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Plasticity

The various forms of sensorimotor plasticity following limb amputation and their link with rehabilitation strategies

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INFO ARTICLE

Article history:
Received 2 June 2021
Received in revised form
6 September 2021
Accepted 21 September 2021
Available online 14 October 2021

Keywords:
Amputation
Sensorimotor plasticity
Sensorimotor deprivation
Use-dependent plasticity
Phantom limb pain.

ABSTRACT

Limb amputation is characterized by complex and intermingled brain reorganization processes combining sensorimotor deprivation induced by the loss of the limb per se, and compensatory behaviors, such as the over-use of the intact or remaining limb. While a large body of evidence documents sensorimotor representation plasticity following arm amputation, less investigations have been performed to fully understand the use-dependent plasticity phenomenon and the role of behavioral compensation in brain reorganization. In this article, I will review the findings on sensorimotor plasticity after limb amputation, focusing on these two aspects: sensorimotor deprivation and adaptive patterns of limb usage, and describe the models that attempt to link these reorganizational processes with phantom limb pain. Two main models have been proposed: the maladaptive plasticity model which states that the reorganization of the adjacent cortical territories into the representation of the missing limb is proportional to phantom pain intensity, and the persistent representation model, which rather suggests that the intensity of residual brain activity associated with phantom hand movements scales with phantom limb pain intensity. I will finally illustrate how this fundamental research helps designing new therapeutic strategies for phantom plain relief.

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https://doi.org/10.1016/j.neurol.2021.09.003

1. Introduction

Limb amputation results in a deprivation of sensory inputs to the primary somatosensory cortex (S1), and the loss of muscle targets for efferent fibres coming from the primary motor cortex (M1). Clinically, approximatively 80% of amputees report the presence of a phantom limb which corresponds to the persistence of sensory and motor perceptions in the amputated limb [1]. It includes different sensory modalities i.e., interoceptive, exteroceptive or proprioceptive, with characteristics such as shortening or referred sensations. Proprioceptive sensations include a general perception of size, shape and position of the phantom limb [2]. Patients also report the ability to evoke movements with their phantom limb. In patients who report a residual phantom limb, phantom limb pain (PLP) is present in up to 80% of them. PLP can be very disabling and is often resistant to most of the antalgic therapies [3].

Limb amputation is a very rich scientific model allowing researchers to question a multitude of important concepts, such as brain plasticity following sensorimotor deprivation or following compensatory motor behaviours. These reorganization processes can be studied in relationship with certain perceptive phenomena in particular phantom limb pain, giving rise to different models attempting to explain the development of phantom limb pain (e.g., the maladaptive plasticity model or the residual representation model). In this review paper, I will focus on the main central theories and neglect peripheral accounts such as the neuroma model which considers that PLP arise from spontaneous activity of residual limb injured axons [4]. We will examine how these central theories have paved the way to the development of therapeutic strategies, mostly targeting the sensorimotor cortex contralateral to the amputation.

2. The conceptual frameworks of post-amputation sensorimotor plasticity

Gross somatotopic organization is the hallmark of the primary somatosensory and motor cortex (S1 and M1). The idea that a cortical region is systematically organized to control movements of body parts was first conceptualized by Hughlings Jackson in the 1870s, who noticed sequential convulsive movements starting from one body part to the adjacent during seizures of epileptic patients. Then finer maps of body segments representations in M1 were progressively reported, until Penfield's homunculus [5]. Penfield and colleagues reported a relatively precise body-part map (somatotopy) along M1 and later on, along the postcentral gyrus (S1) by recording the verbal reports of awake patients [6].

Discrete boundaries between body parts can be found in S1, while M1 has not a systematic point-to-point mapping of control of different body parts along its mediolateral axis [7–9]. This can be explained by the highly complex dimensionality of the information processed in M1 to accomplish multi-joints movements for instance. Another feature of the sensorimotor maps is the ''functional instability of cortical motor points'', first observed by Leyton and Sherrington when trying to define cortical motor maps in monkeys [10]. They noticed that faradization, which consists in applying induced alternating electric current on a given point of motor cortex resulted in facilitation, reversal, or deviation of the movement evoked when stimulating the same point subsequently. This phenomenon of brain plasticity has been later defined as the ability of the brain to modify its connections or re-wire itself in response to experience and reported in the sensorimotor domain. Brain plasticity has been later reported in different contexts such as after sensory or motor training [11], immobilization [12], stroke [13] or amputation [14].

2.1. *Deprivation-triggered plasticity*

Early electrophysiology studies in monkeys identified extensive changes to the sensory maps' organization following amputation of a single digit [14], deafferentation of a nerve [15] or the entire arm [16]. Reorganization of the motor maps were initially studied in rats after amputation of a forelimb or the section of a motor nerve to the moveable vibrissa of the face. In these animals, electrical stimulation of locations that initially evoked movements of the forelimb or facial vibrissae, produced movements of adjacent remaining body parts [17]. Once neurons are deprived of their primary input, they become responsive to stimulation that activates the cortical neighbours of the deprived area. Reciprocally in the motor territories, neurons belonging to the deefferented cortex appear to activate muscles that control body parts proximal to the amputation. These phenomena are most likely driven by unmasking of already existing inputs, plus eventually some long-term potentiation-like mechanisms [18]. Then, inputs that already have access to the deprived cortex, especially topographic neighbours, are more likely to be expressed after amputation.

The development of non-invasive neuroimaging technics allowed the investigation of sensorimotor maps in humans using PET [19], MEG [20], task-based fMRI [21], functional resting-state or structural connectivity (e.g. DTI tractography) [Behrens et al., 2003]. Recent technological and analytical advances further enable multivariate investigations or cortical mapping at a millimeter scale resolution [22–25].

Studies in human amputees report an inter-hemispheric asymmetry of the face representation in M1 and S1 [26–28], and the majority also described that the resulting shift in the existing body segment boundaries, especially the face/lips area correlates with phantom limb pain [27–31]. This correlation supports the maladaptive plasticity model, which postulates that representations of body parts adjacent to the missing limb's representation expand and invade the deprived cortex, and that this ''invasion'' leads to phantom limb pain. This model is further supported by evidence that interventions that reduce phantom limb pain also reduce the inter-hemispheric asymmetry of the face representation [32–34]. Furthermore, similar findings have been reported in other models of neuropathic pain. For example, the cortical representations of both the digits and the lips appear to shift and shrink in unilateral upper-limb chronic regional pain syndrome type 1 (CRPS1) and the extent of their shift is correlated with pain intensity [35,36].

In a paper published in 2016, we found that the topological arrangement of the lip and elbow representations within the motor cortex were not symmetrical in the two hemispheres of upper-limb amputees [31] (Fig. 1). Furthermore, we found that reorganization of these body parts might partly be driven by PLP intensity but also by the ability to move the phantom limb. Interestingly, these factors did not equally influence the reorganization of both body part representations. This paper provides further support for the maladaptative plasticity model but also demonstrates that this reorganization is not limited to the face but extends to the medial part of the sensorimotor cortex, and that pain is not the only perceptual correlate of post-amputation reorganization.

The role of phantom limb motor control has been neglected in the past, but we made the assumption that it might instead be a key factor in driving/preventing brain reorganization. More generally, data from patients with movements disorders such as writer's cramp, motor stroke, cerebral palsy, or Parkinson's disease show that disorganized upper-limb representations are associated with decreased distal motor control [37,38]. Another piece of evidence comes from the efficacy of non-pharmacological antalgic therapies such as phantom limb training or mirror therapy that are based on phantom limb movements [39–41] (see section III.1). Finally, our finding of substantial activity in the deprived motor cortex during intact hand movements, which strongly correlates with the ability to move the phantom, suggests that the synergistic movement of the intact and phantom limbs during intact hand movements might help shape and reactivate the deprived cortex. This would in turn, facilitate voluntary

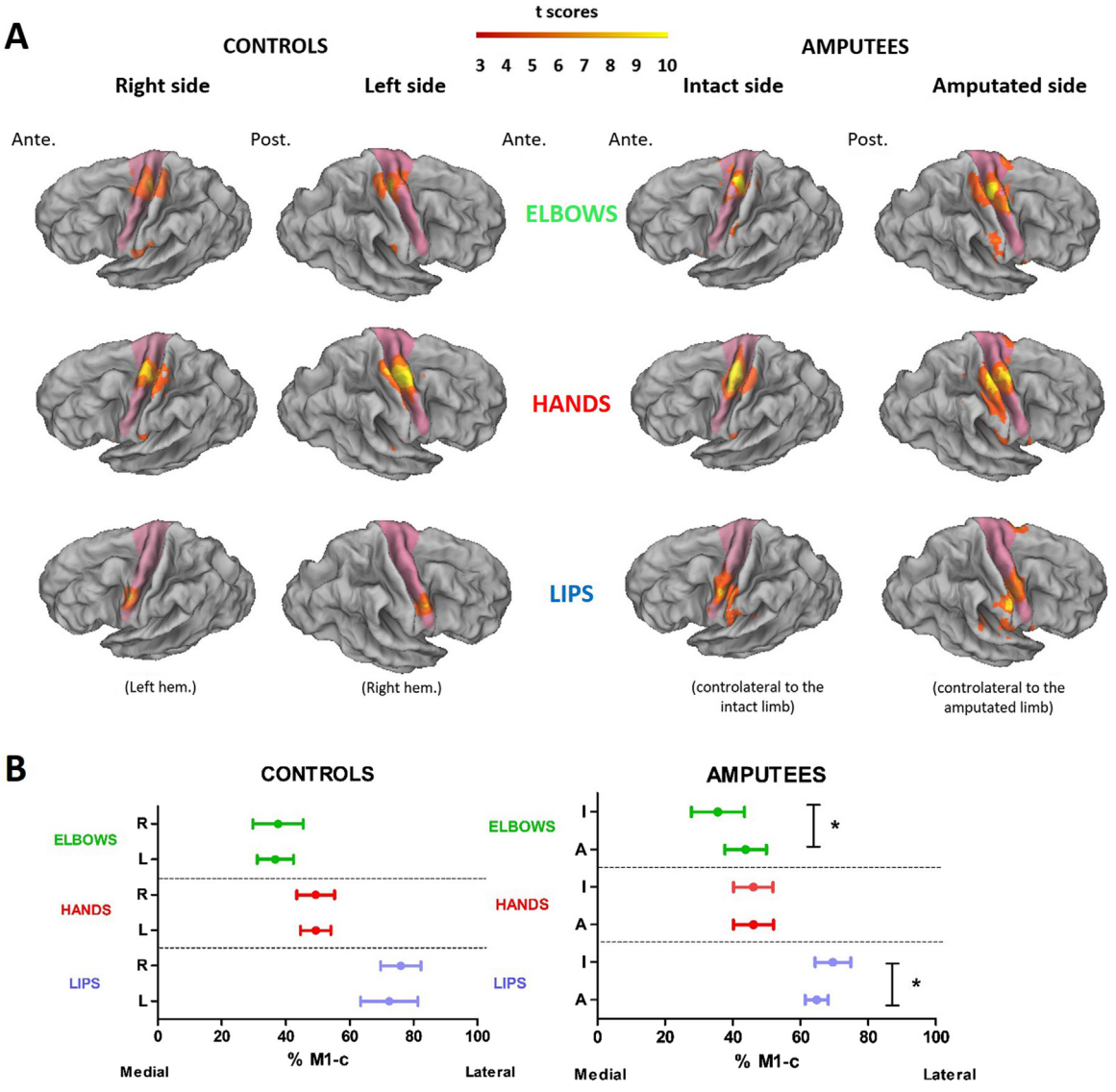

Fig. 1 – A. Group activation maps showing sensorimotor activity during elbows, hands and lips movements of a control group and a group of upper-limb amputees; B. Geodesic distance between the midline and the centre of gravities of the respective motor cortex clusters for the elbows, hands and lips from the hemisphere contralateral to the intact limb (I) and the amputated limb (A). In the amputated group, the elbows and lips representations were found to be asymmetrical (adapted from Raffin et al., 2016).

phantom hand movements, protect against reorganization of the motor cortex contralateral to the amputation, and thereby reduce phantom pain. This seems to be the case for S1 as well since amputees with greater self-report phantom kinaesthetic sensations were found to have better individuated digit representation in the contralateral S1 during fingers' movements of the phantom hand [42].

The original maladaptative plasticity model however assumes a ''take-over'' by other body parts rather than a ''cohabitation'' [43]. Indeed, for decades, this maladaptive plasticity model ignored the persistence of the missing limb's representation [44,45]. However, in a previous paper, we demonstrated that motor execution with both the phantom and intact limbs recruits brain areas typically activated during movement execution in healthy subjects, including the primary motor and sensory cortices, the SMA, the dorsal premotor cortex and the cerebellum [46,47]. These findings are consistent with previous amputee studies in which movements of the phantom limb activated a network similar to the one activated by contralateral intact limb movements [28,48,49]. Reilly and colleagues also demonstrated the engagement of the full motor pathways with measureable EMG activity from the denervated motor neurons [45]. More recently, multivariate analyses were applied to the activation induced by phantom limb movements in two amputees and similar representational features were identified as compared to a normal hand even decades after amputation [50].

The same team also found in their cohort of amputees that the activity elicited by phantom hand movements in the deprived sensorimotor cortex positively correlates with phantom limb pain, i.e., people who experience more chronic PLP also showed greater activity when moving their phantom hands [51,52]. On the basis of their structural and functional MRI data, Makin and colleagues proposed an alternative model: the persistent representation model [52]. This model postulates that persistent pain is associated with preserved structure and function in the former hand area rather than reorganization of neighbouring body parts [52].

The authors suggest that the mechanisms that maintain the missing hand representation in the sensorimotor cortex may also be relevant for PLP. Although there is still no convincing mechanistic interpretation supporting this model, this idea however finds some justification in a study where a single session of anodal transcranial direct current stimulation (a-tDCS) over the deprived sensorimotor cortex significantly relieved PLP, with effects lasting at least 1 week [53]. The antalgic effects were associated with reduced activity in the S1/M1 missing hand cortex after stimulation. The authors also report early activity changes in the mid- and posterior insula and secondary somatosensory cortex (S2).

Intuitively, these two models, i.e., the maladaptative plasticity and the persistent representation models, seem to be contradictory, but there are evidence showing that one does not exclude the other.

Interestingly, using computational modelling to simulate the self-organizing sensorimotor maps, Boström et al., showed that the amount of reorganization and the level of cortical activity during phantom movements were both enhanced with severe phantom pain [54]. Their results further yielded to a similar underlying mechanism, driven by an abnormally enhanced spontaneous activity of deafferented nociceptive channels, driven by a deafferentation-related disinhibition [55]. Muret and Makin lately suggested that if deprivation triggers remapping of the adjacent body parts through the unmasking of pre-existing latent activity, it might correspond to a latent form of activity along the homunculus, which in turn, elicits homeostatic regulations through the maintenance of the persistent representation of a missing hand [56]. They further suggest that since the activity of the latent connections was already present, remapping could somehow correspond to functional stability of the sensorimotor system rather than reorganisation. These ideas brings another concept of activity-dependent homeostatic plasticity of cortical circuits into play after the loss of a limb.

2.2. *Use-dependent plasticity*

The remapping demonstrated above might not only be driven by deprivation but also by increasing inputs from other body parts. Along these lines, the persistent representation model predicts that the intact hand activates the former hand area [57]. We then re-examined the ipsilateral motor cortex activity generated during hand movements. Our results revealed that 73% of amputees recruited the ipsilateral motor cortex when moving their phantom hand and 55% when moving their intact hand compared with only 18% in the control group [31]. Furthermore, among those subjects who activated their ipsilateral motor cortex, we found that the ipsilateral M1 activation clusters in amputees were larger than in controls when amputees moved either their intact or their amputated hand. Interestingly, 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 ($r = 0.87$, $P = 0.01$, Bonferroni-Sidak corrected) [31].

Multiple other studies have documented increased activity in the sensorimotor missing hand cortex for the intact hand [42,58–60]. Interestingly this ''abnormal'' ipsilateral activity appears to be activity dependent. Makin et al. showed that following acquired limb loss, individuals who intensively use their residual arm, show less activation during intact hand movements in the deprived cortex. Conversely, when they extensively rely on their intact hand, have a greater representation of their intact hand in the ipsilatateral cortex [60].

Complementarily, this activity seems to be performance-dependent as well: Precision drawing using the non-dominant intact hand has been found to be associated with increased recruitment of the ipsilateral former sensorimotor hand territory. This result suggests that ipsilateral hand territory may play a functional role in improved performance after chronic forced use of the non-dominant hand [59,61]. This is in line with studies reporting that left-handed people forced to switch from left-handed to right-handed writing in childhood, show greater bilateral engagement of parietal and premotor regions when writing with the non-dominant hand [62].

This series of findings reveal the potential importance of activity-dependent plasticity in maintaining the functional organization of the sensorimotor cortex when deprivation occurs in adulthood. It has been suggested that these plasticity mechanisms follow each other in time. The initial remapping

triggered by deprivation will be further refined by inputs due to alternative behavioural strategies that circumvent impairments to enable the performance of daily life activity by the intact body parts [26,63].

3. Plasticity outside the primary sensorimotor cortex

Extensive literature focused on post-amputation reorganization of the primary somatosensory or motor cortex, but little is known about reorganization outside these areas or at the network level. The primary somatosensory and motor cortex are interconnected with other primary sensory areas like the primary visual cortex, and with higher-order sensorimotor and association areas (e.g. premotor, parietal or prefrontal cortices), therefore these local topographical changes are likely to translate into cortical reorganization in remote interconnected areas. Additionally, there is a body and hand representation outside S1/M1 area. Some form of topographical representations of body parts have been found in numerous regions, for instance in the cerebellum, basal ganglia [64], operculum and insula [65], supplementary motor cortex [66], occipitotemporal cortex [67], parietal cortex [64,68]. One piece of evidence is the association between non-painful phantom sensations and frontal and parietal activity [69]. Moreover, it is likely that the brain circuits involved in chronic pain (e.g., the primary and secondary somatosensory cortex, anterior cingulate cortex (ACC), the prefrontal and orbitofrontal cortex or the Insula) or in emotional (e.g., the Amygdala), motivational (e.g., prefrontal cortex) and cognitive (posterior parietal cortex, ACC) processes are involved in phantom limb pain [55,70–72]. Interestingly, amputees with and without PLP can be dissociated by the absence of increase in grey matter in the visual cortex found in amputees without PLP [73]. Then, compensatory visual processing might occur in pain-free amputees.

The investigation of these non-primary sensorimotor regions is associated with other theoretical models of post-amputation reorganization and PLP. For instance, the neuromatrix model introduced by Melzack states that phantom limb pain originates from a mismatch between the unchanged body representation despite limb amputation, involving the thalamus and the limbic system [74]. An interesting recent contribution proposes a framework that unifies pain processing circuitry and phantom limb movements (The Stochastic Entanglement hypothesis) [75]. Finally, it is likely that sensorimotor cortical remapping also reflect changes in sub-cortical areas (e.g. brainstem, basal ganglia) or cerebellum [76].

Overall, all these studies also points towards the importance of considering multiple modalities (e.g., sensory versus motor assessment), the interaction between the two types of plasticity mentioned earlier (the deprivation- and use-dependent plasticity), the type of data analysis, contextual factors such as the body representation and psychological variables which will highly modulate the outcome of the measured plasticity and its relationship with PLP. This non-exhaustive review highlights the fact that there are existing and apparently contradicting theories that might not be mutually exclusive. All of them involve several intertwined potential mechanisms by which different types of therapies have been tested to alleviate PLP.

4. Clinical applications

The next section will focus on a few clinical interventions targeting sensorimotor plasticity as a mean of decreasing phantom limb pain.

4.1. *From phantom motor execution to myoelectric prosthesis*

There are converging evidence of a relationship between the ability to move the phantom limb and PLP [53,77,78]. Therefore, producing phantom movements by recruiting the appropriate central and peripheral circuits, ultimately resulting in muscular activation at the stump might have an antalgic effect by itself, besides improving phantom-mobility based prosthesis control [79]. One promising and innovative example involving the entire sensorimotor loop is the myoelectric decoding of motor volition at the stump, ensuring that movement execution is actually taking place. Muscular contraction is the ultimate physiological response to motor execution, and by decoding phantom motor volition from residual muscular activity at the stump, the authors ensure that the related central and peripheral circuitry is activated [80]. In their setup, these authors provide a visual feedback of the intended movement via virtual or augmented reality, while taking advantage of serious gaming to maintain subject engagement throughout the therapy [75,80].

An alternative option, when phantom limb execution is impossible to perform or in case of kinesiophobia is motor imagery. However, randomized controlled clinical trials demonstrated that motor imagery is ineffective [39,81,82]. Motor imagery is used currently in such a way as part of Graded Motor Imagery (GMI), a therapy model that consists in lateralization (right/left limb identification), motor imagery, and mirror therapy, with increasing task complexity [83]. Based on a few randomized and controlled trials [84], GMI has been found to be better than routine physiotherapy for reducing PLP. Based on the clinically meaningful reduction in PLP, and the ease of application, GMI might be a viable treatment for treating PLP. However, this treatment has only sparsely been implemented in clinical practice.

4.2. *Mirror therapy*

To facilitate motor sensations, patients suffering from phantom limb pain are sometimes offered a form of rehabilitation that involves visual feedback training in which they see modified visual feedback of their missing limb using either mirrors [39,85] or pre-recorded and flipped videos of movements of their intact hand [40,41]. During this training they are encouraged to move their phantom limb in synchrony with the movements they observe. Foell and colleagues showed that mirror training can effectively reactivate the former somatosensory representation and they demonstrated a clear relationship between PLP relief and the normalization

of the S1 organization, as evidenced by the degree of representational shift away from the missing hand area compared to the intact hemisphere [86]. These studies show that S1 changes and treatment-induced reductions in PLP covary, but the direction of the relationship, i.e. if the brain changes are a cause or consequence of the change in PLP cannot be determined from these studies. Studies that can assess causal relationships are needed. The restitution of the visual feedback is thought to be the main factor explaining its therapeutic effect [87] but there are conflicting evidence in this regard [39,88]. In clinical contexts, mirror therapy is considered today as the non-pharmacological treatment of choice, being simple, implementable at home, and very inexpensive. Although the level of evidence contributed by most studies could be improved, most of the clinical trials succeeded in decrease pain levels [89].

4.3. *Sensory stimulation*

On the somatosensory side, Flor et al. proposed a sensory discrimination training program focused on the stump [33]. Using eight electrodes positioned over the stump area, patients received ten daily 90 min sessions of feedback-guided sensory training, during which they had to discriminate the frequency and location of high intensity non-painful electric stimuli. They showed that training on spatial or frequency sensory discrimination increased perceptual ability in the stump and this was associated with reduced PLP. They also demonstrated a reversal of the cortical shift of the lip representation into the former hand area. However, it is important to note that the stump representation was not mapped, so no conclusion can be drawn on whether their finding could be attributed to an enlargement of the stump representation. The home-based version also appeared to provide significant pain relief [90]. The same team published later an extension of this approach that they called the multimodal sensory-motor training combining phantom motor execution enriched with sensory (tactile and visual) feedback of the moving phantom arm [91]. They obtained 30% reduction in PLP and importantly, greater consistency across non-painful phantom characteristics compared to mirror therapy. However, this approach was stopped due to the lack of strong clinical benefit.

4.4. *Non-invasive brain stimulation*

Several case studies have been published testing the effect of high/low frequency repeated transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) of the affected/unaffected M1 or S1, leading to a transient reduction in pain intensity [92,93]. Real or sham high-frequency rTMS was applied in M1 contralateral to the amputated leg in fifty-four patients with PLP, 20 minutes a day for 10 days [94]. The results show that the active rTMS condition induced a significantly greater pain reduction 15 days after the treatment compared to sham rTMS, but this effects failed down after 30 days.

Several clinical trials combined behavioural strategies (e.g., mirror therapy, [95]) with NIBS, but only a few have already been published. Using transcranial direct current stimulation (tDCS) to manipulate activity in the missing hand area, Kikkert et al., demonstrated successful PLP reduction after one single session of tDCS over the S1/M1 representation of the missing hand area [53]. This pain relief was associated with reduced phantom hand activity, in contrast to the studies on mirror treatment. Of note, these studies used different activation paradigms (active phantom movement versus mirrored movements) and the differences in activation changes might also be attributed to use-dependent changes related to the intact hand which is actively recruited during mirror training (see [96] for a discussion).

An alternative approach consists in altering nociceptive processing and pain perception with cerebellar transcranial direct current stimulation (ctDCS) [97]. This study showed that anodal ctDCS significantly reduced paradoxical pain as well as non-painful phantom limb sensations and phantom limb movements whereas PLP and stump pain did not change compared to the sham condition.

These NIBS approaches appear promising especially when combined with another behavioural or training strategy. However, there is insufficient evidence to determine the efficacy of rTMS for treating PLP, preventing a full clinical implementation. Therefore, further studies are needed to validate the effects of rTMS on pain relief.

5. Conclusion

This review highlights the existence of multiple types of sensorimotor plasticity taking place after the loss of a limb and different mechanisms driving those phenomenon. Their relationship with perceptual sensations emanating from the phantom limb are still poorly understood. The co-existence of central (either maladaptive or preserved reorganization) or peripheral origins of phantom limb pain point to the complexity of the phenomenon, but these accounts are not necessarily exclusive. Additionally, sensorimotor plasticity after amputation as described in this review might be associated with reorganization of nociceptive pathways, spatially and temporally correlating with different components of phantom limb pain. Amputees with phantom limb pain show also reduced activation in secondary somatosensory cortex, insula, orbitofrontal cortex, anterior cingulate cortex, or in the striatum. This complexity is further empirically evidenced by the beneficial effects of multimodal strategies which engage multiple behavioural and neural resources such as visual, proprioceptive feedbacks, haptic sensations and even more cognitive facets like reward or motivation.

Disclosure of interest

The author declares that she has no competing interest.

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