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An Introduction to Phantom Limb Pain

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With amputation comes many new experiences and sensations. Most credit the discovery and early characterization of phenomena associated with amputation to Ambroise Paré (16th century) and, nearly 250 years later, Silas Weir Mitchell in 1866 (Finger and Hustwit, 2003; Kline, 2016). Since then, substantial research has been conducted to further understand the consequences, mechanisms, and phenomena associated with amputation through the investigation of physical and psychological changes after amputation. This chapter has several goals. The first is to introduce the topic of amputation and the associated sequelae. Second, discuss the epidemiology and several proposed etiologies of the sequelae, focusing on phantom limb pain (PLP). Third, review methods for measuring the manifestation of PLP, specifically with respect to psychophysical aspects and cortical representation. Fourth, explore the proposed treatments of PLP and consider a potential new therapy paradigm.

Multiple studies have estimated the prevalence of limb loss and the subsequent effects of amputation. As many as 185,000 amputations occur every year in the United States (Owings and Kozak, 1998; Ziegler-Graham et al., 2008). It was estimated that 1.6 million Americans were living with the loss of a limb in 2005, which translates to a ratio of 1:190 Americans; 65% of these individuals have lower extremity amputations (Ziegler-Graham et al., 2008). Fifty-four percent of amputation cases occur after diagnosis of dysvascular

disease and 70% of amputees with dysvascular disease (or 38% of the amputee population) were noted to have a comorbidity of diabetes (Ziegler-Graham et al., 2008). An unfortunate reality for many amputees is a relatively high rate of reamputation (26% among those with dysvascular amputation (Dillingham et al., 2005; Ziegler-Graham et al., 2008)). Reamputation refers to those who underwent an additional procedure or additional procedures to the previously amputated limb or the contralateral limb within 12 months of the original procedure. In 1996, US medical care costs exceeded $4 billion yearly for dysvascular amputations alone (Dillingham et al., 2005), which is only about half (54%) of the amputee community (Ziegler-Graham, 2008). Ziegler-Graham et al. predict the number of amputees in the United States will reach beyond 3 million by the year 2050. This, coupled with the high prevalence of postamputation pain (PAP) and the high degree of pain experienced, easily makes the case that phantom pain is a relevant problem. To further complicate the issue, the amputee community is ill-informed in regards to PLP; 41.6% of amputees have never heard of the phenomenon (Kern et al., 2012).

1.1 Epidemiology and Etiology of Phenomena and Sequelae Associated with Amputation

Individuals commonly notice the presence of a phantom limb shortly after amputation. This phenomenon, known as phantom limb sensation (PLS), is the mental construction of the limb that is no longer present postamputation. The phantom limb, or phantom, can be represented in a number of forms, from normal orientations to those that are not easily described or even physically possible. The phantom can also present pain to the amputee in many varieties, such as tingling, burning, stabbing, etc. This phenomenon is known as PLP or phantom pain. PLP is a subset of PLS where the sensations specifically cause discomfort. Amputees also experience other common painful phenomena, such as neuropathic pain (NP) and residual limb pain (RLP; also known as stump pain). NP is pain due to the damage or dysfunction of the somatosensory nervous system and RLP is pain in the remaining portion of the amputated limb. All of these painful phenomena fall under the umbrella of PAP.

1.1.1 Phantom Limb Sensation (PLS)

While the mechanism of the PLS phenomenon is not clear, it is common among amputees; as many as 80–90% of amputees experience PLS (Jensen

et al., 1983; Ehde et al., 2000; Casale et al., 2009). In arm or leg amputees, PLSs are generally localized to the distal region of the phantom, i.e., the hand, foot, fingers, or toes, and are typically not constant (Jensen et al., 1985). Rather, the sensations peak intermittently, sometimes on a monthly basis and sometimes several times a week (Ehde et al., 2000; Kooijman et al., 2000). Sensations can be provoked in various ways, such as stump movement, touching the stump, and urination (Jensen et al., 1983). In a study involving 255 amputees, 79% reported nonpainful PLS, and of those individuals 27% (most common) described the sensations as tingling, 26% as itching, 13% as feeling asleep, among others (Ehde et al., 2000). Another related phenomenon is perceived movement of the phantom, where the amputee is able to consciously move the orientation or sense movement of the phantom. Eight days after amputation, 36% of amputees felt movement of the phantom with 19% feeling spontaneous movements (i.e., movements that were not consciously driven) (Jensen et al., 1983). Similarly, another study by Kooijman et al. found 38% to experience movement (Kooijman et al., 2000).

For some amputees, electromyogram (EMG) patterns in the stump during imagined movements of the phantom limb are distinguishable and non-random, indicating hand motor commands are preserved after amputation and there exists an inherent understanding of how to manipulate/move the phantom (Reilly et al., 2006). The modulation of signal seen in the stump did not appear in experiments with the intact limb, which supports current theories postamputation reorganization at some level.

The efforts to move the phantom were not only observed through muscle movements, but also through peripheral nerve activity, i.e., Dhillon et al. recognized nerve activity in the residual limb during attempted movements. Furthermore, they recognized activity in the central nervous system (CNS), specifically in the motor cortex, during phantom movements (Dhillon et al., 2004). These findings emphasize the current understanding of phenomena associated with amputation; the sensorimotor cortices and related peripheral innervation are actively involved in the perception of the phantom limb.

An altered kinesthesia is also common. For example, as many as 30% of amputees experience telescoping, which is the gradual shortening or retraction of the phantom limb, as depicted in Figure 1.1 (Jensen et al., 1983; Hill, 1999). In some amputees, the phantom limb no longer reflects the original anatomy. In this example, the phantom limb shortens and is drawn into the stump. In these situations, the residual limb and phantom hand or foot are no longer in an orientation that matches the original volume or limb, which causes confusion and concern to many amputees. Telescoping has also been linked to increased levels of phantom pain (Flor et al., 2006).

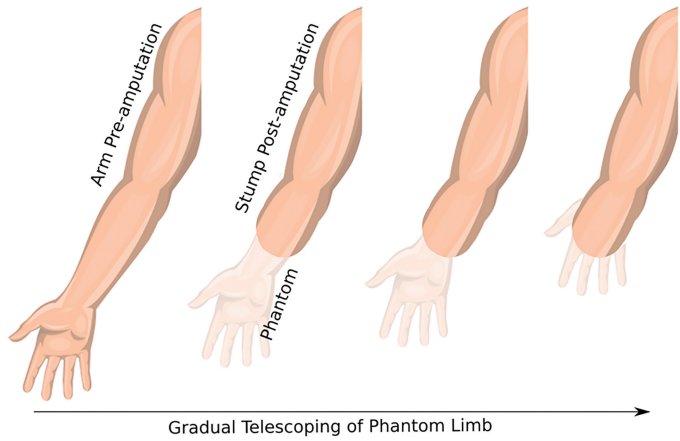

Figure 1.1 Among the peculiar potential pathological changes that occur after amputation is telescoping. Telescoping is a phenomenon in which the amputees sensory body image changes resulting in an alteration in the phantom sensations with respect to the sensations from the normal parts of the body. With time, the phantom sensation gradually moves or shrinks, for example as shown above, into odd or impossible positions or joint angles. This results in a state of sensory confusion, and concern for the amputee that potentially contributes to the increase in phantom limb pain.

In some circumstances, PLSs can be helpful in adjusting to the use of a prosthetic device, where the phantom limb embodies the prosthesis (Gallagher et al., 2008). Murray describes the embodiment phenomenon as a transition of a prosthesis from an extracorporeal structure to a corporeal one, meaning the prosthesis becomes part of the identity of self. This fits into the field of psychoprosthetics, which uses a psychological framework to analyze and explain the phenomena associated with prostheses and the amputation rehabilitation process. Corporeal embodiment does not occur in all amputees, which is not well understood. Murray attributes this embodiment transformation to practice, i.e., increased use of the prosthesis (Gallagher et al., 2008). Despite the possible utility of PLSs, in many cases the phantom sensation evolves into the form of PLP, which can be not only a hindrance, but also a phenomenon that has a strong negative effect on the amputee's quality of life (Knežević et al., 2015).

The phantom limb can also be debilitating when the sensations are painful; 54% of amputees who experience painful phantom sensations, or PLP, regarded the pain as somewhat bothersome (27% said extremely bothersome) (Ephraim et al., 2005).

Phantom sensations are not pathognomonic to amputation of a limb (Buonocore, 2015). In fact, studies have recognized phantom sensations in other sensory systems. Phantom eye syndrome has been found to affect as many as 51% of patients with orbital exenteration with 26% feeling pain (Roed Rasmussen et al., 2009). Phantom eye sensations most commonly came in the form of elementary visual hallucinations such as white light or colored light and were triggered by darkness, stress, and fatigue, among others (Roed Rasmussen et al., 2009).

Another argued case of phantom sensation is tinnitus, where individuals experience phantom auditory sensations, most commonly described as ringing in the ears, steady tones, or hissing. Tinnitus has been linked to hearing loss, i.e., up to 90% of cases are linked to hearing loss (Shore et al., 2016). Like PLS, tinnitus describes false perceptions; however, tinnitus is unique because it also occurs in individuals who are otherwise healthy. Sectioning of relevant cranial nerves has not proven successful for the treatment of tinnitus, lending to support the current proposed mechanism of maladaptive neural plasticity (House and Brackmann, 1981; Shore et al., 2016).

1.1.2 Phantom Limb Pain (PLP)

The prevalence of PLP, or phantom pain, widely varies in literature. A survey by Ephraim et al. (with 914 respondents), phantom pain was reported in 79.9% of amputees with 38.9% reporting the pain as severe ($\geq$7 on a 0–10 analog scale) (Ephraim et al., 2005). Ephriam et al. recognized no significant difference of the rates of phantom pain based on etiology, age, or level of amputation; they also noted that the rate of PLP for upper limb amputees was 83%, consistent with the rest of the study population. Eleven percent of the amputees in this study were upper limb (10% unilateral), leaving 89% as lower limb (79% unilateral). The mean pain intensity for phantom pain of all study participants was 5.5 $\pm$ 2.6 (Ephraim et al., 2005). Others have found prevalence rates ranging between 40% and 85% (Sherman and Sherman, 1983; Ehde et al., 2000; Kooijman et al., 2000; Schley et al., 2008; Kern et al., 2012). Various explanations have been offered for discrepancies in the prevalence, such as response rates and bias from choice of study population. However, the clear cause of the differences is not known. The range for PLP prevalence in amputees generally referenced in literature is 50–80%.

The quantification and description of PLP is important in understanding the effectiveness of treatment. From the standpoint of self-reporting scales, pain can be defined in terms of intensity, affect, quality, and location (Jensen

and Karoly, 2010). Most research studies have opted to primarily measure intensity and bothersomeness using the visual analog scale (VAS) or the discrete version called the numeric rating scale (NRS). Average ratings of pain, in terms of the VAS, fall in the range of 5.1–5.5 out of 10 (Ehde et al., 2000; Ephraim et al., 2005). Ehde et al. found that when asked how bothersome the pain is (scale of 0–10, 0 being not at all bothersome, 10 being as bothersome as could be) 32% of respondents reported pain as being severely bothersome ($\geq$7) and only 10% rated the PLP as not bothersome at all (Ehde et al., 2000). Likewise, Ephraim et al. found only 19% of respondents not to be bothered by the PLP they experienced (Ephraim et al., 2005). Amputees tend to describe PLP as knife-like (stabbing), sticking, burning, squeezing, etc. (Jensen et al., 1983; Jensen et al., 1985; Montoya et al., 1997).

A final metric or description of PLP is needed to quantify frequency and length-of-time of the pain. Efforts have been taken to define how often amputees felt PLP, and how long the pain was present. Amputees suffering from PLP experience the pain at different intervals; 31% report a frequency less than 1 episode per month, 14% a few times a day, and 7% have constant pain (Schley et al., 2008). Another study found 14%, 24%, and 24% for the same time frames, respectively (Kooijman et al., 2000). Kooijman et al., in the same work, found a fairly uniform distribution among frequencies of phantom pain attacks from feeling PLP a few times per year, month, week, day and constant pain, ranging from 14% to 24%. Kern et al. found of those experiencing PLP, 56.1% have pain lasting less than 5 h daily and many (27%) felt pain constantly (Kern et al., 2012). Ephraim et al. reported frequency in terms of never, sometimes, and always (20.1%, 58.7%, and 21.2%, respectively) (Ephraim et al., 2005). Ehde et al. found 81% of amputees to experience intermittent PLP, between once a week or less and four to six times per week (Ehde et al., 2000). Among these studies the rates are different for frequency of pain, as shown in Figure 1.2.

The median follow-up period for the study by Schley et al. was 3.2 years while the median follow-up period for the study by Kooijman et al. was 19.1 years. Also, the events leading to amputation (i.e., the study population) were slightly different among studies, where 98% of the Schley et al. data came from traumatic cases (Schley et al., 2008), 78% from traumatic cases in the study by Kooijman et al. (2000), and 50% for the study by Kern et al. (2012). Conversely, frequency and duration of PLP have also been found to decrease within 6 months after amputation (Jensen et al., 1985); this contradicts the discrepancy in the constant pain rate between Schley et al. (7% at 3.2 years after amputation) (Schley et al., 2008) and Kooijman et al. (24% at 19.1 years after amputation) (Kooijman et al., 2000). It is not clear which findings are

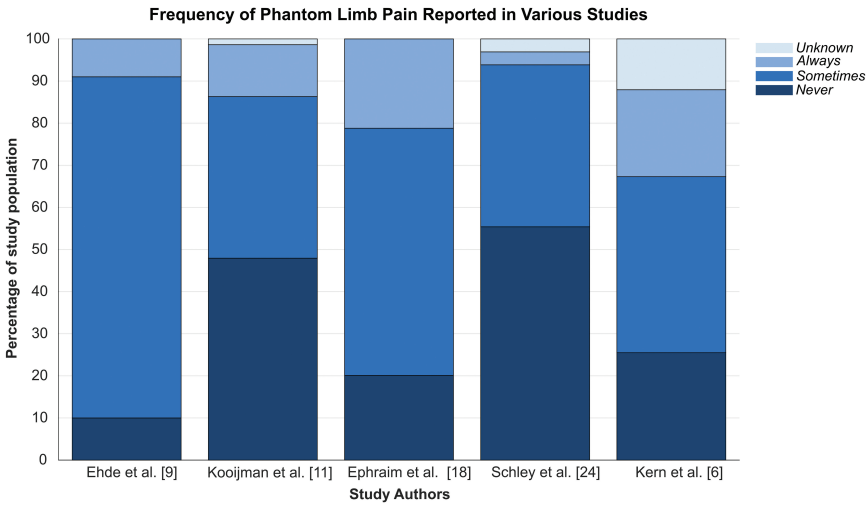

Figure 1.2 Various rates have been reported in literature for the frequency of PLP episodes. Most respondents reported PLP as occurring at a frequency somewhere between never and always. Several variables could explain discrepancies among studies, including epidemiology and etiology of amputation, years since amputation, size of sample population, etc. The effect of these factors on PLP presentation is not well understood.

more representative of the general amputee population. Ephraim et al. found of amputees 10+ years postamputation; 74% were experiencing phantom pain (Ephraim et al., 2005). The measure of length-of-time of pain has been reported in several ways, which makes it difficult to compare among reports in literature. PLP tends to flare episodically for seconds to minutes, but some have reported pain lasting several hours to a day or even longer (Jensen et al., 1985; Montoya et al., 1997; Ehde et al., 2000).

1.1.2.1 Triggers of PLP

Some have sought to understand the common comorbidities and triggers associated with phantom pain. Those who indicate a depressed mood are more likely to report severe pain and pain that is extremely bothersome (Ephraim et al., 2005). Phantom pain comes in many forms with many triggers. Often times PLP can flare during emotional distress, stump pressure, urination, cold temperature, or while coughing (Jensen et al., 1983). Preamputation pain has been recognized in several studies to be associated with phantom pain after the amputation (Jensen et al., 1983; Jensen et al., 1985; Schley et al., 2008). Many have suggested a correlation of PLP and RLP; however, Kooijman et al. suggested that RLP acts as a trigger of PLP (Kooijman et al., 2000).

This claim has not been substantiated by subsequent research. Giummarra et al. suggest several categories of triggers, the most frequent of which is "Movement and 'behavioral schema' triggers"; these include activities such as scratching an itch, gesturing with the phantom, etc. (Giummarra et al., 2011).

1.1.3 Residual Limb (stump) Pain (RLP)

A substantial number of amputees experience pain in their residual limb. As with other descriptors of pain, the rates vary widely in literature. Rates of stump pain span from 22% to 76% (Jensen et al., 1983; Smith et al., 1999; Kooijman et al., 2000; Ephraim et al., 2005; Schley et al., 2008; Bekrater-Bodmann et al., 2015). More recent surveys support rates on the higher side (61–67.7%) (Ephraim et al., 2005; Schley et al., 2008; Bekrater-Bodmann et al., 2015). Ehde et al. reported that, in response to asking which pain is the worst, the highest rated site (33%) was the residual limb, over phantom limb, back, and others (Ehde et al., 2000). RLP was also found in another study to be more impairing than PLP or back pain (Marshall et al., 2002). Only 4–13% of amputees experiencing RLP think of it as not bothersome at all (Ehde et al., 2000; Ephraim et al., 2005). On average, the intensity of the RLP falls in the moderate pain range at 5.4 on a 0–10 scale and is commonly described as aching or burning (Ehde et al., 2000). This is supported by Ephraim et al., who found that for the individuals experiencing RLP, the pain was almost uniformly spread among mild, moderate, and severe (41.8%, 28.3%, and 29.9%, respectively), with mild being slightly more prevalent (Ephraim et al., 2005). Similar to PLP, RLP tends to present itself in episodes and can last seconds, minutes, hours, or longer (Ehde et al., 2000). RLP does not tend to diminish with time after amputation (Ephraim et al., 2005). Looking for the possible cause behind the pain is an elusive question. O'Reilly et al. propose the pain is a result of neuromata (O'Reilly et al., 2013, 2016), which are sensitive bundles of nerve endings that result from inability to reconnect with the target tissue (Fried et al., 1991). Taken together, the high rate of prevalence and the impact on the quality of life highlight the degree to which RLP is a debilitating problem that needs to be addressed. A clear path to treating the issue of RLP is to look at treatment methods for NP. Neuromata are often associated with this type of pain, since inherently neuromata are a result of damage to the peripheral nervous system (PNS).

Amputees, often times, cannot distinguish between PLP and RLP (Hill, 1999; Flor, 2002). Generally, this confusion arises when pain is felt in the

vicinity of the amputation site, where the phantom and residual limbs meet. RLP and PLP tend to correlate, especially in intensity (Ehde et al., 2000). Schley et al. found that 86% of amputees experiencing phantom pain also experienced stump pain (Schley et al., 2008).

1.1.4 Neuropathic Pain (NP)

NP plays a role in phantom phenomena (Buonocore, 2015). Casale et al. suggest that there is a significant link between neuromata and PLP (Casale et al., 2009). Neuromata make the surrounding area more sensitive to stimuli (mechanical, chemical, electrical), which explains correlations of pain and various triggers (e.g., touch, mood, stress, etc.) (Casale et al., 2009). Many of the descriptors of PLP and RLP reflect what would be expected of NP, i.e., burning, stabbing, etc., which leads one to conclude that PLP and RLP are forms of NP, and may link to the development of neuromata in the stump. Neuromata are the most common cause of pain in one study (O'Reilly et al., 2016). However, not all neuromata result in pain. For example, the same study found 159 neuromata in the sample population, but only 91 (57%) were painful in response to transducer pressure (O'Reilly et al., 2013). Another study supports this finding with similar rate of pain occurrence at 67% (O'Reilly et al., 2016). Furthermore, neuroma excision is not always successful. In a small case study, neuroma excision relieved pain in only two of the six patients (Nikolajsen et al., 2010). On the other hand, retrospective studies of neuromata removal found surgery to be a very successful method for relinquishing pain (Ducic et al., 2008; Sehirlioglu et al., 2009). Nevertheless, even though the links among neuromata, PLP and RLP are uncertain, it does not rule out that PLP and RLP arise from NP origins. Nikolajsen et al. found a link of PLP to N-methyl D-aspartate (NMDA) receptors through treatment with ketamine and concluded that PLP and RLP have mechanisms linked to both peripheral and central systems (Nikolajsen et al., 1996).

NMDA is an excitatory neurotransmitter which interacts with NMDA receptors. NMDA receptors are known to be associated with neural plasticity, having a role in long-term potentiation and long-term synaptic depression. They are also involved in sensory transmission; A-delta and C fibers use NMDA receptors among others in transmitting painful stimuli up nociceptive pathways at synapses in the Rexed laminae of the dorsal horn (Bleakman et al., 2006). Furthermore, having these roles gives way to one of the current, proposed mechanisms for NP, which points to NMDA receptors as a culprit for injury-induced central sensitization leading to secondary pain

presentations such as allodynia and hyperalgesia (Bleakman et al., 2006; Collins et al., 2010). For this reason, as discussed later, NMDA receptors are a popular target for medicinal treatment approaches to alleviate NP (Collins et al., 2010).

Whereas, PLP is pain in the phantom and RLP is pain in the stump, linking the two to NP offers an explanation that neither form of pain would exist without injury to the PNS. This also assumes that RLP and PLP are not generated through traditional means of activating nociceptor pathways. Although, this theory does not explain all observed conditions of phantom pain, e.g., people who are congenitally limb-deficient. As many as 20% of these individuals experience phantom limbs at some level (either sensation or pain), even though there is no injury, per se (Melzack et al., 1997).

1.1.5 Secondary Effects of PAP

It is not just the rate of amputations and the severity of the pain that makes this problem relevant, but also the impact of PAP on an individual's everyday life. The multifaceted attack of PAP through various mediums, such as PLP, RLP, and other forms, interferes with daily activities (Marshall et al., 2002). Amputation and PAP negatively affect the self-perceived quality of life through fatigue and diminished mood (Trevelyan et al., 2016). This leads to high rates of depression among amputees (as high as 41%) presenting a vicious cycle, as there are substantial links among depression, level of pain, and bothersomeness of pain for PLP and RLP (Cansever et al., 2003; Ephraim et al., 2005). Depression secondary to amputation could be remediated by educating the population on the risks of amputation and providing mental health services (Darnall et al., 2005).

1.2 The Proposed Loci and Mechanisms of PLP

1.2.1 Neurologic Locus of PLP

The root cause of PLP is not clear as effects of amputation appear in each level of the nervous system, indicating multiple compounding sources of pain. Evidence suggests that PLP is the result of a multifaceted, combined system response from cortical, peripheral, segmental, and even psychological origins (Flor et al., 2006). Most propositions of mechanisms discuss cause and effect on the level of the CNS or PNS. Because of the many proposed mechanisms, further partitioning is necessary. Therefore, mechanisms are discussed below

according to the relevant neurologic locus: peripheral, spinal, supraspinal, and cortical (Flor et al., 2006; Hsu and Cohen, 2013).

1.2.2 Predominant Mechanisms of the Peripheral Neurologic Locus

The Tinel sign (also "tingling" sign) was originally proposed to identify regions of peripheral nerve regeneration, specifically regarding cases of nerve injury (Davis and Chung, 2004). Similarly, one can use the Tinel sign on an amputee to locate nerve injuries that cause sensations or pain in the stump or phantom (referred sensation or RS). Commonly, the location that causes sensation or pain is at the site of a severed nerve, which has morphed into a neuroma. These neuromata (known as terminal neuromata) are typically formed within 1–12 months after nerve transection (Boutin et al., 1998), but start to form within hours (Fried et al., 1991). A study in rats found that ectopic discharges from injured peripheral nerves have a role in initiating NP, but do not have a significant role in the maintenance of NP (Sun et al., 2005). The onset of ectopic discharges is correlated with the onset of allodynia (pain from a stimulus that would normally be nonpainful) shortly after nerve transection, indicating these are responses to or results of injury (Sun et al., 2005). However, in animal studies ectopic discharges diminished over time, while tactile allodynia was maintained (Sun et al., 2005; Flor et al., 2006). These circumstances in the periphery seem to demonstrate two effects of nerve transection, but do not identify the source or mechanism of pain. For example, neuromata have been found to be sensitive to mechanical and chemical stimuli (Fried et al., 1991; Flor et al., 2006), so much so that PLP can be heightened from tapping (Nystrom and Hagbarth, 1981). However, a study on two amputees found that PLP persisted even after blocking PLP associated neuromata with lidocaine (Nystrom and Hagbarth, 1981). This causes further suspicion that PLP and other phantom phenomena are not caused by peripheral mechanisms; rather, they are merely accentuated by peripheral factors.

1.2.3 Predominant Mechanisms of the Spinal Neurologic Locus

Deafferentation of the dorsal horn is thought to be linked to PAP, specifically through central sensitization, which is the increased activity of the dorsal

horn afferent targets due to decreased suppression from the brainstem (Iacono et al., 1987; Hsu and Cohen, 2013).

Deafferentation could be a result of amputation, or it could be another type of injury such as brachial plexus injury. Jensen et al. proposed that pain may be induced from atrophy of deafferented dorsal horn neurons and changes to receptive fields in the spinal cord (Jensen et al., 1983).

Spinal reorganization has also been recognized in functionally inactive regions and is reversible if the relevant nerves regenerate (Devor and Wall, 1981; Hsu and Cohen, 2013). It has also been manipulated through operant conditioning of spinal reflexes (a well-known mechanism for learning). Thompson and Wolpaw reviewed several studies that took advantage of the operant conditioning paradigm to alter reflexes (Thompson and Wolpaw, 2014). Because of the integration of sensory information in the spinal cord (especially connections involved in gating through suppressive inhibitory interneurons), spinal mechanisms are important to consider (Teixeira et al., 2015).

1.2.4 Predominant Mechanisms of the Supraspinal Neurologic Locus

Florence and Kaas found in animal studies that cortical reorganization was linked to reinnervation and sprouting afferents subcortically in the brainstem and thalamus (Florence and Kaas, 1995). Some have linked amputation to significant changes to the cuneate nucleus in the brainstem, which typically projects to the thalamus and transmits afferent sensory information, especially from the hand (Florence and Kaas, 1995; Wu and Kaas, 2002). Xu and Wall found changes in the cuneate nucleus to occur within minutes to hours after injury in primates (Xu and Wall, 1997). Further evidence of supraspinal reorganization was demonstrated in adult squirrel monkeys (Churchill et al., 2001). Churchill et al. found that somatotopic reorganization of the thalamus and brainstem was of a similar extent to what is reported for the cortex (Churchill et al., 2001).

1.2.5 Predominant Mechanisms of the Cortical Neurologic Locus

A traditional theory, as proposed by Ramachandran et al., is that cortical reorganization is the primary mechanism of PLP, which is typically discussed in terms of plasticity of the primary somatosensory cortex (S1) (Ramachandran et al., 1992, Flor et al., 2000). Directly following amputation, the mapping of

S1, i.e., Penfield's Homunculus, no longer matches the anatomical structure. Changes occur in the sensory and motor cortices adapting to both the altered anatomy and the loss of sensory input (Flor et al., 2000). Specifically, the plasticity of the cortex allows neighboring regions of the somatosensory homunculus to take over the region that previously mapped to the, now deafferented, limb (Ramachandran et al., 1992). However, this mechanism also has missing links when looking at clinical experiences. A case study of two amputees found that some experience RS in the phantom hand while touching the ipsi- or contra-lateral foot (Grüsser et al., 2004). Another study found RSs in the upper leg and genitals that mapped to the phantom in upper limb amputees (Giummarra et al., 2011). Flor et al. found significant differences in activity among amputees experiencing phantom pain compared to those not experiencing PLP in regions such as SI, the secondary somatosensory cortex (S2), and the posterior parietal cortex (PPC) (Flor et al., 2000). Other cortical changes have also been evaluated, such as unmasking of preexisting synapses of neighboring cortical regions, e.g., of SI, and of preexisting transcommissural connections, e.g., for coordinated movements of multiple limbs (Giummarra et al., 2007). The latter is of particular interest because it may explain cortical reorganization ipsi-lateral to the amputation as seen by (Schwenkreis et al. 2003; Garry et al., 2005).

1.2.5.1 Referred sensation and related mechanisms

While all phantom sensations are in a sense "referred," the definitions of PLS and RS are slightly different. PLSs are generally understood to be any sensation felt in the phantom limb, whereas RSs are perceived feelings in a body part when another body part is being stimulated (such as the residual limb or the face). RS is a common occurrence in amputees (Ramachandran et al., 1992; Flor et al., 2000). While it is possible to feel RSs without nerve injury by stimulating proximal regions of a peripheral nerve as demonstrated by Forst et al. (2015), RSs typically are amplified in amputees (i.e., more regions of the body such as the face and ear map to the phantom limb). Similar to amputation, substantial RSs have been noted in individuals with type I complex regional pain syndrome (CRPS) (McCabe et al., 2003), spinal cord injury (Moore et al., 2000; Soler et al., 2010), and other nerve-related ailments. As with other aspects of phantom phenomena there is debate on the mechanism of RSs. This phenomenon is thought to originate from mechanisms that are separate from other phantom phenomena, as they are non-neuropathic in nature (Buonocore, 2015). Flor et al. found correlation of RSs to increased activity of the PPC (Flor et al., 2000),

while Ramachandran et al. supported reorganization of S1 to be the primary mechanism (Ramachandran et al., 1992). Stimulation of the remaining nerve in the residual limb has also elicited RSs; Dhillon et al. achieved this through stimulation with implanted electrodes (Dhillon et al., 2004). Similarly, Forst et al. were able to evoke RSs through surface electrical stimulation in healthy subjects by placing surface electrodes over the ulnar and median nerves (Forst et al., 2015).

The mapping of RSs requires the analysis of three primary locations: (1) the area being stimulated, (2) the area being referred, and (3) the cortical location of somatosensory processing. Several questionnaires call for a subject to locate the areas of pain (Melzack, 1975), but because nonpainful sensation are generally not bothersome (Smith et al., 1999), the location and mapping of RSs have not been addressed except cortically. This is a useful measure to determine changes in the presentation of pain. RSs can be evoked by touch; the Tinel sign is a simple method for identifying these regions (Trotter and Davies, 1909; Davis and Chung, 2004).

Several interesting phenomena, which likely have different mechanisms, are considered RSs. For example, the RSs evoked by touching the face of an amputee (as done by Ramachandran et al.) likely has a mechanism primarily in the cortex (Ramachandran et al., 1992; Flor et al., 2000). However, an RS evoked from stimulation of the proximal region of a peripheral nerve (as done by Dhillon et al.) likely can be explained by peripheral and/or spinal mechanisms (Dhillon et al., 2004; Forst et al., 2015).

1.2.6 Psychological Aspects of Pain

Emotional and psychological states have a large role in interfering with amputees' lives (Shukla et al., 1982; Kashani et al., 1983; Cansever et al., 2003). The initiative on methods, measurement and pain assessment in clinical trials (IMMPACT) recommends testing effects on emotional functioning when conducting pain-related clinical trials (Dworkin et al., 2008). Since amputees have exhibited differences from the general population in this respect, it is reasonable to assume that it also plays a role in the experience of PLP and other postamputation phenomena. In general, PLP is not a symptom of psychological distress (Katz, 1992). Katz and Melzack reported that depression and anxiety were not predictors of PLP (Katz and Melzack, 1990). This is further supported by Darnall et al. who found extremely bothersome RLP or PLP lead to increased odds of depressed symptoms, but depressed symptoms do not necessarily indicate bothersome RLP or PLP. They concluded that one of the highest risk factors for depressive symptoms

is PAP (Darnall et al., 2005). Both Hill and Katz cautioned researchers on the assumptions related to depression and PLP saying claims of psychological explanations of pain are unsubstantiated and study populations may be inherently biased (Katz, 1992; Hill, 1999). Along the same lines, some have suggested that the causal relationship between pain and mood is only unidirectional, i.e., negative mood states are a result of pain, but pain is not a result of negative mood (Blågestad et al., 2016). Even though the relationship of PAP and depression is still under investigation, the relationship of depression and amputation seems to be quite clear. In addition to depressive symptoms, evidence of anxiety, insomnia, and other psychological ailments are prevalent (Shukla et al., 1982). This demonstrates a need for mental health services among the amputee population.

1.3 "Phantom" Pain in Nonamputees – A Complicated Issue

The traditional definition of PLP refers to pain in a limb that is not present. However, there are also instances of sensation and pain in a limb that has lost connection to the CNS (deafferentation), from brachial plexus avulsion (BPA) or intraspinal injury, for example. These scenarios have been dubbed as "phantom" because the individual does not experience pain or even sensation through typical nociceptive and sensory pathways, because they are no longer connected. In this regard "phantom" sensations have been found in individuals who have brachial plexus injuries (Sweet, 1975; Son and Ha, 2015; Tsao et al., 2016). In addition to the similar descriptions of pain, after BPA individuals experience RSs in the deafferented limb from touching the ipsilateral face (Tsao et al., 2016). Brachial plexus injuries also lead to cortical reorganization (Qiu et al., 2014). Most often pain is described as tingling, pins and needles, burning, sharp, or paroxysmal (Parry, 1980), which is reason to believe BPA causes NP (Teixeira et al., 2015). The underlying mechanisms of pain as a result of BPA are not well defined. In comparing symptoms, one must consider that brachial plexus injuries are often incomplete, meaning the limb remains partially sensate because it is still partially neurologically intact. If individuals with BPA or intraspinal injury experience PLP, the phantom pain and phantom sensations convolute with trace sensations from the limb. Furthermore, the presence of the limb further complicates discriminating phenomena as phantom or not. While the pain presents in a similar fashion to that of pain as a result of amputation, the presence of the limb makes it difficult to know if the mechanisms are the same.

1.4 Theories of Why PLP Presents

In the study of phenomena associated with amputation, an important thought to consider is that a single mechanism will likely not explain all phenomena. This idea was proposed by Sherman et al. in their evaluation of the mechanism of PLP, which concludes that different presentations of pain should be treated differently clinically, but does not suggest how (Sherman et al., 1989). Several theories have been proposed over the years to explain PAP and phantom phenomena. Ronald Melzack and Patrick Wall have had many contributions to this list and evolution of theories including the Gate theory of pain, the Neuromatrix theory, and others, which are discussed further.

1.4.1 Gate Theory

Gate theory is a prominent pain theory developed in the 1960s (Melzack and Wall, 1965). The concept in its most basic form can be summarized as a complex multi-input, multilayered system, where inputs at various layers can relay "off" or "on" signals, which cascade to determine whether or not pain is perceived (Melzack and Wall, 1965; Mendell, 2014). More specifically, Gate theory suggests that portions of the dorsal horns, such as the substantia gelatinosa, and the brain are active contributors to the system, which excite, suppress, and modulate signals to downstream targets (Melzack, 1999). Wall reinforced the theory after a few years discussing new findings in the field and how they relate to the previously proposed theory (Wall, 1978). In development of the theory there were many unknowns as to how the theory was implemented physiologically. In returning to the topic Wall proposed that descending control involves the periaqueductal grey matter and nucleus raphe magnus (Wall, 1978).

The theory was proposed ahead of its time, pushing the field forward to better understand mechanisms of pain (Mendell, 2014). Since its introduction, Gate theory has evolved over several decades to account for new findings (Wall, 1978; Mendell, 2014). It provided the framework for future theories of mechanisms that incorporate the CNS and an individual's unique life experiences (Hill, 1999; Melzack, 1999). Melzack proposed a new theory as a derivative from Gate theory called the Neuromatrix theory, which emphasizes a sense of self in the perception of pain (Melzack, 1999).

1.4.2 Neuromatrix Theory

The Neuromatrix theory relies on the concept of a network of neurons that defines a genetically determined feeling of self (Melzack, 1990, 1992). The neuromatrix is thought to extend beyond the somatosensory areas of the cortex to the limbic and thalamocortical systems (Giummarra et al., 2007). Melzack proposed the neuromatrix could be molded by sensory input and is comprised of "thalamocortical and limbic loops," which cyclically process and synthesize input and output patterns. These patterns are what Melzack deemed the neurosignature, an individual's pattern of synaptic connections impressed on the neuromatrix (Melzack, 1990). An altered neurosignature, due to amputation, for example, would result in the experience of a phantom limb through sensations and possibly pain (Flor, 2002). The Neuromatrix theory considers sensory input and transmission on a "level of equal importance" as hormonal mechanisms of stress, meaning pain does not exist solely in a space of neural mechanisms, but also has psychological factors (Melzack, 1990). The diffuse nature of the theory, i.e., pain (or even phantom sensation) being the output of a large, complex psychophysical system, makes it difficult to isolate and test clinically (Hill, 1999; Flor, 2002; Giummarra et al., 2007). Furthermore and even more perplexing, the theory does not offer an explanation for why some amputees experience phantom pain or phantom sensation and others do not (Flor, 2002). Giummarra et al. offer examples of seven phantom limb-related experiences that are not explained by the Neuromatrix theory and concludes that Neuromatrix theory may provide explanations of PLP, but not PLS (Giummarra et al., 2007). While Neuromatrix theory is intriguing and will likely spark discovery in the current age of pain research (like Gate theory did in the 1960s), it lacks some explanation for phantom phenomena.

1.4.3 Maladaptive Cortical Plasticity

The idea of maladaptive cortical plasticity is that the sensorimotor cortex reorganizes in a way that causes pain post deafferentation. Whereas, it is clear that the cortex reorganizes postamputation, the extent of the relationship between reorganization and pain is unclear (Flor et al., 2006). Evidence supporting this theory compared hand and lip movements among upper limb amputees and healthy controls, where amputees experiencing PLP showed reorganization of the mouth and hand region of S1 and the primary motor cortex (M1) (Lotze

et al., 2001). In a study of brain-machine interfaces with patients experiencing phantom pain, Yanagisawa et al. found that attempting to merge and amplify neural signaling to cortical representation of the phantom actually increased pain (Yanagisawa et al., 2016).

1.4.4 Pain Memory

The pain memory hypothesis supposes that phantom pain mimics preamputation pain because of implicit pain "memories" established in the somatosensory system (Flor, 2002; Flor et al., 2006). The hypothesis relies on plasticity of the somatosensory cortex due to nociception (Flor et al., 2006). In a small study involving capsaicin injection, sensitivity of SI to nociception has been measured, improving validity of the hypothesis (Sörös et al., 2001). Further support for the hypothesis is that phantom pain commonly embodies pain that was experienced preamputation (Katz and Melzack, 1990), and several studies have found correlations between preamputation pain and phantom pain (Jensen et al., 1983; Nikolajsen et al., 1997). However, this theory does not account for the amputees who experience PLP but do not experience pain preamputation. Furthermore, some amputees feel pain due to the phantom limb being in an unnatural or biologically impossible orientation, which does not support this hypothesis.

1.4.5 Sensory Confusion

The hypothesis of sensory confusion assumes that pain is a result of ramping due to broken feedback mechanisms. While feedback loops exists subcortically, evidence also points to involvement of frontal and parietal brain areas in the "incongruence of motor intention and sensory feedback" (Harris, 1999; Flor et al., 2006). Similar to Gate theory, this hypothesis relies on closed-loop control of peripheral and central mechanisms, which modulate sensorimotor information during movement. Harris compares this effect to the feeling of nausea when senses do not agree on body position or balance (Harris, 1999).

1.5 Measuring PLP

Pain has both behavioral and physical properties and can be largely subjective. Intensity, affect, quality, and location are the primary experiential dimensions of pain (Jensen and Karoly, 2010). Pain intensity refers to the extent of the pain and can be subjective based on historical experience of the

individual reporting the pain. Pain affect refers to the "emotional arousal or changes in action readiness caused by the sensory experience of pain," as so eloquently put by Jensen and Karoly (Jensen and Karoly, 2010). In essence, pain intensity refers to the extent of pain while pain affect refers to the emotional experience related to pain or the extent to which the individual is bothered by the pain. Pain quality refers to the descriptors of pain with respect to sensation, such as tingling, burning, sharpness, etc. and also includes the time-related aspects of pain, such as frequency, length-of-time of pain, etc. Pain location defines the area pain is perceived. Each of these four dimensions of pain is important to measure when studying the effectiveness of treatments and therapies for PLP. However, the measurement of PLP is a complicated issue. When measuring pain in a research setting (clinical or animal), there are additional considerations, such as the effects of habituation and sensitization (Johnson, 2016). Because of these barriers, pain-researchers utilize multiple measures and consider behavioral presentations of discomfort in analysis (Huskisson, 1974). Across studies of proposed therapy methods, various pain measures and scales have been utilized; in regards to PLP, studies tend to describe the degree of pain and the extent the pain interferes with the individual's life through various psychophysical measurement modalities (Hill, 1999). This variety of methods makes comparisons of results difficult.

1.5.1 Psychophysical Measures of Pain

In order to understand the effects of a given therapy modality, one must measure the various aspects of pain. Several validated measures are available to do this. The instruments used in the present study for effect determination are the VAS, neuropathic pain symptom inventory (NPSI), profile of mood states-short form (POMS-SF) and are discussed further.

1.5.1.1 Self-report questionnaire

While self-report questionnaires are an obvious way to gather information and understand the pain being perceived, the subject-to-subject (intersubject) variation cannot be predicted. For example, Dar et al. found, in a small study of injured veterans, that severely injured individuals have a higher pain tolerance and higher pain threshold than lightly injured individuals (Dar et al., 1995). In a study of thermal pain thresholds, Wasner et al. explored preconditioning as a means of testing sources of intersubject variations; however, in terms of pain thresholds, the study found no difference in subjects who were preconditioned and subjects who were not preconditioned (Wasner and Brock, 2008). This is a relevant finding because of the concern for scale

recalibration presenting a potential source of variability in self-report data. The proposition of scale recalibration is an issue that is not addressed in the realm of PLP. However, in other research areas, this has not been validated as a source of variation. Lacey et al. found no evidence of scale recalibration in individuals suffering from chronic illness (specifically with regards to quality of life ratings) (Lacey et al., 2008). Nevertheless, studies typically rely on validated instruments and assessments to characterize pain and understand the effects of a given treatment for a population.

1.5.1.2 The visual analog scale (VAS)

Psychophysical measures involve those that describe an individual's perception. A commonly used instrument is the VAS. With respect to pain intensity, an individual experiencing pain ranks the pain somewhere between "no pain" and the "pain as bad as it could be" by marking a line spanning between the two extremes (commonly separated by 10-cm). The individual's severity of pain can be enumerated by measuring the length from 0 (no pain) to the marking (Huskisson, 1974). The primary measure of most studies describing the prevalence of PLP is typically some version of pain intensity; most often this is done with the VAS (Hill, 1999). The VAS and the discrete version, NRS, can be used for any measure in which there are two extremes. The VAS has been used to understand other aspects of phantom phenomena, such as intensity of PLS (Sherman and Sherman, 1983), and it can be useful in describing the effect of a treatment or therapy. In fact, it is used frequently outside of the realm of PLP (Huskisson, 1974). When describing the intensity of phantom pain, the VAS is often used along with the interpretation or adaptation into mild, moderate, and severe pain. Jensen et al. attempted to standardize these descriptors to pain ranges, 1–4, 5–6, and 7–10, respectively, by considering factors such as pain interference and impact on quality of life (Jensen et al., 2001).

1.5.1.3 The neuropathic pain symptom inventory (NPSI)

The idea of using a VAS or NRS has been adopted and adapted to quantify other unmeasureables because of its dependability (Huskisson, 1974). The NPSI utilizes several NRSs to quantify the qualities of NP (Bouhassira et al., 2004). Ultimately, the responses are combined to form subscores, which represent different aspects of NP, i.e., burning, pressing, paroxysmal, evoked, and paresthesia (or dysesthesia), and overall NP. In the case of NPSI, paresthesia/dysesthesia are defined by the same subscore, which is related to feeling pins and needles and feeling tingling (Bouhassira et al., 2004).

The usefulness of the NPSI is that it not only demonstrates the presence of NP, but also the presentation of the pain. Having this capability offers the opportunity to study the effects of treatment on subtypes of NP as well as the effects on overall NP. Mackey et al. proposed extracting information on NP from the short-form McGill pain questionnaire (SF-MPQ; discussed further in subsection\ref{opm}); this method takes advantage of an existing questionnaire, but it is not as specific as other measures, such as NPSI (Mackey et al., 2012). Other measures specifically related to NP exist, such as the neuropathic pain scale (NPS) (Galer and Jensen, 1997), the neuropathic pain questionnaire (NPQ) (Krause and Backonja, 2003), the "neuropathic pain four questions" (DN4) (Bouhassira et al., 2005), the Leeds assessment of neuropathic symptoms and signs (LANSS) (Bennett, 2001), among others; however, these alternative instruments are either not strongly validated, not detailed enough, or are designed to differentiate non-NP from NP and not to assess NP (Bouhassira et al., 2004). The NPSI has been validated in several languages among various populations (Bouhassira et al., 2004; Sommer, 2011; Matsubayashi et al., 2015). A German study found NPSI test-retest reliability to be suboptimal (Sommer, 2011), compared to the original study (Bouhassira et al., 2004). Although, in the German study the time lag was 24 h (compared to 3 h in the original study (Bouhassira et al., 2004)). While this is a notable finding, it does not change the validation of the instrument as it is reasonable to expect changes in the presentation of pain in a 24 h period; temporal variation is a known characteristic of NP (Gilron et al., 2006).

1.5.1.4 The profile of mood states-short form (POMS-SF)

In traumatic lower limb amputees, the prevalence of depression was 41.6% (Cansever et al., 2003). In a broader population base of various etiologies, significant depressive symptoms were seen in 28.7% (Darnall et al., 2005) (compared to 4.9% point prevalence) and 17.1% life-time prevalence in the general population (Blazer et al., 1994).

Ephraim et al. aptly noted the correlation of depression and the presence of PLP, where increased pain intensity corresponded to heightened depressive symptoms (Ephraim et al., 2005). The finding suggests that there is a need to continuously monitor and swiftly treat depression in amputees (Ephraim et al., 2005). In a more general sense, mood correlates to the intensity and perception of pain greatly (Blågestad et al., 2016). Some attempts have been made to treat pain using the class of drugs called antidepressants and through psychological treatments of pain Gilron et al., 2006; Alviar et al., 2016; however, these have been ineffective (Eccleston et al., 2015). Mood does not

act as an effective target for treatment. However, it may act as an indicator of positive or negative effect because of its correlation to pain.

The POMS-SF is comprised of 37 descriptors of mood. Each descriptor is ranked by the study subject on a five-point scale (1 = "Not at all," 5 = "Extremely") and is incorporated into a subscale, which can be used to characterize the individual's mood. The subscales are depression, vigor, confusion, tension, anger, and fatigue. Whereas depression has been shown to positively correlate with pain, other mood descriptors could provide more insight on the relationship of PLP and psychological state.

1.5.1.5 The brief pain inventory-interference scale (BPI-IS)

The brief pain inventory (BPI) has been adapted into a more succinct questionnaire as the BPI-short form (BPI-SF), which is a validated instrument for pain interference (Tan et al., 2004; Osborne et al., 2006; Raichle et al., 2006). The final series of questions is known as the BPI-IS. Questions are nonspecific to phantom pain and describe how pain has interfered with daily living over the past 24 h. The seven-question interference scale utilizes 11-item NRSs to describe pain's interference with general activity, mood, walking ability, normal work, relationships with other people, sleep, and enjoyment of life. The NRSs span from 0 ("Does not interfere") to 10 ("Completely interferes").

1.5.1.6 Problems with measuring PLP and other phantom phenomena

One factor not addressed by Jensen et al. when describing the standardization of the VAS with respect to PLP is the associated anchors of the VAS (Jensen et al., 2001). Anchors are defined as the descriptions of the minimum and maximum scores. Jensen et al. used a scale of 0–10 with anchors of "0 = no pain" and "10 = pain as bad as it could be" (Jensen et al., 2001). A prime example of this inconsistency in research related to PLP can be found in reports of the intensity of pain. In Table 1.1, several examples demonstrate how intensities are reported among various authors. The outcome of not utilizing a standard instrument for measuring pain intensity is data that are not directly comparable. While it may be possible to normalize the various scales back to the standard scale proposed by Jensen et al., correlations have not been proposed among the various scales.

Furthermore, interpretation of changing VAS scores is nontrivial. Jensen et al. suggest that a change in pain intensity from "7 to a 4 might be considered more beneficial and more clinically relevant than a reduction from a 4 to a 1,

Table 1.1 Different investigators use VAS pain scales that quantify pain intensities using different anchors, making it difficult to compare the measures between studies

Reference	Pain Scale	Anchors
Sherman and Sherman (1983)	0–100	Anchors not described
Montoya et al. (1997)	0–10	No pain / Unbearable pain
Smith et al. (1999)	0–100	Extremely mild / Extremely intense
Ehde et al. (2000)	0–10	No pain / Pain as bad as it could be
Marshall et al. (2002)	0–10	No pain / Pain as bad as it could be
Ephraim et al. (2005)	1–10	Mild pain / Extremely intense pain
Schley et al. (2008)	0–100	Anchors not described

at least in terms of the impact of the treatment on function and quality of life" (Jensen et al., 2001). This conclusion suggests that both the change in pain intensity as well as the baseline or reference pain intensity are important factors to keep track of in establishing effective treatments and therapies.

1.5.2 Other Proposed Self-report Measures of PLP

Because of the lack of standardization, several questionnaires and instruments have been developed or adapted for measuring PLP. Hill notes in a literature review of PLP, the MPQ and SF-MPQ have been used in several studies (Hill, 1999). The MPQ and its variants have significantly contributed to the understanding of pain (in general) and PLP, and it acts as a primary instrument in many pain studies (Katz and Melzack, 2010).

Alternate measures of depression include the Center for Epidemiological Studies-depression questionnaire (CES-D) (Ephraim et al., 2005). The chronic pain grade (CPG) (Von Korff et al., 1992; Ehde et al., 2000; Marshall et al., 2002) distributes an individual's pain into one of four grades based on intensity and disability associated with pain. Grade I is the least intense and least disabling, while Grade IV is the most intense and most disabling (Von Korff et al., 1992). Flor et al. and Montoya et al. used a 122-item phantom-and-stump phenomena interview as a primary instrument (Flor et al., 1995; Ehde et al., 2000). The interview is a compilation of several standard instruments to separately analyze stump and phantom sensations and pain, including a modified version of the MPQ, several VASs to describe average pain severity and intensity of nonpainful sensations, descriptors of sensations, along with several open-ended questions (Ehde et al., 2000). Montoya et al. also utilized the West Haven-Yale multidimensional pain inventory (MPI) to evaluate the severity and interference of stump and phantom pain (Ehde et al., 2000). Smith et al. (1999) used the prosthesis evaluation questionnaire (PEQ;

developed by Legro et al. (1998)). The PEQ highlights intensity, frequency, and bothersomeness of phantom, stump, and back pain as well as phantom sensations (Smith et al., 1999). Further evidence of lack of standardization is that study designs have opted to utilize self-designed questionnaires such as the Groningen questionnaire problems after arm amputation (GQPAA) by Kooijman et al. (2000).

1.5.3 Measuring Cortical Reorganization

Cortical plasticity or cortical reorganization is a popular topic in the study of postamputation phenomena. This is mainly because of the desire to understand the underlying mechanisms. While plasticity is not unique to the cortex (Florence and Kaas, 1995), it gets particular attention because of the relationship of the somatosensory mapping and observations of RSs in the facial region (Ramachandran et al., 1992). From the perspective of characterization, studies have investigated the differences in cortical activity among amputees and healthy controls. Lotze et al. studied the locus of activation for hand and lip movements using functional magnetic resonance imaging (fMRI), comparing amputees with PLP ($n = 7$), amputees without PLP ($n = 7$) and healthy controls ($n = 7$) (Lotze et al., 2001). Reorganization of the hand and lip areas in M1 and S1 was recognized in patients with PLP but not others. Many studies have also investigated the cortical differences between the activities utilizing the affected limb versus the individual's healthy limbs. This paradigm attempts to have an individual serve as his or her own control. Measurement of changes to the cortex can be done through several modalities. Blood oxygen level dependent (BOLD) fMRI is used most often because of the ability to relate activation to particular cortical structures. Most studies that use event-related BOLD fMRI to look at cortical reorganization focus on S1 and M1 (Flor et al., 1995; Lotze et al., 2001). Other instruments include electroencephalogram (EEG) coupled with some type of somatosensory evoked potential (SEP) in the periphery, such as tactile evoked potential (TEP) or laser evoked potential (LEP) (Flor et al., 2000; Zhao et al., 2016). Coupling both EEG and MRI, Flor et al. used EEG to record cortical activation during RSs elicited by TEP, and used the activation map to overlay an anatomical image captured via magnetic resonance imaging (Flor et al., 2000).

Some disadvantages should be considered when using BOLD fMRI to study cortical differences. The main disadvantage is the length of time required for measurement. BOLD fMRI contrast relies on the hemodynamic

response function (HRF), which is an increase in oxygenated blood (specifically oxyhemoglobin) compared to a resting state. The underlying assumption is that the increase in blood in a particular region is a causal, time-delayed effect of increased neuronal activity. These details reveal a reason behind the intensive time requirements of fMRI, as stimuli do not elicit instantaneous responses. Beyond the time dynamics of the biological system, the larger contributors to lengthy experimentation paradigms are issues of signal-to-noise ratio (SNR). To alleviate the poor SNR, fMRI paradigms typically utilize signal averaging, thus longer measurement times. Analysis of fMRI results involves an understanding of both estimation efficiency (ability to estimate the HRF) and detection power (ability to detect activation) as described by (Liu and Frank 2004; Liu, 2004). Furthermore, a recent study attempting to validate fMRI statistical analysis methods found high rates of false positives (Eklund et al., 2016).

1.5.4 Pros and Cons of Different Measurement Approaches

If relating back to the four primary dimensions of pain (intensity, affect, quality, and location), various instruments have positive aspects and points of weakness. For this reason, several research studies have implemented multiple instruments. Depending on the study design this could have different effects on self-report data. Thorough questionnaires and interviews (such as the MPQ or the phantom-and-stump phenomena interview) allow for detailed description of the pain, but take substantial time and concentration for the study participant. This could cause frustration and bias if the participant is enrolled in a study of temporal effects of treatment and having to complete a questionnaire multiple times, for example. Substantial effort should be taken to consider the length of time a study participant spends responding to questionnaires and the number of times a study participant responds to a particular questionnaire. On the other hand, there are disadvantages of being too brief (Jensen and Karoly, 2010). Brevity is just one consideration in the list of primary trade-offs, where targets should be set to reduce the required contact time between the health care provider (HCP) and patient, while maximizing the collection of relevant pain characterization data.

1.6 Current Treatment/Pain Management Methods

The proposition of treating PLP has been under study for decades. In 1980, Sherman et al. reported on 68 different possible methods (Sherman et al.,

1980; Sherman, 1980). To this day, a concise method for treatment has not been identified. Flor suggested more than 30 commonly used treatments for PLP in 2002, only a small fraction of which have shown any success in randomized controlled trials (RCTs) (Flor, 2002). Ideally, treatment methods of PAP and phantom limb phenomena would be developed from a mechanistic approach, i.e., the mechanism of pain would be utilized to address and reverse the pain. Since the mechanisms are not well understood, therapies tend to treat the symptoms, leading to a high number of available treatments, low rates of success, and high rates of dissatisfaction among patients (Sherman et al., 1980; Vernadakis et al., 2003). Current treatments of PAP can be broken down into medicinal and nonmedicinal methods. Medicinal treatments of pain utilize various methods of application: topical, oral, and local injection. A wide variety of nonmedicinal treatments have been explored, taking advantage of mechanical and electrical sensitivity of PAP. Other methods have used traditional pain management techniques, while some have ventured into the psychological treatment of pain. All-in-all treatment of any form of PAP has been largely unsuccessful.

1.6.1 Current Standard of Care

In 1983, a study found that only 17% of amputees were offered treatment for PLP even though 61% reported experiencing PLP (Sherman and Sherman, 1983). Several authors have noted a variety of responses from physicians to those suffering from PLP such as, "it is in your head" or PLP is "psychogenic" (Flor, 2002; Sherman et al., 1984; Mortimer et al., 2004; Sherman et al., 1987). Conversely, while the limb may no longer be present, the pain and sensations seem real. Another study in 1997 found nearly one-third of amputees who discussed PLP with their doctor were told no treatment was available (Wartan et al., 1987). Kern et al. attempted to study the success rates of relevant treatment methods by surveying amputees. Seventy-one percent ($N = 537$) of the amputees suffering from PLP had never received or sought after treatment; 19% felt their doctors were incompetent on the topic (Kern et al., 2012). Of those who did receive treatment for phantom pain, the treatment with the highest success rate was opioids via oral or IV administration at 67%. The second highest treatment method was opioid injection via intrathecal pump at 58%. Neither of these treat the root problem but only temporarily mask the pain (Kern et al., 2012). Whereas the medical and scientific communities are more accepting of the reality of PLP, the current standard of care is still up for debate. A focus group of health

professionals found that information given to patients experiencing PLS and PLP is grossly inconsistent, indicating a necessity for a standard of care to be developed (Mortimer et al., 2004).

1.6.2 Medicinal Treatments

Medicinal treatments are among the most successful at alleviating PLP. Opioids/Opiates have shown a success rate as high as 67.4% (Kern et al., 2012), in particular morphine via injection and oral administration has shown successful reduction of but not elimination of PLP and RLP in a randomized controlled trial (Wu et al., 2002, 2008; Alviar et al., 2016). However, long-term analgesic efficacy has not been verified (Kern et al., 2012; Alviar et al., 2016). Anticonvulsants have also shown moderate success (52%) (Kern et al., 2012). Gabapentin is a commonly used anticonvulsant, which has had controversial results in RCTs. Bone et al. showed reduction of PLP in comparison to a placebo but no significant change in secondary measures, such as depression, mood, or sleep interference (Bone et al., 2002). Conversely, a separate RCT showed no significant difference between gabapentin and placebo groups (Smith et al., 2005). Some side effects were noted; however, these were not significantly different from the control groups (Bone et al., 2002; Smith et al., 2005).

Alviar et al. reviewed three NMDA receptor antagonists as possibilities: memantine, dextromethorphan, and ketamine (Alviar et al., 2016). The review identified only ketamine (Eichenberger et al., 2008) and dextromethorphan (Ben Abraham et al., 2003) to provide pain relief from this class of pharmacologic interventions (Alviar et al., 2016); however, both studies were underpowered (Alviar et al., 2016) and treatment with ketamine had substantial side effects, including dizziness, light hallucinations, and hearing impairment (Eichenberger et al., 2008). NMDA receptor antagonists have shown moderate success at relieving pain. The unsuccessful cases may be related to the mode of administration; each memantine trial reviewed utilized oral administration while other studies of this intervention method were successful with injection (Alviar et al., 2016).

Various other options have been explored and proposed for treatment including antidepressants, calcitonins, and local anesthetics (Alviar et al., 2016). In patient surveys, antidepressants have shown to be ineffective. Only 36.4% noted this method as effective (Kern et al., 2012). This ineffectiveness was supported in a RCT of amitriptyline that failed to show positive results (Robinson et al., 2004; Alviar et al., 2016). Furthermore, amitriptyline had

a significant adverse effect of dry mouth over the placebo (Robinson et al., 2004). Local anesthesia was largely ineffective according to patient surveys (21.6% success) (Kern et al., 2012); RCTs of intravenous infusion with Lidocaine have shown successful treatment of RLP but not of PLP (Wu et al., 2002).

1.6.3 Nonmedicinal Treatments

Several nonpharmacological approaches have been proposed and tested as possible treatments for PLP, such as proper stump management, electrical stimulation, and mental imagery. Treatments vary significantly in regards to stimulus modality, psychological demand, and efficacy. Many therapies are proposed in case studies and uncontrolled trials, but either do not reach the stage of conducting a RCT or are not successful in a RCT, which makes identifying potential effective treatments in literature difficult (Halbert et al., 2002). Some of the more prominent methods are discussed further.

1.6.3.1 Nerve and stump management

Several methods have been proposed to thwart PAP related to neuromata; a universal method has not been accepted (Ducic et al., 2008; Vernadakis et al., 2003). Proper care of the stump and preventative measures in surgery are crucial to mediate pain. Painful neuromata are common among amputees; nearly 30% undergo surgery after amputation with the hopes of relieving neuroma-related pain (Kern et al., 2012). Often they form from improper surgical technique during the original amputation (Vernadakis et al., 2003). Studies have shown that simply excising the neuroma and applying traction to the nerve (encouraging the nerve to retreat into the stump) is not a successful procedure, only demonstrating successful results 33% of the time (Tupper and Booth, 1976). Over the years several techniques have emerged to ameliorate this painful phenomenon (Vernadakis et al., 2003). A recent review of neuromata treatment and prevention found nearly 200 techniques, supporting the perfect solution has not yet been found (Vernadakis et al., 2003). Some techniques have proven successful and appear notable; excision with silicone capping (83% success (Swanson et al., 1977)) or centrocentral anastomosis (94–95% success (Kon and Bloem, 1987; Barberá and Albert-Pampló, 1993)) are prime examples (Vernadakis et al., 2003). On the other hand, techniques such as these also present unnecessary risks to the patient. Silicone capping involves the introduction of a foreign body, which risks immunological response and inflammation in the stump (Ducic et al., 2008). Centrocentral

anastomosis lengthens the time of surgery due to the meticulous nature of microsurgery, which means more opportunities for infection (Ducic et al., 2008).

One of the most notable techniques is nerve transposition (Vernadakis et al., 2003). Mackinnon et al. demonstrated the capability of minimizing neuroma formation in an animal model (Mackinnon et al., 1985). Rerouting the transected nerve into adjacent muscle without tension, resulted in significantly smaller neuromata compared to control groups in primate models (Mackinnon et al., 1985). Mackinnon and Dellon revisited the technique emphasizing the importance of separating the nerve ending from the scar tissue (Mackinnon and Dellon, 1987). This study found different success rate depending on a patient's previous experience ranging from 56% to 100% for good or excellent results (Mackinnon and Dellon, 1987). The nerve transposition technique had good or excellent results in 81% of cases (42 patients).

Another method that has had some success is targeted muscle reinnervation (TMR) (Souza et al., 2014). This is the act of intentionally ligating the original innervation of a nearby muscle to direct alternative peripheral nerves to the muscle. Generally, TMR utilizes a muscle that is no longer providing functional advantages to the patient with the hopes of the muscle acting as a target for the nerve. The long-term goal for these patients is that they could intuitively move their phantom, which would cause muscle activity in the targeted muscle; then, this muscle activation could be recorded, e.g., via EMG, to manipulate an active prosthetic. Conveniently, this method serves a dual purpose by also preventing the formation of neuromata. In a retrospective study 6 months after surgery, the method appears to be successful (Souza et al., 2014). All patients in this study reporting pain reported reduced or eliminated pain, and just under 90% were able to operate a TMR-controlled prosthesis.

Peripheral nerve surgery, such as TMR, is a treatment option for managing pain related to neuromata that has shown success in several studies, and is an excellent example of advancement in the field (Vernadakis et al., 2003); however, the degree of functionality provided by this method is often not necessary for lower extremity amputees. Rather than transferring the transected afferent nerve fibers to an alternative muscle or region, some have suggested merely tying the sensory nerves to nearby muscle away from areas forming scar tissue. If done during the amputation surgery, it could prevent formation and excision of the neuroma postamputation, thus lowering overall patient risk through reduction of procedures and procedural time (Ducic et al., 2008).

This procedure, proposed by Ducic et al. as an outpatient operation has had great success in a retrospective study of 21 neuroma excisions; patients reported an the average preoperative pain of 8.04 that decreased to 1.07 on the VAS (ranging 0–10) (Ducic et al., 2008). Furthermore, 85% reported improved quality of life. The key to this technique involved suturing the nerve-ending (after neuroma excision) to the nearby muscle. Some have proposed applying light traction to the nerve is sufficient, but an important detail to many of the techniques is to keep the nerve tension free (Vernadakis et al., 2003).

1.6.3.2 Electrical stimulation

Electrical stimulation of the residual limb, especially transcutaneous electrical nerve stimulation (TENS) or functional electrical stimulation (FES), has had success in case studies and small trials. However, as is the case with other therapy methods, the effectiveness of TENS has not been shown with a RCT (Johnson et al., 2015). Other forms of electrical stimulation have shown promise as well. Peripheral nerve stimulation showed significant improvement in regards to pain and quality of life, but the study lacked a placebo and had a small number of participants (Rauck et al., 2014). Others have attempted applying TENS to areas other than the residual limb, such as the contralateral limb (Tilak et al., 2016) and the ears (Katz and Melzack, 1991). Both of these methods showed a positive effect in small, short-term trials, but neither was compared to placebo groups. Sensory discrimination training using TENS has shown positive results (reduction in PLP and effect in cortical reorganization) in a small comparative study of 10 amputees (Flor et al., 2001). This method involved the application of random, nonmeaningful stimulation patterns of varying frequency, intensity, and location. Trial subjects were instructed to identify different patterns with the hypothesis that distraction from the pain actually reduces the pain (Flor et al., 2001). Success indicates there is a positive relationship among discrimination ability, cortical reorganization, and decreased PLP; although, the long-term effects of this method were not reported in (Flor et al., 2001).

1.6.3.2.1 *Considerations for FES of peripheral nerves*

Studying the effect in cats, Agnew et al. found that 8 h of high-rate, high-amplitude electrical stimulation resulted in irreversible damage of sciatic nerve axons (Agnew et al., 1999). In an earlier paper (McCreery et al., 1997), this effect was referred to as stimulation-induced depression of neuronal excitability (SIDNE). SIDNE, which according to the authors differs

from long-term depression (LTD) because it does not involve a change in efficacy of the synapses and does not worsen day-to-day, can occur in the CNS if axons are subjected to "prolonged, high-frequency microstimulation" (McCreery et al., 1997). McCreery et al. stimulated the posteroventral cochlear nucleus (PVCN) for 7 h per day to find that with high enough intensity SIDNE could be induced, but was still reversible. The speculated mechanism attributed the effect to the entry of calcium into the neurons activating second messengers and several downstream pathways.

Lu et al. studied the effects of electrical stimulation on peripheral nerve regeneration in Sprague-Dawley rats (Lu et al., 2008). Methods involved transecting the right sciatic nerve, separating the nerve endings by 10-mm, and surrounding the nerve endings by a silicone rubber chamber. Stimulation was applied for 15 min every other day at 1 mA (1, 2, 20, 200 Hz depending on group). Results included histological samples as well as tests of nerve conductivity that showed the 2-Hz stimulation group to have the most mature structure. Lu et al. concluded that in regards to peripheral nerve regeneration, stimulation (depending on frequency) can have a positive or negative effect. Note, control group had 100% success in regenerating a nerve cable spanning the 10-mm gap; however, the conclusion was that the nerves generated under 2-Hz stimulation were healthiest (Lu et al., 2008). Cogan et al. suggest many culprits when it comes to the cause of tissue damage and that macroelectrodes and microelectrodes have different challenges when it comes to preventing tissue damage (especially charge density and charge per phase), but they did not address continuous stimulation (Cogan et al., 2016). Patel and Butera used stimulation frequency of up to 70 kHz to block nerves, but did not report on the possible effects of continuously stimulating at these high frequencies (Patel and Butera, 2015). Prodanov et al. (2003) reviewed FES in 2003 and pointed to two other articles by McCreery et al., which also discussed the negative effects of continuous electrical stimulation (McCreery et al., 1992, 1995). The 1995 McCreery paper indicates that low-frequency stimulation does not lead to early axonal degeneration, independent of stimulus amplitude.

1.6.3.3 Imagery

Mental imagery coupled with various techniques, such as muscle relaxation (Brunelli et al., 2015) or virtual visual feedback (Ramachandran and Rogers-Ramachandran, 1996; Mercier and Sirigu, 2009), present enlightening results that may reveal psychological aspects of PLP. Ipsi-lateral cortical reorganization could be a target for mental imagery, especially when utilizing

coordinated bimanual movements through visual feedback (Schwenkreis et al., 2003; Garry et al., 2005). Mental imagery and muscle relaxation showed a significant reduction in PLP, PLS, and pain interference compared to a positive control group (Brunelli et al., 2015). The positive control group maintained the same physical therapy schedule as the test group, while the test group exercised mental imagery, in addition to the physical therapy. The success of this trial demonstrates an advantage of coupling physical stimulus with psychological exercise. Graded motor imagery (GMI) utilizes gradual training in three strategies: (1) implicit motor imagery, (2) explicit motor imagery, and (3) mirror visual feedback (Priganc and Stralka, 2011). Implicit motor imagery training involves laterality recognition or identification of images representing left limbs versus right limbs; explicit motor imagery practices movement of the phantom limb, or focusing on consciously manipulating the phantom; and, mirror visual feedback exercises the movement of the phantom while the patient utilizes visual feedback. Typically, the visual feedback involves placing the contralateral limb in front of the mirror, the amputated limb behind the mirror, and simultaneously moving both the contralateral and phantom limbs. Bowering et al. reviewed studies, including work on PLP by Moseley (2006), using this multipronged approach and found it to successfully treat chronic pain (Bowering et al., 2013). While the method has been proposed to treat PLP and PAP, the effects have not been thoroughly evaluated in this context (Limakatso et al., 2016). Some have compared the effects of mental imagery through virtual visual feedback (also known as mirror therapy) to that of TENS when applied to the nonamputated limb (Tilak et al., 2016). Both groups showed reduction in pain over a 4-day treatment phase, but neither group performed significantly better than the other.

This type of mental imagery could be considered a form of conditioning, where participants actively and consciously reinforce imagined movement with feedback (e.g., visual or tactile).

Imagery is supported by Macuga and Frey (2012), who found that imagery, i.e., actively simulating movements, stimulates more brain regions than passive observation. Studies on operant conditioning have shown to alter CNS organization in the spinal cord, specifically through retraining of spinal-cord-mediated reflexes (Thompson and Wolpaw, 2014). Thus, in these circumstances psychological treatment has physiological implications. Psychological treatments have had positive results for the treatment of NP in a few, small studies; however, treatment recommendations for NP have moved toward a multimodal approach incorporating psychological treatment

with pharmacological or nonpharmacological methods (Turk et al., 2010). This serves as a possible opportunity that has not yet been thoroughly explored in the realm of PAP, through the combination of psychological and nonpharmacological treatment.

No single treatment method seems to be a superior method for alleviating PLP. This may be due to the nature of nonmechanism-based therapy development, treating symptoms rather than the root cause. In order to develop successful therapies, we should first seek to understand the primary mechanisms driving PLP in the background (Hsu and Cohen, 2013). We should also seek to understand the effects of various methods by reporting results in a consistent way. Several studies and the measured effects have been reported and reviewed; the unfortunate reality is that many of the therapy methods are difficult to compare in terms of effect because there is not a standard metric for PLP.

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