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Neuroimaging: A Key Unlocking Phantom Limb Pain

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Abstract

Post Amputation Pain (PAP) is highly prevalent after limb amputation but unfortunately, the pathophysiology along with consistently effective treatments remain elusive. However, recent advances in neuroimaging and neurophysiology are rapidly expanding our understanding of Phantom Limb Pain (PLP) and have paved a way for mechanism directed treatment approaches. The purpose of this article is to review recent advances in neuroimaging that has led to better understanding of PLP mechanism and how understanding of these mechanisms has been contributing in developing new treatment approaches. We have discussed different proposed mechanism and treatments of PLP in short with emphasis on how neuroimaging has led us to unveil these facts about PLP and how with further advancement in neuroimaging, we would be able to dig in deeper into yet unanswered questions.

Keywords: Phantom limb pain, Maladaptive plasticity, Cortical reorganization, fMRI, fcMRI

Introduction

PLP first described by French military surgeon, Ambrose Pare, is defined as a painful sensation in the location of an amputated limb, which gets its present name as "phantom limb pain" by a famous civil war surgeon Silas Weir Mitchellis [1-3]. PLP is a common phenomenon occurring in 72% of amputees within the first week of surgery, with 60% continuing to experience pain at 6 months. No change in this prevalence occurs during the next 5 years. Factors that correlate to the development of phantom pain include pain that lasts longer than 1 month before amputation, increased post-surgical pain, and psychological factors, including anxiety [1]. The paradigms of proposed mechanisms for PLP have shifted over the past years from the psychogenic theory to peripheral and central neural changes involving cortical reorganization. More recently, the role of mirror neurons in the brain has been proposed in the generation of phantom pain. A wide variety of treatment approaches have been employed, but mechanism-based specific treatment guidelines are yet to evolve [2]. Mechanism-based pain treatment is generally considered to be superior to etiologic-based therapy but the obstacles involved in identifying the predominant mechanisms can become nearly insurmountable for a condition as phenotypically and pathogenetically disparate as PAP [4]. Over the recent years, neuroimaging has revolutionized our understanding of the physiological responses to PLP thereby, paving the way for better treatment approaches directed towards the mechanisms.

Neuroimaging Modalities

All noninvasive neuroimaging modalities are based on biophysical signals related to either brain electrophysiology or hemodynamics/metabolism. Neuronal activity intensifies electrophysiological signals, such as action potentials and post-synaptic potentials, which serve as the primary messengers for communication among neurons. In addition, neuronal activity is also coupled with metabolic and hemodynamic processes. As brain function requires sustained blood flow to supply oxygen to compensate for cerebral metabolic energy consumption, changes in neuronal activity often induce cascade of changes in Cerebral Metabolic Rate of Oxygen ($CMRO_2$), Cerebral Blood Flow (CBF), Oxygen Extraction Fraction (OEF), Cerebral Blood Volume (CBV), etc. In contrast to electrophysiological signals, metabolic and hemodynamic responses are much slower and reflect the indirect and secondary effects of neuronal activity [5]. Electro Encephalo Graphy (EEG) [6] and Magneto Encephalo Graphy (MEG) [7] are based on electrophysiological principles. Functional Magnetic Resonance Imaging (fMRI) [8-10], Positron Emission Tomography (PET) [11,12], Single-Photon Emission Computed Tomography (SPECT) and Near-Infrared Spectroscopy (NIRS) are based on hemodynamic and/or metabolic principles. EEG and MEG measure external electric potenials and magnetic fluxes respectiveley. Both of these electricomagnetic signals, electric potenials and magnetic fluxes, arises collectively from mass neuronal responses within the brain and is then propagated (virtually) instantaneously from the activated neuronal tissues via volume conduction to the recording sites on/above the scalp surface [13-16]. In contrast to EEG and MEG, fMRI is based on changes in oxygenation of hemoglobin that is associated with neural activity. Deoxyhemoglobin (dHb) is paramagnetic whereas oxyhemoglobin is diamagnetic on fMRI [17,18].

As neuronal activity elevates, the concomitant alternation of local oxyhemoglobin versus deoxyhemoglobin content gives rise to a so-called Blood Oxygen Level Dependent (BOLD) Magnetic Resonance (MR) signal [19]. In contrast to the traditional task-based approach (e.g., fMRI), resting state studies (e.g., fcMRI) observe the brain in the absence of overt task performance or stimulation. In these studies, subjects are generally asked to lie quietly under "resting" conditions such as eyes closed or while fixating on a crosshair. Spontaneous modulations in the BOLD signal in the absence of any explicit input or output are then recorded and analyzed. The resting human brain represents only 2% of total body mass but consumes 20% of the body's energy, most of which is used to support of ongoing neuronal signaling. Task-related increases in neuronal metabolism are usually small (<5%) when compared to this large resting energy consumption.

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Table 1: Different Proposed Mechanism of Phantom Limb Pain.

Mechanisms	Central	Supraspinal	Cortical plasticity
			Body schema
			Neuvromatrix and Neurosignature
			Mirror neuron
		Spinal	Central sensitization
	Peripheral		
	Psychogenic		

Differences in these task-related changes between normal and pathological populations are smaller still, often less than 1%. When attempting to study disease or diagnose patients based on task-related changes, one is therefore focusing on only a very small fraction of the brain's overall activity. Ongoing spontaneous activity may provide a window onto the neural processing that appears to consume the vast majority of the brain's resources and so may prove a richer source of disease-related signal changes [20]. Importantly, resting state fcMRI may enjoy several practical and theoretical advantages over task based fMRI for clinical applications, including improved signal to noise, reduced need for patient compliance, avoidance of task performance confounds, and expanded patient populations [21]. Other imaging modalities like Diffusion Tensor Imaging (DTI) have also been used to study brain connectivity and plasticity. The various indices extracted from DTI enhance image specificity for distinct brain structures (e.g. Fractional Anisotropy (FA) is used to characterize the organization of white matter fibers) [22]. Significant changes in DTI parameters were reported in the relevant white matter pathways after training [23-25], leading to speculation that DTI can detect structural brain plasticity in both gray and white matter [26]. However, the biological and morphological meanings of these changes remain unclear.

Combined Imaging Modalities

A number of efforts in recording technology, multimodal data fusion and the neurovascular modeling, have collectively led to a promising fMRI-EEG/MEG integrated functional neuroimaging approach, which holds the potential to reach millimeter spatial resolution and millisecond temporal resolution, thereby opening a unique and noninvasive window to investigate dynamic brain activity and connectivity. Electrophysiological and hemodynamic/metabolic signals reflect distinct but closely coupled aspects of the underlying neural activity [27]. Thus, combining EEG with Transcranial Magnetic Stimulation (TMS) allow us to fully characterize dynamic properties of local and distributed brain cortical activity by offering a behaviorally independent input of quantifiable and parametrically scalable magnitude applicable across ages, individuals, and neural states which can be further elucidated by obtaining simultaneous neuroimaging with fMRI thereby investigating whole brain response to and recovery from patterned stimulation [28].

Application of Imaging in PLP Treatment

Neuroimaging is not only used to explore mechanism involved with neuropathic pain but also used in monitoring treatments. One of the treatment methods, Transcranial Magnetic Stimulation (TMS), can be integrated with several imaging methods for better understanding. TMS is based on electromagnetic induction and while it can be used to explore brain-behavior relations, map sensory, motor, and higher-order cognitive functions, and examine the excitability, connectivity and plasticity of different cortical regions, it can also be used as a therapeutic intervention in a variety of nervous system disorder. TMS stimulation can evoke muscle twitching measurable by Electro Myo Graphy (EMG); this activity is known as Motor-Evoked Potentials (MEP) and that is how changing coil position of TMS over motor cortex, can induce MEP in a somatotopical fashion. Applied to non-motor cortical regions, TMS evokes a local field potential that can be recorded with EEG, and represents a measure of cortical reactivity to TMS [1]. Fundamentally, single-pulse TMS combined with EMG, EEG, fMRI or other brain imaging methods can be used to quantify cortical reactivity before and following a given intervention [29].

Mechanisms and Treatments

Central neural mechanism

Supra-spinal mechanism

a) Cortical plasticity

Although plastic changes have mainly been documented in cortical areas, similar changes occur on all level of neuroaxis, including spinal cord, the brainstem and the thalamus [30].

At Cortical level

Following limb amputation, the loss of afferent input allows for invasion of neighboring cortical region into the cortical areas representing the amputated extremity in both primary somatosensory and motor cortex [4,31,32]. Some Researchers believe that reorganization in motor cortex maybe secondary to changes in somatosensory cortex [33]. According to them, somatosensory cortex has projections to layers of motor cortex, which plays important role in acquisition of motor skills and stimulation of somatosensory cortex. And these projections, from somatosensory cortex to motor cortex, might induce Long-Term Potentiation (LTP) in the motor cortex. An alternative possibility would be reorganization in the thalamus modulates motor plasticity. At synaptic level it has been believed that use-dependent changes in synaptic strength such as LTP and Long-Term Depression (LTD) may serve as a key mechanism of cortical plasticity [34]. Several studies derived evidence from imaging modalities, electroencephalography [35-37], TMS [38-41], magnetoencephalography [42], and fMRI [43-45] to demonstrate changes in primary Sensory (S1) and Motor (M1) cortices following limb amputation or deafferentation.

At Subcortical level

Edward et al., [46] electrophysiologically mapped the thalamus of Macaca fascicularis monkeys and showed extensive reorganization of the body map in a thalamus in which the upper limb representation was affected by severe transneuronal degeneration, and thus they proposed that a progressive, slow atrophy of cells in the cuneate nucleus, whose efferent axons slowly die or are withdrawn from the upper limb part of the Ventral Posterior Lateral nucleus (VPL) leads to an even slower atrophy of many cells in the upper limb representation of VPL; and the accompanying breakdown of the arcuate lamella (undoubtedly due to loss of incoming axons) progressively brings Ventral Posterior Medial nucleus (VPM) and VPL cells, normally innervated by inputs from the face or trunk, into close proximity. Degeneration or retraction of the axons of atrophic

Table 2: Different Available Treatment Methods for Phantom Limb Pain.

Treatments	Central	Supraspinal	Deep brain stimulation
			Motor cortex stimulation
			Hypnosis, biofeedback, guided imagery
			Mirror therapy
			Opioids, anticonvulsants
		Spinal	Spinal cord stimulation
			Sodium channel blockers
			NMDA antagonists, opioids
	Peripheral	Pharma-cological	Perineural botulinum toxin, local anesthetic injections
		Non-pharma-cological	Pulsed radiofrequency
			Peripheral nerve stimulation
			Surgery

thalamic upper limb cells in the somatosensory cortex should permit the divergent axon branches of thalamic face cells to be expressed functionally in the cortex. Previously silent inputs from the lower face region to thalamic cells whose dominant inputs from the upper limb have been silenced could also be uncovered thereby indicating that the reorganization of cortex is also a progressive phenomenon dependent on slow degenerative changes in both the cuneate and VP nuclei. Several studies have cleared that reorganization within the somatosensory pathways also occurs at subcortical levels, such as the thalamus [47-55], brain stem [56-63], and spinal cord [64].

Synaptic mechanism of cortical plasticity

A fundamental property of the brain is plasticity, i.e., the ability to change in response to experience and use. Plasticity allows the brain to learn and remember patterns in the sensory world, to refine movements, to predict and obtain reward, and to recover function after Injury. The two main mechanisms proposed to explain reorganization after peripheral lesions are unmasking of previously present but functionally inactive connections and growth of new connections (collateral sprouting). Unmasking of latent synapses can be due to several mechanisms and include increased excitatory neurotransmitter release, increased density of postsynaptic receptors, changes in membrane conductance that enhance the selection of weak or distant inputs, displacement of pre synaptic elements to a more favorable site, decreased inhibitory inputs or removing inhibition from excitatory inputs (unmasking excitation) [34,65,66]. Among these possibilities, the evidence is strongest for removal of inhibition to excitatory synapses, which is likely due to reduction of Gamma-Amino Butyric Acid (GABA) ergic inhibition, in mediating short-term plastic changes. Reduction in activity, based on sensory deprivation will reduce amounts of inhibitory neurotransmitter GABA, which in turn may allow normally suppressed input originating from long range horizontal collaterals of pyramidal neurons located in cortex adjacent to deafferented area to become disinhibited. Mechanism for Long-term plastic change may include LTP, which requires N-methyl-D-aspartate (NMDA) receptor activation and increased intracellular calcium concentration. The NMDA receptors regulate the flow of calcium ions into neurons, which in turn strengthens the spared inputs (synapses) during deprivation-induced plasticity. Axonal regeneration and sprouting with alterations in synapse shape, number, size and type may also be involved [65]. Increased activity of peripheral nociceptors (e.g., due to an amputation-related transection of nerves) leads to an enduring changes in the synaptic structure of the dorsal horn in the spinal cord and supra-spinal centers, a process called central sensitization [30]. In addition reorganization across a larger distance may involve actual axonal growth and re-innervation [67].

b) Body schema

The body schema can be thought of as a template of entire body in the brain [68], and is derived from multiple sensory and motor inputs (e.g., proprioceptive, vestibular, tactile, visual, efference copy-the neural copy of a movement command) that interacts with motor systems by generating or initiating movements and actions [69,70]. Any change to this body schema, such as amputation, might results in perception of phantom limb [69,71]. A further expansion of the body schema concept is the "neuromatrix and neurosignature" hypothesis proposed by Ronald Melzack in 1989 [2].

c) Neuromatrix and neurosignature

While initially it was broadly assumed that pain could be explained and understood as a consequence of nociceptive specific activity in primary (S1) and secondary (S2) somatosensory cortices. Neuroimaging revealed anterior cingulate cortex as a key area necessary for pain experience. And over the time with refinement in neuroimaging modalities, further areas were found to be involved in pain perception. With establishment of the fact that pain involves sensory, affective, and cognitive components, neuroimaging made researcher to propose a term pain neuromatrix and neurosignature [72]. The neuromatrix can be conceptualized as a network of neurons within the brain that integrates numerous inputs from various areas including somatosensory, limbic, visual, and thalamocortical components. It then results in an output pattern that evokes pain or other meaningful experiences. The term "neurosignature" was proposed by Melzack to refer to the patterns of activity generated within the brain that are continuously being updated based upon one's conscious awareness and perception of the body and self [2]. While multiple sensory inputs are integrated to create the body–self neuromatrix, amputation and deafferentation are commonly associated with cortical re-organization, and spontaneous bursts of activity that produce output patterns that resemble activity associated with pain and thus lead to the conscious experience of phantom pain [73]. Raj [74] proposed that the active body-neuromatrix, in the absence of modulating inputs from the limbs or body, produces a neurosignature pattern, including the high-frequency, bursting pattern that typically follows deafferentation, which is transduced in the sentient neural hub into a hot or burning quality. The cramping pain, however, may be due to messages from the action-neuromodule to move muscles in order to produce movement. In the absence of the limbs, the messages to move the muscles become more frequent and "stronger" in the attempt to move the limb. The end result of the Output Message may be felt as cramping muscle pain. Shooting pains may have a similar origin, in which action-neuromodules attempt to move the body and send out abnormal patterns that are felt as shooting pain.

d) Mirror neurons

Recent neuroimaging data indicates that the human brain is

endowed with a "mirror neuron system", putatively containing mirror neuron, which was first found in macques monkey in ventral premotor cortex and later in infraparietal lobule, and other neuron for matching the observation and execution of actions. Neuroimaging studies showed that mirror neurons on manipulation fire both, when the animal manipulates an object in a specific way and when it sees another animal (or the experimenter) perform an action that is more or less similar. Mirror neuron can be conceptualized as retrieving the desired memory item based on sensory stimulus (e.g., visual observation) or the motor plan (intention) [75]. In a study by Buccino et al. [76] fMRI was used to localize brain areas that were active during the observation of actions made by another individual. They found that during action observation there was a recruitment of the same neural structures which would have been normally involved in the actual execution of the observed action, thereby, supporting the concept of the action observation/execution matching system (mirror system) [76]. In addition to action understanding, mirror neurons are involved in other domains of perception and perceptual understanding, including emotion [77], disgust [78], touch [79], and pain [80-82]. When observing another person in pain, we not only consciously comprehend that the other is in pain, but we also automatically interpret the experience throughout the same cortical networks that mediate personal experience of pain. While there may be mirror neuron activity in the pain matrix of healthy people without actual perception of pain, mirror neuron system in amputees, may be dis-inhibited, leading to empathically perceived pain when another is in pain [69,83]. Anterior Insular Cortex (AIC) and the Anterior Cingulate Cortex (ACC) which are involved in both the personal experience of pain and its empathic experience also process feelings of "emotional pain", such as social rejection or frustration. The ACC receives visual information from the superior temporal areas, and through its outputs to the premotor and motor areas, cause similar motor action responses to a painful stimulus when it is either personally experienced, or observed to be experienced by another person that is; proposed Superior Temporal Sulcus (STS) 'sees' the action, whereas the ventral premotor cortex (F5) 'executes' the action [69].

Proposed mechanism for mirror synasthesia

While atypical connectivity reducing pruning of synapses in early development has been proposed as potential mechanism of developmental mirror-sensory synasthesia in an individual without identifiable cause, atypical connectivity in an amputee may be a result of cortical re-organization, suggesting that the unmasking of synaptic connection between visual and somatosensory areas may be implicated in acquired sensory synasthesia. An alternate mechanism is that mirror-sensory synaesthesia may result from hyperactivity of otherwise normal brain areas for touch or pain. Atypically, activation in mirror areas is greater when one experiences a sensation, or an emotion, or carries out an action compared to when the same experience is observed in another because of absence of, or reduction in, normal inhibitory mechanisms within these mirror systems leading to the experience of that touch or pain–mirror-sensory synaesthesia [69,75,83].

Spinal mechanism

Increased activity of peripheral nociceptors (e.g., due to an amputation-related transsection of nerves) leads to an enduring change in the synaptic structure of the dorsal horn in the spinal cord, a process called central sensitization [30] where the increase in synaptic strength enables previously sub-threshold inputs to activate nociceptive neurons, reducing their threshold, enhancing their responsiveness, and expanding their receptive fields [84]. Presynaptic functional changes after peripheral nerve injury that increase synaptic strength include alterations in the synthesis of transmitters and neuromodulators and in calcium channel density. Postsynaptic changes involve phosphorylation of NMDA subunits and increased receptor density due to trafficking and enhanced synthesis of ion channels and scaffold proteins [85]. This is followed by a phenomenon called the "windup phenomenon" in which there is an up-regulation of those receptors in the area [2]. This process brings about a change in the firing pattern of the central nociceptive neurons. The target neurons at the spinal level for the descending inhibitory transmission from the supraspinal centers may be lost. There also may be a reduction in the local intersegmental inhibitory mechanisms at the level of the spinal cord, resulting in spinal disinhibition and nociceptive inputs reaching the supra spinal centers. This lack of afferent input and changes at the level of the spinal cord has been proposed to result in the generation of PLP [2]. To determine the presence of central sensitization in patients, information assessed by MRI such as, what changes in sensitivity occurs, as well as where and when these changes combine together with objective measures of central activity, is needed [86]. The utility of diagnostic criteria for the presence of central sensitization would not only be insight into the pathophysiological mechanisms responsible for producing pain, but more so in defining potential treatment strategies. Neuroimaging studies have found changes in the brainstem that are apparently specific to central sensitization, in addition to the changes in the primary somatosensory cortex that are related to the intensity of pain [87-89].

Peripheral mechanism

Axonal nerve damage during an amputation cause disruption of the normal pattern of afferent nerve to the spinal cord followed by process called deafferentation and regenerative sprouting which results in a neuroma [2,4,31]. Afferent fibers in the neuroma develop ectopic activity, mechanical sensitivity, and chemosensitivity to catecholamines. Altered expression of transduction molecules, up-regulation of voltage-sensitive sodium channels, down-regulation of potassium channels, and the development of new nonfunctional connections between axons (ephapses) all serve to increase spontaneous afferent input to the spinal cord [31].

Treatments

Non invasive therapy

Pharmacological

a) Acetaminophen and nonsteroidal anti-inflammatory

The analgesic mechanism of acetaminophen is not clear but serotonergic and multiple other central nervous system pathways are likely to be involved. Non-Steroidal Anti Inflammatory Drugs (NSAIDs) inhibit the enzymes needed for the synthesis of prostaglandin and decrease the nociception peripherally and centrally [2].

b) Opioids

Beneficial in the treatment of PAP due to its mechanism of action at both the spinal level, where it inhibits pain signaling pathways, and supraspinal level, where it may diminish the degree of cortical reorganization associated with pain intensity [4].

c) NMDA receptor antagonist

NMDA receptor antagonists including ketamine, dextromethorphan, and memantine are thought to block a cascade of events leading to sensitization of dorsal horn wide dynamic range neurons [4].

d) Antidepressant

The analgesic action of tricyclic antidepressant is attributed mainly to the inhibition of serotonin- norepinephrine uptake blockade, NMDA receptor antagonism, and sodium channel blockade [2].

e) Anticonvulsants

Gabapentin as a treatment for established PAP have been conflicting with both positive and negative trial results. Carbamazepine has been reported to reduce the brief stabbing and lancinating pain associated with PLP. Oxcarbazepine and pregabalin may also play a role in the treatment of PLP, but further studies are required [2,4].

f) Calcitonin

The mechanism of action of calcitonin in treatment of PLP is not clear. Studies relative to its therapeutic role have been mixed [2].

g) Other medications

The beta-blocker propranolol and the calcium channel blocker nifedipine have been used for the treatment of PLP. However, their effectiveness is unclear and further studies are needed. Flupirtine, an NMDA antagonist and potassium channel agonist, has been reported to be effective when used together with opioids in cancer related neuropathic pain but needs further studies for other etiologies [2]. Dextromethorphan, topical application of capsaicin, intrathecal opiods, various anaesthetic blocks and injections of botulinum toxian and topiramate have been claimed to be effective in phantom pain, but none of them have been proven effective in well controlled trials with a sufficient number of patients [90].

Non-pharmacological

For such brain stimulation therapies neuroimaging has been used to identify (a) the brain areas that the applied current passes through, and (b) the neural circuits that it modulates (which may extend beyond the site of stimulation through brain networks), to improve their therapeutic potential [91].

a) Transcutaneous Electrical Nerve Stimulation (TENS)

Although there are multiple reports of TENS use in PLP advocating low-frequency and high intensity TENS as more effective than other doses [92], a recent systematic review [93] revealed lack of evidence from randomized controlled trials on which effectiveness of transcutaneous electrical nerve stimulation for PLP could be judged.

b) TMS

TMS exerts its effects on brain structures via electrical currents induced by a powerful magnetic field delivered with a magnetic coil over the scalp [94]. More recently, repetitive Transcranial Magnetic Stimulation (rTMS) has been introduced as a tool to block the maladaptive plasticity in the sensorimotor cortex. It has been suggested that the administration of high-frequency rTMS over the motor cortex enhances its excitability leading to an indirect activation of inhibitory projections towards the thalamus, resulting in a modulation of ascending nociceptive signal pathways. Furthermore, this modulation of ascending nociceptive signal pathways may influence other brain pain-related networks such as the orbitofrontal, anterior cingulate gyri, and the periaqueductal gray matter, which are related with the affective–emotional components of nociception [95]. Previous studies had shown some beneficial effects of rTMS on PLP [96-98].

Transcranial direct current stimulation (tDCS)

tDCS is a noninvasive method that modulates spontaneous neuronal activity with anodal stimulation enhancing cortical excitability and cathodal inducing an opposite effect. Recently, tDCS has been explored as a neurorehabilitory tool for the treatment of chronic PLP. Bolognini et al. [99] studied the effect of anodal tDCS over M1 contralateral to the amputated limb in 8 patients with unilateral lower and upper limb amputation of different etiologies. The authors reported a pain relief immediately after the 5 sessions and up to 1 week of the last stimulation session.

c) Mirror therapy

Mirror therapy was first reported by Ramachandran and Rogers-Ramachandran in 1996 and is suggested to help PLP by resolving the visual-proprioceptive dissociation, that is resolve a conflict between motor intention and sensory feedback, in the brain [100,101]. The visuo-proprioceptive mismatch and the reduced limb representation in premotor and primary motor cortical areas can be overcome by activation of the so-called mirror neuron system that is; since the activation of mirror neurons modulates somatosensory inputs, their activation may block protopathic pain perception in the phantom limb [102,103]. Parasagittally placed mirror between arms or legs lead virtual limb to replace the phantom limb, thereby, giving the illusion that the amputated limb is present and can be purposefully moved [4].

d) Motor imagery

Motor imagery is based on percepts or sensations generated internally by the brain, a mental representation of an actual sensation or movement [104]. Moseley et al. [105] showed that the application over several weeks of graded motor imagery led to a significant reduction of phantom pain. The patients were instructed, among other exercises, how they should carry out movements with the amputated limb. A controlled neuroimaging study of motor imagery in PLP [104] showed evidence of cortical reorganization of motor and somatosensory cortices and its correlation with patients' pain scores prior to the motor imagery training. The training resulted in a significant decrease of intensity and unpleasantness of pain, which correlated with reduction (improvement) of cortical reorganization.

e) Biofeedback, integrative and behavioral methods.

Biofeedback (learned control over autonomic physiologic

processes) is mostly anecdotal [4]. Although there are earlier reports suggesting temperature biofeedback to be helpful for burning sensation of PLP, there is no specific evidence to match specific types of PLP with specific biofeedback techniques. There is also a case report of visual feedback helpful in reduction of phantom pain [2]. Guided imagery, (creating mental images that help promote relaxation and healing) relaxation techniques, and hypnosis have been employed in the treatment of different neuropathic pains and may also be useful for PLP [106-108]. There are case reports of the beneficial effect of acupuncture for PLP [109,110]. The effectiveness of cognitive behavioral therapy in neuropathic pain syndromes has been reported in a number of case studies [111,112].

Invasive neuromodulation

Advances in imaging techniques allowed a direct visualization of the target with high-resolution Magnetic Resonance (MR) imaging thereby allowing better electrode positioning in such neuromodulation treatments. By detecting cortical reorganization, fMRI contributes to the indication for motor cortex stimulation for phantom pain and aids in electrode positioning [91].

Chronic motor cortex stimulation (CMCS)

Motor Cortex Stimulation (MCS) is an electrical stimulation of the precentral gyrus using epidural surgical leads and sub-threshold stimulation [113-117]. Although chronic motor cortex stimulation is used increasingly for neuropathic pain, its mechanisms of action are not entirely known. Furthermore, its effectiveness is variable and inaccurate electrode placement has been implicated as the most likely cause for this variability [118]. Because fMRI can detect functional areas of the brain, it can be coupled with neuronavigation to improve positioning. Sol et al., [118] proposed the mechanism leading to pain control according to clinical results and fMRI data. Sol et al., [118] found that after CMCS the three patients experienced decrease in phantom limb sensation. fMRI results showed that primary motor cortex, stimulation has strong inhibiting effects on the primary sensorimotor cortex as well as on the contralateral primary motor corticess and found it to be consistent with the hypothesis described by Tsubokawa et al., [119] in which chronic cortical stimulation inhibits the hyperactivity of deafferented nociceptive neurons.

Deep brain stimulation (DBS)

DBS is an electrical stimulation performed after stereotactic implantation of thin stick leads into subcortical areas such as the thalamus or basal ganglia. It has been hypothesized that DBS generates a depolarizing blockade that mimics the effects observed following lesioning of the same structures, but the exact underlying mechanisms remain unclear. DBS directly alters brain activity in a controlled manner, and unlike lesioning techniques, it is adjustable and reversible. Pereira et al., [120] through his study demonstrated efficacy of DBS at 1 year for chronic neuropathic pain after traumatic amputation and advocated ventroposterolateral nucleus of the sensory thalamus rather than periventricular gray as the first target of choice for a neurosurgeon commencing DBS for limb pain.

Spinal cord stimulation (SCS)

SCS involves the placement of electrodes in the epidural space adjacent to the spinal area presumed to be the source of pain. An electric current is then applied to achieve sympatholytic and other neuromodulatory effects [121]. Typically, the first phase of treatment involves the temporary placement of an electrical stimulator. Patients are monitored over a period of time to determine the pain reduction. Only patients positively responding to the stimulation would be considered for a permanent implantation [122].

Conclusion

Neuropathic pain, an expression of maladaptive plasticity, is contributed by multiple alterations such as ectopic generation of action potentials, facilitation and disinhibition of synaptic transmission, loss of synaptic connectivity and formation of new synaptic circuits, and neuroimmune interactions, distributed widely across the nervous system and predisposed on this neural lesion is genetic polymorphisms; gender, and age factors leading to persistent pain. Thus, treatment needs to move from merely suppressing symptoms to a disease-modifying strategy aimed at both preventing maladaptive plasticity and reducing intrinsic risk [123]. Imaging studies provide us an opportunity to obtain objective measures of subjective sensations to identify which areas of the brain are likely involved in the processing of neuropathic pain and to evaluate the location and mechanisms of treatment effects (Becerra et al. 2006). However, although neuroimaging has increased our understanding of PLP, it seems to represent only the tip of iceberg. More studies are needed to further refine and validate the mechanism and provide an evidence-based foundation to guide current and future treatment approaches.

References

1. Henry DE, Chiodo AE, Yang W. Central nervous system reorganization in a variety of chronic pain states: a review. PM R. 2011; 3: 1116-1125.
2. Subedi B, Grossberg GT. Phantom Limb Pain: Mechanisms and Treatment Approaches. Pain Res Treat. 2011; 2011: 864605.
3. Weeks SR, Anderson-Barnes VC, Tsao JW. Phantom limb pain: theories and therapies. Neurologist. 2010; 16: 277-286.
4. Hsu E, Cohen SP. Postamputation pain: epidemiology, mechanisms, and treatment. J Pain Res. 2013; 6: 121-136.
5. He B, Liu Z. Multimodal Functional Neuroimaging: Integrating Functional MRI and EEG/MEG. IEEE Rev Biomed Eng. 2008; 1: 23-40.
6. Casson A, Yates D, Smith S, Duncan J, Rodriguez-Villegas E. Wearable electroencephalography. What is it, why is it needed, and what does it entail? IEEE Eng Med Biol Mag. 2010; 29: 44-56.
7. Cohen D. Magnetoencephalography: evidence of magnetic fields produced by alpha-rhythm currents. Science. 1968; 161: 7: 84-786.
8. Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H, et al. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. Proc Natl Acad Sci USA. 1992; 89: 5951-5955.
9. Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, et al. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc Natl Acad Sci USA. 1992; 89: 5675-5679.
10. Bandettini PA, Wong EC, Hinks RS, Tikofsky RS, Hyde JS. Time course EPI of human brain function during task activation. Magn Reson Med. 1992; 25: 390-397.
11. Fox PT, Raichle ME. Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. Proc Natl Acad Sci USA. 1986; 83: 1140-1144.

12. Fox PT, Raichle ME, Mintun MA, Dence C. Nonoxidative glucose consumption during focal physiologic neural activity. Science. 1988; 241: 462-464.

13. Nunez PL. Electric Fields of the Brain: The Neurophysics of EEG. New York Press. 1981.

14. Hamalainen M, Hari R, Ilmoniemi RJ, Knuutila J, Lounasmaa OV. Magnetoencephalography-theory, instrumentation, and applications to noninvasive studies of the working human brain. Reviews of Modern Physics. 1993; 65: 413-497.

15. Kozińska D, Tarnecki R, Nowiński K. Presentation of brain electrical activity distribution on its cortex surface derived from MR images. Technol Health Care. 1998; 6: 209-224.

16. Ding L, Zhang N, Chen W, He B. Three-dimensional Imaging of Complex Neural Activation in Humans from EEG. IEEE Trans Biomed Eng. 2009; 56: 1980-1988.

17. Ogawa S, Lee TM, Nayak AS, Glynn P. Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. Magn Reson Med. 1990; 8: 68-78.

18. Pauling L, Coryell CD. The Magnetic Properties and Structure of Hemoglobin, Oxyhemoglobin, and Carbonmonoxyhemoglobin. Proc Natl Acad Sci USA. 1936; 8: 210-216.

19. Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci USA. 1990; 87: 9868-9872.

20. Fox MD, Greicius M. Clinical Applications of Resting State Functional Connectivity. Front Syst Neurosci. 2010; 4: 19.

21. Fox MD, Halko MA, Eldaief MC, Pascual-Leone A. Measuring and manipulating brain connectivity with resting state functional connectivity magnetic resonance imaging (fcMRI) and transcranial magnetic stimulation (TMS). Neuroimage. 2012; 62: 2232-2243.

22. Blumenfeld-Katzir T, Pasternak O, Dagan M, Assaf Y. Diffusion MRI of structural brain plasticity induced by a learning and memory task. PLoS One. 2011; 6: e20678.

23. Schlaug G, Marchina S, Norton A. Evidence for plasticity in white-matter tracts of patients with chronic Broca's aphasia undergoing intense intonation-based speech therapy. Ann N Y Acad Sci. 2009; 1169: 385-394.

24. Bengtsson SL, Nagy Z, Skare S, Forsman L, Forssberg H, Ullen F. Extensive piano practicing has regionally specific effects on white matter development. Nat Neurosci. 2005; 8: 1148-1150.

25. Scholz J, Klein MC, Behrens TEJ, Johansen-Berg H. Training induces changes in white matter architecture. Nat Neurosci. 2009; 12: 1370-1371.

26. Voss HU, Schiff ND. MRI of neuronal network structure, function, and plasticity. Prog Brain Res. 2009; 175: 483-496.

27. Laufs H, Daunizeau J, Carmichael DW, Kleinschmidt A. Recent advances in recording electrophysiological data simultaneously with magnetic resonance imaging. Neuroimage. 2008; 40: 515-528.

28. Pascual-Leone A, Freitas C, Oberman L, Horvath JC, Halko M, Eldaief M, et al. Characterizing brain cortical plasticity and network dynamics across the age-span in health and disease with TMS-EEG and TMS-fMRI. Brain Topogr. 2011; 24: 302-315.

29. Freitas C, Farzan F, Pascual-Leone A. Assessing brain plasticity across the lifespan with transcranial magnetic stimulation: why, how, and what is the ultimate goal? Front Neurosci. 2013; 7: 42.

30. Flor H. Maladaptive plasticity, memory for pain and phantom limb pain: review and suggestions for new therapies. Expert Rev Neurother. 2008; 8: 809-818.

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

32. Ramachandran VS, Brang D, McGeoch PD. Dynamic reorganization of referred sensations by movements of phantom limbs. Neuroreport. 2010; 21: 727-730.

33. Karl A, Birbaumer N, Lutzenberger W, Cohen LG, Flor H. Reorganization of motor and somatosensory cortex in upper extremity amputees with phantom limb pain. J Neurosci. 2001; 21: 3609-3618.

34. Zhuo M. Cortical Depression and Potentiation: Basic Mechanisms for Phantom Pain. Exp Neurobiol. 2012; 21: 129-135.

35. Karl A, Birbaumer N, Lutzenberger W, Cohen LG, Flor H. Reorganization of motor and somatosensory cortex in upper extremity amputees with phantom limb pain. J Neurosci. 2001; 21: 3609-3618.

36. Grusser SM, Winter C, Muhlnickel W, Denke C, Karl A, Villringer K, et al. The relationship of perceptual phenomena and cortical reorganization in upper extremity amputees. Neuroscience. 2001; 102: 263-272.

37. Flor H, Muhlnickel W, Karl A, Denke C, Grusser S, Kurth R, et al. A neural substrate for nonpainful phantom limb phenomena. Neuroreport. 2000; 11: 1407-1411.

38. Cohen LG, Bandinelli S, Findley TW, Hallett M. Motor reorganization after upper limb amputation in man. A study with focal magnetic stimulation. Brain. 1991; 114: 615-627.

39. Pascual-Leone A, Peris M, Tormos JM, Pascual AP, Catala MD. Reorganization of human cortical motor output maps following traumatic forearm amputation. Neuroreport. 1996; 7: 2068-2070.

40. Roricht S, Meyer BU, Niehaus L, Brandt SA. Long-term reorganization of motor cortex outputs after arm amputation. Neurology 1999; 53: 106-111.

41. Mercier C, Reilly KT, Vargas CD, Aballea A, Sirigu A. Mapping phantom movement representations in the motor cortex of amputees. Brain. 2006; 129: 2202-2210.

42. Flor H, Elbert T, Knecht S, Wienbruch C, Pantev C, Birbaumer N, et al. Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. Nature 1995; 375: 482-484.

43. Lotze M, Grodd W, Birbaumer N, Erb M, Huse E, Flor H. Does use of a myoelectric prosthesis prevent cortical reorganization and phantom limb pain? Nat Neurosci. 1999; 2: 501-502.

44. Giraux P, Sirigu A, Schneider F, Dubernard JM. Cortical reorganization in motor cortex after graft of both hands. Nat Neurosci. 2001; 4: 691- 692.

45. Grusser SM, Muhlnickel W, Schaefer M, Villringer K, Christmann C, Koeppe C, et al. Remote activation of referred phantom sensation and cortical reorganization in human upper extremity amputees. Exp Brain Res. 2004; 154: 97-102.

46. Jones EG, Pons TP. Thalamic and brainstem contributions to large-scale plasticity of primate somatosensory cortex. Science. 1998; 282: 1121-1125.

47. Alloway KD, Aaron GB. Adaptive changes in the somatotopic properties of individual thalamic neurons immediately following microlesions in connected regions of the nucleus cuneatus. Synapse. 1996; 22: 1-14.

48. Florence SL, Hackett TA, Strata F. Thalamic and cortical contributions to neural plasticity after limb amputation. J Neurophysiol. 2000; 83: 3154-3159.

49. Garraghty PE, Kaas JH. Functional reorganization in adult monkey thalamus after peripheral nerve injury. Neuroreport. 1991; 2: 747-750.

50. Jones EG, Pons TP. Thalamic and brainstem contributions to large-scale plasticity of primate somatosensory cortex. Science. 1998; 282: 1121-1125.

51. Kiss ZH, Dostrovsky JO, Tasker RR. Plasticity in human somatosensory thalamus as a result of deafferentation. Stereotact Funct Neurosurg. 1994; 62: 153-163.

52. Rasmusson DD. Changes in the response properties of neurons in the ventroposterior lateral thalamic nucleus of the raccoon after peripheral deafferentation. J Neurophysiol. 1996; 75: 2441-2450.

53. Rhoades RW, Belford GR, Killackey HP. Receptive-field properties of rat ventral posterior medial neurons before and after selective kainic acid lesions of the trigeminal brain stem complex. J Neurophysiol. 1987; 57: 1577-1600.

54. Nicolelis MA, Chapin JK, Lin RC. Thalamic plasticity induced by early whisker removal in rats. Brain Res. 1991; 561: 344-349.

55. Verley R, Onnen I. Somatotopic organization of the tactile thalamus in normal adult and developing mice and in adult mice dewhiskered since birth. Exp Neurol. 1981; 72: 462-474.

56. Chiaia NL, Shah A, Crissman RS, Rhoades RW. Prevention of galanin upregulation following neonatal infraorbital nerve transection or attenuation of axoplasmic transport does not rescue central vibrissae-related patterns in the rat. Eur J Neurosci. 2001; 13: 25-34.

57. Jain N, Florence SL, Qi HX, Kaas JH. Growth of new brainstem connections in adult monkeys with massive sensory loss. Proc Natl Acad Sci USA. 2000; 97: 5546-5550.

58. Kalaska J, Pomeranz B. Chronic paw denervation causes an age-dependent appearance of novel responses from forearm in "paw cortex" of kittens and adult cats. J Neurophysiol. 1979; 42: 618-633.

59. Northgrave SA, Rasmusson DD. The immediate effects of peripheral deafferentation on neurons of the cuneate nucleus in raccoons. Somatosens Mot Res. 1996; 13: 103-113.

60. Panetsos F, Nunez A, Avendano C. Local anaesthesia induces immediate receptive field changes in nucleus gracilis and cortex. Neuroreport. 1995; 7: 150-152.

61. Pettit MJ, Schwark HD. Receptive field reorganization in dorsal column nuclei during temporary denervation. Science. 1993; 262: 2054-2056.

62. Rasmusson DD, Northgrave SA. Reorganization of the raccoon cuneate nucleus after peripheral denervation. J Neurophysiol. 1997; 78: 2924-2936.

63. Waite PM. Rearrangement of neuronal responses in the trigeminal system of the rat following peripheral nerve section. J Physiol. 1984; 352: 425-445.

64. Wu CW, Kaas JH. The effects of long-standing limb loss on anatomical reorganization of the somatosensory afferents in the brainstem and spinal cord. Somatosens Mot Res. 2002; 19: 153-163.

65. Kaas JH. Plasticity of sensory and motor maps in adult mammals. Annu Rev Neurosci. 1991; 14: 137-167.

66. Ramachandran VS, Hirstein W. The perception of phantom limbs. The D. O. Hebb lecture. Brain. 1998; 121: 1603-1630.

67. Florence SL, Kaas JH. Large-scale reorganization at multiple levels of the somatosensory pathway follows therapeutic amputation of the hand in monkeys. J Neurosci. 1995; 15: 8083-8095.

68. Freund HJ. Somatosensory and motor disturbances in patients with parietal lobe lesions. Adv Neurol. 2003; 93: 179-193.

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

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

71. Fox MD, Greicius M. Clinical applications of resting state functional connectivity. Front Syst Neurosci. 2010; 4: 19.

72. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron. 2007; 55: 377-391.

73. Melzack R. From the gate to the neuromatrix. Pain. 1999; 6: 121-126.

74. Melzack R. Evolution of the neuromatrix theory of pain. The Prithvi Raj Lecture: presented at the third World Congress of World Institute of Pain, Barcelona 2004. Pain Pract. 2005; 5: 85-94.

75. Oztop E, Kawato M, Arbib MA. Mirror neurons: functions, mechanisms and models. Neurosci Lett. 2013; 540: 43-55.

76. Buccino G, Binkofski F, Fink GR, Fadiga L, Fogassi L, Gallese V, et al. Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. Eur J Neurosci. 2001; 13: 400-404.

77. Ruby P, Decety J. How would you feel versus how do you think she would feel? A neuroimaging study of perspective taking with social emotions. J Cogn Neurosci. 2004; 16: 988-999.

78. Wicker B, Keysers C, Plailly J, Royet JP, Gallese V, Rizzolatti G. Both of us disgusted in my insula: the common neural basis of seeing and feeling disgust. Neuron. 2003; 40: 655-664.

79. Keysers C, Wicker B, Gazzola V, Anton JL, Fogassi L, Gallese V. A touching sight: SII/PV activation during the observation and experience of touch. Neuron. 2004; 42: 335-346.

80. Jackson PL, Meltzoff AN, Decety J. How do we perceive the pain of others? A window into the neural processes involved in empathy. Neuroimage. 2005; 24: 771-779.

81. Morrison I, Lloyd D, di Pellegrino G, Roberts N. Vicarious responses to pain in anterior cingulate cortex: is empathy a multisensory issue? Cogn Affect Behav Neurosci. 2004; 4: 270-278.

82. Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, Frith CD. Empathy for pain involves the affective but not sensory components of pain. Science. 2004; 303: 1157-1162.

83. Fitzgibbon BM, Enticott PG, Rich AN, Giummarra MJ, Georgiou-Karistianis N, Bradshaw JL. Mirror-sensory synaesthesia: Exploring 'shared' sensory experiences as synaesthesia. Neurosci Biobehav Rev. 2012; 36: 645-657.

84. Vranken JH. Mechanisms and treatment of neuropathic pain. Cent Nerv Syst Agents Med Chem. 2009; 9: 71-78.

85. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response to nervous system to damage. Annu Rev Neurosci. 2009; 32: 1-32.

86. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011.

87. Baron R, Baron Y, Disbrow E, Roberts TP. Brain processing of capsaicin-induced secondary hyperalgesia: a functional MRI study. Neurology. 1999; 53: 548-557.

88. Lee MC, Zambreanu L, Menon DK, Tracey I. Identifying brain activity specifically related to the maintenance and perceptual consequence of central sensitization in humans. J Neurosci. 2008; 28: 11642-11649.

89. Maihofner C, Jesberger F, Seifert F, Kaltenhauser M. Cortical processing of mechanical hyperalgesia: a MEG study. Eur J Pain. 2010; 14: 64-70.

90. Nikolajsen L. Post amputation Pain: studies on mechanisms. Dan Med J. 2012.

91. Jog MV, Smith RX, Jann K, Dunn W, Lafon B, Truong D, et al. *In-vivo* Imaging of Magnetic Fields Induced by Transcranial Direct Current Stimulation (tDCS) in Human Brain using MRI. Sci Rep. 2016; 6: 34385.

92. Cruccu G, Aziz TZ, Garcia-Larrea L, Hansson P, Jensen TS, Lefaucheur JP, et al. EFNS guidelines on neurostimulation therapy for neuropathic pain. Eur J Neurol. 2007; 14: 952-970.

93. Mulvey MR, Bagnall AM, Johnson MI, Marchant PR. Transcutaneous electrical nerve stimulation (TENS) for phantom pain and stump pain following amputation in adults. Cochrane Database Syst Rev. 2010.

94. Reis J, Swayne OB, Vandermeeren Y, Camus M, Dimyan MA, Harris-Love M, et al. Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control. J Physiol. 2008; 58: 325-351.

95. Malavera A, Silva FA, Fregni F, Carrillo S, Garcia RG. Repetitive Transcranial Magnetic Stimulation for Phantom Limb Pain in Land Mine Victims: A Double-Blinded, Randomized, Sham-Controlled Trial. J Pain. 2016; 17: 911-918.

96. Topper R, Foltys H, Meister IG, Sparing R, Boroojerdi B. Repetitive transcranial magnetic stimulation of the parietal cortex transiently ameliorates phantom limb pain-like syndrome. Clin Neurophysiol. 2003; 114: 1521-1530.

97. Khedr EM, Kotb H, Kamel NF, Ahmed MA, Sadek R, Rothwell JC. Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. J Neurol Neurosurg Psychiatry. 2005; 76: 833-838.

98. Di Rollo A, Pallanti S. Phantom limb pain: low frequency repetitive transcranial magnetic stimulation in unaffected hemisphere. Case Rep Med. 2011; 2011: 130751.

99. Bolognini N, Spandri V, Ferraro F, Salmaggi A, Molinari AC, Fregni F, et al. Immediate and Sustained Effects of 5-Day Transcranial Direct Current Stimulation of the Motor Cortex in Phantom Limb Pain. J Pain. 2015; 16: 657-665.

100. Ramachandran VS, Rogers-Ramachandran D. Synaesthesia in phantom limbs induced with mirrors. Proc Biol Sci. 1996; 263: 377-386.

101. Feinberg TE. Brain and self: bridging the Gap. Conscious Cogn. 2011; 20: 2-3.

102. Rossi S, Tecchio F, Pasqualetti P, Ulivelli M, Pizzella V, Romani GL, et al. Somatosensory processing during movement observation in humans. Clin Neurophysiol. 2002; 113: 16-24.

103. Ramachandran VS, Rogers-Ramachandran D. Sensations referred to a patient's phantom arm from another subjects intact arm: perceptual correlates of mirror neurons. Med Hypotheses. 2008; 70: 1233-1234.

104. Maclver K, Lloyd DM, Kelly S, Roberts N, Nurmikko T. Phantom limb pain, cortical reorganization and the therapeutic effects of mental imagery. Brain. 2008; 131: 2181-2191.

105. Moseley GL. Graded motor imagery for pathologic pain: a randomized controlled trial. Neurology. 2006; 67: 2129-2134.

106. Maclver K, Lloyd DM, Kelly S, Roberts N, Nurmikko T. Phantom limb pain, cortical reorganization and the therapeutic effects of mental imagery. Brain. 2008; 131: 2181-2191.

107. Ramachandran VS, Brang D, McGeoch PD. Size reduction using Mirror Visual Feedback (MVF) reduces phantom pain. Neurocase. 2009; 15: 357-360.

108. Cassileth BR, Keefe FJ. Integrative and behavioral approaches to the treatment of cancer-related neuropathic pain. Oncologist. 2010; 15: 19-23.

109. Bradbrook D. Acupuncture treatment of phantom limb pain and phantom limb sensation in amputees. Acupunct Med. 2004; 22: 93-97.

110. Jacob MB, Niemtzow RC. Treatment of Phantom Limb Pain with Laser and Needle Auricular Acupuncture: A Case Report. Medical Acupuncture. 2011; 23: 57-60.

111. Wetering EJ, Lemmens KM, Nieboer AP, Huijsman R. Cognitive and behavioral interventions for the management of chronic neuropathic pain in adults--a systematic review. Eur J Pain. 2010; 14: 670-681.

112. Prakash S, Golwala P. Phantom headache: pain-memory-emotion hypothesis for chronic daily headache? J Headache Pain. 2011; 12: 281-286.

113. Garcia-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Bonnefoi F, et al. Positron emission tomography during motor cortex stimulation for pain control. Stereotact Funct Neurosurg. 1997; 68: 141-148.

114. Garcia-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Le Bars D, et al. Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. Pain. 1999; 83: 259-273.

115. Mertens P, Nuti C, Sindou M, Guenot M, Peyron R, Garcia-Larrea L, et al. Precentral cortex stimulation for the treatment of central neuropathic pain: results of a prospective study in a 20-patient series. Stereotact Funct Neurosurg. 1999; 73: 122-125.

116. Roux FE, Ibarrola D, Lazorthes Y, Berry I. Chronic motor cortex stimulation for phantom limb pain: a functional magnetic resonance imaging study: technical case report. Neurosurgery. 2001; 48: 681-688.

117. Saitoh Y, Shibata M, Hirano S, Hirata M, Moshimo T, Yoshimine T. Motor cortex stimulation for central and peripheral deafferentation pain. Report of eight cases. J Neurosurg. 2000; 92: 150-155.

118. Sol JC, Casaux J, Roux FE, Lotterie JA, Bousquet P, Verdie JC, et al. Chronic motor cortex stimulation for phantom limb pain: correlations between pain relief and functional imaging studies. Stereotact Funct Neurosurg. 2001; 77: 172-176.

119. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Chronic motor cortex stimulation in patients with thalamic pain. J Neurosurg. 1993; 78: 393-401.

120. Pereira EA, Boccard SG, Linhares P, Chamadoira C, Rosas MJ, Abreu P, et al. Thalamic deep brain stimulation for neuropathic pain after amputation or brachial plexus avulsion. Neurosurg Focus. 2013.

121. Oakley JC, Prager JP. Spinal cord stimulation: mechanisms of action. Spine (Phila Pa 1976). 2002; 27: 2574-2583.

122. Knotkova H, Cruciani RA, Tronnier VM, Rasche D. Current and future options for the management of phantom-limb pain. J Pain Res. 2012; 5: 39-49.

123. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. Annu Rev Neurosci. 2009; 32: 1-32.

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