Noninvasive Brain Stimulation, Maladaptive Plasticity, and Bayesian Analysis in Phantom Limb Pain

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ABSTRACT

Introduction: Phantom limb pain (PLP) is a common and poorly understood pathology of difficult medical control that progressively takes place after amputation occurs.

Objective: This article discusses the multifactorial bases of PLP. These bases involve local changes at the stump level, spinal modifications of excitability, deafferentation, and central sensitization, leading to the development of maladaptive plasticity, and consequentially, defective processing of sensory information by associative neural networks. These changes can be traced by neurophysiology and imaging topographical studies, indicating a degree of cortical reorganization that perpetuates pain and discomfort.

Intervention: Noninvasive brain stimulation can be an alternative way to manage PLP. This article discusses two techniques—transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS)—that have shown promising results for controlling PLP. The modulation that both techniques rely on is based on synaptic mechanisms linked to long-term potentiation and long-term depression phenomena. By applying tDCS or rTMS, clinicians can target processes associated with central sensitization and maladaptive plasticity, while promoting adequate sensory information processing by integrative cognitive behavioral techniques in a comprehensive rehabilitation program.

Conclusions: Understanding PLP from a dynamic neurocomputational perspective will help to develop better treatments. Furthermore, Bayesian analysis of sensory information can help guide and monitor therapeutic interventions directed toward PLP resolution.

Keywords: phantom limb pain, noninvasive brain stimulation, maladaptive plasticity, Bayesian model

INTRODUCTION

PHANTOM LIMB PAIN (PLP) is a neurologic condition that has fascinated physicians from a clinical viewpoint and the prolific imagination of laypeople. From authors to artists without medical training, people are trying to understand how this phenomenon occurs. For a patient suffering with this problem, the origin and causes of such odd—and mostly painful—sensations are less im-

portant, as pain relief becomes the priority in order to have an acceptable quality of life (QoL). Phantom perception is extremely common among people who have undergone amputation; somatosensory deprivation leads to phantom perception in 90%–98% of patients suffering from limb amputation. This happens immediately after an amputation in 75% of these patients, and, in a delayed fashion, after 2–3 weeks, in the remaining 25% of such patients.¹

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Amputations in war veterans represent one of the most detrimental injuries affecting QoL and overall health status. The prevalence of PLP has been reported to be high among war veterans and is similar to the prevalence in the civilians who undergo amputation.² PLP in veterans is often aggravated by the presence of psychiatric or neurologic comorbidities; therefore, it is extremely important to understand the neurocognitive mechanisms associated with this condition, as this might help to uncover neural network changes associated with maladaptive plasticity in pain and other associated neuropsychiatric disorders.

Treatment options for PLP remain limited, and successful pain relief is not always possible for all patients affected by this problem.³ Integrative and complementary medicine has added some options to the battery of therapeutic interventions. Mindfulness,⁴ adaptive yoga,⁵ or acupuncture⁶ are some of the therapies currently being used. Unfortunately, research is still scarce, which prevents physicians from gaining a full understanding of the mechanisms and evidence behind such therapeutic alternatives.

Relatively recently, the field of neuromodulation became active with the rediscovery of noninvasive brain stimulation (NIBS). In the past 3 decades, there has been a proliferation of publications describing and applying different techniques, such as transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS). Both approaches have flourished thanks to the advancements in functional imaging, elegant neurophysiologic assessments, computer-generated modeling, and, most importantly, the groundwork of well-designed research methodology. While the evidence for the efficacy of these neuromodulatory therapies is mounting, well-controlled and large-scale studies are still needed.⁷

NIBS has been used as a neuromodulatory intervention in clinical research for addressing different pathologies and also to explore cognitive functioning in neurotypical subjects. NIBS techniques usually involve applying electrical currents to the most superficial areas of the cortex, modifying the neural process being generated under the area covered by the tDCS electrode montage or where the magnetic coil is being positioned in the case of repetitive TMS (rTMS). Both tDCS and rTMS have shown effects on plasticity and learning processes mediated by long-term potentiation (LTP), and long-term depression (LTD), cortical connectivity, and by coactivation when specific tasks are introduced to facilitate cognitive processing and performance.

Both tDCS and TMS techniques are becoming suitable options for PLP applications as modulators of pain perception by promoting changes in cortical excitability and by inhibiting aberrant neuroplastic changes over specific networks. NIBS can also help clinicians to recognize how amputation alters sensory input and processing of perception, by evaluating neurophysiologic responses of cortical excitability after patients are exposed to NIBS treatments.

After amputation, a series of changes develop along the pathway that used to innervate the lost limb. From the distal stump to the spinal segment and its ascension to the central level, the phantom sensations and pain are frequently generated by the genesis of ectopic action potentials in the interrupted nerve fibers. However, in some cases, the generator can also be proximal to the neural axis, (e.g., at the posterior horn and sensory afferent columns through segmental hyperexcitability) or localized to subcortical and cortical structures (e.g., as in the case of thalamocortical dysrhythmia). Sometimes phantom sensations are not created by the stimulation of somatosensory fibers with a missing territory, but can be the result of central sensitization or neuroplastic changes that allow for the convergence of impulses coming from different body parts (referred sensations), one of which is missing.⁸

Although each of these anatomical compartments seem to play specific roles in the genesis of phantom perception, the discussion in this article is focused on the mechanisms occurring at higher neural centers. The purpose is to enhance understanding of how noninvasive brain stimulation—specifically, tDCS and TMS—can be used to modulate phantom perception. A proposal based on how transcranial stimulation modulates aberrant circuitry formation, either by facilitating or inhibiting substrates of use-dependent and lesion induce plasticity, is reviewed.

Special considerations are necessary when reviewing the neural mechanisms involved in sensory processing information and PLP. The application of computational methods on neural circuitry function is of particular importance, as this application will improve understanding of the role of neural plasticity in circuit and network reorganization. By learning how the brain fills in the lack of sensory input, it might be possible for researchers to develop new assessment tools that can be used to detect and monitor these changes occurring in the brain and show how it compensates after amputation.

NEURAL CHANGES IN MALADAPTIVE PLASTICITY

Pain, as a result of maladaptive neuroplasticity, involves sensory, cognitive, and emotional experiences. Current investigations have demonstrated that plastic changes take place in the spinal cord and brain structures—particularly cognitive-affective structures and somatosensory cortical areas—as responses to persistent pain. These changes are far too subtle to represent functional adaptive processes, but rather a continuum into the progression of circuitry dysfunction, where consequential aberrant plasticity promotes generation of pain and discomfort in patients who undergo amputation.

It is important to consider the directionality involved in these changes, from distal to central, from nociceptor to

spinal neuron, and from thalamus to somatosensory cortex. However, what happens at the cortical level and its feedback in the opposite direction might explain the generation of PLP. Thus, it is conceivable that the *periphery* could modulate the *center* and *vice versa* in response to external stimuli or stressors.⁹

Plasticity responsible for clinical pain hypersensitivity has two general forms: modulation and modification. Modulation represents reversible changes in excitability of primary sensory and central neurons, mediated by post-translational alterations induced in receptors and ion channels by activation of intracellular transduction cascades. Modification represents long-lasting alterations in expression of transmitters/receptors/ion channels or in the structure, connectivity and survival of neurons, such that the system is grossly modified, distorting its normal stimulus–response characteristics.¹⁰

These mechanisms are of paramount importance in the genesis of PLP. Immediately after nerve damage, inflammatory processes trigger a biochemical cascade promoting depolarization of the nociceptor with subsequent spinal-cord transmission to the central nervous system, where excitatory synaptic activity for pain is mediated by glutamatergic receptors. Imaging studies have demonstrated maladaptive structural plastic changes in patients with persistent peripheral pain.

Subjects suffering from carpal tunnel syndrome (CTS)—a condition characterized by entrapment neuropathy that produces pain and paresthesia in the affected hand—had extensive and stronger contralateral sensorimotor cortical representations from the digits innervated by the entrapped median nerve, when these were stimulated during functional magnetic resonance imaging (fMRI) evaluation.¹¹ Moreover, these changes in cortical fMRI activation were negatively correlated with peripheral nerve dysfunction and the anatomical distance between digit separations, indicating that abnormal peripheral nerve conductance might trigger structural central changes in the sensorimotor areas. Nonetheless, these changes seemed to be partially reversed when a neuromodulatory technique was used for symptom relief. When subjects with CTS were exposed to electroacupuncture (EA), the severity of their symptoms decreased, and nerve conduction and anatomical separation of cortical digit representations evaluated by fMRI also showed improvements in these subjects.¹² These results showed that, despite the development of aberrant plasticity, these changes can be modulated and somewhat reversed by applying sensory and electrical stimulation in the form of EA.

Overstimulation of nociceptive pathways induced by chronic pain in a stump can lead to a massive maladaptive rearrangement at the spinal level and disorganization in pain-related neural structures. This phenomenon, also termed central sensitization, promotes secondary hyperalgesia and allodynia. When neurons in the dorsal horn of

the spinal cord are subject to central sensitization, they develop: (1) an increase in spontaneous activity; (2) a reduction in the threshold for activation by peripheral stimuli; (3) an increase in response to suprathreshold stimulation; and (4) an enlargement of their receptive fields.^{10,13} Central sensitization induces conversion of nociceptive-specific neurons to wide-dynamic-range neurons that respond to both innocuous and noxious stimuli.¹⁴ Activation of pain at the nociceptors, generates depolarizing currents in response to noxious stimuli. This triggers fast excitatory synaptic transmission in pain pathways mediated by glutamate acting on α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate ligand-gated ion channels.¹⁵ The excitation is focused by segmental and descending activation of inhibitory neurons, most of which co-release glycine and γ -aminobutyric acid (GABA).¹⁶

While the precise neurobiology of these maladaptive plastic changes is becoming understood, conceptualization of how the cortex and subcortical structures process the information from these deviant circuits remains unclear. PLP must be considered within the context of all these factors—from the neurobiology behind plastic changes and the neural processes needed to generate the perception of pain.

Deafferentation and Sensitization: The Building After Neural Insult

Pain because of deafferentation can be considered the result of partial or complete afferent activity disruption. This kind of pain results from lesions interrupting spinothalamic pathways at any level of the nervous system. Amputation or deafferentation (complete or incomplete) of a limb or another body part is usually followed by a global feeling that the missing limb is still present (phantom limb awareness), as well as specific sensory and kinesthetic sensations (phantom sensations).¹⁷ A common feature after complete or partial nerve injury is the manifestation of “Tinel’s sign.” This sign has been used to identify hyperreactive nerves and denotes local or referred pain covered by the damaged nerve’s territory of innervation and occurring as a response to mechanosensitivity of ectopic pacemakers’ sites (neuromas, regenerating sprouts, demyelination) at the injured nerve.¹⁸

PLP may be described as burning or tingling at the time of onset and can eventually evolve into severe crushing, pinching, or shooting pain that could become extremely intense. These descriptions suggest that PLP involves both superficial and deep-tissue pain sensations. Somatosensory deafferentation leads to sensory deprivation, which, in turn, limits the amount of information the brain needs to process to find the amputated limb in the bodily space. Because of this faulty detection, dramatic changes occur at the higher cortical level.

The most common theory of PLP caused by deafferentation is based on the concept of maladaptive

reorganization. The key evidence supporting this is the correlation between pain and topographic reorganization of sensorimotor cortical maps as revealed by imaging¹⁹ and neurophysiologic data.²⁰ A cascade of events—starting with hyperpolarization at peripheral structures, with transitions from short- to long-term neural modifications at the central level—is characterized by a continuum of such dynamic plastic changes. It has been reported that anesthetic treatments do not always ease PLP in animal models.²¹ Clinicians are also aware of the lack of pain control after local stump infiltration or spinal anesthesia in some patients, indicating that not only local factors are involved but rather intrinsic modifications of neural circuits.

Central sensitization, as a result of modulation in pain pathways, is triggered by peripheral nociceptor activity, resulting in enhanced responsiveness of pain transmission neurons. This, in turn, outlasts the initiating input or requires a low-level peripheral threshold to keep it active.²² In this regard, overactivity at the dorsal root ganglia, as a result of increased sprouting of the primary afferent fibers, leads to an increase in excitatory signaling and, consequentially, reduced inhibitory synaptic activity. The changes can be limited to a local stimulated synapse or can spread to neighboring synapses. Most excitatory inputs to the pain pathway neurons are subthreshold inputs, and increased gain results in recruitment of these inputs to the output of the neurons, causing them to fire to normally ineffective inputs.^{13,23}

These changes are the foundation of central sensitization and are responsible for pain produced by low-threshold afferent inputs and the spread of hypersensitivity to regions beyond injured tissue.²⁴ Enhanced excitatory cortical activity in chronic pain correlates with increased amplitude of motor-evoked potential as measured by TMS, demonstrating enlarged recruitment of corticospinal tracts. Moreover, this spreading out in pyramidal neuron activations is mediated by glutamatergic activity.

This disinhibition of the hyperexcitatory state occurs through multiple neurobiologic systems—including the *N*-methyl-D-aspartate and AMPA receptors, Ca^{2+} , and activation of calcium/calmodulin-dependent kinase II—that can amplify sensory pain signals to the neural pain matrix.²⁵ The reverse of this phenomenon (a gradual loss of inhibitory tone) can be seen in GABAergic neurons.²⁶ This loss on inhibition can be measured by the long-interval cortical inhibition (LICI) metric of TMS. It is thought LICI is mediated by GABA_B ; a decrease in LICI might be the result of decreased GABA_B receptor-mediated inhibitory postsynaptic potentials.²⁷ The imbalance in cortical excitability facilitates circuit modifications and structural reorganization. Therefore, the increase in excitatory activity by ectopic neuromas or anomalous pacemakers will lead to persistent spinal transmission to thalamocortical circuits favoring hyperexcitability while decreasing regulatory inhibitory activity.

NIBS AS A THERAPEUTIC OPTION FOR PLP

NIBS techniques have been used for >200 years.²⁸ NIBS technology development and research has advanced in parallel with the main goal of achieving a better understanding of neural physiology and the effects of electrical stimulation on excitable tissue. Methods of neuromodulation are being recognized as technology making an impact on the neural interface. In addition, NIBS is emerging as an interesting alternative for this interface to act upon neurologic and psychiatric conditions. NIBS has a therapeutic potential to modulate maladaptive plasticity. For example, in the case of dystonia, clinical studies have revealed efficacious and long-lasting neuromodulatory effects of rTMS at 1 Hz over the primary somatosensory area²⁹ and rTMS at 0.2 Hz or 1 Hz over the premotor cortex.³⁰ Similarly, cathodal tDCS has decreased seizure frequency and interictal epileptiform discharges in patients with mesial temporal lobe epilepsy.³¹

These studies are examples of how techniques with clear effects on network modulation, can disrupt maladaptive plasticity in reverberant circuitries. Chronic pain—specifically PLP, where nociceptor-induced spinal and central sensitization of the somatosensory system has a strong effect promoting plastic changes—makes the system hyperalert and the risk for further damage is high, for instance, immediately after exposure to an intense or damaging stimulus.³²

Transcranial Direct Current Stimulation

tDCS is a noninvasive technique capable of modulating cortical excitability while offering symptom relief in a variety of conditions. The transcranial application of weak direct currents to the human cerebral cortex elicits membrane changes through subthreshold mechanisms. The nature of these modulations depends on tDCS polarity and scalp-site localization.³³ In summary, cerebral excitability is diminished by cathodal stimulation, which hyperpolarizes neurons, while anodal stimulation facilitates neuronal depolarization, leading to an increase in excitability.³⁴ These changes occur with a safety profile that has not yet shown serious adverse events, making the technique suitable for human applications. Manipulation of these neurophysiologic effects demonstrates how modulation can be used as an operational technique to promote activation or inhibition of higher neuronal processes.

Furthermore, tDCS is capable of inducing duration-dependent, long-lasting modulatory effects that outlast the duration of the stimulation period. This method of stimulation has been shown to affect a range of motor, somatosensory, visual, affective, and cognitive functions.³⁵ There has been a limited number of trials exploring the effects of tDCS on PLP. In the last decade, radiologic neuroimaging techniques have enhanced the study of mechanisms involved in the development and maintenance of neuropathic pain.

Findings in 2010 suggested that neuropathic pain in certain pain syndromes—including PLP—is associated with a functional reorganization and hyperexcitability of the somatosensory and motor cortex, and that tDCS could be a suitable method for modulating the cortical excitability imbalance.³⁶

According to this rationale, one of the first trials³⁷ showed that a single session of anodal tDCS of the supplementary motor complex (SMC or M1) induced a selective short-lasting decrease of PLP, whereas cathodal tDCS of the posterior parietal cortex (PPC) induced a selective short-lasting decrease of nonpainful phantom sensations. This indicated that PLP is associated primarily with cortical excitability shifts in the sensorimotor network. Increasing excitability in this system by anodal tDCS has an analgesic effect on PLP.

Conversely, nonpainful phantom sensations are associated with hyperexcitation of the PPC that can be normalized by cathodal tDCS.³⁷ A follow-up study by some members of the same group of researchers, explored the effects of 5 days of stimulation.³⁸ The results demonstrated that active, but not sham, anodal tDCS induced a sustained decrease in background PLP and in the frequency of PLP paroxysms. These effects lasted for 1 week after the end of treatment. Moreover, on each day of active tDCS, patients reported immediate relief of their PLP along with an increased ability to “move” their phantom limbs.³⁸

These studies offered insight about anodal stimulation over M1 or PPC. However, sample size is still a problem, and no definitive conclusion can be drawn from these results. Currently, the Neuromodulation Laboratory at Spaulding Rehabilitation Hospital is performing a large prospective study on the effects of tDCS and mirror therapy (MT) in PLP with a larger sample ($N=132$) in a factorial design. Interestingly, the objective of this study is to evaluate the efficacy of tDCS and MT as rehabilitative tools for managing PLP. The factorial design will provide relevant data for evaluating whether tDCS combined with MT is more effective than each therapy alone.³⁹ The idea to combine two neuromodulatory techniques is attractive, especially to favor treatment efficacy for a condition that is difficult to manage. Moreover, this study includes fMRI and TMS assessments, which will help elucidate some of the questions surrounding tDCS + MT as therapeutic options for PLP.

Repetitive Transcranial Magnetic Stimulation

As a therapeutic alternative, rTMS has been used to mitigate PLP. The technique is based on the electromagnetic induction principle. Electromagnetic induction can elicit suprathreshold neuronal depolarization by applying coils placed over a patient’s scalp. When this depolarization occurs in a repetitive way, cortical modulation may persist even after the stimulus is removed. Cortical facilitation or inhibition depends on the frequency and intensity of the pulse repetitions. It has been proposed that increasing

motor cortex activity with high-frequency rTMS could augment its inhibitory influence on spinal excitability via the cortico–thalamic–spinal tract, hence, reducing α and γ neuron hyperactivity and, thus, phantom pain. One of the first studies testing this principle failed to demonstrate superiority of high-frequency rTMS over inhibitory rTMS or sham stimulation.⁴⁰ The crossover design and small sample size of that study compromised its statistical power. Furthermore, the methodology highlighted the role of medical devices in promoting placebo effects, which is a common phenomenon driven by expectations regarding new and advanced medical technology.

A case report exploring the effects of inhibitory rTMS over M1 in the contralateral hemisphere (the unaffected hemisphere), show that rTMS was efficacious for reducing PLP.⁴¹ This study tested the hypothesis of transcallosal inhibition, wherein the unaffected hemisphere inhibits modulation of hyperexcitability on the affected hemisphere. The rationale supporting this hypothesis is based on the premise that transhemispheric reorganization occurs after deafferentation in the affected sensorimotor cortex.

Researchers conducted a randomized trial exploring the analgesic effect of high-frequency rTMS (20 Hz) on chronic PLP, using contralateral M1 as a target of stimulation for 5 consecutive days. The researchers reported a significant reduction of visual analogue scale (VAS) scores in a verum stimulation group immediately after the fifth session (55%) that was maintained after 2 months (39%), compared with what occurred in a sham “stimulation” group.⁴² Although this trial produced positive results, the methodology prevented the researchers from generalizing their results.

Recently, Malavera et al., demonstrated a significant analgesic effect on PLP, using a well-designed protocol with a more heterogeneous sample (active: 27 subjects; sham: 27 subjects). The researchers tested the effects of 10 sessions of 10 Hz rTMS on the primary motor cortex contralateral to the amputated lower limb. Active rTMS induced a significant reduction in pain intensity on VAS scores 15 days after treatment, compared to what occurred in group who received sham “stimulation” ($-53.38 \pm 53.12\%$ versus $-22.93 \pm 57.16\%$; mean between-group difference = 30.44%; 95% confidence interval: 0.30–60.58; $P=0.03$).⁴³ These results extended beyond previous rTMS studies on PLP and provided a more-reliable estimate of the effect size of this intervention.

In an example of technology development that increased treatment efficacy, Lee et al. presented a case report of a successful application of navigated rTMS in a subject with a right transfemoral amputation. The patient was suffering from severe PLP. The researchers targeted the affected SMC or M1, using a neuronavigation system with 800 stimuli at 1 Hz rTMS. rTMS over the SMC dramatically reduced this patient’s VAS ratings of PLP from 7 to 0. However, 1 Hz rTMS over the premotor cortex (PMC) failed to reduce this patient’s pain. Although this was just a case report, it demonstrated the advantages offered by a

better targeting approach, with use and applications of navigated TMS.⁴⁴

Summary

Overall, there is some promising evidence coming from a handful of tDCS and rTMS clinical trials, that both techniques seem to capitalize in their potential for modulating maladaptive plasticity in PLP. More and better-designed protocols are needed to sustain PLP research exploring new treatments options for adequate pain relief. International collaboration appears to be a good strategy when patient recruitment is a challenge that many scientists encounter on a regular basis.

BAYESIAN MODELS OF SENSORY INTEGRATION IN PLP

The most accepted models of information processing and sensation differentiate perception as a function of interpretation of sensory inputs and their transformation into meaningful information that one can use for recognition and understanding of the environment. Human senses provide a variety of independent cues for the three-dimensional (3-D) components of objects. For instance, tactile and physical information—generated from Meissner's corpuscles, mechanoreceptors, proprioceptors, nociceptors, or thermoreceptors—all provide information from the limbs and their relation to positions and structural integrity within the context of space. A large associative network is needed to process all these sensory cues. This specialized network adds inputs from visual and motor systems and integrates these inputs to correct for ambiguity.

Role of Previously Acquired Storage

Previously acquired storage through experience acts as a reference for computational processing for the new incoming sensory, visual, and motor inputs. Within the context of this general plan of processing and organization, the sensory-fugal pathways—which sequentially convey sensory information from primary sensory to unimodal (S1, M1, premotor, and V1), heteromodal, paralimbic, limbic, and hypothalamic areas of the brain⁴⁵—play a crucial role in shaping cognition and behavior associated with the awareness of limb representation within a 3-D context.

Bayesian Probability Theory

To gain a better understanding of how PLP produces physical discomfort when a bodily limb is missing, it is necessary to move beyond neuroanatomical/physiologic boundaries and incorporate a probabilistic analysis approach. This can enable a superior understanding within the realms of sensory-information processing.

Bayesian probability theory provides a normative framework for modeling how an observer should combine information from multiple cues and from prior knowledge about objects in the world to make perceptual inferences.⁴⁶ The theory also provides a framework for developing predictive theories of how human sensory systems make perceptual inferences about the world from sensory data. These are predictions that can be tested psychophysically.⁴⁷ An in-depth analysis of Bayesian methods for sensory cue integration is beyond the scope of this article. Yet, an introduction to the basic principles is presented here to build a reference for additional understanding of maladaptive plasticity and network processing failure in PLP.

To demonstrate the elementary concept of Bayesian computations for sensory integration cues consequential to a limb, one needs to consider the position of the limb (l) from visual and proprioceptive cues, (V and Pr). The optimal Bayesian computation can be used to calculate the conditional density function, $p(l \mid V, Pr)$. The Bayesian's rule states the following:

$$p(l \mid V, Pr) = \frac{p(V, Pr \mid l)p(l)}{p(V, Pr)}$$

where $p(V, Pr \mid l)$ represents the relative likelihood of sensing the given data for different limb values (l) and its prior probability $p(l)$ as a reference for different values of l . Given that there is ambiguity and statistically independent noise also captured by visual and sensory systems, the associative network must process the resulting uncertainty effectively to generate perceptual representations of the limb and to guide its actions.

To reach this objective, a different computation is necessary to decompose the likelihood function into the product of functions associated with the visual and proprioceptive cues based on prior information, respectively:

$$p(V, Pr \mid l) = p(V \mid l)p(Pr \mid l)$$

where $p(V \mid l)$ and $p(Pr \mid l)$ represent the information provided by visual and proprioceptive systems about the limb's position. The posterior density function is proportional to the product of three functions, the likelihood of functions associated with each cue (limb, visual, and proprioceptive), and the prior density function representing the relative probability of the limb's dimensional situation at any given position.

Thus, Bayesian sensory integration at the neural level can be conceptualized as a probability "machine" that constantly makes predictions about the world and then updates them based on what the "machine" senses.⁴⁸ In phantom sensations and PLP, the faulty information and lack of content is what generates uncertainty. The redundancy of a present limb is what is already known and serves as a protection against errors in information transmission. Once the

limb's information is deleted due to amputation, a series of errors are generated by ectopic neuromas, the hyperexcitable spinal segment, and, ultimately, deafferentation. All of these errors are somewhat corrected following predictions produced by Bayesian computations. Unfortunately, what comes out of this processing is also defective information that induces perception of phantom phenomena.

For completely predictable stimuli, there is no information content that can reduce the uncertainty of the limb further with respect to the environment. Yet, information content that can reduce the uncertainty is present in changes occurring in the environment (e.g., observing the remaining limb, or sensations triggered by ectopic neuromas). The uncertainty can also be reduced by generating an endogenously generated signal to be used as an allusion to the missing limb. Thus, a phantom sensation develops in an attempt to correct for the uncertainty.

If biologic systems compute intrinsic and extrinsic signals with the goal of keeping low uncertainty, then any interventions must account for this and allow recovery of function by preventing processes of maladaptive plasticity and by reducing generation of noise caused by the lack of sensory and proprioceptive inputs. In this scenario, the proposed methodology by Pinto et al. of combining tDCS and mirror therapy³⁹ is an attractive alternative for treating PLP.

CONCLUSIONS

Phantom sensations and PLP are complex experiences and indicate abnormal processing of sensory and proprioceptive information. Moreover, hyperexcitable responses originated at diverse levels of the neuroaxis facilitates the rearrangement of neural circuits promoting maladaptive plasticity. Future treatments and interventions will need to approach the disruption of aberrant circuitry and the correction of defective information promoted by the lack of reliable sensory inputs.

Noninvasive brain stimulation techniques, such as tDCS and rTMS, can modulate large and focal networks, respectively. Both techniques are capable of affecting plasticity by inducing LTP/LTD mechanisms, based on how the electrical current is delivered and how the stimulation parameters are used. The brain applies Bayesian processing of information through active sensory and proprioceptive monitoring, so a human being can sense the environment and where his or her body is positioned spatially. After limb amputation, phantom perceptions might be the result of Bayesian adaptations nurtured by maladaptive plasticity. Therefore, the combination of NIBS plus cognitive-behavioral interventions can target the neural and computational substrates involved in PLP.

Based on the presented information, it is clear that more and better-designed studies are needed to generate enough

evidence to support the use of NIBS techniques. Further technological developments for monitoring and analysis will help researchers to understand the changes associated with amputation. But more importantly, these developments can guide and optimize treatment alternatives for patients with PLP.

ACKNOWLEDGMENTS

Dr. Morales-Quezada received funding support from an Institutional National Research Service Award from the National Center for Complementary and Integrative Health grant T32AT000051, the Ryoichi Sasakawa Fellowship Fund, and the Program in Placebo Studies at Beth Israel Deaconess Medical Center.

AUTHOR DISCLOSURE STATEMENT

The author has no conflicts of interest to declare.

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