New developments in the understanding and management of persistent pain

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Purpose of review
It is proposed that central rather than peripheral factors may be important in pain chronicity. We review recent empirical findings on these processes and discuss implications for treatment and prevention.

Recent findings
The literature on neuroimaging of pain and on learning processes shows that learning-induced functional and structural brain changes involving sensorimotor, as well as limbic and frontal, areas are important in the transition from acute to chronic pain. These alterations share many similarities with brain changes in emotional disorders and the specificity for pain needs to be determined. Further important contributors to chronic pain may be disturbed processing of the body image, impaired multisensory integration and faulty feedback from interoceptive processes. These findings have led to new treatment approaches that focus on the extinction of aversive memories, restoration of the body image and normal brain function and include approaches such as brain stimulation, mirror training, virtual reality applications or behavioral extinction training.

Summary
We propose that chronic pain is characterized by learning-related and memory-related plastic changes of the central nervous system with concomitant maladaptive changes in body perception. These alterations require new treatments that focus on the alteration of central pain memories and maladaptive body perception.

Keywords
body perception, brain plasticity, chronic pain, extinction, learning, memory

INTRODUCTION

Recent scientific evidence suggests that chronic pain is greatly determined by learning processes that are accompanied by plastic changes on multiple levels of the nervous system [1▪▪,2▪▪]. A fundamental distinction of memory mechanism is that of implicit or nondeclarative and explicit or declarative memory processes. Implicit memory processes refer to often nonconscious changes in behavior as a consequence of experience and involve nonassociative learning such as habituation and sensitization but also associative processes such as operant and respondent conditioning. Explicit learning usually refers to semantic and episodic memory processes that rely on the conscious reproduction of an encoded memory item. These memory processes also involve different brain structures and neuronal networks and may be differentially interacting in health and disease. For example, explicit memory depends on intact hippocampal structures, whereas some types of implicit emotional memory require an intact amygdala or striatum. Although both types of learning and memory processes are important in chronic pain, we have proposed that implicit learning processes may be more pronounced in chronic pain. As implicit learning processes change behavior without the person knowing about it, they may, therefore, be especially difficult to extinguish. We assume that the extinction or 'unlearning' rather

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KEY POINTS

- Learning and memory processes are important in pain chronicity.
- They lead to site-specific maladaptive structural and functional brain changes.
- These learning processes are accompanied by changes in body perception.
- Treatments must focus on the extinction of these maladaptive memory processes.

than the acquisition of pain memories is the main problem in chronic pain; central and peripheral memory traces are closely interwoven and lead to alterations in the body image; and treatment can be viewed as extinction and relearning and needs to be provided on the basis of learning principles.

LEARNING PROCESSES IN CHRONIC PAIN

Implicit learning processes involve sensitization, operant and respondent conditioning, as well as priming and social learning. Sensitization refers to a nonassociative learning process wherein the repeated or extended application of a stimulus leads to an increased response that can be described on the physiological level, usually referred to as 'central sensitization', or the psychological level, usually referred to as 'perceptual sensitization'. Its counterpart is the process of habituation, wherein repeated stimulation leads to a reduction of the response to the stimulus, which can also be described on the physiological or behavioral level.

In a number of chronic pain syndromes, perceptual sensitization has been observed, which is also accompanied by enhanced activation in the central nervous system. For example, in patients with fibromyalgia syndrome or patients with chronic back pain, enhanced perception of tonic painful stimuli or repetitive painful stimulation has been observed [3▪].

Operant conditioning is another mainly implicit learning mechanism that can lead to chronicity. The operant view proposes that acute 'pain behavior' such as limping may come under the control of external contingencies of reinforcement and thus develop into a chronic pain problem. Pain behavior may be directly positively reinforced, maintained by the escape from noxious stimulation or deficient reinforcement of 'well behavior' (e.g. activity, working). The pain behavior originally elicited by somatic factors may thus come to occur, totally or in part, in response to reinforcing environmental events. Not only observable pain behaviors but also verbal expressions of pain and physiological variables may come under the control of the contingencies of reinforcement. Becker *et al.* [4▪▪] showed that increases or decreases of pain perception can serve as implicit reinforcers and that this operant conditioning of sensitization or habituation is differentially altered in patients with fibromyalgia with or without irritable bowel syndrome.

As the experience of pain is a very important biological stimulus, it is immediately evident that respondent (Pavlovian) conditioning might play an important role when pain is repeatedly experienced, as is the case in the transition from acute to chronic pain. In the typical classical conditioning paradigm, a previously neutral variable (later the conditioned stimulus), when paired with a biologically significant stimulus (unconditioned stimulus), comes to elicit a conditioned response that resembles the response to the unconditioned stimulus, the unconditioned response. For example, if a certain movement has been associated with pain, just thinking about the movement may already elicit fear and muscle tension (previously elicited by pain) and may then motivate avoidance behaviors. Once an acute pain problem exists, fear of motor activities that the patient expects to result in pain may develop and motivate avoidance of activity. Nonoccurrence of pain is a powerful reinforcer for reduction of activity and thus the original respondent conditioning may be followed by an operant learning process, whereby the nociceptive stimuli and the associated responses need no longer be present for the avoidance behavior to occur. In acute pain states it may be useful to reduce movement, and consequently avoid pain, to accelerate the healing process. Pain related to sustained muscle contractions might, however, also be conceptualized as a unconditioned stimulus in the case wherein no acute injury was present and sympathetic activation and tension increases might be viewed as unconditioned responses that might elicit more pain, and conditioning might proceed in the same fashion as outlined above. Thus, although the original association between pain and pain-related stimuli results in anxiety regarding these stimuli, with time the expectation of pain related to activity may lead to avoidance of adaptive behaviors even if the nociceptive stimuli and the related sympathetic activation are no longer present. Fear of pain and activity may become conditioned to an expanding number of situations. Avoided activities may involve simple motor behaviors, but also work, leisure and sexual activity. In addition to the avoidance learning, pain may be exacerbated and

maintained in these encounters with potentially pain-increasing situations due to the anxiety-related sympathetic activation and muscle tension increases that may occur in anticipation of pain and also as a consequence of pain. Thus, psychological factors may directly affect nociceptive stimulation and need not be viewed as only reactions to pain. Aversive emotional conditioning with painful stimuli as unconditioned stimulus has been shown to be exaggerated in chronic back pain patients, as well as patients with tension type headache [5▪▪,6], and leads to increased muscle tension responses. Meulders *et al*. [7▪▪] showed that movement can be a conditioned stimulus that can be associated with pain and itself elicit fear of movement, an aversive motivational state and avoidance of movement. Social learning or modeling related to viewing pain in others may be an additional important learning process that can also play a role in chronicity. Although empathy for pain is a prerequisite for social learning, social learning goes beyond emotional involvement in others' pain, especially when the pain of another person is experienced as if it were one's own pain [8▪]. This might itself be an important stimulus for pain chronicity.

CENTRAL CHANGES RELATED TO LEARNING AND PAIN

The increase or decrease of sensory input into the brain leads to adaptive changes in the primary sensory and motor areas. For example, in patients with amputations, the map in primary sensorimotor cortex changes in such a manner that input from neighboring areas occupies the region that formerly received input from the now amputated limb [9]. Interestingly, reorganizational changes were only found in amputees with phantom limb pain after amputation but not in amputees without pain. This suggests that nociceptive input may contribute to the changes observed and that the persisting pain might also be a consequence of the plastic changes that occur. Similar observations were made in patients with complex regional pain syndrome [10▪]. In addition to functional changes, structural changes have also been related to chronic pain. For example, Gustin *et al*. [11▪▪] showed gray matter volume reductions in the primary somatosensory cortex, anterior insula, putamen, nucleus accumbens, and thalamus, whereas gray matter volume was increased in the posterior insula in patients with trigeminal neuropathic pain but not in those with temporomandibular disorders. Furthermore, in trigeminal neuropathy patients, magnetic resonance spectroscopy revealed a significant reduction in the N-acetylaspartate/creatine ratio, a biochemical marker of neural viability, in the region of thalamic volume loss. Structural changes have been documented in many types of chronic pain [12▪], but the specificity and the underlying mechanisms have not yet been explored. It has, however, been shown that they change with successful treatment [13▪▪]. Connectivity of large-scale brain networks is also altered in chronic pain and has been associated with pain symptoms [14▪].

But also increased behaviorally relevant input related to nonneuropathic pain leads to changes in the cortical map and other brain regions. This might underlie the changes in functional and structural plasticity seen in many musculoskeletal pain disorders. For example, Diesch and Flor [15] documented changes in primary somatosensory cortex as a consequence of Pavlovian conditioning with painful stimuli. More recent evidence has focused on the affective and cognitive processing of pain and how this might be altered in chronic pain. Spontaneous fluctuations in chronic pain were found to be associated with increased prefrontal activation in chronic pain patients; and it was also shown that chronic pain alters the motivational value of pain; in that chronic pain patients do not attribute the same value to the cessation of acute pain as healthy controls do (cf. [16,17▪▪]). Eck *et al*. [18▪] showed that the mere imagination of pain-related words activated brain regions involved in the affective processing of pain. However, many of the brain activations seen may not be specific for pain but may rather be involved in saliency detection and multisensory processing [19▪▪,20▪].

BODY IMAGE, BODY PERCEPTION AND CHRONIC PAIN

Changes in sensory and affective brain regions are also associated with alterations in the perception of the body and perceptual acuity. Neuropathic pain syndromes such as complex regional pain syndrome or phantom limb pain are accompanied by deterioration of tactile acuity and disturbances of the body image [21]. This was also observed in musculoskeletal pain [22] and is also reflected in altered and maladaptive central representations of muscles in the affected body part [23▪▪].

LEARNING, PLASTICITY AND PAIN: IMPLICATIONS FOR TREATMENT

Learning influences subjective, behavioral, neurophysiological and biochemical aspects of pain that outlast the phase of acute pain and may contribute to the experience of chronic pain. Extinction of

learnt pain associations may especially be impaired in chronic pain patients and needs to be the focus of pain management. There are site-specific peripheral and central changes related to pain memory processes that may potentially have to be addressed separately. It is not only the physical stimulus but the learning history that determines the response to noxious stimulation, and thus the learning history must be assessed and included in treatment.

In contrast to the acquisition of a pain-related response, which generalizes easily across stimuli and responses, the extinction or unlearning of a pain response is specific to the stimulus and the response. This means that training a patient to extinguish pain-related responses may be much more difficult than their acquisition. Moreover, extinction involves the learning of an inhibitory process, not just the erasure of an old memory trace. Further characteristics of extinction are that the changes in memory fade with the passage of time, whereas acquired emotional memories often become stronger with time. In addition, a change of context can reactivate the extinguished memory, a phenomenon that has been termed renewal. In memory acquisition, generalization of stimuli and responses occurs, in contrast, making the acquired response very resistant to extinction. Finally, stressful events such as a new episode of pain can function like an unconditioned stimulus and can reactivate the extinguished memory (reinstatement). This is problematic in chronic pain patients in whom new stress and pain episodes are likely to occur. For treatment, this means that massed practice in varying contexts during stress and nonstress conditions is necessary. This can be achieved by specific operant-based extinction training, but also by cognitive–behavioral or respondent (biofeedback) approaches [24▪].

The alteration of maladaptive brain plasticity is also possible by directly modifying the maladaptive learnt brain response to pain by methods, such as imagery, mirror training or the use of virtual reality, that make use of the fact that the brain processes the perceived rather than the physical reality and could thus reverse maladaptive changes in pain-related memories such as phantom limb pain [25,26]. Stimulation-related procedures were also found to be effective. Noninvasive techniques such as transcranial magnetic stimulation and transcranial direct current stimulation have been applied with good initial results on pain relief [27▪▪]. Brain changes might also be modified by the use of brain computer interfaces that can directly target maladaptive plastic changes [28]. It has also been suggested [29▪▪] that the combination of sensory training and vagus nerve stimulation might be an especially powerful tool to restore normal brain function.

The reversal, as well as prevention, of chronic pain might also be possible by using pharmacological agents that are known to prevent or reverse cortical reorganization, although they are less specific than behavioral interventions. Among these substances, γ-aminobutyric acid agonists, *N*-methyl-D-aspartate (NMDA) receptor antagonists and anticholinergic substances seem to be the most promising [30]. In the treatment of phobia the effects of exposure therapy related to aversive fear memories could be enhanced by combining the treatment with a partial NMDA receptor agonist (D-cycloserine) [31]. NMDA receptor agonists have also been shown to be effective in relieving pain in conjunction with noninvasive brain stimulation (cf. [32▪]). As extinction is context-specific, training as many varied behaviors as possible, training in many different environments and the use of stress and pain episodes to train relapse prevention are important parts of this training. Moreover, chronic pain must be prevented as early as possible by pharmacological and psychological interventions in order to keep pain memories from being established.

CONCLUSION

Although recent scientific evidence has shown that chronic pain leads to changes in many brain regions, the responsiveness of pain to plastic changes also opens the door for new intervention methods, which rely on stimulation, behavioral training or pharmacological interventions that prevent maladaptive memory formation or enhance extinction. This article focused on the role of learning and memory mechanisms in the development and maintenance of chronic pain and outlined implications for new treatment approaches.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

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

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 160).

1. ■■ Apkarian AV, Hashmi JA, Baliki MN. Pain and the brain: specificity and plasticity of the brain in clinical chronic pain. Pain 2011; 152:S49–S64.

This article reviews the brain changes related to acute and chronic pain and proposes a model for the transition from acute to chronic.

2. ■■ De Ridder D, Elgoyhen AB, Romo R, Langguth B. Phantom percepts: tinnitus and pain as persisting aversive memory networks. Proc Natl Acad Sci U S A 2011; 108:8075–8080.

De Ridder *et al.* review the similarities between tinnitus and pain based on the notion that they are learnt chronic conditions.

3. ■ Graven-Nielsen T, Arendt-Nielsen L. Assessment of mechanisms in localized and widespread musculoskeletal pain. Nat Rev Rheumatol 2010; 6:599–606.

These authors describe the mechanisms that contribute to sensitization in chronic musculoskeletal pain.

4. ■■ Becker S, Kleinbohl D, Baus D, Holzl R. Operant learning of perceptual sensitization and habituation is impaired in fibromyalgia patients with and without irritable bowel syndrome. Pain 2011; 152:1408–1417.

This elegant study used an operant learning protocol based on intrinsic reinforcement of pain and showed that habituation and sensitization are modified by learning and that this mechanism is altered in patients with fibromyalgia with and without irritable bowel syndrome. It shows how pain chronicity could be learnt.

5. ■■ Klinger R, Matter N, Kothe R, *et al.* Unconditioned and conditioned muscular responses in patients with chronic back pain and chronic tension-type headaches and in healthy controls. Pain 2010; 150:66–74.

Klinger *et al.* present evidence that chronic musculoskeletal pain can be influenced by Pavlovian conditioning and lead to long-lasting changes in pain perception.

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7. ■■ Meulders A, Vansteenwegen D, Vlaeyen JW. The acquisition of fear of movement-related pain and associative learning: a novel pain-relevant human fear conditioning paradigm. Pain 2011; 152:2460–2469.

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8. ■ Fitzgibbon BM, Giummarra MJ, Georgiou-Karistianis N, *et al.* Shared pain: from empathy to synaesthesia. Neurosci Biobehav Rev 2010; 34:500–512.

Viewing others in pain not only elicits empathy but can also induce pain in the observer, is the argument of the authors.

9. Flor H, Nikolajsen L, Staehelin Jensen T. Phantom limb pain: a case of maladaptive CNS plasticity? Nat Rev Neurosci 2006; 7:873–881.

10. ■ Goebel A. Complex regional pain syndrome in adults. Rheumatology 2011; 50:1739–1750.

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11. ■■ Gustin SM, Peck CC, Wilcox SL, *et al.* Different pain, different brain: thalamic anatomy in neuropathic and nonneuropathic chronic pain syndromes. J Neurosci 2011; 31:5956–5964.

These authors show that different types of facial pain are accompanied by different changes in brain structure.

12. ■ May A. Structural brain imaging: a window into chronic pain. Neuroscientist 2011; 17:209–220.

An excellent review of structural changes in chronic pain, including putative mechanisms.

13. ■■ Seminowicz DA, Wideman TH, Naso L, *et al.* Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. J Neurosci 2011; 31:7540–7550.

This study shows that structural and functional brain changes can be reversed with effective treatment.

14. ■ Napadow V, LaCount L, Park K, *et al.* Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. Arthritis Rheum 2010; 62:2545–2555.

One of a growing number of studies that focus on resting state brain activity and the connectivity of brain regions involved in different networks, and finds associations with chronic pain.

15. Diesch E, Flor H. Alteration in the response properties of primary somatosensory cortex related to differential aversive Pavlovian conditioning. Pain 2007; 131:171–180.

16. Baliki MN, Chialvo DR, Geha PY, *et al.* Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. J Neurosci 2006; 26:12165–12173.

17. ■■ Baliki MN, Geha PY, Fields HL, Apkarian AV. Predicting value of pain and analgesia: nucleus accumbens response to noxious stimuli changes in the presence of chronic pain. Neuron 2010; 66:149–160.

These authors present evidence that the transition from acute to chronic pain involves a change in the signal value of pain involving the nucleus accumbens.

18. ■ Eck J, Richter M, Straube T, *et al.* Affective brain regions are activated during the processing of pain-related words in migraine patients. Pain 2011; 152:1104–1113.

These authors show that imagery of pain-related words activates brain regions involved in the affective processing of pain and this gives evidence of the important role of associative learning mechanisms in pain.

19. ■■ Legrain V, Iannetti GD, Plaghki L, Mouraux A. The pain matrix reloaded: a salience detection system for the body. Prog Neurobiol 2011; 93:111–124.

These authors challenge the notion of a pain matrix and point out that activation in these brain regions is also present in other types of salient sensory events.

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23. ■■ Tsao H, Danneels LA, Hodges PW. ISSLS prize winner: smudging the motor brain in young adults with recurrent low back pain. Spine 2011; 36:1721–1727.

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26. Ramachandran VS, Altschuler EL. The use of visual feedback, in particular mirror visual feedback, in restoring brain function. Brain 2009; 132:1693–1710.

27. ■■ Zaghi S, Thiele B, Pimentel D, *et al.* Assessment and treatment of pain with noninvasive cortical stimulation. Restor Neurol Neurosci 2011 (in press).

Presents an excellent overview of the possibilities of using noninvasive cortical stimulation in chronic pain.

28. Birbaumer N, Ramos-Murguialday A, Weber C, Montoya P. Neurofeedback and brain–computer interface clinical applications. Int Rev Neurobiol 2009; 86:107–117.

29. ■■ Engineer ND, Riley JR, Seale JD, *et al.* Reversing pathological neural activity using targeted plasticity. Nature 2011; 470:101–104.

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30. Cramer SC, Sur M, Dobkin BH, *et al.* Harnessing neuroplasticity for clinical applications. Brain 2011; 134:1591–1609.

31. Kantak KM, Hofmann SG. Cognitive enhancers for the treatment of neuropsychiatric disorders: clinical and preclinical investigations. Pharmacol Biochem Behav 2011; 99:113–115.

32. ■ Antal A, Paulus W. A case of refractory orofacial pain treated by transcranial direct current stimulation applied over hand motor area in combination with NMDA agonist drug intake. Brain Stimul 2011; 4:117–121.

An interesting case study that combined an NMDA receptor antagonist and brain stimulation to treat chronic pain.