Meredith Conroy
Dr. Bartholomew and Dr. Roy
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“Phantom Limb Pain: It’s Not ‘All in my Mind, it’s in my Neurons!’”

Abstract:

Phantom limb pain (PLP) is a burning, stabbing, shooting, aching, and/or throbbing pain that an amputee feels in his or her amputated limb. According to recent statistics, PLP affects 50-80% of amputees—over one million amputees in the United States alone. With this condition being so widespread and detrimental to patients' day to day life it is important to understand its mechanisms. However, there is a great deal of debate as to whether PLP is neurological or psychological. Those who side with the neurologists argue that PLP functions through three main mechanisms: maladaptive brain plasticity, referred pain, and atrophy of neural structures. Researchers have proposed treating PLP by disrupting these neurological mechanisms through electrode therapy, mirror therapy, acupuncture, and pharmaceuticals. More experimental therapies include robot hand therapy and gaming therapies. Those who believe PLP is largely psychological argue that amputees have high levels of anxiety and depression due to their vulnerability, dependency on others, and drastic lifestyle changes. Anxiety and depression have been linked to a number of psychosomatic symptoms including chronic nerve pain. Therefore, they argue that the experience of PLP is largely caused by psychological factors. However, the evidence supporting this theory is both weak and contradictory. Many studies that support the idea that PLP is primarily psychological have weak evidence, lack controls, and have small sample sizes. Conversely, the evidence supporting the idea that PLP functions through maladaptive brain plasticity, referred pain, and neural atrophy is strong and well supported by other scientists. However, there is still room for further research. It remains unclear why PLP affects some amputees but not others. Furthermore, researchers do not know which mechanism (maladaptive brain plasticity, referred pain, or neural atrophy) is the most dominant and why. Overall, it is clear that PLP is caused primarily by drastic neurological changes resulting in excessive and confused neuronal firing. Though psychology plays a role in PLP, as it does in many illnesses, it is not the primary mechanism of the syndrome. Thus, healthcare companies should provide adequate neurological/pharmacological care for patients suffering from PLP.

Introduction:

In the United States alone there are two million existing amputees and just under 200,000 new incidents each year. According to recent statistics, 50-80% of these amputees will experience phantom limb pain following their amputation (Le Feuvre and Aldington 2014). Phantom limb pain is defined as burning, stabbing, shooting, aching, and/or throbbing pain localized in an amputee's missing limb (Ferraro et al. 2016). PLP should not be confused with "stump pain" which is pain that is strictly localized to the site of the amputation (Barbina et al. 2016). PLP onset typically occurs within six months of the initial amputation and can last anywhere from a few months to several years. However, there is no relationship between the

type of injury that lead to the amputation and subsequent PLP symptoms (Le Feuvre and Aldington 2014). Intensity can range anywhere from mild to severe and the pain can be either chronic or acute, depending on the patient. Therefore, it can severely interfere with a patient's quality of life. It is clear, based solely on PLP's prevalence and debilitating nature, that PLP is a serious issue today which is why both its mechanisms as well as potential treatments must be studied extensively.

It was previously thought that phantom limb pain was a psychosomatic disorder with minimal (if any) neurological mechanism. The accepted theory was that patients suffering from PLP were only imagining the pain to be real because they were traumatized by the injury, were used to having the limb there, or had another mental illness (de Roos et al 2010). However, in recent years scientists have come to understand that PLP is largely neurological. Despite the mass amount of evidence supporting this, there is still some debate as to whether or not psychology plays an important role. Here, I will discuss the neurological and psychological mechanisms of PLP and how health care providers can effectively treat patients.

Neurological Mechanisms of Phantom Limb Pain:

The first major way that phantom limb pain is initiated and propagated neurologically is through the atrophy of neural structures (Jiang et al 2015). Every limb/part of the body is associated with a different region of the somatosensory and premotor cortexes. When a limb gets amputated there is no longer neural signals being sent to its corresponding cortical regions. Thus, the dormant neural tissue begins to atrophy. Jiang et al (2015) describes an experiment in which the cortical thickness and fractional anisotropy of white matter of seventeen lower limb amputees and eighteen healthy controls' brains using MRI and diffusion tensor imaging. They ultimately found that the amputees had a number of deteriorating structures including: thinning premotor

cortexes as well as visual-to-motor regions, decreased fractional anisotropy in the right superior corona radiata as well as the inferior fronto-occipital fasciculus (Jiang et al 2015). Each of these affected neural structures are associated with movement, sensation, and processing visual information. Therefore, when they are compromised it can have a slew of neurological consequences including maladaptive brain plasticity.

Maladaptive brain plasticity is when the brain attempts to quickly correct a neural trauma by converging adjacent neural pathways onto the affected site thus creating neural confusion and excess neuronal firing (Le Feuvre and Aldington 2014). Initially the damage caused by the amputation increases the firing of peripheral nociceptors which ultimately alters the anatomy of the dorsal horn and root of the spinal cord so that it becomes more excitable (Le Feuvre and Aldington 2014). The more excited dorsal root has the ability to also excite adjacent neurons. These factors increase the patients' sensitivity to pain. In the brain itself, the somatosensory region originally associated with movement of the (now phantom) limb atrophies and becomes relatively dormant. This causes adjacent neural structures to converge on the deafferented cortical amputation zone (Le Feuvre and Aldington 2014). Raffina et al (2016) considered patients with amputated hands for instance. In this study the central sulcus and BOLD responses within the brain of eleven hand amputees and seventeen healthy controls were studied during hand, elbow, and lip movement. The experimenters found that the brain had formed little to no reorganization patterns where the amputee's hand would have synapsed in the brain. However, the cortical regions pertaining to lip and elbow movement began to converge on the deafferented cortical region where the hand nerves once synapsed. This occurred because the hand, lip, elbow and even eye share neural pathways and are connected through peripheral nerves. Therefore, when one region is affected it causes a cascade effect on the rest of the neural pathway. In other

words, different nerves connect a variety of different body parts and thus share pathways. The connectedness of neural pathways is heavily associated with the second neurological mechanism of phantom limb pain, referred pain.

Referred pain is when stimulation to one region causes sensation in another and it is both central and peripheral mechanism of phantom limb pain (Collins et al 2017). Due to maladaptive brain plasticity, when a limb gets amputated, adjacent neural pathways in the brain attempt to converge on the site of the amputation to correct the damage. However, this convergence causes neural confusion and excessive firing thus resulting in increased nociception. An example of this is in upper extremity amputees; when an upper extremity is amputated, the nerves of the face converge on the dormant extremity region of the brain. This causes the neural pathways of the amputated limb and the face to cross paths. Thus when the face is stimulated the patient will often feel the sensation in their phantom limb. This can also cause painful sensations in the phantom limb due to excessive firing and overstimulation (Collins et al 2017). One experiment attempted to further investigate the mechanisms of referred sensation by stimulating the facial nerves of nineteen upper extremity patients using electrodes on the skin. 42.1% of the patients felt referred sensation in their phantom limbs while others experienced sensation in other areas. This supports the claim that PLP is influenced by referred pain mechanisms (Collins et al 2017). However, there are still other factors at play in PLP sensation.

Another way in which PLP is initiated is through peripheral factors. The initial amputation cuts peripheral nerves. The axons of these nerves attempt to re-sprout which can then cause a neuroma on the residual limb to form. The neuroma will then secrete ectopic discharges (a nociceptive signal) that can then cause the patient to experience PLP. In addition to ectopic discharges, an infected wound could also cause PLP (Le Feuvre and Aldington 2014). Infection

at the amputation sight would cause inflammation and subsequent stimulation to the adjacent neural pathways. This stimulation would create referred pain in the phantom limb. Another factor that would cause PLP is increased levels of epinephrine in the body. Increased epinephrine levels are caused by sympathetic secretions which are typically caused by bodily or emotional stress (Le Feuvre and Aldington 2014). Epinephrine increases the body's nociception thus making the patient more vulnerable to PLP. Overall, there is a clear relationship between peripheral factors, chemical signals, and PLP.

Accepted Treatments for Phantom Limb Pain and How They Target Neural Mechanisms:

Due to the multifaceted nature of phantom limb pain, there are a number of different proposed treatments and each range in their efficacy based on the individual. The most common treatments include (but are not limited to): mirror therapy, acupuncture, electrode therapy, and pharmaceuticals (Mayo Clinic Staff 2014). Mirror therapy is a technique during which a patient places a mirror between his or her real limb and their phantom limb (facing the real limb) to give the appearance of symmetry. The patient will then be asked to perform a series of movements with their real limb and pretend to perform the task with their phantom limb while looking at the mirror (Le Feuvre and Aldington 2014). This gives the illusion that they are performing the task with both limbs rather than just one and tricks the brain (it is often considered both a psychiatric and neurological therapy). The goal is to revert maladaptive brain plasticity and adjust the neural pathways to reduce excess firing. Various studies have claimed that mirror therapy is effective in treating PLP but provide little evidence to support their claims (Barbina et al 2016). Barbina et al (2016) conducted a systematic review of twenty mirror therapy experiments and found that all of them lacked sufficient evidence to support the efficacy of MT as a treatment of PLP. The lack of evidence mainly stemmed from the fact that most of the papers did not have controls.

Furthermore, MT varies in its effectiveness. Sometimes it helps patients significantly, sometimes it does nothing, and sometimes it makes pain worse (Barbina et al 2016). The exact reasoning for why MT ranges in effectiveness is not known. Therefore, it is not always recommended for treating PLP.

Another proposed treatment for PLP is acupuncture therapy (Mayo Clinic Staff 2014). Acupuncture therapy is considered a complementary medicine and has been practiced by the Chinese for hundreds of years. During this therapy, small needles are placed into specific "chi" points on the body and left in for twenty to thirty minutes. "Chi" points are associated with different nerves and muscles (typically knots in the muscles). Sometimes the needles will be stimulated with electrical currents, heat, or pressure. For PLP patients the needles can be placed in the stump itself or more proximal to the body, depending on the patient's pain capacity and sensitivity to stimulation. Though there are a number of proposed theories of how acupuncture therapy works neurologically, it is generally accepted that it works by altering brain activity patterns associated with pain perception and by increasing the amount of endorphins, serotonin, ATP, and other neurotransmitters in the body (Baeulmer et al 2014). Trevelyan et al 2016 describes an experiment that tested the efficacy of acupuncture therapy on fifteen lower limb amputees (seven acupuncture treated, and eight controls) over the course of four weeks. A numerical pain-rating scale, the Short-Form McGill Pain Questionnaire 2, EQ-5D-5 L, Hospital Anxiety and Depression Scale, Perceived Stress Scale 10-item, Insomnia Severity Index, and Patient Global Impression of Change surveys were conducted at the baseline, weekly, and one month post completion of the experiment. The experimenters found that pain was significantly reduced in the acupuncture group (5.44-2.75) but not in the usual care group (5.43-4.43). Patients also noted that acupuncture was both relaxing and enjoyable, despite their initial apprehensions

about it (Trevelyan et al 2016). These findings suggest that acupuncture is a viable treatment for PLP but future experiments with larger samples and more diverse demographics should be conducted.

Electrode therapy is a commonly used treatment for PLP because it is noninvasive and relatively risk free (Mayo Clinic Staff 2014). During electrode therapy, electrode patches will be placed on the amputee's stump and adjacent nerves (Mayo Clinic Staff 2014). Electrical impulses are then sent through the patches to the patient's amputated limb to engage with the nervous system. These impulses act antagonistically to the excessive neural signals caused by damaged nerves thus reducing pain. The electrodes elicit various sensations such as tingling, gripping, touch, or vibration at the site of the patches and (often times) in referred locations (Forst et al 2015). For PLP patients the referred location is typically the phantom limb. Forst et al (2015) describes an experiment in which the median and/or ulnar nerves of thirty five healthy patients were stimulated using electrodes. The location, strength, and duration of their resulting perception of this stimulus was then recorded. All subjects felt the sensation in their hand rather than the site of the electrodes thus highlighting the connectedness of neural pathways and how it is possible to engage areas (such as a phantom limb) that is not directly being stimulated. Therefore, experimenters proposed that electrode therapy could be effective in treating PLP. Other studies such as Collins et al (2017) found that electrode therapy was successful in creating referred sensation in phantom limbs and could thus be used as a treatment.

Pharmaceuticals are often used to treat PLP by targeting specific chemical messengers, reducing neuronal firing, and/or blocking the brain's perception of pain (Mayo Clinic Staff 2014). Anti-epileptics (gap junction inhibitors) such as gabapentin, pregabalin, and carbamazepine are often prescribed because they reduce excessive neuronal firing thus quieting

excessive neural signaling and reducing pain (Alivar, Hale, and Dungca 2011) . Codeine or morphine are narcotics that can be used to block the brain's nociception thus reducing PLP. N-methyl-d-aspartate (NMDA) receptor antagonists such as ketamine and dextromethorphan function by binding to NMDA receptors in the brain and blocking glutamate reception (a nerve signaling molecule) (Alivar, Hale, and Dungca 2011). Finally, anti-depressants such as Celexa, Zoloft, Paxil, or Pristiq can be prescribed to help mood changes and to help the patient sleep, which in turn helps naturally reduce pain (Bostwick 2010). These will be discussed later in psychological mechanisms and treatments.

Experimental Treatments of Phantom Limb Pain Show Promise:

Though the above described treatments are commonly used there is still a lot of room for improvement when treating PLP. Therefore, a number of experimental treatments have been proposed. They include (but are not limited to): robot hand therapy and gaming therapy. Robot hand therapy is an experimental therapy described by Yanagisawa et al (2015) during which experimenters use brain-machine interface based on real time magnetoencephalography signals to reconstruct hand movements with a robotic hand for upper extremity amputees. In other words, electrodes are placed on the amputee's stump and the patient is asked to "move" their phantom limb in specific ways. The neural signals sent by the brain and propagated through the stump are picked up by the electrodes and used to calibrate the robotic hand. The goal of this stimulation is to create the illusion that the patient has a fully operating hand to activate deafferented pathways and reverse maladaptive brain plasticity. Using fMRI imaging before and after the therapy the experimenters were able to see that the therapy was able to induce neural changes. Contrary to their expectations, they found that when the robotic hand's movements were synced with the patient's movements PLP increased. However, when the robotic hand's

movements were dissociated from the patients' movements, pain decreased. This suggests that there is a relationship between visual stimuli and sensorimotor functioning that can be used and manipulated when experimenting with alternative treatments.

Another experimental therapy that shows promise for treating PLP is gaming therapy. This therapy utilizes machine learning, augmented and virtual reality, and gaming to rework neural pathways in the brain by taking advantage of the relationship between the visual and somatosensory cortexes (Ortiz-Catalan et al 2016). Experimenters place electrodes on the amputee's stump and ask them to mimic movements on a computer screen with their amputated limb. The electrodes sense the resulting neural impulses and use this to calibrate the machine. The patients then perform a series of exercises and games using augmented and virtual reality (i.e. matching a specific movement, race car driving, etc.). During one experiment, fourteen upper extremity amputees with chronic PLP were given gaming therapy for twelve two hour sessions. They were given surveys that assessed their pain at the baseline, weekly, as well as one, three, and six months post completion of the therapy. The experimenters found that all the patients had significant PLP reduction (Ortiz-Catalan et al 2016). This would suggest that gaming therapy is a viable treatment option for chronic PLP patients. However, this experiment had a relatively small sample size (n=14). Therefore, future research is needed.

Psychological Mechanisms of Phantom Limb Pain:

It is clear that there are a number of neurological factors at play in phantom limb pain. However, we would be remiss to say that psychology does not play a role. Studies have shown that anxiety, depression, and PTSD can increase pain intensity, duration, and frequency (Lotchting et al 2017, Eccleston et al 2015). Lochting et al (2017) aimed to determine the degree to which patients' perception of their injury as well as mental health affected their pain intensity,

duration, and frequency. To do so, they studied two hundred and three chronic lower back pain patients by giving them a series of surveys that assessed their mental health as well as their physical health over the course of twelve months. They were looking to see if the patients that had higher levels of depression and anxiety and more negative outlooks on their recovery process had higher levels of pain as well as longer recovery times. Though they did not find a relationship between mental illness and pain perception they did find that patients with a negative outlook on their recovery had worse pain as well as longer recovery times. This would suggest that there is a relationship between the psychological and the physiological in pain sensation. Furthermore, despite the data gathered from this trial, other studies have found that depression and anxiety are closely related with pain symptoms such as headache, abdominal pain, musculoskeletal pain, and back pain (Eccleston et al 2015). In fact, patients suffering from PTSD or another psychological trauma, on average, are 2.7 times more likely to experience chronic widespread pain, fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, or temporomandibular disorder (Afari et al 2014). These studies suggest that there is a relationship between the mind and the body in pain propagation. They seem to suggest that when an individual is experiencing mental or emotional pain it can translate into physical pain, regardless of whether or not there is an injury. In the case of PLP patients, this would contradict the theory that their pain is neurological based because studies have shown that PLP patients are subject to high levels of anxiety and depression.

Amputees are often subject to a wide array of mental illnesses ranging from anxiety and depression to PTSD. These illnesses are caused, in large, by the amputation disrupting their normal day-to-day life. Many find it difficult to adjust to a new life with a missing limb. They require more assistance with a variety of tasks and thus can experience feelings of humiliation,

hopelessness, anger, anxiety, and sadness. Padovani et al (2015) described an experiment in which twenty seven lower limb amputees were given a series of surveys that assessed their levels of depression and anxiety as well as the level of difficulty they had performing certain tasks like showering, eating, sleeping, etc. The study revealed that amputees in the 18-38 age range had high levels of anxiety while those living in the 60-80 range had high levels of depression. It can be deduced that those in the 18-38 age range had higher levels of anxiety because they were worried about how the amputation would affect the rest of their life, their relationships with others, work performance, etc. There is a great deal of anxiety hidden in the unknown. Those in the 60-80 age range likely had higher levels of depression because they are already aging and starting to see their body deteriorate. Thus they are beginning to rely on others for physical assistance. The addition of an amputation makes them even more reliant and hopeless thus causing them to feel humiliated and dependent. When looking at this article in juxtaposition with the findings of Afari et al (2014), Eccleston et al (2015), and many others, one starts to see the relationship between psychology and PLP; amputations cause feelings of anxiety and depression, anxiety and depression cause pain symptoms to be worse, thus amputees experience pain.

There is an undeniable relationship between the mind and the body. However, what bridges these two entities? The answer, in short, is simple—hormones. Emotional or mental stress causes the release of cortisol and epinephrine. To release cortisol, the brain recognizes a stressor thus causing the hypothalamus to release corticotropin releasing hormone (CRH) which then tells the anterior pituitary gland to release adrenocorticotropin hormone (ACTH). ACTH then tells the adrenal glands to release cortisol. Cortisol then binds to a glucocorticoid receptor in the cytosol which then activates genes such as *NR3C1, CLOCK*, and *Per* (Wiley, Higgens, and Athey 2016). When these pathways are constantly activated it causes fatigue, high blood

pressure, irritable bowel syndrome, body aches, and more (Wiley, Higgens, and Athey 2016). High cortisol levels are associated with various psychiatric disorders such as anxiety, depression, and bipolar disorder (Wiley, Higgens, and Athey 2016). Similarly, stressful events cause the release of epinephrine. When the brain recognizes an event as stressful the hypothalamus signals the adrenal medulla to release epinephrine. Epinephrine causes increased blood pressure, heart rate, sweating, as well as increase neuronal firing (Le Feuvre and Aldington 2014). Increases in neural activity can elicit painful sensations.

Accepted Psychological Treatments for Phantom Limb Pain:

When attacking phantom limb pain from a psychological standpoint there are a couple different routes that can be taken. The two most common treatments are talk therapy and anti-depressants or anti-anxiety medications. Talk therapy is an overarching term used to describe any type of doctor-patient based therapy designed to change cognitive patterning and subsequent behavior of a patient (Gianluca et al 2016). One popular talk therapy is cognitive behavioral therapy (CBT) during which doctors will attempt to help patients devise new ways to think and cope with their emotional problems so that they can process stress as it comes. Another popular therapy (especially in trauma patients) is eye movement desensitization and reprocessing therapy (EMDR). The goal of EMDR is to help patients face and overcome their previous traumas by showing disturbing images to provoke stress responses and help devise ways to cope with them (Gianluca et al 2016). Hypnosis is also commonly used to help the patient cope with unconscious stressors to cause subconscious changes in how the person processes stress. There are numerous other forms of talk therapy, including but not limited to: acceptance and commitment therapy, relaxation training, psychodynamic therapy, guided meditation, and more (Gianluca et al 2016). All of these therapies aim to create healthy coping mechanisms and cognitive processing to

alleviate the psychological stress that is causing excessive release of hormones like cortisol and epinephrine. This will ultimately help the patient to feel more relaxed and at peace mentally and physically. Studies have shown that psychotherapies such as these can be effective in treating phantom limb pain. Gianluca et al (2016) conducted a systematic review of 400 psychotherapy studies including: CBT, EMDR, mindfulness therapy, hypnosis, acceptance and commitment therapy, mirror therapy, and more. The authors ultimately found that these therapies were effective in slightly reducing pain but are more effective when used in conjunction with other things (pharmaceuticals, neural therapy, etc.)

In addition to talk therapy, anti-depressants are often prescribed to treat PLP. It is thought that chronic anxiety and depression are caused by imbalance of monoamine neurotransmitters in the brain such as serotonin, dopamine, norepinephrine, and epinephrine (Bostwick 2010). Though diverse in their chemical structure, all antidepressants aim to balance these monoamine levels in the brain. Examples include: tricyclics (Pamelor, Norpramin, Amitrptyline), selective serotonin reuptake inhibitors (SSRIs) (Celexa, Lexapro, Prozac, Paxil, Zoloft), serotonin and norepinephrine reuptake inhibitors (SNRIs) (Effexor and Pristiq), serotonin antagonists (Remeron), and norepinephrine and dopamine reuptake inhibitors (Wellbutrin) (Bostwick 2010). SSRIs SNRIs, and norepinephrine and dopamine reuptake inhibitors work by inhibiting the reuptake of serotonin, norepinephrine, and dopamine (respectively) to allow higher levels in the brain (Bostwick 2010). Doctors still do not fully understand why antidepressants help alleviate pain but a few assumptions can be made. The first is that serotonin, dopamine, and norepinephrine are all involved in proper neural signaling (Koch N.d) This would indicate that when their levels are imbalanced it can cause excessive or improper neural firing thus causing pain. Second, it has been shown that regulating monoamine levels can help patients sleep better

and relax (Mayo Clinic 2014). Getting more sleep not only helps the body recover physically but it also helps the patient to relax and handle stress more easily (Mayo Clinic Staff 2014). As mentioned earlier, high stress levels cause the release of epinephrine and cortisol which have been known to act as nociceptive signals (Le Feuvre and Aldington 2014). Most importantly, however, antidepressants help the patient's mood so that he or she can cope with stress as it comes and have a more positive outlook on his or her recover. Padovani et al (2015) highlights the importance of a positive mindset in the recovery process; it can help reduce pain intensity, frequency, and duration. However, when ill prescribed, antidepressants are associated with a number of side effects such as: sleep disturbances, sedation, nausea, dry mouth, hypotension, sexual dysfunction, weight gain, and more (Bostwick 2010). Therefore, it is important to find the right medication and monitor the patient closely.

Conclusion: Which is the Stronger Argument; is PLP Neurological or Psychological?

It is clear that phantom limb pain is complex in nature. There is much debate about how it is initiated as well as prolonged. However, the scientific evidence supporting the theory that PLP is primarily a neurological disorder outweighs the evidence that suggests it is psychological. First, we know that the brain is capable of incredible adaptations through neural plasticity. For instance, children with uncontrollable epilepsy are able to have entire hemispheres of their brain removed and still lead normal lives due to the brain making new neural connections (Winston et al 1992). In the case of PLP there are a number of studies that use fMRI images before and after PLP neurological treatment that show structural and neural changes. These changes would indicate that PLP is affected by neural mechanisms (maladaptive brain plasticity, referred pain, and atrophy of neural structures) (Yanagisawa et al 2016, Le Feuvre and Aldington 2014). Furthermore, diffusion tensor imaging reveals that there are major structural changes to the brain

following an amputation as mentioned earlier in the Jiang et al (2015) paper. It is hard to dispute concrete quantitative evidence such as this especially when comparing it to more subjective data such as mental health assessment surveys.

The biggest weakness in the psychology argument is that mental illness is not unique to phantom limb patients. In fact, at least 6.5% of the United States population is diagnosed with clinical depression ("Mental Health—United States" 2010). It is true that PLP patients are subject to a great deal of stress due to their severely altered lifestyle, vulnerability, and feelings of humiliation. However, the rest of the population also struggles with similar issues and heart break caused by other factors (lost loved ones, other debilitating diseases, financial stress, etc.). Therefore, PLP patients are not necessarily more prone to mental illness than the rest of the population and thus any more likely to experience nerve pain caused by psychological stressors. To test this, Durmus et al (2015) conducted an experiment in which fifty one amputees and fifty one healthy controls were given a series of surveys that assessed their mental health as well as pain levels. PLP was measured using a visual analog scoring method, psychiatric symptoms were determined using Symptom Checklist-90-R, Beck Depression Inventory, Pittsburgh Sleep Quality Index, Rosenberg Self-Esteem Scale, and State-Trait Anxiety Inventory. The results showed that though PLP patients had higher levels of anxiety than the controls, they had no other statistically significant differences in psychiatric symptoms from the healthy controls (Durmus et al 2015). This suggests that PLP patients are not any more vulnerable to mental illness (with the exception of anxiety) than the rest of the population is. Additionally, when Lochting et al (2017) studied the mental health as well as pain intensity, frequency, and duration of 203 chronic lower back pain patients they found no correlation between anxiety and depression and pain perception. This would contradict the idea that pain is initiated and intensified by mental illness.

Furthermore, many studies that study mental illnesses in PLP patients lack controls (such as the Padovani et al. 2015). Therefore, there is a significant lack of evidence supporting the idea that mental illness causes PLP.

Overall, there is an undeniable relationship between extreme neural changes and phantom limb pain. Thus, it can be concluded that PLP is initiated and prolonged through maladaptive brain plasticity, referred pain, and neural atrophy. If, on top of severe neural damage/changes, a patient suffers from mental illnesses like depression and anxiety, pain can be intensified due to hormonal imbalances. However, the present research on the relationship between mental illness and PLP is both weak and contradictory thus it requires future research with stronger controls and more concrete data. At the present moment, it is also unclear what treatment option is most effective for PLP patients. Neurological interventions seem effective most of the time but do not work for everyone. Psychological interventions can be helpful but are not always effective. Therefore, further research is required for treatment methods as well.

Direction of Future Research:

Despite the mass amount of literature on phantom limb pain, its exact mechanisms are still unknown. As mentioned earlier, PLP affects between 50-80% of amputees (Le Feuvre and Aldington 2014). However, it remains unclear why it affects certain people and not others. There is no relationship between the type of injury and subsequent PLP (Le Feuvre and Aldington 2014). This would suggest that there is a genetic, environmental, and/or physiological component to its onset. To test this theory experimenters could perform genetic testing on healthy amputees and PLP patients to search for similarities and differences among their genetic codes, specifically genes that code for cortisol (NR3C1), epinephrine and norepinephrine (ADRB1), serotonin (5-H2TA), and dopamine (DRD4), receptors (Wiley, Higgens, and Athey

2016, Allen, Yadav, and Roth 2008, Ptácek, Kuzelová, Stefano 2011, "ADRB1" 2017). Perhaps these genes would be mutated in some way so that they are more or less active than wildtype genes thus causing them to excessively or minimally bind to these hormones and neurotransmitters. This would alter brain chemistry and could potentially affect whether or not amputees experience PLP. Experimenters could also use MRI and fMRI to image the brains of healthy amputees and PLP patients to see if there are any major structural differences between the two that would lead to increased pain (i.e. larger or damaged hypothalamus, more C-Fibers that carry nociceptive signals, a larger amygdala leading to more anxiety and depression, etc.). To test this, experimenters would need adequate controls (PLP free amputees) and experimental groups (PLP patients) from a wide range of demographics. Determining why PLP affects certain people over others is essential in understanding both the mechanisms of PLP and how to most effectively treat it.

The exact mechanisms of PLP remain unclear. So far it has been proposed that PLP is caused by maladaptive brain plasticity, referred pain, atrophy of neural structures, anxiety, depression, and/or PTSD. To determine the exact pathology of PLP experimenters could take MRI and fMRI images of patients with planned amputations (i.e. diabetes patients, cancer patients, those with severe infections, etc.) before and after the procedure and monitor if and how the surrounding cortical structures converge on the deafferented cortical region and/or any other notable cortical changes. They could also measure levels of all monoamine neurotransmitters in the brain before, immediately after, one month, and six months post amputation to determine if the amputation initiated major hormonal changes.

Overall, there have been a number of experiments that aimed to dissect the exact mechanisms of PLP and how certain treatments could potentially help. However, many of the

experiments lacked adequate controls and had miniscule sample sizes. Thus their results are not necessarily trustworthy. Therefore, experiments that test the efficacy of robot hand therapy, gaming therapy, electrode therapy, acupuncture and especially mirror therapy should be repeated with larger sample sizes, controls, and more diverse demographics. Finally, there should be experiments that test how these therapies work in conjunction with one another; does combining therapies increase efficacy of treatment? Neurological therapies should also be combined with psychological therapies (talk therapy and pharmaceuticals) to see if PLP improves. Overall much is known about PLP but there is still a great deal that has yet to be learned.

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