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Review

Cortical changes in complex regional pain syndrome (CRPS)

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ABSTRACT

Recent research suggests that changes in cortical structures can contribute to the pathophysiology of Complex Regional Pain Syndrome (CRPS). This review provides an overview of studies showing cortical involvement in CRPS, including mislocalizations of tactile stimuli, changes in size and organization of the somatosensory map, changes in motor cortex representation and body perception disturbances. In addition, we review experimental treatment approaches, such as mirror therapy and motor imagery programs, aimed at restoring the integrity of neural processing in the sensory-motor cortex in individuals with CRPS. The intervention effects are promising and can be theoretically motivated on the basis of established principles of neural organization, although important questions concerning the precise neural mechanisms of action remain unanswered.

1. Introduction

Complex regional pain syndrome (CRPS) is a disabling condition characterized by burning pain, increased sensitivity to tactile stimuli, and sensations of pain in response to normally non-painful stimuli (Birklein et al., 2000; Wasner et al., 2003). In addition, the syndrome is characterized by motor disturbances such as weakness, tremor and muscle spasms (Veldman et al., 1993), and sympathetic dysfunction, such as changes in vascular tone, temperature changes and increased sweating (Birklein et al., 1998; Wasner et al., 2001). In most cases the upper or lower limb is affected, but also other body parts, or different body parts at the same time can be involved (Stanton-Hicks et al., 1995). According to Bruehl and Chung (2006), CRPS should be understood as a biopsychosocial disorder, whereby psychological, behavioral and pathophysiological factors interact in a complex manner. Most studies of CRPS have focussed on the peripheral and spinal mechanisms responsible for the origin and development of the syndrome. However, there is an emerging view that the peripheral (autonomic and somatosensory) changes in CRPS must be viewed as a manifestation of changes in the brain (Jänig and Baron, 2002). Importantly, CRPS has unexpected similarities with phantom limb sensations and phantom pain (Giummarra et al., 2007; Maihöfner et al., 2004). This paper gives an overview of our current knowledge concerning cortical changes in CRPS (especially involving the sensory-motor cortex), and it discusses novel experimental therapies that directly target the disorganized cortex in an attempt to alleviate some of the symptoms of CRPS. The emphasis of the review will be on mechanisms of neural reorganization and cortical plasticity.

2. Background

CRPS is often preceded by a noxious event, such as a trauma or surgical procedure, after which CRPS may develop in the corresponding part of the body (Stanton-Hicks et al., 1995). However, in some cases no clear eliciting event can be identified (Veldman et al., 1993). The spontaneous pain or hyperalgesia is disproportional to the severity of the trauma and is not limited to the area of the trauma (Stanton-Hicks et al., 1995). Two types of CRPS are typically distinguished. In CRPS-1 no neural damage is evident, whereas in CPRS-2 pain can be traced to an identifiable nerve injury, like a lesion or a tumor (Stanton-Hicks et al., 1995; Jänig and Baron, 2002). The symptoms of the two types are similar, and it has been suggested that the distinction between the two types is more apparent than real (e.g., Oaklander et al., 2006).

The incidence of CRPS in the Netherlands was recently investigated by De Mos et al. (2006) in a search among 600,000 electronic patient records of a general practice research database. It was found that each year about 26 out of 100,000 people develop CRPS. In the Netherlands this amounts to 4300 new sufferers every year. Women in the age of 61–70 years are most at risk. The upper limb is affected more frequently than the lower limb, and in 44% of the cases the syndrome is preceded by a fracture (De Mos et al., 2006). Another study investigated the incidence of CRPS in a rural area in the USA (Sandroni et al., 2003). That study revealed an incidence of 5.46 per 100,000 persons years at risk and a prevalence of 20.57 per 100,000 persons. Again, women were more at risk than men,

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and the most frequently affected area was the upper limb (see also Veldman et al., 1993).

Although CRPS seems to occur mainly in adults, the syndrome may also develop in children, with a somewhat different symptomatology (Lebel et al., 2008; Tan et al., 2008). The lower limb is more frequently affected (Low et al., 2007; Tan et al., 2008) and neurological and sympathetic symptoms seem to be less pronounced (Tan et al., 2008). Interestingly, the functional neuroimaging study of Lebel et al. (2008) showed that the underlying neural mechanisms of CRPS in children and adults are actually quite similar. Again, the syndrome occurs more frequently in girls (Low et al., 2007).

Although a wide range of treatment options exists for CRPS, their efficacy seems to be limited. For example, a review of randomized controlled trials (RCT) found limited evidence for the analgesic effectiveness of sympathetic suppression (Perez et al., 2001). As another example, Forouzanfar et al. (2002) reviewed RCTs of the effectiveness of commonly used therapeutic interventions in CRPS such as sympathetic blocks, radical scavenging, prednisolone administration, acupuncture and manual lymph drainage. The authors concluded that there is limited evidence for the efficacy of such interventions, although calcium-regulating drugs and exercises seemed to be more promising treatment modalities. It is now acknowledged that CRPS is a multifactorial disorder, requiring multidisciplinary treatment (Bruehl and Chung, 2006). Current treatment approaches also include cognitive-behavioural therapy, such as relaxation training, and replacing catastrophizing cognitions with adaptive cognitions (e.g., Bruehl and Chung, 2006). A small number of experimental studies (described below) took a different approach, and asked whether treatments aimed at the cortical representation of the affected limb might be effective.

2.1. Cortical reorganization

It has been hypothesized that a common feature in many chronic pain syndromes is distortion of the cortical topographic representation of the body (i.e., the Penfield 'homunculus'; e.g., Harris, 1999). A clear signature of distorted body representation is the phenomenon of referred sensations, which is the experience of somatosensory feelings that originate from a body part other than the part being stimulated (Giummarra et al., 2007; Ramachandran and Rogers-Ramachandran, 2000). Referred sensations are often reported by amputees or deafferented individuals, who experience sensations in their missing ("phantom") limb when certain areas of the face are touched (e.g., Ramachandran and Hirstein, 1998). Brain imaging studies have revealed that following loss of a limb the somatosensory cortex may undergo plastic changes. The cortical regions that receive no further afferent input (e.g., the amputated arm) are 'invaded' by adjacent cortical areas, such as the lower face area (e.g., Flor et al., 1995; Ramachandran, 1993; Yang et al., 1994). One consequence of this central remapping phenomenon is the experience of referred sensations. Given the commonalities between phantom limb pain and pain in CRPS, a number of studies (described below) have sought for evidence of referred sensations in CRPS.

McCabe et al. (2003a) provided the first demonstration of referred sensations in CRPS-1 patients. Participants had to describe any sensations they experienced, with their eyes-closed, while being stimulated with light touch, pinprick and vibration at various places of their body. Out of 16 individuals with CRPS-1, five reported sensations in their affected limb when they received stimulation at another site of their body. The referred sensations were modality specific and consistent with the Penfield homunculus. That is, the referred sensations were experienced in that part of the body that is adjacent to the stimulated area on the cortical map. No referred sensations were experienced with the eyes open.

Referred sensations in CRPS were also observed by Maihöfner et al. (2006). They applied non-noxious mechanical stimulation to one of two digits (D1 and D5) of a CRPS-affected hand and to the same digits in the contralateral unaffected hand. The authors observed mislocalization in a third of their subjects (8 out of 24), both in CRPS-1 and CRPS-2. Referred sensations occurred only when the affected hand was stimulated and consisted of the experience of being touched at another place within the same hand. For example, when the finger tip of the little finger was stimulated, some subjects reported a sensation at the back of their hand near the wrist. Another finding was that the presence of mechanical hyperalgesia was a significant predictor for the occurrence of tactile mislocalizations. Maihöfner et al. (2006) concluded that CRPS may induce a blurred cortical representation of the fingers, which would then result in intra-manual referred sensations.

Cortical involvement in CRPS was also demonstrated by Acerra and Moseley (2005). In this study the unaffected limb was stimulated with light touch, pinpricks or cold, while a mirror was placed between the subjects' limbs. The subjects watched the unaffected limb in the mirror, with the affected limb hidden behind the mirror. This condition was compared with an eyes-closed condition, in which the affected limb was stimulated without the use of the mirror. A major finding was that watching a mirror image of the stimulated – unaffected – limb evokes pain in the affected limb when the stimulated area corresponded to the area of allodynia. Acerra and Moseley (2005) dubbed this phenomenon "dysynchiria", that is, non-painful touch in one limb is simultaneously experienced as pain or increased sensitivity in the affected limb. They concluded that the central somatosensory representation of the limb can be activated by visual input, possibly mediated by the "mirror neuron" system. This result bears close resemblance to the phenomenon of "cross-referencing" in amputees, i.e., sporadic mirror sensations of pain, itch, touch etc. in both the phantom limb and the intact limb. These sensations are possibly mediated by changes in transcallosal synaptic weights, as evidenced by findings of cortical reorganization ipsilateral to the deafferented limb (Giummarra et al., 2007).

Other studies used functional neuroimaging to examine the purported cortical reorganization in CRPS more directly. Maihöfner et al. (2003) used magnetoencephalography (MEG) to investigate the representation of the primary somatosensory cortex (S1) of a group of twelve CPRS-1 patients with an affected upper limb. During scanning, digits 1 and 5 and the lower lip of both the affected and unaffected side were repeatedly stimulated using air puffs. The results showed that the area of the cortex subserving the hand of the affected side was reduced in size, and that it was shifted in the direction of the representation of the lip. A similar change in cortical topography has been observed repeatedly in amputees with phantom limb sensations (e.g., Ramachandran and Hirstein, 1998). Furthermore, the amount of change in cortical organization in the study of Maihöfner et al. (2003) was correlated with the intensity of pain and the extent of hyperalgesia.

In a follow-up study Maihöfner et al. (2004) tested ten out of twelve subjects from the previous study. Between the tests, all patients had received treatment consisting of physical therapy and anti-inflammatory drugs, and after about one year there was a significant reduction in reported pain. A major finding was that at follow-up the cortical reorganization, that was previously observed, was now largely reversed. Furthermore, the amount of cortical normalization was correlated with the reduction of CRPS pain. These neuroimaging studies thus clearly demonstrate the involvement of cortical reorganization in CRPS, but the relationship between referred sensations and the organization of the somatosensory cortex remains to be established.

Given that CRPS is not only characterized by disturbances of the somatosensory system (as described above) but also by motor dis-

turbances, a recent study (Maihöfner et al., 2007) sought to determine whether adaptive cortical changes also occur within the motor system in CRPS. Ten patients diagnosed with CRPS-1 and a group of twelve healthy controls participated. Subjects made unimanual rhythmic tapping movements during fMRI scanning. One of the findings was that the area of motor cortex contralateral to the affected side was significantly enlarged compared to the ipsilateral (unaffected) side. This is a somewhat surprising finding, because the opposite pattern of results was observed in studies of the somatosensory cortex, viz. a significant reduction in cortical area in CRPS. The authors suggested that the increase in motor cortex representation could actually be due to an increased ipsilateral activation in homologous motor areas via transcallosal fibres. This additional activation is presumably due to increased cognitive processing needed to produce and maintain the required motor pattern.

2.2. Pain and body perception

The importance of central nervous system (CNS) involvement in CRPS is further underscored by the repeated observation of so-called "neglect-like" symptoms in CRPS, which suggests that attention (or lack thereof) of the affected limb co-determines the complex symptomatology of CRPS. According to Galer and Jensen (1999) individuals with CRPS often describe their affected limb as foreign, or not belonging to them, and they need to focus conscious attention on their limb when making voluntary movements. It has also been observed, using psychophysical procedures, that the tactile spatial acuity of the affected limb is significantly reduced relative to controls and relative to the contralateral unaffected limb (Maihöfner and DeCol, 2007). These symptoms are paradoxical, because on the one hand sensory awareness of the limb is reduced in a neglect-like manner, whereas on the other hand the limb has clearly been sensitized to touch and pain, suggesting hypervigilance to the limb. The neglect-like symptoms provide further evidence for a changed cortical representation, and signify some sort of "body perception disturbance" (Lewis et al., 2007) in CRPS. Body perception was investigated using self report in the study of Galer and Jensen (1999). A group of people with CRPS filled out a questionnaire concerning the perception of their affected limb. One of the results was that 60% of the respondents agreed with the statement that "My painful limb feels as though it is not part of my body" (which the authors dubbed "cognitive neglect"), and 56% agreed with the statement that "I need to focus all of my attention on my painful limb to make it move the way I want to" (dubbed "motor neglect").

Similar findings were reported by Förderreuther et al. (2004) in a group of 114 CRPS patients. A major finding was that classical neglect symptoms and signs of extinction were absent in CRPS and that, in contrast to classical neglect, there was no difference between left and right CRPS, which led the authors to suggest that the phrase "neglect-like" may represent a misnomer. One of the conclusions was that body perception disturbance was clearly present in CRPS, but that the current state of knowledge precluded drawing a causal link between body perception disturbance and changes in cortical representation.

More recently, Lewis et al. (2007) conducted a semi-structured interview to examine the extent of body perception disturbance in CRPS. It was found that subjects often experienced their affected limb as not belonging to them. In addition, patients often reported that they were hardly aware of the exact position and orientation of their limb. Lewis et al. (2007) argued that these findings were in agreement with the notion of an altered central representation of the body, and that treatments should be targeted at modifying the central remapping in CRPS, for example using mirror therapy (to be described below). According to Giummarra et al. (2007) the body schema, that is "the internal, dynamic representation of the spatial and biomechanical properties of one's body" (p. 223), is generated in the parietal cortex. Various sensory (e.g., visual and proprioceptive) and motor (movement and efference copy) systems converge to create the representation of the body schema. When one of these systems is damaged, or when a mismatch occurs between converging neural inputs, this can give rise to various perceptual disturbances, such as phantom limb sensations, phantom pain, and probably also pain in CRPS.

Interestingly, Buchner et al. (2000) found that pain, attention, and cortical reorganization are intimately intertwined. In their study they exposed digits 4 and 5 of healthy subjects to a painful condition (ice water), whereas in another condition subjects had to focus their attention on the digits. The peripheral nerves of digits 2 and 3 were electrically stimulated, and subsequently the changes in electrical activity in the brain were recorded to detect cortical reorganization. The analysis of the somatosensory evoked potentials revealed that focussed attention immediately shifts the representation of digits 2 and 3 medially, which was accompanied by an expansion of the representation of the stimulated digits. After the painful stimulation the cortical representation was also expanded, yet after a prolonged period of time, and the reorganization was still evident after the painful stimulation stopped. It was concluded that both pain and spatial attention may induce cortical reorganization, yet the observed differences in time course, extent, and direction of the reorganization suggest dissimilar neural mechanisms.

The underlying mechanisms responsible for body perception disturbance in CRPS are unclear, but it is likely that the disturbance is due to prolonged and active attempts of the patient to suppress sensory and motor activity in the painful, sensitized, and disfigured limb (Frettlöh et al., 2006), so that the limb is no longer integrated in the body schema. Prolonged non-use of the affected limb may lead to a vicious cycle whereby immobility, loss of cortical representation, and atrophic changes reinforce each other (e.g., Bruehl and Chung, 2006; Tichelaar et al., 2007), thereby aggravating the symptoms.

3. Therapeutic opportunities

The observed effects of referred sensations, cortical reorganization, and the normalization of the cortex with CRPS recovery are strongly suggestive of CNS involvement in CRPS. Could pain similarly be explained, and possibly treated, by shifting our perspective to the disorganized cortex? A leading explanation of pain in phantom limbs states that pain arises due to a mismatch between motor intention and proprioceptive feedback (Flor et al., 2006; Harris, 1999). Put simply, the motor cortex has no way of knowing that a limb is missing, and continues to transmit motor commands. The proprioceptive system in the parietal lobes, in contrast, receives no incoming signals from the same body part, and it is this mismatch that creates painful sensations in the amputated limb (e.g., Ramachandran and Hirstein, 1998; Ramachandran and Rogers-Ramachandran, 2000). A successful approach for treating phantom limb pain is to resolve this mismatch using mirror therapy (Ramachandran, 2005; Ramachandran and Rogers-Ramachandran, 1996). The amputee places the intact limb in a mirror box and is looking at the reflection of the unaffected limb, such that the received visual feedback of the amputated limb is replaced by visual feedback of the intact limb. When the intact hand makes a movement, the visual feedback of the mirror creates a vivid impression that the movements originate from the amputated hand. Amputees respond positively to mirror therapy, and some of them experience a permanent reduction in pain (Ramachandran, 2005; Ramachandran and Rogers-Ramachandran, 1996). It has been suggested that the mismatch between motor intention and

sensory feedback of the moving limb underlies not only phantom pain, but also a range of other chronic pain conditions, such as low back pain and CRPS (Harris, 1999), and a handful of studies have now been published aimed at resolving this cortical mismatch in CRPS patients.

The first study that attempted to restore the integrity of processing in the sensory-motor cortex in CRPS was that of McCabe et al. (2003b), who investigated how this patient group would respond to mirror therapy. The authors conducted a controlled pilot study involving eight individuals with CRPS-1. During a 6-week period the participants could use a mirror as frequently as they wished to exercise both limbs at home, with a maximum duration of 10 min each time. The subjects had to write down the frequency of this practice and the pain they experienced, using a visual analogue scale (VAS) score. At baseline and after 6 weeks measures of pain at rest and movement related pain were recorded, again using a VAS-score. In addition to these pain measures, vasomotor changes that are influenced by skin temperature were measured by infrared thermography. It was found that after visual mirror feedback the patients with early CRPS (<8 weeks, $N = 3$) reported a significant reduction in pain intensity. At baseline, the pain returned when the mirror was removed, but when the mirror was used more frequently the pain free period also increased. Separate control conditions revealed that these beneficial effects could not be accounted for by visualization or selective attention. In patients with an intermediate disease duration (>8 weeks and <2 years, $N = 2$) the use of the mirror led to an immediate reduction in stiffness, which facilitated movement. At 6 weeks vasomotor changes had occurred in these patients. In contrast, in chronic CRPS patients (>2 years, $N = 3$) mirror therapy had no effect. In sum, the study of McCabe et al. (2003b) suggests a beneficial effect of visual mirror feedback on pain severity and on vasomotor function, at least in the early stages of CRPS. The analgesic benefit of mirror therapy is likely due to the false, yet congruent visual feedback provided via the mirror, which serves to re-establish the balance between sensory feedback and motor intention within cortical areas.

Moseley (2004) also tried to modulate the cortical abnormalities in CRPS using a combination of techniques that were aimed at targeting the disorganized cortical networks. In that study pain scores in two groups of subjects were compared: an experimental group, consisting of thirteen CRPS-1 subjects with upper limb symptoms, and a control group that received standard medical care. Moseley (2004) developed a so-called motor imagery program (MIP) consisting of three stages: a limb laterality recognition task, an imagined limb movement task, and mirror therapy. In the limb laterality recognition task the participants had to identify a pictured hand as a left or a right limb. It was assumed that performing this task would activate the pre-motor cortex. In the second stage of the MIP subjects had to imagine that they adopted a limb posture similar to the one shown in a picture. It was assumed that mentally adopting one of several postures would activate both the pre-motor cortex and the primary motor cortex. Finally, during the mirror therapy stage, the subjects had to actually adopt limb postures shown in each picture with both hands. Importantly, in this stage the hands were put in a mirror box, such that the affected limb was concealed from view, and subjects watched the reflection of their unaffected limb. Each stage of the MIP was performed for two weeks on a daily basis. It was found that the treatment had a strong beneficial effect on pain and limb swelling and that the effect was maintained for several weeks. Furthermore, 6 weeks after the treatment, about 50% of the subjects did no longer meet the criteria of the diagnosis of CRPS-1. Moseley (2004) suggested that the cortical activation induced by the MIP caused subjects to consciously focus attention on their affected limb, thereby alleviating the neglect-like symptoms reported earlier, and reversing the learned disuse of the limb. Thus, the established principle in rehabilitation to 'train the brain' can also be applied to CRPS, although many questions regarding the time course, frequency, and optimal structure of the imposed pattern remain to be answered.

In a later study Moseley (2006) evaluated the same graded motor imagery program using a more heterogeneous group of CRPS-1 patients, and also using a group of amputees, to test whether the similarities between the syndromes also results in similar reactions to the MIP. A group of CRPS-1 patients with upper or lower limb deficits ($N = 37$) and a group of phantom limb pain patients ($N = 14$) participated, and subjects were randomly assigned to the experimental or the control group. The experimental group participated in the graded motor imagery program, whereas the control group received a physical therapy program and ongoing medical care. Similar to the previous study (Moseley, 2004), each stage of the program had a duration of two weeks. Outcome measures were the patient-specific task-related numerical rating scale (NRS), the McGill Pain Questionnaire (MPQ) to determine current pain intensity, and a VAS-score to measure the average level of pain intensity over the past two days. Moreover, the symptoms were assessed at pre and post test. The results clearly showed a significant improvement in primary outcome measures (decrease in pain, increase in function) between the experimental and control group. Another major finding was that within the experimental group the CRPS-1 patients and amputees benefited to an equal degree from the program. The correspondence between these two patient groups suggests that sensory-motor incongruence underlies both syndromes, and that re-activation of disused neural circuits may resolve this incongruence, leading to reduced symptoms. These are very compelling results, but the conclusion would receive further support if the measures were complemented with neuroimaging data. For example, Birklein and Maihöfner (2006) pointed out that some of the effects might actually be due to reduced anxiety and not to reduction of sensory-motor incongruency, and neuroimaging studies could help rule out alternative explanations. It is conceivable that the motor imagery program works by inducing plastic changes in motor cortical areas. Maihöfner et al. (2007) clearly showed a significant reorganization of central motor circuits in a group of 12 CRPS patients, which was accompanied by a reduced ability to perform smooth reach-to-grasp movements. This opens up the possibility of reversing this process of neural plasticity by using therapies aimed at central motor representations (e.g., motor imagery or motor practice), which might lead to a reduction in motor disturbances.

Recently, Tichelaar et al. (2007) piloted the effect of the combination of both mirror therapy and cognitive-behavioural therapy in three individuals with CRPS-1. The patients first gradually stopped using analgesics, and then received mirror therapy three times a day, a whole week, with a duration of two times 5 min. From the third week the intensity of the mirror therapy was increased to 5 sessions a day. Pain intensity, with the use of a VAS-score, range of limb motion, muscle strength, and area of allodynia and hyperalgesia were measured once a week and at follow-up. It was found that two patients experienced a reduction in pain after treatment. In addition, range of motion improved in both patients, and one of them also had improved strength. The third patient showed no improvement on any of the outcome measures. Unexpectedly, the area of hyperalgesia increased in all three subjects. The authors concluded that the combination of the therapies might be helpful in rehabilitation of CRPS-1, but that success also depended on the duration of the syndrome.

If pain in CRPS is the result of a mismatch between cortical areas that control limb movements and areas that monitor the sensory consequences of these movements, then it should be possible to experimentally induce pain in healthy subjects, by artificially inducing such a mismatch. McCabe et al. (2005) provided

empirical support for this hypothesis. They investigated in healthy subjects whether a conflict between sensory feedback and motor output would give rise to spontaneous sensations of pain and peculiarity. Sensory mismatch was introduced by asking subjects to perform rhythmic bilateral movements of the upper or lower limbs while viewing a mirror reflection of one of their limbs, with the other limb hidden from view. The bilateral movements were either congruent (symmetric flexions and extensions) or incongruent (anti-symmetric flexions and extensions). It was found that within 20 s the majority of subjects experienced anomalous sensations, such as tingling, numbing, stiffness, or acute pain. Furthermore, these sensations were most often reported in the incongruent condition (66%). Thus, pain can be induced in a relatively simple fashion in the complete absence of a noxious event. Pain is then caused by sensory-motor mismatch, which arguably results in an impaired efference copy of the motor signal. The results provide indirect evidence for the theoretical rationale behind mirror therapy: since a mirror can be used to induce a sensory-motor mismatch, and since this mismatch (as in CRPS) can be corrected with a mirror as well, it is likely that common neuroplastic mechanisms are at work here.

Therapies such as mirror box therapy are directly aimed at reducing the sensory-motor mismatch, and hence at restoring the disorganized body schema (Harris, 1999). There is evidence that not only chronic pain cases (phantom limb pain and CRPS), but also stroke survivors may benefit from therapies aimed at restoring or renormalizing cortical activity (e.g., Giummarra et al., 2007; Ramachandran, 2005). In a review of mirror box therapy and CRPS, McCabe et al. (2008) concluded that this form of therapy, possibly in combination with motor imagery, is promising, yet still in its infancy. Similarly, Moseley et al. (2008) concluded that the beneficial effect of mirror therapy for CRPS is still anecdotal, and should be investigated using methodologically more rigorous studies. Importantly, the precise neural mechanisms of action are unknown, and need to be studied using a combination of behavioural and neuroimaging approaches. The consensus in the literature seems to be that the disorganized parietal cortex generates some of the symptoms of CRPS, such as pain and inattention, but there is also evidence that the prefrontal cortex (McCabe et al., 2008) and the ipsilateral motor cortex (Maihöfner et al., 2007) play a role.

The interventions described in this review seem to have their effect by reducing the mismatch between motor output and sensory feedback. From these studies it has become evident that this can be accomplished in several ways, for example by providing (false) visual feedback or by engaging in mental imagery. In principle, there exists a range of other possibilities to eliminate this mismatch, but these have not been explored. For example, one could attempt to artificially manipulate proprioceptive feedback of the limb, in a manner akin to the mirror box, by providing a novel pattern of force feedback elicited by limb movements. Also visual feedback can be manipulated in more challenging ways with the help of virtual reality environments, which can be used to provide whole new mappings between (real) limb movements and experienced sensory consequences. Another possibility to restore the mismatch between the neural divisions would be to directly influence cortical excitability using repetitive transcranial magnetic stimulation (rTMS). As a case in point, it has been reported that symptoms of unilateral neglect can be temporarily ameliorated by applying rTMS over the unaffected hemisphere (e.g., Fierro et al., 2006). Some of the options described here may not (yet) be technically feasible, but they all have in common that they attempt to "hijack" the disorganized cortex via a particular entry point, which can than be used to apply novel and consistent structured patterns of neural activity which may, in turn, lead to long-term neural changes.

4. Conclusions

CRPS is no longer seen as an exclusively peripheral problem, and nowadays the role of the neocortex in the pathogenesis and chronicity of the syndrome is also recognized. Mislocalizations, changes in the size and organization of the somatosensory map, changes in motor cortex representation and body perception disturbances are strongly suggestive of cortical involvement in CRPS. We reviewed experimental treatment options, such as mirror therapy and motor imagery programs, that attempt to directly influence disorganized cortical representations in people with CRPS. Although the number of studies that investigate the effects of these interventions is limited, the results of the studies are promising. Mirror box therapy seems to be beneficial especially in early CRPS (e.g., McCabe et al., 2003b), but promising results with chronic CRPS and motor imagery were found (Moseley, 2004). To our knowledge, the studies by Moseley (2004, 2006) are the only ones that meet the criteria of a randomized controlled trial.

The beneficial effects of the experimental treatments are consistent with Robertson and Murre's (1999) notion of guided recovery, according to which a lesioned or disorganized network can undergo plastic changes due to a combination of patterned stimulation and Hebbian learning. Within this framework, providing mirror visual feedback would constitute an instance of bottom-up specific stimulation, whereas efforts to direct conscious attention to the limb, e.g., using visual imagery, would constitute an instance of top-down specific stimulation. Whether a pattern of stimulation is externally imposed (bottom-up) or internally generated (top-down) is of secondary importance; the main issue is whether the neural pattern is effective in inducing restitutive changes in the circuit (Robertson and Murre, 1999). The neural mechanisms underlying central reorganization are likely diverse (Nudo, 2006). Broadly speaking, cortical changes arise from alterations in connectivity between neural networks, such as unmasking or disinhibition of previously silent inputs, long-term potentiation, axonal or dendritic sprouting, increased density of postsynaptic receptors, decreased inhibitory inputs, and modulation of neurotransmitter activity (Flor et al., 2006; Nudo, 2006). This process of neuroplasticity can take place at different time scales and is strongly dependent on patterned neural activity (Robertson and Murre, 1999). Consistent sensory stimulation of the neural network or disruption of stimulation has clear effects on sensory-motor maps, as is the case in phantom limbs, and this cortical reorganization is probably mediated by a process of Hebbian learning (Robertson and Murre, 1999). We believe that a similar mechanism is at work in CRPS, but here the cortical changes are probably the result of consistent self-generated activity aimed at reducing sensory stimulation. It is this process of prolonged and active inhibition that sets in motion a vicious cycle of non-use, inattention, body perception changes, and abnormal sensory integration in the cortex (Bruehl and Chung, 2006; Ramachandran, 2005). As a case in point, there is evidence to suggest that pharmacological agents such as GABA agonists can block changes in S1 cortex. This blockade prevents the formation of pain memories and thus of phantom pain (Flor, 2002; Flor and Birbaumer, 2000). This state of affairs of course underscores the importance of early behavioral and pharmacological intervention, so as to bring the process of maladaptive cortical reorganization to an early halt.

In conclusion, recent research provides empirical support for cortical reorganization and body perception disturbances in CRPS and for the efficacy of therapies that target the disorganized cortical network. Despite the fact that a limited number of studies have evaluated the effect of interventions that target cortical networks, these approaches seem very promising in people with CRPS. Therefore, mirror therapy and motor imagery programs can complement

existing management schemes in the treatment of CRPS, as they are non-invasive and cost effective. Moreover, these new therapeutic options can be theoretically motivated on the basis of established principles of neural organization.

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