Recent neuroscientific evidence has revealed that the adult brain is capable of substantial plastic change in such areas as the primary somatosensory cortex that were formerly thought to be modifiable only during early experience. These findings have implications for our understanding of chronic pain. Functional reorganisation in both the somatosensory and the motor system was observed in neuropathic and musculoskeletal pain. In patients with chronic low back pain and fibromyalgia the amount of reorganisation increases with chronicity; in phantom limb pain and other neuropathic pain syndromes cortical reorganisation is correlated with the amount of pain. These central alterations may be viewed as pain memories that influence the processing of both painful and nonpainful input to the somatosensory system as well as its effects on the motor system. Cortical plasticity related to chronic pain can be modified by behavioural interventions that provide feedback to the brain areas that were altered by somatosensory pain memories or by pharmacological agents that prevent or reverse maladaptive memory formation.

Key words: cortical reorganisation, chronic pain, phantom limb, behavioural training, memory for pain


INTRODUCTION

Over the last two decades our understanding of the modifiability of the primary sensory and motor areas of the brain has greatly changed. Whereas it was previously assumed that plastic changes in these cortical areas are limited to an early period in development it is now an accepted fact that substantial plastic changes of the primary cortical areas occur throughout life (for review see 1–3). Cortical reorganisation has been observed as a consequence of both injury and stimulation. For example, in the owl monkey, the amputation of a digit led to a ‘take-over’ of the cortical representation zone of this digit by neuronal input from adjacent digits (4). This ‘shift’ of neighbouring areas into the amputation zone developed over the course of several weeks and might be due to the unmasking of normally inhibited connections as well as the sprouting of new axonal connections (5). An even larger cortical reorganisation was observed by Pons et al. (6) in the macaque monkey subsequent to long-standing dorsal rhizotomies. Here the representation of the face ‘invaded’ the representation of the deafferented arm and hand – a shift that was in the range of several centimetres and is probably related to altered thalamocortical projections (7).

Cortical representation zones are not only altered by injury but also by behaviourally relevant stimulation and training. For example, Jenkins et al. (8) observed that sensory discrimination training of individual fingers led to an expansion of the cortical representation zone of the trained fingers. This change occurred only if the training was behaviourally relevant; it was not observed after passive stimulation.

CHRONIC BACK PAIN AND CORTICAL REORGANISATION

Animal models have shown that long-lasting and/or intense states of pain (e.g. when an inflammation is present) lead to the sensitisation of spinal cord neurons (e.g. 9) as well as to an altered representation of the painful area in the thalamus (10) and the cortex (11). In chronic pain patients hyperreactivity to tactile or noxious stimuli was also observed (e.g. 12, 13). For example, perception and pain thresholds as well as pain tolerance levels were found to be significantly lower in patients with chronic back pain and episodic headaches and these thresholds were lower the more chronic the pain had become (12). Although peripheral as well as spinal and thalamic mechanisms have been implicated in some of these changes in nociception, cortical changes may also play a role in these alterations of nociceptive sensitivity. We (14) have reported elevated responses to painful and nonpainful tactile stimulation as assessed by magnetoencephalography in chronic back pain patients. Stimulation at the affected back but not at the finger led to a significantly higher magnetic field in the time window less than 100 msec, whereas both types of stimulation caused higher fields in the later time windows in the patients as compared to the controls. This hyperreactivity of the somatosensory system increased with chronicity. When the source of this early activity was localised, it was shown to originate in primary somatosensory cortex. Whereas the localisation of the fingers was not significantly different between patients and controls, the localisation of the back was more inferior and medial in the pa-
patients indicating a shift and expansion toward the cortical representation of the leg. These data suggest that chronic pain leads to an expansion of the cortical representation zone related to nociceptive input much like the expansions of cortical representations that have been documented to occur with other types of behaviourally relevant stimulation. Nociceptive input is of high relevance for the organism and it might be useful to enhance the representation of this type of stimulation to prepare the organism for the adequate response. The amount of expansion of the back region was positively correlated with chronicity, suggesting that this pain-related cortical reorganisation develops over time (see Fig. 1). Using functional magnetic resonance imaging, Gracely et al. (15) recently reported a similar hyperreactivity to painful stimulation in a number of brain regions, including SI cortex in patients with fibromyalgia.

This type of cortical alteration may correspond to what Katz & Melzack (16) have termed a somatosensory pain memory in phantom limb pain patients. Although they referred mainly to explicit memories, i.e. the patients’ recollection that the phantom pain was similar to previously experienced pains, somatosensory memories may also be implicit. Implicit pain memories are based on changes in the brain that are not open to conscious awareness but lead to behavioural and perceptual changes – such as hyperalgesia and allodynia – that the patient is not aware of. It is therefore impossible for the patient to counteract these pain memories. This type of memory trace may lead to pain perception in the absence of peripheral stimulation, since an expansion of a representational zone is related to higher acuity in the perception of tactile input (cf. 4).

LEARNING AND CORTICAL REORGANISATION

Implicit pain memories can be altered by learning processes such as habituation and sensitisation, operant and classical conditioning or priming. There is now ample evidence that learning not only affects pain behaviours and the subjective experience of pain but also the physiological processing of painful stimulation. For example, a spouse who habitually reinforces pain can also influence the pain-related cortical response. When patients were stimulated with electric impulses at either the finger or the back in either the presence or absence of the spouse, spouse presence influenced the electroencephalographic (EEG) potentials that were recorded from the patients’ skull. Whereas spouses who habitually ignored the pain or punished their partners for expressing pain had no effect, spouses who habitually reinforced pain behaviours caused a 2.5-fold increase in the patients’ brain response to pain applied to the back. At the finger no difference for the presence or absence of spouse was observed, nor was there a difference for the healthy controls (17). The main difference between these conditions was observed in an area that corresponds to the location of the anterior cingulate cortex that has been shown to be involved in the processing of the emotional aspects of pain (18).

Direct verbal reinforcement of pain has been identified as an additional important modulator of the pain response. When patients and healthy controls were reinforced for increasing or decreasing their verbal pain responses, both groups learned this task equally well, although the patients showed a delay in the extinction of the response. When the somatosensory-evoked potentials to the pain stimuli were examined, the late event-related responses (>200 msec) were unaltered and showed mainly habituation. However, the early response (N150) was affected by the conditioning and remained high in the chronic pain group that had been reinforced for higher pain ratings, thus indicating a direct effect of verbal reinforcement on the early cortical processing of nociceptive information (19). This lack of extinction in the cortical domain suggests that learning processes related to verbal and behavioural conditioning may exert long-lasting influences on the cortical response to pain-related stimuli, forming implicit pain memories.

Further evidence for pain-related memories comes from studies that used pain-related words such as aching and burning and compared them to body-related words such as sweating and breathing and neutral words such as working and eating. When evoked responses to these words were examined in patients with chronic back pain or subchronic patients, they showed enhanced early evoked responses (N100) to the pain-related words, indicating a classical or Pavlovian conditioning process that had transferred special meaning to these words (20, 21). A direct classical conditioning experiment that paired pseudowords (i.e. words the subjects had never heard and could not attach any prior meaning to) with electric shock yielded exactly the same results: subjects acquired an elevated N100 response to the words that had been
paired with shock, with a preponderance of the response over the left (language-related) hemisphere (22).

In addition to operant conditioning, classical conditioning has been identified as an important modulator of pain-related responses. This effect pertains not only to the ascending nociceptive system but also to descending pain-modulatory systems. The fact that stress positively influences the pain response and activates the descending pain-inhibitory system has commonly been described by the term stress-induced analgesia or hypoalgesia. Animal studies have shown that stress analgesia can be conditioned and that some forms of both conditioned and unconditioned stress analgesia are mediated by the endogenous opioid system. It was recently shown that stress analgesia can be classically conditioned in humans as well and that this conditioned analgesia is mediated by the release of endogenous opioids (23, 24). To what extent deficient descending pain inhibition is involved in chronic pain has not yet been established, nor do we know enough about the role of learning and memory process in the inhibition of pain.

In summary, chronic pain states lead to the development of somatosensory pain memories that manifest themselves in alterations in the somatotopic map in somatosensory cortex and may contribute to hyperalgesic states in the absence of peripheral nociceptive stimulation. These pain memories can be influenced by psychological processes such as operant and classical conditioning, which may establish additional and potentially more widespread implicit memories and enhance existing memories. In addition to local representational changes, chronic states of pain are associated with increased cortical excitation that may significantly contribute to cortical reorganisation. Pain-inhibitory systems are also influenced by learning and memory processes and may be altered in chronic pain.

PHANTOM LIMB PAIN AND CORTICAL REORGANISATION

As noted above, not only enduring nociceptive input but also the loss of input, for example, subsequent to amputation or nerve injury, can alter the cortical map. Several studies examined cortical reorganisation after amputation in humans. These studies were instigated by the report of Ramachandran et al. (25) that phantom sensation could be elicited in upper extremity amputees when they were stimulated in the face. There was a point to point correspondence between stimulation sites in the face and the localisation of sensation in the phantom. Moreover, the sensations in the phantom matched the modality of the stimulation, e.g. warmth was perceived as a warm phantom sensation, painful touching was perceived as pain. The authors assumed that this phenomenon might be the perceptual correlate of the type of reorganisation previously described in animal experiments. The invasion of the cortical hand or arm area by the mouth representation might lead to activity in the cortical amputation zone, which

would be projected into the no longer present limb. Subsequently, Elbert et al. (26) and Yang et al. (27) used a combination of magnetoencephalographic recordings and structural magnetic resonance imaging to test this hypothesis. They observed a significant shift of the mouth representation into the zone that formerly represented the now amputated hand or arm; however, this shift occurred in patients with and without phantom sensation referred from the mouth. Flor et al. (28) showed that phantom limb pain rather than referred sensation was the perceptual correlate of these cortical reorganisational changes. Patients with phantom limb pain displayed a significant shift from mouth representation to hand representation, whereas this was not the case in patients without phantom limb pain. The intensity of phantom limb pain was significantly positively correlated with the amount of displacement of the mouth representation. It was later shown that referred sensations such as those described by Ramachandran et al. (25) can also be elicited from areas far removed from the amputated limb, for example from the foot in arm amputees. This led to the conclusion that alterations in the organisation of S1 – where arm and foot are represented far apart – are most likely not the neuronal substrate of referred phantom sensations (29, 30).

Similar results were obtained when the motor cortex was investigated. For example, a functional magnetic resonance imaging (fMRI) study, where upper extremity amputees had to perform puckering lip movements, showed that the representation of the lip in primary motor cortex had also shifted into the area that formerly occupied the amputated hand (31) (Fig. 2). The magnitude of this shift was also highly significantly correlated with the amount of phantom limb pain experienced by the patients, thus suggesting parallel processes in the somatosensory and motor system. A high concordance of changes in the somatosensory and the motor system was also reported by Karl et al. (32) who used transcranial magnetic stimulation to map the motor cortex and neuroelectric source imaging (that combines the determina-
tion of cortical sources by evoked potential recordings with structural magnetic resonance imaging) to map the somatosensory cortex. This close interconnection of changes in the somatosensory and motor system suggests that rehabilitative efforts directed at one modality may also affect the other.

The close association between cortical alterations and phantom limb pain was further underscored by a study by Birbaumer et al. (33). In upper limb amputees, anaesthesia of the brachial plexus led to the elimination of phantom limb pain in about 50% of the amputees whereas phantom limb pain remained unchanged in the other half. Neuroelectric source imaging revealed that cortical reorganisation was also reversed in those amputees that showed a reduction of phantom limb pain. Patients who continued to have phantom limb pain during the elimination of sensory input from the residual limb had an even more reorganised mouth representation. These data suggest that in some patients peripheral factors might be important in the maintenance of phantom limb pain, whereas in others pain and reorganisation processes might have become independent of peripheral input. As Devor (34) and others have pointed out, it is not yet clear on which level of the neuraxis the cortical changes that have been observed in imaging studies originate. In addition to intracortical changes alterations might be present in the dorsal root ganglion, the dorsal horn, the brain stem or the thalamus. Recent imaging studies (e.g. 35) have also shown that not only the primary and secondary somatosensory cortex and the posterior parietal cortex are involved in the processing of phantom phenomena but also regions such as the insula and the anterior cingulate. Similar alterations in the cortical processing of sensory information have recently also been reported in patients with complex regional pain syndromes (36).

Based on these findings and the results obtained on somatosensory memories in chronic back pain it can be assumed that prior pain memories might also be important in the development of phantom limb pain, even if it is highly unlikely that they are the sole factors. Thus, when pain has occurred prior to amputation, alterations in somatosensory cortex and other brain areas might have occurred that would later – when activated by neighbouring input subsequent to the amputation – lead to the sensation of phantom limb pain (see 37). Initial evidence from a longitudinal study (38) suggests that chronic pain before the amputation is a much more important predictor of later phantom limb pain than acute pain at the time of the amputation, thus supporting this assumption. In addition, peripheral changes related to the amputation may contribute to enhanced cortical reorganisation and phantom limb pain. For example, Calford & Tweedale (39) have shown that the loss of C-fibre input leads to an expansion of receptive fields in S1 due to a loss of inhibition that is mediated by C-fibres. Thus, the selective loss of C-fibres that has been observed in peripheral deafferentation might lead to disinhibition and unmasking and further cortical reorganisation. It was found that stimulation on the stump – both with q-tips and with pin prick – will lead to an increase in phantom sensation, especially in painful sensations. Microneurographic recordings from nerves supplying the former hand region (cf. 40) suggest that considerable spontaneous activity is present in these nerves, which may also originate in the dorsal root ganglion that seems to be of a random nature. This suggests in turn that the spontaneous activity might be an additional source of activation of cortical reorganisation, since random input seems to increase shifts in the cortical map (see 41).

In summary, somatosensory pain memories represented by alterations in the topographic map of S1 cortex may underlie the development of phantom limb pain. Long-standing states of chronic pain prior to the amputation may be instrumental in the formation of these pain memories by inducing representational and excitability changes. Deafferentation does not alter the original assignment of cortical representation zones to peripheral input zones and leads to double coding. Peripheral factors such as loss of C-fibre activity, spontaneous activity from neuroma, or psychophysiological activation may also influence the cortical representational changes. Learning processes are instrumental in the development and maintenance of these cortical changes.

**TREATMENT OF CHRONIC PAIN BY BEHAVIOURAL INTERVENTIONS**

The discussion in the preceding sections suggests that the alteration of somatosensory pain memories might be an influential method for reducing both chronic musculoskeletal and neuropathic pain. This could be achieved by altering the peripheral input that enters the brain region that coded a pain memory, e.g. by using EMG or temperature biofeedback (for reviews see 42, 43) or by employing a sensory simulation protocol that provides relevant correlated sensory input to the respective brain region. It would also be possible to directly alter the brain response to pain by providing feedback of event-related potential components or EEG rhythms. Most of these methods have not yet been tested in a systematic manner and their effects on cortical reorganisation are unknown so far. Alternatively, pharmacological interventions could be used that prevent or reverse the establishment of central memory traces.

In phantom limb pain, it was assumed that the pain is maintained by cortical alterations fed by peripheral random input. In this case the provision of correlated input into the amputation zone might be an effective method for influencing phantom limb pain. fMRI was used to investigate the effects of prosthesis use on phantom limb pain and cortical reorganisation (44). Patients who systematically used a myoelectric prosthesis that provides sensory and visual as well as motor feedback to the brain showed much less phantom limb pain and cortical reorganisation than patients who used either a cosmetic prosthesis or none at all. The relationship between phantom limb pain and the use of a myoelectric prosthesis was entirely mediated by cortical reorganisation. When it was partialled out from the correlation, phantom limb pain and prosthesis use were no longer associated. This sug-
gests that sensory input to the brain region that formerly represented the now absent limb may be beneficial in reducing phantom limb pain. These studies were performed in patients with chronic phantom limb pain. An early fitting and training with a myoelectric prosthesis would probably be of great value not only in the rehabilitation of amputees but also in preventing or reversing phantom limb pain.

These assumptions were further confirmed in an intervention study where the patients received feedback on sensory discrimination of the residual limb (45). Eight electrodes were attached to the residual limb and provided high intensity non-painful electric stimulation of varying intensity and location that led to the experience of intense phantoms. The patients were trained to discriminate the location or the frequency of the stimulation (alternating trials) of the stimulation and received feedback on the correct responses. The training was conducted for 90 min/day and was spread over a time period of two weeks (10 days of training). Compared to a medically treated control group that received an equal amount of attention, the trained patients showed significantly better discrimination ability on the stump. They also experienced a more than 60% reduction of phantom limb pain and a significant reversal of cortical reorganisation with a shift of the mouth representation back to its original location. The alterations in discrimination ability, pain and cortical reorganisation were highly significantly correlated (Fig. 3).

In a related study (47) asynchronous tactile stimulation of the mouth and hand region was used over a time period of several weeks. This training was based on the idea that synchronous stimulation leads to fusion and asynchronous stimulation leads to a separation of cortical representation zones. In this case it was postulated that input from the mouth representation that would now activate the region that formerly represented the now amputated hand and arm would be eliminated and with it the phantom phenomena that would be projected to the amputated limb. This intervention also showed a reduction in phantom limb pain and cortical reorganisation.

PHARMACOLOGICAL PREVENTION AND TREATMENT OF PHANTOM LIMB PAIN

In addition to behavioural interventions, pharmacological interventions may also be useful in the treatment of both chronic musculoskeletal and neuropathic pain. The prevention of pain memories might be made possible by using pharmacological agents that are known to also prevent or reverse cortical reorganisation. Among these substances, GABA agonists, N-methyl-D-aspartate (NMDA) receptor antagonists and anticholinergic substances seem to be the most promising. A recent double-blind placebo-controlled study that used the NMDA receptor antagonist memantine in the perioperative phase in acute amputations reported a decrease of the incidence of phantom limb pain from 72 to 20% one year after the amputation (48). The pharmacological intervention was most effective in patients for whom treatment had been started before or immediately after the amputation. This study could explain why the results of different controlled prospective studies about the effect of preemptive analgesia initiated at least 24 h before the amputation on the incidence of phantom limb pain are inconsistent. For example, a well-controlled study by Nikolajsen et al. (49) showed no effect of preemptive analgesia on phantom limb pain. If a preexisting pain memory is important in the development of phantom limb pain, the use of preemptive analgesia,
which eliminates afferent barrage in the perioperative phase but does not alter previously formed neuronal changes, may be ineffective.

Treatment of chronic phantom limb pain with pharmacological agents has also yielded inconsistent results. 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 (50), there are no controlled studies for phantom limb pain. Controlled studies have been performed for opioids (51), calcitonin (52) and ketamine (53) all of which were found to effectively reduce phantom limb pain. Memantine, also an NMDA receptor antagonist like ketamine, however, was not effective (54). We found positive effects from both opioids (51) and memantine (Köppe et al. unpublished data) on both chronic phantom limb pain and cortical reorganisation, suggesting that more work is necessary to determine the circumstances under which various pharmacological agents can effectively reverse the maladaptive plastic changes that are a consequence of amputation and chronic pain (Fig. 4).

CONCLUSIONS

The empirical evidence discussed above suggests that neuroplastic changes in the central nervous system play an important role in the development and maintenance of chronic pain. It is not yet clear to what extent changes in the spinal cord, the brain stem or the thalamus contribute to the changes in cortical reorganisation and to what extent cortical reorganisation affects the lower levels. Longitudinal studies and controlled outcome studies are needed to elucidate in greater detail the efficacy and mechanisms of feedback-based interventions designed to alter cortical pain memories.

REFERENCES


