ARTICLES

Interactions between Pain and the Motor Cortex: Insights from Research on Phantom Limb Pain and Complex Regional Pain Syndrome

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ABSTRACT

Purpose: Pain is a significantly disabling problem that often interacts with other deficits during the rehabilitation process. The aim of this paper is to review evidence of interactions between pain and the motor cortex in order to attempt to answer the following questions: (1) Does acute pain interfere with motor-cortex activity? (2) Does chronic pain interfere with motor-cortex activity, and, conversely, does motor-cortex plasticity contribute to chronic pain? (3) Can the induction of motor plasticity by means of motor-cortex stimulation decrease pain? (4) Can motor training result in both motor-cortex reorganization and pain relief?

Summary of Key Points: Acute experimental pain has been clearly shown to exert an inhibitory influence over the motor cortex, which can interfere with motor learning capacities. Current evidence also suggests a relationship between chronic pain and motor-cortex reorganization, but it is still unclear whether one causes the other. However, there is growing evidence that interventions aimed at normalizing motor-cortex organization can lead to pain relief.

Conclusions: Interactions between pain and the motor cortex are complex, and more studies are needed to understand these interactions in our patients, as well as to develop optimal rehabilitative strategies.

Key Words: motor control, motor cortex, pain, plasticity, rehabilitation

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RÉSUMÉ

Objectif : La douleur est considérablement invalidante et présente souvent des interactions avec d'autres déficits au cours du processus de réadaptation. L'objectif de cet article est d'analyser donnée supportant la présence d'interactions entre la douleur et le cortex moteur afin de tenter de répondre aux questions suivantes : (1) La douleur aiguë nuit-elle à l'activité du cortex moteur? (2) La douleur chronique altère-t-elle l'activité du cortex moteur et, réciproquement, la réorganisation du cortex moteur contribue-t-elle à la douleur chronique? (3) L'induction de la plasticité motrice par stimulation du cortex moteur peut-elle réduire la douleur? (4) L'entraînement moteur peut-il amener à la fois une réorganisation du cortex moteur et un soulagement de la douleur?

Résumé des principaux points : Il a été clairement démontré que la douleur aiguë expérimentale exerce une influence inhibitoire sur le cortex moteur, qui peut entraver les capacités d'apprentissage moteur. Les donnée actuelles suggèrent également qu'il existe une relation entre la douleur chronique et la réorganisation du cortex moteur, mais il n'est pas clair que l'un provoque l'autre. Il existe toutefois des preuves de plus en plus nombreuses que les interventions visant à normaliser l'organisation du cortex peuvent amener un soulagement de la douleur.

Conclusions : Les interactions entre la douleur et le cortex moteur sont complexes et d'autres études sont nécessaires pour comprendre ces interactions chez nos patients et pour concevoir des stratégies de réadaptation optimales.

Mots clés : contrôle moteur, cortex moteur, douleur, plasticité, réadaptation

INTRODUCTION

Pain is one of the most common and disabling symptoms of numerous diseases. For many years, pain was considered and treated as a symptom of pathology or injury and as a sensory phenomenon only.[1] Steering away from this view of pain as a purely sensory process, contemporary integrative models of pain now include a sensory–discriminative component (processing infor-

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mation about the location and the type of pain) and a motivational–affective component (processing the subjective feeling of unpleasantness associated with pain).[2,3] Brain-imaging techniques have revealed a complex network of cerebral structures associated with the different dimensions of pain, including the primary (S1) and secondary (S2) somatosensory, insular (IC), anterior cingulate (ACC) and prefrontal (PFC) cortices, and thalamus (Th).[4,5] In addition to this brain network, which is classically associated with pain processing, some functional neuro-imaging studies have also reported haemodynamic changes in brain regions related to motor function during pain, including the primary motor cortex (M1), although this aspect of pain-related brain activity is rarely discussed.[5,6] These neuro-imaging results do not necessarily indicate that motor areas are involved in pain processing and perception, but they certainly raise the possibility of interactions between pain and motor function. Although the possible link between pain and motor functions was recognized several years ago,[7] research into the nature and extent of these interactions is very recent.

Physiotherapists are generally aware that pain can interact with other functions during the rehabilitation process, and particularly with motor functions, but these motor dysfunctions are often simply regarded as a consequence of movement-related pain or anticipated movement-related pain (e.g., kinesiophobia). The interactions between pain and motor control are much more complex, however, and more in-depth knowledge about these interactions is necessary to understand the physiology of the motor and nociceptive systems in patients suffering from both pain and motor deficits, as well as to develop rehabilitative strategies that take these interactions into account. One important aspect to consider from a rehabilitation perspective is that these interactions may be bidirectional—that is, pain may have an effect on motor-cortex activity, but motor-cortex activity may also have an impact on pain. The aim of this paper is to review evidence on interactions between pain and motor-cortex activity in an effort to answer the following four questions:

1. Does acute pain interfere with motor-cortex activity?
2. Does chronic pain interfere with motor-cortex activity, and, conversely, does motor-cortex plasticity contribute to chronic pain?
3. Can the induction of motor plasticity by means of motor-cortex stimulation decrease pain?
4. Can motor training result in both motor-cortex reorganization and pain relief?

As these four questions target the motor cortex rather than the motor system in general, the effect of pain on the muscle itself and on spinal reflexes will not be addressed in detail here. The effects of focal muscle pain on muscle activity during rest, contraction, and fatigue have been reviewed elsewhere.[8,9] This review focuses mainly on two models of chronic neuropathic pain: phantom limb pain and complex regional pain syndrome (CRPS). As the idea of maladaptive plasticity within the sensorimotor cortex as a potential cause of chronic pain (or of pain maintenance) has emerged from research in the field of neuropathic pain,[10,11] most existing research on the interaction between motor-cortex plasticity and pain was conducted in these populations.

DOES ACUTE PAIN INTERFERE WITH MOTOR-CORTEX ACTIVITY?

Plasticity has been clearly observed in the sensory systems in response to both acute and chronic pain, including changes in the dorsal horn, thalamus, and the somatosensory cortex,[11–14] but the idea that pain may also affect the motor system is relatively new.[15] Most studies that have focused on the interactions between pain and motor function have dealt with the effects of experimental acute pain on spinal-cord reflexes (see Sandrini et al.[16] and Clarke and Harris[17] for reviews). During the withdrawal reflex response, nociceptive information from skin, muscles, and/or joints makes synapses with motoneurons located in various spinal-cord segments, inducing a complex flexion synergy of the stimulated limb.[16,18] This flexion synergy plays a protective role against potential limb damage[16] and attests that interactions between pain and motor function occur as early as in the spinal cord. Interestingly, applications of previous noxious stimuli to specific regions of the limb, as well as the presence of certain injuries, have been shown to increase the magnitude of the withdrawal reflex response (see Clarke and Harris[17] for a review). These increased withdrawal responses are thought to be caused by changes occurring at the sensory level (e.g., central sensitization) that would enhance the protective function of the withdrawal reflex after tissue injury.[17,19]

It has been demonstrated that pain leads to a reduction of maximal voluntary contraction, a decrease in endurance during submaximal contraction, and changes in coordination during dynamic tasks (see Graven-Nielsen and Arendt-Nielsen[8] and Arendt-Nielsen and Graven-Nielsen[9] for reviews). Moreover, recent studies using intra-muscular electromyography (EMG) recordings have shown that pain (induced in either muscular or non-muscular tissue) results in changes in the motor-unit recruitment strategy, revealing that the effect of pain is not limited to a uniform inhibition of the motoneuron pool but, rather, includes more subtle changes in the distribution of output to the motoneuron pool.[20,21] However, it is still unclear whether these alterations in motor function observed at the muscular level reflect changes at the peripheral, spinal, or cortical level.

Two different models have been proposed for the inter-

actions between pain and movement: the vicious circle model[22] and the pain-adaptation model.[23] The vicious circle model suggests that musculoskeletal pain is sustained by the fact that pain-related muscle spasms lead to muscle ischemia, which in turn increases pain and contributes to its maintenance.[22] However, this model has not received much support from experimental data.[8,23] The pain-adaptation model, on the other hand, predicts a reduction of the agonist motoneuron output and an increase in antagonist motoneuron firing during movement in the presence of pain.[23] According to this model, changes in motor output in response to pain result when interneurons receive convergent afferent information and have a reciprocal effect on agonist and antagonist muscles in the spinal cord and brainstem. Two common features of these models of interaction between pain and movement are (1) that they have arisen from clinical observations and experiments focused on localized muscle pain and (2) that they focus on changes in the spinal cord and periphery, without considering any potential role for cortical mechanisms.

More recently, several studies using transcranial magnetic stimulation (TMS) have shown that pain also influences the excitability of the primary motor cortex.[6] TMS is a method of stimulating the brain non-invasively. The rapid time-varying magnetic field generated by the TMS coil penetrates the scalp and skull and induces electrical currents in the area of the brain beneath the coil that activate the axons of neurons in the cortex. Stimulation of the motor cortex evokes muscle responses, termed *motor evoked potentials* (MEPs), that are measured using EMG. A variety of parameters of MEPs can be studied in order to assess changes in cortico-spinal or intra-cortical excitability. The motor threshold is generally defined as the minimal intensity of stimulation required to produce an MEP of small amplitude in 50% of trials. Therefore, a decrease in motor threshold reflects an increased excitability of the cortico-spinal tract, and vice versa. The size of the MEP (amplitude, duration, or area) also reflects the excitability of the cortico-spinal pathway, which can be affected by a number of mechanisms at both cortical and spinal levels. Paired pulse stimulation, whereby a supra-threshold test stimulus is preceded by a sub-threshold conditioning stimulus, can be used to gain insight into the contribution of local inhibitory and excitatory interneurons in order to assess changes in intra-cortical facilitation or intra-cortical inhibition mechanisms. TMS can also be used to create a cortical map of a target muscle's representation by measuring MEP amplitudes evoked by TMS applied to different positions over the motor cortex. This allows researchers to study the extent and the location (often defined by the centre of gravity of the cortical map) of the cortical representation of a given muscle target.

Although the effect of pain on the motor system can vary depending on variables such as duration of the painful stimulus (phasic vs. tonic pain), submodality (deep vs. superficial pain), and location (proximal vs. distal pain), a common finding of TMS studies is that acute experimental pain exerts an inhibitory influence on cortico-spinal excitability.[24–29] This inhibitory effect of experimental pain, however, was not observed by Romaniello et al.[30] Changes in responses evoked by TMS do not necessarily reflect changes at the motor-cortex level; alternatively, they could be the result of changes occurring in various neural structures between the primary motor cortex and the motoneurons in the spinal cord. However, there is evidence that the origin of these effects can be at least partially attributed to the cortex. For example, laser-evoked pain was found to attenuate motor responses to TMS but not to transcranial electrical anodal stimulation (which directly activates the pyramidal tract rather than activating cortical interneurons).[24,27] Another study showed that during the initial phase of tonic pain induced by injection of hypertonic (5%) saline, there was a reduction of motor responses evoked by TMS stimulation in the absence of any effect on the H-reflex (H-reflex amplitude was decreased in a later phase, about 1 minute after the peak in pain, which suggests that the change initially occurred at the motor-cortex level).[25] Pain induced by application of capsaicin on the skin was also found to reduce the amplitude of motor responses evoked by TMS without alteration of spinal excitability.[26] It is noteworthy that these different experimental pain models recruit different types of nociceptive afferents. For example, injection of hypertonic saline, often used to mimic musculoskeletal pain, excites nociceptive muscle afferents (groups III and IV),[31,32] while capsaicin- or laser-evoked pain selectively activates Aδ and C fibres in the superficial skin layers.[33,34] Even though nociceptive inputs from muscle and skin have been shown to induce distinct changes in trigeminal motoneuronal excitability,[35] changes at the motor-cortex level appear to be consistently inhibitory across the different pain models (muscle vs. cutaneous pain, phasic vs. tonic pain).[24–29]

In patients with motor deficits who experience acute pain, the inhibitory influence of pain on the motor cortex may hamper optimal motor-cortex activation during voluntary movement and preclude motor improvement during rehabilitation. There is striking evidence supporting this view from a recent study in healthy individuals showing that acute pain can prevent motor-cortex plasticity associated with novel motor training and impair the ability to learn a new motor task.[36] In this study, healthy volunteers participated in two crossover training sessions in which they were trained in a tongue-protrusion task. Prior to each training session, a cream was applied to the tongue that contained either capsaicin (inducing moderate intra-oral tonic pain) or an inert substance (control condition). Although participants'

performance in the motor task was improved following training in both painful and non-painful conditions, the improvement was significantly less when the training was performed in the presence of pain (capsaicin condition). Moreover, measurements of cortico-spinal excitability with TMS showed that the presence of pain suppressed training-induced motor-plasticity effects (e.g., increased excitability) observed in the control condition, despite a similar amount of practice. Although these results were obtained in healthy individuals, they strongly suggest that pain can interfere with the effect of motor rehabilitation, both at the cortical and behavioural levels.

DOES CHRONIC PAIN INTERFERE WITH MOTOR-CORTEX ACTIVITY, AND, CONVERSELY, DOES MOTOR-CORTEX PLASTICITY CONTRIBUTE TO CHRONIC PAIN?

While increased inhibition has been systematically observed in acute experimental pain models, changes in motor-cortex excitability in patients with chronic pain are less consistent. Some TMS studies report increased motor-cortex excitability (reflected in decreased motor threshold, increased map volume, or reduced intracortical inhibition) in patients with chronic pain from diverse origins,[37–41] but the opposite has also been found.[42–44] Studying the relationship between pain and changes within the motor cortex in patients with chronic pain is very complex, as these patients have other sensorimotor deficits that are likely to have an impact on motor-cortex excitability. The presence of these sensorimotor deficits may explain why there is more variability in the results of studies on clinical pain than in those of studies on acute experimental pain. In order to illustrate the complex nature of the relationship between motor-cortex changes, motor deficits, and pain in patients with chronic pain disorders, we discuss two examples of neuropathic chronic pain: phantom limb pain and complex regional pain syndrome (CRPS).

Phantom Limb Pain, Phantom Limb Movement, and Motor Reorganizations

One particularly interesting model used to study interactions between the motor system and pain is the phantom limb phenomenon, which is the vivid sensation that a missing body part is still present after an amputation. Between 50% and 80% of amputees also report pain in the missing limb, a phenomenon called *phantom limb pain*. Phantom limb pain often persists chronically and is recognized as very difficult to treat.[45] Interestingly, most amputees (including those with and without phantom limb pain) feel that they are able to perform voluntary movements with their phantom limb.[46–52] Most amputees are able to move their phantom limb easily soon after the amputation, but in many cases this ability diminishes over time, so that the phantom limb becomes more and more difficult to move and, in some cases, becomes completely paralyzed.[49–51] Clinical observations and experimental data provide some evidence of interactions between pain and motor control in the phantom limb phenomenon. As the physical limb is no longer there, it is likely that these interactions reflect central mechanisms, and the phantom limb phenomenon is therefore an interesting model for studying interactions between changes in the motor cortex and pain.

Amputees often report feeling that if they could move the limb into a new position, this would ease their pain. However, moving the phantom limb is often difficult, and attempts to move it tend to increase the pain.[49] We recently developed an approach to assess phantom limb motor control and showed that distinct movements of the phantom limb were associated with distinct patterns of EMG activity in the remaining stump muscles.[46,51] Using this method, we demonstrated that phantom limb motor control is decreased in patients with pain relative to amputees who are pain free.[46] Indeed, phantom movement speed was systematically decreased in subjects with phantom limb pain relative to amputees who were pain free, which suggests decreased phantom limb motor control in patients with phantom limb pain.[46] Furthermore, the presence of a clear phase-dependent modulation of stump-muscle EMG activity during phantom hand movements was associated with more severe phantom limb pain. Since movement-related EMG patterns in above-elbow stump muscles during phantom hand movements can be considered a marker of motor-system reorganization (because above-elbow muscles are not normally activated during hand movements), this result indirectly supports the hypothesis that amputation-induced plasticity in the motor system is associated with the severity of phantom limb pain.[46]

At the cortical level, this amputation-induced plasticity is observable as a marked increase in the excitability of the representation of stump muscles relative to the same muscles on the intact side,[37,53–56] although it is important to note that in most studies, this asymmetry in excitability was not found to be related to severity of pain. Indeed, only one study found such an association, with an increase in excitability of the representation of stump muscles (i.e., muscle responses evoked by TMS were larger) relative to the intact side in patients with phantom limb pain but not in patients who were pain free.[37] The idea of an association between pain and cortical excitability has been challenged by the findings of another study, which showed that the reduction of cortical excitability in patients with chronic phantom limb pain following treatment with memantine was not paralleled by a reduction in the intensity of phantom pain.[57] Thus the relationship between motor excitability and phantom limb pain remains unclear, and it is possible that deafferentation/deefferentation plays a larger

role than post-amputation pain in post-amputation excitability changes. Evidence to the contrary comes from neuro-imaging studies, whose findings generally support the existence of a relationship between phantom limb pain and the spatial extent of amputation-induced reorganization in the motor cortex, this reorganization being characterized as a medial shift of the face muscle representation in upper-limb amputees (i.e., displacement toward the former hand area).[37,58–60] As these studies have shown that more reorganization is associated with more pain, this reorganization induced by amputation is generally considered an example of maladaptive plasticity. Taken together, the results of studies using EMG, TMS, and other neuro-imaging techniques suggest the existence of some relationship between motor reorganization and pain after amputation, but the exact nature of this relationship remains unclear.

Complex Regional Pain Syndrome and Motor Reorganization

Complex regional pain syndrome type I (CRPS-I) is a painful disorder that develops after trauma (or even in the absence of trauma) and is characterized by pain and related sensory abnormalities that are disproportionate to the initial problem. These abnormalities include edema, autonomic dysfunction, motor symptoms, and trophic changes.[61] There is some evidence of motor-cortex reorganization in patients with CRPS-I. Although TMS studies found no significant inter-hemispheric difference in the motor thresholds,[38,40,42] the size of the cortical representation of muscles on the affected side was found to be reduced relative to the unaffected side.[42] In addition, intra-cortical inhibition has been found to be decreased in the motor cortex contralateral to the affected limb or bilaterally.[38,40] Interestingly, in one study this reduction in intra-cortical inhibition of the motor cortex contralateral to the affected limb was linked with pain severity.[38] Consistent with this decreased inhibition, an fMRI study showed greater activation within the motor cortex (among other regions) during a finger-tapping task performed with the affected hand relative to activations for the unaffected hand or activations seen in healthy controls.[62] Moreover, the degree of activation within the motor cortex was correlated with the amount of motor impairment evaluated during reach-to-grasp movements. However, no significant correlation was found between pain intensity and deficits in motor performance.

Summary

Overall, it can be concluded based on studies in these two clinical populations that reorganization occurs within the motor cortex of patients with different chronic pain syndromes but that this reorganization is not always consistent with what is seen in acute experimental pain models (increased excitability and/or decreased inhibition in these chronic pain populations vs. decreased excitability and/or increased inhibition with acute experimental pain). There are several possible explanations for these differences. First, it is possible that the effect of pain on the motor cortex changes depending on the duration of the exposure to pain. Second, several factors other than pain may contribute to the changes observed in motor excitability in clinical populations, such as lack of somatosensory input, disuse of the limb, and loss of muscle targets; for example, in the absence of pain, immobilization has been shown to induce motor-cortex reorganization.[63–65] Finally, it is possible that the cortical changes vary depending on the pain population. Such a hypothesis finds support in studies observing the changes that occur at the level of the somatosensory cortices, which showed that the representation of the painful area decreased both in patients with phantom limb pain and in patients suffering from CRPS[42,59] but increased in patients with low back pain and in patients suffering from fibromyalgia.[59,66,67] Because of the high concordance of changes in the somatosensory and motor systems,[37] it is conceivable that these opposite changes could also be present in the motor cortex. In that sense, the experimental pain models (using stimulations that recruit peripheral nociceptors) are quite different from the clinical pain experienced by patients suffering from neuropathic pain. Additional studies focusing on the changes in excitability of the motor cortex in patients suffering from somatic pain are needed if we are to better understand the relationship between chronic pain and motor-cortex activity.

At the moment, therefore, it is not possible to give clear answers to the questions, *Does chronic pain interfere with motor-cortex activity?* and *Does motor-cortex plasticity contribute to chronic pain?* In the two clinical populations discussed above, there is evidence of some associations among changes within the motor cortex, changes in motor control, and pain intensity. However, such associations do not allow us to reach any conclusions with respect to causal relationships, and it is still unclear whether these associations indicate that pain drives plasticity within the motor cortex or, conversely, that motor-cortex plasticity contributes to the development of chronic pain. The presence of relationships between changes at the motor-cortex level and pain suggests that existing models (i.e., the vicious circle model and the pain-adaptation model) are incomplete and cannot account for observations made in patients with neuropathic pain. It is important to keep in mind that these models were developed based on models of musculoskeletal pain. That said, reorganization of trunk-muscle representation has recently been shown in the motor cortex of individuals with recurrent low back pain, and this reorganization was shown to be associated with deficits in postural control.[41] Although motor-cortex reorganization has been much less studied in popula-

tions with musculoskeletal pain than in populations with neuropathic pain, this finding suggests that alterations within the motor cortex should be taken into consideration in a model of pain–movement interactions, even in the context of musculoskeletal pain.

One way to gain more insight into the causal relationships between pain and changes in motor-cortex activity is to examine whether interventions that induce changes in motor performance and/or in motor-cortex organization also modify pain. The next two sections address the impact of motor-cortex stimulation (which presumably induces motor-cortex plasticity) and motor training on chronic pain.

CAN THE INDUCTION OF MOTOR PLASTICITY BY MEANS OF MOTOR-CORTEX STIMULATION DECREASE PAIN?

Chronic motor-cortex stimulation (MCS) with surgically implanted electrodes has been performed in people with neuropathic pain for the past 20 years, and the results of several studies indicate that MCS is useful in alleviating neuropathic pain of either central or peripheral origin.[68,69] Given that electrical stimulation of the motor cortex can induce analgesic effects, researchers have wondered whether similar effects could be induced using TMS. Repetitive TMS (rTMS) is a non-invasive method that can induce immediate and lasting changes in cortical excitability.[70] Over the past decade, several studies have shown that rTMS applied over the motor cortex can also, at least temporarily, alleviate neuropathic pain.[71–74] To date, about 20 studies have assessed the efficacy of rTMS in more than 300 persons with drug-resistant chronic neuropathic pain of diverse origins (including post-stroke pain, CRPS, trigeminal neuralgia, amputation, spinal-cord injury, and brachial plexus avulsion),[74] and recent meta-analyses showed that high-frequency rTMS is associated with significant pain relief.[72,73]

Does the reduction in pain following stimulation of the motor cortex indicate that motor-cortex plasticity is a cause of chronic neuropathic pain? Not necessarily. The neurophysiological changes at the origin of the analgesic effects induced by motor-cortex stimulation may be far from the stimulation site. In fact, electrophysiological and positron emission tomography (PET-scan) studies in people receiving MCS have so far failed to demonstrate significant changes within the primary motor cortex.[75] Current hypotheses suggest that MCS may act through other mechanisms, such as (1) activation of perigenual cingulate and orbitofrontal areas modulating the emotional appraisal of pain; (2) top-down activation of brainstem periaqueductal grey matter driving descending inhibition toward the spinal cord; and (3) triggering of mechanisms resulting in the secretion of endogenous opioids.[75] However, changes within the motor cortex itself may also contribute to the effect of motor-cortex stimulation. It has been shown that 10 Hz rTMS applied over the motor cortex can restore defective intra-cortical inhibition in people with neuropathic hand pain.[76] Interestingly, the increase in intracortical inhibition was found to be correlated with concomitant pain relief. This result suggests that restoring defective inhibitory mechanisms within the motor cortex may contribute to pain relief, but more TMS studies on the relationship between local changes induced by rTMS and pain relief are needed if we are to draw definitive conclusions as to whether motor plasticity induced by rTMS (or by MCS) can decrease pain.

CAN MOTOR TRAINING RESULT IN BOTH MOTOR-CORTEX REORGANIZATION AND PAIN RELIEF?

Another way to look at the relationship among motor-cortex reorganization, motor control, and pain is to examine whether motor-cortex plasticity driven by motor training is associated with pain relief. The changes driven by motor training are of particular interest for physiotherapists, who commonly use such strategies (motor relearning, therapeutic exercises) in various pain populations. In addition to the changes that occur at the level of the musculoskeletal system, activation of the motor system by means of therapeutic exercises may indeed help to explain how active rehabilitation (focusing on movement and exercises) can assist in decreasing pain. This question has received particular attention in the field of research on phantom limb pain.

The first line of evidence that motor training can affect both motor-cortex organization and pain comes from the observation that intensive use of a prosthetic hand controlled via stump-muscle contractions (which can be considered a type of motor training involving the residual limb) is associated with less sensorimotor reorganization (presumably a reversal of the maladaptive plasticity) and also with reduced phantom limb pain.[58,77] However, not all studies have found an association between prosthesis use and decreased pain and/or cortical reorganization.[78,79] Moreover, the two studies that did find an association used transversal or retrospective designs, which makes it difficult to ascertain whether this association indeed reflects a causal relationship. A larger cohort of patients and longitudinal follow-up are needed if we are to be able to relate motor-cortex reorganization to amount of motor training and to pain relief. At this stage it is also difficult to determine whether it is the motor act of controlling the prosthesis that is important in the reversal or prevention of the maladaptive plasticity or whether other factors are involved—for example, the visual feedback provided by the artificial limb or the cutaneous stimulation of the stump.

A second line of evidence that motor training affects both motor-cortex organization and pain comes from longitudinal intervention studies showing that rehabili-

tation interventions can induce pain relief that is associated with changes in motor control of the phantom limb and/or motor-cortex activity in people with amputations. These rehabilitative approaches, which target motor control of the phantom limb, emerged from the observation that viewing a virtual limb moving (by looking at the reflection of the intact arm in a mirror box, an approach called *mirror therapy*) can induce sensations of movement in the phantom limb and alleviate pain.[80] These observations led to the idea that performing a motor-training task with the phantom limb while receiving visual feedback congruent with the movements attempted with the phantom limb might lead to a parallel improvement in motor control of the phantom limb and a reduction in phantom pain. Two randomized controlled studies have shown that such approaches lead to significantly greater improvement in pain and in the ability to move the phantom limb than repeated attempts to move the limb without visual feedback or mental visualization of movements of the limb.[81,82] Pain reduction was also found in patients with amputation or brachial plexus avulsion using visuo-motor training in which a virtual image of a missing or paralyzed limb performing different movements was presented while the patient was asked to follow the movements with his or her phantom limb.[49,83] Interestingly, in one of these studies, an fMRI examination performed before and after the intervention showed that the amount of activity in the primary motor cortex during attempts to move the phantom hand increased after treatment in the two patients who experienced pain relief, while no change occurred in the patient who did not experience a decrease in pain.[83]

Another fMRI study focused on cortical reorganization within primary motor and somatosensory cortices prior to and after mental-imagery training that included movements of the phantom limb.[60] After training, the reduction in constant pain scores co-varied significantly with the decreased activation of the contralateral hand/arm area within the motor cortex during a lip-purse movement, indicating a reversal of the presumably maladaptive motor reorganization. Patients also reported improvement in freedom of movement of the phantom limb as training progressed. Studies in patients with CRPS-I have also shown that mirror therapy or a graded imagery programme—including tasks of recognition of limb laterality (implicit motor imagery), imagined movements (explicit motor imagery), and mirror therapy—can provide a sustained decrease in pain and disability.[84–86] However, none of the studies in patients with CRPS-I documented whether these treatments resulted in motor-cortex reorganization, which makes it impossible to ascertain from their results whether the analgesic effect was related to motor changes.

CONCLUSION

Acute experimental pain has been clearly shown to exert an inhibitory influence on the motor cortex. This inhibition can hamper proper motor-cortex activation and not only limit the immediate ability to perform a motor task but also interfere with the ability to learn a new one. Current evidence also suggests that there is a relationship between chronic pain and motor-cortex reorganization, but the causality of this relationship remains unclear. That said, there is growing evidence that rTMS approaches and rehabilitation treatments whose goal is to normalize motor-cortex organization can reduce pain in patients with chronic pain. One important aspect to consider, from a rehabilitation perspective, is that these interactions may be bidirectional and sometimes paradoxical. For example, on the one hand, pain can restrain learning during motor training, while on the other hand, interventions based on motor training can alleviate pain. Taken together, the evidence reviewed here indicates that interactions between pain and the motor cortex are complex. The findings demonstrate a need for new models of interaction between pain and movement that will take cortical mechanisms into account and will contribute to our understanding of neuropathic pain. These observations also underline the importance of conducting further research to better understand these interactions in patients suffering from both pain and motor deficits, as well as of developing optimal rehabilitative strategies that take these interactions into account.

KEY MESSAGES

What Is Already Known on This Topic

Physiotherapists are generally aware that pain can interact with other functions during the rehabilitation process, and particularly with motor functions. These motor dysfunctions are often regarded simply as a consequence of movement-related pain or anticipated movement-related pain (e.g., kinesiophobia).

What This Study Adds

This review shows that the interactions between pain and motor control are much more complex. Acute pain exerts an inhibitory influence over the motor cortex that can interfere with motor learning capacities. Current evidence also suggests a relationship between chronic pain and motor-cortex reorganization, but it is still unclear whether one causes the other. Interestingly, there is growing evidence that interventions aimed at normalizing motor-cortex organization can lead to pain relief.

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