Phantom limb pain and bodily awareness: current concepts and future directions

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Purpose of review

Phantom pain is a frequent consequence of amputation or deafferentation. There are many possible contributing mechanisms, including stump-related pathology, spinal and cortical changes. Phantom limb pain is notoriously difficult to treat. Continued consideration of the factors associated with phantom pain and its treatment is of utmost importance, not only to advance the scientific knowledge about the experience of the body and neuropathic pain, but also fundamentally to promote efficacious pain management.

Recent findings

This review first discusses the mechanisms associated with phantom pain and summarizes the current treatments. The mechanisms underlying phantom pain primarily relate to peripheral/spinal dysfunction, and supraspinal and central plasticity in sensorimotor body representations. The most promising methods for managing phantom pain address the maladaptive changes at multiple levels of the neuraxis, for example, complementing pharmacological administration with physical, psychological or behavioural intervention. These supplementary techniques are even efficacious in isolation, perhaps by replacing the absent afferent signals from the amputated limb, thereby restoring disrupted bodily representations.

Summary

Ultimately, for optimal patient outcomes, treatments should be both symptom and mechanism targeted.

Keywords

behavioural therapy, neuropathic pain, treatment

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Introduction

Intuitively, one might predict that amputation, or complete denervation of a body part, would result in an instantaneous disembodiment of that part; however, this is seldom the case. Most patients continue to experience a phantom [1]. Phantom limbs are usually of a 'normal' size, shape and posture; however, about 20% of amputees experience a shortened or telescoped phantom [2•], and about 80% experience it as painful (regardless of the cause of amputation [3,4]), and/or occupying an abnormal or anatomically impossible posture [2•]. Impossible phantom limb configuration can even be experimentally induced through mental imagery of impossible movement trajectories in amputees [5].

The impact of phantom pain extends beyond the amputation and beyond the phantom itself. Phantom pain is frequently associated with disabling pain in the residual limb, the contralateral, nonamputated, limb, the neck and the back [6,7,8•]. Not surprisingly, psychosocial dysfunction is also common. In particular, when compared with amputees without phantom pain, those with phantom pain exhibit reduced physical and mental health-related quality of life [9], poorer adaptation to the limitations of amputation [10•], amplification of depression and anxiety in the first 3 years after surgery [11] (particularly in women [12•]) and maladaptive coping strategies; for example, pain-related catastrophizing [13,14]. This review will present the latest literature on the mechanisms underlying phantom pain and its treatment.

Mechanisms underlying phantom pain

Three principal mechanisms are associated with phantom pain: peripheral factors; spinal factors and central brain changes. Each of these factors can account for the frequent triggers of phantom phenomena, including physical triggers (e.g., referred sensations), psychological and emotional triggers (e.g., thinking about the amputation,

or others in pain) and weather-induced triggers (e.g., temperature or changes in weather) [10•]. The mechanisms associated with phantom pain will now be discussed.

Peripheral and spinal factors

The peripheral consequences of amputation are well established. Lesion to the peripheral nerves supplying a limb leads to structural and functional changes within the peripheral nerve and is often associated with the development of neuromata. Each of these changes has been studied for some time and the effect on sensory input is, in general, an increase in ectopic activity and a loss of inhibitory control at the dorsal horn [15–19]. Although there is little doubt that peripheral factors can contribute to phantom limb pain, there is also little doubt that they are not sufficient – indeed, their ubiquitous presence after amputation is clearly not always associated with pain. This review focuses on recent developments, the most relevant of which concern supraspinal and cortical changes associated with phantom limb pain.

Supraspinal and cortical changes

A fundamental property of biological systems is their capacity to adapt. There is extraordinary redundancy in the central nervous system (e.g., see [20]), enabling huge capacity for adaptation and reorganization. For example, in the primary sensory cortex (S1) representation of the left hand is larger in violinists than in non-violinists (i.e., more S1 cells are involved in representing the left hand of violinists, which affords smaller receptive fields and, therefore, greater sensory acuity) [21]. Phantom pain, however, corresponds to maladaptive reorganization of the thalamus [22] and body representations in somatosensory and motor cortices (see [23,24] for reviews), whereby neighbouring regions of sensorimotor homunculi overlap with representations of the missing limb. These neuroplastic changes involve both immediate loss of inhibitory inputs from one region to another, evident even during temporary regional anaesthesia [25•], and sprouting of new connections over longer periods of time [26,27]. Reorganization of body maps is evident in other maladaptive pain conditions, such as complex regional pain syndrome (CRPS) [28•,29], or following congenital limb aplasia in which there is a functional shift in the limbs that have formed (e.g., when the feet and toes are used for writing and gesturing [30]). Phenomenologically, plastic changes to body maps may correspond to the experience of referred sensations [10•], which can often be elicited by external stimulation, especially if the stimulated body part cannot be seen [31,32•]. This implicates that referred sensations are less frequent when the stimulation is reafferent (i.e., corresponding to sensory signals resulting, and predicted, from self-generated actions), or can be 'over-ridden' by visual input. The absence of valid visual and proprioceptive feedback to corroborate efference copy of motor commands targeting the phantom limb has been found to be associated with phantom pain [4,33–37] (see Fig. 1). The observation of sensorimotor and pain experiences in others, however, may be involved in generating and maintaining phantom limb phenomena, that is, via mirror neuron systems (MNS) [1], which are active during both first-hand and observed movement or sensory experiences [38•]. Such mirrored activity has a gating effect on the processing of somatosensory information arising from the observer's own body [39•,40•].

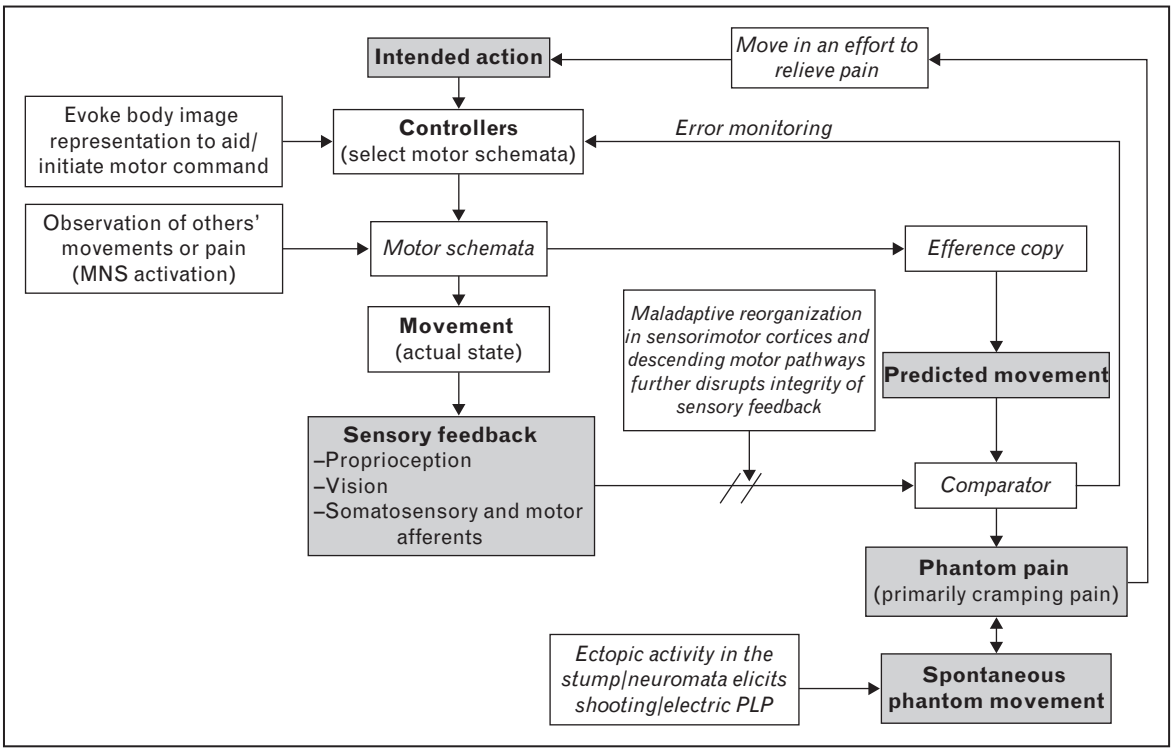
Key points

- Phantom pain fundamentally corresponds to central changes in homuncular body map reorganization.
- Although peripheral factors, including afferent input from neuromata and dorsal root ganglion, may contribute to these brain changes, targeted treatment of peripheral factors will only bring about long-term benefits if they are combined with treatments that target the maladaptive plasticity in the brain itself.
- Mirror neuron systems are implicated in the experience of maladaptive synaesthetic phantom pain, and may also underlie the beneficial pain reducing effects evident in the latest movement imagery studies.
- Many treatments to date have shown little benefit in pain reduction, particularly pharmacological treatments and invasive treatments involving surgery.
- Physical, psychological and behavioural treatments that replace or substitute the absent afferent signals from the amputated limb show the greatest promise for reducing phantom pain.

Disinhibition of mirror neuron systems and phantom limb phenomena

Phantom limb manifestation – particularly in people with congenital aplasia – is thought to partially arise through embodied action via MNS activation [1,30,41–44]; however, to date few studies have investigated this hypothesis. Adaptive involvement of MNSs have been implicated by the finding that observing another's hand being touched from a self-oriented perspective [45], or other-oriented perspective [46,47], can induce the experience of phantom touch or reduce phantom pain. Maladaptive involvement of MNSs is implicated in the experience of synaesthetic pain in amputees [48••,49]. Synaesthetic pain occurs when the observation or imagination of pain in another induces a similar somatosensory experience in the pain synaesthete. In amputee pain synaesthetes, this manifests in phantom pain being triggered by observing others in pain. Up to 16% of amputees [50•] and 30% of healthy individuals [51], experience

Figure 1 Model of phantom limb movement and phantom pain, based on an 'internal forward model' of movement whereby both efference copy of outgoing motor commands and afferent sensory signals estimate the current and immediate future state of the limb



Adapted with permission from [36,37].

acquired and congenital variants of synaesthesia for pain, respectively. There are a number of discrepancies between congenital and acquired synaesthesia for pain. Acquired pain synaesthetes typically report high-intensity pain in a presensitized body part that corresponds to prior pain qualities in that region, but without any significant relationship with empathy [50•,52••]. Acquired pain synaesthetes are hypervigilant to threatening stimuli, and exhibit cognitive inhibition when observing others in pain [53•], and, in addition to reporting synaesthetically triggered pain, execute spontaneous movements with the phantom in response to threat [52••]. Congenital pain synaesthetes, on the contrary, report synaesthetic pain in the same location as the observed injury, characterized by low-intensity sensory qualities. Like congenital synaesthesia for touch [54], congenital synaesthesia for pain is associated with heightened empathy [51]. Considering these disparate findings, it may be that synaesthesia for pain varies along a continuum with an adaptive congenital manifestation associated with heightened empathy, through to a maladaptive clinical presentation with disinhibition of pain MNSs following trauma and/or chronic pain.

A large number of treatments have been used to manage phantom pain, with limited success in most cases. The latest evidence suggests that unless the mechanisms underlying phantom pain are clarified and, in particular, identified within the presenting patient, phantom pain treatment will remain difficult [55]. Treatments of phantom pain will now be summarized.

Update on phantom pain treatment

There are two primary levels at which interventions most successfully manage phantom pain: symptom-specific pharmacological intervention and tailored psychological, physical and behavioural paradigms. Surgical intervention is sometimes attempted with varying levels of success, for example, targeted management of stump neuromata, which typically involves invasive surgical procedures or injections into nerve endings to desensitize pain conduction pathways [56,57]. However, the long-term efficacy of these procedures in managing neuromata [19,58], and reducing phantom pain [17], is questionable, particularly in amputees whose pain corresponds to central changes. Mechanism-based phantom pain treatments (also see [23] for a review) are as follows:

(1) surgical and pharmacological treatments:
    (a) surgical stump revision,
    (b) alter nerve endings (e.g., using silicone capsor transposing it into vein, muscle or bone),

(c) injections into nerve endings (e.g., with norepinephrine, lidocaine, local anaesthesia);
(2) surgical and pharmacological treatments:
(a) dorsal root entry zone lesions,
(b) dorsal column tractotomy,
(c) intrathecal fentanyl and/or epidural morphine,
(3) surgical treatments:
(a) stereotaxic lesions of thalamus and cortex;
(4) pharmacological treatments:
(a) conventional analgesics,
(b) tricyclic antidepressants (e.g., fluoxetine),
(c) antipsychotic neuroleptics (e.g., phenothiazines),
(d) anticonvulsants/relaxant (e.g., gabapentin, carbamazepine and clonazepam),
(e) opioids,
(f) muscle relaxants (e.g., botulin toxin),
(g) antiangina/antihypertensive medications (e.g., mexiletine, clonidine and propranolol),
(h) N-methyl D-aspartate receptor agonists (e.g., ketamine),
(i) calcitonin,
(j) capsaicin;
(5) psychological intervention:
(a) eye movement desensitisation and reprocess ing,
(b) cognitive–behavioural pain management,
(c) hypnosis;
(6) behavioural intervention
(a) mirror visual feedback,
(b) movement imagery training,
(c) prosthesis use and training;
(7) psychophysical, electrical and sensory stimulation:
(a) acupuncture,
(b) electromyographic biofeedback,
(c) sensory discrimination training,
(d) electrical stimulation: transcutaneous electrical nerve stimulation (TENS); caloric vestibular stimulation; spinal cord stimulation; deep brain stimulation; transcranial magnetic stimulation and electroconvulsive therapy,
(e) massage, vibration and manipulation,
(f) electromagnetic stump liner.

Pharmacological treatments

Preamputation pain is associated with increased phantom pain [59]. Although pre-emptive analgesia enables anaesthesiologists to control acute postoperative pain [7,60], it does not reduce the long-term incidence or modify the sensory qualities of phantom and stump pain [3,4,61••,62•,63•]. Indeed, preamputation opioids may even increase phantom pain [64]. Intense or long-lasting noxious input prior to amputation (e.g., from preamputation functional impairment, infection and surgery) does, however, appear to influence the incidence and characterization of somatosensory pain memories in the phantom [65].

Pharmacological agents that are frequently prescribed to treat phantom pain include tricyclic antidepressants, anticonvulsants and opioids. Agents such as N-methyl-D-aspartate receptor antagonists may also be prescribed to prevent or reverse cortical reorganization [17]. Other agents target the specific types of phantom pain, including antiangina/antihypertensive medications (e.g., nifedipine) to increase blood flow to the stump for burning pain; and muscle relaxants, botulin toxin [55], lidocaine [66] or phenol instillation of stump neuroma [19] for cramping phantom pain [17]. Although there seem to be several pharmacological targets for phantom pain, an earlier systematic review concluded that there was insufficient evidence to support the efficacy of any of them [67]. That said, new pharmacological approaches to all types of pain are being developed and may offer new opportunities, which should also be interrogated with the usual methods: randomized controlled trials. If phantom pain is indeed dependent on numerous pathological processes, including cortical changes, then physical, behavioural and psychological treatments might be helpful.

Physical, behavioural and psychological treatments

Most psychophysical interventions aim to normalize the cortical processes that are thought to underpin and/or contribute to phantom pain. These interventions can usually be integrated into a multimodal rehabilitation approach, potentially in conjunction with pharmacological or surgical strategies.

Electrical and sensory stimulation

Electrical stimulation has long been held to be effective for phantom pain (e.g., see [68]). However, as is often the case, most supportive data come from noncontrolled comparisons or single case studies, which limits the strength and generalizability of these findings (e.g., see a Cochrane review of TENS for phantom pain, which found only low-level evidence for its efficacy [69]). Positive results have been reported for TENS of the contralateral limb [70•] or ear [71]; caloric vestibular stimulation [72]; spinal cord stimulation [73]; deep brain stimulation [74]; transcranial magnetic stimulation [75]; electroconvulsive therapy [17,76]; and massage, manipulation, or vibration of the stump [77]; however, further rigorous studies into these techniques are required. One of the few treatments for which there is randomized-controlled-trial evidence is sensory discrimination training (i.e., learning to distinguish the location and frequency of sensory stimuli), which brings about significant reductions in phantom pain and, notably, correlated normalization of cortical reorganization [78,79]. Sensory discrimination training has also been shown to be effective in CRPS [80,81], which shares some important pathophysiological characteristics with phantom pain [82].

Psychological intervention

Phantom pain is frequently triggered by emotional factors [10•], and may be treated through cognitive behavioural therapy [83] or 'reprogramming' of pain memories related to amputation with eye movement desensitization and reprocessing (EMDR) [84–87,88•]; however, again, robust data are lacking.

Visual illusions

One of the most innovative techniques to be employed in phantom pain management involves restoration and manipulation of body representations using mirror visual feedback and immersive virtual reality (see [89] for a review). One randomized controlled trial showed significant treatment effects of mirror therapy [90]; however, there is limited systematic evidence [91], and the paradigm appears to be counterproductive during early rehabilitation [92]. Pre-existing body representations or maladaptive cortical reorganization may impede the efficacy of this therapy considering, in a once-off treatment, congenital amputees [93], and those with chronic phantom pain [94••] do not activate contralateral sensory and motor cortices during mirror visual therapy. Anecdotally, mirror therapy may restore 'normal' phantom limb perception or posture, for example, one patient was able to 'release' a metal bar that was felt to restrict phantom limb movement [95]. Responsiveness to the therapy seems to be heightened in patients whose pain has deep-tissue-mediated qualities (e.g., cramping) [96]. Together, these findings suggest that long-term patients with muscular-type phantom pain might benefit most from movement-based mirror therapy.

Manipulation of the mirror so that the 'virtual' limb looks smaller may have additional analgesic effects. In a recent study using a randomized repeated measures design, patients with CRPS moved their painful arm and watched it through magnifying or minimizing lenses [97]. When the arm appeared bigger, increases in pain and swelling were larger than if they watched it without distortion; however, if the arm appeared smaller, the increase in pain and swelling was smaller than if they watched it without distortion. Similar modulatory effects have been reported in a single amputee with phantom pain [98], but replication in larger studies is required. Indeed, exploring visual and other perceptual illusions as a means to modify cortical representations of different body parts is an exciting new area of enquiry and may, eventually, lead to new treatments (see [99•] for a relevant review).

Movement therapy

Although phantom limb movement can be associated with phantom limb pain [35], phantom movement therapy has been shown to reduce phantom pain [100•]. Mental imagery alone can modify the cortical map representing the amputated limb [5] and relieve pain in some amputees [101–103], but may exacerbate pain in other amputees [104], or in patients with CRPS [105,106], or spinal cord injury [107]. One approach that may get 'under the radar' of an overprotective pain system is to begin movement therapy with implicit motor imagery [108]. For example, when making judgements about whether a pictured limb belongs to the left or right side of the body, we subconsciously mentally rotate the corresponding body part to match that shown in the picture [109]. Following implicit motor imagery with imagined movements, and then mirror therapy, might have an added effect by activating MNSs to restore the efficacy and accuracy of sensory processing [100•], although neuroimaging studies are required to confirm this explanation. Therapeutic benefits have also been reported in patients with spinal cord injury performing a visual illusion task in which their paralysed lower body appears to be moving when in fact, the patient's own torso and upper limbs are superimposed onto a film of a walking model [110,111••].

Prosthesis use and embodiment

Upper-limb amputees who use functional or myoelectric prostheses experience more vivid phantom limb phenomena [112] and reduced phantom pain [3,113]. When amputees actively engage with the prosthetic limb, their innate sense of proprioception extends to embody the prosthesis [2•,114,115]. Amputees may even 'use the phantom' to control a prosthetic device [116]. However, sometimes the phantom feels as if it is too short, too large, or in an inconsistent posture for the prosthesis, which produces a conflict between perceived and actual limb experience [2•,117••]. Prosthesis embodiment is enhanced in amputees whose phantom is extended [2•] and corresponds to a sensory map on the stump [118]. Further, embodiment of a prosthetic limb in the rubber-hand-illusion paradigm is most profound in more recent amputees [119•], and when the prosthesis provides cutaneous feedback to the residual limb [120••]. Together, these findings indicate that prosthesis use brings about reduced levels of phantom pain when users experience prosthetic limb movement and touch that corresponds visually and functionally to representations of the limb and discharged motor output.

Conclusion

In summary, phantom pain emerges through altered afferent input from the affected limb and dorsal root ganglia, together with disrupted sensory processing and derangement of body representations at the supraspinal and cortical level. The numerous pathological contributions to phantom pain demands that different treatments should be considered, and be both symptom and mechanism based. Across therapeutic disciplines, the evidence-base for treating phantom pain is fragile.

Randomized controlled trials and systematic reviews are rare, and where they do exist, the conclusions are not encouraging. Recent progress includes the development of treatments that directly target cortical mechanisms which have been linked to phantom pain. The initial data for these treatments are encouraging, but limited. Robust multicentre randomized controlled trials are warranted.

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Conflicts of interest

None declared.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 594).

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