Phantom Pain

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Almost anyone with a limb amputation experiences phantom sensations. Moreover, the majority of amputees experience pain. This phenomenon is known as 'Phantom pain' and is described as the pain felt from a body part, usually a limb, which is no longer present. Several mechanisms have been proposed in attempt to explain this phenomenon with some being more prevalent than others. Cortical remapping seems to explain a substantial part of the occurrence of phantom pain and will be focused upon throughout this review. Since the exact mechanism underlying phantom limb pain is unknown, treatment for this condition is still quite primitive and is mostly by trial and error. However, 'Mirror Therapy' has recently been suggested which seems to show promising results for the effective treatment of phantom pain.

Overview on Phantom Pain

Allegedly, one might think that amputation or complete denervation of a body part would result in immediate disembodiment of that part, however, this is rarely the case (Melita J. Guimarra and G. Lorimer Moseley, 2011). As a matter of fact between 90 and 98 percent of amputees experience a vivid impression that the amputated limb is still present. This phenomenon is known as 'Phantom Sensation'. In 75 percent of cases, phantoms appear immediately after surgery as soon as the anaesthetic wears off. In the remaining 25 percent, the appearance of the phantom is delayed, usually by a few days or weeks (V.S Ramachandran and Wiliam Hirstein, 1998).

In 80 percent of the cases the phantom limb is painful (Melita J. Guimarra and G. Lorimer Moseley, 2011). Phantom pain is defined as a painful or unpleasant sensation in the distribution of the lost or deafferentated body part. (Eugene Hsu and Steven P Cohen et al., 2013). It is also referred to as 'Post-amputation Pain'. Pain, together with touch, vibration, temperature and pressure, makes up the exteroceptive perceptions of phantom (Sharon R. Weeks, Victoria C. Anderson-Barnes et al., 2010; Eugene Hsu and Steven P Cohen et al, 2013).

Phantom pain can be present for a couple of days, weeks or else it can persist for years. The longest duration reported is that of 57 years (Browder and Gallagher, 1948). Phantom pain can be a constant dull throbbing pain which lasts several hours, or else it can be a sharp shooting pain which lasts only a few seconds, the latter one being the most common (V.S Ramachandran and Wiliam Hirstein, 1998; K.MacIver, D.M Lloyd et al., 2008). It can take several forms including tingling, itching, stabbing, burning, cramping and even feeling 'pins and needles' (Sharon R. Weeks, Victoria C. Anderson-Barnes et al., 2010). Moreover, the pain could be present all over the missing limb or else localised to just one area. It is most often localised on the hands and feet where there is a high degree of cortical mapping (Eugene Hsu and Steven P Cohen et al, 2013). Post-amputation pain may also result as the phantom takes up an awkward and uncomfortable position. The is known as a kinaesthetic sensation which can be painful (Sharon R. Weeks, Victoria C. Anderson-Barnes et al., 2010; Eugene Hsu and Steven P Cohen et al, 2013). These amputees usually have very specific sensations, for example a reported case of a soldier who had a grenade explode in his hand leaving behind a phantom hand cramped in that position (Browder and Gallagher, 1948). This habitual posture taken up by the phantom may be temporary or even permanent.

The occurrence of phantom pain is regardless of the cause, level and location of the amputation. Gender, age, social and marital status do not affect the incidence of phantom pain in any way (V.S Ramachandran and Wiliam Hirstein, 1998).

Factors which do enhance the appearance of phantoms include firstly the pre-amputation history. Amputation following a pre-existing painful limb pathology or a traumatic limb loss usually results in a vivid, persistent and painful phantom. This is especially in contrast to pre-planned amputations where the limb is not painful which are far less likely to result in post-amputation pain. The reason for this may be due to 'pain memories' of the existing painful limb which persist in the phantom. A second factor which effects the appearance of phantoms is the condition of the stump. If there is

no stump pathology such as scarring or neuromas and the stump heals nicely and quickly, the phantom is dulled rapidly. Hitting the stump can also elicit phantom pain. Resting, tranquility and distraction can alleviate the pain whereas stress and emotional turmoil will make it worse (V.S Ramachandran and Wiliam Hirstein, 1998). Phantom limb pain has also been found to be more prevalent in upper extremity amputees than lower extremity amputees (Bishnu Subedi and GT. Grossberg, 2011).

Phantom pain has not just been reported in limbs, although this is the most common, but also in other body parts. There have been several reports of phantom menstrual cramps following hysterectomy, acute appendicitis following appendectomy (V.S Ramachandran and Wiliam Hirstein, 1998), phantoms following mastectomy (Aglioti, 1994; Björkman B. et al., 2008) phantom ulcer pains following partial gastrectomy (Szasz, 1949) and even phantom facial pain after parts of the face have been removed (Hoffman, 1955). Phantom sensations of flatus and faeces as well as sensation of haemorrhoids and hard stool that would rupture the rectum have been reported after resection of the rectum or the sigmoid colon (Oversen P. et al., 1991; Reategui C. et al., 2013). Patients with their penis removed have also reported having phantom erections and ejaculation (Fisher CM., 1999; Wade NJ. and Finger S., 2010).

Phantom pain may also be experienced by children with congenital amputations although these are far less common. This is because the brain has already developed several neural connections (but not all) involving the perception of the body. Congenital phantoms are experienced in 20 percent of child amputees. Apart from this, 50 percent of children who lose a limb at the age of 5 years or younger develop a phantom limb. In amputees over 8 years of age the incidence is the same as in adults (V.S Ramachandran and Wiliam Hirstein, 1998).

There are numerous proposed mechanisms underlying the pathophysiology and aetiology of phantom limb pain with some theories being more prevalent than others. In this next section I will discuss the most prevalent ones.

Mechanisms Underlying Phantom Pain

Post-amputation pain was primarily thought to be a form of mental disorder (Bishnu Subedi and George T. Grossberg, 2011) until in the mid-16th century, French military surgeon Ambrose Pare introduced the concept. Years after, this concept was described and given the term 'Phantom Pain' by Mitchell in 1871. It is only until recent decades that this condition was researched and given more importance, and this is due to the ongoing conflicts in Iraq and Afghanistan which have caused a significant rise in amputee patients (Sharon R. Weeks, Victoria C. Anderson-Barnes et al., 2010).

Over time there have been several proposed theories of the mechanisms underlying phantom pain. Some of these have been discarded whilst others are being supported but still need further research to be confirmed and accepted by all scientists. One of the strongest and most supported model is that proposed by Ramachandran and Hirstein. This hypothesis includes several sources which these scientists believe provide a contribution to the occurrence of phantom pain and in fact, describe phantom pain as a multifactorial phenomenon (Sharon R. Weeks, Victoria C. Anderson-Barnes et al., 2010; V.S Ramachandran and Wiliam Hirstein, 1998).

The Multifactorial Model

According to Ramachandran and Hirstein, a number of factors are involved in the pathophysiology of phantom pain and all of these factors reinforce one another.

Residual Limb Neuroma

One of the factors, that of residual limb neuroma was the first standard explanation for the occurrence of phantom pain. A neuroma is a non-neoplastic tumour which occurs as the nerves supplying the limb are lacerated (Sharon R. Weeks, Victoria C. Anderson-Barnes et al., 2010; Melita J. Guimarra and G. Lorimer Moseley, 2011). Although residual limb pain, or more commonly called stump pain, does contribute to the occurrence of phantom limb pain, it is not the causative agent producing the pain (V.S Ramachandran and Wiliam Hirstein, 1998). In fact, as has been discussed, congenital amputees also experience phantom limb pain which shows that there is a much more complex representation of the limb. Apart from this, administration of local anaesthesia to the stump or surgical removal of the neuroma does not always relieve the pain. Ramachandran and Hirstein believe that the sympathetic nervous system contributes highly to the intensified phantom pain in the presence of neuromas. Spontaneous activity or excitation of the cortex, which could be due to several factors including emotional instability as well as weather changes, causes an increase in firing rate of the pre-ganglionic sympathetic neurons. At the sympathetic ganglion the pre-ganglionic sympathetic neurons synapse with the post-ganglionic sympathetic neurons and the these fibres fire. The post-ganglionic sympathetic fibres could either be noradrenergic or cholinergic. The noradrenergic (vasomotor) fibres innervate the blood vessels and when excited cause vasoconstriction whilst the cholinergic (sudomotor) fibres innervate sweat glands. Apart from this the release of noradrenaline and acetylcholine at the stump causes excitation of primary afferent fibres trapped in the neuroma. These afferents synapse at the dorsal horn and from here the impulses can either reach and synapse at the sympathetic ganglia or else reach the cortex, either way, this sympathetic cycle can be repeated (V.S Ramachandran and Wiliam Hirstein, 1998). If this cycle keeps on going, the pain will also continue to be perceived , once it stops, the pain will go away.

Cortical Factors

A second factor which contributes highly to phantom pain is cortical remapping. It is only until recent decades that the concept of cortical remapping was accepted amongst a number of researchers and scientists. Primarily, it was believed that the cortex remains stable throughout life and that one will die with the neural connections that were established in infancy. The first clear experimental study of cortical plasticity was demonstrated by Patrick Wall and his

team. After a case of partial denervation, these scientists managed to record changes in the receptive field size of a single neuron in the dorsal column (Wall, 1977). Nowadays, thanks to advances in technology, we are able to observe this phenomenon of cortical remapping using Magnetoencephalogram (MEG).

We now know that the somatosensory cortex comprises a complete map of the body. Parts of the body which have a higher sensory function than others, such as the lips and hands have more cortical representation. This is represented by the sensory homunculus. After amputation there is a decrease in the sensory input from the lost limb to the cortex. The area which once corresponded to the hand is now taken over by adjacent areas, these being the face and also the shoulder in upper limb amputation. Therefore, the sensory input from the face is received by the cortical areas of the face itself and also that of the hand (V.S Ramachandran and Wiliam Hirstein, 1998). This can happen even just a few hours after the amputation (V.S Ramachandran, 1998). This phenomenon could be observed in several studies performed by Ramachandran and Hirstein. In one case, a 17-year old boy who was involved in a car accident had his left arm amputated above the elbow. Tactile stimuli using a cotton swab were applied to the boy's left side of the face with his eyes closed at all times. The boy could accurately perceive the stimuli as coming from the face and also simultaneously mis-localised the stimuli as tingling sensations coming from his phantom hand. When the cotton swab was stroked along the boy's face, he could feel a sensation of stroking along his phantom hand. The areas on the face which corresponded to the areas on the phantom hand were very specific and stable over successive tests. Apart from this, these mis-localised stimuli were only perceived when touching the face, whilst other body parts such the tongue, neck and shoulder did not produce the same effect. These tests were performed again a week after and the results were found to be exactly the same. In another case these same results were obtained but conversely a second map present on the deltoid was observed. This was also stable and topographically organised. Other tests were done but this time using the sensations of warmth and cold. When a drop of warm water was placed on the amputee's face he felt the warm sensation on his phantom arm. When this drop trickled down his face he could also feel the warm water trickling down his phantom arm. The topographical arrangement of the sensation of warmth and cold was found to be roughly the same as that of the tactile stimulation. This referral from the face or deltoid to the phantom arm/hand is quite common and one might assume that the same thing would happen with phantom legs or feet, although this is not the case. Ramachandran and Hirstein have reported only two cases of lower limb amputees experienced sensation of their phantom leg during sexual intercourse. In addition to this form of referral there have also been a few reported cases of referral from the other intact arm. This referral occurred for touch but not for pain and temperature. In fact, a painful prick on the intact arm was perceived as an indentation on the phantom. These results propose that there are connections linking the two hands conveying the sensation of touch. These may be too weak when both limbs are intact but when one limb is amputated the input may be strengthened resulting in this referral of touch (V.S Ramachandran and Wiliam Hirstein, 1998).

Ramachandran and Hirstein also discussed the reasons why the referral of pain is not always constant as could be seen in the two cases mentioned above. The first reason for this is that the hypothesis of cortical remapping could be totally wrong or missing some parts. Also, in this hypothesis we are assuming that the remapping takes place only at the primary somatosensory cortex but in actual fact, it could be occurring anywhere in the cortex including the thalamus. Another reason could be that the somatosensory maps vary from one person to another. Moreover, this referral is also influenced by external factors. For example, some patients may learn to disregard the referred sensations. Apart from this, certain patients continually use their stump for everyday activities and this may encourage cortical reorganisation of the hand to be referred to the stump instead of the face or shoulder (V.S Ramachandran and Wiliam Hirstein, 1998). This process of cortical reorganisation may cause pain in a number of amputees because it is a pathological process. These sudden maladaptive changes in the cortex may be labelled as pain or paraesthesiae in the phantom by the nervous system (V.S Ramachandran and Wiliam Hirstein, 1998). In fact scientists have found out that there is actually a relationship between the extent of cortical remapping and the potency of the phantom limb pain; the higher the extent of cortical remapping the more potent is the phantom pain (Flor et al., 2006). This hypothesis of cortical remapping is partially supported by a study in which 9 patients who had a focal lesion of the parietal lobe had a complete disappearance of the phantom. Even though this theory manages to give us several answers on phantom pain, it fails to explain a number of things such as the phantom movements perceived by the subject, the paralysis of the phantom and the presence of phantoms in several cases, including those with a congenital absence of a limb. In fact congenital phantoms may strongly suggest that the brain constructs a body image which is partly genetically determined but can also be modified to undergo drastic changes, since it is affected by sensations such as touch, vision, hearing, balance and proprioception. The body image may also explain the rest of the cases because although the body image is subject to change the brain is predisposed to retain a complete body image, regardless of the actual appearance (Sharon R. Weeks, Victoria C. Anderson-Barnes et al., 2010; V.S Ramachandran and Wiliam Hirstein, 1998). The mechanism underlying cortical remapping, which is still primitive, is thought to be mediated by N-methyl-D-aspartate (NMDA) receptors. These receptors intensify the connection between two inputs coming together which will eventually result in a long-term Hebbian (neurons that fire together, wire together) potentiation of synapses (LTP) (V.S Ramachandran and Wiliam Hirstein, 1998). They are most commonly found at the anterior cingulate cortex, which is an area that controls pain and cognition. Glutamate is the major fast excitatory neurotransmitter present in the anterior cingulate cortex whilst gamma-amino butyric acid (GABA) is the major inhibitory neurotransmitter. When there is a reduction in the sensory activity, as in the case of amputation, the amount of GABA neurotransmitter will be reduced.

Therefore, NMDA receptors have a greater chance of being activated. This increased activation will cause calcium ions, an intracellular messenger, to be released in the dendritic spines. At the cells calcium binds to calmodulin and activates calcium-stimulated signalling pathways. This will cause synapses which were previously inhibited to be disinhibited. This will result in more long-term Hebbian connections to be set up which will in turn contribute to cortical remapping. At the anterior cingulate cortex, long-term depression of synapses (LTD) can also be set up but unlike the LTP's, this ability is thought to be lost after amputation. The ability to reset any enhanced synapses is lost after amputation (Min Zhuo, 2012; V.S Ramachandran and Wiliam Hirstein, 1998). The enhanced LTP's together with the diminished LTD's may be involved directly with the occurrence of phantom pain due to the maladaptive plasticity. In fact a promising treatment for phantom pain is resetting the enhanced synapses or recovering the ability for neurons to undergo LTD's (Min Zhuo, 2012).

Another cortical factor which is thought to contribute to the perception of phantom pain is corollary discharge. Corollary discharge is defined as the copy of a motor output in order to inform various parts of the brain that a movement will be performed. After amputation, the brain still continues to provide motor input to the missing limb, but after some time the brain realises that it is not receiving any sensory or proprioceptive inputs from the limb and thus discontinues the signals to that limb. Thus the phantom disappears over time. However, this is not the case in every individual, in congenital amputees the phantom limb usually persists longer. This is because the brain has never relied on any sensory inputs from the phantom as it has never received any. There is also the concept of 'learned paralysis', which most commonly happens when the limb is paralysed before the amputation. The brain has already learned that the arm is immobile through repeated messages from the motor cortex in effort to move limb. The visual stimulus will then inform the brain that the limb is paralysed. This concept happens as well after amputation but in this case the brain does not receive visual or any other stimulus input as the limb is missing. Thus, the ability to control the phantom is lessened to such a great extent which results in paralysis (V.S Ramachandran and Wiliam Hirstein, 1998; Sharon R. Weeks, Victoria C. Anderson-Barnes et al., 2010).

Proprioceptive Memory

Even though the visual stimuli are not present after amputation it is thought that proprioceptive stimuli still exist. This is because the proprioceptive memory remains in the individual. This may also further explain the concept of learned paralysis. In most of the investigated cases, patients undergoing surgery perceive the phantom to be in the last position as it was just before local anaesthesia was administered. Memories of motor and sensory information could still be recalled in the limb through proprioceptive memory. The proprioceptive memory of the paralysed limb after amputation together with the absence of visual stimuli, causes the proprioceptive memory to perceive the phantom as being paralysed. The proprioceptive memory is also thought to be involved in the underlying mechanisms of several experiences reported by patients. These include reports of patients who still feel their wedding ring on their phantom finger. Apart from this, a number of patients have reported the sensation of a clenched fist and the feeling that their nails are digging into their palm. In all of these patients this sensation was accompanied by agonising pain which in some lasted for a couple of minutes, while in others lasted for hours. It is thought that the motor cortex sends signals to the phantom hand to clench the fist. This action is normally lessened by proprioceptive feedback, but in this case it is only the proprioceptive memory which remains and this has no control over the signalling from the motor cortex. Thus the motor cortex fires more and this overflow of motor input to the phantom may be interpreted as pain (V.S Ramachandran and Wiliam Hirstein, 1998; Sharon R. Weeks, Victoria C. Anderson-Barnes et al., 2010).

Pain Memory

Apart from the proprioceptive memory Ramachandran and Hirstein also believe that the actual pain memory in the spinal cord remains intact after the amputation, possibly due to the process of central sensitisation. Since the amputation in itself results in severe tissue injury hyperalgesia takes place. There is an increase in the activity of nociceptive afferents which causes an increase in the excitability of neurons present in the dorsal horn. Moreover, nociceptive afferents which were once sub-threshold are now active which results in an increase in pain sensitivity and thus, more firing of the dorsal horn neurons. This hyper-excitability state is not influenced in any way by a local anaesthetic but it has been found that NMDA antagonists can block the spinal cord and prevent this central sensitisation process (V.S Ramachandran and Wiliam Hirstein, 1998). NMDA antagonist are sometimes given to patients before and during surgery to prevent the occurrence of phantom pain after amputation (Melita J. Guimarra and G. Lorimer Moseley, 2011).

Peripheral Nervous System Theory

A peripheral nervous system theory for the development of phantom pain due to stump neuroma suggests that the severe tissue and nerve injury after the amputation causes abnormal peripheral activity. Intracellular sodium at the neuroma increases as there is build-up of molecules that increase the expression of sodium channels. This results in loss of inhibitory control at the dorsal horn and therefore hyper-excitability (Sharon R. Weeks, Victoria C. Anderson-Barnes et al., 2010; Melita J. Guimarra and G. Lorimer Moseley, 2011; Bishnu Subedi and George T. Grossberg, 2011). Peripheral injections which alter the intracellular sodium concentration at the stump have been used for research and also as part of treatment. Peripheral injection of gallamine increases the sodium concentration in the neuroma by blocking acetylcholine. This has shown to increase phantom limb pain. Furthermore, injection of lidocaine showed a decrease in phantom limb pain as it blocks the sodium channels (Sharon R. Weeks, Victoria C. Anderson-Barnes et al., 2010). This hypothesis only attempts to explain part of the cause of phantom pain and therefore cannot be regarded as an effective theory.

Conclusion

If the discussed hypothesis on phantom pain is true, that is it includes several number of factors, most significantly cortical and physical factors that reinforce each other to cause pain, then both pharmacological and behavioural methods of treatment need to be taken into consideration in order to effectively treat phantom pain. This formula of carefully combined methods of treatment in order to effectively and consistently treat phantom pain in a majority of patients has not yet been established and much more work still needs to be done. One could say that treatment options for phantom limb pain depend upon the level of understanding of the mechanisms and nature of phantom limb pain. Since this comprehension is still relatively poor, phantom limb pain continues to be a ghostly phenomenon.

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