How imaging will guide rehabilitation

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Purpose of review

Human ischemic stroke is a multistage disorder with different options for recovery. Imaging has opened a window to explore the pathophysiology and recovery mechanisms of ischemic stroke *in vivo*.

Recent findings

It was shown that in the acute phase, arterial recanalization and reperfusion are the most important determinants for recovery. This is followed by functional and structural changes in the perilesional tissue and in large-scale bihemispheric networks that continue with different dynamics for weeks to months. Evidence is presented that the behavioral gains induced by repetitive and mental training are paralleled by changes in functional representations.

Summary

This review emphasizes that neuroimaging has a great potential for monitoring the hemodynamic, functional and structural factors determining recovery from stroke. It is shown that combining neuroimaging with electrophysiological methods will be instrumental for developing neuroscience-based strategies in rehabilitation.

Keywords

cognitive training, cortical stimulation, functional MRI, stroke, transcranial magnetic stimulation

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Introduction

Stroke induces acute deficits of motion, sensation, cognition and emotion, which may or may not regress subsequently. The regression of the neurological deficits evolves substantially in the early period after ischemic stroke but continues to do so at a lower pace usually for up to 2 years. The recovery of activities of daily living usually develops within 6 months after the insult and is often accompanied by compensatory hand use [1,2]. In the acute phase of stroke, it has been proved difficult to predict the degree of ultimate recovery. But prediction becomes progressively better the more specific and differentiated the physiological assessment measures and the longer the time since the stroke [3–5]. Notably, patients older than 65 years benefit as much as younger patients from intensive rehabilitation [6,7], but younger patients typically improve more on mobility, balance, walking and grip strength [8]. Rehabilitation of hemiparesis includes passive movements of the limbs to prevent joint contractures, synergistic facilitation of movements of the affected limb and enhancement of active training of the affected limb. Although the effect of traditional physiotherapy such as Bobath therapy is difficult to quantify [9–12], recent rehabilitative strategies have been proposed that aim at preventing learned nonuse of the affected limb, improving function by cognitive or imaginative training and by external interventions. These approaches are hypothesis-driven and based on novel findings in systems physiology and on results of neuroimaging proof-of-concept studies.

Neuroimaging can visualize the human brain structures and the disease-related changes of the brain in three dimensions of space. Thereby, it provides in-vivo correlations of the infarct-induced clinical changes that can be assessed quantitatively using neurophysiological measures. Functional imaging is a physiological tool which allows the study of brain activity related to specific activation states as well as its changes related to adaptation to the lesion, to deficit compensation and to re-learning. A critical issue, however, is if imaging can predict

(1) whether a patient will recover from his stroke-induced neurological deficit and if so,
(2) by which mechanisms (both spontaneous and/or rehabilitative) and
(3) to what extent.

Recent publications pertinent for these questions will be discussed in this review.

Role of lesion

The infarct lesion is considered as the anatomical focus causing a neurological deficit. With respect to

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the functional implication, there is the need for an accurate anatomical localization of the brain lesion in the individual patient. This information is then transferred to and compared with a generalized reference system for comparison across patients and across patient groups from different institutions. Tiny, circumscribed brain lesions may specifically erase a well defined function, which inversely engages this very same area when probed in healthy individuals [13,14]. In contrast, larger brain lesions usually affect multiple brain systems, resulting typically in complex neurological syndromes. In these instances, probabilistic lesion mapping contrasting well defined patient groups has been shown to be effective in identifying the critical cortical and subcortical grey matter structures whose damage causes the specific clinical deficit in question, for example, hemispatial neglect or apraxia [15,16•,17].

In addition to the location, the degree of damage of a functional system within a lesion and the lesion volume are important. Measures of functional damage have been found to explain best the degree of functional impairment and to play an important role in predicting recovery from stroke [18–22]. This is not only valid for the motor system but has been shown also for language functions, the somatosensory system and the visual system [19–24]. Regarding lesion volume, it is important to remember that stroke lesions develop dynamically from the initial regional hypoperfusion via changes of water diffusion to the final infarct lesion. As secondary changes, such as shrinkage of the lesion and the surrounding brain tissue, result in external and internal brain atrophy, lesions continue to evolve for up to 90 days [25,26]. By 30 days, lesion volume, in general, approaches final infarct volume as assessed in fluid-attenuated inversion recovery sequence [27]. In the acute stage of stroke, the area of impaired brain perfusion typically exceeds the area of abnormal diffusion causing the so-called perfusion–diffusion mismatch (Fig. 1) [28,29•,30••]. The perfusion–diffusion mismatch has been assumed to be the target for acute stroke treatment and, thus, to play a prominent role for stroke recovery [31]. This was tested in large clinical trials. In the Diffusion and perfusion imaging Evaluation For Understanding Stroke Evolution (DEFUSE) trial, it was found that a good clinical outcome after thrombolysis performed 3–6 h after stroke onset was associated with less infarct growth in patients with a perfusion–diffusion mismatch [32]. Likewise, an acute perfusion–diffusion mismatch of more than 20% in the left Brodmann area 37 was strongly associated with acute improvement of naming on days 3–5 [33•]. Similarly, in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET), it was shown that recanalization was strongly correlated with reperfusion as assessed with MRI at days 3–5 [34]. These data probably explain why early recanalization is predictive of reduced infarct growth and good outcome as compared with failed recanalization [29•].

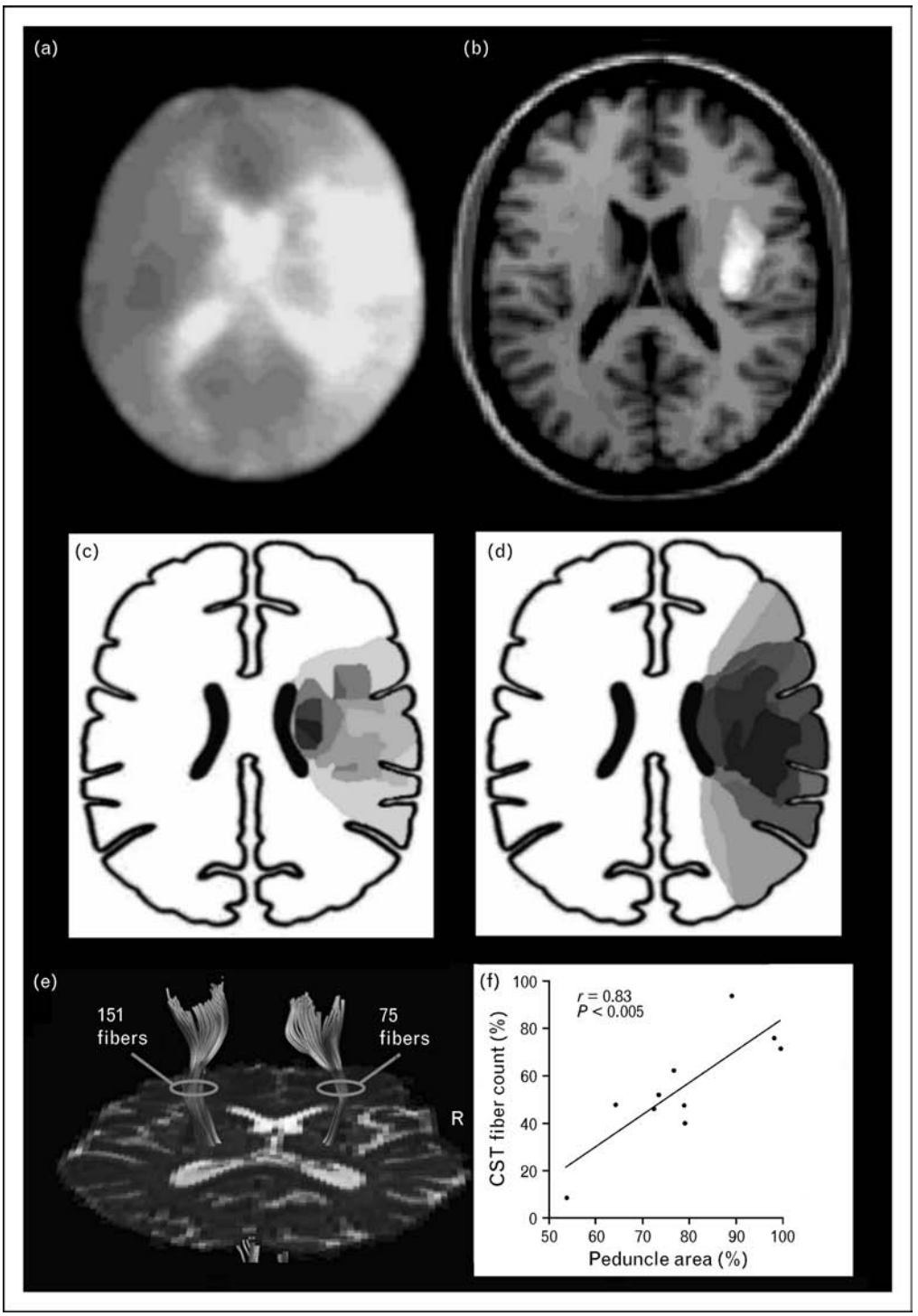
These and other studies have also shown that the abnormal area in diffusion-weighted imaging signifies the area of most severely deprived perfusion, which typically transforms into the final infarct lesion (Fig. 1).

Regarding arterial recanalization, the residual flow at the site of the intracranial occlusion before systemic thrombolysis predicts the likelihood of rapid recanalization and the long-term neurological outcome: no flow in transcranial Doppler indicates the least chance to achieve recanalization [35]. In addition, the arterial collaterals are also of importance, as patients with poor collaterals had larger areas of perfusion delay and greater infarct growth than those with good collaterals [36,37].

Perilesional tissue

Owing to the fact that the area of acute ischemia typically exceeds the final infarct lesion, an important factor contributing to functional recovery is the behavior of the perilesional tissue. The perilesional tissue is supposed to be structurally intact but functionally altered due to transient ischemia and subsequent reperfusion. Both factors evoke a large number of biochemical, metabolic, electrical and immunological processes that evolve sequentially [38,39]. Notably, the binding of flumazenil, a gamma-aminobutyric acid ($GABA_A$) receptor antagonist, as measured with PET was found to be reduced in this area in proportion to the initial hypoperfusion as assessed with perfusion computed tomography (CT) [40]. This suggests loss of inhibitory interneurons in the peri-infarct area, resulting in increased cortical excitability, similarly to what is shown with transcranial magnetic stimulation (TMS) [41•,42]. Behaviorally, the functionally abnormal perilesional tissue contributes to the clinical deficit, which will affect an activation-related functional MRI (fMRI) signal. Thus, fMRI performed approximately 2 days after stroke revealed an area in the ipsilesional postcentral gyrus and posterior cingulate that correlated with motor recovery approximately 3 months after stroke [43]. Also, restoration of hand function 3 months after stroke was associated with progressively lateralized activation of the affected sensorimotor cortex [44]. Similarly, in chronic stroke-induced aphasia, repetitive 4-Hz TMS over the left inferior frontal gyrus rather than the contralateral side resulted in an increase of reaction time or error rate in a semantic task, suggesting recruitment of perilesional tissue in the left hemisphere during recovery [45]. This kind of recovery pattern was again observed in bilinguals [46]. Accordingly, when an impaired function is probed in an activation study, the activation most likely reflects adaptation of the injured brain to the functional deficit owing to plastic changes in the perilesional tissue.

Figure 1 Neuroimaging determinants of recovery in hemiparetic stroke



Mean perfusion deficit involving the central portion of the MCA territory and sparing the basal ganglia (a) exceeding the abnormality of diffusion-weighted imaging which was limited to the hemispheric white matter (b), adapted from [28]. Patients with good recovery show a small area of lesion overlap (c), whereas patients with poor recovery have a large lesion overlap in the hemispheric white matter (d), adapted from [29•]. Note the correspondence of the lesion location to the abnormality of diffusion-weighted imaging. Patients with limited recovery from hemiparesis exhibit a prominent reduction in fiber density in the corticospinal tract as assessed with diffusion tensor imaging (e), which correlates with brain atrophy in the cerebral peduncles (f). Figure 1e and f are reprinted with permission of Elsevier. Adapted from Fig. 2a and c of [30••], copyright of Elsevier. CST, corticospinal tract; MCA, middle cerebral artery.

Impact of white matter injury

In hemispheric brain infarcts, the involvement of the white matter has been less appreciated than that of the cortex. Stereotactic lesion mapping revealed that particularly middle cerebral artery (MCA) stem infarctions induce a prominent lesion overlap in the hemispheric white matter in addition to the peri-insular cortex and basal ganglia [29•]. This white matter damage is particularly prominent in hemispatial neglect, apraxia and severe hemiparesis [15,16•,17,28]. Accordingly, the integrity of the corticospinal tract was found to predict motor recovery as assessed physiologically by motor-evoked potentials (MEPs) or by diffusion tensor imaging (DTI) [18,21,22,30••,47,48]. The integrity of the corticospinal tract as derived from DTI correlates with the overall atrophy of the cerebral peduncles (Fig. 1). The integrity of the corticospinal tract also correlates with the movement-related motor cortex activation [18,21]. In chronic patients without MEPs, there was no recovery if the fractional anisotropy of the posterior part of the internal capsule, as assessed by DTI, was asymmetric across the hemispheres [18]. In these patients bilateral fMRI activations were observed in relation to finger movements, whereas in the patients with a lower asymmetry there was an activation lateralized to the affected hemisphere.

However, there are changes not only in the efferent motor fiber tracts but also in the cortico-cortical loops and probably also in cortico-subcortical fiber tract systems. Motor cortical connectivity was shown by DTI to be enhanced after stroke [49]. More so, orientation uncertainty and greater white matter complexity correlated with functional outcome [49,50]. Notably, these DTI measures correlated with lesion volume, suggesting that the repair processes are possibly triggered by functional demands. Another interesting observation is that intracortical excitability is increased in motor cortex of both hemispheres regardless of subcortical or cortical location of infarction [41•,42]. It is tempting to speculate that both the enhanced cortical excitability and the ipsilesional white matter changes provide a physiological basis for an abnormal recruitment in the hemiparetic patients, as ipsilesional MEPs are more easily elicited from proximal muscles in stroke patients than in healthy individuals [51–53]. Finally, the interhemispheric connectivity is also altered after stroke, as the interhemispheric inhibition from motor cortex of the lesioned onto the nonlesioned hemisphere was decreased, whereas it was normal from the nonlesioned onto the lesioned hemisphere [41•].

Network changes underlying recovery

The perilesional cortex is not the only system activated during recovery. Rather, it is anatomically linked to a large number of brain structures that become engaged as a functional network upon the generation of activity and in relation to spontaneous recovery. Well established since the first functional neuroimaging studies in focal brain lesions is that there are large-scale changes that affect the contralateral cerebral cortex and subcortical structures in a highly structured pattern. These patterns most likely reflect the functional intracerebral connectivity. More recently, it was reported that patients with poorer motor skill recovery had reduced fractional anisotropy in both corticospinal tracts than patients with better motor skills [31]. Importantly, an involvement of both cerebral hemispheres becomes apparent when the impaired functional system is probed by specific activation as, for example, during simple finger movements in hemiparesis [43,54]. The functional changes are enhanced in comparison to controls, largely reminiscent of re-learning, and essentially transient in nature [41•,42,55].

Network type of analysis methods have shown that in patients with a single subcortical stroke, there is a pathological interhemispheric interaction between the ipsilesional and contralesional motor cortex as well as between the ipsilesional supplementary motor area (SMA) and contralesional motor cortex [56••]. In unilateral movements of the affected hand, there was an inhibitory influence from the contralesional to the ipsilesional motor cortex, which correlated with the degree of motor impairment. In bimanual movements, the interaction of the ipsilesional SMA and the contralesional motor cortex was reduced which correlated with impaired bimanual performance. This can be related to the observation that there was less activation in contralesional motor cortex when the motor task did not require working memory demands and even no change when the task required online visual feedback monitoring [57]. Also, the premotor cortex was bilaterally less active when there was no working memory demand but increased activity upon online visual feedback monitoring, although there was no difference in performance.

Effect of training

Behaviorally, rehabilitative training after stroke is known to improve the functionality and to enhance the spectrum of activities of daily living. Evidence from functional neuroimaging shows that training has a significant impact on the cerebral activation patterns. Constraint-induced movement therapy, which is composed of focussing the patient's attention to the affected side and imposing repetitive training, results in improved motor function and enhanced activation in the partially damaged sensorimotor cortex [21,58] as well as in other gray areas including the hippocampus [59]. Similarly, repetitive training of the affected arm resulted in an increase of

activation in the sensorimotor cortex related to hand movements. This initially persisted for weeks after training completion and then decreased in magnitude in relation to the functional gain [60,61]. Further, a 3-week training of robot-assisted movements in chronic stroke patients resulted in gains of hand motor function that was associated with a greater fMRI signal in sensorimotor cortex related to performance of the trained movements [62]. This increase was task-specific, as it did not occur in relation to a nontrained supination/pronation movement with the affected hand and movements of the nontrained hand. Similarly, treadmill training was found to improve walking velocity, which correlated with brain activity in the posterior cerebellum [63]. Even passive training of wrist movements was reported to be clinically effective and to change the cortical activation [64], although evidence from three-dimensional motor analysis showed that successful hand shaping and grasping of objects did not occur when there was not sufficient volitional control of finger and thumb extensions [65].

More recently, cognitive training strategies have been promoted. It has been assumed that the inferior frontal cortex plays a critical role in motor recovery, as there are so-called mirror neurons that become active not only in relation to motor activity but also in response to observation and imagery of the same type of movements. In controlled trials, mirror therapy early after stroke was found to improve the neurological status immediately after the intervention and at long-term follow-up [66,67]. Similarly, mental training was reported to result in better functionality of the upper extremity and in greater gains of activities of daily living than did standard physiotherapy [68,69•]. fMRI revealed that motor imagery activated a widespread network of cerebral areas in motor, premotor and parietal cortex in both cerebral hemispheres. However, activation of Brodmann area 4a was lower, while dorsal premotor cortex activation was similar [69•,70•]. Notably, ipsilesional area 4p activation in relation to motor imagery and hand movements correlated with motor performance.

Similarly, a daily treatment combining observation of movements with physical training for 4 weeks resulted in a significant increase in motor functions, which lasted for at least 8 weeks after training [71]. This was associated with a significant overactivation in the bilateral ventral premotor cortex, bilateral superior temporal gyrus, the SMA and the contralateral supramarginal gyrus related to an object manipulation task.

It needs to be mentioned, however, that the capacity to perform motor imagery can be weakened by limb loss or disuse. In contrast, the temporal characteristics of motor imagery may not be affected [72]. This is important, as first-person imagery of hand movements strongly activates the left inferior parietal lobe (parietal operculum and SII) in healthy volunteers, particularly with postures compatible to a previously seen right hand movement [73]. Notably, the secondary somatosensory cortex is particularly activated in successful recovery from hemiparesis [43,74]. Further, kinetic imagery showed more activity in motor-associated structures and in the inferior parietal lobule, whereas visual imagery engaged primarily occipital regions and the superior parietal lobules [75].

New therapeutic interventions

A recent development in neurorehabilitation is the translation of findings obtained in basic neuroscientific research in clinical testing. Specifically, strategies aiming at restoring the disturbed balance of cortical excitability following stroke have been elaborated and proposed as possible targets.

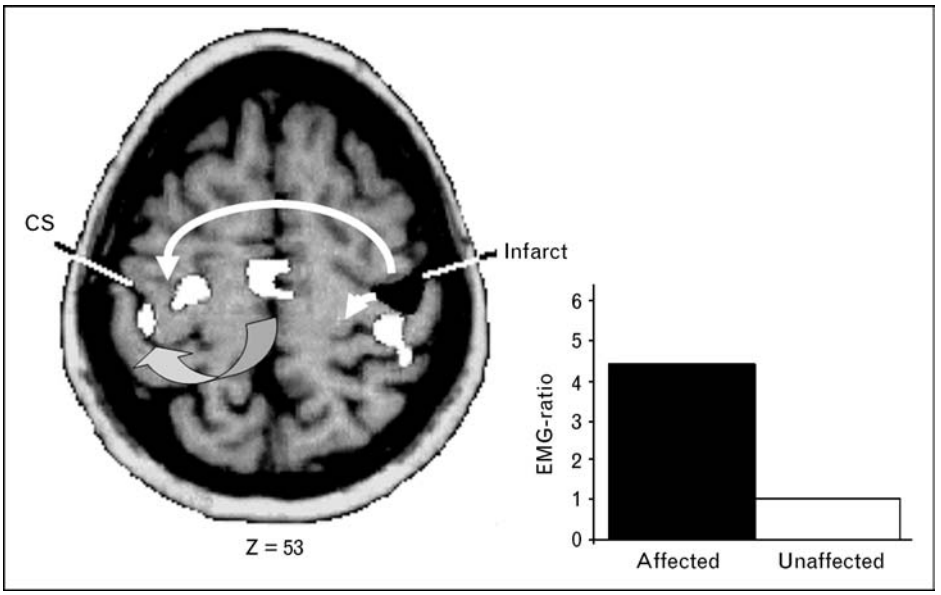
One example is the active–passive bilateral arm therapy. It was described that it can produce sustained improvements in upper limb motor function in chronic stroke patients. This was paralleled by an enhanced ipsilesional motor cortex excitability and an increased transcallosal inhibition from ipsilesional to contralesional motor cortex [76].

Furthermore, anodal stimulation of the affected motor cortex can augment motor skill acquisition [77]. Conversely, application of 1-Hz repetitive TMS (rTMS) of 10 min duration to the contralesional motor cortex, which downregulates the contralesional motor cortex, improved the kinematics of finger and grasp movements in the affected hand. This resulted in overactivity in the contralesional motor and premotor cortical areas [78]. Although there was no correlation to the behavioral improvement for motor cortex activation, overactivity in contralesional premotor cortex and ipsilesional medial frontal cortex predicted improvement in movement kinematics. Probably, the medial frontal cortex exerts an inhibitory influence onto the disinhibited contralesional motor cortex (Fig. 2).

Also interventions in the peripheral nervous system are promising. For example, combining peripheral nerve stimulation to the affected hand with anodal direct current stimulation of the affected motor cortex facilitates motor performance beyond levels reached with either intervention alone [79•]. Likewise, Galvanic stimulation of the median nerve resulted in a source displacement in the affected hemisphere as compared with the nonaffected hemisphere in proportion to clinical recovery after stroke [80].

The combination of electromyographically triggered electrical stimulation of finger extensor muscles at

Figure 2 Relationship of the brain activation pattern and cortical excitability after complete recovery from lacunar motor cortical stroke



There was no change of muscle activity in the ipsilesional nonaffected hand as evident from electromyography as compared with rest. The transfer of the enhanced cortical excitability from the perilesional tissue to the contralesional motor cortex is indicated. Note also, the enhanced activity in the presupplementary motor area in the medial frontal cortex that is suited to antagonize the enhanced excitability of the contralesional motor cortex. CS, central sulcus; EMG, electromyographic. Adapted from [41•].

50 Hz and tracking training for 1 h over 2–3 weeks improved the dexterity of the affected hand as assessed with the Jebson test [81]. Patients with an intact motor cortex showed a greater improvement than those who had direct involvement of the motor cortex. However, only in the combination group did functional improvement correlate with a change of the laterality index in sensorimotor cortex and premotor cortex activation, indicating greater ipsilesional control. There was a negative correlation with the blood-oxygen-level-dependent (BOLD) signal intensity change in the ipsilesional sensorimotor cortex and the SMA [81].

Recently, the effect of 5 days of anodal stimulation of the injured motor cortex was found to improve consolidation but not long-term retention of a motor task [77]. One may wonder whether long-term retention can be achieved by long-lasting stimulation or by the combination of voluntary action and direct brain stimulation.

Conclusion

Imaging is a powerful tool to explore the structure and function of the human with high spatial and good temporal resolution *in vivo*. It has become increasingly clear that the human brain has the capability to regain functions that are impaired by insults such as ischemic stroke. Restitution of functionality is paralleled by structural changes in cerebral grey and white matter and normalization of functional representations involving neural networks in both cerebral hemispheres. Initial attempts to apply neuroscience principles in neurorehabilitation are promising to enhance recovery. Currently, electrophysiological stimulation paradigms are considered as potential amplifiers.

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The author has no conflicts of interest to declare.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 93).

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