Restorative Neurology and Neuroscience 22 (2004) 207–229
IOS Press

Reorganisation of cerebral circuits in human ischemic brain disease

Rüdiger J. Seitz[a,b,*], Cathrin M. Bütefisch[c], Raimund Kleiser[a,c] and Volker Hömberg[c,d]
[a]*Department of Neurology, University Hospital Düsseldorf, Moorenstrasse 5, 40225 Düsseldorf, Germany*
[b]*Biomedical Research Centre, Heinrich-Heine-University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany*
[c]*Neurological Therapy Centre, Hohensandweg 37, 40591 Düsseldorf, Germany*
[d]*St. Mauritius Therapy Clinic, Strümper Strasse 111, 40670 Meerbusch, Germany*

Abstract. Animal experiments suggest that reorganisation of cerebral representations is the neurobiological basis of post-lesional recovery. In human ischemic brain disease recovery is a dynamic and sustained process beginning after stroke manifestation. The mechanisms underlying recovery can be investigated non-invasively in the human brain using functional neuroimaging and transcranial magnetic stimulation (TMS).
In the acute stage, the mismatch area of the perfusion deficit and the impaired water diffusion as assessed by magnetic resonance imaging (MRI) shows the brain tissue that potentially can be rescued by thrombolysis or emergency carotid endarteriectomy. Since spontaneous motor recovery is a function of the corticospinal tract integrity, early reperfusion of ischemic tissue is critical. In the subacute and chronic stage after stroke, recovery of motor function was shown to take place irrespective of a concomitant affection of the somatosensory system. Functional MRI with simultaneous recordings of the electromyogram provides evidence that the abnormal activation of motor and premotor cortical areas in both hemispheres related to finger movements has a large interindividual variability. As evident from TMS, recovery results from regression of perilesional inhibition and from remote intracortical disinhibition. Repetitive training, constraint induced training and motor imagery can augment recovery promoting a re-emerging activation in the affected hemisphere.
Evolution of altered local perilesional and large-scale bihemispheric circuits appears to allow for post-lesional deficit compensation.

Keywords: Stroke, plasticity, recovery, motor system, functional neuroimaging, lesion morphometry, transcranial magnetic stimulation, perfusion weighted imaging, diffusion weighted imaging

1. Introduction

Middle cerebral artery (MCA) infarction is the most common manifestation of stroke and characterized by contralateral hemiplegia and neuropsychological deficits such as apraxia and aphasia [67]. Most frequently, both motor functions and somatosensation are impaired while either system may be affected preferentially. The majority of patients recovers such that they become ambulatory again regaining independence in activities of every-day life [12,107]. There is increasing evidence that neurorehabilitation can support clinical recovery [112,114]. Issues of interest are what the clinical course and the neurobiological basis of recovery are. It is now widely assumed that reorganisation of functional representations in the human brain mediate postlesional recovery [27]. The underlying assumption is fostered by recent experimental work in animals which provided evidence for plastic changes in the brain in relation to input and output manipulations.

During the past two decades experimental studies in animals have demonstrated that the adult brain main-

*Corresponding author: Dr. R.J. Seitz, Department of Neurology, University Hospital Düsseldorf, Moorenstrasse 5, 40225 Düsseldorf, Germany. Tel.: +49 211 81 18974; Fax: +49 211 81 18485; E-mail: seitz@neurologie.uni-duesseldorf.de.

tains the ability to reorganise throughout life. Cortical reorganisation or plasticity as defined by Donoghue is "any enduring change in the cortical properties either morphological or functional" [55]. Since the pioneering work of Merzenich and his colleagues (for review see [132]) it is known that the overuse or disuse of limbs lead to an increase or decrease of the corresponding cortical representations, respectively. Motor cortical representations can reorganise rapidly in response to different stimuli, such as peripheral nerve lesions [56,179], ischemic nerve block [14] or motor performance [149].

The pivotal question for restorative neurology of whether such plasticity also operates after cortical damage was approached in specific ablation experiments. For example, Nudo et al. [149], observed that the cortical finger representations adjacent to partly damaged finger representations became enlarged with rehabilitation, while they remained unchanged in the untreated monkeys. In such experiments evidence was provided showing that reorganisation occurs in the adult nervous system both adjacent to a focal brain damage leading to plastic changes of the representation within the affected system. Furthermore, destruction of areas 1, 2 and 3 in the hand area of primary somatosensory cortex of the monkey (SI) has been shown to lead to an immediate unresponsiveness of the hand representation in SII, the second somatosensory cortex, a functionally related but distinct co-operative area [158]. More importantly, however, twenty-four hours later the formally unresponsive hand area in SII was occupied by a foot representation. Later it was shown that focal lesions of the cerebral cortex typically induce plastic changes remotely in cortical and subcortical locations in lesion-related systems [232]. The underlying mechanisms involve the unmasking of existing, but latent, horizontal connections (for review [177]) or modulation of synaptic efficacy such as long-term potentiation (LTP) [84,85] or long-term depression (LTD) [86]. The neurotransmitter systems involved in mediating these effects include the inhibitory GABAergic system [84, 86] as well as the excitatory glutamatergic system with activation of NMDA receptors [85].

The availability of non-invasive neuroimaging and electrophysiological techniques allow us today to study reorganisation in-vivo also in the human brain. The functional neuroimaging techniques include measurements of the regional cerebral blood flow (rCBF), regional cerebral metabolism of glucose or oxygen (rCMRGlu, rCMRO2) and of neuroreceptor and neurotransmitter systems using positron emission tomography (PET). In more recent years diffusion weighted imaging (DWI) and perfusion imaging (PWI) using magnetic resonance imaging (MRI) have been developed. Furthermore, rCBF-measurements with PET and measurements of blood oxygen level dependent changes with functional MRI (fMRI) allow to map the cerebral structures that participate in motion, sensory perception, or in cognitive problem solving. These functional neuroimaging techniques have not only been employed for studying normal brain function but also for the study of brain plasticity related to learning (for review see [214]). More recently, PET and fMRI have even been used for studying the reorganisation of functional representations in relation to recovery from human brain diseases including cerebral ischemia [27]. This issue is not straightforward, since a fundamental problem when studying patients with focal brain lesions or psychiatric disorders, such as psychosis, is that one has to differentiate between the task-specific activation patterns and the disease-related functional changes the latter of which may obscure the task-specific activation patterns [160,161].

Transcranial magnetic stimulation (TMS) provides additional information on processes involved in cerebral reorganisation. Changes of the human corticospinal motor output system such as changes of the maps of cortical excitability related to use or injury of the brain can be studied. More recently, paired-pulse TMS has provided means to study intracortical inhibitiory and excitatory activity thereby allowing to study the differential regulation of intracortical neuronal networks involved in reorganisation of the brain [22,122]. Further, by combining TMS with drugs that either block or enhance TMS evoked responses, neurotransmitter systems mediating the observed effects can be identified [19,204,239], for review Cohen et al. [42]. Also, "artificial reversible brain lesions" can be introduced with single pulse and repetitive TMS which allow to probe the specific role of a cortical area for a given behavioral task [88,96,171].

Here, we will review in which way neuroimaging techniques and TMS have enabled us to study cerebral mechanisms of recovery after lesions to the central nervous system. The thereby acquired knowledge is a prerequisite to develop neurobiologically based strategies for neurorehabilitative interventions. We will focus on brain infarction for two reasons. First, in the majority of patients, brain infarction is a well defined localised lesion to the brain with a clear temporal onset. In this sense it is comparable to experimental lesions in animals. Second, brain infarction in the territory of the

middle cerebral artery leading to hemiparesis provides a means to study the lateralised sensorimotor system which allows to differentiate perilesional from remote changes related to recovery of arm and hand function. Specifically, we will address the pathophysiology and treatment options in the acute phase of stroke, the impact of the structural stroke lesion, the role of the cerebral structures on motor recovery, the changes of excitability of the cortical motor output system, and the effect of dedicated training.

2. Recovery in the acute phase of stroke

In patients with a functional impairment recovery may result from restitution of tissue function after a short-lasting ischemia or from reorganisation within the remaining functional network adjacent to a small brain lesion. The pathogenetically leading mechanism, e.g. ischemia, can now be studied in humans with MRI techniques such as perfusion and diffusion weighted imaging (PI, DWI). Interruption of circulation due to cerebral artery occlusion induces immediate suppression of cerebral electrical activity causing perinfarct depolarisation with repeated episodes of metabolic stress and growth of the infarction up to 24 hours post-occlusion [82,91,116,121,135]. Clinically, a middle cerebral artery (MCA) occlusion becomes manifest by contralateral hemiplegia within 60 seconds [15]. During ischemia the thresholds for selective neuronal and tissue necrosis are a function of rCBF reduction [90]. PI is based on the dynamic recording of the passage of an intravenously administered contrast agent through the brain and thereby provides means to assess the regional cerebral perfusion including estimation of the rCBF. During stroke evolution the hypoperfused area is typically larger than the ischemic core that is irreversibly affected and evident in DWI [128, 145,170,215]. The resulting PI-DWI mismatch shows the portion of brain tissue which is potentially salvable and, therefore, may correspond to the so-called penumbra. The penumbra has been defined as an area with misery perfusion and enhanced oxygen extraction [82, 118]. Accordingly, recovery may well be the consequence of restoration of perfusion due to rapid vessel recanalisation (Fig. 1). Recanalisation of the occluded cerebral artery with partial restoration of perfusion occurs spontaneously in the majority of patients within 24 hours [72,80]. However, good leptomeningeal collaterals and early recanalisation of middle cerebral arterial occlusion, in particular during thrombolytic therapy, critically increase the chances of functional restitution with favourable clinical outcome [165,216,217]. The beneficial role of early recanalisation was shown by functional imaging [81,103] and monitoring with transcranial Doppler sonography [2,3].

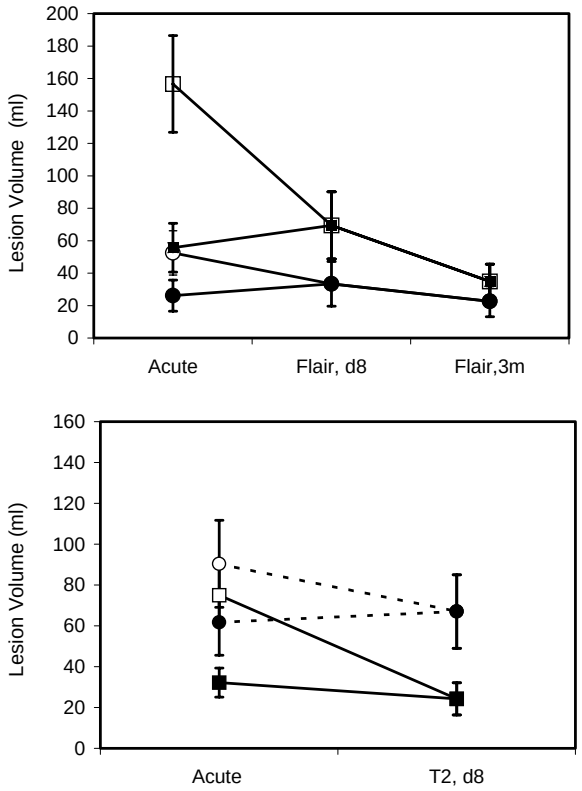

Fig. 1. Salvage of ischemic brain tissue at risk of infarction by systemic thrombolysis with rtPA (top) and emergency carotid artery surgery (bottom). The structural stroke lesions as visualized on day 8 in FLAIR or T2-images are smaller than the acute PWI-lesions before treatment but virtually identical to the acute DWI-lesions. At three months the stroke lesions had regressed in volume. Squares: treated patients, dots: non-treated control patients; in acute stage open symbols: PWI-lesions; filled symbols: DWI-lesions.

Thus, recovery of function in brain infarction is critically determined by the spatial extent, duration, and severity of focal ischemia [104]. While hemiplegia and depression of rCBF produced by temporary carotid artery balloon occlusion have been shown to normalise completely with 15 minutes [15], hyperglycemia adds to brain damage even in early reperfusion after thrombolysis [59,152].

3. Evolution of the chronic stroke lesion

The pathophysiologically most important factor for post-stroke recovery is the affection of the impaired

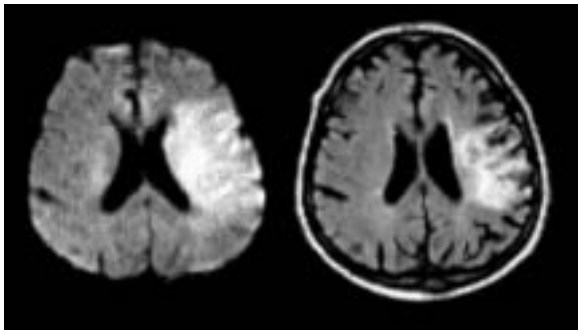

Fig. 2. Regression of the chronic stroke lesions as visualized in a FLAIR-image four months after stroke (right) as compared with the acute DWI lesion (left).

functional system. Therefore, due to the toporegional organisation of the brain lesion assessment is critical. In human stroke the area with severely compromised perfusion undergoes necrosis. This necrotic core is visualised with DWI in the acute phase and after couple of days with structural MRI or CT (Fig. 2). Assessing the actual size of the ischemic infarction is important because the volume of the lesion is one factor determining the degree of recovery. In addition, the lesion location within the affected hemisphere but also lesion location in the right versus left hemisphere are important determinants for post-stroke recovery [11,12,33, 53,153,208]. This point is well illustrated by the famous case of Foerster [65]. The patient underwent ablation of motor cortex for intractable focal epilepsy and later, at autopsy, showed complete unilateral pyramidal tract degeneration. He had regained the capacity to lift his arm straight over his head and to hold a pen. However, his fractionated finger movements remained severely handicapped. Further evidence for the important role of the pyramidal tract for motor recovery was obtained from morphometric measurements and from MR diffusion tensor imaging [11,70,224,231].

As described above, however, the PI-abnormality in acute stroke is typically larger than the irreversibly damaged ischemic brain lesion. Thus, any possible reorganisation processes at the border of the manifest ischemic brain lesion will take place in brain tissue which was critically compromised in blood supply but remained structurally intact. The persisting depressions of cerebral metabolism or blood flow beyond the necrotic core of brain infarction within the affected perfusion area are probably the result of selective ischemic nerve cell damage in the presence of viable glia [82, 198,230]. This implies that a chronic structural brain lesion as evident in CT and MRI reflects only a portion of the total amount of brain tissue affected by ischemia in the acute stage of brain infarction (Fig. 2). This is also apparent from recent morphometric studies on structural MRI which showed a profound atrophy of the perilesional brain tissue [168,188]. Consecutively, the neuronal loss after transient ischemia significantly exceeds the area of DWI abnormality [121].

4. Post-stroke recovery investigated with functional activation studies

Functional imaging studies using rCBF-PET or fMRI in patients who had recovered from their first hemiparetic stroke involving the internal capsule and the basal ganglia consistently showed a spatially enhanced recruitment of cortical areas ipsilateral to the infarction during movement activity of the affected hand [37,131,227]. Interestingly, the task-related rCBF-increases were as high as in normal controls which probably corresponded to normal MEPs of the affected hand [225,226]. Thus, there are good reasons to believe that the motor cortex of the affected hemisphere was actively involved in task performance in these patients who had recovered from subcortical stroke.

In contrast, after recovery from hemiparetic stroke in the MCA territory with predominant involvement of the pericentral cortex, there may be a lack of activation in motor cortex and SI, although the corticospinal tract and the afferent somatosensory tract were largely functional as assessed by evoked potential and metabolic studies [53,195]. Thus, no activity changes related to finger movements of the affected hand were observed in sensorimotor cortex adjacent to the stroke lesion (Fig. 3). This was the case in the chronic phase in PET studies and in the subacute phase in fMRI studies. In contrast, fMRI showed activation areas related to sensorimotor activity just adjacent to the lesion within 24 hours after stroke onset, while they were somewhat displaced in the subacute stage at four weeks after stroke (Fig. 3). Similarly, diminished rCBF increases due to sensorimotor stimulation have been reported even after transient cortical ischemic attacks [159]. Possibly, these observations corresponded to the reported uncoupling of rCBF (no response) and rCMRGlu (persistent response) which was explained by an ischemia-induced inhibition of the neuronal nitric oxide synthetase [36].

Other functional imaging studies in patients with cortical brain infarction showed a regional reorganisation of cortical representations. For example, a systematic posterior shift of the activation was observed after re-

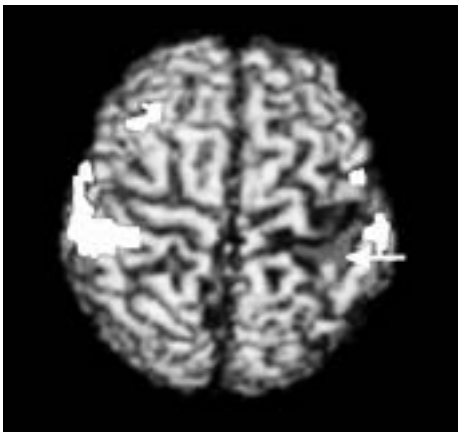

Fig. 3. Displaced haemodynamic response in related to tactile exploration movements of the affected hand in a patient with good motor recovery. Note also the contralesional activation area in the motor-premotor cortex. The arrow indicates the infarct lesion in the precentral gyrus.

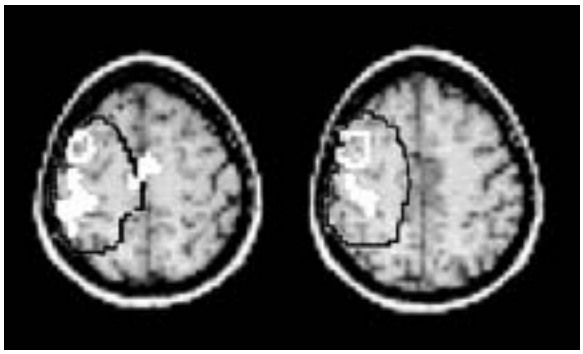

Fig. 4. Coregistration of the perfusion abnormalities, the manifest lesion and cerebral activations after recovery in a patient with right-hemispheric infarction in the middle cerebral artery territory. Shown are two adjacent axial slices at the level of the cortical hand/arm representation. The DWI-lesion is outlined in white, the large area of impaired perfusion is outlined in black. The activation areas related to finger movement of the recovered hand adjacent to the DWI-lesion and in the midline corresponding to the supplementary motor area (white).

covery from stroke [29,155]. Further, there was also evidence that activation related to sensorimotor activity was restricted to the somatosensory cortex after infarction of motor cortex and to the motor cortex after infarction of somatosensory cortex [45]. These findings resembled the displacement of the hand representation in brain tumours [196,237] suggesting a local reorganisation of cortical representation by the plastic capacity of the underlying perilesional neural machinery [191].

Analysis of imaging data in individual patients, however, revealed large differences of rCBF increases related to sensorimotor activity of the affected limb [89, 225,229]. These differences were probably due to individual lesion location and extent, differences in performance, and possibly due to inter-individual functional variability [44,225,229]. Group data of patients with fairly homogenous infarct types and lesions, however, showed that the dorsal premotor cortex in the affected hemisphere was more active after prolonged recovery than early after stroke [24]. This area seemed to coincide with a premotor cortical area being more active in elderly as compared to young subjects during sensorimotor activity [26].

More recently, event-related fMRI was used to investigate the time course of activation in motor cortex after right subcortical stroke [147]. The major observation was that the hemodynamic response was delayed particularly in the right motor cortex during activity of the paretic contralateral left hand. In contrast, in healthy subjects the hemodynamic response was well timed. One may, therefore, speculate that this impairment of the hemodynamics in the stroke patients was due to structural changes in the supplying artery, to functional abnormalities of hemodynamic signalling of the formerly ischemic brain tissue, or to both. In fact, activation after stroke may occur next to the DWI-lesion within the formerly critically hypoperfused brain tissue which was salvaged from transition into ischemic necrosis due to thrombolysis (Fig. 4).

In addition to the abnormalities in the affected hemisphere, there is clinical evidence showing that the motor system in the contralesional hemisphere plays an important role for deficit compensation in postischemic reorganisation [64]. The first to show contralesional motor cortex activation in brain lesions acquired in adulthood were Chollet et al. [37] using PET. Later is was replicated by Cao et al. [28] using fMRI. One aspect of this contralesional activation was that those patients who exhibited significant rCBF increases in motor cortex contralateral to the cerebral infarction had associated movements of the non-affected hand [229]. This corresponded to electromyographic findings in healthy subjects in whom effort, force and activity with the non-dominant hand were accompanied by increased muscle activity in the homologue muscles contralateral to the moving hand [57,58]. Notably, the associated rCBF increases in the motor cortex of the non-affected hemis phere occurred in those patients with limited recovery [225,229]. Nevertheless, fMRI showed that the ipsilateral activation did not occur in a strictly homologue location compared with the contralateral motor cortical representation but in different locations along the contralesional motor cortex [44]. Again, there is

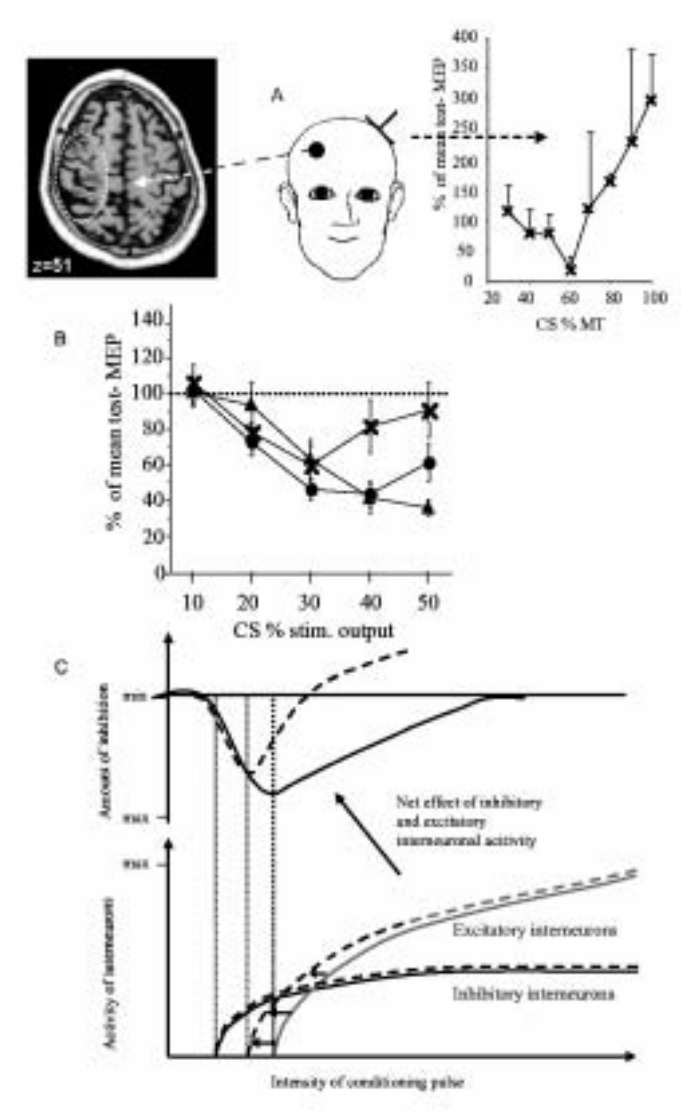

Fig. 5. Increased recruitment of ipsilateral motor areas when moving the affected hand in one patient with right hemispheric brain infarction. A. Contrast between performance of motor task with the paretic left hand and rest. In this study the patient is performing a finger sequence with the affected left hand while the right non-affected hand is relaxed. Activation of ipsilateral precentral gyrus is evident (level of the axial view is given in z-coordinate of Talairach space, p gives the threshold). Electromyographic recording of the extensor digitorum communis muscle of both hands during the motor performance (inset) confirmed that this increased recruitment was not due to co-activation of the non-affected hand. The ratio of EMG activity while performing the task and at rest was calculated. As indicated by the EMG ratio of 1 for the right hand, this hand was relaxed during the performance of the left hand. In contrast the EMG ratio of about 3 indicates that this hand was active during the the task B. The location of the infarction is illustrated in the axial slices of the schematic brain in Talaraich space. The levels of the axial slices are given in z-coordinates.

considerable interindividual variability of the cortical activations. This variability may be partially accounted for by differences in task performance and associated electromyographic activity (Fig. 5).

In patients with cortical MCA infarctions there was activation in the frontomesial cortex including the supplementary motor area (SMA) as shown in Figs 4 and 5 which contrasts to patients who had recovered from striatocapsular infarction [52,225]. Activation of the SMA probably corresponded to the initiative role of the SMA in movement control [95,130]. From longitudinal studies on recovery from hemispheric stroke it became apparent that the activity of the SMA was enhanced early after stroke but declined as learning pro-

ceeded [29]. The lack of SMA activation in the striatocapsular infarctions was probably due to damage of the corticospinal projection from the SMA to the basal ganglia by the infarct. These patients appeared to activate instead the contralesional premotor cortex [225] underscoring the impact of lesion location for the activation pattern related to sensorimotor recovery.

The contralesional premotor cortex may be of critical importance for recovery from middle cerebral artery infarction [195]. First, one may argue that recovery was brought about by recruitment of ipsilateral corticospinal projections originating in the contralesional hemisphere [7,31,60,120]. Usually, this leads to initial reoccurrence of proximal movements compared to the later recovery of distal movements [43,117]. Conversely, there is an ipsilesional impairment of forearm function in the acute stage after stroke [99]. Similarly, active and passive sensorimotor tasks were reported to show a largely bilateral activation pattern as recovery progressed [26,142]. Remarkably, the more symmetric the activations in both cerebral hemispheres were, the greater was the white matter affection and the worse the clinical outcome [163,172]. Second, the premotor cortex is of particular importance for control of temporally or sequentially complex finger movements as evident in learning, motor adaptation, and post-stroke recovery [50,192,207]. While in single movement tasks the premotor cortex did not become engaged [30], inhibition of the contralesional premotor cortex was reported to impair motor performance in patients who have recovered from stroke [98]. These observations may provide an explanation for the fact that stroke patients with involvement of premotor cortex exhibited an additional motor deficit that counteracted recovery [68,134].

It is noteworthy that a combined activation of the SMA and parietal cortex was shown to be related to the exertion of force [51]. It is, therefore, reasonable to assume that parietal activation reflected reorganisation of the sensorimotor system to meet the task demands of the sensorimotor activation paradigm. Contralesional activation of the anterior parietal cortex after stroke was reported both in relation to active somatosensory object discrimination and passive arm movements [143, 195]. Kinematic evidence showed that patients with parietal cortex lesions retained abnormal finger movements when required to explore macrogeometric objects after recovery from hemiparesis [10]. It is, therefore, possible, that the rCBF increases in the contralesional parietal cortical regions during somatosensory discrimination of macrogeometric objects [195] were related to deficit compensation. Notably, they occurred in an area that in normal subjects seems to participate in voluntarily controlled forelimb movement [9,194]. In addition, there was abnormal prefrontal cortex activation suggesting enhanced cognitive control for a task that is relatively difficult for patients as compared with healthy subjects [24,195]. Continued training with passive arm movements enhanced the bilateral activation of the cortex lining the intraparietal sulcus and premotor cortex even further [142]. Since the parietal cortex subserves sensorimotor integration being heavily interwoven with executive functions mediated in the frontal motor cortical areas [225], these data substantiated the importance of the non-affected hemisphere for post-stroke recovery of sensorimotor functions.

Furthermore, recovery from hemiplegia may be connected also with activation of other parts of the sensorimotor circuitry. Similarly to activation of the lower premotor cortical areas in recovery from aphasia [101, 106,228] there was inferior frontal cortex activation ipsilateral to the moving hand during execution of fast and sequential finger movements with the recovered hand [195,229]. Since this area was activated in healthy subjects during learning of finger movement sequences [97,187] but not after skill acquisition [197], it is a key area for establishing the motor program. Probably, this function is mediated by the property of this area to relate perception of movements such as gestures to body movement production [8,13,48,151].

More recently, the dynamics of the cerebral activation maps related to the course of motor recovery have been studied (Table 1). It was found that there are complex modulations of activity that were determined by the stroke lesion. For example, it was observed that areas showing progressively increasing or sustained activity were located in contralesional prefrontal and premotor cortex as well as the contralesional cerebellum [25,62,66,201]. Conversely, areas in the contralesional hemisphere were reported to become progressively less engaged when motor cortex was spared [62]. However, patients with poor recovery showed far less cortical and cerebellar activation [29,201]. The latter observations are of particular relevance, since they emphasise that the cerebellar route participates critically in motor recovery substantiating earlier observations [6]. Further, patients with poor recovery did not seem to endogenously activate the motor system in contrast to motor imagery in healthy subjects [8,48,115,205]. Nevertheless, the changes in the well recovering patients reflected more or less the pattern in recovery brought about by dedicated physiotherapy. The time course of cerebral activations is probably even greater than the

Table 1
Lateralization of motor cortex activation as evident from fMRI during recovery of finger movements of the affected hand

Early (day 5)	subacute (2 weeks)	chronic (after 4 weeks)
0.5 +/− 0.6	−0.6 +/− 0.5	1.0 +/− 0.1

Legend: Data shown for 8 patients with infarctions in the pre- or postcentral gyrus with initial loss of hand function followed by progressive clinical recovery. Note that there is a lateralization to the contralesional side in the subacute phase due to transient lack of motor cortex activation inspite of finger movement activity. In the chronic stage the activation is clearly lateralized to the ipsilesional side, i.e. normalized.

relatively slow changes in haemodynamics observable with functional imaging. Recently, it was shown with event-related electroencephalography after subcortical stroke that in movements of the recovered hand activate both sensorimotor cortices. However, the activation of the cortex ipsilateral to the affected hand joined in shortly after the ipsilesional cortex which was different from healthy controls [219].

Apart from recovery mediated within the original sensorimotor domain, shifts in the strategy of task performance have to be considered. These included the resumption of abnormal movement patterns [69] as well as abnormal movement guidance. For example, monkeys with focal ischemic lesions in motor cortex visually inspect their hand when retrieving objects with the affected hand [150]. In humans, it was observed that patients who had recovered from ischemic stroke differed significantly from healthy controls by the recruitment of a predominantly contralesional network, involving visual cortical areas, prefrontal cortex, thalamus, hippocampus, and cerebellum during the blind-folded performance of sequential finger movements [192]. Greater expression of this cortical-subcortical network correlated with a more severe sensorimotor deficit in the acute stage after stroke, reflecting its greater role for post-stroke recovery (Fig. 6). Thus, a visuomotor brain system appeared to compensate a sensorimotor deficit in patients who had recovered from hemiparetic stroke. This observation corresponded to animal models of focal brain lesions and to the developing human visual and auditory systems [38,41,146,176], suggesting that postlesional reorganisation involved a network usually not active in sensorimotor activity.

In addition, it was shown that the lesion-affected and the recovery-related network in stroke patients shared the same structures in the contralesional thalamus and bilateral in visual association areas [193]. Thus, these sharing structures accommodated simultaneously passive lesion effects and active recovery-related changes

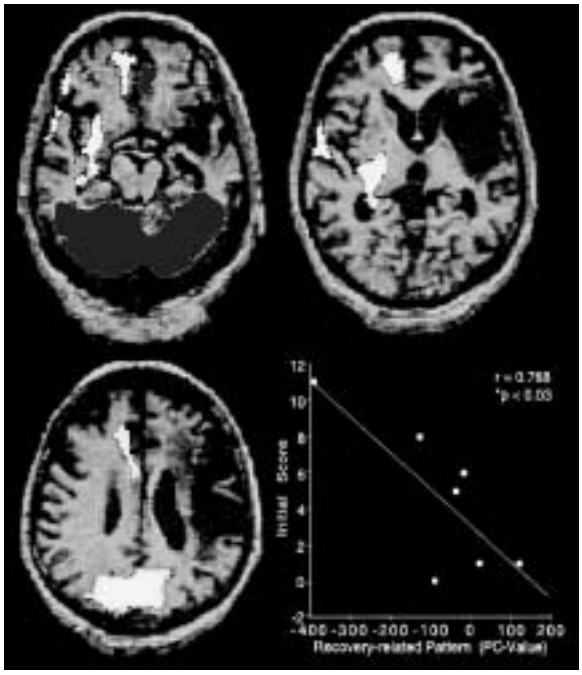

Fig. 6. Recruitment of a contralesional hemispheric network involving the thalamus and visual association cortex, and bilateral the cerebellum in patients with recovery from middle cerebral artery infarction. The greater the initial motor deficit the greater expression of this pattern. Results of a prinicipal component analysis of PET rCBF-data [192].

in locations remote to the site of the brain infarction. This observation corresponded to the original conception of diaschisis as a restorative mechanism in functional recovery. That is, recovery was mediated by areas that had regained activity after initial inhibition by a distant brain lesion as originally suggested in the concept of diaschisis by von Monakov [222]. Thus, postlesional reorganisation was not only effective in the perilesional vicinity but appeared as a task-related rewiring of intrinsic cerebral networks [191]. Similar conclusions were proposed recently also for psychologically impaired patients [160,161]. As evidenced by activation studies in patients who had recovered from hemiplegic stroke, such unused, but functionally related pathways may take on back-up or facilitatory functions [37,225,229]. Likewise, disturbances of complex motor behaviour such as neglect and limb kinetic apraxia also tend to disappear with time [58, 78].

In summary, there is a temporally dynamic evolution of brain activation in cortical structures in the affected and the non-affected hemisphere as well as in subcortical structures related to post-lesional recovery from stroke.

5. Relevance of the motor output system for stroke recovery

Transcranial magnetic stimulation (TMS) is a non-invasive technique in which a focused magnetic field pulse is used to evoke an electrical discharge of cortical neurones. If the resulting discharge is of sufficient magnitude, a motor evoked potential (MEP) is measurable in the muscle where the cortical neurones project to (target muscle). The size of the MEP depends on the intensity of the magnetic stimulus, the excitability and number of cortical neurones and on the integrity of the entire cortico-spinal tract. Following injury to the brain TMS has been used to prognosticate the functional outcome, to study mechanisms of recovery and to assess the efficacy of rehabilitative strategies.

Following brain infarction, at least part of the recovery process involves resolution of the reversible pathophysiologic events that follow injury to the brain i.e. edema and diaschisis (for review [232]). As one of the most important factors influencing motor recovery appears to be the integrity of the cortico-spinal motor output system. Within the first 72 hours after stroke, absent MEP has been related to poor functional recovery [11, 77,141,154]. This negative relation was still true when MEPs were measured one to two months after brain infarction of either cortical or subcortical location [23, 54,129,206,218]. In a systematic review the predictive value of the presence of MEPs obtained within the first week after infarction was consistently high with odds ratios varying between 5.49 and 13.50 for functional recovery [83]. Upon recovery, good functional outcome was associated with an increase of the initially reduced MEP amplitudes and regression of corti cospinal tract damage as assessed morphometrically by MRI during the first four weeks after stroke [11]. However, there are a few patients with excellent recovery of motor function despite an absent MEP or late MEP reappearance [22, 218], for review [83]. In these patients recovery of motor function may occur through increased recruitment of other neuronal networks such as the contralesional motor area (Fig. 5). Similarly, there are patients with severe motor deficits despite normal MEPs in whom increased cortical inhibitory activity may cause the motor deficit [40]. An example for this exaggerated inhibition is given for a patient with thalamocapsular infarction (Fig. 7). This increased perilesional inhibition may depress the hemodynamic response upon activation probably by an increase of relative inhibitory input into the activated region of cortex.

Cerebral reorganisation is likely to play an important role in the functional recovery that follows injury to the central nervous system and is modulated by post-injury experience [148]. When studying cerebral reorganisation in humans, changes in (a) the MEP amplitude, (b) the rise of MEP amplitude with increasing stimulus intensities (stimulus response curve) and (c) the number of cortical sites from where a MEP is elicited (cortical map) are used to measure changes in the excitability of the motor output zone. Patients with upper limb paresis due to brain infarction undergoing a neurorehabilitative training program showed an increase in the number of cortical sites from where an MEP of the paretic hand could be elicited [122,124,133,218,234]. Although the extent of a map is influenced by other factors such as excitability of the motor cortex and excitability at the level of the spinal cord, this may indicate that the cortical representation of the target muscle (muscle map) enlarged. The cortical site of these changes is supported by the finding of shifts in motor maps. Moreover, a shift of the muscle map [124,234] or the increased number of abnormal location of some of these cortical sites [218] indicates that reorganisation of the cortical motor output-zone may have occurred in the adjacent spared cortex, involving cortical area previously not dedicated to this muscle as previously shown for monkeys [149]. Following subcortical infarction, the majority of patients showed some degree of cortical reorganisation as indicated by a shift of motor map when compared to the non-affected side [23].

6. Mechanisms of perilesional reorganisation

The cellular and synaptic processes underlying cerebral reorganisation have been shown in animal experiments to involve the unmasking of existing, but latent, horizontal connections (for review [177]) or modulation of synaptic efficacy such as long-term potentiation (LTP) or long-term depression (LTD) [55,86]. Such modification of synaptic efficacy was recently demonstrated in the horizontal connections of rats that underwent a training of a skilled motor task [166]. The neurotransmitter systems involved in mediating these effects include the inhibitory GABAergic system [84, 86] as well as the excitatory glutamatergic system with activation of NMDA receptors [84].

Regulation of excitatory and inhibitory neurotrans mitter-systems in the cerebral cortex may play a role also in the reorganisation process that occurs after stroke [148]. In the photothrombosis model of the rat

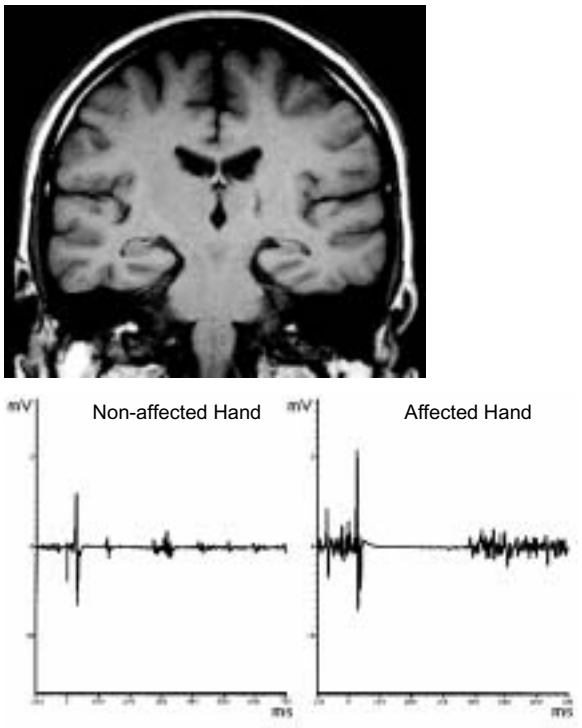

Fig. 7. Silent period in a patient with partial recovery after lacunar stroke with initial severe disabling hemiparesis. Coronary MR image showing the left thalamocapsular lesion in the 50 year old man seven month after infarction. At that time the patient suffered from a moderate spastic ataxic hemiparesis on the right with slowed individual finger movements. TMS showed normal motor evoked potentials with normal central conduction latencies on both sides. However, the silent period was prolonged on the affected right side.

small focal cortical lesions led to perilesional changes that were monitored by electrophysiological, anatomical and audioradiographic methods. Specifically, it was found that the stimulation threshold increased while simultaneously the intracortical inhibition decreased leading to distinctly altered spontaneous activity and stimulus response characteristics within the affected hemisphere [233]. In close accordance, receptor studies revealed a diversified pattern of altered GABA receptor expression which initially resembled the juvenile expression pattern [71,186]. In addition, there was an increase in glutamate receptor densities. These changes persisted over many weeks. The implication of these prolonged changes for functional restoration and the co-operation of these perilesional area with the remaining network is to be explored further.

In the intact human brain changes of the intracortical excitability of inhibitory and excitatory neuronal networks can be studied using TMS. First, the paired pulse TMS technique in which a suprathreshold test pulse is preceded by a subthreshold conditioning pulse (CS) at different interstimulus intervals [111] and different intensities [22,184] allows to study excitatory and GABAA-inhibitory system of human motor cortex [241,242]. Second, following a single suprathreshold magnetic stimulus there is a transient silence of the electromyogram in the activated target muscle [94, 169]. This EMG silence (silent period) is mainly of cortical origin and mediated by intracortical inhibitory neuronal networks. Thus, TMS is suited to characterise perilesional and remote changes in excitability in humans. This is illustrated in Fig. 7 in apatient who recovered astonishingly well from hemiplegic stroke but had a lacunar infarct lesion in the left thalamocapsular region.

A shortened silent period, indicating decreased inhibition in the intracortical neuronal network tested with this technique, occurred after infarctions within motor cortex [102,221]. This disinhibition is likely to arise from perilesional cortex and may reflect processes involved in cerebral reorganisation. However, a prolonged silent period was found also in patients with hemiparesis due to infarction of mainly subcortical structures [40,221]. Importantly, inhibition regressed in parallel with the clinical recovery [40]. Since in these patients the infarction spared the primary motor cortex and pyramidal tract as evident from CT or MRT, the increased inhibition early after stroke probably caused the initial severe motor deficit. It may be speculated that loss of afferent projections to the motor cortex may have decreased the excitatory input to the pyramidal tract and inhibitory neurones and thereby led to an overactivity of inhibitory inter-neurones. That different neuronal populations can be affected after stroke when motor cortex is spared is apparent from the observation that decreased inhibition as measured with the silent period occurred simultaneously with increased inhibition as measured with paired pulse TMS [125]. In fact, several inhibitory networks were identified using different stimulation techniques [35,180]. However, as one can only look at the net effect of intracortical inhibitory and excitatory activitiy [22,164] dynamic changes of intracortical inhibition and excitability may occur during the course of recovery [21].

7. Mechanisms underlying remote changes

Depression in the cerebral metabolism and changes in the excitatory and inhibitory neurotransmitter systems in brain areas remote from a lesion have been re-

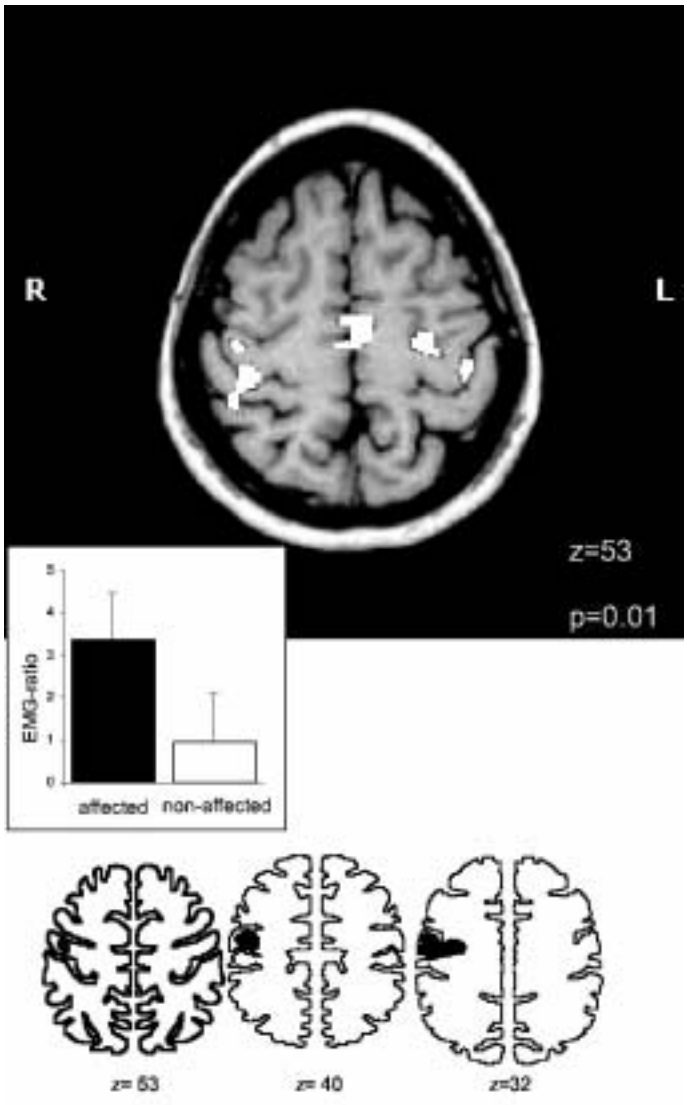

Fig. 8. A. Paired pulse excitability in a single patient with good recovery. The infarct of this patient's brain is shown in the MRI (Talaraich coordinate of the axial slice is given). The schematic head gives the position of the infarct (black dot) and site of TMS (stimulating coil is indicated by the bar). Inhibition and facilitation produced by paired pulse TMS at a constant ISI of 2ms with the conditioning pulse (CS) at different intensities of the stimulator output in this patient. CS is expressed as percentage of the patients motor threshold (MT). B. Paired pulse excitability in patients with good ($n = 13$) and poor ($n = 5$) recovery and healthy age-matched controls ($n = 13$). Inhibition and facilitation produced by paired pulse TMS at a constant ISI of 2 ms with the conditioning pulse (CS) at different intensities of the stimulator output in normal volunteers (filled dots), patients with good recovery (cross), and patients with poor recovery of hand function (triangle). Responses were recorded in the relaxed FDI muscle of the non-affected hand. The MEP amplitudes at different CS intensities were calculated as a percentage of the mean amplitude of the test pulse alone. CS intensity is expressed as percentage of stimulator output. Note the similarity of the slope on the left in patients and healthy volunteers while inhibition fades rapidly with increasing CS intensities in patients with good recovery (right) suggesting that in patients the balance of excitatory and inhibitory activity was shifted towards an increase of excitatory activity or lowered threshold for excitatory interneurons. This was not seen in patients with persistent hemiplegia. Mean and $\pm$ SE. C Schematic excitatory and inhibitory activity: In the lower part of the diagram the intracortical excitatory (black) and inhibitory (grey) interneuronal activity of normal subjects (solid line) and patients (dotted line) is plotted against the intensity of the conditioning pulse. With increasing CS intensity both intracortical inhibitory and excitatory activity increase. In either group the inhibitory interneurons are recruited at lower CS intensities when compared to the excitatory interneurons. In patients however the threshold for the excitatory interneurons is shifted towards lower intensities as indicated by the shift of the dotted line to the left (arrows). In the upper diagram the net effect of inhibitory and excitatory activity as measured by the inhibitory effect of the CS on the conditioned MEP amplitude (amount of inhibition) is plotted against the intensity of CS. Because of the earlier recruitment of excitatory interneurons in patients, the net effect of inhibitory and excitatory activity is shifted towards less inhibition (modified after [22]).

ported in animals and humans and owing to the concept of diaschisis been implicated as mechanisms relevant for functional recovery [61,148,193]. In rats, following an ischemic lesion in the primary motor cortex, long-term changes in the inhibitory and excitatory neurotransmitter systems of the homotopic cortex of the non-affected hemisphere have been described and implicated as processes relevant for functional recovery after stroke (for review [232]). More specifically, following a lesion of the primary motor cortex, down-regulation of GABAA-receptor function has been described in the non-affected contralateral motor cortex [16,17,144, 162,186]. Similarities to the mechanisms shown as relevant for reorganisation processes after experimental brain injury were identified in man using TMS.

Since intracortical inhibitory interneurones have a lower threshold for TMS when compared to the excitatory interneurons [35,184] different intensities for the conditioning pulse allow to differentiate these two processes in greater detail (Fig. 8). The similarity of the left portion of the MEPs in the stroke patients studied and healthy volunteers for low intensity of the conditioning stimulus suggests that the threshold for activation and the activity of inhibitory interneurones are similar in healthy subjects and patients. In contrast to normals however, inhibition fades rapidly with increasing CS intensities in patients suggesting that in patients, the balance of excitatory and inhibitory activity was shifted towards an increase of excitatory activity or lowered threshold for the activation of excitatory inter-neurons [22]. This was associated with good recovery while it was not seen in patients with persistent hemiplegia.

In contrast, ischemic infarction of the primary motor output system of the hand did not elicit gross changes in corticomotoneuronal excitability of the non-affected homotopic motor cortex of patients as indicated by the similarity of motor threshold, MEP magnitude, and the recruitment curves in patients and healthy volunteers [22,123,200].This was similar for patients with poor and good recovery [22]. However, there are some patients with decreased MT of about 4% [105] indicating that there may be subgroup behaving differently.

8. Training strategies in neurorehabilitation

As was described in this chapter, neurological recovery after brain ischemia can occur by different processes (Fig. 9). An important aspect is spontaneous and pharmacologically facilitated reperfusion in the acute

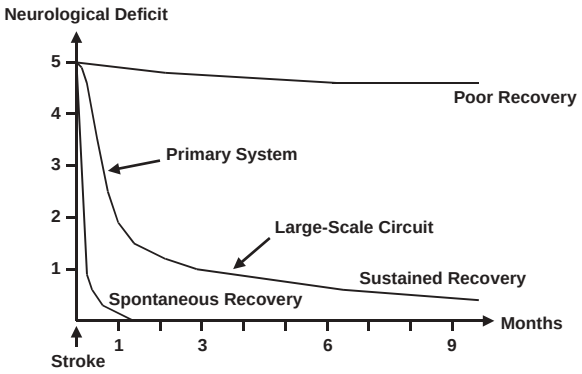

Fig. 9. Schematic graph of the recovery process after hemiparetic stroke. Fast complete motor recovery in the spontaneous group, slight further improvement after acute recovery in the sustained recovery group and lack of recovery in most severe stroke. The initial recovery is mostly due to salvage of the primary system, the second slope due to therapy-related reorganisation in neighbouring brain systems.

stage after stroke onset allowing the salvage of brain systems at risk of persistent ischemic damage. These processes can be monitored effectively by perfusion imaging (PI), diffusion weighted imaging (DWI), and magnetic resonance angiography [103,145,173,235]. The acute phase is followed by a subacute phase of approximately four weeks in which recovery of a neurological deficit is mostly due to spontaneous regression of brain edema and perilesional dysfunction, which can be monitored by fMRI and TMS [11,13,40]. With a longer temporal course of months spontaneous normalisation of abnormally enhanced neural excitability in locations remote from the infarct lesion and active reorganisation of functional representations were documented in longitudinal studies [22,24,30,62,143,200, 201,218]. This sustained reorganisation is a good candidate for therapeutic enhancement by external interventions such as rehabilitation strategies (Fig. 9).

To analyse the contribution of the motor system for recovery from hemiparesis is particularly attractive, since the cerebral circuits controlling arm and hand movements are quite well understood. Further, the lateralised organisation of the motor system allows to differentiate perilesional changes in the affected cerebral hemisphere from contralesional changes in the unaffected hemisphere. Thus, recovery from hemiparesis is a good model for understanding the probably complex cerebral processes underlying recovery of function. Last but not least, to study the recovery of manual skills is of great functional implication, since the hand is the organ with which we interact with our environment and sample tactile information.

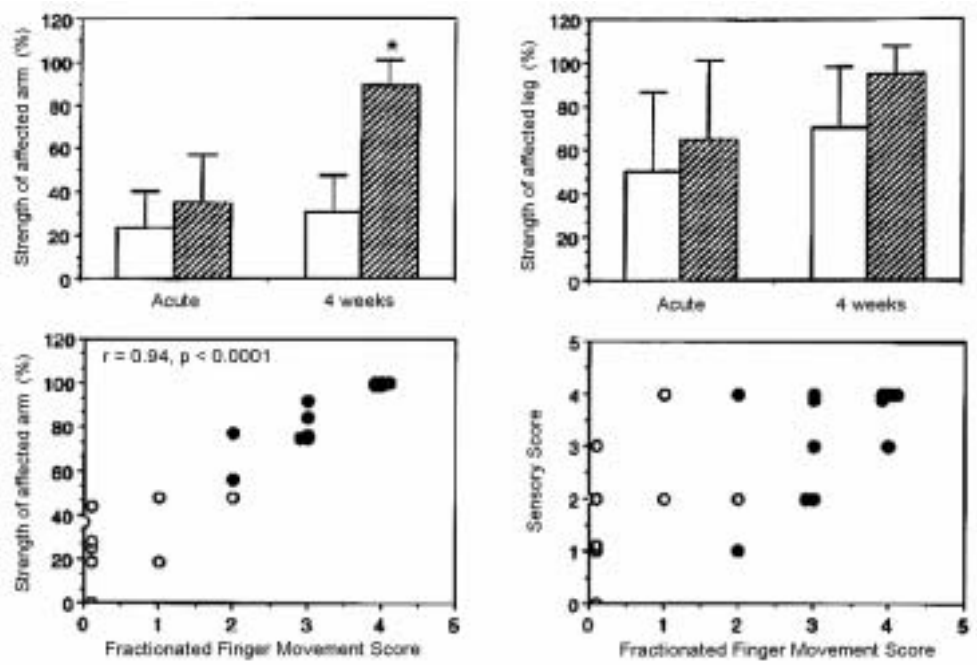

Fig. 10. Motor recovery in patients after middle cerebral artery infarction. Note the different degree of recovery of hand function in contrast to the slight, non-significant recovery of leg function in patients with poor recovery (white bar) and in patients with good recovery (shaded bar, $p < 0.05$). High correlation of maximal hand grip force and ability to perform fractionated finger movements in contrast to the lack of correlation between motor and somatosensory functions; patients with good recovery (dots) and poor recovery (circle) behaved similarly. (Further details in [6]).

In fact, the close relationship between the sensory and motor system was repeatedly demonstrated. For example, in monkeys, removal of the primary sensory cortex produces a small, temporary motor deficit [4]. Conversely, a focal lesion in the motor hand representations appears to produce a sensory deficit [150]. Apart from the cortical motor output system, feedback provided by the use of a partly compromised limb may play a major role for the reshaping of the remaining circuits, because the lack of active limb movement precludes motor related feedback [174]. Evidence from combined clinical and electrophysiological studies in stroke patients support this view, since the presence of SSEPs indicated good recovery [63]. Furthermore, illusory arm movements in healthy subjects have been reported to activate beyond motor areas also the somatosensory cortex [140]. However, although passive and active movements may activate similar structures, a training consisting of passive movements thereby providing some proprioceptive feedback had no enhancing effect on the performance [127]. In fact, recovery of the motor and somatosensory representations may be independent leaving patients with persistent somatosensory deficits in the presence of good motor recovery (Fig. 10). Moreover, in patients with a lesion of the somatosensory cortex recovery of object exploration was mediated by enlarged finger movements [10]. Since there is no overlapping somatotopy of digit representation in the somatosensory cortex [209] in contrast to the hand representation in motor cortex [178,185, 181], the exaggerated exploratory finger movements evoke a spatially enhanced input which is likely to be processed in an abnormally large portion of the sensorimotor cortex. Furthermore, after focal lesions of the primary somatosensory cortex the somatosensory representations become enlarged during skill recovery [238]. Similarly, there is evidence suggesting that patients with hemianopia can learn to perform enlarged saccadic eye movements to compensate for their visual field defect [157,243].

Studies of normal motor learning have shown that highly trained subjects perform motor task in a highly stereotypic fashion. These learnt movements build up on movement segments (for review [5]). In patients with hemiparesis due to brain infarction repetitive training of stereotyped movement segments improved the performance of the trained movement segments but also more complex motor tasks [20,87,92,

113]. Even rhythmic movement facilitation as well as robot training appeared to be beneficial for motor recovery [1,213,220]. Repetitive training of voluntary contraction of the affected muscles facilitate motor cortical activity as shown by TMS [1,75]. These data corresponded to evidence from animal experiments showing an enlargement of the motor cortical representation in monkeys that were subjected to motor training after experimental stroke in motor cortex [149]. In a detailed study of behavioral outcome and lesion location and size within the primary motor cortex of non-human primates, a correlation between size, location and mode of recovery was found. In both groups recovery was associated with an increasing percentage of highly stereotype movement pattern. However, those monkeys with larger lesions that affectedcortical representation of finger movements developed compensatory movement strategies while those monkey with smaller lesions affecting wrist movements re-acquired the pre-infarct movement strategies [69]. In correspondence to observations in sport physiology [47,49], also cognitive imaginative training can improve hand function in patients after stroke similarly to repetitive training (Fig. 11). In view of these observations it is conceivable that patients recovering from stroke select an alternative strategy to compensate for their neurological deficit. Nevertheless, subtle motor and cognitive deficits may persist after stroke due to the damaged brain systems even after excellent clinical recovery [136,156,226].

Compensatory strategies seem to evolve when immediately after the injury the pre-infarct movement patterns are not rewarded. As a consequence alternative movement patterns are favoured while the pre-existing movements cease altogether [211,212] . This concept of "learned non-use" was implemented in new approaches of rehabilitative strategies in patients with brain infarction [211,236]. This concept imposed constraints on the unaffected limb by keeping it in a cast forcing the subject to use the residual functions of the affected arm for daily purposes. This so called "constrained induced" therapy has now been shown to be successful even when applied in the chronic state to severely affected patients and induces cerebral activity changes similar to those in spontaneous recovery [29, 119,124,212,234]. This beneficial effect is likely not only due to prevention of the possible detrimental effect of learned non-use but also due to the beneficial effect of increasing the amount of movements of the affected limb (thereby enhancing the chance of repetition of movements) and establishing reafferent somatosensory information from the partly compromised limb. However this concept of learned non-use seems to contradict rehabilitative strategies employing bilateral arm movements and to apply a number of motor tasks for training; although both ways proved successful to improve recovery [32,137,202]. These approaches make use of the transmodal transfer of learning or of skill generalisation which are supposed to be prominent modes for learning [190].

As revealed by functional imaging studies, in addition to primary motor cortex, there are other areas such as premotor cortex, supplementary motor cortex and cingulate cortex in which motor representations can be found (see above). These non-primary motor areas are likely to participate in recovery of function [27, 126]. The situation is different in congenital hemispheric brain lesions involving the pre- and postcentral gyrus. In these patients motor function in the contralateral hand may be remarkable and even allows for independent finger movements probably by unmasking of ipsilateral corticospinal motor projections that are usually difficult to excite in healthy people [7,31,60, 139,175,203,240]. It should be stressed, however, that in these patients injury to the brain occurred also very early in life and processes mediating the cortical reorganisation for recovery of motor functions occurred very early in life. Considering the limited post-lesional changes seen in adult rats [108] and adult humans after focal injury to the brain (see above), it appears likely that the capacity for cerebral reorganisation of the focally damaged adult brain may be less extensive. Nevertheless, also elderly patients gain profoundly from stroke treatment [107,110].

Mechanisms operating in experience dependent cerebral reorganisation may enhance rehabilitation efforts. To study them, TMS may be combined with drugs that influence synaptic plasticity [18,19,182, 183]. Specifically, a short training period consisting of simple voluntary repetitive thumb movements in a specific direction, elicits reorganisation of the cortical representation of the thumb that encodes the kinematic details of the practiced movements as measured with TMS. This form of use-dependent plasticity was substantially reduced by dextromethorphan, an NMDA receptor blocker and lorazepam, a GABAA-receptor-positive allosteric modulator. These results identified NMDA receptor activation and GABAergic inhibition as mechanism operating in this form of plasticity [19].

Another recent approach is derived from animal experiments where the activity of GABAergic inhibition was important in controlling the extent of reorgani-

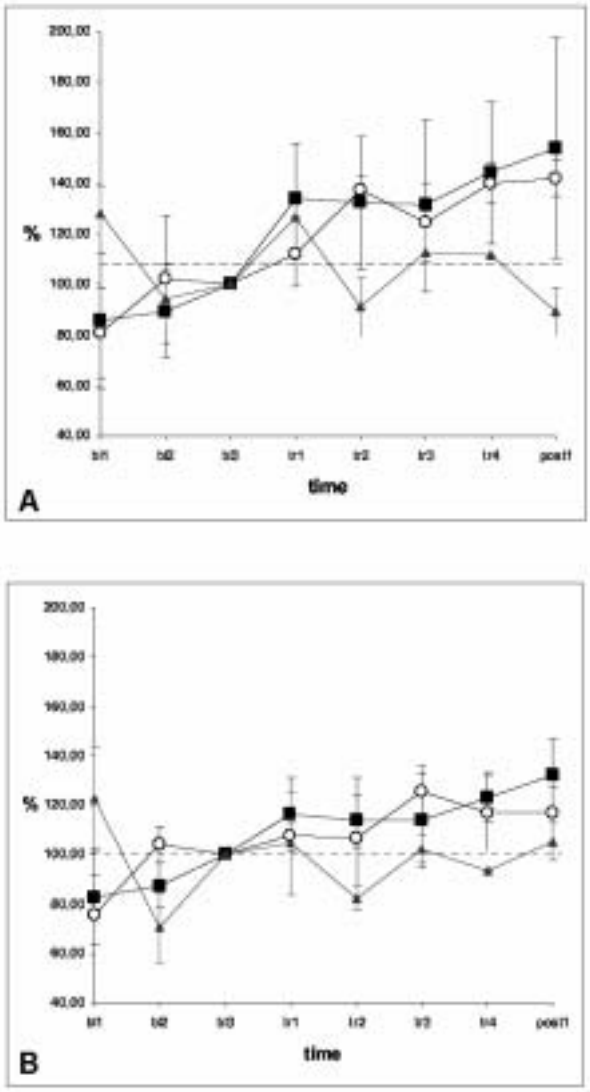

Fig. 11. Effect of different training strategies on motor recovery after stroke. The effect of imagining the performance of a finger sequence (open circle, $n = 4$) and execution of a finger sequence (black square, $n = 5$) was compared to conventional physical therapy (grey triangle, $n = 3$). Pinch grip of the affected (A) and non-affected (B) hand was measured during a baseline period of two weeks (bl1-bl3). Following baseline patients were randomly assigned to one of three different treatment arms. All patient received 30 min training per day of the assigned treatment type for four weeks. At the end of each week pinch grip was tested for both hands (tr1-tr4). One week after completion of the training pinch grip was tested (post1). Mean and SE is shown for each group.

sation. There is some evidence in baboons and humans that decreased labelling of the GABA-B receptors indicated irreversibly damaged brain tissue [74, 76,79,199,210]. However, despite these abnormalities the perilesional area cannot be visualised by imaging methods even not at high field (7 Tesla), [189]. Nevertheless, deafferentation of body parts is a means to decrease GABAergic inhibition as assessed with TMS and thereby to induce rapid plastic changes resulting in an increased cortical representation of the adjacent body parts [239]. In patients with brain infarction, deafferentation of the upper arm produced by regional anaesthesia improved hand function dramatically [138]. Increasing sensory input to the pharynx is an approach that induces changes in cortical motor representation as measured with TMS [66,73] affected the cortical activation as measured with fMRI and improved swallowing function [66].

It is still unclear when rehabilitative training should be initiated, although recovery appears as a continuous process with different dynamics (Fig. 9). Epidemiologic studies showed that early physiotherapy and patient mobilisation after stroke is beneficial [100]. It is unclear at present how these data obtained in humans can be reconciled with observations in animal experiments showing that training during the first days aggravates postischemic brain lesions [109,167]. Recently a rTMS protocol was developed, which produces a decrease of cortical excitability [34]. The effect of such stimulation continued after rTMS had ceased. Depending on the duration of the rTMS trains itself, such suppressing effect can last up to 15 minutes.

9. Conclusions

Using the combination of TMS techniques and functional neuroimaging, brain areas activated by a specific task can be identified topographically and their participation can be tested functionally. This approach has the advantage of studying brain areas in a hypothesis based, systematic manner, as opposed to studying patients with chronic individual brain lesions. Further, since the patients' baseline before the onset of the impairment is usually not known (for review [223]), longitudinal studies combining different neuroimaging methods and TMS studies will enhance our knowledge about the processes underlying functional recovery. The knowledge we have obtained from the motor system make it feasible to reveal the physiological processes underlying recovery even of cognitive functions such as attention, language, and memory.

Acknowledgements

The studies reported in this paper are supported by the Sonderforschungsbereich 194, Kompetenznetz Schlaganfall of the Bundesministerium für Bildung und Forschung, and the Brain Imaging Center West. C.M. Bütefisch is holding a Lise-Meitner Grant provided by the State North-Rhine Westphalia.

References

[1] M.L. Aisen, H.I. Krebs, N. Hogan, F. McDowell and B.T. Volpe BT. The effect of robot-assisted therapy and rehabilitative training on motor recovery following stroke, *Arch Neurol* **54** (1997), 443–446.

[2] A.V. Alexandrov, W.S. Burgin, A.M. Demchuk, A. El Mitwalli and J.C. Grotta, Speed of intracranial clot lysis with intravenous tissue plasminogen activator therapy: sonographic classification and short-term improvement, *Circulation* **103** (2001), 2897–2902.

[3] A.V. Alexandrov, A.M. Demchuk, R.A. Felberg et al., High rate of complete recanalization and dramatic clinical recovery during tPA infusion when continuously monitored with 2-MHz transcranial doppler monitoring, *Stroke* **31** (2000), 610–614.

[4] H. Asanuma and K. Arissian, Experiments on functional role of peripheral input to motor cortex during voluntary movements in the monkey, *J Neurophysiol* **52** (1984), 212–227.

[5] H. Asanuma and C. Pavlides, Neurobiological basis of motor learning in mammals, *Neuroreport* **8** (1997), 1–6.

[6] N.P. Azari, F. Binkofski, K.D. Pettigrew, H.J. Freund and R.J. Seitz, Enhanced regional cerebral metabolic interactions in thalamic circuitry predicts motor recovery in hemiparetic stroke, *Hum Brain Mapp* **4** (1996), 240–253.

[7] R. Benecke, B.U Meyer and H.J. Freund, Reorganisation of descending motor pathways in patients after hemispherectomy and severe hemispheric lesions demonstrated by magnetic brain stimulation, *Exp Brain Res* **83** (1991), 419–426.

[8] F. Binkofski, K. Amunts, K.M. Stephan et al., Broca's area subserves imagery of motion: a combined cytoarchitectonic and MRI study, *Hum Brain Mapp* **11** (2000), 273–285.

[9] F. Binkofski, G. Buccino, S. Posse, R.J. Seitz, G. Rizzolatti and H. Freund, A fronto-parietal circuit for object manipulation in man: evidence from an fMRI-study, *Eur J Neurosci* **11** (1999), 3276–3286.

[10] F. Binkofski, E. Kunesch, C. Dohle, R.J. Seitz and H.J. Freund, Tactile Apraxia: unimodal apractic disorder of tactile object exploration associated with parietal lobe lesions, *Brain* **124** (2001), 132–144.

[11] F. Binkofski, R.J. Seitz, S. Arnold, J. Classen, R. Benecke and H.J. Freund, Thalamic metbolism and corticospinal tract integrity determine motor recovery in stroke, *Ann Neurol* **39** (1996), 460–470.

[12] F. Binkofski, R.J. Seitz, T. Hackländer, D. Pawelec, J. Mau and H.J. Freund, The recovery of motor functions following hemiparetic stroke: a clinical and MR-morphometric study, *Cerebrovasc Dis* **11** (2001), 273–281.

[13] E. Bonda, M. Petrides, S. Frey and A. Evans, Neural correlates of mental transformations of the body-in-space, *Proc Natl Acad Sci USA* **92** (1995), 11180–11184.

[14] J.P. Brasil-Neto, J. Valls-Sole, A. Pascual-Leone et al., Rapid modulation of human cortical motor outputs following ischaemic nerve block, *Brain* **116** (1993), 511–525

[15] J.A. Brunberg, K.A Frey, J.A. Horton and D.E. Kuhl, Crossed cerebellar diaschisis: occurrence and resolution demonstrated with PET during carotid temporary balloon occlusion [see comments], *AJNR Am J Neuroradiol* **13** (1992), 58–61.

[16] I. Buchkremer-Ratzmann, M. August, G. Hagemann and O.W Witte, Electophysiological transcortical diaschisis after cortical photothrombosis in rat brain, *Stroke* **27** (1996), 1105–1111.

[17] I. Buchkremer-Ratzmann and O.W. Witte, Extended brain disinhibition following small photothrombotic lesions in rat frontal cortex, *Neuroreport* **8** (1997), 519–522.

[18] C.M. Bütefisch, B.C. Davis, L. Sawaki et al., Modulation of use-dependent plasticity by d-amphetamine, *Ann Neurol* **51** (2002), 59–68.

[19] C.M. Bütefisch, B.C. Davis, S.P. Wise et al., Mechanisms of use-dependent plasticity in the human motor cortex, *Proc Natl Acad Sci USA* **97** (2000), 3661–3665.
[20] C.M. Bütefisch, H. Hummelsheim, P. Denzler and K.H. Mauritz, Repetitive training of isolated movements improves the outcome of motor rehabilitation of the centrally paretic hand, *J Neurol Sci* **130** (1995), 59–68.
[21] C.M. Bütefisch, J. Netz, R.J. Seitz and V. Hömberg, Dynamik kortikaler Inhibition und Exitation im Verlauf der postischämischen Funktionserholung, *Neurologie Rehabilitation*, 2001. Ref Type: Abstract
[22] C.M. Bütefisch, J. Netz, M. Weßling, R.J. Seitz and V. Hömberg, Remote changes in excitability after stroke, *Brain* **126** (2003), 470–481.
[23] M.L. Byrnes, G.W. Thickbroom, B.A. Phillips, S.A. Wilson and F.L. Mastaglia, Physiological studies of the corticomotor projection to the hand after subcortical stroke, *Clinical Neurophysiology* **110** (1999), 487–498.
[24] C. Calautti, F. Leroy, J.Y. Guincestre and J.C. Baron, Dynamics of motor network overactivation after striatocapsular stroke: a longitudinal PET study using a fixed-performance paradigm, *Stroke* **32** (2001), 2534–2542.
[25] C. Calautti, F. Leroy, J.Y. Guincestre, R.M. Marie and J.C. Baron, Sequential activation brain mapping after subcortical stroke: changes in hemispheric balance and recovery, *Neuroreport* **12** (2001), 3883–3886.
[26] C. Calautti, C. Serrati and J.C. Baron, Effects of age on brain activation during auditory-cued thumb-to-index opposition: A positron emission tomography study, *Stroke* **32** (2001), 139–146.
[27] C. Calautti and J.C. Baron, Functional neuroimaging studies of motor recovery after stroke in adults. A review, *Stroke* **34** (2003), 1553–1566
[28] Y. Cao, L. D'Olhaberriague, E.M. Vikingstad, S.R. Levine and K.M. Welch, Pilot study of functional MRI to assess cerebral activation of motor function after poststroke hemiparesis, *Stroke* **29** (1998), 112–122.
[29] J.R. Carey, T.J. Kimberley, S.M. Lewis et al., Analysis of fMRI and finger tracking training in subjects with chronic stroke, *Brain* **125** (2002), 773–788.
[30] L.M. Carey, D.F. Abbott, G.F. Egan, G.J. O'Keefe, G.D. Jackson, J. Bernhardt and G.A. Donnan, Evolution of brain activation with good and poor motor recovery after stroke, *J Neurol*, in press, 2003.
[31] L.J. Carr, L.M. Harrison, A.L. Evans and J.A. Stephens, Patterns of central motor reorganization in hemiplegic cerebral palsy, *Brain* **116** (1993), 1223–1247.
[32] J.H. Cauraugh and S. Kim, Two coupled motor recovery protocols are better than one: electromyogram-triggered neuromuscular stimulation and bilateral movements, *Stroke* **33** (2002), 1589–1594.
[33] C.L. Chen, F.T. Tang, H.C. Chen, C.Y. Chung and M.K. Wong, Brain lesion size and location: effects on motor recovery and functional outcome in stroke patients, *Arch Phys Med Rehabil* **81** (2000), 447–452.
[34] R. Chen, J. Classe, C. Gerloff et al., Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation, *Neurology* **48** (1997), 1398–1403.
[35] R. Chen, A. Tam, C.M. Bütefisch et al., Intracortical inhibition and facilitation in different representations of the human motor cortex, *J Neurophysiol* **80** (1998), 2870–2881.
[36] N. Cholet, J. Seylaz, P. Lacombe and G. Bonvento, Local uncoupling of the cerebrovascular and metabolic responses to somatosensory stimulation after neuronal nitric oxide synthase inhibition, *J Cereb Blood Flow Metab* **17** (1997), 1191–1201.
[37] F. Chollet, V. DiPiero, R.J. Wise, D.J. Brooks, R.J. Dolan and R.S. Frackowiak, The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography, *Ann Neurol* **29** (1991), 63–71.
[38] R.E. Clark and E.R. Delay, Reduction of lesion-induced deficits in visual reversal learning following cross-modal training, *Restor Neurol Neurosci* **3** (1991), 247–255.
[39] J. Classen, J. Liepert, S.P. Wise, M. Hallett and L.G. Cohen, Rapid plasticity of human cortical movement representation induced by practice, *J Neurophysiol* **79** (1998), 1117–1123.
[40] J. Classen, A. Schnitzler, F. Binkofski et al., The motor syndorme associated with exaggerated inhibition within the primary motor cortex of patients with hemiparetic stroke, *Brain* **120** (1997), 605–619.
[41] L.G. Cohen, P. Celnik, A. Pascual-Leone et al., Functional relevance of cross-modal plasticity in blind humans, *Nature* **389** (1997), 180–183.
[42] L.G. Cohen, U. Ziemann, R. Chen et al., Studies of neuroplasticity with transcranial magnetic stimulation. [Review] [215 refs], *J Clin Neurophysiol* **15** (1998), 305–324.
[43] J.G. Colebatch and S.C. Gandevia, The distribution of muscular weakness in upper motor neuron lesions affecting the arm, *Brain* **112** (1989), 749–763.
[44] S.C. Cramer, S.P. Finklestein, J.D. Schaechter, G. Bush and B.R. Rosen, Activation of distinct motor cortex regions during ipsilateral and contralateral finger movements, *J Neurophysiol* **81** (1999), 383–387.
[45] S.C. Cramer, G. Nelles, R.R. Benson et al., A functional MRI study of subjects recovered from hemiparetic stroke, *Stroke* **28** (1997), 2518–2527.
[46] S.C. Cramer, G. Nelles, J.D. Schaechter, J.D. Kaplan, S.P. Finklestein and B.R. Rosen, A functional MRI study of three motor tasks in the evaluation of stroke recovery, *Neurorehabil Neural Repair* **15** (2001), 1–8.
[47] J. Decety and M. Jeannerod, Mentally simulated movements in virtual reality: does Fitts's law hold in motor imagery? *Behav Brain Res* **72** (1995), 127–134.
[48] J. Decety, J. Grezes, N. Costes et al., Brain activity during observation of actions. Influence of action content and subject's strategy, *Brain* **120** (1997), 1763–1777.
[49] C. Deschaumes-Molinaro, A. Dittmar and E. Vernet-Maury, Relationship between mental imagery and sporting performance, *Behav Brain Res* **45** (1991), 29–36.
[50] L. Deecke, Electrophysiological correlates of movement initiation, *Rev Neurol* **146** (1990), 612–619.
[51] C. Dettmers, G.R. Fink, R.M. Lemon et al., Relation between cerebral activity and force in the motor areas of the human brain, *J Neurophysiol* **74** (1995), 802–815.
[52] C. Dettmers, K.M. Stephan, R.N. Lemon and R.S.J. Frackowiak, Reorganization of the executive motor system after stroke, *Cerebrovasc Dis* **7** (1997), 187–200.
[53] V. DiPiero, F.M. Chollet, P. MacCarthy, G.L. Lenzi and R.S. Frackowiak, Motor recovery after acute ischaemic stroke: a metabolic study, *J Neurol Neurosurg Psychiatry* **55** (1992), 990–996.
[54] M. Dominkus, W. Grisold and V. Jelinek, Transcranial electrical motor evoked potentials as a prognostic indicator for motor recovery in stroke patients, *J Neurol Neurosurg Psychiatry* **53** (1990), 745–748.
[55] J.P. Donoghue, G. Hess and J. Sanes, Substrates and mechanisms for learning in motor cortex, in: *Acquisition and mech-*

anisms for learning in motor cortex, J. Boedel, ed., 1996, pp. 363–386.
[56] J.P. Donoghue, S. Suner and J.N. Sanes, Dynamic organization of primary motor cortex output to target muscles in adult rats. II Rapid reorganization following motor nerve lesions, *Exp Brain Res* **79** (1990), 492–503.
[57] H.F. Durwen and A.G. Herzog, Electromyographic investigation of mirror movements in normal adults. variation of frequency with side of movements, handedness, and dominance, *Brain Dysfunct* **2** (1989), 84–92.
[58] H.F. Durwen and A.G. Herzog, Electromyographic investigation of mirror movements in normal adults. Variation of frequency with site, effort and repetition of movements,*Brain Dysfunct* **2** (1992), 310–318.
[59] T. Els, J. Klisch, M. Orszagh et al., Hyperglycemia in patients with focal cerebral ischemia after intravenous thrombolysis: influence on clinical outcome and infarct size, *Cerebrovasc Dis* **13** (2002), 89–94.
[60] S.F. Farmer, L.M. Harrison, D.A. Ingram and J.A. Stephens, Plasticity of central motor pathways in children with hemiplegic cerebral palsy, *Neurology* **41** (1991), 1505–1510.
[61] D.M. Feeney and J.C. Baron, Diaschisis, *Stroke* **17** (1986), 817–830.
[62] A. Feydy, R. Carlier, A. Roby-Brami et al., Longitudinal study of motor recovery after stroke: recruitment and focusing of brain activation, *Stroke* **33** (2002), 1610–1617.
[63] H. Feys, J. Van Hees, F. Bruyninckx, R. Mercelis and W. De Weerdt, Value of somatosensory and motor evoked potentials in predicting arm recovery after a stroke, *J Neurol Neurosurg Psychiatry* **68** (2000), 323–331.
[64] C.M. Fisher, Concerning the mechanism of recovery in stroke hemiplegia, *Can J Neurol Sci* **19** (1992), 57–63.
[65] O. Foerster, Motorische Felder und Bahnen, in: *Allgemeine Neurologie*, O. Bumke and O. Foerste, eds, Berlin: Julius Springer Verlag, 1936, pp. 1–357.
[66] C. Fraser, M. Powerand, S. Hamdy et al., Driving plasticity in human adult motor cortex is associated with improved motor function after brain injury, *Neuron* **34** (2002), 831–840.
[67] H.J. Freund, Abnormalities of motor behavior after cortical lesions in humans, *Handb. Physiology*, Philadelphia: American Physiological Society, 1987, pp. 763–810.
[68] H.J. Freund and H. Hummelsheim, Lesions of premotor cortex in man, *Brain* **108** (1985), 697–733.
[69] K.M. Friel and R.J. Nudo, Recovery of motor function after focal cortical injury in primates: compensatory movement patterns used during rehabilitative training, *Somatosens Mot Res* **15** (1998), 173–189.
[70] K. Fukui, I. Iguchi, A. Kito, Y. Watanabe and K. Sugita, Extent of pontine pyramidal tract Wallerian degeneration and outcome after supratentorial hemorrhagic stroke, *Stroke* **25** (1994), 1207–1210.
[71] G. Hagemann, C. Redecker, T. Neumann-Haefelin, H.J. Freund and O.W. Witte, Increased long-term potentiation in the surround of experimentally induced focal cortical infarction, *Ann Neurol* **44** (1998), 255–258.
[72] A.M. HakimM, R.P. Pokrupa, J. Villanueva et al., The effect of spontaneous reperfusion on metabolic function in early human cerebral infarcts, *Ann Neurol* **21** (1987), 279–289.
[73] S. Hamdy, J.C. Rothwell, Q. Aziz, K.D. Singh and D.G. Thompson, Long-term reorganization of human motor cortex driven by short-term sensory stimulation, *Nature Neuroscience* **1** (1998), 64–68.
[74] J. Hatazawa, T. Satoh, E. Shimosegawa et al., Evaluation of cerebral infarction with iodine 123-iomazenil SPECT, *J Nucl Med* **36** (1995), 2154–2161.
[75] B. Hauptmann and H. Hummelsheim, Facilitation of motor evoked potentials in hand extensor muscles of stroke patients: correlation to the level of voluntary contraction, *Electroencephalogr Clin Neurophysiol* **101** (1996), 387–394.
[76] K. Hayashida, Y. Hirose, Y. Tanaka et al., Reduction of 123I-iomazenil uptake in haemodynamically and metabolically impaired brain areas in patients with cerebrovascular disease, *Nucl Med Commun* **17** (1996), 701–705.
[77] A. Heald, D. Bates, N.E. Cartlidge, J.M. French and S. Miller, Longitudinal study of central motor conduction time following stroke. 2. Central motor conduction measured within 72 h after stroke as a predictor of functional outcome at 12 months, *Brain* **116** (1993), 1371–1385.
[78] K.M. Heilman, E. Valenstein and R.T. Watson, The neglect syndrome, *Clinical Neuropsychology*, Amsterdam: Elsevier, 1985, 153–183.
[79] W.D. Heiss, M. Grond, A. Thiel et al., Permanent cortical damage detected by flumazenil positron emission tomography in acute stroke, *Stroke* **29** (1998), 454–461.
[80] W.D. Heiss, M. Grond, A. Thiel, H.M. von Stockhause and J. Rudolf, Ischaemic brain tissue salvaged from infarction with alteplase [letter], *Lancet* **349** (1997), 1599–1600.
[81] W.D. Heiss, M. Grond, A. Thiel et al., Tissue at risk of infarction rescued by early reperfusion: a positron emission tomography study in systemic recombinant tissue plasminogen activator thrombolysis of acute stroke, *J Cereb Blood Flow Metab* **18** (1998), 1298–1307.
[82] W.D. Heiss, M. Huber, G.R. Fink et al., Progressive derangement of periinfarct viable tissue in ischemic stroke, *J Cereb Blood Flow Metab* **12** (1992), 193–203.
[83] H. Hendricks, M. Zwarts, E. Plat and J. van Limbeek, Systematic review for the early prediction of motor and functional outcome after stroke by using motor-evoked potentials, *Arch Phys Med Rehabil* **83** (2002), 1303–1308.
[84] G. Hess, C. Aizenman and J.P. Donoghue, Conditions for the induction of long-term potentiation in layer II/III horizontal connections of the rat motor cortex, *J Neurophysiol* **75** (1996), 1765–1778.
[85] G. Hess and J.P. Donoghue, Long-term potentiation of horizontal connections provides a mechanism to reorganize cortical motor maps, *J Neurophysiology* **71** (1994), 2543–2547.
[86] G. Hess and J.P. Donoghue, Long-term depression of horizontal connections in rat motor cortex, *Eur J Neurosc* **8** (1996), 658–665.
[87] S. Hesse, C. Bertelt, M.T. Jahnke et al., Treadmill training with partial body weight support compared with physiotherapy in nonambulatory hemiparetic patients, *Stroke* **16** (1995), 976–981.
[88] C.C. Hilgetag, H. Theoret and A. Pascual-Leone, Enhanced visual spatial attention ipsilateral to rTMS-induced "virtual lesions" of human parietal cortex, *Nature Neuroscience* **4** (2001), 953–957.
[89] M. Honda, T. Nagamine, H. Fukuyama, Y. Yonekura, J. Kimura and H. Shibasaki, Movement-related cortical potentials and regional cerebral blood flow change in patients with stroke after motor recovery, *J Neurol Sci* **146** (1997), 117–126.
[90] K.A. Hossmann, Viability thresholds and the penumbra of focal ischemia, *Ann Neurol* **36** (1994), 557–565.
[91] K.A. Hossmann, M. Fischer, K. Bockhorst and M. Hoehn-Berlage, NMR imaging of the apparent diffusion coefficient

(ADC) for the evaluation of metabolic suppression and recovery after prolonged cerebral ischemia, *J Cereb Blood Flow Metab* **14** (1994), 723–731.
[92] H. Hummelsheim, B. Hauptmannand S. Neumann, Influence of physiotherapeutic facilitation techniques on motor evoked potentials in centrally paretic hand extensor muscles, *Electroencephalogr Clin Neurophysiol* **97** (1995), 18–28.
[93] T.V. Ilic, F. Meintzschel, U. Cleff, D. Ruge, K.R. Kessler and U. Ziemann, Short-interval paired-pulse inhibition and facilitation of human motor cortex: the dimension of stimulus intensity, *J Physiol* **545** (2002), 153–167.
[94] M. Inghilleri, A. Beradelli, G. Cruccu and M. Manfredi, Silent period evoked by transcranial stimulation of the human cortex and cervicomedullary junction, *J Physiol* (*Lond*) **466** (1993), 521–534.
[95] M. Jahanshahi, I.H. Jenkins, R.G. Brown, C.D. Marsden, R.E. Passingham and D.J. Brooks, Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects, *Brain* **118** (1995), 913–933.
[96] M. Jahanshahi and J. Rothwell, Transcranial magnetic stimulation studies of cognition: an emerging field, *Exp Brain Res* **131** (2000), 1–9.
[97] I.H. Jenkins, D.J. Brooks, P.D. Nixon, R.S. Frackowiak and R.E. Passingham, Motor sequence learning: a study with positron emission tomography, *J Neurosci* **14** (1994), 3775–3790.
[98] H. Johansen-Berg, M.F. Rushworth, M.D. Bogdanovic, U. Kischka, S. Wimalaratna and P.M. Matthews, The role of ipsilateral premotor cortex in hand movement after stroke, *Proc Natl Acad Sci USA* **99** (2002), 14518–14523.
[99] R.D. Jones, I.M. Donaldson and P.J. Parkin, Impairment and recovery of ipsilateral sensory-motor function following unilateral cerebral infarction, *Brain* **112** (1989), 113–132.
[100] H.S. Jorgensen, LP. Kammersgaard, J. Houth et al., Who benefits from treatment and rehabilitation in a stroke Unit? A community-based study, *Stroke* **31** (2000), 434–439.
[101] H. Karbe, J. Kessler, K. Herholz, G.R. Fink and W.D. Heiss, Long-term prognosis of poststroke aphasia studied with positron emission tomography, *Arch Neurol* **52** (1995), 186–190.
[102] K.R. Kessler, A. Schnitzler, J. Classen and R. Benecke, Reduced inhibition within primary motor cortex in patients with poststroke focal motor seizures, *Neurology* **59** (2002), 1028–1033
[103] C.S. Kidwell, J.L. Saver, J. Mattiello et al., Thrombolytic reversal of acute human cerebral ischemic injury shown by diffusion/perfusion magnetic resonance imaging, *Ann Neurol* **47** (2000), 462–469.
[104] C.S. Kidwell, J.L. Saver, S. Starkman et al., Late secondary ischemic injury in patients receiving intraarterial thrombolysis, *Ann Neurol* **52** (2002), 698–703.
[105] V. Kimiskidis, G. Dimopoulos, S. Papgiannopoulos, D. Kazis, A. Kazis and K. Mills, Corticomotor threshold in stroke: the unaffected hemisphere, *Clin Neurophysiol* **113** (2002), S46 (23-02).
[106] D.S Knopman, A.B. Rubens, O.A. Selnes, A.C Klassen and M.W. Meyer, Mechanisms of recovery from aphasia: evidence from serial xenon 133 cerebral blood flow studies, *Ann Neurol* **15** (1984), 530–535.
[107] P.L. Kolominsky-Rabas, C. Sarti, P.U. Heuschmann, C. Graf, S. Siemonsen, B. Neundoerfe, A. Katalinic, E. Lang, K.G. Gassmann and T.R. von Stockert, A prospective community-based study of stroke in Germany–the Erlangen Stroke Project (ESPro): incidence and case fatality at 1, 3, and 12 months, *Stroke* **29** (1998), 2501–2506
[108] M. Kossut, P.J. Hand, J. Greenberg and C.L. Hand, Single vibrissal cortical column in SI cortex of rat and its alterations in neonatal and adult vibrissa-deafferented animals: a quantitative 2DG study, *J Neurophysiol* **60** (1988), 829–852.
[109] D.A. Kozlowski, D.C. James and T. Schallert, Use-dependent exaggeration of neuronal injury after unilateral sensorimotor cortex lesions, *J Neurosci* **16** (1996), 4776–4786.
[110] C. Kugler, T. Altenhoner, P. Lochner and A. Ferbert, Hessian Stroke Data Bank Study Group ASH. Does age influence early recovery from ischemic stroke? A study from the Hessian Stroke Data Bank, *J Neurol* **250** (2003), 676–681.
[111] T. Kujirai, M.D. Carami, J.C. Rothwell et al., Corticocortical inhibition in human motor cortex, *J Physiol* (*Lond*) **471** (1993), 501–519.
[112] G. Kwakkel, R.C. Wagenaar, B.J. Kollen and G.J. Lankhorst, Predicting disability in stroke – a critical review of the literature, *Age Ageing* **25** (1996), 479–489.
[113] G. Kwakkel, R.C. Wagenaar, J.W. Twisk G.J. Lankhorst and J.C. Koetsier, Intensity of leg and arm training after primary middle-cerebral-artery stroke: a randomised trial, *Lancet* **354** (1999), 191–196.
[114] G. Kwakkel, B.J. Kollen, J. van der Grond and A.J. Prevo, Probability of regaining dexterity in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke, *Stroke* **34** (2003), 2181–2186
[115] M.F. Lafleur, P.L. Jackson, F. Malouin, C.L. Richards, A.C. Evans and J. Doyon, Motor Learning Produces Parallel Dynamic Functional Changes during the Execution and Imagination of Sequential Foot Movements, *Neuroimage* **16** (2002), 142–157.
[116] L.J. Lee, C.S. Kidwell, J. Alger, S. Starkman and J.L. Saver, Impact on stroke subtype diagnosis of early diffusion-weighted magnetic resonance imaging and magnetic resonance angiography, *Stroke* **31** (2000), 1081–1089.
[117] R.N. Lemon, R.S. Johansson and G. Westling, Modulation of corticospinal influence over hand muscles during gripping tasks in man and monkey, *Can J Physiol Pharmacol* **74** (1996), 547–558.
[118] G.L. Lenzi, R.S. Frackowiak and T. Jones, Cerebral oxygen metabolism and blood flow in human cerebral ischemic infarction, *J Cereb Blood Flow Metab* **2** (1982), 321–335.
[119] C.E. Levy, D.S. Nichols, P.M. Schmalbrock, P. Keller and D.W. Chakeres, Functional MRI evidence of cortical reorganization in upper-limb stroke hemiplegia treated with constraint-induced movement therapy, *Am J Phys Med Rehabil* **80** (2001), 4–12.
[120] J.D. Lewine, R.S. Astur, L.E. Davis, J.E. Knight, E.L. Maclin and W.W. Orrison Jr., Cortical organization in adulthood is modified by neonatal infarct: a case study, *Radiology* **190** (1994), 93–96.
[121] F. Li, K.F. Liu, M.D. Silva et al., Transient and permanent resolution of ischemic lesions on diffusion- weighted imaging after brief periods of focal ischemia in rats: correlation with histopathology, *Stroke* **31** (2000), 946–954.
[122] J. Liepert, H. Bauder, W.H.R. Miltner, E. Taub and C. Weiller, Treatment-induced cortical reorganization after stroke in humans, *Stroke* **31** (2000), 1210–1216.
[123] J. Liepert, F. Hamzei and C. Weiller, Motor cortex disinhibition of the unaffected hemisphere after acute stroke, *Muscle Nerve* **23** (2000), 1761–1763.

[124] J. Liepert, W.H. Miltner, H. Bauder et al., Motor cortex plasticity during constraint-induced movement therapy in stroke patients, *Neurosci Lett* **250** (1998), 5–8.
[125] J. Liepert, P. Storch, A. Fritsch and C. Weiller, Motor cortex disinhibition in acute stroke, *Clin Neurophysiol* **111** (2000), 671–676.
[126] Y. Liu and E.M. Rouiller, Mechanisms of recovery of dexterity following unilateral lesion of the sensorimotor cortex in adult monkey, *Exp Brain Res* **128** (1999), 149–159.
[127] M. Lotze, C. Braun, N. Birbaumer and L.G. Cohen, Motor learning elicited by voluntary drive, *Brain* **126** (2003), 866–72.
[128] K.O. Lovblad, A.E. Baird, G. Schlaug et al., Ischemic lesion volumes in acute stroke by diffusion-weighted magnetic resonance imaging correlate with clinical outcome, *Ann Neurol* **42** (1997), 164–170.
[129] R.A. Macdonell, G.A. Donnan and P.F. Bladin, A comparison of somatosensory evoked and motor evoked potentials in stroke, *Ann Neurol* **25** (1989), 68–73.
[130] C.D. MacKinnon, S. Kapur, D. Hussey, M.C. Verrier, S. Houle and W.G. Tatton, Contributions of the mesial frontal cortex to the premovement potentials associated with intermittent hand movements in humans, *Hum Brain Mapp* **4** (1996), 1–22.
[131] R.S. Marshall, G.M. Perera, R.M. Lazar, J.W. Krakauer, R.C. Constantine and R.L. DeLaPaz, Evolution of cortical activation during recovery from corticospinal tract infarction, *Stroke* **31** (2000), 656–661.
[132] M.M. Merzenich and K. Sameshima, Cortical plasticity and memory, *Curr Opinion Neurobiol* **3** (2000), 187–196.
[133] W.H. Miltner, H. Bauder, M. Sommer, C. Dettmers and E. Taub, Effects of constraint-induced movement therapy on patients with chronic motor deficits after stroke: a replication, *Stroke* **30** (1999), 586–592.
[134] I. Miyai, T. Suzuki, J. Kang, K. Kubota and B.T. Volpe, Middle cerebral artery stroke that includes the premotor cortex reduces mobility outcome, *Stroke* **30** (1999), 1380–1383.
[135] J.P. Mohr, M.A. Foulkes, A.T. Polis et al., Infarct topography and hemiparesis profiles with cerebral convexity infarction: the Stroke Data Bank, *J Neurol Neurosurg Psychiatry* **56** (1993), 344–351.
[136] S. Mori, S. Sadoshima, S. Ibayashi, K. Lino and M. Fujishima, Relation of cerebral blood flow to motor and cognitive functions in chronic stroke patients, *Stroke* **25** (1994), 309–317.
[137] M.H. Mudie and T.A. Matyas, Can simultaneous bilateral movement involve the undamaged hemisphere in reconstruction of neural networks damaged by stroke? *Disabil Rehabil* **22** (2000), 23–37.
[138] W. Muellbacher, C. Richards, U. Ziemann et al., Improving hand function in chronic stroke, *Arch Neurol* **59** (2002), 1278–1282.
[139] F. Muller, E. Kunesch, F. Binkofski and H.J. Freund, Residual sensorimotor functions in a patient after right-sided hemispherectomy, *Neuropsychologia* **29** (1991), 125–145.
[140] E. Naito, H.H. Ehrsson, S. Geyer, K. Zilles and P.E. Roland, Illusory arm movements activate cortical motor areas: a positron emission tomography study, *J Neurosci.* **19** (1999), 6134–6144.
[141] R. Nardone and F. Tezzon, Inhibitory and excitatory circuits of cerebral cortex after ischaemic stroke: prognostic value of the transcranial magnetic stimulation,*Electromyogr Clin Neurophysiol* **42** (2002), 131–136.
[142] G. Nelles, W. Jentzen, M. Jueptner, S. Muller and H.C. Diener, Arm training induced brain plasticity in stroke studied with serial positron emission tomography, *Neuroimage* **13** (2001), 1146–1154.
[143] G. Nelles, G. Spiekramann, M. Jueptner et al., Evolution of functional reorganization in hemiplegic stroke: a serial positron emission tomographic activation study, *Ann Neurol* **46** (1999), 901–909.
[144] T. Neumann-HaefelinT and O.W. Witte, Periinfarct and remote excitability changes after transient middle cerebral artery occlusion, *J Cereb Blood Flow Metab* **20** (2000), 45–52.
[145] T. Neumann-Haefelin, H.J. Wittsack, F. Wenserski et al., Diffusion- and perfusion-weighted MRI. The DWI/PWI mismatch region in acute stroke, *Stroke* **30** (1999), 1591–1597.
[146] H.J. Neville and D. Bavelier, Neural organization and plasticity of language, *Curr Opin Neurobiol* **8** (1998), 254–258.
[147] J. Newton, A. Sunderland, S.E. Butterworth, A.M. Peters, K.K. Peck and P.A. Gowland, A pilot study of event-related functional magnetic resonance imaging of monitored wrist movements in patients with partial recovery, *Stroke* **33** (2002), 2881–2887.
[148] J.R. Nudo, Recovery after damage to motor cortical areas, *Cur Opinion Neurobiol* **9** (1999), 740–747.
[149] J.R. Nudo, B.M. Wise, F.S. SiFuentes and G.W. Milliken, Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct, *Science* **272** (1996), 1791–1794.
[150] R.J. Nudo, K.M. Friel and S.W. Delia, Role of sensory deficits in motor impairments after injury to primary motor cortex, *Neuropharmacology* **39** (2000), 733–742.
[151] L.M. Parsons, P.T. Fox, J.H. Downs et al., Use of implicit motor imagery for visual shape discrimination as revealed by PET, *Nature* **375** (1995), 54–58.
[152] M.W. Parsons, P.A. Barber, P.M. Desmond et al., Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study, *Ann Neurol* **52** (2002), 20–28.
[153] P.M. Pedersen, H.S. Jorgensen, H. Nakayama, H.O. Raaschou and T.S. Olsen, Impaired orientation in acute stroke: frequency, determinants, and time- course of recovery. The Copenhagen Stroke Study, *Cerebrovasc Dis* **8** (1998), 90–96.
[154] G. Pennisi, G. Rapisarda, R. Bella, V. Calabrese, A. Maertens De Noordhout and P.J. Delwaide, Absence of response to early transcranial magnetic stimulation in ischemic stroke patients: prognostic value for hand motor recovery, *Stroke* **30** (1999), 2666–2700.
[155] R. Pineiro, S. Pendlebury, B.H. Johansen and P.M. Matthews, Functional MRI detects posterior shifts in primary sensorimotor cortex activation after stroke: evidence of local adaptive reorganization? *Stroke* **32** (2001), 1134–1139.
[156] T. Platz, P. Denzler, B. Kaden and K.H. Mauritz, Motor learning after recovery from hemiparesis, *Neuropsychologia* **32** (1994), 1209–1223.
[157] K. Pommerenke and H.J. Markowitsc, Rehabilitation training of homonymous visual field defects in patients with postgeniculate damage of the visual system, *Restor Neurol Neurosci* **1** (1989), 47–63.
[158] T.P. Pons, P.E. Garraght and M. Mishkin, Lesion-induced plasticity in the second somatosensory cortex of adult macaques, *Proc Natl Acad Sci USA* **85** (1988), 5279–5281.

[159] W.J. Powers, P.T. Fox and M.E. Raichle, The effect of carotid artery disease on the cerebrovascular response to physiologic stimulation, *Neurology* **38** (1988), 1475–1478.
[160] C.J. Price and K.J. Friston, Scanning patients with tasks they can perform, *Hum Brain Mapp* (1999), 102–108.
[161] C.J. Price, E.A. Warburton, C.J. Moore, R.S. Frackowiak and K.J. Friston, Dynamic diaschisis: anatomically remote and context-sensitive human brain lesions, *J Cogn Neurosci* **13** (2001), 419–429.
[162] M. Qü, T. Mittmann, H.J. Luhmann, A. Schleicher and K. Zilles, Long-term changes of ionotropic glutamate and GABA receptors after unilateral permanent focal cerebral ischemia in the mouse brain, *Neuroscience* **85** (1998), 29–43.
[163] H. Reddy, N. De Stefano, M. Mortilla, A. Federico and P.M. Matthews, Functional reorganization of motor cortex increases with greater axonal injury from CADASIL, *Stroke* **33** (2002), 502–508.
[164] M.C. Ridding, R. Inzelberg and J.C. Rothwell, Changes in excitability of motor cortical circuitry in patients with Parkinson's disease, *Ann Neurol* **37** (1995), 181–188.
[165] E.B. Ringelstein, R. Biniek, C. Weiller, B. Ammeling, P.N. Nolte and A. Thron, Type and extent of hemispheric brain infarctions and clinical outcome in early and delayed middle cerebral artery recanalization, *Neurology* **42** (1992), 289–298.
[166] M.S. Rioult-Pedotti, D. Friedman, G. Hess and J.P. Donoghue, Stengthening of horizontal cortical connections following skill learning, *Nature Neuroscience* **1** (1998), 230–234.
[167] A. Risedal, J. Zeng and B.B. Johansson, Early training may exacerbate brain damage after focal brain ischemia in the rat, *J Cereb Blood Flow Metab* **19** (1999), 997–1003.
[168] A. Ritzl, S. Meisel, H.J. Wittsack, M. Siebler, U. Moedde and R.J. Seitz, Development of Brain Infarct volume as assessed by magnetic resonance imaging: T2- and FLAIR-follow-up of DWI lesions, *JMRI* **20** (2004), 201–207.
[169] H. Roick, H.J. von Giesen and R. Benecke, On the origin of the postexcitatory inhibition seen after transcranial magnetic brain stimulation in awake human subjects, *Exp Brain Res* **94** (1993), 489–498.
[170] G. Rordorf, W.J. Koroshetz, W.A. Copen et al., Regional ischemia and ischemic injury in patients with acute middle cerebral artery stroke as defined by early diffusion-weighted and perfusion-weighted MRI, *Stroke* **29** (1998), 939–943.
[171] S. Rossi, S.F. Cappa, C. Babiloni et al., Prefrontal cortex in long-term memory: an "interference" approach using magnetic stimulation, *Nature Neuroscience* **9** (2001), 948–952.
[172] P.M. Rossini, F. Tecchio, V. Pizzella et al., On the reorganization of sensory hand areas after mono-hemispheric lesion: a functional (MEG)/anatomical (MRI) integrative study, *Brain Res* **782** (1998), 153–166.
[173] J. Rother, P.D. Schellinger, A. Gass et al., Effect of intravenous thrombolysis on MRI parameters and functional outcome in acute stroke $<$6 hours, *Stroke* **33** (2002), 2438–2445.
[174] J.C. Rothwell, M.M. Traub, B.L. Day, J.A. Obeso, P.K. Thomas and C.D. Marsden, Manual motor performance in a deafferented man, *Brain* **105** (1982), 515–542.
[175] U. Sabatini, D. Toni, P. Pantano et al., Motor recovery after early brain damage, A case of brain plasticity, *Stroke* **25** (1994), 514–517.
[176] N. Sadato, A. Pascual-Leone, J. Grafman, M.P. Deiber, V. Ibanez and M. Hallett, Neural networks for Braille reading by the blind, *Brain* **121** (1998), 1213–1229.
[177] J.N. Sanes and J.P. Donoghue, Plasticity and primary motor cortex, *Annu Rev Neurosci* **23** (2000), 393–415.
[178] J.N. Sanes, J.P. Donoghue, V. Thangaraj, R.R. Edelman and S. Warach, Shared neural substrates controlling hand movements in human motor cortex, *Science* **268** (1995), 1775–1777.
[179] J.N. Sanes, S. Suner, J.F. Lando and J.P. Donoghue, Rapid reorganisation of adult rat motor cortex somatic representation patterns after motor nerve injury, *Proc Natl Acad Sci USA* **85** (1988), 2003–2007.
[180] T.D. Sanger, R.R. Garg and R. Chen, Interactions between two different inhibitory systems in the human motor cortex, *J Physiol* (*Lond*) **530** (2001), 307–317.
[181] K.C. Sato and J.Tanji, Digit-muscle responses evoked from multiple intracortical foci in monkey precentral motor cortex, *J Neurophysiol* **62** (1989), 959–970.
[182] L. Sawaki, B. Boroojerdi, A. Burstein et al., Cholinergic influences on use-dependent plasticity, *J Neurophysiol* **87** (2002), 166–171.
[183] L. Sawaki, G. Cohen, J. Classen, B.C. Davis and C.M. Bütefisch, Enhancement of use-dependent plasticity by d-amphetamine, *Neurology* **59** (2002), 1262–1264.
[184] M. Schäfer, J.C. Biesecke, A. Schulze-Bonhage and A. Ferbert, Transcranial magnetic double stimulation: influence of the intensity of the conditioning stimulus, *Electroencephalogr Clin Neurophysiol* **105** (1997), 462–469.
[185] M.H. Schieber and L.S. Hibbard, How somatotopic is the motor cortex hand area? *Science* **261** (1993), 489–492.
[186] K. Schiene, C. Bruehl, K. Zilles et al., Neuronal hyperexcitability and reduction of GABAA-receptor expression in the surround of cerebral photothrombosis, *J Cereb Blood Flow Metab* **16** (1996), 906–914.
[187] G. Schlaug, U. Knorr and R. Seitz, Inter-subject variability of cerebral activations in acquiring a motor skill: a study with positron emission tomography, *Exp Brain Res* **98** (1994), 523–534.
[188] T. Schormann and M. Kraemer, Voxel-guided morphometry ("FGM") and application to stroke, *IEEE Trans Med Imaging* **22** (2003), 62–74.
[189] M. Schroeter, C. Franke, G. Stoll and M. Hoehn, Dynamic changes of magnetic resonance imaging abnormalities in relation to inflammation and glial responses after photothrombotic cerebral infarction in the rat brain, *Acta Neuropathol* (*Berl*) **101** (2001), 114–122.
[190] R.J. Seitz and T. Matyas, Acquisition and guidance of actions: theory and neuroimaging results, in: *Frontiers of human memory*, A. Yamadori, R. Kawashima, T. Fuji and K. Suzuki, eds, Sendai: Tohuku University Press, 2002, pp. 37–47.
[191] R.J. Seitz and N.P. Azari, Cerebral reorganization in man after acquired lesions, *Adv Neurol* **81** (1999), 37–47.
[192] R.J. Seitz, U. Knorr, N.P. Azari, H. Herzog and H.J. Freund, Recruitment of a visuomotor network in stroke recovery, *Restor Neurol Neurosci* **14** (1999), 25–33.
[193] R.J. Seitz, N.P. Azari, U. Knorr, F. Binkofski, H. Herzog and H.J. Freund, The role of diaschisis in stroke recovery, *Stroke* **30** (1999), 1844–1850.
[194] R.J. Seitz, A.G. Canavan, L. Yaguez et al., Representations of graphomotor trajectories in the human parietal cortex: evidence for controlled processing and automatic performance, *Eur J Neurosci* **9** (1997), 378–389.
[195] R.J. Seitz, P. Hoflich, F. Binkofski, L. Tellmann, H. Herzog and H.J. Freund, Role of the premotor cortex in recovery from middle cerebral artery infarction, *Arch Neurol* **55** (1998), 1081–1088.

[196] R.J. Seitz, Y. Huang, U. Knorr, L. Tellmann, H. Herzog and H.J. Freund, Large-scale plasticity of the human motor cortex, *Neuroreport* **6** (1995), 742–744.
[197] R.J. Seitz and P.E. Roland, Learning of sequential finger movements in man: a combined kinematic and positron emission tomography study, *Eur J Neurosci* **4** (1992), 154–165.
[198] R.J. Seitz, G. Schlaug, A. Kleinschmidt et al., Remote depressions of cerebral metabolism in hemiparetic stroke: topography and relation to motor and somatosensory functions, *Hum Brain Mapp* **1** (1994), 81–100.
[199] G. Sette, J.C. Baron, A.R. Young et al., In vivo mapping of brain benzodiazepine receptor changes by positron emission tomography after focal ischemia in the anesthetized baboon, *Stroke* **24** (1993), 2046–2057.
[200] T. Shimizu, A. Hosaki, T. Hino et al., Motor cortical disinhibition in the unaffected hemisphere after unilateral cortical stroke, *Brain* **125** (2002), 1896–1907.
[201] S.L. Small, P. Hlustik, D.C. Noll, C. Genovese and A. Solodkin, Cerebellar hemispheric activation ipsilateral to the paretic hand correlates with functional recovery after stroke, *Brain* **125** (2002), 1544–1557.
[202] W.R. Staines, W.E. McIlroy, S.J. Graham and S.E. Black, Bilateral movement enhances ipsilesional cortical activity in acute stroke: a pilot functional MRI study, *Neurology* **56** (2001), 401–404.
[203] M. Staudt, W. Grodd, C. Gerloff, M. Erb, J. Stitz and I. Krageloh-Mann, Two types of ipsilateral reorganization in congenital hemiparesis: a TMS and fMRI study, *Brain* **125** (2002), 2222–2237.
[204] K. Stefan, E. Kunesch, R. Benecke, L.G. Cohen and J. Classen, Mechanisms of enhancement of human motor cortex excitability induced by interventional paired associative stimulation, *J Physiol* (*Lond*) **543** (2002), 699–708.
[205] K.M. Stephan, G.R. Fink, R.E. Passingham et al., Functional anatomy of the mental representation of upper extremity movements in healthy subjects, *J Neurophysiol* **73** (1995), 373–386.
[206] K.M. Stephan, J. Netz and V. Homberg, Prognostic value of MEP and SSEP in patients with chronic UMN lesions after stroke, *Cerebrovasc Dis* **5** (1995), 407–412.
[207] K.M. Stephan, W.H. Thaut, G. Wunderlich et al., Conscious and subconscious sensorimotor synchronization–prefrontal cortex and the influence of awareness, *Neuroimage* **15** (2002), 345–352.
[208] A. Sunderland, D. Tinson and L. Bradley, Differences in recovery from constructional apraxia after right and left hemisphere stroke? *J Clin Exp Neuropsychol* **16** (1994), 916–920.
[209] W.W. Sutherling, M.F. Levesque and C. Baumgartner, Cortical sensory representation of the human hand: size of finger regions and nonoverlapping digit somatotopy, *Neurology* **42** (1992), 1020–1028.
[210] W. Takahashi, Y. Ohnuki,T. Ohta, H. Hamano, M. Yamamoto and Y. Shinohara, Mechanism of reduction of cortical blood flow in striatocapsular infarction: studies using [123I]iomazenil SPECT, *Neuroimage* **6** (1997), 75–80.
[211] E. Taub, J.E. Crago, L.D. Burgio et al., An operant approach to rehabilitation medicine: overcoming learned nonuse by shaping, *J Exp Anal Behav* **61** (1994), 281–293.
[212] E. Taub, G. Uswatte and R. Pidikiti, Constraint-Induced Movement Therapy: a new family of techniques with broad application to physical rehabilitation–a clinical review, *J Rehabil Res Dev* **36** (1999), 237–251.
[213] M.H. Thaut, G.C. McIntosh and R.R. Rice, Rhythmic facilitation of gait training in hemiparetic stroke rehabilitation, *J Neurol Sci* **151** (1997), 207–212.
[214] A.W. Toga and J.C. Mazziotta, *Brain mapping*, The systems, San Diego: Academic Press, 2000.
[215] D.C. Tong, M.A. Yenari, G.W. Albers, M. O'Brien, M.P. Marks and M.E. Moseley, Correlation of perfusion- and diffusion-weighted MRI with NIHSS score in acute ($<$ 6.5 hour) ischemic stroke, *Neurology* **50** (1998), 864–870.
[216] D. Toni, M. Fiorelli, S. Bastianello et al., Acute ischemic strokes improving during the first 48 hours of onset: predictability, outcome, and possible mechanisms. A comparison with early deteriorating strokes, *Stroke* **28** (1997), 10–14.
[217] D. Toni, M. Fiorelli, E.M. Zanette et al., Early spontaneous improvement and deterioration of ischemic stroke patients. A serial study with transcranial Doppler ultrasonography, *Stroke* **29** (1998), 1144–1148.
[218] R. Traversa, P. Cicinelli, A. Bassi, P.M. Rossini and G. Bernardi, Mapping of motor cortical reorganization after stroke. A brain stimulation study with focal magnetic pulses, *Stroke* **28** (1997), 110–117.
[219] R. Verleger, S. Adam, M. Rose, C. Vollme, B. Wauschkuhn and D. Kompf, Control of hand movements after striatocapsular stroke: high-resolution temporal analysis of the function of ipsilateral activation, *Clin Neurophysiol* **114** (2003), 1468–1476.
[220] B.T. Volpe, H.I. Krebs, N. Hogan, L. Edelsteinn, C.M. Diels and M.L. Aisen, Robot training enhanced motor outcome in patients with stroke maintained over 3 years, *Neurology* **53** (1999), 1874–1876.
[221] H.J. von Giesen, H. Roick and R. Benecke, Inhibitory actions of motor cortex following unilateral brain lesions as studied by magnetic brain stimulation, *Exp Brain Res* **99** (1994), 84–96.
[222] C. von Monakow, *Lokalisation im Gehirn und funktionelle Störungen induziert durch kortikale Läsionen*, Wiesbaden, Germany: Bergmann, J.F., 1914.
[223] V. Walsh and A. Cowey, Transcranial magnetic stimulation and cognitive neuroscience, [Review] [95 refs], *Nature Reviews Neuroscience* **1** (2000), 73–79.
[224] T. Warabi, K. Inoue, H. Noda and S. Murakami, Recovery of voluntary movement in hemiplegic patients. Correlation with degenerative shrinkage of the cerebral peduncles in CT images, *Brain* **113** (1990), 177–189.
[225] B. Weder, U. Knorr, H. Herzog et al., Tactile exploration of shape after subcortical ischaemic infarction studied with PET, *Brain* **117** (1994), 593–605.
[226] B. Weder and R.J. Seitz, Deficient cerebral activation pattern in stroke recovery, *Neuroreport* **5** (1994), 457–460.
[227] C. Weiller, F. Chollet, K.J. Friston, R.J. Wise and R.S. Frackowiak, Functional reorganization of the brain in recovery from striatocapsular infarction in man, *Ann Neurol* **31** (1992), 463–472.
[228] C. Weiller, C. Isensee, M. Rijntjes et al., Recovery from Wernicke's aphasia: a positron emission tomographic study, *Ann Neurol* **37** (1995), 723–732.
[229] C. Weiller, S.C. Ramsay, R.J. Wise, K.J. Friston and R.S. Frackowiak, Individual patterns of functional reorganization in the human cerebral cortex after capsular infarction, *Ann Neurol* **33** (1993), 181–189.
[230] C. Weiller, E.B. Ringelstein, W. Reiche, A. Thron and U. Buell, The large striatocapsular infarct. A clinical and pathophysiological entity, *Arch Neurol* **47** (1990), 1085–1091.

[231] D.J. Werring, C.A. Clark, G.J. Barker et al., The structural and functional mechanisms of motor recovery: complementary use of diffusion tensor and functional magnetic resonance imaging in a traumatic injury of the internal capsule, *J Neurol Neurosurg Psychiatry* **65** (1998), 863–869.

[232] O.W. Witte, Lesion-induced plasticity as a potential mechanism for recovery and rehabilitative training, *Cur Opinion Neurol* **11** (1998), 655–662.

[233] O.W. Witte, H.J. Bidmon, K. Schiene, C. Redecker and G. Hagemann, Functional differentiation of multiple perilesional zones after focal cerebral ischemia, *J Cereb Blood Flow Metab* **20** (2000), 1149–1165.

[234] G.F. Wittenberg, R. Chen, Ishii, Kenji, K.O. Bushara, E. Taub, L.H. Gerber, M. Hallett and L.G. Cohen, Constraint-induced therapy in stroke: Magnetic-stimulation motor maps and cerebral activation, *Neurorehabilitation and Neural Repair* **16** (2003), 1–10.

[235] H.J. Wittsack, A. Ritzl, G.R. Fink et al., MR imaging in acute stroke: diffusion-weighted and perfusion imaging parameters for predicting infarct size, *Radiology* **222** (2002), 397–403.

[236] S.L. Wolf, D.E. LeCraw, L.A. Barton and B.B. Jann, Forced use of hemiplegic upper extremities to reverse the effect of learned nonuse among chronic stroke and head-injured patients, *Exp Neurol* **104** (1989), 125–132.

[237] G. Wunderlich, U. Knorr, H. Herzog, J.C. Kiwit, H.J. Freund and R.J. Seitz, Precentral glioma location determines the displacement of cortical hand representation, *Neurosurgery* **42** (1998), 18–26.

[238] C. Xerri, M.M. Merzenich, B.E. Peterson and W. Jenkins, Plasticity of primary somatosensory cortex paralleling sensorimotor skill recovery from stroke in adult monkeys, *J Neurophysiol* **79** (1998), 2119–2148.

[239] U. Ziemann, M. Hallett and L. Cohen, Mechanisms of deafferentation-induced plasticity in human motor cortex, *J Neurosci* **18** (1998), 7000–7007.

[240] U. Ziemann, K. Ishii, A. Borgheresi et al., Dissociation of the pathways mediating ipsilateral and contralateral motor-evoked potentials in human hand and arm muscles, *J Physiol* **518** (1999), 895–906.

[241] U. Ziemann, S. Lonnecker, B.J. Steinhoff and W. Paulus, Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study, *Ann Neurol* **40** (1996), 367–378.

[242] U. Ziemann, S. Lonnecker, B.J. Steinhoff and W. Paulus, The effect of lorazepam on the motor cortical excitability in man, *Exp Brain Res* **109** (1996), 127–135.

[243] J. Zihl and D. von Cramon, Visual field recovery from scotoma in patients with postgeniculate damage. A review of 55 cases, *Brain* **108** (1985), 335–365.