

Neurorehabilitation of Chronic Pain: Relationships among Pain, Motion, and Perception

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Current Status of the Neurorehabilitation of Pain

Chronic pain emerges not only because of the injury of peripheral organs or a plastic change in spinal nerves, but also because of plasticity in the brain [1]. Therefore, the development of interventions dedicated to the rehabilitation of pain must occur via approaches that cause changes in the brain, instead of approaches that treat only peripheral organs. In particular, pain is composed of three facets, including a sensory aspect, a cognitive aspect, and an emotional aspect [2]. Thus, the rehabilitation of the brain represents an approach to that will address the cognitive and emotional aspects in particular.

A plasticity is observed in the brain when chronic pain persists for a certain period; this is true not only for pain caused by brain damage and for neuropathic pain, but also for pain caused by motor system diseases [3]. Somatosensory areas are the main centers involved in the sensory aspect of pain and are considered to be responsible for acute pain. Therefore, direct intervention in these areas via neurorehabilitation is not likely. However, the application of neurorehabilitation to elicit effective changes in other areas responsible for pain, including the parietal lobe, insular cortex, anterior cingulate gyrus, amygdala, and prefrontal cortex, has gained attention recently [4]. The parietal lobe and prefrontal cortex are mainly involved in the cognitive aspect of pain; conversely, the insular cortex, anterior cingulate gyrus, and amygdala are mainly involved in its emotional aspect.

Neurorehabilitation has been reported to be effective in perception and motor imagery tasks [5]. These tasks subdivide perception, integration of visual and somatic sensations, and consistency between images and feedback information based on actual motion. In addition, methods that facilitate and suppress directly the neural activity of the brain using transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) have been developed recently and applied clinically.

In contrast, the prefrontal area and the periaqueductal grey (PAG) are involved in diffuse noxious inhibitory controls (DNIC) and placebo pain relief. Because hypofunction of the prefrontal area is considered to cause the chronicity of pain, the activation of this area is key for the clinical effect of neurorehabilitation in some cases.

Neural Plasticity Induced by Immobility

Several studies have shown that, generally, somatotopic representations of the primary sensory area and primary motor area are modulated by changes in the perceptual experience of the body in patients with chronic pain. These degrees of somatotopic representation of the cortex and strength of pain are correlated. The changes in somatotopic representation are influenced by the duration of illness, immobility, and reduction of the somatosensory input caused by immobility. This is based on a neural mechanism in which pain-induced suppression of motion and taking actions to avoid the pain cause learned nonuse, the continuance of which leads to a narrowed somatotopic representation of the affected body part; this results in hypofunction of the area of the cortex that is involved in pain suppression and in consequent chronic pain (Figure 1) [6]. This is originally the mechanism that explains the development of movement disorder after brain damage, i.e., the pathology of paralysis

[7]. However, the secondary brain dysfunction is caused by the nonuse of the body also in patients with pain who develop no brain damage normally, because of pain instead of paralysis. Such failure of the pain-suppression mechanism due to cortical dysfunction influences the severity of pain and motor function. In addition, disinhibition occurs in the primary motor area of patients with complex regional pain syndrome (CRPS) [8]. Thus, it is currently well known that long-lasting immobility causes brain dysfunction.

Discrepancy between Motor Simulation and Perception

In acute pain, the addition of a sensory input to the body leads to the overactivity of the pain-related region, which results in the occurrence or enhancement of pain, even if it is not an invasive stimulation. In chronic pain, a mechanism has been reported in which no appropriate activation of a brain region is observed at the time of simulation and imaging, leading to chronicity of the pain via the occurrence of a sensory discrepancy (Figure 2) [9]. For example, CRPS patients exhibit activation of sensory and motor areas during actual movement, whereas no activity similar to that of motor execution is observed when motor imagery [10]. The brain activities during motor execution and the motor imagery are normally equivalent. However, a dissociation

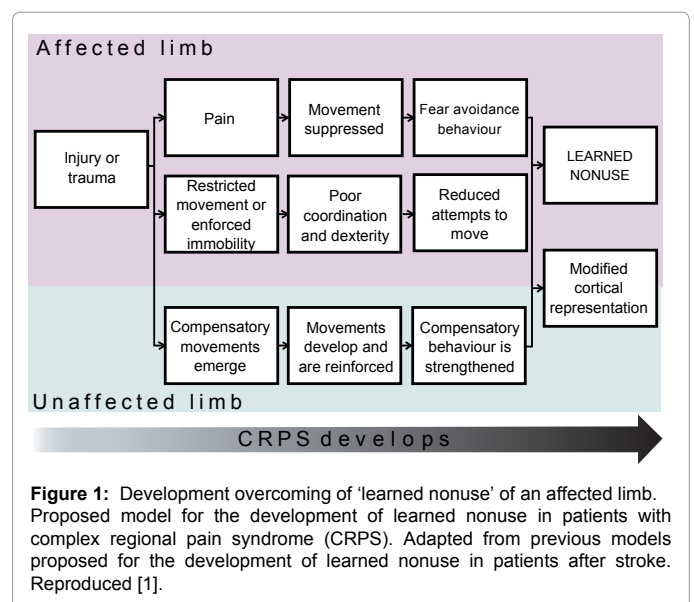


Figure 1: Development overcoming of 'learned nonuse' of an affected limb. Proposed model for the development of learned nonuse in patients with complex regional pain syndrome (CRPS). Adapted from previous models proposed for the development of learned nonuse in patients after stroke. Reproduced [1].

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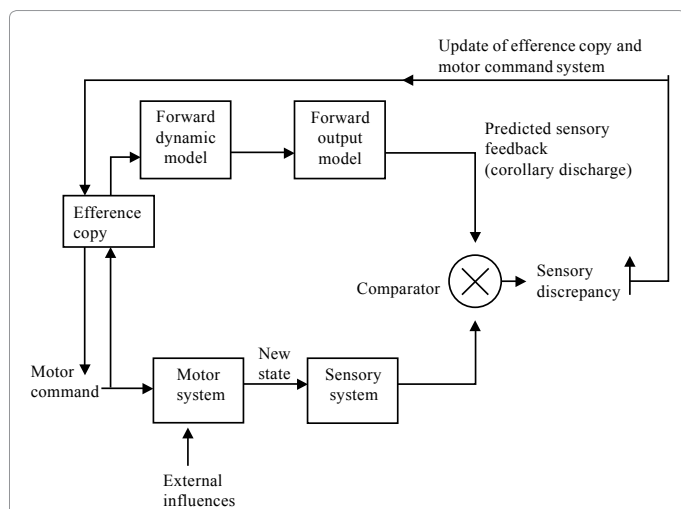


Figure 2: Schematic diagram depicting the role of the efference copy in the motor control system. Information from current state variables (e.g. joint position sense) is used to create a prediction of the sensory consequences of any motor command. This prediction, or efference copy, is compared (comparator) with the actual sensory consequences of that new activity. When a discrepancy is noted this information is fed back to the motor command system to update the state variables and thereby inform future efference copies [4].

between the two is observed in CRPS patients who exhibit no activation during the motor imagery. Thus, failure of the perception–motion loop occurs in patients with chronic pain. This information discrepancy observed in patients with chronic pain seems to be the cause of neglect-like symptoms [11]. This phenomenon consists of two symptoms, including cognitive neglect, in which patients do not feel that their diseased limbs are their own body, and motor neglect, in which patients cannot move their diseased limbs without paying excessive attention to their visual sensation. Table 1 presents the concrete evaluations of this phenomenon [12]. CRPS patients often have neglect-like symptoms, as they exhibit finger agnosia, size-perception disorder, elevated somatosensory threshold of diseased limbs, and reduction of brain activity during the motor imagery of the diseased limbs. These symptoms are similar to those of asomatognosia, which is a higher brain dysfunction that occurs after brain damage. We reported that these neglect-like symptoms occur in motor system diseases as well [13].

Rehabilitation Using Motor Illusion Based on Vibratory Stimulation

In the duration of immobility, it is also important in the sense of preventing chronicity how to maintain the somatotopic representation. However, when pain emerges, it is difficult to input afferent information into the brain from the periphery via compulsory motion. In addition, casting the affected part after injuries such as ligament damage or bone fracture, or after surgery, is a classical medical treatment and is considered to be useful for facilitating the healing process of the damaged tissues. However, around 40–50% of patients develop CRPS or allodynia because of cast-caused immobility [14].

As shown above, if the brain activities recorded at the time of motor execution or motor imagery are equivalent, body-part-related brain activities may be maintained by inducing motor imagery or motor illusion, which may prevent the chronicity of pain. Several rehabilitation approaches based on this theory have been devised. Among them, an intervention that uses the motor illusion or the motor

imagery is garnering attention. For example, one method induces a motor illusion in which the patient feels as if the motion of his/her own joint has occurred by perceiving that the muscle has been extended due to the stimulation by an afferent input from the projection of the muscle spindle, caused by the vibratory stimulation of a tendon. Recently, we showed that, in this case, the brain is also activated equivalently to the motor execution. Because the motor illusion motivated by the vibratory stimulation of a tendon causes no actual motion, it can induce motor illusion by causing less pain. Whether the motor illusion caused by vibratory stimulation influences pain or joint range of motion has been investigated. It was reported that more enhanced and instant effects of pain reduction are remarkable in the group given vibratory stimulation in addition to the normal 10 weeks of rehabilitation, such as massage, drainage, occupational therapy, physiotherapy, and electric stimulation [15]. Conversely, it was reported that appropriate activity of motion-related regions, including the primary motor area, occurred during the movement of the hand after the removal of a cast of the hand and finger joints that caused immobility during the period (5 days) in which vibratory stimulation was added, whereas the activity of those regions was reduced in the group that did not receive vibratory stimulation [16]. We performed an intervention to induce the motor illusion in patients that necessitated a cast after surgery for a fracture of the distal edge of the radius by adding vibratory stimulation for 7 days to the hand joint that developed no pain in the unaffected side; we found that only the groups that were given the vibratory stimulation exhibited the effect on pain and range of motion of the hand joint after removal of the cast [17]. We also demonstrated that the tactile identification task administered to two patients whose limbs were amputated because of diabetic gangrene revealed the pain-reducing effect of the phantom limb pain, although this does not constitute an motor illusion caused by vibratory stimulation [18].

Rehabilitation Using Motor Illusion Based on Visual Perception

A mirror box is a box with two mirrors in the center (one facing each way), invented by Ramachandran to help alleviate phantom limb pain, in which patients feel they still have a limb after having it amputated. It is called mirror therapy. This is based on the principle of the existence of consistency between the memory information based on the somatic sensation of the lost hand (somatic sensation) and the information based on the induction of visual illusion (visual perception) [19]. In fact, the mitigation of phantom limb pain using this intervention has been reported [20-22]. Among the various verified intervention effects of mirror therapy on pain, the study performed by Sumitani et al. [22]. is interesting. Their report revealed that cases showing an intervention effect experienced pain with proprioceptive sensibility-related characteristics (e.g. twisted), whereas the intervention was not so effective for pain with cutaneous receptive sensibility-related characteristics (such as being pierced by a knife). Moreover, those authors mentioned the usefulness of self-care of phantom limb pain using voluntary movement of the phantom limbs acquired by mirror therapy. They also reported that, in the case of the involuntary

Item 1	If I don't focus my attention on my painful limb it would lie still, like dead weight.
Item 2	My painful limb feels as though it is not part of the rest of my body.
Item 3	I need to focus all of my attention on my painful limb to make it move the way I want it to.
Item 4	My painful limb sometimes moves involuntarily, without my control.
Item 5	My painful limb feels dead to me.

Table 1: Neurobehavioral Questionnaire by Galer.

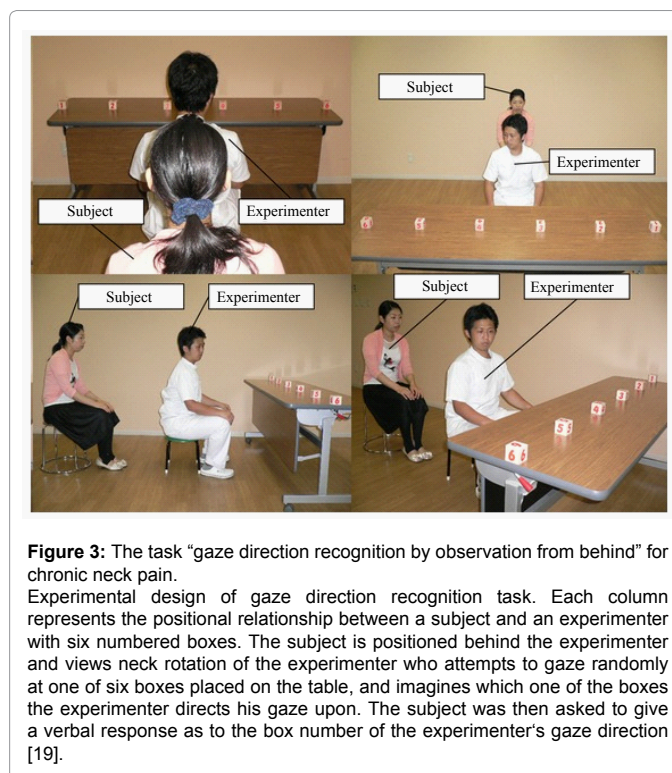
emergence of uncomfortable phantom limb sensation accompanied by kinesthesia, making a voluntary movement of phantom limbs, and thus antagonizing the involuntary movement, allows the self-care of pain. This is not only a very interesting fact regarding patient education, but also shows that the appropriate simulation of motion may control pain. In contrast, it is known that the subjective recognition of CRPS patients' own midline is biased toward the affected side. Sumitani et al. [23] administered the prism adaptation test for 2 weeks, in which CRPS patients pointed an index by wearing prism adaptation task and reported that their recognition of the body's midline was normalized and that the pain, edema, and skin-color changes improved. Such pain caused by a distortion of the body image seems to be caused by the failure of sensorimotor integration and is considered to be due to bidirectional network failure between the premotor area and the posterior parietal lobe [9]. We confirmed the activity of the parietal lobe and premotor area during the prism adaptation task [24].

Rehabilitation Using Motor Imagery

Several studies have shown that motor imagery causes positive effects of pain reduction. For example, the intervention devised by Moseley consisted of 1) the left-right orientation test of the hand in which the subject identifies the hand in a photograph presented as being the left or right hand, 2) the imagery test of mentally requested motions, and 3) mirror therapy. The administration of these interventions in the order of 1) to 3) has been reported to lead to pain reduction [25]. The improvement of the dissociation shown in figure 2 is considered as the mechanism underlying this pain reduction. Briefly, the motor-simulation function is made consistent with the afferent information generated by a motor execution via imagery enhancement of the motion. Although the rehabilitation approach using vibratory simulation described above generates illusory motion in the brain in a bottom-up manner using afferent information from the periphery, this motor imagery leads to the formation of the illusive motion in a top-down manner based on memory in the brain. However, care must be taken regarding the intervention using motor imagery, because pain has been reported to conversely increase in association with motor imagery. The evocation of the emotional aspect of pain, such as fear and uneasiness, by motor imagery may cause remembrance of the pain. We developed a motion-observation therapy based on gaze recognition, as shown in figure 3, as a measure to overcome this problem [26,27]. This task was devised for patients with neck pain. In this task, the patient observes the circular movement of the head and neck of another person and is asked to guess what the other person intended to observe based on that motion. When assuming this intention, the patient has to simulate the motion by observing the motion of another person from the back, as if the patient is making the circular movement. This resulted in significant pain reduction and increase in neck-joint range of motion in the group that simulated the neck motion by attempting to read which index the other person intended to observe compared with the group that simply observed another person's motion without assuming their intention. The level of this effect was significantly higher than that observed in groups that received intervention via physiotherapy, including electric stimulation and traction therapy. Prior to this intervention, we showed that the movement-related regions were activated during this test using a brain imaging technique.

Influence of Exercise on Pain Suppression

Studies that investigated the influence of the type of exercise on pain reported that the score of emotional expression on the McGill pain questionnaire decreased after running compared with after walking [28]. Conversely, the pain threshold and score of subjective sensation



after the administration of stimulation were not different between the two conditions. In addition, the expression of b-endorphin, which causes euphoria and pain relief, was increased in the running condition [29]. We confirmed that the administration of a medium-level exercise test using a bicycle ergometer enhanced serotonin release. In contrast, a study that investigated the brain regions that showed changes in opioid binding associated with pain relief after running confirmed that opioid binding was decreased (endogenous opioids were released) in the frontal lobe, cingulate gyrus, insular cortex, and hippocampus [30]. Thus, although there is evidence of pain relief due to the release of endogenous opioids caused by motion, there is also an indication that no pain relief effect occurs in patients with chronic pain because of that absence of release of endogenous opioids. For that reason, a certain measure is required when performing an intervention using a gross movement. For example, it has been shown that requesting motions of a body part closely located to the pain-developing part is an effective intervention. At any rate, because of the existence of a relationship between body activity and pain, the addition of their relationship with brain function would allow us to say that an increase in body activity leads to increased activity in the regions that regulate pain, such as the dorsolateral part of the prefrontal area, during pain stimulation. Conversely, lower activity leads to increased activity at the time of pain stimulation in the regions involved in the sensory aspect of pain, such as the primary sensory area and the parietal lobe. Such series of achievements will allow us to say that performing a given motion is also important for activating the neural mechanisms that suppress pain. New neurorehabilitation such techniques should be applied to patients with chronic pain.

Pain-relief Effects of Neuromodulation Techniques by TMS or tDCS

Repeated TMS (rTMS) therapy for chronic pain is being increasingly adopted since its original report by Migita et al. [31].

The stimulations used in rTMS are broadly classified into three types: administered to the primary motor area of the opposite side of the affected part, administered to the dorsolateral part of prefrontal area, and administered to the parietal lobe. Hirayama et al. [32] reported that, among the stimulations administered to several regions of patients with chronic pain using rTMS, only the stimulation of the primary motor area yielded a reduction effect on pain. The principle of this therapy is the normalization of the function of the primary motor area, the corresponding region in the affected side, by causing its disinhibition via the suppression of the activity of the primary motor area, the corresponding region in the unaffected side. We estimate that pain was reduced by this adjustment of brain activities. In contrast, another report has stated that the therapy given to manage facial pain after tooth removal in the case of depression using rTMS in the dorsolateral part of the prefrontal area resulted in pain reduction [33]. Moreover, a recent report showed that a therapy for chronic pain and depressive symptoms using TMS in the dorsolateral part of the prefrontal area led to the observation of the same effect [34]. When a chronic pain persists, depressive symptoms are observed and the prefrontal area exhibits hypofunction. These series of interventions are based on the theory according to which pain is reduced as a result of an attempt to improve depressive symptoms via the induction of excitement in the prefrontal area by rTMS. Data associated with tDCS are also accumulating. Several studies have confirmed the effect of the noninvasive adjustment of cortical neuronal membrane potential, such as that obtained using tDCS, on the pain relief associated with the sensory aspect of pain [35,36]. In addition, regarding the effect of tDCS on the emotional aspect of pain, it was confirmed that tDCS in the prefrontal area significantly reduces unpleasantness in the subjective evaluation [37]. As we confirmed that tDCS reduced unpleasantness in the emotional aspect of pain, and that at that time the prefrontal area was activated (decrease in the frequency of the α -band and increase in the frequency of the β -band) [38], the application of neuromodulation techniques for the therapy of chronic pain will gain attention in the future. However, the long-term prognosis of these neuromodulation techniques has not been reported. This is a future task.

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