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REVIEW

A Dissociation Between Primary Motor Cortex Reorganization and Correlation with Pain Intensity in Phantom Limb Pain: A Systematic Review of fMRI Studies

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Background: Phantom limb pain (PLP) constitutes a diagnostic and therapeutic challenge with an unknown pathophysiology that likely comprises a combination of cerebral, spinal, and peripheral nervous system pathways. A novel therapeutic field in chronic pain targets cortical areas as treatment foci for neuropathic pain. One studied target in phantom limb pain is the primary motor cortex (M1). Given some promising results of noninvasive brain stimulation to reduce PLP, understanding further the role of M1 in the mechanisms of PLP would provide important future insights to further develop this therapeutic target.

Objective: To synthesize neuroimaging evidence on M1 reorganization in PLP and evaluate its association with pain intensity.

Methods: Six databases (Ovid MEDLINE, Cochrane Library, CINAHL, Scopus, Web of Science and EMBASE) were searched.

Results: Of the 2582 articles, 13 articles met our criteria and were included. Evidence demonstrated cortical reorganization in the contralateral M1, characterized by increased activation and maintained functional representation of the absent limb, lasting decades post-amputation. Patients with PLP showed significant activation in M1 and the somatosensory cortex during phantom limb movements, alongside reduced interhemispheric functional connectivity. However, results regarding the relationship between M1 reorganization and PLP intensity were inconsistent.

Conclusion: M1 cortical reorganization plays a substantial role in PLP mechanisms, making it a viable therapeutic target. The inconsistent correlation between M1 activity and PLP severity highlights the complexity of PLP pathophysiology. Future research should standardize imaging protocols, control for confounding variables, and investigate interactions between M1 and other brain regions to improve therapeutic approaches.

Keywords: phantom limb pain, motor cortex, motor cortex representation, brain activation

Introduction

Phantom limb pain (PLP) belongs to a group of neuropathic pain syndromes and is characterized by the perception of pain in a missing limb or following partial or complete deafferentation.[1,2] The incidence of PLP ranges from 42.2 to 78.8%, with a reported prevalence of 45–85%. PLP onset can begin immediately or many years after amputation, occurring in 82.7% of cases within the first 12 months.[2–5] In most cases, PLP subsides over time regardless of the cause of amputation, but it persists for several years in 5–10% of cases.[6,7]

Despite the high incidence in amputees and impact on their quality of life,[8,9] PLP remains one of the most challenging chronic pain syndromes to treat, often responding poorly to conventional therapies.[1,2,10–12] Although central and

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peripheral factors have been implicated in the development of PLP, the former is believed to be the major contributor. It has been proposed that the phenomenon is initiated by changes arising in the periphery that alter the afferent input into the brain and spinal cord.[1,3,10,13] In that way, the region that represents the missing limb in the primary somatosensory cortex (S1) becomes deprived of its primary input, resulting in functional changes in the gray and white matter, prominently in the primary sensory (S1) and motor (M1) cortices.[14–18]

Neuroimaging techniques such as fMRI have thus been employed to investigate these neural alterations and guide rehabilitative strategies for PLP. fMRI has proven valuable for evaluating cortical reorganization, somatotopic representation changes, task-related activation, and treatment-related neural responses.[19,20] For instance, when amputees with PLP attempt to move their phantom limbs, activation in the corresponding sensorimotor areas appears in fMRI, and this activation is similar to real executed movements in able-bodied subjects.[19] Significant task-related activation in the superior temporal gyrus, medial temporal gyrus, and M1 contralateral to the executed movement has been documented in other studies.

Furthermore, greater dependence on the intact limb has been associated with decreased white matter degeneration, improved limb representation, and cortical expansion of S1 cortex into the deprived cortex.[13] It has also been proposed that brain functional network recovery occurs through progressive restoration of functional connectivity between subcortical and cortical regions, particularly involving the supplementary motor area (SMA) and the contralateral S1M1.[21,22]

Despite previous reviews addressing the phantom limb pain mechanisms broadly or focusing on the therapeutic interventions, the precise role of primary motor cortex (M1) reorganization in PLP perception and intensity remains unclear.[23] Neuroimaging studies have reported inconsistent findings—some showing positive associations between M1 activity and pain intensity, while others show null or contradictory results. Moreover, understanding M1 involvement is clinically relevant, as this area is targeted by rehabilitation strategies such as motor imagery, mirror therapy, and non-invasive brain stimulation, which aim to reverse maladaptive cortical changes and alleviate pain. This systematic review synthesizes the available neuroimaging evidence on M1 reorganization in PLP, with an emphasis on its relationship to pain intensity and its implications for therapy.

Materials and Methods

This review was conducted with the PRISMA 2020 statement (Page MJ, McKenzie JE, Bossuyt PM, et al, 2020), and an a priori protocol was registered with PROSPERO (CRD42022383423).

Search Strategy

We applied a search strategy developed in collaboration with an experienced librarian (MH) in Ovid MEDLINE, Cochrane Library, CINAHL, Scopus, Web of Science and EMBASE. The search was performed from each dataset's inception until March 2023 by using controlled vocabulary, supplemented with keywords related to phantom limp pain and neuroimaging techniques. There was no language restriction placed on the search. No additional filters (eg, publication year) were set. A manual search was also conducted to find other potential articles based on references identified in the individual articles. Our full search strategy is available in the Supplemental Digital content-Search strategies.

Eligibility Criteria

We included original articles and case reports that had interventions with positive or negative outcomes in the primary motor cortex by using neuroimaging techniques in adults with a limb amputation and suffering from PLP. Outcomes expected: (1) structural changes in M1. (2) increased, decreased, or absence of neuronal activation in the M1 after imagined phantom limb movements or TDCs. There was no language restriction placed on the search.

Exclusion Criteria

The following criteria were used to exclude studies: (1) wrong patient population: studies that included adults with any limb amputation, but without PLP. (2) wrong intervention: studies that did not use neuroimaging techniques in patients with PLP (3) wrong outcomes: studies that included amputees with PLP who underwent any of the neuroimaging

modalities but did not report either positive or negative outcomes in the primary motor cortex. (4) wrong study design: (a) animal studies; (b) review articles; (c) letters to the editor; (d) editorials. Duplicated studies were also removed.

Data Collection and Management

Two independent reviewers (IG, EL) screened the abstracts and assessed them for inclusion and exclusion criteria. Duplicated records were removed. Then, full texts were read and assessed for eligibility. Any discrepancies were discussed between the two reviewers initially and if no agreement was reached, this was solved by another reviewer (HA). Extraction of relevant results was checked (10% of the time) by a second reviewer (HA). Due to the heterogeneity in study designs and outcome reporting, a meta-analysis was not feasible. Instead, a narrative synthesis was conducted. Findings were grouped and interpreted based on task type (eg, motor execution vs imagery) and reported associations between M1 activity and phantom limb pain intensity.

Protocol Deviations

Following PROSPERO registration (CRD42022383423), a number of adjustments were made to improve the comprehensiveness of the review. These included (1) expanding the databases searched to include CINAHL and Scopus, (2) removal of the language restriction to capture a broader range of studies, and (3) inclusion of both case-control and cross-sectional studies. These changes were implemented to capture a more representative and updated evidence base and are transparently reported here.

Risk of Bias Assessment

One reviewer (HA) independently assessed the risk of bias of the studies according to the Newcastle -Ottawa quality assessment scale,[24] and the results were displayed using the "robvis" package.[25] Three domains were evaluated: subject selection, comparability, and the assessment of the exposure. The evaluation was reported as "low", "some concerns" or "high", as summarized in Figure 1.

Results

Studies Retrieval

The results of the search strategy are summarized in Figure 2 as PRISMA statement flow diagram. The literature search resulted in 1494 articles after duplicates were removed. Based on titles and abstracts screening, 1196 articles were excluded. The remaining 298 articles underwent full-text screening to identify studies reporting M1 findings in PLP patients using neuroimaging techniques. Although our initial search included a broad range of neuroimaging modalities, only studies employing functional MRI (fMRI) met our criteria for inclusion. In this phase, 281 articles were excluded as

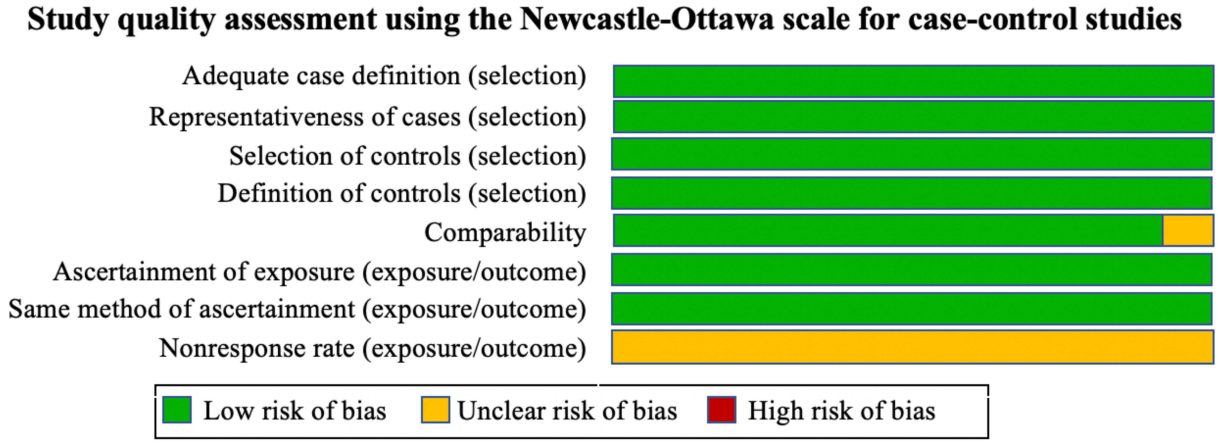

Figure 1 Literature search flow-chart.

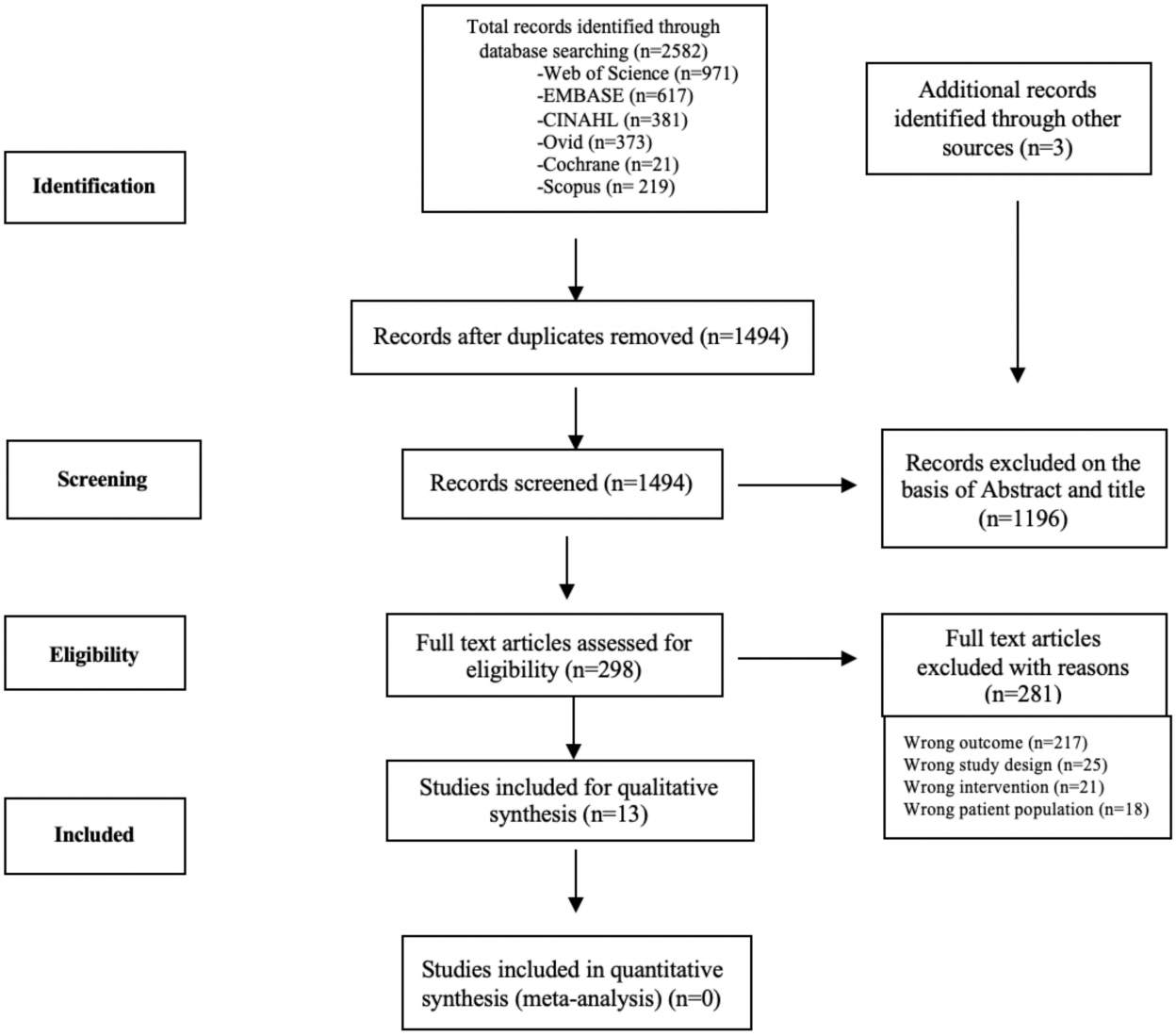

Figure 2 Risk of bias assessment.

they did not report M1 findings, did not include PLP patients, or had an inappropriate study design (eg, review articles). Therefore, 13 articles were included: 1 case report, 10 case-controls studies, and 2 cross-sectional studies.

Overall Characteristics

Among the patient's characteristics, the predominant cause of amputation was trauma. Most of the studies involved upper-limb amputees, and only four studies included lower-limb amputees. The right upper limb was the most affected, and only 5 studies mentioned the use of prostheses. The time since amputation ranged from 1.5 years to 21.3 years (mean 14.27 years). fMRI was the most common neuroimaging used to evaluate cortical reorganization after performing tasks, imaginary/mental training, or undergoing neurostimulation. Most of the studies included healthy patients without amputation as controls. Only one study used subjects as their own control, comparing against the participants' ipsilateral hemisphere to the amputation.

One study evaluated transcranial direct current stimulation over the primary sensorimotor missing cortex (S1/M1) to alleviate PLP. Eleven studies assessed cortical reorganization in M1/S1 in imagined phantom limb movements, mental imagery, and mirror therapy. The characteristics of the included articles are summarized in Table 1. Study heterogeneity prevented data pooling.

Table 1 Characteristic of Included Studies

Authors, Year, and Sample Size	Study Design	Type of Amputation	Time Since Amputation (Mean)	Gender	Prosthesis Use (N)	Handedness Before Amputation	Amputation Side
Ersland et al (1997)[26] (n=1)	Case report	**UL** Traumatic	1.5 years	M	N/A	R	R
Lotze et al (2001)[27] (n=14)	Case control	**UL** 11 traumatic 1 infection 2 cancer	17.21 years	4 F/10 M	N/A	9 R/ 5 L	9 R/ 5 L
Dettmers et al (2001)[28] (n=16)	Case control	**UL** 13 traumatic, 2 infection, 1 pathological fracture	12 years	2 F/14 M	N/A	N/A	10 R/6 L
Roux et al (2003)[29] (n=10)	Case control	**UL** (8)/**LL** (2) 9 traumatic 1 ischemic	13 years	4 F/6 M	N/A	10 R	6 RUL/ 2 LUL/ 2 RLL 1 LLL
MacIver et al (2008)[30] (n= 13)	Case control	**UL** 12 traumatic 1 cancer	24 years	2 F/11 M	8	N/A	9 R/ 4 L
Raffin et al (2016)[31] (n=11)	Case control	**UL** 11 traumatic	7.5 years	4 F/ 7 M	5	11 R	5 R/ 6 L
Makin et al (2013)[32] (n=18)	Case control	**UL**	18 years	N/A	N/A	6 R/ 12 L	13 R/ 5 L
Foell et al (2014)[33] (n=13)	Case control	**UL** 12 traumatic 1 vascular disease	21.3 years	4 F/ 9 M	5	12 R/1 L	5 R/8 L
Kikkert et al (2017)[34] (n=15)	Case control	**UL** 13 traumatic 1 vascular disease 1 cancer	16 years	4 F/11 M	11	10 R/ 5 L	6 R/ 9 L
Kikkert et al (2018)[35] (n=15)	Case control	**UL** 13 traumatic 1 cancer 1 vascular disease	16 years	4 F/11 M	13	11 R/4 L	6 R/11 L
Duarte et al (2020)[36] (n=18)	Cross-sectional study	**LL**	N/A	8 F/10 M	N/A	N/A	8 R/10 L
Andoh et al (2020)[37] (n=20)	Case control	**UL**	18 years	10F /10M	N/A	N/A	10 R/10 L
Zheng et al (2020)[13] (n=20)	Cross-sectional study	**LL** 11 traumatic 7 cancer 2 vascular disease	3 years	7 F/23 M	N/A	N/A	9 R/11 L

Abbreviations: UL, upper limb; LL, lower limb; M, male; F, female; R, right; L, left; RUL, right upper limb; LUL, left upper limb; RLL, right lower limb; LLL, left lower limb.

Clinical Findings-Role of the Primary Motor Cortex in Imaginary Movements

Reorganization in M1/S1 contralateral to the amputation side has been suggested to be the main neural correlate of PLP. Supporting this idea, Lotze et al[27] studied upper limb amputees and found that only patients with PLP presented a shift of the lip representation into the deafferented primary motor and somatosensory hand areas during lip movements and

Table 2 Summary of Functional MRI Findings Reported in Studies of Phantom Limb Pain

Authors, Year	Assessment	Task Performed	Major Findings
Ersland et al (1997)[26]	Evaluation of cortical activation after imagined finger movements of the amputated arm	Imagined phantom limb movement	Increased neuronal activation in the contralateral M1 during imaginary finger tapping. Slight delay in onset of activation of contralateral hemisphere during imaginary movements.
Lotze et al (2001)[27]	To evaluate patients during the execution of hand and lip movements and imagined movements of the phantom limb	Imagined phantom limb movement	A shift of the lip representation into the deafferented primary motor and somatosensory hand areas during lip movements was evidenced only in patients with PLP and it was positively correlated to the severity of PLP. Higher activation in the contralateral M1 and somatosensory cortex during imagined phantom limb movements.
Dettmers et al (2001)[28]	Evaluation of primary sensorimotor cortex (SMC) during the execution of finger tapping, repetitive eye closing, and anteflexion of the amputated arm.	Imagined phantom limb movement	Greater activation in SM1 and supplementary motor area (SMA) in PLP patient contrast to patients without PLP.
Roux et al (2003)[29]	To study cortical areas involved in the phantom-limb sensation	Imagined phantom limb movement	Contralateral sensorimotor areas, M1, activation with phantom limb movements in amputees. Supplementary motor area activation with imaginary movement in the intact limb.
MacIver et al (2008)[30]	To evaluate cortical reorganization after 6-week training in mental imagery	Imagined phantom limb movement	Activation of bilateral M1 and S1, expanding from lip area to hand area during lip purse, imagined movement of the phantom hand, and executed movement of the intact hand. Increased ipsilateral activation in the M1 and S1 hand areas during movement of the intact limb that at baseline correlated with the intensity of constant pain. Mental imagery results in pain relief and reduction in cortical reorganization
Raffin et al (2016)[31]	To evaluate the cortical reorganization	Imagined phantom limb movement	Larger ipsilateral M1 activation in amputees than in controls when amputees moved either their intact or their amputated hand. The amount of ipsilateral activity in the former hand area while moving the intact hand was strongly correlated with the ability to move the phantom.
Makin et al (2013)[32]	Evaluate maladaptive cortical organization and disruptive interregional connectivity	Imagined phantom limb movement	Significant activation in the primary somatosensory cortex contralateral to the phantom hand in nearly all amputees. Activation during phantom movements correlated with subjective ratings of chronic phantom pain magnitude in amputees.
Foell et al (2014)[33]	To evaluate the effects of daily mirror training	Mirror therapy	No significant correlation between the cortical shift in ipsilateral M1 and reduction of PLP. Pain relief induced by mirror therapy is accompanied by a reversion of cortical reorganization in S1.
Kikkert et al (2017)[34]	Evaluation after the execution of finger-tapping task with the phantom limb	Imagined phantom limb movement	Slower phantom hand movements were coupled with stronger activity in the primary sensorimotor phantom hand cortex and worse chronic PLP.
Kikkert et al (2018)[35]	Task-Noninvasive brain stimulation via task-concurrent NIBS over the primary sensorimotor missing hand cortex (S1/M1) to alleviate PLP	TDCs	PLP relief and reduced activity in the S1/M1 missing hand cortex after stimulation. Increased activity in the ipsilateral insula, S2, and other pain-related areas during stimulation was predictive of subsequent PLP relief
Duarte et al (2020)[36] (n=18)	To evaluate the cortical reorganization	N/A	Increased activity in M1 and a shift in motor cortex representation not related to PLP intensity. They were directly correlated with time since amputation; and there was an association between increased activity in M1 with a lack of itching sensation.
Andoh et al (2020)[37] (n=20)	To assess the relationship between task-related activation maxima and PLP intensity in S1 and M1	Imagined phantom limb movement	Neural activity in M1 was positively related to PLP intensity.

(*Continued*)

Table 2 (Continued).

Authors, Year	Assessment	Task Performed	Major Findings
Zheng et al (2020)[13] (n=20)	Evaluate cortical reorganization in M1/S1 when executing tasks	Imagined phantom limb movement	Cortical activation in the contralateral M1/S1 when imaginary phantom limb movement. The contralateral SMA was activated when PLP-free amputees and controls made an imagined movement in their amputated limb.

Abbreviations: SMA, Supplementary motor area; SM1, Primary sensorimotor cortex; S1, Somatosensory cortex; TDCs, Transcranial Direct Current Stimulation.

imagined movements of the phantom hand. Moreover, the displacement of the lip representation in the primary motor and somatosensory cortex was positively correlated to the intensity of PLP (Table 2).

Contrary to the shift in motor cortex representation mentioned previously, Raffin et al[31] and Kikkert et al[35] found that maintained representation of the missing limb in the primary somatosensory cortex seems to be associated with chronic PLP. They consider that PLP is associated with the preservation of the grey matter volume in the cortical area of the missing limb. Additionally, Makin et al[32] found that individuals suffering more from PLP have a greater reduction in interhemispheric functional connectivity, which could explain the decrease in callosal white-matter fractional anisotropy in lower limb amputees documented by Simões et al.[38] Therefore, multiple factors interact to preserve the local structural and functional representations, but, at the same time, disrupt the interhemispheric connectivity.

In addition, most of the studies found that during the imagination of moving the phantom hand, a significant activation in the contralateral primary motor (M1) and somatosensory cortices was present compared with imagination hand movements in the control groups. However, only the patients with PLP during the imagined movement of the phantom activated the neighboring face cortical area and had increased activation in the M1/S1 lip area contralateral to the amputation side. Thus, the increased neuronal activation in the contralateral M1 during imaginary limb movements proves that the cortical areas of the missing limb are still functional even decades after amputation.[13,39]

Likewise, the imaginary movement of the phantom limb activates cortical areas that differ from the intact limb movement. Roux et al[29] found that the activation during imaginary movement in control subjects did not activate the precentral or postcentral gyri. In its place, activation was mainly in the SMA region. Supporting this idea, Romero et al[40] studied lower limb amputees and found that the brain activation during the imagery movement tasks of the amputated lower limbs involves the superior temporal gyrus, contralateral M1, and contralateral SMA.

Interestingly, activation of the basal ganglia loop was not seen during the imagery movement task of the intact toes in amputees or the healthy control group. Only during imaginary limb movements, increased activation was found in the contralateral basal ganglia at the medial globus pallidus, substantia nigra, and thalamus.[40] The increased activation in the basal ganglia–thalamus–cortex pathway during imaginary movement of the phantom toes may reflect an abnormal open loop functioning of the thalamocortical system underlying the conscious awareness of the phantom phenomenon.[40]

Regarding the intensity of pain in amputee patients, the contradictory results in the studies cannot provide certain evidence about the role of M1 in modulating pain. Makin et al,[32] Kikkert et al,[35] and Andoh et al[41] found an association between the degree of activation in the contralateral M1 during phantom movement and the intensity of pain in amputees, with greater activation in individuals with a worse history of PLP. In contrast to that, Duarte et al[36] found that PLP intensity is not associated with signal changes in M1 and a shift in motor cortex representation. Instead, signal changes in M1 are inversely correlated with time since amputation. Thus, longer periods of amputation lead to compensatory changes in sensory-motor areas with fewer changes in the contralateral M1. Duarte et al[36] conclude that signal changes in the visual cortex seem to be more related to greater pain.

Clinical Correlation—M1 Activation and Pain Relief

Elimination of cortical reorganization—evidenced by reduced activation in the contralateral M1 and S1 of the missing limb—has been associated with decreased intensity and unpleasantness of chronic pain in amputees. Supporting this, Maclver et al[30] studied 13 upper-limb amputees and found that after 6-week training in mental imagery, patients presented a significant reduction in both the intensity and unpleasantness of persistent pain and its exacerbations,

accompanied by a reversal of cortical reorganization.[30] Before training, cortical activation during lip pursuing extended abnormally from the lip area into the deafferented hand region of M1 and S1 a pattern that correlated with pain severity.

Foell et al[33] investigating the effects of mental imagery on PLP found similar changes.[33] The study showed that the pain relief induced by mirror therapy is associated by a reversion of dysfunctional cortical reorganization, but mainly in S1. As PLP decreased, the representation of the missing limb in the somatosensory cortices become similar, possibly returning to their normal state. However, for the motor cortex, no connection was found. Instead, pain reduction after mirror training was related to a decrease in activity in the inferior parietal cortex (IPC), an area connected to the interpretation of sensory information, and pain generation. That might suggest that the ability to relate the mirror image to one's phantom influence the treatment effectiveness to alleviate pain.[42] They also found no significant correlation between time since amputation and the treatment effects of mirror therapy.

Some evidence suggests that other pain-related areas are involved in the physiopathology of PLP. Kikkert et al[35] found that using task-concurrent NIBS stimulation in the mid and posterior insula and S2 reduced activity in the S1/M1 of the missing hand cortex. The reduced activity in M1/S1 was correlated with PLP relief. However, this study provides additional evidence that highlights the causal role of the mid and posterior insula in alleviating PLP, possibly through S1/M1 modulation.

Raffin et al[31] found that the amount of ipsilateral activity in the former hand area (M1) while moving the intact hand is correlated with the ability to move the phantom. Therefore, these findings correlated with the studies that found the reactivation of the deprived cortex (M1) when moving the intact and phantom limbs during mirror or imagery therapy.[26,28] Hence, this evidence reinforces the utility of these therapies to protect against reorganization of the motor cortex contralateral to the amputation and reduce phantom pain.

Clinical Correlation-Control Group Findings

Although the exact mechanisms behind the mode of action of mirror therapy (MT) are not clear, it has been proposed that there is representational restoration in the brain of the missing limb by the conjunction of visual and proprioceptive input. Foell et al[33] used the hemispheres ipsilateral to the amputation as controls for the measured changes in cortical activity after 4 weeks of MT. The study found no significant association between the cortical shift in the ipsilateral S1 and M1 with treatment benefit. Therefore, any changes in the ipsilateral hemisphere after MT did not influence PLP relief. In contrast to a reduction of dysfunctional reorganization in the contralateral S1 that was correlated with pain relief.

Discussion

Our review highlights cortical organization at a network-level scale, with reduced interhemispheric functional connectivity of the contralateral M1 and S1.[43–45] The findings in the studies suggest that cortical reorganization leads to PLP, and it is accompanied by the persistence of the missing limb's representation. Amputees who suffer from PLP seem to have greater cortical reorganization compared to amputees without pain.[46,47] The amount of cortical reorganization in some studies has been strongly related to the intensity of PLP4.[45] Zhang et al[20] and Lotze et al[27] found that the cortical shift is positively correlated with the PLP intensity.[20] In other words, PLP has a negative correlation with cortical reorganization and the reduction in pain intensity.[48] In contrast, Gunduz et al[46] and Pacheco et al[49] did not find any correlation between motor cortex reorganization and level of pain. Pacheco et al[49] conclude that the amount of cortical reorganization could be associated with the presence of pain instead of its severity.[49]

Hence, neuroplasticity-based methods that strengthen the cortical representation of the phantom and decrease the cortical reorganization have been used for the relief of PLP.[50–56] Among these PLP therapies, motor imagination, mirror therapy, and repetitive magnetic stimulation (rTMS) have shown inconsistent results. Repetitive magnetic stimulation (rTMS) over M1 has been revealed to temporarily alleviate the painful cramping sensation in the phantom limb and even provoke a sensation of movement.[4,21,38,57–59]

M1 plays a role in alleviating pain relief in PLP patients by mechanisms that are contradictory and not well understood. As described by Duarte et al,[36] the posterior M1 is linked to nonmotor regions including sensory and attentional brain areas that can suggest its modulation in pain.[36] Therefore, this could explain the reversibility of neuroplastic changes in patients after transcranial direct current stimulation over the M1. In addition, since M1 is

involved in the planning of action and execution of a motor task, the virtual reality mirror box (VRMB) has also been used to bring back the representation of the missing hand and reverse the maladaptive brain plasticity. In amputees, VRMB has shown significant task-related activation in the primary motor (MI) and somatosensory cortex (SI) contralateral to the executed movement.[21,56] Likewise, there is increased functional connectivity between the M1 (contralateral to the executed movement) and the medial occipital cortex, bilateral precuneus, caudate, superior frontal and superior medial frontal cortices, and angular gyrus.[21,60] Although similar brain areas are activated in motor imagery and execution, the degree of activation is different. For example, excitatory coupling between the thalamus and primary motor cortex is present during motor execution, but not in motor imagery.[22,61]

Taken together, the findings confirm that different components of pain (cognitive, affective, and discriminative) can be assigned to different brain regions and these areas play a role in the distinctive pain experienced by each individual (see Figure 3).[55] Pacheco et al[49] suggested that PLP intensity may be more related to neuronal circuits associated with emotional processing.[49] Therefore, the maladaptive cortical reorganization seems to activate pain circuits and the circuits related to emotional affective processing regulate the pain intensity. As described, the somatosensory cortex seems to be associated with the sensory-discriminative component, but the thalamus and limbic structures may determine their significance for the generation of affective and cognitive aspects of pain. Likewise, the insula may have a causal role (and other pain-related areas) in alleviating PLP, potentially through S1/M1 modulation.

There is also an important role of self-perception and corporeal awareness of body integrity that is optimized with a mirrored image of intact limbs.[28,62] That concept is supported by the ability of the visual cortex to generate kinesthetic motor imagery of own body movement.[61,63] Therefore, mirror therapy demonstrates the capacity to incorporate visual inputs in tasks by using similar approaches as motor execution (M1 activation). Moreover, the decrease of activity in the inferior parietal cortex (IPC) after mirror therapy also suggests its influence on the interpretation of sensory information and alleviation of pain.[33]

Similarly, the presence of itching in PLP patients as a compensatory mechanism to decrease neuropathic pain was suggested by Duarte et al.[36] They evidenced an association between the decreased activity in M1 and itching sensation compared with subjects without itching. Pain and itching have been found to partially activate the same cortical areas in healthy individuals (the anterior cingulate cortex, the anterior insula, the basal ganglia and the pre-supplementary motor

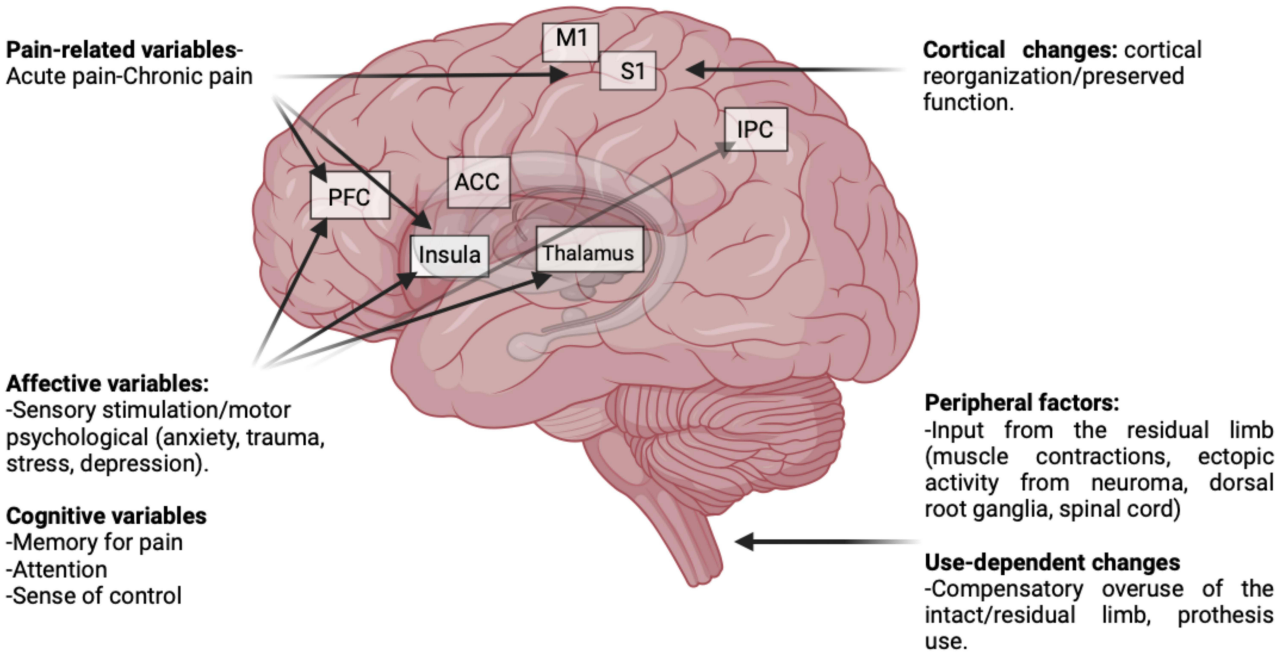

Figure 3 Factors determining the outcome of PLP.[43]
Abbreviations: M1, Primary motor cortex; S1, Primary somatosensory cortex; PFC, Prefrontal cortex; IPC, inferior parietal cortex.

https://doi.org/10.2147/IJGM.S526262

area) which suggest that the two sensations may be interlinked on a neurophysiological level.[64] However, only pain has been found to induce an activation of the thalamus, and being significantly correlated to pain sensation. These findings support the idea that the thalamus and S2 are important components for pain perception and demonstrate the central mechanisms of itching distinct from pain.[64]

Due to the rapid appearance of symptoms in some cases after amputation, cortical reorganization has been proposed to be a result of unmasking occult synapses in the somatosensory cortex, rather than specific anatomical changes.[39] A theory states that PLP may also arise from errors occurring in that cortical remapping process and leading to over-amplification of the pain experienced. This is the result of a lack of inhibitory activity in the sensory-cortical feedback pathways with a continued efferent motor cortical command. These are hypotheses and the current therapies have provided some clues about the physiopathology of PLP.

Given the controversial findings, larger studies evaluating the neurophysiological and structural changes in patients with PLP are needed, specifically focusing on the different brain areas that interlay and interact with the primary motor cortex to modulate pain. Likewise, a challenge to PLP research begins with how PLP is quantified. Most of the PLP treatment outcomes are measured by self-report, and as mentioned previously, PLP is heterogeneous like the experience (quality, intensity, frequency, time of onset, etc) and its association with other phantom sensations. Münger et al[65] found that 90% of patients with PLP experience at least 1 phantom sensation such as electric sensations, itching, and movement.[65]

Therefore, if the symptoms are assessed by trained research staff instead of questionnaire-based, the risk of response bias is reduced. Consequently, an analysis of the fMRI series can provide detailed and accurate results about the precise cortical areas activated in pain. Lastly, one limitation of retrospective pain assessments before the amputation is the recall bias. Patients with chronic pain may have difficulties rating their pre-amputation pain correctly when the amputation occurred months or years previously.

Finally, more longitudinal studies with larger sample sizes, and more homogeneous populations, considering the different factors associated with PLP are needed. The studies should include patients with low-intensity PLP or without pain as controls to assess the amount of reorganization more precisely with the presence of PLP and identify potential patients with an increased risk of developing phantom pain.

Limitations

This review has several limitations. First, the number of included studies was relatively small, which limits the breadth and statistical robustness of the findings. Second, there was substantial heterogeneity in study designs, participant characteristics, neuroimaging protocols, and the tasks employed (eg, motor execution vs imagery), making direct comparisons difficult. Third, the majority of research relied on self-reported, subjective measures of phantom limb pain, which are subject to recall and reporting bias. Fourth, due to the variability in outcomes and reporting, no quantitative synthesis or meta-analysis was conducted, and between-study heterogeneity was not formally assessed.

As a result, the synthesis was descriptive and qualitative, which limits the generalizability of conclusions. Fifth, the possibility of publication bias cannot be ruled out, particularly given the limited number of studies and the tendency to publish significant findings. Finally, most included studies involved upper-limb amputees, which may limit the generalizability of the findings to lower-limb amputees or other amputation contexts. Despite these limitations, this review offers valuable insights into the role of M1 in PLP and highlights directions for future research.

Conclusion

This systematic review highlights the involvement of the M1 in the pathophysiology of PLP, with fMRI studies demonstrating cortical reorganization that may correlate with pain persistence or response to therapy. These findings suggest that M1 could serve as a potential target for neuromodulatory interventions. However, M1 does not operate in isolation. Several studies also reported changes in regions such as SI, SMA, and temporal gyri, indicating that PLP is mediated by a distributed cortical and subcortical network. These broader findings warrant further integration into neurorehabilitation strategies.

Despite the progress in functional imaging, inconsistencies in study design, outcome measures, and imaging paradigms limit the comparability of existing findings. Future research should prioritize standardized imaging protocols, stratification by limb type (upper vs lower extremity), and control for key confounders such as prosthesis use, time since amputation, handedness, and pre-amputation pain history. Longitudinal studies with larger and more diverse populations will be essential to clarify causal mechanisms and support personalized therapeutic approaches. In addition, the inclusion of control groups in future studies would allow for direct comparison, thereby enhancing the interpretability and robustness of the results.

Neuroimaging continues to offer a valuable insight into the central mechanisms underlying PLP and has the potential to guide more targeted and effective treatments as evidence accumulates.

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