NEUROIMAGING AND PAIN: IMPLICATIONS FOR PREVENTION AND TREATMENT

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ABSTRACT

This article reports our contribution to the meeting held in Siena in November 2010 in honour of Giancarlo Carli, who has worked extensively on animal and human models of pain and, in particular, on the cognitive dimensions of chronic pain. The paper deals with the brain changes related to acute and chronic pain in muscular and neuropathic pain patients. The long-term influence of perinatal pain on sensitization and pain processing is discussed as well as the influence of learning processes such as operant or classical conditioning. The review closes with implications for behavioural interventions.

Key words: brain changes, chronic pain, learning, preterm, sensitization, behavioural interventions

It was a pleasure for us to join the meeting held in Siena in honour of Giancarlo Carli on the occasion of his retirement. In fact, we share with him a deep interest in pain and, more specifically, in the environmental and individual factors possibly influencing the experience of chronic pain (Carli et al., 2002; Huber et al., 2007, 2008, 2009; Carli, Huber et al., 2008; Carli, Suman et al., 2008; Gabriel et al., 2010). This paper reports our contribution to the congress.

BRAIN CHANGES IN CHRONIC NEUROPATHIC AND MUSCULOSKELETAL PAIN

In persons with amputations it has been shown that the region of the somatosensory cortex that formerly received input from the now amputated limb reorganizes and subsequently processes input from neighbouring regions (e.g. Elbert et al., 1994; Yang et al., 1994; Flor et al., 1995; Price et al., 2006). These changes are mirrored in motor cortex (Cohen et al., 1991; Kew et al., 1994; Karl et al., 2001; Lotze et al., 2001; Karl, Muhlnickel et al., 2004). Interestingly, reorganizational changes were only found in amputees with phantom limb pain after amputation, but not in amputees without pain (Flor et al., 1995). This suggests that pain may contribute to the changes observed and that the persisting pain might also be a consequence of the plastic changes that occur. In several studies carried out on human upper-extremity amputee patients, displacement of the lip representation in the primary motor and somatosensory cortex was positively correlated with the intensity of phantom limb pain, and was not present in pain-free amputee patients or healthy control subjects (e.g. Flor et al., 1995; Diers et al., 2010). In addition, in the patients with phantom limb pain, but not in the pain-free amputee patients,

imagined movement of the phantom hand was shown to activate the neighbouring face area (Lotze et al., 2001). This co-activation probably occurs due to the high overlap of the hand, arm, and mouth representations.

Similar observations have been made in patients with complex regional pain syndrome (CRPS). In these patients, the representation of the affected hand tends to be smaller compared with that of the unaffected hand and the individual digit representations had moved closer together (Juottonen et al., 2002; Maihöfner et al., 2003, 2006; Schwenkreis et al., 2003; Pleger et al., 2005). The extent of the pathological change in the cortical representations correlated with the intensity of pain or motor dysfunction (Maihöfner et al., 2004, 2007; Pleger et al., 2005), but was additionally related to a degradation of sensibility in the affected hand. It was, however, unrelated to a loss of motor function (Maihöfner et al., 2007). It is so far not known how an expansion of adjacent representations and a shrinking of adjacent representations as observed in phantom limb pain and CRPS, respectively, can both be associated with pain. It is also not known to what extent nociceptive and non-nociceptive neurons interact in this process and how inhibitory and excitatory mechanisms influence each other.

Not only decreased input related to deafferentation but also increased behaviourally relevant input related to non-neuropathic pain leads to changes in the cortical map in chronic musculoskeletal pain syndromes such as chronic back pain (CBP) or fibromyalgia (FM) (Flor, Braun et al., 1997; Gracely et al., 2002; Giesecke et al., 2004; Tsao et al, 2008 Burgmer et al., 2009). For example, Flor, Braun et al. (1997) reported a close association between the chronicity of back pain and enhanced excitability and map expansion of the back representation in primary somatosensory cortex in patients with non-neuropathic back pain. The back representation had expanded and shifted towards the leg representation the longer the pain had persisted. This was site-specific since the hand representation was unaffected. Similar changes were reported by Giesecke et al. (2004) using functional magnetic resonance imaging. Recently, Tsao et al. (2008) observed a close interaction between changes in motor cortex and postural control in patients with CBP suggesting an intricate interaction between peripheral and central traces of plastic changes related to chronic pain.

Greatly enhanced representations of painful stimulation were also found in patients with fibromyalgia. Gracely et al. (2002) reported that comparable levels of subjectively reported painful stimulation resulted in cerebral activation patterns that were similar in FM patients and healthy controls. However, similar stimulation intensities resulted in stronger activation in regions specific for pain processing in FM patients, supporting the hypothesis of augmented pain processing in FM patients. Cook et al. (2004) examined painful heat stimuli (47°C) to the non-dominant thenar in patients with FM and healthy controls and observed activations in primary and secondary somatosensory cortex, the anterior cingulate cortex, the supplementary motor area, and the insular cortex. Contrasts between both groups revealed significantly more activation for the FM group in the contralateral insular cortex. For perceptually equivalent pain ratings FM patients failed to respond to pain provocation in the descending pain regulating system (the rostral anterior cingulate cortex) (Jensen et al., 2009).

These changes were present in cortical activation maps as well as in areas involved in the affective and cognitive processing of pain (Burgmer et al., 2009). Catastrophizing was found to be significantly associated with increased activity in brain areas related to anticipation of pain (medial frontal cortex, cerebellum), attention to pain (dorsal anterior cingulate cortex, dorsolateral prefrontal cortex), emotional aspects of pain (claustrum, closely connected to amygdala),

and motor control when depressive symptomatology was controlled for (Gracely et al., 2004). Symptoms of depression and the presence of major depressive disorder were associated with the magnitude of pain-evoked neuronal activations in brain regions associated with affective pain processing (the amygdalae and contralateral anterior insula cf., Giesecke et al., 2005). Patients with major depressive disorder show hyperalgesia, but the hyperalgesia is more pronounced in FM and a deficit in pain inhibition is specific to FM (de Souza et al., 2009; Normand et al., 2010). A recent study with 83 subjects showed that depressive symptoms, anxiety, and catastrophizing scores were correlated, but did not correlate with ratings of clinical pain or with sensitivity to pressure pain (Jensen et al., 2010). Brain activity during experimental pain was not modulated by depressive symptoms, anxiety, or catastrophizing (Jensen et al., 2010). The general and widespread nature of pain in FM suggests the involvement of central mechanisms via spinal and/or supraspinal modulation of experimental peripheral input. The exact interplay of pain, anxiety, depression, and catastrophizing needs to be further investigated and can be different in different subgroups of patients (Flor & Turk, 2011).

In addition to changes in functional activation, structural and biochemical changes and changes in brain connectivity have also been reported for musculoskeletal pain syndromes (e.g. Kuchinad et al., 2007; Schmidt-Wilcke et al., 2007; Staud & Spaeth, 2008). They might, however, be a consequence rather than a cause of the pain (Seifert & Maihöfner, 2011).

PRETERM SENSITIZATION

An especially interesting example of brain changes correlated to injury and stimulation related to pain are changes that occur as a consequence of painful stimulation early in life. Whereas formerly it was assumed that there is no pain perception in the neonate, more recent evidence shows not only that neonates perceive pain but that pain leads to long-lasting negative consequences (Thewissen & Allegaert, 2011). The neonatal period is a particularly sensitive time window for experience-induced neuronal plasticity due to the ongoing maturation of the nociceptive (Fitzgerald & Jennings, 1999) and the sensory systems (Berardi et al., 2000). In animal studies it has been shown that neonatal pain experiences can induce long-term hypoalgesia or hyperalgesia (Anand et al., 1999; Lidow, 2002). Similar findings have been obtained in humans. Twelve years after treatment in a neonatal intensive care unit both preterm and full-term children showed greater perceptual sensitization to tonic heat and elevated heat pain thresholds compared to control children without neonatal intensive care unit experience (Hermann et al., 2006). In response to tonic heat pain preterm children showed significantly higher activations in primary somatosensory cortex, anterior cingulate cortex, and insula compared to controls (Hohmeister et al., 2010). This suggests that repeated pain experience in neonates may induce activity-induced changes in the functioning of pain pathways that persist well beyond infancy.

A changed pain perception has also been observed in school-aged children who suffered during the age of 6–24 months from moderate or severe burn injuries. Moderately burned children had significantly higher mechanical detection thresholds and significantly lower mechanical pain thresholds and significantly greater perceptual sensitization to repetitive mechanical stimuli compared to controls (Wollgarten-Hadamek et al., 2009). Severely burned children had elevated heat pain thresholds and significantly greater perceptual sensitization to thermal stimuli compared to controls (Wollgarten-Hadamek et al., 2009). This suggests that early traumatic and painful injuries can induce global, long-term alterations in sensory and

pain processing also on body sites not affected by the burn injury. It is possible that sensitized excitatory pain pathways result in a disturbed endogenous pain inhibitory mechanism and can be tested with stress-induced analgesia, a reduced nociceptive response after stress exposure, which is mediated by descending inhibitory opioid and non-opioid brain circuits (Akil et al, 1976; Willer et al., 1981; Flor & Grüsser, 1999; Flor et al., 2002; Yilmaz et al., 2010). Moderately burned children and controls showed intact stress-induced analgesia whereas severely burned children failed to show significant stress-related changes (Wollgarten-Hadamek et al., 2011). In addition, in neonates brain regions involved in pain inhibition were underactivated whereas brain regions that reflect especially the affective component of pain were overactivated (Hohmeister et al., 2010). A counter-irritation-induced analgesia with a cold pressor pain stimulus reduced heat pain intensity ratings in term-born children and preterm children with few painful interventions at birth, but not in preterm children with numerous painful procedures during the neonatal period (Goffaux et al., 2008). This suggests that pain and stress exposure in neonates and infants may be associated with an attenuated stress-induced activation of endogenous pain inhibitory mechanisms later in childhood and adolescence.

LEARNING MECHANISMS IN CHRONIC PAIN AND SENSITIZATION

In addition to sensitization (a non-associative learning process), associative learning such as operant or Pavlovian conditioning can influence the processing of pain on all levels—the verbal-subjective, the behavioural, and the physiological (Fordyce, 1976; Linton & Gotestam, 1985; Flor & Turk, 2011). Fordyce (1976) proposed that positive as well as negative reinforcement of pain behaviours (such as sighing or grimacing) and a lack of positive reinforcement of healthy behaviours (such as movement or smiling) can increase the expression of pain behaviours and over time lead to behaviourally induced chronic pain problems. Direct verbal reinforcement of pain has been identified as an important modulator of the pain response. When patients and healthy controls were reinforced for increasing or decreasing their verbal pain responses both patients and controls learned this task equally well; however, the patients showed a delay in the extinction of the verbal pain response.

When somatosensory evoked potentials to the pain stimuli were examined, the late event-related responses (> 250 ms) were unaltered and showed mainly habituation. However, the early response (N150) was affected by the conditioning procedure and remained high in the chronic pain group that had been reinforced for higher pain ratings during extinction. This indicates a direct effect of verbal reinforcement on the early cortical processing of nociceptive information (Flor et al., 2002). This lack of extinction in cortical processing implies that maladaptive learnt physiological responses may greatly contribute to pain chronicity. Chronic pain patients might also have learned to increase muscle tension in anticipation of painful stimuli to reduce pain. This would result in negative reinforcement (because a negative consequence, pain, is eliminated) and could lead to short-term pain reduction, but on the long term stimulate and sensitize nociceptors and thus increase pain. During painful stimuli on the lower arm or back, chronic back pain patients were instructed to increase their muscle tension or keep it low. During the tension increase condition, the CBP patients but not the healthy controls showed higher N150 and N150/P260 amplitudes (Knost et al., 1999). Thus, operantly conditioned muscle tension could contribute to chronicity.

In a study in which pain was implicitly reinforced, a series of tonic painful heat stimuli were applied to the dominant hand. Patients had to adjust the temperature at the end of each trial to the subjective temperature felt at the beginning of each trial, which was objectively not changed. The temperature was increased or decreased in each subsequent trial, depending on the adjustment in the trial before. Thus the behaviour of the subjects was reinforced without their knowledge. It was shown that increased or decreased pain sensitivity could be implicitly learned (Hölzl et al., 2005). In another study sensitization could be modulated by implicit reinforcement (Becker et al., 2008). Thus, operant learning mechanisms based on intrinsic reinforcement may provide an explanation for the gradual development of sustained hypersensitivity during pain that is becoming chronic (Becker et al., 2008). Using this paradigm in patients with FM, one subgroup with and one without irritable bowel syndrome (IBS), it was shown that FM patients without IBS sensitized in the habituation learning condition. FM patients with IBS demonstrated neither learning of sensitization nor habituation. Thus, operant perceptual learning seems to be impaired in patients with FM (Becker et al., 2011).

Another type of learning that is important for pain modulation is Pavlovian conditioning where originally neutral stimuli become associated with pain and can later by themselves enhance pain perception and induce chronicity. In a typical aversive Pavlovian differential delay conditioning procedure, aversive pictures were paired with painful electric stimulation, whereas positive pictures were paired with the absence of shock (Schneider et al., 2004). Chronic back pain patients showed an enhanced muscular response of the left forearm (where the unconditioned stimulus was applied) to the reinforced conditioned stimulus already in the pre-conditioning phase indicative of more anticipatory anxiety towards the painful stimulus. During learning the painful muscle showed an increased response to the reinforced conditioned stimulus and an increased response to the reinforced and unreinforced conditioned stimulus in the extinction phase. These data were complemented by brain changes that were indicative of an altered anticipatory brain response as evidenced by the contingent negative variation that develops between the conditioned and the unconditioned stimulus.

Diesch and Flor (2007) showed that non-painful tactile stimulation can change the organization of the primary somatosensory cortex. Non-painful stimuli to the finger were used as conditioned stimuli and painful electrical stimuli to the back as unconditioned stimuli. This study in healthy controls showed that humans easily acquire a conditioned muscular response in this conditioning paradigm compared to an unconditioned control group where the stimuli were randomly distributed. The cortical representation of the conditioned finger increased and shifted in the direction of the back compared to the control finger. These data can be interpreted as reflecting the development of a cortical network that associates more and more formerly neutral stimuli into a 'pain network' that then triggers pain perception and behavioural pain responses. It should be noted that there is considerable overlap between the processing of pain and other negative emotions and that these networks interact (Legrain et al., 2011).

There is also indirect evidence of conditioning for pain-related words. Several studies found that painful words such as 'burning', 'sticking', and 'pricking' led to changed brain responses and hyper-reactivity in chronic pain patients compared to non-pain-related bodily sensations such as 'sweating' or 'breathing' or neutral words such as 'walking' or 'standing'. The early component (N100–N150) of the event-related potential was increased for the pain-related words in both chronic and subchronic pain patients (Flor et al., 1997; Knost et al., 1997) and showed

increased blood-oxygen-level dependence in the left orbitofrontal cortex and anterior insula in migraine patients (Eck et al., 2011).

Another study showed that this effect can be induced in a learning process in healthy subjects. In a classical conditioning study pairing pseudo-words with painful electrical stimuli an increased N100 response, especially over the left hemisphere, was found after the conditioning procedure (Montoya et al., 1996). Thus chronic pain can lead to the development of a somatosensory memory for pain with changed maps in the somatosensory cortex and changes in other brain areas, as well as hyperalgesia in the absence of peripheral nociceptive stimuli. These processes lead to more attention to the formerly neutral stimuli because they increase their salience and attentional processes can further enhance the learning and brain changes (Rainville et al., 1997; Buchner et al., 1999; Valet et al., 2004). Learning and attentional processes thus cause additional and widespread implicit memory traces and reinforce the existing pain memory via connections with affective brain areas. In addition to local changes a general cortical excitability was found in chronic pain (e.g. Larbig et al., 1996; Karl, Diers et al., 2004).

BEHAVIOURAL INTERVENTIONS

The assumption that chronic pain is greatly influenced by learning and memory processes suggests that treatment should focus on the alteration of these memory traces. Behavioural and cognitive methods or their combination are especially well suited for this purpose because they can specifically alter the brain change that is prominent in a specific condition whereas pharmacological treatments act in a more unspecific manner. Patients who show high levels of pain behaviours and are much incapacitated by their pain should profit from operant behavioural treatment. The goals of this treatment are: the decrease of pain behaviours in an effort to extinguish pain; the increase of activity levels and healthy behaviours related to work, leisure time, and the family; medication reduction and management; and the change of the behaviour of significant others (Fordyce, 1976). The overall goal is to reduce disability by reducing pain and increasing healthy behaviours. Medication is switched from a pain contingent to a fixed time schedule, where medication is given at certain times of the day to avoid negative reinforcement learning. 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 such as FM (Thieme et al., 2003, 2006) and is especially effective in reducing pain behaviours.

The cognitive-behavioural model of chronic pain emphasizes the role of cognitive, affective, and behavioural factors in the development and maintenance of chronic pain. The central tenet of this treatment is to reduce feelings of helplessness and uncontrollability, and to establish a sense of control over pain in patients. This is achieved by the modification of pain-eliciting and maintaining behaviours, cognitions, and emotions. The cognitive-behavioural 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 and use of imagery or relaxation that increase self-efficacy. Several studies have examined the efficacy of cognitive-behavioural pain management, which must be considered as a very effective treatment of chronic pain (Hoffman et al., 2007). Whereas operant treatment reduces especially pain behaviours and also pain intensity, cognitive-behavioural therapy has a special effect on the affective and cognitive aspects of pain (Thieme et al., 2006). Since extinc-

tion is more difficult than acquisition, principles of extinction training need to be considered (Flor, 2009).

Previous studies have used hypnosis to differentially modulate the sensory or affective component of pain and have shown differential changes of the primary somatosensory cortex or the anterior cingulate, respectively (Rainville, Carrier et al., 1999; Rainville, Hofbauer et al., 1999). Several studies have shown that hypnosis also effectively influences pain in chronic conditions and that it produces sizeable pain reductions (Carli, Huber et al., 2008; Carli, Suman et al., 2008; Dufresne et al., 2010). For example, hypnosis improved pain intensity in multiple sclerosis as well as cognitive restructuring with the best effects for the combined treatment (Jensen et al., 2011). Hypnosis was shown to have effects on both cortical pain modulation (by attention) (Rainville, Carrier et al., 1999; Rainville, Hofbauer et al., 1999; Derbyshire et al., 2009) and spinal pain modulation (Kiernan et al., 1995; Danziger et al., 1998).

Treatments that combine pharmacological interventions with behavioural and cognitive-behavioural interventions might be even more effective. 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. 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 in several studies (Ressler et al., 2004; Hofmann et al., 2006). D-cycloserine has also been shown to reduce neuropathic pain by itself in an animal model of neuropathic pain (Millecamps et al., 2007). In addition, cannabinoids have been identified as important modulators of extinction (Marsicano et al., 2002; Wotjak, 2005) and might be interesting compounds to support extinction training. Since pain seems 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 behaviours 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 (Flor, 2009).

CONCLUSION

Recent scientific evidence has shown that chronic pain leads to changes in many brain regions. In particular the neonatal period is a sensitive time window for experience-induced neuronal plasticity due to the ongoing maturation of the pain system. As classical and operant conditioning procedures are involved in the development of chronic pain, cognitive-behavioural treatments are very effective.

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