldiers at Walter Reed Army Medical Center in Washington, DC, the majority of patients we have encountered have reported experiencing phantom sensations and PLP.<sup>35</sup> Theories as to why sensations and pain develop and persist in absent limbs are highlighted later.

### THEORIES OF PLP

There are numerous theories surrounding the pathophysiology and etiology of PLP in the literature. Both central and peripheral nervous system mechanisms have been proposed, and some experts suggest that phantom pain is a combination of both. Below is a description of the various theories that have been proposed to explain the occurrence of PLP in amputees.

#### Central Nervous System Theories

##### Cortical Reorganization and Neuroplasticity

Cortical reorganization is the most commonly cited reason for the existence or development of phantom pain. Extensive experimental evidence has shown that the somatosensory and motor cortices undergo neuroplastic changes following limb amputation.<sup>36–39</sup> The literature suggests that cortical areas representing the amputated extremity are taken over by neighboring representational zones in both the primary somatosensory cortex (S1) and motor cortex (M1).<sup>8,37,40–42</sup>

---

*Cortical areas representing the amputated extremity are taken over by neighboring representational zones in both the primary somatosensory cortex (S1) and motor cortex (M1).*

---

Patrick Wall<sup>43</sup> was a pioneer in demonstrating plasticity in the adult central nervous system. Since then, human and animal models have been used to investigate the extent of cortical reorganization that occurs in the central nervous system following deafferentation or amputation. Magnetoencephalography, transcranial magnetic stimulation, functional magnetic resonance imaging, and direct electrical stimulation of the cortex have all been used to demonstrate changes in the organizational map of cortical neurons after amputation.<sup>41,44–47</sup> One of the first animal studies to prove cortical plasticity following amputation used microelectrodes on adult owl monkeys. Researchers found that when 1 finger was amputated, the sensory input from adjacent digits took over.<sup>45</sup> Furthermore, the amount of cortical reorganization has been found to be dependent upon the size of the deafferented region(s); the greater the deafferentation, the greater the cortical reorganization.<sup>41</sup>

Ramachandran et al<sup>46</sup> used magnetoencephalography to demonstrate cortical reorganization in humans following amputation. They investigated 4 upper extremity amputees, and determined that the Penfield map, which shows the organization of the sensory-motor cortex in humans, can be reorganized by at least 2 or 3 cm in the adult brain. Their findings were the first to confirm that large-scale reorganization of topography can occur over several centimeters in the brain of adults.<sup>8,46</sup> Furthermore, Flor et al<sup>37</sup> conducting imaging studies, have confirmed that there is a relationship between S1 reorganization and the intensity of PLP—the greater the extent of S1 reorganization, the more intense the PLP experience. One other study used functional magnetic resonance imaging to study intact hand and lip movements, as well as phantom limb movements, in 14 upper extremity amputees.<sup>48</sup> These data were compared with a healthy control group that performed hand and lip movements, as well as imagined hand movements. Patients with PLP were the only group to exhibit reorganization of the S1 and M1 regions. During lip movements, the representation of the lip region shifted to the area that previously corresponded to the deafferented hand.

As is evident from the literature, many researchers have investigated cortical reorganization as a plausible explanation for the occurrence of PLP. However, other theories have also been posited.

##### Body Schema

Originally proposed by Head and Holmes in 1912,<sup>49</sup> the concept of a “body schema” refers to a continually changing representation in the brain of the different positions one’s limbs could occupy. The body schema is modified by nerve impulses from the cutaneous, proprioceptive, visual, and vestibular systems, and is, therefore, plastic and acquired throughout experiences.<sup>49,50</sup> Brodmage and Melzack,<sup>51</sup> in contrast, while agreeing that the body schema promotes important postural functions, proposed that the body schema is fixed and possibly inherited. Many years later, Schwoebel et al<sup>52</sup> defined body schema as a dynamic representation of the relative positions of body parts derived from multiple sensory and motor inputs (eg, proprioceptive, vestibular, tactile, visual, efference copy—the neural copy of a movement command) that interacts with motor systems by generating or initiating movements and actions. The body schema can be thought of as a template of the entire body, and changes to the body—such as an amputation—results in the perception of a phantom limb.<sup>12,53</sup> Studies investigating congenital limb deficiencies have even suggested that the brain is naturally inclined to retain an intact and fully functional image of the body, regardless of the body’s true appearance.<sup>12,54</sup> These theories are supported by the observation that congenital amputees often experience PLP.<sup>55–57</sup>

## Neuromatrix Theory

Ronald Melzack<sup>58</sup> introduced the “neuromatrix theory” to account for meaningful experiences of the limb, such as phantom limb sensation or pain. The proposed theory can be thought of as an extension to previous theories regarding the body schema. Specifically, the neuromatrix theory proposes that the “body-self neuromatrix” is a network of neurons within the brain that integrates numerous inputs from the body, including somatosensory, limbic, visual, and thalamocortical components, and results in an output pattern that evokes pain or other meaningful experiences.<sup>59,60</sup> The neuromatrix involves the sensory, affective, and cognitive dimensions of the experience of pain.<sup>60</sup> The neuromatrix retains a central representation of each limb, and upon life experiences, this representation can be changed or modified to account for each new experience.

The theory proposes that the internal awareness of one’s body is created within the brain, and is activated by various perceptual inputs. The inputs received by the brain are plentiful, and according to Melzack,<sup>60</sup> include the following: (1) somatosensory inputs; (2) visual inputs; (3) phasic and tonic cognitive and emotional inputs; (4) intrinsic neural inhibitory modulation; and (5) inputs that relate to the body’s stress system (ie, cytokine, endocrine, autonom, immune, and opioid systems). The exact architecture of the pain neuromatrix, however, is determined by genetic and sensory modalities. The term “neurosignature” was proposed by Melzack<sup>58</sup> to refer to the patterns of activity generated within the brain that are continuously being updated based upon one’s conscious awareness and perception of the body and self. Melzack proposed that phantom pain is caused by the deprivation of various inputs from the limbs to the neuromatrix, causing an abnormal neurosignature to be produced.<sup>58,60</sup>

This theory has been reviewed by other researchers in the field and has gained mixed reviews. Giummarra et al<sup>12</sup> have criticized the validity of the theory, emphasizing that while it may address various aspects of phantom phenomena, it cannot be tested on phantom sensations that are pain-free. As a result, the theory is difficult to establish as the sole reason for the existence of phantom limbs.

## Additional Theories

Ramachandran and Hirstein<sup>8</sup> have proposed several theories surrounding the onset and occurrence of PLP. They first put forth the suggestion that the PLP experience develops because tactile and proprioceptive inputs from the face and tissues near the residual limb take over specific regions of the brain. This theory ultimately leads to their version of “cortical remapping” as an explanation for the development of PLP. However, recognizing that remapping cannot explain the entire occurrence of PLP in every individual with the condition, they have proposed a more in-depth model of phantom limbs—the “multifactorial model.”

With perception in mind, Ramachandran and Hirstein<sup>8</sup> suggest that there are at least 5 different sources that contribute to the PLP experience: (1) residual limb neuromas; (2) cortical remapping; (3) monitoring of corollary discharge from motor commands to the limb; (4) one’s body image; and (5) vivid somatic memories of painful sensations or posture of the original limb being “carried” over into the phantom. Perhaps the most important aspect of the theory is the emphasis that all 5 components work together and reinforce each other. As a result, individual experiences with PLP may differ.

An additional theory proposed by Ramachandran and Hirstein<sup>8</sup> is termed “learned paralysis.” This theory relates to the occurrence of volitional control over a phantom arm.

The learned paralysis is most applicable, for example, to the clinical scenario of a paralyzed arm due to brachial plexus avulsion which occurs prior to limb amputation. In this theory, the brain has ample time to “learn” that the limb is immobile because when messages are sent from the motor cortex to the “paralyzed” limb, the visual feedback that is relayed to the brain informs the individual that the limb cannot move. As a result, this message is continually received and repeated in the neural circuitry of the parietal lobe, and results in the brain “learning” that the arm is fixed in that position. Ramachandran and Hirstein<sup>8</sup> suggest that a similar situation may occur after a surgical amputation. Rather than the brain receiving information that the limb is immobile, it fails to receive feedback from a newly amputated limb to confirm that a motor command has been followed. As a result, an individual has volitional control over his or her phantom limb directly after an amputation; however, after a certain period of not receiving confirmation that the command was followed, the ability to control limb movement diminishes and the phantom is experienced as “paralyzed.”

Finally, a theory put forth by our group suggests that PLP is the result of a phenomenon which we term “proprioceptive memory.”<sup>61</sup> Proprioception refers to the internal awareness of limbs and limb location, and proprioceptive memories refer to memories of specific limb positions. Our hypothesis proposes that proprioceptive memories remain in an individual, even after a limb has been amputated. Presumably, the brain mechanisms that pertain to memory have not changed; therefore, it is likely that memories of motor and sensory information for a limb can continue to be recalled at will. Because memories remain intact, proprioception occurs as it did prior to amputation. The realization that a limb is missing arises through the visual system, but not the proprioception system. The rest of the body continues to work as it always has; nerves that are associated with the missing limb are still active, resulting in a false misrepresentation of the limb’s presence. In the case of a “paralyzed” phantom limb, perceived sensations of muscle cramping or joint fatigue, for example, might be explained by the existence of such proprioceptive memories.

---

*A theory put forth by our group suggests that phantom limb pain is the result of a phenomenon which we term “proprioceptive memory.”*

---

Further support for this hypothesis is provided by a study conducted by Gentili et al<sup>62</sup> who investigated patients’ perceptions of limb location under regional anesthesia. They found that the actual position of the limb and the patients’ perceived position of the limb frequently differed. The authors postulated that patients undergoing regional anesthesia seem to only take into account the last input received by the proprioception system, just prior to the time at which the anesthetic becomes effective. They concluded that patients perceive their last memory of limb position to be the only location the limb occupied throughout the operation. Following the onset of regional anesthesia, patients were unaware that their limb had been moved to occupy a different position. When they were questioned about limb position after surgery, the patients reported that their limb was occupying the same position as it did before surgery.<sup>62</sup>

Many hypotheses have been proposed to account for the pain that develops in the phantom limbs of amputees and subsequently

tested, yet it remains to be established which theory (or theories) portray(s) the most accurate explanation for the existence of PLP. In addition to the many cortical theories that have been put forward, some researchers believe PLP is caused by peripheral mechanisms.

### Peripheral Nervous System Theories

One of the strongest arguments for peripheral causes of PLP arises from the correlation seen between PLP and residual limb pain. Amputees with chronic residual limb pain experience PLP significantly more frequently.<sup>5</sup> The mechanisms for this relationship are not clear. However, in the residual portions of amputated limbs, neuromas commonly form at the site of a nerve transection. These neuromas exhibit abnormal activity following mechanical or chemical stimulation.<sup>31</sup> Two studies have independently shown that repetitive touching of the residual limb results in increased PLP.<sup>30,63</sup> Furthermore, studies have shown that PLP decreases with the resolution of pain in the residual limb.<sup>16</sup> Although these correlations are compelling, they are not sufficiently informative to explain why some researchers do not show a significant correlation between residual limb pain and PLP.<sup>5</sup> Congenital amputees also sometimes experience PLP, meaning that neuromas cannot entirely explain the experience of pain.<sup>55,57,64</sup> A possible explanation for this inconsistency is that there are many confounding factors at work in the study of the residual limb pain-PLP relationship. Residual limb pain, for example, can interfere with prosthetic use and rehabilitation.<sup>30</sup> However, multiple reports claim that functional use of a prosthesis and successful rehabilitation decreases PLP.<sup>65,66</sup> Although the reasons for this correlation were outside the scope of the studies, it is possible that incorporation of the prosthesis into a patient's body schema on some level results in reduced PLP. Amputees remain cognizant of their limb loss and, therefore, likely do not fully represent the artificial limb at the cortical level. However, it has been shown that wearing a prosthesis helps maintain a body schema in which the phantom limb remains similar to the intact one, as such a representation is necessary for movements to be carried out properly.<sup>67</sup>

Peripheral causes of PLP are also implicated based upon research examining peripheral injections of locally active drugs. One study reported the perineuronal injection of the acetylcholine blocker gallamine, which increases sodium intracellular concentrations, produces PLP in amputees while the injection of lidocaine (which blocks sodium channels nonspecifically) into neuromas of the residual limb, blocks PLP.<sup>68</sup>

The theory proposed by Ramachandran and Hirstein<sup>8</sup>—that there are at least 5 different sources that contribute to phantom pain (residual limb neuromas, cortical remapping, corollary discharge, body image, and somatic memories)—is perhaps the strongest hypothesis linking phantom pain to both cortical and peripheral mechanisms as it uses pathways from both systems to explain the range of phantom limb sensations reported. However, the authors do not address the degree of contribution to PLP that arises from the central and peripheral nervous systems. Nevertheless, other experts promote only cortical or only peripheral mechanisms. Clearly, more research is needed to ascertain the mechanisms that truly account for PLP.

### TREATMENT OPTIONS

Treatment options for PLP have generally been limited, and there is no clear consensus on an optimal treatment regimen. It is possible that some treatments will be more efficacious for specific patient cohorts. Several pharmacologic studies have been carried out to examine the effectiveness of various drug interventions on PLP. However, the results from these studies failed to reveal an optimal treatment algorithm or the usefulness of individual drugs. Some of the most common medications used to treat PLP are opioids,

anticonvulsants, lidocaine/mexiletine, clonidine, ketamine, amitriptyline, nonsteroidal anti-inflammatory drugs, and calcitonin.

Despite multiple problems with the use of opioids to treat acute pain, they remain one of the common prescriptions to complement both oral analgesics and regional anesthesia. Opioids bind to opioid receptors peripherally and centrally, providing analgesia without loss of touch, proprioception, or consciousness.<sup>69</sup> Opioid medications include piperidine, morphine, methadone, hydromorphone, and fentanyl. There is further evidence that opioids may diminish cortical reorganization, thereby disrupting one of the possible mechanisms through which it is believed that PLP originates.<sup>8,40,70–72</sup> Morphine has been shown to be effective in decreasing PLP in some instances,<sup>73,74</sup> but the high rate of undesirable side effects frequently makes it an unattractive solution for providers and patients alike. In our experience, war-wounded service members who have been taking high doses of methadone have not experienced any relief of PLP.<sup>35</sup>

In addition to opiates, anticonvulsants have long been used in the treatment of PLP. Gabapentin, for example, a drug that is effective in treating several syndromes of neuropathic pain, has been shown to relieve pain in up to two-thirds of patients in one study<sup>75</sup> and to be significantly more effective than placebo in another.<sup>76</sup> However, 2 additional studies both showed that gabapentin did not substantially affect pain in adults with PLP, either in the immediate postoperative period<sup>31</sup> or when used for chronic pain.<sup>77</sup> In contrast, another anticonvulsant, carbamazepine, was shown to reduce intense and brief stabbing pains of PLP but not other types of PLP.<sup>78,79</sup> Consequently, the role of anticonvulsants in treating PLP remains unclear.

Similarly, studies have reported that amitriptyline, a tricyclic antidepressant, appears to provide excellent and stable PLP control in one study<sup>80</sup> but failed to effectively control pain in another.<sup>81</sup> However, secondary amines such as nortriptyline and desipramine are perhaps equally effective and have fewer side effects. These drugs were demonstrated by Panerai et al<sup>82</sup> to be effective in resolving central pain syndromes, but their study group was not limited to patients with PLP. In an open-label case series conducted by Kuiken et al,<sup>83</sup> mirtazapine, an antidepressant without the multiple side effects typically seen with tricyclic antidepressants, treatment of 4 patients resulted in marked decrease in PLP by at least 50%.

In addition, clinical studies examining the effect of calcitonin simultaneously question<sup>84</sup> and support<sup>85</sup> the usefulness of the drug in chronic PLP. Other suggested pharmacologic agents for treating PLP include oral tramadol tablets<sup>80</sup>; perioperative epidural infusion of a diamorphine, clonidine, and bupivacaine cocktail<sup>86</sup>; a clonidine and mexiletine combination regimen<sup>87</sup>; and intravenous ketamine.<sup>88</sup> Nonsteroidal anti-inflammatory drugs are also considered promising in the treatment of PLP as the most recent agents in the class decrease nociception both peripherally and centrally.<sup>89</sup> Despite their initial promising results, these drugs have not been tested in controlled trials.

Although pregabalin has been used in the treatment of neuropathic pain,<sup>90</sup> and some providers have used it successfully off label to treat PLP, to date there have been no definitive studies examining its efficacy. The oral NMDA receptor antagonist, memantine, has been shown in 2 case studies to significantly reduce severe PLP.<sup>91</sup> Although previous controlled trials using memantine to treat chronic PLP following amputation showed little success,<sup>92–94</sup> a more recent double-blinded placebo-controlled trial of memantine administration for the 4 weeks following amputation showed significance decrease in PLP.<sup>95</sup> In their review of the literature, Buvanendran and Kroin<sup>96</sup> concluded that memantine may

be a useful supplement when used soon after amputation to treat PLP but less useful for established chronic neuropathic pain.

In addition to pharmacologic interventions, many nontraditional therapies for pain have been applied to PLP with varying degrees of success. These therapies include transcutaneous electrical nerve stimulation (TENS), deep brain and spinal cord stimulation, acupuncture, and virtual reality/mirror therapies. Although the mechanisms of pain relief for these treatments are not fully understood, there are promising results that warrant further study.

Controlled experiments examining the effect of brief, intense transcutaneous electrical stimulations at triggers points on the residual limb or along the course of the peripheral nerve of the residual limb led to an average PLP decrease of 66%, significantly more effective than placebo contributions to pain reduction.<sup>97</sup> It has also been suggested that TENS on the healthy side of the body may give better long-term improvement than stimulating the affected, painful area.<sup>98,99</sup> However, more recent reports found no significant difference in the analgesic requirements or reported prevalence of PLP after treatment for postoperative pain or chronic PLP with active low frequency TENS compared with sham TENS, although treatment did result in faster residual limb healing.<sup>100</sup> A case report suggests that TENS applied to the contralateral leg was significantly more effective than a placebo in decreasing the intensity of phantom sensations.<sup>101</sup> Further research revealed a moderate, yet statistically significant decrease in pain 10 minutes after onset of auricular TENS.<sup>102</sup>

Temporary and immediate relief of PLP has also resulted from deep brain stimulation of the ventral caudal thalamic nucleus.<sup>97,99,103–105</sup> Stimulation of the posterior columns of the spinal cord led to reduction of pain levels by 25% in 65% of patients immediately following surgery. However, only about half of those experiencing pain reduction derived long-term relief from PLP.<sup>106,107</sup> Subsequent reports have not replicated these findings.<sup>108,109</sup> Likewise, epidural spinal cord stimulation does not appear to help decrease the intensity or frequency of PLP.<sup>110,111</sup>

Other treatments for PLP that have been reported to have mixed results include anesthetic and surgical neuroablation<sup>112</sup> as well as psychological interventions<sup>113</sup> that include cognitive and behavioral methods. Acupuncture has been reported in multiple cases to temporarily relieve PLP,<sup>114,115</sup> but an additional case report noted that acupuncture failed to provide PLP relief following a traumatic limb amputation.<sup>115</sup> The results from studies of these treatments, like many of the pharmacologic interventions, show that the therapies do not consistently reduce or relieve PLP in patients nor are their mechanisms of action fully understood.

Perhaps the most promising therapy for treating PLP is mirror therapy, first reported by Ramachandran and Rogers-Ramachandran in 1996.<sup>116</sup> In this treatment, the patient views the reflection of their intact limb moving in a mirror placed parasagittally between the arms or legs while simultaneously moving the phantom hand or foot in a manner similar to what they are observing. The virtual limb in the mirror appears to be the missing limb. Patients have reported a relief of cramping and “frozen limb” phantom pains as a result of even one session with the mirror.<sup>8</sup> Efficacy of mirror therapy was reported to be 60% (9/15 upper limb amputees). The only randomized, sham-controlled, crossover study of mirror therapy was conducted by Chan et al<sup>117</sup> in lower limb amputees. In this study, subjects viewed the reflection of their contralateral leg and foot in a plane mirror placed parasagittally along their body (Fig. 1). For 15 minutes each weekday for 4 weeks, subjects performed simple movements of the foot/leg with their intact limb, viewed the virtual image in the mirror, and mimicked the movements with their phantom. The movements included toe flexion and extension, foot dorsi- and plantar flexion, rotation about the ankle and inversion/



FIGURE 1. Mirror therapy for lower extremity amputee.

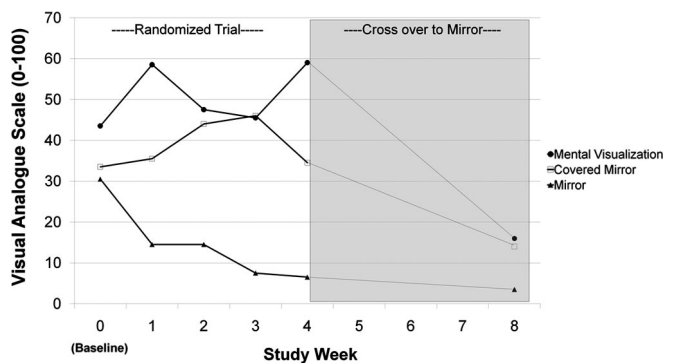


FIGURE 2. Results of a sham-controlled, randomized, cross-over trial of mirror therapy to treat phantom limb pain.<sup>117</sup> Unilateral lower limb amputees who underwent mirror therapy daily for 4 weeks to treat PLP showed significant decreases in pain compared with those patients undergoing mental visualization therapy or using a covered mirror. When the 2 control groups were crossed over to mirror therapy at the 4-week point of the study, they also showed a significant decrease in PLP scores after 4 weeks of mirror therapy. Reprinted with permission from Chan BL, Witt R, Charrow AP, et al. Mirror therapy for phantom limb pain. *N Engl J Med.* 2007;357:2206–2207. Copyright © 2007 Massachusetts Medical Society. All rights reserved.

eversion, and knee flexion and extension (for above knee amputees). Pain scores were measured daily using a 100-mm visual analogue scale, where 0 mm was no pain and 100 mm the most severe pain. The study showed significant decreases in PLP in patients who underwent mirror therapy compared with 2 control groups (covered mirror and mental visualization therapies) (Fig. 2).

*Perhaps the most promising therapy for treating phantom limb pain is mirror therapy.*

The mechanisms of pain relief are unclear, although Ramachandran suggested that mirror therapy resolves the visual-proprioceptive dissociation proposed as an explanation for PLP. The

**TABLE 3.** Summary of Treatment Options for Phantom Limb Pain

Treatment	Type of Study	Significant Effects	Reference
Level I (at least 2 randomized, controlled studies)			
Morphine	R, PC, DB, CO; N = 31	SBP	73
	R, PC, DB, CO; N = 56	SBP	74
	R, PC, DB, CO; N = 12	SBP	70
Gabapentin	Meta-analysis of 15 studies; N = 1468	Effective in neuropathic pain, including PLP; ineffective for acute pain	75
	R, PC, DB, CO; N = 14	SBP	76
	R, PC, DB; N = 41	NDP	121
	R, PC, DB, CO; N = 24	NDP	77
Level II (randomized controlled study and other evidence)			
Amitriptyline and tramadol†	R, PC, DB, CO; N = 84	Both drugs SBP	80
Amitriptyline	R, PC, DB; N = 39	NDP	81
Tricyclic antidepressants, including Chlorimipramine	R, PC, DB, CO; N = 39	Decreases central pain syndromes	82
Nortriptyline		SBP and nortriptyline	
Calcitonin	R, PC, DB, CO; N = 20	Question effectiveness	84
	R, PC, DB, CO; N = 21	Support effectiveness	85
TENS	Case report, PC*, N = 1	SBP	101
	PC, N = 53	SBP	97
Mirror therapy	R, PC, CO; N = 21	SBP	117
	Case studies		8
Ketamine	PC, DB, CO; N = 20	Significant decrease in PLP	84
	Case series, N = 11	Decreases in PLP	88
Memantine	R, PC, DB, CO; N = 19	NDP	92
	R, PC, DB; N = 36	NDP	93
	R, PC, DB, CO; N = 8	NDP	94
	R, PC, DB; N = 19	SBP over 1, 6 mo	95
	Two case studies	NDP over 12 mo	
Level III (other evidence)			
Carbamazepine	Case series, N = 5	Decreases PLP	78
			79
Mirtazapine	Open-label case study, N = 4	Decreases PLP by at least 50%	83
Diamorphine/clonidine/bupivacaine—perioperative epidural infusion	PC; N = 24	SBP	86
Clonidine/mexiletene	Open-label, N = 31	Significant decrease in PLP	87
Acupuncture	Case series, N = 9	Decreases PLP	114
	Case series, N = 3	Decreased PLP in <sup>2/3</sup>	115

\*Subject received real and placebo TENS during separate sessions.

†Double blind compared to placebo for both medications. Open label comparison of medications to each other.

SBP indicates significantly better than placebo in treating PLP; NDP, no significant difference when compared to placebo; PC, placebo controlled; DB, double-blinded; R, randomized; CO, crossover; N, number of subjects.

success of mirror therapy compared with both covered mirror and mental visualization therapies indicates that vision is the critical component in resolving pain and that the visual feedback provided by mirror therapy might allow vision to dampen any mismatch in brain signal perception.<sup>117</sup> Whereas all 6 patients in the mirror therapy group had decreased PLP, use of covered mirror and mental visualization treatments, which lack the overt visual input generated by viewing the intact limb moving in a mirror, not only did not significantly reduce phantom pain, in some instances these therapies actually worsened pain.<sup>117</sup> Such results are consistent with the visual-proprioception dissociation theory.

Although the results of the Chan et al<sup>117</sup> study appear to provide further support for the postulate that a mismatch between

visual and proprioceptive inputs contribute to the generation of PLP, it is not clear why a mismatch would cause pain. Rossi et al,<sup>118</sup> however, offer further evidence to explain the success of mirror therapy, while giving insight to a possible mechanism of pain relief. Their findings expand upon those of Rizzolatti et al,<sup>119</sup> who found the existence of mirror neurons in monkeys—neurons that fire both when the animal performs an action, as well as when it observes the same action performed. Rossi et al discovered homologous neurons in humans.<sup>118</sup> Ramachandran and Rogers-Ramachandran<sup>120</sup> provided further evidence for the presence of these mirror neurons by finding that “touching” the virtual image of the limb in the mirror is sufficient to elicit tactile sensations on the phantom limb. These experiments explained why a person with intact limbs only empa-

thize with the person they observe, rather than feeling it themselves, because of the null input from their intact limb. Patients with missing limbs do not receive such null input. As a result, activation of mirror neurons in an amputee may create a perception of tactile sensation. Consequently, since the activation of these mirror neurons modulate somatosensory inputs, their activation may have blocked protopathic pain perception in the phantom limb. A summary of the evidence for each treatment modality for PLP is shown in Table 3.

### THE WALTER REED EXPERIENCE: A MILITARY PERSPECTIVE OF PLP

The recent wars in Iraq and Afghanistan have resulted in a new population of amputee patients who are younger than typical amputee populations and are much more physically fit, active, and motivated in their rehabilitation efforts. As a result, new research is necessary to investigate the special considerations for this population and perhaps offer new insights into the mechanisms of PLP itself.

Since the beginning of the conflicts in Iraq and Afghanistan, over 900 amputees have been treated at Walter Reed Army Medical Center in Washington, DC. As part of routine treatment efforts, the patients are asked to describe their experience with phantom sensation and phantom pain. There have been a plethora of responses regarding the onset, duration, description, and location of phantom sensations and phantom pains from those queried. Furthermore, some explain they have volitional control over their phantom, and can move their phantom at will, while others report their phantoms being fixed in a specific position. Some even report the inability to make movements with the phantom, despite the presence of a strong sensation or pain emanating from their residual limb. For example, one service member reported that his phantom hand was in a distinct position: he felt he was pulling the trigger on his rifle with his index finger, and was unable to move his hand to a different position. He also felt cramping pains in his hand muscles. Another service member, a bilateral, above knee amputee, described the feeling of heavy legs, asserting that the feeling was similar to weights attached to his calf muscles. He also described that it felt as though his combat boots were on too tightly. Many other unique and interesting reports have been offered by other injured service members, demonstrating the need to continue research on phantom limbs and the associated characteristics of this phenomenon. We are currently conducting a randomized, controlled trial of mirror therapy with upper extremity amputees to assess whether the response rate is similar to that for lower extremity amputees. In addition, we are also using functional magnetic resonance imaging to examine what changes occur in the brain after 4 weeks of mirror therapy. In 10 patients who have participated in either study or who were treated with mirror therapy for their PLP, 8 (80%) experienced pain relief.

---

*We are currently conducting a randomized, controlled trial of mirror therapy with upper extremity amputees to assess whether the response rate is similar to that for lower extremity amputees.*

---

Of the theories that have been proposed thus far, it seems likely that a combination of cortical and peripheral mechanisms must interact and result in the phantom pain experience, as no single pathway seems to account for the spectrum of phantom sensations experienced by each amputee. For example, cortical reorganization,

one of the best supported theories, cannot by itself explain phantom pain, as it fails to account for the experience of phantom sensations or phantom pain in children with congenitally missing limbs. The same can be said for the remaining theories that have been proposed to provide an explanation for PLP; the body schema, neuromatrix, and learned paralysis theories all have strengths, but each theory by itself does not account for the entire spectrum of PLP. Therefore, we are led to conclude that phantom pain is likely to be the result of a combination of cortical and peripheral mechanisms, as well as visual and proprioceptive inputs.

---

*We are led to conclude that phantom pain is likely to be the result of a combination of cortical and peripheral mechanisms, as well as visual and proprioceptive inputs.*

---

### CONCLUSION

Our knowledge of PLP has drastically increased since it was first articulated as a clinical problem several hundred years ago. We are significantly more aware of its incidence, severity, and manifestations. In addition, there are some promising therapies, pharmacologic and otherwise, for its treatment and a multitude of theories have been developed to try to explain what we observe in amputee patients. However, we continue to lack evidence and a clear explanation as to why some individuals develop PLP and some do not, why some pain subsides over time and other PLP persists, and what molecular and biologic mechanisms are at work. With the exception of opioids and mirror therapy, many of the other reported treatment modalities lack robust studies to support their effectiveness. Further studies are critical to discover the answers to these questions, to evaluate therapies, and to improve the care we can provide to amputee patients who experience this unique condition.

### REFERENCES

- Weinstein SM. Phantom limb pain and related disorders. *Neuropathic Pain Syndr.* 1998;16:919–935.
- Mitchell SW. *Injuries of Nerves and Their Consequences.* Philadelphia, PA: JB Lippincott; 1872.
- Melzack R. Phantom limb pain: implications for treatment of pathologic pain. *Anesthesiology.* 1971;35:409–419.
- Sherman RA, Arena JG, Sherman CJ, et al. The mystery of phantom pain: growing evidence for psychophysiological mechanisms. *Biofeedback Self Regul.* 1989;14:267–280.
- Sherman RA, Sherman CJ. Prevalence and characteristics of chronic phantom limb pain among American veterans: results of a trial survey. *Am J Phys Med.* 1983;62:227–238.
- Staps T, Hoogenhout J, Woobes T. Phantom breast sensations following mastectomy. *Cancer.* 2006;56:2898–2901.
- Ovesen P, Kroner K, Ornholt J, et al. Phantom-related phenomena after rectal amputation: prevalence and clinical characteristics. *Pain.* 1991;44:289–291.
- Ramachandran VS, Hirstein W. The perception of phantom limbs: the D. O. Hebb lecture. *Brain.* 1998;121:1603–1630.
- Fisher CM. Phantom erection after amputation of penis. Case description and review of relevant literature on phantoms. *Can J Neurol Sci.* 1999;26:53–56.
- Biley FC. Phantom bladder sensations: a new concern for stoma care workers. *Br J Nurs.* 2001;10:1290–1296.
- Brena SF, Sammons EE. Phantom urinary bladder pain—case report. *Pain.* 1979;7:197–201.



12. Giummarra MJ, Gibson SJ, Georgiou-Karistianis N, et al. Central mechanisms in phantom limb perception: the past, present and future. *Brain Res Rev*. 2007;54:219–232.
13. Sörös P, Husstedt IW, Evers S, et al. Phantom eye syndrome: Its prevalence, phenomenology and putative mechanisms. *Neurology*. 2003;60:1542–1543.
14. Marbach JJ. Is phantom tooth pain a deafferentation (neuropathic) syndrome? *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1993;75:95–105.
15. Henderson WR, Smyth GE. Phantom limbs. *J Neurol Neurosurg Psychiatry*. 1948;11:88–112.
16. Carlen PL, Wall PD, Nadvorna H, et al. Phantom limbs and related phenomena in recent traumatic amputations. *Neurology*. 1978;28:211–217.
17. Shukla GD, Sahu SC, Tripathi RP, et al. Phantom limb: a phenomenological study. *Br J Psychiatry*. 1982;141:54–58.
18. Steinbach TV, Nadvorna H, Arazi D. A five year follow-up study of phantom limb pain in post traumatic amputees. *Scand J Rehabil Med*. 1982;14:203–207.
19. Jensen TS, Krebs B, Nielsen J, et al. Phantom limb, phantom pain and stump pain in amputees during the first 6 months following limb amputation. *Pain*. 1983;17:243–256.
20. Sherman RA, Sherman CJ, Parker L. Chronic phantom and stump pain among American veterans: results of a survey. *Pain*. 1984;18:83–95.
21. Pohjolainen T. A clinical evaluation of stumps in lower limb amputees. *Prosthet Orthot Int*. 1991;15:178–184.
22. Houghton AD, Nicholls G, Houghton AL, et al. Phantom pain: natural history and association with rehabilitation. *Ann R Coll Surg Engl*. 1994;76:22–25.
23. Montoya P, Larbig W, Grukke N, et al. The relationship of phantom limb pain to other phantom limb phenomena in upper extremity amputees. *Pain*. 1997;72:87–93.
24. Nikolajsen L, Ilkjaer S, Kroner K, et al. The influence of preamputation pain on postamputation stump and phantom pain. *Pain*. 1997;72:393–405.
25. Watan SW, Hamman W, Wedley JR, et al. Phantom pain and sensation among British veteran amputees. *Br J Anaesth*. 1997;78:652–659.
26. Wilkins KL, McGrath PJ, Finley GA, et al. Phantom limb sensations and phantom limb pain in child and adolescent amputees. *Pain*. 1998;77:7–12.
27. Kooijman CM, Dijkstra PU, Geertsen JH, et al. Phantom pain and phantom sensations in upper limb amputees: an epidemiological study. *Pain*. 2000;87:33–41.
28. Schley MT, Wilms P, Toepfner S, et al. Painful and nonpainful phantom and stump sensations in acute traumatic amputees. *J Trauma*. 2008;65:858–864.
29. Ewalt JR, Randall GC, Morris H. The phantom limb. *Psychosom Med*. 1947;9:118–123.
30. Nikolajsen L, Jensen TS. Phantom limb pain. *Br J Anaesth*. 2001;87:107–116.
31. Nikolajsen L, Jensen TS. Phantom limb. In: McMahon SB, Koltzenberg M, eds. *Wall and Melzack's Textbook of Pain*. 5th ed. Oxford, United Kingdom: Elsevier; 2006:961–977.
32. Jensen TS, Krebs B, Nielsen J, et al. Immediate and long-term phantom limb pain in amputees: incidence, clinical characteristics and relationship to preamputation limb pain. *Pain*. 1985;21:267–278.
33. Wall R, Novotny-Joseph P, Macnamara TE. Does preamputation pain influence phantom limb pain in cancer patients? *South Med J*. 1985;78:34–36.
34. Lacoux PA, Crombie IK, Macrae WA. Pain in traumatic upper limb amputees in Sierra Leone. *Pain*. 2002;99:309–312.
35. Tsao JW. *Unpublished Clinical Observations and Data*. Washington, DC: Walter Reed Army Medical Center; 2005–2009.
36. Chen R, Cohen LG, Hallett M. Nervous system reorganization following injury. *Neuroscience*. 2002;111:761–773.
37. Flor H, Nikolajsen L, Jensen TS. Phantom limb pain: a case of maladaptive CNS plasticity? *Nature Rev Neurosci*. 2006;7:873–881.
38. Hall EJ, Flament D, Fraser C, et al. Non-invasive brain stimulation reveals reorganized cortical outputs in amputees. *Neurosci Lett*. 1990;116:379–386.
39. Mackert BM, Sappok T, Grusser S, et al. The eloquence of silent cortex: analysis of afferent input to deafferented cortex in arm amputees. *Neuroreport*. 2003;14:409–412.
40. Elbert T, Flor H, Birbaumer N, et al. Extensive reorganization of the somatosensory cortex in adult humans after nervous system injury. *Neuroreport*. 1994;5:2593–2597.
41. Lotze M, Moseley GL. Role of distorted body image in pain. *Curr Rheumatol Rep*. 2007;9:488–496.
42. MacIver K, Lloyd DM, Kelly S, et al. Phantom limb pain, cortical reorganization and the therapeutic effect of mental imagery. *Brain*. 2008;131:2181–2191.
43. Wall PD. The presence of ineffective synapses and the circumstances which unmask them. *Philos Trans R Soc Lond B Biol Sci*. 1977;278:361–372.
44. Chen R, Corwell B, Yaseen Z, et al. Mechanisms of cortical reorganization in lower-limb amputees. *J Neurosci*. 1998;18:3443–3450.
45. Merzenich MM, Nelson RJ, Stryker MP, et al. Somatosensory cortical map changes following digit amputation in adult monkeys. *J Comp Neurol*. 1984;224:591–605.
46. Ramachandran VS, Rogers-Ramachandran D, Stewart M, et al. Perceptual correlates of massive cortical reorganization. *Science*. 1992;258:1159–1160.
47. Pons TP, Garraghty PE, Ommaya AK, et al. Massive cortical reorganization after sensory deafferentation in adult macaques. *Science*. 1991;252:1857–1860.
48. Lotze M, Flor H, Grodd W, et al. Phantom movements and pain: an fMRI study in upper limb amputees. *Brain*. 2001;124:2268–2277.
49. Head H, Holmes G. Sensory disturbances from cerebral lesions. *Brain*. 1912;34:102–254.
50. Riddoch G. Phantom limbs and body shape. *Brain*. 1941;64:197–222.
51. Bromage PR, Melzack R. Phantom limbs and the body schema. *Can Anaesth Soc J*. 1974;21:267–274.
52. Schwoebel J, Boronat CB, Branch Coslett H. The man who executed “imagined” movements: evidence for dissociable components of the body schema. *Brain Cogn*. 2002;50:1–16.
53. Aglioti S, Smania N, Manfredi M, et al. Disownership of left hand and objects related to it in a patient with right brain damage. *NeuroReport*. 1996;8:293–296.
54. Berlucchi G, Aglioti S. The body in the brain: neural bases of corporeal awareness. *Trends Neurosci*. 1997;20:560–564.
55. LaCroix R, Melzack R, Smith D, et al. Multiple phantom limbs in a child. *Cortex*. 1992;28:503–507.
56. Melzack R, Israel R, Lacroix R, et al. Phantom limbs in people with congenital limb deficiency or amputation in early childhood. *Brain*. 1997;120:1603–1620.
57. Saadah ES, Melzack R. Phantom limb experiences in congenital limb-deficient adults. *Cortex*. 1994;30:479–485.
58. Melzack R. Phantom limbs and the concept of a neuromatrix. *Trends Neurosci*. 1990;13:88–92.
59. Katz J, Melzack R. Pain “memories” in phantom limbs: review and clinical observations. *Pain*. 1990;43:319–336.
60. Melzack R. From the gate to the neuromatrix. *Pain Suppl*. 1999;6:S121–S126.
61. Anderson-Barnes VC, McAuliffe C, Swanberg KM, et al. Phantom limb pain—a phenomenon of proprioceptive memory? *Med Hypotheses*. 2009;73:555–558.
62. Gentili ME, Verton C, Kinirons B, et al. Clinical perception of phantom limb sensation in patients with brachial plexus block. *Eur J Anaesthesiol*. 2002;19:105–108.
63. Nystrom B, Hagbarth KE. Microelectrode recordings from transected nerves in amputees with phantom limb pain. *Neurosci Lett*. 1981;27:211–216.
64. Ramachandran VS. Behavioral and magnetoencephalographic correlates of plasticity in the adult human brain. *Proc Natl Acad Sci USA*. 1993;90:10413–10420.
65. Weiss T, Miltner WH, Adler T, et al. Decrease in phantom limb pain associated with prosthesis-induced increased use of an amputation stump in humans. *Neurosci Lett*. 1999;272:131–134.
66. Pezzin LE, Dillingham TR, MacKenzie EJ. Rehabilitation and the long-term outcomes of persons with trauma-related amputations. *Arch Phys Med Rehabil*. 2000;81:292–300.
67. Mayer A, Kudar K, Bretz K, et al. Body schema and the awareness of amputees. *Prosthet Orthot Int*. 2008;32:363–382.
68. Chabal C, Jacobson L, Russel L, et al. Pain responses to perineuromal injection of normal saline gallamine, and lidocaine in humans. *Pain*. 1989;36:321–325.
69. Stoelting RK, Miller RD. Opioids. In: *Basics of Anesthesia*. 5th ed. Edinburgh, United Kingdom: Churchill Livingstone; 2006:112–123.
70. Huse E, Larbig W, Flor H, et al. The effect of opioids on phantom limb pain and cortical reorganization. *Pain*. 2001;90:47–55.
71. Flor H, Elbert T, Knecht S, et al. Phantom-limb pain as a perceptual

- correlate of cortical reorganization following arm amputation. *Nature*. 1995; 375:482–484.
72. Birbaumer N, Lutzenberger W, Montoya P, et al. Effects of regional anesthesia on phantom limb pain are mirrored in changes in cortical reorganization. *J Neurosci*. 1997;17:5503–5508.
  73. 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;96:841–848.
  74. Wu CL, Agarwal S, Tella PK, et al. Morphine versus mexiletine for treatment of postamputation pain: a randomized, placebo-controlled, crossover trial. *Anesthesiology*. 2008;109:289–296.
  75. Wiffen PJ, McQuay HJ, Rees J, et al. Gabapentin for acute and chronic pain. *Cochrane Database Syst Rev*. 2005;3:CD005452.
  76. Bone M, Critchley P, Buggy D. Gabapentin in postamputation phantom limb pain: a randomized, double blind, placebo controlled, cross-over study. *Reg Anesth Pain Med*. 2002;27:481–486.
  77. Smith DG, Ehde DM, Hanley MA, et al. Efficacy of gabapentin in treating chronic phantom limb and residual limb pain. *J Rehabil Res Dev*. 2005;42: 645–654.
  78. Elliott F, Little A, Milbrandt W. Carbamazepine for phantom-limb phenomena. *N Engl J Med*. 1976;295:678.
  79. Patterson JF. Carbamazepine in the treatment of phantom limb pain. *South Med J*. 1988;81:1100–1102.
  80. Wilder-Smith CH, Hill LT, Laurent S. Postamputation pain and sensory changes in treatment-naïve patients: characteristics and responses to treatment with tramadol, amitriptyline, and placebo. *Anesthesiology*. 2005;103: 619–628.
  81. Robinson LR, Czerniecki JM, Ehde DM, et al. Trial of amitriptyline for relief of pain in amputees: results of a randomized controlled study. *Arch Phys Med Rehabil*. 2004;85:1–6.
  82. Panerai AE, Monza G, Movilia P, et al. A randomized, within-patient, cross-over, placebo-controlled trial on the efficacy and tolerability of the tricyclic antidepressants chlorimipramine and nortriptyline in central pain. *Acta Neurol Scand*. 1990;82:34–38.
  83. Kuiken TA, Schechtman L, Harden RN. Phantom limb pain treatment with mirtazapine: a case series. *Pain Pract*. 2005;5:356–360.
  84. Eichenberger U, Neff F, Svetcic G, et al. Chronic phantom limb pain: the effects of calcitonin, ketamine, and their combination on pain and sensory thresholds. *Anesth Analg*. 2008;106:1265–1273.
  85. Jaeger H, Maier C. Calcitonin in phantom limb pain: a double-blind study. *Pain*. 1992;48:21–27.
  86. Jahangiri M, Jayatunga AP, Bradley JW, et al. Prevention of phantom pain after major lower limb amputation by epidural infusion of diamorphine, clonidine, and bupivacaine. *Ann R Coll Surg Engl*. 1994;76:324–326.
  87. Davis RW. Successful treatment for phantom pain. *Orthopedics*. 1993;16: 691–695.
  88. Nikolajsen L, Hansen CL, Nielsen J, et al. The effect of ketamine on phantom pain: a central neuropathic disorder maintained by peripheral input. *Pain*. 1996;67:69–77.
  89. Hallivris R, Derkson TA, Meyr AJ. Peri-operative pain management. *Clin Pediatr Med Surg*. 2008;25:443–463.
  90. Gilron I, Watson CP, Cahill CM, et al. Neuropathic pain: a practical guide for the clinician. *CMAJ*. 2006;175:265–275.
  91. Hackworth RJ, Tokarz KA, Fowler IM, et al. Profound pain reduction after induction of memantine treatment in two patients with severe phantom limb pain. *Anesth Analg*. 2008;107:1377–1379.
  92. Nikolajsen L, Gottrup H, Kristensen AG, et al. Memantine (a N-methyl-D-aspartate receptor antagonist) in the treatment of neuropathic pain after amputation or surgery: a randomized, double-blinded, cross-over study. *Anesth Analg*. 2000;91:960–966.
  93. 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;103:277–283.
  94. Wiech K, Kiefer RT, Topfner S, et al. A placebo-controlled randomized crossover trial of the N-methyl-D-aspartic acid receptor antagonist, memantine, in patients with chronic phantom limb pain. *Anesth Analg*. 2004;98: 408–413.
  95. Schley M, Topfner S, Wiech K, et al. Continuous brachial plexus blockage in combination with the NMDA receptor antagonist memantine prevents phantom pain in acute traumatic upper limb amputees. *Eur J Pain*. 2007; 11:299–308.
  96. Buvaendran A, Kroin JS. Early use of memantine for neuropathic pain. *Anesth Analg*. 2008;107:1093–1094.
  97. Melzack R. Prolonged relief of pain by brief, intense transcutaneous somatic stimulation. *Pain*. 1975;1:357–373.
  98. Laitinen L. Placement of electrodes in transcutaneous stimulation for chronic pain [in French]. *Neurochirurgie*. 1976;22:517–526.
  99. Carabelli RA, Kellerman WC. Phantom limb pain: relief by application of TENS to contralateral extremity. *Arch Phys Med Rehabil*. 1985;66:466–467.
  100. Finsen V, Persen L, Lovlien M, et al. Transcutaneous electrical nerve stimulation after major amputation. *J Bone Joint Surg Br*. 1988;70:109–112.
  101. Katz J, France C, Melzack R. An association between phantom limb sensations and stump skin conductance during transcutaneous electrical nerve stimulation (TENS) applied to the contralateral leg: a case study. *Pain*. 1989;36:367–377.
  102. Katz J, Melzack R. Auricular transcutaneous electrical nerve stimulation (TENS) reduces phantom limb pain. *J Pain Symptom Manage*. 1991;6: 73–83.
  103. Long DM. Cutaneous afferent stimulation for relief of chronic pain. *Clin Neurosurg*. 1974;21:257–268.
  104. Shealy CN. Transcutaneous electrical stimulation for control of pain. *Clin Neurosurg*. 1974;21:269–277.
  105. Winnem MF, Amundsen T. Treatment of phantom limb pain with TENS. *Pain*. 1982;12:299–300.
  106. Krainick JU, Thoden U, Riechert T. Spinal cord stimulation in postamputation pain. *Surg Neurol*. 1975;4:167–170.
  107. Krainick JU, Thoden U, Riechert T. Pain reduction in amputees by long-term spinal cord stimulation: long-term follow-up study over 5 years. *J Neurosurg*. 1980;52:346–350.
  108. Nielson KD, Adams JE, Hosobuchi Y. Phantom limb pain: treatment with dorsal column stimulator. *J Neurosurg*. 1975;42:301–307.
  109. Wester K. Dorsal column stimulation in pain treatment. *Acta Neurol Scand*. 1987;75:151–155.
  110. Kumar K, Nath R, Wyant GM. Treatment of chronic pain by epidural spinal cord stimulation: a 10-year experience. *J Neurosurg*. 1991;75:402–407.
  111. Lang P. The treatment of chronic pain by epidural spinal cord stimulation—a 15 year follow-up; present status. *Axone*. 1997;18:71–73.
  112. Fisher A, Meller Y. Continuous postoperative regional analgesia by nerve sheath block for amputation surgery: a pilot study. *Anesth Analg*. 1991;72: 300–303.
  113. Muraoka M, Komiyama H, Hosoi M, et al. Psychosomatic treatment of phantom limb pain with post-traumatic stress disorder: a case report. *Pain*. 1996;66:385–388.
  114. Xing G. Acupuncture treatment of phantom limb pain—a report of 9 cases. *J Tradit Chin Med*. 1998;18:199–201.
  115. Bradbrook D. Acupuncture treatment of phantom limb pain and phantom limb sensation in amputees. *Acupunct Med*. 2004;22:93–97.
  116. Ramachandran VS, Rogers-Ramachandran D. Synaesthesia in phantom limbs induced with mirrors. *Proc Biol Sci*. 1996;263:377–386.
  117. Chan BL, Witt R, Charrow AP, et al. Mirror therapy for phantom limb pain. *New Eng J Med*. 2007;357:2206–2007.
  118. Rossi S, Tecchio F, Pasqualetti P, et al. Somatosensory processing during movement observation in humans. *Clin Neurophysiol*. 2002;113:16–24.
  119. Rizzolatti G, Fogassi L, Gallese V. Mirrors of the mind. *Sci Am*. 2006;295: 54–61.
  120. Ramachandran VS, Rogers-Ramachandran D. Sensations referred to a patient's phantom arm from another subjects intact arm: perceptual correlates of mirror neurons. *Med Hypotheses*. 2008;70:1233–1234.
  121. Nikolajsen L, Finnerup NB, Kramp S, et al. A randomized study of the effects of gabapentin on postamputation pain. *Anesthesiology*. 2006;105: 1008–1015.