EXPERT
REVIEWS

Maladaptive plasticity, memory for pain and phantom limb pain: review and suggestions for new therapies

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A number of studies have shown that phantom limb pain is associated with plastic changes along the neuraxis, with a close correlation between changes in the cortical representation of the affected limb and phantom limb pain. Mechanisms underlying these maladaptive plastic changes are related to a loss of GABAergic inhibition, glutamate-mediated long-term potentiation-like changes and structural alterations such as axonal sprouting. These plastic changes and phantom limb pain seem to be more extensive when chronic pain precedes the amputation. Behavioral interventions, stimulation, feedback and pharmacological interventions that are designed to reverse these maladaptive memory traces and enhance extinction may be beneficial for the treatment and prevention of phantom limb pain.

Phantom limb pain or phantom pain is defined as pain felt in the place of a missing body part. It may be related to a certain position or movement of the phantom and may be elicited or exacerbated by a range of physical (e.g., changes in weather or pressure on the residual limb) and psychological factors (e.g., emotional stress). It seems to be more intense in the distal portions of the phantom and may have a number of different qualities such as stabbing, throbbing, burning or cramping. Phantom limb pain is often confused with pain in the area adjacent to the amputated body part. This phenomenon is referred to as residual limb pain or stump pain, and is usually positively correlated with phantom limb pain. In addition, post-amputation pain at the site of the wound must be distinguished from acute post-operative pain in the residual limb and phantom limb pain, which may all co-occur in the early phase after amputation and may contribute to later (chronic) phantom limb pain. It may also be useful to assess acute and chronic pre-amputation pain, which was found to be related to the incidence, type and severity of phantom limb pain in the phase following amputation. Phantom pain must be viewed in the context of nonpainful phantom sensation that involves phantom limb awareness as well as discrete phantom sensations, phantom limb movement and body perception, as well as body ownership in general [1]. Phantom limb pain is commonly classified as neuropathic pain and is assumed to be related to damage of central or peripheral neurons. Although phantom limb pain is more common after the amputation of an arm or leg, it may also occur after the surgical removal of other body parts, such as a breast, rectum, penis, testicles, eyes, tongue or teeth. Both peripheral and central factors have been discussed as determinants of phantom limb pain. Psychological factors do not seem to contribute to the etiology of the problem, but may rather affect the course and the severity of the pain. The general view today is that of multiple changes along the neuraxis contributing to the experience of phantom limb pain [2,3].

Cortical reorganization & phantom limb pain

Neuroscientific evidence has shown that the adult cortex is malleable and that it adapts to injury and environmental challenges [4]. As a

10.1586/14737175.8.5.809 © 2008 Expert Reviews Ltd ISSN 1473-7175

consequence of limb amputation input from cortical representation areas adjacent to the representation of the amputation zone can activate the region which lost its input. The potential functional significance of these changes for the understanding of phantom phenomena was pointed out by Ramachandran *et al.* who reported that they could elicit phantom sensation in the amputated arm when they used tactile stimulation on the face in persons with upper extremity amputations [5]. They found a point-to-point correspondence between stimulation sites on the face and perceived phantom sensations, and also reported that the sensations were modality-specific. Ramachandran *et al.* proposed that the reorganizational changes in somatosensory cortex might be the neural substrate of these 'referred sensations' and termed the phenomenon 'facial remapping'. To assess the functional significance of this type of cortical reorganization in more detail, Flor *et al.* used neuromagnetic source imaging combined with a comprehensive assessment of painful and nonpainful phantom phenomena, and referred sensation in persons with unilateral upper limb amputations [6]. Consistent with previous results, they found a significant medial and superior shift of the mouth representation towards the former hand representation in the primary somatosensory cortex (S1) contralateral to the amputation, but only the subjects with painful and not those with nonpainful phantom phenomena showed cortical reorganization. The persons with nonpainful phantoms were not significantly different in their cortical reorganization from the healthy controls, suggesting a unique relationship of phantom limb pain and cortical reorganization. This result was replicated in several subsequent studies for both the primary somatosensory

and the motor cortex [7]. FIGURE 1 illustrates the reorganization assessed in primary somatosensory and motor cortex related to lip movement using functional MRI.

It has not yet been clarified to what extent these maladaptive plastic changes in the CNS are a cause, a consequence or an epiphenomenon of phantom limb pain, since painful input itself alters the cortical map [8]. In addition to changes in primary somatosensory and motor cortex, phantom limb pain is related to changes in areas involved in the affective processing of pain. For example, Willoch *et al.* used hypnosis to induce painful phantom sensations and observed activation in brain areas, such as the insula and the anterior cingulate cortex [9], regions that have been identified as important in the processing of affective pain components, thus confirming animal studies that had shown alterations and disinhibition in anterior cingulate cortex [10]. Finally, a generally increased excitability of many brain areas has been found in phantom limb pain, which may enhance map reorganization [11]. Although plastic changes have mainly been documented in cortical areas, similar changes occur on all levels of the neuraxis, including the spinal cord, the brain stem and the thalamus [3]. In addition, peripheral changes can greatly influence the plastic alterations in the cortex. For example, Birbaumer *et al.* used peripheral anesthesia to eliminate all sensory input to S1 and studied the effects of this procedure on the map in S1 and on phantom limb pain [12]. Brachial plexus anesthesia completely eliminated cortical reorganization and phantom limb pain in 50% of the people with amputations; in the remaining half both cortical reorganization and phantom limb pain remained unchanged. This result suggests that in some people with amputations, cortical reorganization and phantom limb pain may be maintained by peripheral input, whereas in others central, possibly intracortical changes or changes in the dorsal root ganglion may be more important.
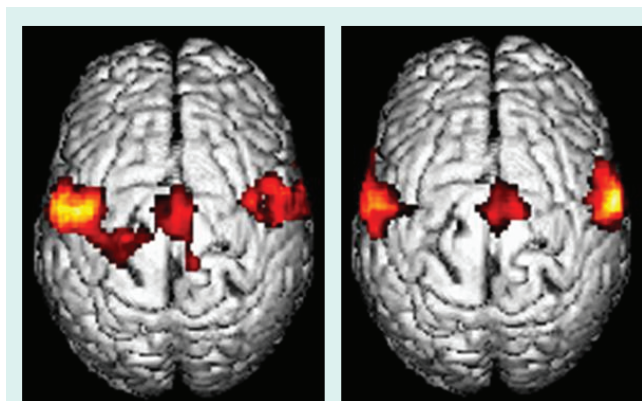

Figure 1. Reorganization in primary somatosensory and motor cortex in a group of people with unilateral upper limb amputation and phantom limb pain (left), and persons after amputation of one arm without phantom limb pain (right). The participants had the task to puck their lips at a metronome paced speed while functional MRI were taken. Note that only in people with actions and phantom limb pain a shift of the cortical mouth representation into the hand representation has occurred, whereas the people with amputation and without pain do not display a similar shift.

Mechanisms of maladaptive brain plasticity

Increased activity of peripheral nociceptors (e.g., due to an amputation-related transsection of nerves) leads to an enduring change in the synaptic structure of the dorsal horn in the spinal cord and supraspinal centers, a process called central sensitization [13]. Central sensitization is characterized by increased excitability of neurons, the reduction of inhibitory processes and structural changes at the central nerve endings of the primary sensory neurons, the interneurons and the projection neurons. This central sensitization is mediated by the NMDA receptor and its transmitter glutamate. Animal studies suggest that the pronounced topographic changes that occur during the protracted phase of recovery after deafferentation depend in part on NMDA receptors, possibly due to Hebbian-like changes in synaptic strength [14]. A mechanism of special relevance to phantom phenomena may be the invasion of central representation zones where the deafferented limb was previously represented. This process may be due to unmasking of previously silent connections or the sprouting of new connections,

and seems to be primarily a cortical phenomenon [15]. Thalamic stimulation and recordings in people with amputations have revealed that reorganizational changes also occur at the thalamic level, and are closely related to the perception of phantom limbs and phantom limb pain [16]. Studies in animals have shown that these changes can be relayed from the spinal and brain stem level [17], but changes on the subcortical levels may also originate in the cortex, which has strong efferent connections to the thalamus and lower structures [18]. Axonal sprouting as well as changes in dendritic arborization within the cortex were identified as other mechanisms underlying the reorganizational changes [19,20]. Structural changes have also been observed in people with amputations; however, their relationship to phantom limb pain is not clear [21]. GABA is the most important inhibitory neurotransmitter in the brain, and alterations in GABAergic inhibition can induce rapid changes in cortical excitability immediately after an amputation and can also influence lower brain centers [22,23]. In models of spinal cord injury Waxman and Hains reported a substantial calcium channel-mediated upregulation of activity in supraspinal pathways [24].

Memory for pain

Longstanding or intense acute pain in the limb prior to or during the amputation might lead to the establishment of a somatosensory pain memory. The original assumption of pain memory, as noted by Katz and Melzack [25], was based on findings that many people with amputations report phantom limb pain that is similar in both quality and location to pain experienced before the amputation. However, several articles have noted that these explicit memories of pre-amputation pain are rare and may be of less importance in chronic phantom limb pain [26]. Pain memories are, however, more likely implicit and not readily accessible to conscious recollection. The term 'implicit pain memory' refers to central changes related to nociceptive input, for example the somatosensory cortex, that lead to subsequent altered processing in the somatosensory system [27]. These alterations do not require changes in conscious processing of the pain experience, but are characterized by enduring physiological changes. In patients with chronic back pain, it was shown that increasing chronicity of pain is positively correlated with an enlargement of the representation zone of the back in primary somatosensory cortex [28]. These data suggest that long-lasting noxious input may lead to long-term changes at the central level and especially at the cortical level. It has long been known that the primary somatosensory cortex is involved in the processing of pain and that it may be important for the sensory-discriminative aspects of the pain experience [29]. If a somatosensory pain memory has been established, subsequent deafferentation and an invasion of the amputation zone by neighboring input may preferentially activate cortical neurons coding for pain. Since the cortical area coding input from the periphery seems to stay assigned to the original zone of input, the activation in the cortical zone representing the amputated limb is referred to the
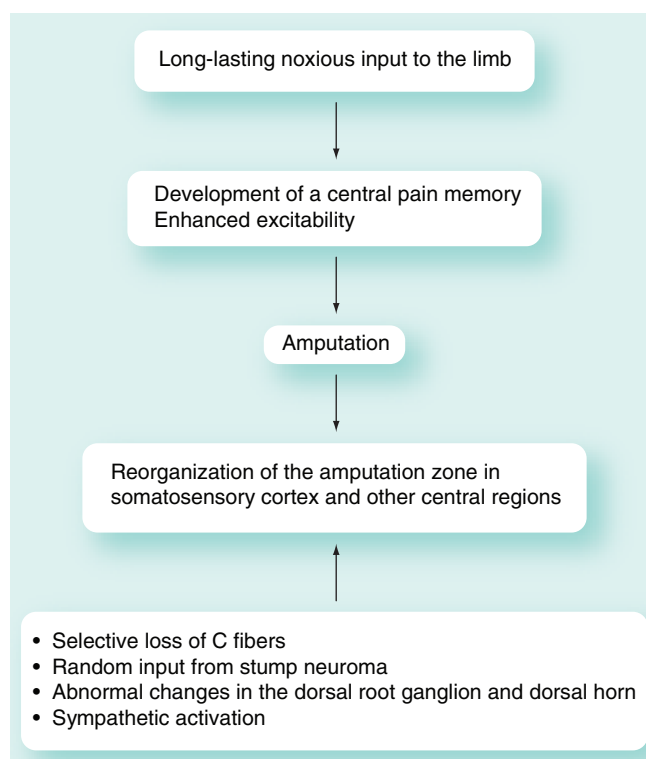

Figure 2. Schematic diagram incorporating the main factors thought to be relevant for the development of phantom limb pain.

phantom limb and the activation may be interpreted as phantom sensation and phantom limb pain [30]. FIGURE 2 illustrates these changes assumed to take place in patients with phantom limb pain. The fact that some patients develop phantom pain although they never experienced chronic pain before suggests that peritraumatic mechanisms and additional yet unknown mechanisms (e.g., genetic predisposition) may also contribute to phantom limb pain.

Current treatments for phantom limb pain

Several studies, including large surveys of people with amputations, have shown that most treatments for phantom limb pain are ineffective and fail to consider the mechanisms underlying the production of the pain [31,32]. Most studies are uncontrolled short-term assessments of small samples of phantom limb pain patients. The maximum benefit reported from a host of treatments (e.g., local anesthesia, sympathectomy, dorsal root entry zone lesions, cordotomy and rhizotomy, neurostimulation methods) or pharmacological interventions (such as anticonvulsants, barbiturates, antidepressants, neuroleptics and muscle relaxants) seems to be approximately 30%. This does not exceed the placebo effect reported in other studies. BOX 1 summarizes currently available treatments for phantom limb pain and indicates the extent to which controlled studies have been performed.

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Box 1. Commonly employed treatments for phantom limb pain.

Pharmacological

- Conventional analgesics
- Opioids +
- Calcitonin +
- β-blockers
- Neuroleptics
- Anticonvulsives
- Gabapentin + (-)
- Antidepressants
- Amitryptiline -
- Barbiturates
- Muscle relaxants

Surgical

- Stump revision
- Neurectomy
- Sympathectomy
- Rhizotomy
- Cordotomy
- Tractotomy
- Dorsal column stimulation
- Deep brain stimulation

Anesthesiological

- Nerve blocks
- Epidural blockade
- Sympathetic block
- Local anesthesia
- Lidocaine +

Psychological

- Electromyographic biofeedback
- Temperature biofeedback
- Cognitive-behavioral pain management
- Hypnosis

Other

- Transcutaneous electrical nerve stimulation +
- Acupuncture
- Physical therapy
- Ultrasound
- Manipulation
- Electromagnetic stump liner +

+: Denotes that at least one controlled study with a positive effect of phantom limb pain is available; -: Denotes that a controlled study with no effect on phantom pain is available.

Pharmacological interventions include a host of agents, and although tricyclic antidepressants and sodium channel blockers have been indicated as treatments of choice for neuropathic pain [32], there are only few controlled studies for phantom limb pain regarding these substances. For example, Robinson *et al.* found no support for the efficacy of amitriptyline in patients with phantom limb pain [33]. Controlled studies have also been performed for opioids [34] (e.g., calcitonin [35], ketamine [36], dextromethorphan [37] and gabapentin [e.g., [38], but see also [39]]), all of which were found to effectively reduce phantom limb pain. Memantine, also a NMDA receptor antagonist like ketamine was, however, not effective (e.g., [40]) although animal studies suggest that cortical reorganization can be prevented and reversed by the use of NMDA receptor antagonists or GABA agonists. In one controlled study, transcutaneous nerve stimulation yielded a small effect on phantom limb pain [41]. In addition, a recent study reported the effectiveness of an electromagnetically acting stump liner, although the mechanisms of this device are not clear [42].

Mechanism-based treatments are rare, but have been shown to be effective in a few small but mostly uncontrolled studies. Lidocaine was found to reduce phantom limb pain of patients with neuromas (e.g., [43]). Biofeedback treatments resulting in vasodilatation of the residual limb or decreased muscle tension in the residual limb help to reduce phantom limb pain and seem promising in patients where peripheral factors contribute to the pain (for review, see [44]).

Innovative treatments based on research on maladaptive memory & plasticity processes

Based on the findings from imaging studies, changes in cortical reorganization might be related to phantom limb pain. Thus, methods that influence central pain memories and neuroplasticity should also be effective in phantom limb pain. Animal work on stimulation-induced plasticity would suggest that extensive behaviorally relevant (but not passive) stimulation of a body part leads to an expansion of its representation zone and could counteract maladaptive plasticity. These changes could also be instigated by central stimulation. In addition, pharmacological agents that reduce deafferentation-induced hyperexcitability and prevent or reverse maladaptive plasticity and extinguish related memory changes might be useful.

Behaviorally relevant peripheral stimulation

Based on these assumptions, the use of a prosthesis that gives extensive feedback to the brain based on stimulation- and use-related brain activation might be useful. The easiest method to mimic input from the lost arm that might compete with input from adjacent areas is the use of a myoelectric prosthesis. This type of prosthesis is triggered by contractions of the remaining muscles in the residual limb. It enables the user to perform grasp movements and twists of the wrist as well as movements of the elbow joint. Lotze *et al.* showed that intensive use of such

a myoelectric prosthesis was positively correlated with both the reduction in phantom limb pain and cortical reorganization [45]. When cortical reorganization was controlled for, the relationship between prosthesis usage and reduced phantom limb pain was no longer significant, suggesting that cortical reorganization mediates this relationship. The converse, that increased phantom limb pain might have motivated patients to decrease prosthesis usage, is unlikely because no patient reported increased phantom limb pain due to prosthesis use or gave residual limb or phantom limb pain as a reason for discontinuing prosthesis usage. These data suggest that extended use of a myoelectric prosthesis – in contrast to the use of a cosmetic prosthesis or the non-use of prosthesis – might reduce both cortical reorganization and phantom limb pain. Similar effects were reported for the use of a Sauerbruch prosthesis [46]

An alternative approach in patients where prosthesis use is not feasible (e.g., because the residual limb is too short or the stump muscles are too weak) is the application of behaviorally relevant stimulation on an area that is close to the amputation line. The rationale behind this approach is again to provide the brain with afferent information conveyed by the same nerve fibers that supplied the now amputated limb and thus terminate within the cortical representation area of the amputated limb. Flor *et al.* used a 2-week treatment where the patients were trained to discriminate the frequency and location of two of eight possible stimuli to the residual limb [47]. The electrical stimulation that was provided was so intense that it elicited phantom sensation but was never painful. In the course of the training, the discriminability of the stimulus pairs (in terms of frequency and location) was reduced in a shaping procedure. The training comprised ten sessions in a 14-day period with each session lasting 90 min. Verbal and visual feedback was provided. The treatment led to a significant improvement on both frequency and location discrimination, which was also reflected in improved two-point discrimination. It resulted in a more than 60% reduction in phantom limb pain and a significant reversal of cortical reorganization, with a shift of the mouth representation back to its original location. The alterations in discrimination ability, pain and cortical reorganization were significantly positively correlated. A control group of patients who received standard medical treatment and general psychological counseling in this time period did not show similar changes in cortical reorganization and phantom limb pain. These finding were confirmed by a study that used a similar protocol with asynchronous tactile stimulation of the mouth and hand region [48].

Imagery, mirrors & virtual reality treatment

Ramachandran *et al.* who employed a mirror to train patients to move the phantom and reduce phantom limb pain described a cognitive approach [5]. A mirror was placed in a box and the patient inserted his or her intact arm and the arm with the phantom. The patient was then asked to look at the mirror image of the intact arm, which was perceived as an intact arm in the location where the amputated arm used to be. The patients were then asked to make symmetric movements with both the intact and the phantom hand thus suggesting real movement from the lost arm to the brain. This procedure seemed to re-establish control over the phantom and to reduce phantom limb pain in some patients. Extended mirror treatment was highly effective in reducing phantom limb pain in a controlled study, where it was compared with movement without a mirror and imagined movement [49]. However, another controlled study failed to yield specific effects of mirror treatment on phantom pain compared with movement of the intact hand and phantom without a mirror [50]; however, this study included only one trial and no extended training.

Moseley used a tripartite program for patients with complex regional pain syndrome [51]. This program contained a hand laterality recognition task (recognizing a pictured hand to be left or right), imagined movements of the affected hand and mirror therapy (adoption of the hand posture shown on a picture with both hands in a mirror box while watching the reflection of the unaffected hand). After 2 weeks of treatment, pain scores were significantly reduced and it was shown that this effect was not simply attention mediated. Significant effects on phantom limb pain were found in studies that used motor imagery [52,53]. This contradicts the results of Chan *et al.*, who observed no effect of this intervention [49]. However, an 8-week training program during which patients learned to match voluntary 'movements' of the phantom limb with prerecorded movements of a virtual hand revealed significant activation of the motor cortex contralateral to the amputated limb and concomitant decreases in phantom limb pain. These studies suggest that modification of input into the affected brain region by visual feedback and imagery alone may alter pain sensation and cortical plasticity. A virtual reality treatment that uses, for example, movement of the intact limb that is then fed back as movement from the phantom limb in virtual reality might also be a useful treatment option [54]. The contradictory results of some of these studies, however, suggest that the exact training parameters still need to be optimized.

Behavioral intervention

Patients who show high levels of pain behaviors and are very incapacitated by their pain should profit from operant behavioral treatment. The goals of this treatment are: the decrease of pain behaviors in an effort to extinguish pain; the increase of activity levels and healthy behaviors related to work, leisure time and the family; medication reduction and management; and the change of the behavior of significant others [55]. The overall goal is to reduce disability by reducing pain and increasing healthy behaviors. Medication is switched from a *pro re nata* basis to a fixed time schedule, where medication is given at certain times of the day to avoid negative reinforcement learning from occurring. Similar principles are applied to the enhancement of activity, and the reduction of inactivity and invalidity. This approach has been found to be effective in

patients with chronic back pain as well as other pain syndromes [56,57]. The cognitive–behavioral model of chronic pain emphasizes the role of cognitive, affective and behavioral factors in the development and maintenance of chronic pain. The central tenet of cognitive–behavioral treatment is to reduce feelings of helplessness and uncontrollability, and to establish a sense of control over pain in the patients. This is achieved by the modification of pain-eliciting and maintaining behaviors, cognitions and emotions. The cognitive–behavioral approach teaches patients various techniques to effectively deal with episodes of pain. Pain-related cognitions are changed by cognitive restructuring and pain coping strategies, such as attention diversion, use of imagery or relaxation that increase self efficacy. Several studies have examined the efficacy of cognitive-behavioral pain management, which must be considered as a very effective treatment of chronic pain [58]. Both operant and cognitive–behavioral therapy leads to a significant reduction in pain intensity. In addition the cognitive therapy improves cognitive and affective variables, whereas the operant therapy showed significant improvements in physical functioning and behavioral variables, maintained at both the 6- and 12-month follow-ups [57]. Behavioral treatments that focus on the extinction of pain behaviors and the acquisition of healthy behaviors can also alter brain processes related to pain. In anxiety disorders it has been shown that exposure with or without additional pharmacological intervention can alter brain processes related to stimuli that are relevant for the disorder [59]. Similar effects of behavioral interventions in chronic pain still need to be shown.

Central stimulation & brain computer interfaces

In some patients, modulation of cortical excitability to alleviate pain was achieved by electrical stimulation with electrodes implanted over the motor cortex [60]. Although positive results were reported with this method the risk for complications limits its use. More recently noninvasive techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), were proposed as suitable alternatives to achieve this goal. Both techniques have been applied in several hundred subjects (patients and healthy volunteers) worldwide and no significant side effects have been reported to date. For example, in a study by Lefaucher et al., the efficacy of TMS in 60 patients with drug-resistant intractable pain with variable characteristics of pain quality, location and level of sensory loss was assessed [61]. Patients treated with TMS showed significantly greater pain reduction as compared with sham (22 vs 7.8%). Although not all the patients improved with TMS the results are encouraging. For tDCS one controlled study showed positive effects on neuropathic pain after spinal cord injury [62].

If central and especially brain-related maladaptive plastic changes are at the core of phantom limb pain, then the direct modification of the activity of brain regions by brain computer interfaces would be desirable. Although not yet tested in controlled trials, experimental studies have shown that pain perception is altered by the feedback of EEG- or functional MRI-related indicators of the central processing of pain [63,64].

Pharmacological interventions & combined pharmacological & behavioral interventions

As mentioned above, plastic processes in the brain may be a consequence of NMDA receptor-mediated persistent upregulation of neural activity in the CNS following the transsection of peripheral nerves during the amputation. From this it follows that the addition of an NMDA receptor antagonist might reverse cortical reorganization in line with this phantom limb pain. In general, NMDA receptor antagonists been shown to reduce ongoing pain, allodynia, and pathologically decreased pain thresholds in experimental and clinical studies in humans. The partial NMDA receptor agonist D-cycloserine has been found to be effective in enhancing extinction of aversive memories and has been used as an effective adjunct to exposure treatment [65,66]. D-cycloserine has also been shown to reduce neuropathic pain by itself in an animal model of neuropathic pain [67]. In addition, cannabinoids have been identified as important modulators of extinction [68], and might be interesting additive compounds for extinction training. Since pain seem to generally increase excitability, substances that decrease excitation, such as gabapentin or pregabalin, would also seem indicated as enhancers of extinction. Since extinction is context-specific, training should include as many varied behaviors and environments as possible. The use of stress and pain episodes to train relapse prevention are important parts of this training. In addition, cognitive and emotional aspects of pain need to be targeted as outlined above. We have summarized the different approaches in Box 2.

Box 2. New treatment approaches designed to reverse maladaptive memory and plasticity processes.

- Operant behavioral treatment
- Cognitive–behavioral treatment
- Mirror treatment +
- Motor imagery +
- Prosthesis training
- Sensory discrimination +
- Transcranial magnetic stimulation or transcranial direct current stimulation +
- Brain computer interfaces
- NMDA receptor antagonists +
- GABA agonists
- Calcium channel modulators +
- NMDA receptor agonists (e.g. D-cycloserine)
- Cannabinoids

+: Denotes that at least one controlled study with a positive effect of phantom limb pain is available.

Prevention of phantom limb pain: new prospects

Obviously, instead of reversing long-term cortical reorganization and chronic phantom limb pain, it would be useful to prevent their onset or reverse them early on. For the prosthesis approach, this means that an early fitting and training with a myoelectric prosthesis would probably be of great value not only in the rehabilitation of people with amputations, but also in preventing or reversing phantom limb pain. Katz and Melzack emphasized that there are somatosensory pain memories that may be revived after an amputation and lead to phantom limb pain [25]. They have also noted that implicit and explicit memory components can be differentiated, both of which contribute to the experience of phantom limbs and phantom limb pain. They therefore suggested that both memory components need to be targeted in pre-emptive analgesic trials destined to prevent the onset of phantom limb pain; that is, that both general and spinal anesthesia are needed.

Pre-emptive analgesia refers to the attempt to prevent chronic pain by early intervention before acute pain occurs; for example, before and during surgery. Based on the data on sensitization of spinal neurons by afferent barrage, it has been suggested that general anesthesia should be complemented by peripheral anesthesia, thus preventing peripheral nociceptive input from reaching the spinal cord and higher centers. However, pre-emptive analgesia that included both general and spinal anesthesia has not consistently been efficacious in preventing the onset of phantom limb pain [69]. Whereas several studies reported a reduction of the incidence of phantom limb pain when additional epidural anesthesia was used in the pre- and postoperative stage, but some studies failed to find a beneficial effect on phantom limb pain [70]. A pre-existing pain memory that has already led to central and especially cortical changes would not necessarily be affected by a short-term elimination of afferent barrage. As shown by Hanley *et al.* pain before the amputation is predictive of later phantom pain [71]. Thus, it is possible that peripheral analgesia would eliminate new but not pre-existing central changes in the preoperative phase. Here, NMDA-antagonists as well as GABA agonists or calcium channel modulators might be beneficial to prevent both central reorganization and phantom limb pain. A study that used the NMDA receptor antagonist memantine versus placebo in addition to brachial plexus anesthesia in patients undergoing traumatic amputations of individual fingers or a hand found a reduction of phantom limb pain. However its long-term effects were not clear [72]. A study that used gabapentin in the postoperative phase found no significant preventive effect [73].

Expert commentary

The best treatment of phantom limb pain would be the elimination of pain before the amputation. In addition to analgesic medication, the use of pharmacological substances that interfere with the consolidation of aversive memories might be useful. Immediately after amputation additional measures should be taken that prevent adverse effects of previous central changes, or central changes related to the amputation and the postoperative phase. Early use of a myoelectric prosthesis possibly with sensory feedback in combination with virtual reality training and pharmacological intervention might be useful. Chronic phantom pain might best be eliminated by a combination of behavioral and pharmacological interventions.

Key issues

- Phantom limb pain is characterized by central changes that include map reorganization in the primary somatosensory cortex and main areas related to the affective processing of pain.
- The magnitude of the brain changes is correlated with the amount of phantom limb pain.
- An unmasking of normally inhibited connections that involved a lack of GABA, the increase of long-term potentiation through NMDA receptors, and axonal and dendritic sprouting are some of the processes involved in maladaptive plastic changes in phantom pain.
- Pre-existing chronic pain may contribute to the development of phantom limb pain by leading to an expansion of cortical maps and subsequently increased activation of pain-coding neurons.
- Peripheral factors may contribute to central changes and enhance map reorganization.
- Current treatments of phantom limb pain are of little effectiveness and do not address these changes.
- Behavioral and cognitive interventions, such as prosthesis training, mirror training, motor imagery, sensory discrimination training and virtual reality training, may effectively reverse phantom limb pin and maladaptive neuronal plasticity.
- Treatments that directly modify CNS activity, such as transcranial magnetic or transcranial direct current stimulation, or EEG- or functional MRI-based brain computer interfaces might also be effective.
- Pharmacological interventions that enhance extinction and prevent or abolish maladaptive plasticity include cannabinoids, NMDA receptor antagonists and agonists (depending on the time of the intervention), and GABA antagonists. Calcium channel modulators should also be efficacious.
- Preventive measures using NMDA receptor antagonists and calcium channel blockers in the pre- and/or postoperative phase have only had partial success.
- Studies are needed that examine these behavioral and pharmacological interventions systematically in trials that also employ neuroimaging measures to examine the outcome on maladaptive plastic changes.

Five-year view

The finding that central, and especially cortical changes, are important in the development and maintenance of phantom limb pain has led to a new focus on treatments that act at the central level. These include behaviorally relevant peripheral and central stimulation, behavioral interventions, cognitive methods as well as pharmacological agents that target plasticity and memory mechanisms, and enhance extinction. An especially beneficial effect might be related to the combination of behavioral and pharmacological methods because they combine the specificity of behavioral with the power of pharmacological interventions. The development of more powerful treatments for phantom limb pain needs controlled treatment outcome, prospective and double-blind placebo controlled outcome research that also examines the effects of treatments on the central level. Only then will effective evidence-based interventions be available.

References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

1   Giummarra MJ, Gibson SJ, Georgiou-Karistianis N, Bradshaw JL. Central mechanisms in phantom limb perception: the past, present and future. *Brain Res. Rev.* 54, 219–232 (2007).

2   Flor H, Nikolajsen L, Jensen TS. Phantom limb pain: a case of maladaptive CNS plasticity? *Nat. Rev. Neurosci.* 7, 873–881 (2006).

3   Nikolajsen LJ, Jensen TS. Phantom limb. In: *Wall and Melzack's Textbook of Pain* (5th Edition). Koltzenburg M, McMahon SB (Eds). Elsevier, Amsterdam, The Netherlands, 961–971 (2005).

••   **Comprehensive overview of factors that contribute to phantom limb pain as well as treatment options.**

4   Pascual-Leone A, Amedi A, Fregni F, Merabet LB. The plastic human brain cortex. *Annu. Rev. Neurosci.* 28, 377–405 (2005).

5   Ramachandran VS, Rogers-Ramachandran D. Synaesthesia in phantom limbs induced with mirrors. *Proc. R. Soc. Lond. B Biol. Sci.* 263, 377–386 (1992).

6   Flor H, Elbert T, Knecht S *et al.* Phantom limb pain as a perceptual correlate of massive cortical reorganization in upper extremity amputees. *Nature* 357, 482–484 (1995).

•   **First study that showed a close association between cortical plasticity and phantom limb pain.**

7   Lotze M, Flor H, Grodd W, Larbig W, Birbaumer N. Phantom movements and pain: an fMRI study in upper limb amputees. *Brain* 124, 2268–2277 (2001).

8   Soros P, Knecht S, Bantel C, Imai T, Wusten R, Pantev C. Functional reorganization of the human primary somatosensory cortex after acute pain demonstrated by magnetoencephalography. *Neurosci. Lett.* 298, 195–198 (2001).

9   Willoch F, Rosen G, Tolle TR *et al.* Phantom limb pain in the human brain: unraveling neural circuitries of phantom limb sensations using positron emission tomography. *Ann. Neurol.* 48, 842–849 (2000).

10   Wei F, Zhuo M. Potentiation of sensory responses in the anterior cingulate cortex following digit amputation in the anaesthetised rat. *J. Physiol.* 532, 823–833 (2001).

•   **This study showed for the first time that areas involved in affective processing are involved in post-deafferentation changes.**

11   Karl A, Diers M, Flor H. P300-amplitudes in upper limb amputees with and without phantom limb pain in a visual oddball paradigm. *Pain* 110, 40–48 (2004).

12   Birbaumer N, Lutzenberger W, Montoya P *et al.* Effects of regional anesthesia on phantom limb pain are mirrored in changes in cortical reorganization. *J. Neurosci.* 17, 5503–5508 (1997).

13   Woolf CJ, Salter MW. State dependent plasticity. In: *Wall and Melzack's Textbook of Pain* (5th Edition). Koltzenburg M, McMahon SB (Eds). Elsevier, Amsterdam, The Netherlands, 91–105 (2005).

••   **Excellent review of pain-related central changes.**

14   Myers WA, Churchill JD, Muja N *et al.* Role of NMDA receptors in adult primate cortical somatosensory plasticity. *J. Comp. Neurol.* 418, 373–382 (2000).

15   Churchill JD, Garraghty PE. The influence of post-nerve injury survival duration on receptive field size: location, location, location. *Neurosci. Lett.* 405, 10–13 (2006).

16   Davis KD, Kiss ZH, Luo L, Tasker RR, Lozano AM, Dostrovsky JO. Phantom sensations generated by thalamic microstimulation. *Nature* 391, 385–387 (1998).

17   Florence SL, Kaas JH. Large-scale reorganization at multiple levels of the somatosensory pathway follows therapeutic amputation of the hand in monkeys. *J. Neurosci.* 12, 8083–8095 (1995).

18   Ergenzinger ER, Glasier MM, Hahm JO, Pons TP. Cortically induced thalamic plasticity in the primate somatosensory system. *Nat. Neurosci.* 1, 226–229 (1998).

19   Churchill JD, Tharp JA, Wellman CL, Sengelaub DR, Garraghty PE. Morphological correlates of injury-induced reorganization in primate somatosensory cortex. *BMC Neurosci.* 5, 43 (2004).

20   Florence SL, Taub HB, Kaas JH. Large-scale sprouting of cortical connections after peripheral injury in adult macaque monkeys. *Science* 282, 1117–1121 (1998).

21   Draganski B, Moser T, Lummel N *et al.* Decrease of thalamic gray matter following limb amputation. *Neuroimage* 31, 951–957 (2006).

22   Monconduit L, Lopez-Avila A, Molat JL *et al.* Corticofugal output from the primary somatosensory cortex selectively modulates innocuous and noxious inputs in the rat spinothalamic system. *J. Neurosci.* 26, 8441–8450 (2006).

23   Chowdhury SA, Rasmusson DD. Corticocortical inhibition of peripheral inputs within primary somatosensory cortex: the role of $GABA_A$ and $GABA_B$ receptors. *J. Neurophysiol.* 90, 851–856 (2003).

24 Waxman SG, Hains BC. Fire and phantoms after spinal cord injury: Na+ channels and central pain. *Trends Neurosci.* 29, 207–215 (2006).

• **Review of calcium channels and pain.**

25 Katz J, Melzack R. Pain 'memories' in phantom limbs: review and clinical observations. *Pain* 43, 319–336 (1990).

26 Nikolajsen L, Ilkjaer S, Kroner K, Christensen JH, Jensen TS. The influence of preamputation pain on postamputation stump and phantom pain. *Pain* 72, 393–405 (1997).

27 Diesch E, Flor H. Alteration in the response properties of primary somatosensory cortex related to differential aversive Pavlovian conditioning. *Pain* 131(1–2), 171–180 (2007).

28 Flor H, Braun C, Elbert T *et al.* Extensive reorganization of primary somatosensory cortex in chronic back pain patients. *Neurosci. Lett.* 224, 5–8 (1997).

29 Hofbauer RK, Rainville P, Duncan GH, Bushnell MC. Cortical representation of the sensory dimension of pain. *J. Neurophysiol.* 86, 402–411 (2001).

30 Flor H. Phantom-limb pain: characteristics, causes, and treatment. *Lancet Neurol.* 1, 182–189 (2002).

31 Finnerup NB, Sindrup SH, Jensen TS. Chronic neuropathic pain: mechanisms, drug targets and measurement. *Fundam. Clin. Pharmacol.* 21, 129–136 (2007).

•• **State-of-the-art evaluation of treatments of neuropathic pain and new developments.**

32 Moulin DE, Clark AJ, Gilron I *et al.* Pharmacological management of chronic neuropathic pain – consensus statement and guidelines from the Canadian Pain Society. *Pain Res. Manag.* 12, 13–21 (2007).

33 Robinson LR, Czerniecki JM, Ehde DM *et al.* Trial of amitriptyline for relief of pain in amputees: results of a randomized controlled study. *Arch. Phys. Med. Rehabil.* 85, 1–6 (2004).

34 Huse E, Larbig W, Flor H, Birbaumer N. The effect of opioids on phantom limb pain and cortical reorganization. *Pain* 90, 47–55 (2001).

35 Jaeger H, Maier C. Calcitonin in phantom limb pain: a double-blind study. *Pain* 48, 21–27 (1992).

36 Nikolajsen L, Hansen CL, Nielsen J, Keller J, Arendt-Nielsen L, Jensen TS. The effect of ketamine on phantom pain: a central neuropathic disorder maintained by peripheral input. *Pain* 67, 69–77 (1996).

37 Ben Abraham R, Marouani N, Weinbroum AA. Dextromethorphan mitigates phantom pain in cancer amputees. *Ann. Surg. Oncol.* 10, 268–274 (2003).

38 Bone M, Critchley P, Buggy DJ. Gabapentin in postamputation phantom limb pain: a randomized, double-blind, placebo-controlled, cross-over study. *Reg. Anesth. Pain. Med.* 27, 481–486 (2002).

39 Smith DG, Ehde DM, Hanley MA *et al.* Efficacy of gabapentin in treating chronic phantom limb and residual limb pain. *J. Rehabil. Res. Dev.* 42, 645–654 (2005).

40 Maier C, Dertwinkel R, Mansourian N *et al.* Efficacy of the NMDA-receptor antagonist memantine in patients with chronic phantom limb pain – results of a randomized double-blinded, placebo-controlled trial. *Pain* 103, 277–283 (2003).

41 Katz J, Melzack R. Auricular transcutaneous electrical nerve stimulation (TENS) reduces phantom limb pain. *J. Pain. Sympt. Manage.* 6, 73–83 (1991).

42 Kern U, Altkemper B, Kohl M. Management of phantom pain with a textile, electromagnetically-acting stump liner: a randomized, double-blind, crossover study. *J. Pain. Symptom. Manage.* 32, 352–360 (2006).

43 Chabal C, Jacobson L, Russell LC, Burchiel KJ. Pain response to perineuromal injection of normal saline, epinephrine, and lidocaine in humans. *Pain* 49, 9–12 (1992).

44 Sherman RA. (1997). *Phantom Limb Pain.* Plenum Press, New York, USA.

45 Lotze M, Grodd W, Birbaumer N, Erb M, Huse E, Flor H. Does use of a myoelectric prosthesis prevent cortical reorganization and phantom limb pain? *Nat. Neurosci.* 2, 501–502 (1999).

46 Weiss T, Miltner WH, Adler T, Bruckner L, Taub E. Decrease in phantom limb pain associated with prosthesis-induced increased use of an amputation stump in humans. *Neurosci Lett.* 272, 131–134 (1999).

47 Flor H, Denke C, Schaefer M *et al.* Effect of sensory discrimination training on cortical reorganisation and phantom limp pain. *Lancet* 375, 1763–1764 (2001).

• **This study shows that sensor discrimination training reduces both phantom limb pain and cortical reorganization.**

48 Huse E, Preissl H, Larbig W, Birbaumer N. Phantom limb pain. *Lancet* 358, 1015 (2001).

49 Chan BL, Witt R, Charrow AP *et al.* Mirror therapy for phantom limb pain. *N Engl J Med.* 357, 2206–2297 (2007).

50 Brodie EE, Whyte A, Niven CA. Analgesia through the looking-glass? A randomized controlled trial investigating the effect of viewing a 'virtual' limb upon phantom limb pain, sensation and movement. *Eur. J. Pain* 11, 428–436 (2007).

51 Moseley GL. Graded motor imagery is effective for long-standing complex regional pain syndrome: a randomised controlled trial. *Pain* 108, 192–198 (2004).

52 Moseley G L. Graded motor imagery for pathologic pain: a randomized controlled trial. *Neurology* 67, 2129–2134 (2006).

• **Shows the specific effects of motor imagery on pain.**

53 Giraux P, Sirigu A. Illusory movements of the paralyzed limb restore motor cortex activity. *Neuroimage* 20, 107–111 (2003).

54 Murray CD, Patchick E, Pettifer S, Caillette F, Howard T. Immersive virtual reality as a rehabilitative technology for phantom limb experience: a protocol. *Cyberpsychol. Behav.* 9, 167–170 (2006).

55 Fordyce WE. *Behavioral Concepts in Chronic Pain Illness.* Mosby, MO, USA (1976).

•• **The standard source on behavioral intervention in chronic pain.**

56 Thieme K, Gromnica-Ihle E, Flor H. Operant behavioral treatment of fibromyalgia: a controlled study. *Arthritis Rheum.* 49, 314–320 (2003)

57 Thieme K, Flor H, Turk DC. Psychological pain treatment in fibromyalgia syndrome: efficacy of operant behavioural and cognitive behavioural treatments. *Arthritis Res. Ther.* 8, R121 (2006).

58 Hoffman BM, Papas RK, Chatkoff DK, Kerns RD. Meta-analysis of psychological interventions for chronic low back pain. *Health Psychol.* 26, 1–9 (2007).

59 Paquette V, Levesque J, Mensour B *et al.* "Change the mind and you change the brain": effects of cognitive-behavioral therapy on the neural correlates of spider phobia. *Neuroimage* 18, 401–409 (2003).

60 Nguyen JP, Lefaucher JP, Le Guerinel C *et al.* Motor cortex stimulation in the treatment of central and neuropathic pain. *Arch. Med. Research* 31, 263–265 (2000).

61 Lefaucheur JP, Drouout X, Menard-Lefaucher I *et al.* Neurogenic pain relief by repetitive transcranial magnetic cortical stimulation depends on the origin and the site of pain. *J. Neurol. Neurosurg. Psychiatry.* 75, 612–616 (2004).

62   Fregni F, Boggio PS, Lima MC *et al.* A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. *Pain* 122, 197–209 (2006).

63   Lousberg R, Vuurman E, Lamers T *et al.* Pain report and pain-related evoked potentials operantly conditioned. *Clin. J. Pain.* 21, 262–271 (2005).

64   deCharms RC, Maeda F, Glover GH. Control over brain activation and pain learned by using real-time functional MRI. *Proc. Natl Acad. Sci. USA* 102, 18626–181631 (2005).

65   Ressler KJ, Rothbaum BO, Tannenbaum L *et al.* Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. *Arch. Gen. Psychiatry* 61, 1136–1144 (2004).

•   **First study that showed the additive effects of a cognitive enhancer on extinction training.**

66   Hofmann SG, Pollack MH, Otto MW. Augmentation treatment of psychotherapy for anxiety disorders with D-cycloserine. *CNS Drug Rev.* 12, 208–217 (2006).

67   Millecamps M, Centeno MV, Berra HH. D-cycloserine reduces neuropathic pain behavior through limbic NMDA-mediated circuitry. *Pain* 132(1–2), 108–123 (2007).

68   Marsicano G, Wotjak CT, Azad SC *et al.* The endogenous cannabinoid system controls extinction of aversive memories. *Nature* 418, 530–534 (2002).

69   Grape S, Tramer MR. Do we need preemptive analgesia for the treatment of postoperative pain? *Bes. Pract. Res. Clin. Anaesthesiol.* 21, 51–63 (2007).

70   Nikolajsen L, Ilkjaer S, Christensen JH, Kroner K, Jensen TS. Randomised trial of epidural bupivacaine and morphine in prevention of stump and phantom pain in lower-limb amputation. *Lancet* 350, 1353–1357 (1997).

••   **Widely cited study on the insignificant effects of pre-emptive analgesia on phantom limb pain.**

71   Hanley MA, Jensen MP, Smith DG, Ehde DM, Edwards WT, Robinson LR. Preamputation pain and acute pain predict chronic pain after lower extremity amputation. *J. Pain* 8, 102–109 (2007).

72   Schley M, Topfner S, Wiech K *et al.* Continuous brachial plexus blockade in combination with the NMDA receptor antagonist memantine prevents phantom pain in acute traumatic upper limb amputees. *Eur. J. Pain* 11, 299–308 (2007).

73   Nikolajsen L, Finnerup NB, Kramp S, Vimtrup AS, Keller J, Jensen TS. A randomized study of the effects of gabapentin on postamputation pain. *Anesthesiology* 105, 1008–1015 (2006).

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