NeuroRehabilitation 25 (2009) 19–27
DOI 10.3233/NRE-2009-0496
IOS Press

Sensorimotor training and cortical reorganization

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Abstract. Several disorders that involve motor and sensory disturbances such as chronic pain, tinnitus, stroke or dystonia are also characterized by changes in the sensory and motor maps in the sensorimotor cortices. This article reviews training procedures that target these maladaptive changes and the behavioral and cortical changes that accompany them. In addition, we will discuss factors that influence these training procedures and discuss new developments. These procedures include training of perceptual abilities, motor function, direct cortical stimulation as well as behavioral approaches and have been shown to reorganize the altered sensory and motor maps. Treatments that combine several modalities such as imagery or mirror treatment as well as use of prostheses also have beneficial effects. Further research must elucidate the mechanisms of these plastic changes and relate them to disorders and treatments.

Keywords: Sensory training, cortical reorganization, phantom limb pain, complex regional pain syndrome, dystonia, tinnitus, stroke

1. Introduction

An injury- or stimulation-related increase or decrease of sensory input into the brain leads to changes in the respective primary sensory and often also the motor areas and these alterations are associated with unpleasant sensations such as in tinnitus or pain and/or restrictions in motor function such as in focal dystonia. In these disorders sensory or motor training seems to be useful and is increasingly employed. In this review we will focus on chronic pain with phantom limb pain and complex regional pain syndrome as examples, as well as stroke, dystonia, and tinnitus. First, we will briefly describe cortical changes that are characteristic for these disorders and we will then discuss sensorimotor trainings and will focus on their effects, mechanisms and future developments.

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Recovery of function is based on two mechanisms: compensatory processes and restitution (for a review see [79]) and it is likely that both occur simultaneously in many cases. Compensatory processes are described as functional reorganization or functional adaptation and are achieved largely by the reorganization of surviving neural circuits to enable a given behavior over different circuits [55]. Training leads to a redistribution of representations to non-damaged areas of sensory cortex via reorganization [101]. By partial restitution of the impaired neuropsychological processes on the basis of experience-dependent brain plasticity the formerly used brain circuits will reconstitute. Plastic reorganization can occur through two types of processes: First, an alteration in synaptic sensitivity related to unmasking of existing connections through change in the inhibitory dynamics. In contrast to structural changes which take days and weeks to develop, this happens in seconds to minutes [19]. Second, the reduced level of activity in the area of the lesion weakens the synaptic connections between the damaged and undamaged sites leading to a reduced synchronous firing of cells in these two areas and thus weakening synaptic connec-

ISSN 1053-8135/09/$17.00

tivity between them. This loss of connectivity results in depression of function in the structurally undamaged but functionally partly disconnected site. A number of different approaches such as stimulation, bottom-up targeted stimulation, top-down targeted stimulation, manipulation of inhibitory processes, and manipulation of arousal mechanisms can be derived from the model of recovery.

2. Neuropathic pain

2.1. Injury-related brain changes

In persons with amputations it has been shown that the region of the somatosensory cortex that formerly received input from the now amputated limb reorganizes and receives input from neighboring regions [21, 24,76,102]. These changes are mirrored in motor cortex [12,39,41,52]. Interestingly, reorganizational changes were only found in amputees with phantom limb pain after amputation, but not in amputees without pain. This suggests that pain may contribute to the changes observed and that the persisting pain might also be a consequence of the plastic changes that occur. In several studies carried out on human upper-extremity amputee patients, displacement of the lip representation in the primary motor and somatosensory cortex was positively correlated with the intensity of phantom limb pain, and was not present in pain-free amputee patients or healthy control subjects. In addition, in the patients with phantom limb pain, but not in the pain-free amputee patients, imagined movement of the phantom hand was shown to activate the neighboring face area [52]. This co-activation probably occurs due to the high overlap of the hand, arm, and mouth representations.

Similar observations have been made in patients with complex regional pain syndrome (CRPS). In these patients, the representation of the affected hand tended to be smaller compared with that of the unaffected hand and the individual digit representations had moved closer together [38,59,60,74,86]. The extent of the pathological changes in the cortical representations correlated with the intensity of pain or motor dysfunction [57, 61,74], but was additionally related to a degradation of sensibility in the affected hand. It was, however, unrelated to a loss of motor function [57]. It is so far not known how an expansion of adjacent representations and a shrinking of adjacent representations as observed in phantom limb pain and CRPS, respectively, can both be associated with pain.

2.2. Sensory and motor training

In amputees with phantom pain, several stimulation-related procedures were found to be effective. Intense input into the cortical amputation zone by the use of a myoelectric prosthesis or other prosthetic devices, for example, was found to reduce both cortical reorganization and phantom limb pain [53,98]. In patients in whom the use of prosthesis is not possible, sensory discrimination training might be beneficial. In one study, electrodes were closely spaced over the amputation stump in a region where stimulation excites the nerve that supplies the amputated portion of the arm. Patients then had to discriminate the frequency and location of the stimulation in an extended training period that lasted 90 min/day over a 2-week period. Substantial improvements to both two-point discrimination and phantom limb pain were demonstrated in the trained patients. These improvements were accompanied by changes in cortical reorganization, indicating a normalization of the shifted mouth representation [23]. An asynchronous stimulation of the stump and lip area also yielded a significant reduction in phantom limb pain suggesting that the separation of overlapping cortical networks involved in pain may be important [36].

Similar results were found in CRPS where active discrimination between tactile stimuli lead to an improvement in pain intensity and two point discrimination compared to passive stimulation alone [68]. Tactile spatial acuity also improved when a Hebbian stimulation protocol of tactile coactivation [58] was used. The question arises if active stimulation is necessary or if passive stimulation is sufficient. In rats it could be shown that associative (Hebbian) pairing of passive tactile stimulation leads to a selective enlargement of the areas of cortical neurons representing the stimulated skin fields and of the corresponding receptive fields [32]. In humans paired tactile stimulation goes along with an improved spatial discrimination performance [32,33] paralleled alterations of primary somatosensory cortex [31] indicating that fast plastic processes based on co-activation patterns act on a cortical and perceptual level. It is possible that in healthy controls passive stimulation without a task is sufficient for changes on the perceptual and cortical level whereas patients, who are less able to discriminate stimuli [58, 68], may need active stimulation for an improvement in discrimination ability (and pain intensity).

2.3. Mirror and motor imagery training

In 1995 Ramachandran et al. [77] suggested that the use of a mirror might reverse the reorganizational changes observed in patients with phantom limb pain and they provided evidence that viewing movements of one's intact hand in a mirror, which provides the impression of viewing the amputated hand, lead to better movement of and less pain in the phantom limb. In lower limb amputees Brodie [5] reported a significantly greater number of movements in the phantom when a mirror box was used. Hunter et al. [35] showed that a single trial mirror box intervention led to a more vivid awareness of the phantom and a new or enhanced ability to move the phantom. Contrasting a mirror box with executed movement Brodie et al. [4] reported that movements in front of a mirror as well as movements without a mirror attenuated phantom limb pain and phantom sensation. Contrary to these findings, which were based on a single trial, 4 weeks of mirror training led to significantly more decrease in phantom limb pain than training with a covered mirror or using mental visualization in lower limb amputees [11] suggesting that phantom pain can be altered by visual feedback. It is well known that vision tends to take precedence over the other senses (touch included) when conflicting information is presented to vision and another sense [34, 68,80].

Reports on imagined phantom movements in amputees [22,52,54,82,83] showed activation in primary sensorimotor cortex representing the amputated limb and were supported by results from transcranial magnetic stimulation (TMS), which showed that perceived phantom hand movement could be triggered by stimulation over the motor cortex in an area that represented the now amputated limb [63]. Both Giraux and Sirigu [30] and MacIver et al. [56] showed that imagery alone also affects the cortical map representing the amputated limb and relieves phantom limb pain in contrast to Chan et al. [11] who did not find changes in phantom pain related to imagery but did not assess cortical changes. These studies suggest that modification of input into the affected brain region may alter pain sensation.

Moseley used a tripartite program to treat patients with CRPS [65,66]. This program consisted of: a hand laterality recognition task (a pictured hand was to be recognized as left or right); imagined movements of the affected hand; and mirror therapy (patients were asked to adopt the hand posture of both hands shown on a picture in a mirror box while watching the reflection of the unaffected hand). After a 2-week treatment, pain scores were found to be significantly reduced. They replicated this result in CRPS and phantom limb pain patients [67]. In addition, McCabe et al. [55] found a reduction in pain ratings during and after mirrored visual feedback of movement of the unaffected limb in CRPS patients. Gieteling et al. [29] asked CRPS patients with dystonic postures of the right upper extremity to execute or imagine movements during an functional magnetic resonance (fMRI) measurement. Compared with controls, imaginary movement of the affected hand in patients showed reduced activation in the ipsilateral premotor and adjacent prefrontal cortex, and in a cluster comprising the frontal operculum, the anterior part of the insular cortex and the superior temporal gyrus. On the contralateral side, reduced activation was seen in the inferior parietal and adjacent primary sensory cortex. There were no differences between patients and controls when they executed movements, nor when they imagined moving their unaffected hand. Transcranial motor cortex stimulation has also been employed successfully for CRPS (e.g. [73]).

3. Stroke

After unilateral stroke patients often ignore the limb of the affected side and perform their daily activities with their unaffected limb. This led Taub et al. [93,94] to formulate the concept of learned nonuse, which is based on the assumption that an initial inability to move the affected limb is maintained by learning, specifically, positive reinforcement for use of the intact and punishment for use of the affected limb. The enduring nonuse of an affected limb may thus in part be behaviorally conditioned. This lead to the development of Constraint-Induced Movement Therapy (CI therapy), which refers to a family of treatments for motor disability that combines constraint of movement, massed practice, and shaping of behavior to improve the amount of use of the targeted limb [95,97]. Until now CI therapy has been evaluated in several laboratories [45,46,49,50,64,88] and has been implemented in clinical practice [96]. CI therapy leads to activation in the hemisphere ipsilateral to the affected limb in the absence of mirror movements of the unaffected hand [45] and later also to activation contralateral to the affected side in the undamaged hemisphere. Results of an fMRI-study point in the same direction and suggest that gains in motor function produced by CI therapy may be associated with a shift in laterality of motor cortical activation toward the undamaged hemisphere [85]. Another fMRI study observed new activation in the contralateral to the affected hand motor/premotor cortices in three subjects and increased activation of the ipsilateral to the affected hand motor cortex and SMA in two patients after CI therapy [42]. By using focal TMS it could be shown that the originally significantly smaller cortical representation area of the muscle of the affected hand compared with the unaffected hand was significantly enlarged after treatment [49,50]. At the 6-month follow-up the two hemispheres became almost identical, representing a return of the balance of excitability between them towards a normal condition [49]. In another study, motor-evoked potential (MEP) amplitudes induced by TMS increased significantly on the affected side after the intervention and the power spectra of movement-related cortical potentials (MRCP) revealed reduced peak frequency over the supplementary motor area when the affected hand was moved. These results show changes in cortical electrical excitability while performing both involuntary and voluntary movements after 2 weeks of CI therapy and may be seen as a sign of neural reorganization instigated by the intervention [92].

Mirror treatment has also been employed with stroke patients. A mirror is propped up vertically and the patient is encouraged to use both arms while receiving mirror visual feedback. Movement abilities were better after mirror therapy compared to a control condition with a transparent plastic sheet [1]. After massive deafferentation of sensory neurons but intact motor pathways in a stroke patient, mirror therapy lead to an improvement of grip strength and other useful movements (e.g. opening a lock) in the paretic arm [84].

In several studies a positive effect of mirror therapy could be found for upper- [1,17,84,89,103] and lower-extremity motor recovery [91]. From these results it can be concluded that that mirror therapy may accelerate recovery of function. TMS has been used to explore the neural basis of mirror therapy. It could be shown that motor evoked potentials (MEPs) were largest in the mirror condition (viewing a mirror-reflection of the active hand in a mirror oriented in the mid-sagittal plane) compared with both an inactive (viewing the inactive hand) and a central (viewing a mark positioned between hands) viewing condition. The authors concluded that the excitability of MI ipsilateral to unilateral hand movement is facilitated by viewing a mirror reflection of the moving hand [28]. This finding provides neurophysiological evidence supporting the application of mirror therapy in stroke rehabilitation. Motor imagery intervention also lead to an improvement in arm function compared to a control group in acute [72] and chronic [71] stroke patients. In another study the specific instructions for forming a kinesthetic image or to use first person imagery were absent suggesting that these patients did not use motor imagery but instead used imagery in the third person or visual imagery by learning movements for solving daily living tasks compared to a control group [51]. The experimental group improved significantly more on daily living tasks but not in re-learning basic motor skills. This suggests that motor imagery could potentially lead to recovery of basic motor skills, whereas visual imagery might be used for relearning the planning aspects of movements.

4. Dystonia

Focal hand dystonia relates to a loss of control over individual fingers during task-specific activity, possibly actuated by chronic massed practice with the fingers in certain manual occupations or in musicians, which results in co-contraction of flexors and extensors. This goes along with alterations in both the somatosensory representation of the digits and performance [62]. Neuronal changes could be found in musicians with focal hand dystonia showing fused representation of the individual digits in somatosensory cortex compared to control subjects who show greater individuation of the digit representations [2,10,20]. It was suggested that repetitive practice (limb overuse, rather than nonuse as in stroke) could be responsible [6]. An intervention with the aim to individuate the somatosensory representation of the digits reduces the focal hand dystonia through repetitive practice of isolated digit movements in musicians [7–9] and writers' cramp [106]. This is nearly the contrary to the coordinated use of all digits during musical performance. In these studies the most affected digit receives repetitive training while the other digits are restrained with a splint [7–9]. The post-treatment improvement was impressive, and several of the musicians returned to professional performance. A different approach of sensory training for patients with focal dystonia involves training in Braille reading, which resulted in decreased disability after training [104,105]. A recent study focused on the short- and long-term effects of repeated administrations of repetitive-transcranial magnetic stimulation (rTMS, 1 Hz) to the premotor cortex on cortical excitability and handwriting performance compared to sham rTMS and healthy subjects receiving one real rTMS session [3]. After five days of rTMS to premotor cortex, reduced cortical excitability and improved handwriting performance were observed and maintained for at least ten days following treatment. The same results could be found with subthreshold low-frequency (0.2 Hz) (rTMS) in writers' cramp [70].

5. Tinnitus

Tinnitus is characterized by the perception of auditory signals in the absence of any internal or external source of sound. Several studies showed that the auditory cortex is overactive in these patients and that there are alterations in the tonotopic map that are not only explained by hearing loss and that are correlated with tinnitus severity [16,69,75] and that there is also altered motor cortex excitability [47]. Thus, training procedures that normalize the tonotopic map and reduce cortical hyperexcitablity seem feasible. In an auditory discrimination training patients had to discriminate pairs of tones and received feedback on their performance [25] similar to trainings in animals [78]. The results showed a positive dose response effect of auditory discrimination training. Similarly, Searchfield et al. [87] reported positive effects of an object identification and attention training for tinnitus. In several studies TMS over the auditory cortex was used to influence tinnitus (for a review see[44,48]). For example, repetitive TMS was performed at 1 Hz at the patients cortical areas with excessive tinnitus-related activity individually navigated as assessed by $[^{15}O]H_2O$ positron-emission tomography (PET) [75]. A dose-dependent attenuation of tinnitus severity after stimulation of the individual tinnitus-related areas was found. Kleinjung et al. [43] combined low-frequency temporal with high-frequency frontal TMS based on the finding that frontal areas are also altered in tinnitus (e.g. [99]) and achieved major changes in tinnitus at a 3-month follow-up period. These training and stimulation protocols may directly affect tinnitus-related activity rather than ameliorating interference related to tinnitus. These approaches could be augmented by brain stimulation (e.g. [13]), neurofeedback [18], extinction training [90] or virtual reality applications.

6. Discussion and conclusion

Based on neuroscientific evidence on alterations in the primary sensory and motor areas in sensory and motor disorders such as chronic pain, hemipareses after stroke, focal dystonias or tinnitus sensory and motor training methods have been developed. They include training of perceptual abilities, motor function, direct cortical stimulation as well as behavioral approaches and have been shown to reorganize altered sensory and motor maps. In addition, treatments that combine several modalities such as imagery or mirror treatment as well as use of prostheses seem to have beneficial effects. Direct brain stimulation methods such as TMS [3,43, 70,73,75] or transcranial direct current stimulation (tDCS) [26,27,81,100] have also been employed successfully in these disorders. Neurofeedback has been used with EEG [18,37,40], or fMRI [14,15]. These are also very promising approaches. This review has several limitations. First, we have only discussed a selected group of disorders where cortical reorganization occurs. Second, we have only described these changes in humans and have focused on implications for treatment rather than explaining mechanisms. Third, we have not been exhaustive with respect to the stimulation-related approaches but have only described exemplary results. For more comprehensive reviews see [100]. Finally, much work still needs to be done to demonstrate the efficacy of these plasticity-related treatment approaches, which were usually tested in small heterogeneous samples without adequate controls. However, they may point out new approaches to treatment of chronic disorders and rehabilitation for the future. Future research should explore additional benefits which might arise from using brain stimulation methods in conjunction with behavioral trainings, virtual reality applications or plasticity-modifying pharmacological interventions.

Acknowledgements

The completion of this article was facilitated by the Bundesministerium für Bildung und Forschung (01EM0512, German Research Network on Neuropathic Pain, DFNS), the Tinnitus Research Initiative and The State of Baden-Württemberg Research Prize. Further support of this study was provided by the SOMAPS project, which receives research funding from the European Community's Sixth Framework Programme (FP6-NEST 043432 SOMAPS) and the PHANTOM MIND project, which receives research funding from the European Community's Seventh Framework Programme (FP7/2007–2013) / ERC grant agreement n° 230249. This manuscript reflects only the author's views and the Community is not liable for any use that may be made of the information contained therein.

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