Paretic Hand in Stroke: From Motor Cortical Plasticity Research to Rehabilitation

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Abstract: Research in neural plasticity of adult cortical representations brought hope of significant potential for further improvement in therapy after cerebrovascular stroke, but the same processes involved in plasticity also allow for maladaptive changes whether spontaneous or caused by inappropriate therapeutic manipulations. Within the extensive network of multiple and bilateral motor cortical and subcortical areas, this paper focuses on the primary motor cortex. We review selected data from humans and primates regarding its functional anatomy and the mechanisms of adaptive neuroplasticity in the presence of brain insults, and the impact of motor skill learning in normals and rehabilitation therapy in patients. The discussion centers on the potential impact of the mechanisms of motor cortex neuroplasticity, especially of the phenomenon of competition among primary motor cortical representations, on the rehabilitation of paretic hand and shoulder after stroke. Application of results from neurophysiology and functional brain imaging research into the clinical practice is in the initial stages and remains a challenge for the future. Nevertheless, even the available research provides an important message for clinical rehabilitation of stroke patients: the need to widen multimodal and interdisciplinary approaches to rehabilitation of the paretic hand.

Key Words: motor cortex, somatotopy, neuroplasticity, stroke, rehabilitation, shoulder, hand

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Observations of patients with neurologic injury provide evidence for the crucial role of the cerebral cortex in the fine and complex aspects of hand motor activity. Whenever the cerebral motor cortical system is damaged, part of the movement repertoire becomes impaired or unavailable. Importantly, significant recovery from cortical damage is often possible. Recently, it has been experimentally confirmed that even the adult mammalian and primate brain is capable of extensive plastic changes after injury or after changes in motor and sensory experience. It is tempting to assume that neural plasticity underlies most of the observed recovery from impairment after brain lesions.

Early notions of adult motor system plasticity date back to Sherrington's observation of the "instability of the motor point" when mapping the primate motor cortex with electrical surface stimulation.[1] This term describes the observation that repeated stimulations of the same motor cortical point may evoke different movements. Subsequent developments in methodology of cortical mapping, including intracortical microstimulation in experimental animals and, most recently, noninvasive functional imaging methods in humans [positron emission tomography (PET), functional magnetic resonance imaging (fMRI)], allowed a detailed mapping of cortical representations of movement, thus establishing a clear baseline organization, against which plastic changes can be observed and related to different causal factors. Because of these methodological advances, formerly independent studies in the areas of experimental psychology (procedural learning, motor memory, motor skill acquisition), neuroscience (adult brain plasticity), and neurology and rehabilitation (stroke recovery) have begun to converge, providing a more complete picture of these dynamic processes and helping to translate the progress in basic science into clinical benefit.

PRIMATE MOTOR CORTEX ARM AREA CONTAINS SOMATOTOPICALLY ORGANIZED MOVEMENT REPRESENTATIONS

One hundred fifty years of clinical and experimental data provided a clear picture of somatotopic arrangement of the gross major divisions in the primate primary motor cortex (M1)-modules controlling the face, arm, trunk, and leg, located progressively more medially and superiorly along the anterior bank of the central sulcus.[2–5] Although the early maps derived from patients with motor cortex lesions[2,3] depicted only the ordering of major motor cortical subdivisions, the subsequent more detailed maps produced by electrical stimulation specified orderly arrangement even for individual fingers within the hand.[4,5] More recently, detailed microstimulation mapping in monkeys revealed very complex fractionated

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cortical maps of muscles, where each muscle is represented in multiple segregated cortical fields on the millimeter scale. These multiple representations of individual muscles were spatially intermingled and seemed to provide no evidence in support of somatotopy within the gross modules, for example, within the hand area.

Yet the most recent human functional neuroimaging possibly reconciled the old and the newer data: the human motor hand area resembles a complex network involving multiple representations of each finger movement, with overlaps among fingers (in agreement with the detailed monkey data), yet it contains somatotopic spatial gradients following the maps of Foerster and Penfield.[6–8] The remaining apparent differences in monkey and human motor maps can result both from phylogenetic differences in motor cortex organization, for example, increasing fractionation of movement when moving from monkeys to apes to humans,[9] and from differences in animal and human methodology, such as intracortical microstimulation or extracellular recording versus PET/fMRI.

Moving beyond the static functional motor cortical anatomy, the recent discovery of plastic changes in the adult mammalian brain has provided new evidence to explain mechanisms of motor learning and skill development (without nervous system lesion) or of behavioral recovery from lesion-related motor deficits. Most of the research has focused on primary motor and sensory cortices, because the anatomic and functional organization of these areas had been well described, thus simplifying the investigation of plastic changes. Repeated mapping within the same individual allows for detecting changes even in the presence of the observed complexity of cortical motor maps. The following section will briefly review the research on plasticity of the M1, the area most easily correlated to changes in motor function, such as recovery from stroke or motor skill learning.

MOTOR CORTICAL REPRESENTATIONS ARE PLIABLE IN THE PRESENCE OF NERVOUS SYSTEM OR ENVIRONMENTAL CHANGES

Many animal studies have demonstrated that the representations of muscles or movements in adult M1 can undergo plastic changes in response to peripheral or central lesions or altered experience. Motor maps have been shown to change in response to peripheral motor nerve lesions in the rat,[10] repetitive cortical stimulation in the monkey,[11] pharmacologic modulation of intracortical inhibition in the rat,[12] change of rat limb configuration,[13] motor practice,[14] or cortical lesions in the monkey.[15]

Several cellular mechanisms have been implicated to explain the observed plasticity, including unmasking or potentiation of existing but normally ineffective neural connections, axonal sprouting with new synapse formation, or a combination of these. Changes in motor maps after the application of bicuculline, an antagonist of the inhibitory neurotransmitter GABA,[12] have been taken as evidence that a part of the wide network of available neural connections is functionally suppressed through intracortical inhibition. Long-term potentiation of corticocortical synapses has been observed in cat motor cortex after tetanic stimulation within somatosensory cortex[16] as has the appearance of new synapses after damage to deep cerebellar nuclei[17] or long-term thalamic stimulation.[18] Increased synaptogenesis and early immediate gene c-fos expression have been associated with motor acrobatic learning in rat motor cortex.[19] Furthermore, the strength of intrinsic connections in M1 is dynamically modifiable through long-term potentiation.[19] Finally, the extent of horizontal connections has been shown to correlate well with the extent of plastic changes in motor cortical representations after transsection of efferent connections in the rat.[19]

Changes of primary motor cortical organization have also been observed in adult humans. Expansion and shifts in motor maps occurred after central or peripheral neurologic lesion such as stroke,[20] amyotrophic lateral sclerosis,[21] arm amputation,[22,23] and facial paralysis.[24] Remapping within M1 was suggested as one possible mechanism of motor function recovery after stroke.[20] One type of map change observed within M1 as a result of brain injury or disease was a shift of hand area laterally and ventrally, into the presumed face area, over a distance of up to 10 mm.[20,21,24] Cramer and Bastings[25] review further evidence of plasticity after stroke. The reviewed studies used PET, fMRI, or transcranial magnetic stimulation to generate motor and language maps and compare recovered patients to normals or observe the changes when repeatedly studying the same patients during the process of recovery.

Similar changes have been described in the absence of motor system injury. Practice of Braille reading and motor learning caused expansion of scalp area from which movement could be evoked by transcranial stimulation.[26,27] Prolonged leg immobilization, on the other hand, caused shrinking of the scalp area for excitation of a leg muscle.[28] Several studies of human motor learning have observed changes within M1,[29–32] even though M1 is only one of the multiple cerebral areas supposedly involved in motor learning.[33] A newly acquired motor skill may take advantage of movement segments that are formed by combining neural units of M1 (segmental learning) and retrieved during the execution of the acquired skill.[34] The possible anatomical substrate for the coactivation of an ensemble of neurons during skilled movement is the network of horizontal corticocortical connections observed within monkey M1.[35]

MOTOR MAP EXPANSION CORRELATES WITH FUNCTIONAL IMPROVEMENT

If one accepts the assumption that increasing skill and automaticity for a specific movement originates from changes of cortical motor function, the next question regards the character and direction of such changes. There is an intuitive concept that skill reflects efficiency at

the cortical level and that such skill would translate into less cortical activation during functional imaging, implying that existing synapses are less active, the number of active synapses decreases, or both. On the other hand, there is both nonhuman primate and human evidence that practice increases rather than decreases the area of cortex associated with the practiced movement (at least in the time frame of several weeks). These studies were performed after behavioral performance reached a stable plateau.

In nonhuman primates, Nudo et al[14] found expansion of the motor cortical representations of muscles/movements that were used during a several week-long session when monkeys learned to retrieve food pellets from small wells. In another primate study with long-term movement practice, M1 neurons that have been initially silent began firing during the practiced movement.[36] Human motor learning studies have commonly reported that movement practice leads to recruitment of additional M1, with the appearance of new active cortical fields[29] and expansion of the cortical territory corresponding to the practiced muscles/movements of several millimeters up to several centimeters.[27,31,32] Subjects who practiced a 5-finger piano exercise for 2 hours a day for 5 days showed an enlarging motor cortical area targeting the long finger flexors and extensors, followed by a decreased threshold for activation as they learned the skill.[26]

Karni et al[31] compared fMRI activation caused by 2 sequential finger movements involving the same fingers. The sequences had 5 components and each involved fingers 2 to 5 touching the thumb in a particular order. One of the sequences was repeatedly practiced with the nondominant hand over several weeks. Although the extent of cortex activated with either sequence was similar at the beginning of the study, after training the primary cortical activation by the practiced finger sequence was significantly larger than activation caused by the nonpracticed sequence. The area of evoked response in M1 for the trained sequence did not extend beyond the hand representation, which was mapped in a subset of the subjects by independent finger movements. However, the amount of change in the surrounding motor map was not addressed to establish whether the learning was competing for cortical output neurons or instead whether it enhanced the sharing of neurons. The relationship between the observed expansion and the localization of other hand movements was not described either. Finally, no direct relationship was established between the cortical area of motor representations and motor performance.

These outstanding questions were addressed in the study of Hluštík et al,[32,37] where subjects practiced a novel 6-keypress finger sequence with their nondominant hand over 3 weeks although being repeatedly tested and scanned with fMRI. Subjects were divided into an intensive training group with daily behavioral practice sessions of the novel sequential movement and a control group, which practiced only during behavioral testing and during fMRI scanning. Over the training period, subjects' performance on the practiced sequence and also on 3 unrelated tests of general hand performance improved, whereas the primary motor and somatosensory cortical movement representations expanded. This expansion likewise was not limited to the representation of the practiced sequential movement but also included representations of unpracticed simple flexion-extension movements of individual fingers and wrist. The results showed similar changes in both groups, demonstrating that even a limited amount of practice on a complex novel task can lead to both specific and nonspecific improvements in behavior and to an increase in the size of M1 and primary somatosensory cortex (S1) movement representations. The extent of M1 and S1 movement representations was significantly correlated with out-of-scanner performance on sequential finger movement and may reflect the current motor behavioral ability of the individual.

After stroke destroyed a part of the monkey primary motor cortical hand area, spontaneous recovery was associated with loss of hand area outside the lesion itself, whereas rehabilitation caused an increase of the hand area.[38] In this paradigm, however, the size of the hand area was not directly correlated to postinfarct motor experience and training.[39] Possible reasons for this are discussed by Nudo et al,[40] including large individual variability in motor performance, small infarct size, and the resulting good recovery in all animals regardless of postinfarct training.

Correlation has also been sought between very long-term practice of skilled movements and the functional organization of the cerebral motor system. Although right-hand dominance for skilled movements is prevalent in humans, hand preference has also been observed in monkeys.[41] The monkey motor cortex controlling the preferred hand has been found to contain a larger and more complex hand area when studied with intracortical microstimulation.[41] Studies of human M1 structural asymmetry related to handedness have found asymmetry in the depth of the central sulcus, with the left hemisphere larger than the right in right handers, and a less prominent opposite asymmetry in left handers.[42,43] Microstructural asymmetry has been found in postmortem brains, with a larger neuropil compartment (containing dendrites, axons, and synapses) in the left (dominant) motor cortex.[43] The authors suggest that this finding reflects a greater density of intracortical horizontal connections in the cortex serving the dominant hand.[43] However, another anatomic study did not find any asymmetry in the size of the precentral motor cortex in postmortem human brains.[44]

Callosal connections from the opposite motor cortex comprise another possible source of increased connectivity, but callosal connection density is very low in the monkey motor hand areas and seems to be inversely related to the development of independent fine movements.[45] Callosal connections have also been suggested to be a potential hindrance for independent movements of one hand.[46] Nevertheless, recent data show the physiologic impact of transcallosal fibers connecting motor cortices: unilateral cortical lesion involving motor cortex

causes motor cortical disinhibition in the unaffected hemisphere,[47–49] which seems related to the goodness of motor recovery.[50,51]

The effect of long-term bimanual practice (ie, playing a musical keyboard instrument) on brain structure was studied by Amunts et al.[52] The asymmetry of central sulcus depth observed in control subjects was diminished in musicians and this effect was proportional to the age of inception of music training. Similarly, finger-tapping performance of musicians was more symmetrical, due to significantly better performance of the nondominant left hand. A right-larger-than-left difference was found in the strength of cortical magnetic fields evoked by moving left versus right fingers in the M1 of string players.[53] All this evidence seems to further support the notion that long-term practice changes the motor cortex at both microscopic and macroscopic levels.

CHANGES IN MULTIPLE CORTICAL REPRESENTATIONS: ADDITIVE OR COMPETITIVE?

As mentioned above, in the absence of nervous system lesion, practicing a novel complex movement apparently leads to expansion of its motor cortical representation (eg, Karni et al[31]) and expansion of other adjacent motor representations as well.[32] In the latter study, learning-induced cortical changes were noncompetitive, instead enhancing overlaps and sharing of cortex among movement representations (significantly more so in the intensive training group), although somatotopy and the extent of the whole mapped hand area were unchanged. Similar observations of cortical sharing and overlaps were made in the rat somatosensory cortex.[54] In that study, cortical representation of one row of vibrissae expanded with learning whereas the cortical fields of whiskers in adjacent rows remained unchanged. This resulted in increased overlaps among whisker representations and thus more prominent sharing of cortical territory.

Different mechanisms may be at play in the presence of central or peripheral nervous system injury, where competition rather than sharing seems to take place. In primates with focal motor cortical lesions, intracortical stimulation of the unused cortical territory surrounding the infarct and formerly representing the paralyzed hand now evokes movements of adjacent body parts.[15] Similar changes occur with peripheral motor nerve lesions.[10,55] In humans with peripheral nerve injury leading to paralysis, transcranial magnetic stimulation mapping confirms expansion of the cortical area, the stimulation of which evokes motor potentials in unimpaired muscles surrounding the paralyzed ones.[24,56–58]

In the last-mentioned study of a patient in whom cervical C7 and C8 root avulsion had paralyzed the hand 11 years before, fMRI during movement of the adjacent forearm in the same patient confirmed the expansion of the forearm representation laterally toward the hand representation. However, fMRI of mental imagery of moving the paralyzed hand demonstrated that it is still represented in the motor cortex after the long-term paralysis.[58] Ersland et al[59] similarly observed motor cortex activation in an amputee during mental performance of a movement of his amputated hand.

There is thus evidence of 2 processes taking place in the reorganizing motor cortex. On the one hand, the paralyzed body part may still be represented in the motor cortex after long nonuse and the expansion of adjacent body parts increases sharing and overlaps of their motor representations. On the other hand, the functionally relevant corticospinal output of the ''unused'' cortical territory seems to be redirected to movement control of adjacent body parts.

Interestingly, as mentioned above, it has been shown that this spontaneous remapping can be prevented in monkeys by intensive rehabilitation and use of the impaired hand.[38]

PROXIMAL AND DISTAL ARM MOTOR CONTROL IN HEALTHY HUMANS AND PATIENTS WITH HAND PARALYSIS: MOTIVATIONS FOR REHABILITATION

Within the arm, neurophysiologic and clinical data justify treating the proximal and distal arm as separate functional units. In healthy humans, motor control of simple movements of the distal arm relies on contralateral M1, while sparing or even significantly deactivating the ipsilateral primary sensorimotor cortex, even though higher motor areas are active bilaterally with left-sided hemispheric dominance. In contrast, proximal movements significantly activate both primary and higher motor cortices bilaterally.[60] In adult hemiparetic stroke patients, proximal arm function is typically less impaired or recovers faster than more distal movements.[61] The neurophysiologic substrate underlying faster recovery of proximal movements may include the more bilateral motor cortical representation of proximal movements mentioned above, and higher participation of subcortical structures, such as the reticulospinal tract and the uncrossed corticospinal tract. Furthermore, a typical stroke with ischemia in the middle cerebral artery territory damages the primary motor cortical hand area, possibly together with some of the adjacent premotor cortex, whereas the supplementary motor area, which gets its vascular supply from the anterior cerebral artery, escapes unharmed. The anterior cerebral artery also supplies the medial aspects of the motor cortex, controlling primarily the lower limb. However, owing to the extensive overlaps of primary motor representations, this portion of M1 may contain neurons related to proximal arm function as well.

Applying the previously discussed principle of competition among body parts for territory in the sensorimotor cortex, even limited activity of the upper arm might prevent the hand from gaining more control, particularly when the territory is reduced in size because

of the stroke. Muellbacher et al[62] used a paradigm of regional anesthesia-induced deafferentation of the upper arm during hand motor practice in patients with long-term stable hand weakness after stroke. The patients dramatically improved their hand motor function, including some activities of daily living.

Rehabilitation strategies often employ shoulder activation as part of complex movement synergies. Unfortunately, inappropriate training of shoulder movements may further enhance the natural competition between shoulder and hand for sensorimotor cortical territory. In contrast, intensive hand motor rehabilitation should lead to reversal of the pathologic plasticity.[38] These concepts were employed in designing a pilot study, where the shoulder was not deactivated but, instead, more intensive hand therapy was used in addition to the common rehabilitation protocol.

In that study,[63,64] 40 stroke patients with hemiparesis were divided in the treatment and control groups. In the treatment group, daily sessions of differentiated manual treatment and sensory stimulation of the hand and the forearm were performed as add-on therapy. Both groups received standard physical therapy based on the Bobath concept. Both the standard and the add-on therapy were initiated within several days of stroke at the stroke unit. At the beginning and at the end of the investigation period (duration 8 to 12 days), functional assessment of the hand (Jebsen-Taylor test, and a new test developed by the authors—visual assessment of the functional task of the hand) was performed. At the end, functional assessment of the shoulder was performed using the Visual Analog Scale for pain assessment and scored tests of shoulder function.

In the treated group, improvement of hand function was in most test items significantly greater when compared with the control group. Interestingly, significantly better outcome regarding pain symptomatology and function of the affected shoulder was demonstrated in the treated group compared with the control group. In some cases, substantial reduction of neglect with the treatment was observed as well.

This pilot study concluded that the performed differentiated manual treatment and sensory stimulation of the hand and forearm significantly contribute to the functional outcome of the hand and shoulder in stroke patients, recommending such treatment as add-on therapy in the early stages of stroke rehabilitation.[63,64] Further studies with longer therapy duration should be pursued.

CONCLUSIONS

The results of recent neuroimaging and neurophysiologic studies have provided fascinating new insights into processes of the repairing brain after injury, a special case of which is stroke.

The new findings prompt us to revise many neurophysiology concepts whereas they provide new and substantial inspiration for clinical research. The current state of knowledge already indicates that many basic paradigms in clinical rehabilitation of the paretic upper arm after stroke need to be revised as well.

The cornerstone of the new perspective is a move away from training focused on the shoulder girdles toward the earliest and most intensive possible complex sensory and motor training of the hand with all available means, naturally when respecting the patient's state and the laws of neurophysiology.

In contrast, it seems likely that suitable activation of the hand can, on the other hand, contribute to functional centration and desirable activation of the shoulder girdle musculature. Even though this assumption is reasonable, it requires further confirmation in well-designed clinical studies.

In summary, research into neurophysiology of neuroplasticity and of cortical reorganization after stroke has recently brought new perspectives of the rehabilitation of the paretic hand in stroke patients, some of which are discussed in this paper. Several important points and recommendations ensuing from the current knowledge can be outlined as follows:

1. Training of the hand should begin as soon as possible.
2. Training should include differentiated sensory stimulation of the hand region with respect to both slow and fast adapting systems of exteroception and proprioception with special regard to fingers.
3. Training should include repetitive selective and differentiated performance of passive, guided, and active movements of the hand segments, especially fingers.
4. Training oriented toward more complex tasks should be included as soon as it is possible. Manual guidance, orthotic support, slings and further arrangements can be used to support the early task-oriented training of the paretic hand.
5. When considering the functional relation of the hand and the shoulder, the hand should be the primary target for the training. Any isolated overactivity of the shoulder girdle should be, especially in the initial phases of the rehabilitation, avoided. In parallel to the already used latero-lateral restraint, a proximo-distal restraint (suppression of the shoulder, activation of the hand) may be considered in the stroke rehabilitation program, although its benefits need yet to be demonstrated.
6. There is some evidence that early, intensive, and differentiated training of the hand may contribute to the prevention of spasticity, and in some instances also ameliorate neglect and prevent the development of the painful shoulder in stroke patients.
7. Not only rehabilitation professionals but also nursing staff, relatives, and the motivated patient himself/herself can be instructed to perform adapted techniques to support and intensify the process of hand rehabilitation.

There are many other avenues that are promising for rehabilitation in patients with hemiparesis related to brain lesion and are beyond the scope of this paper, such as motor imagery (see elsewhere in this issue).

Hand motor rehabilitation in a neurologic patient represents a typical problem that can be solved only through interdisciplinary collaboration of many experts and areas, ranging from basic neuroscience to clinical practice.

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