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REVIEW

Neurorehabilitation of stroke

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Abstract Despite ongoing improvements in the acute treatment of cerebrovascular diseases and organization of stroke services, many stroke survivors are in need of neurorehabilitation, as more than two-thirds show persisting neurologic deficits. While early elements of neurorehabilitation are already taking place on the stroke unit, after the acute treatment, the patient with relevant neurologic deficits usually takes part in an organized inpatient multidisciplinary rehabilitation program and eventually continues with therapies in an ambulatory setting afterwards. A specialized multidisciplinary neurorehabilitation team with structured organization and processes provides a multimodal, intense treatment program for stroke patients which is adapted in detail to the individual goals of rehabilitation. There are many parallels between postlesional neuroplasticity (relearning) and learning in the development of individuals as well as task learning of healthy persons. One key principle of neurorehabilitation is the repetitive creation of specific learning situations to promote mechanisms of neural plasticity in stroke recovery. There is evidence of achieving a better outcome of neurorehabilitation with early initiation of treatment, high intensity, with specific goals and active therapies, and the coordinated work and multimodality of a specialized team. In this context, interdisciplinary goal-setting and regular assessments of the patient are important. Furthermore, several further potential enhancers of neural plasticity, e.g., peripheral and brain stimulation techniques, pharmacological augmentation, and use of robotics, are under evaluation.

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Introduction

Stroke is the most common cause of long-term disability in adults. Although progress in the acute treatment of stroke (e.g., thrombolysis, the concept of stroke units, dysphagia management) has occurred over recent years, neurorehabilitation (mainly as organized inpatient multidisciplinary rehabilitation) remains one of the cornerstones of stroke treatment. The overall benefit of stroke units results not only from thrombolysis—only a small proportion (about 10–15%) of all stroke patients are treated with this regimen—but also more generally from the multidisciplinary stroke unit management, including treatment optimization, minimization of complications, and elements of early neurorehabilitation [1]. After the acute treatment, stroke patients with relevant neurological deficits should in general be treated by a specialized neurorehabilitation clinic or unit. The best timing for transferring a patient after initial treatment (e.g., on a stroke unit) to a specialized neurorehabilitation ward or clinic is dependent on many individual factors, but early initiation of neurorehabilitation is mandatory for outcome optimization.

A key point in successfully diminishing negative long-term effects after stroke and achieving recovery is the work of a specialized multidisciplinary team with structured organization and processes which provides a multimodal, intense treatment program for the stroke patient which is adapted in detail to the individual goals of rehabilitation. Neurorehabilitation nowadays is considered as a multidisciplinary and multimodal concept to help neurological patients to improve physiological functioning, activity, and

participation by creating learning situations, inducing several means of recovery. In this setting, early initiation of treatment, the application of high intensity with specific goals and active therapies, and the coordinated work and multimodality of a specialized team play a major role [2]. Shared goal-setting and assessment is important. Implications of the International Classification of Functioning, Disability, and Health (ICF, WHO 2001) are now widely accepted as a useful tool in goal-setting, making its way into clinical practice. It adds a social perspective with emphasis on participation.

In the following review, principles of neural plasticity and their promotion by means of neurorehabilitation are described, as well as specific techniques, e.g., brain stimulation techniques and pharmacological augmentation (although not all of them are yet part of routine clinical practice).

Neural plasticity in stroke recovery

While for many decades of the last century it was believed that, "once development is complete, the sources of growth and regeneration of axons and dendrites are irretrievably lost. In the adult brain the nerve paths are fixed and immutable: everything can die, nothing can be regenerated" [3], a paradigm shift has taken place. There have been several reports on observations that therapeutic exercises influence the course of spontaneous recovery of a brain affection [4]. It has been a long way, however, to what is widely accepted now, first by measurement of the effects of rehabilitation: the central nervous system of adult human beings has an astounding potential for recovery and adaptability, which can be selectively promoted [5]. The extent of recovery in stroke is dependent on many factors, the initial size and location of the cerebral lesion and the degree of success of recanalization therapies being predominant factors. With a varying individual relevance, the recovery curve flattens in the course of time from the initial incidence.

Such recovery of the central nervous system over the course of time after onset of stroke is possible due to mechanisms described as neural plasticity or neuroplasticity, which can be observed and investigated by different approaches, e.g., from a clinical to a neurobiological and neuropathological point of view. Hebb [6] first described neuroplasticity with regard to the function of synapses, and later this principle was also linked to the functioning of neurons in the wider context of neuronal networks. The term "neural plasticity" might refer to transiently achieved functional changes in the context of learning and recovery, as well as structural changes (overviewed by [7]) describing the basis for neural plasticity as plastic changes in the nervous system which are supposed to occur in four main ways, including functional changes in synaptic efficacy, modifying protein synthesis and proteinase activity in nerve cells, creation of new anatomical connections or by altering synapses morphologically, and by specific apoptosis. The role of neurogenesis in human adult stroke recovery still remains somewhat unclear.

In this context several overlapping and interacting mechanisms of neural plasticity can be identified [8–13]:

– *Plasticity of areas of cortical representation* was described in animal models in connection with the variable size of cortical representation *loco typico* of motor fields [11] and was also demonstrated in humans. By using transcranial magnetic stimulation (TMS) mapping in stroke patients, the area of cortical representation of the abductor minimi muscle (ADM) transiently increased even after a single training session [14]. These findings suggest a very modifiable functional cortical representation. Using functional positron emission tomography (PET) and functional magnetic resonance tomography imaging (fMRI) different patterns of activation during recovery have been described [12], which partly overlap with the following mechanism:
– *Vicariation* ("vice" = instead of) describes the hypothesis that cortical functions of damaged areas can be taken over by different regions of the brain. In clinical practice this ability may vary widely and may be insufficient for a large group of patients with remaining difficulties after brain damage. With functional imaging, however, it could be demonstrated that vicariation takes place in cortical representation areas. In an illustrative longitudinal study [15], a small group of stroke patients with comparable circumscribed M1 lesions (similar to experimental lesions in animal models) affecting the motor control of the contralateral hand were assessed over several months. In the first follow-up, ipsi- and contralateral activation patterns were noted. After several months, activation was again ipsilesional and closer to the former representation and more dorsal for the function of finger extension as compared with controls, reflecting functional reorganization in the motor cortex adjacent to the lesion.

To summarize fMRI and PET studies after focal ischemic brain lesions resulting in motor deficits with damage to corticospinal tract, it is suggested that interruption of projections from the primary motor cortex (M1) leads to increased recruitment of secondary motor areas such as the dorsolateral premotor cortex and supplementary motor areas [13]. For this

- For the phase of early *compensation* in longitudinal fMRI studies an initial upregulation in primary and secondary motor regions (ipsi- and/or contralateral)

but also activity of other nonprimary structures of the sensorimotor network [13] could be observed, followed by

- More precise activation patterns with more focused and efficient brain activity in a later phase reflecting *recovery* and accordingly reorganization [16], and which are—in case of success—reminiscent of normal activation patterns. A precondition to accomplish this more successful course is the preservation of a sufficient amount of specialized cortical and subcortical brain tissue and especially the pyramid tract.

Persistent activation of many different areas may also indicate less successful or failed reorganization in chronic stroke patients: the greater the involvement of the ipsilesional motor network, the better the recovery. In this respect, interactions between lesional and contralesional hemisphere may also play an important role [17–19]. However, many problems of imaging of stroke recovery remain unsolved.

Basic underlying mechanisms of these findings include both different functional use of existing networks and synapses, but also *structural changes*. In the early course of ischemic stroke, pathophysiological mechanisms in the perilesional region are initiated, which include enhanced expression of plasticity-related proteins, neurotrophic factors (e.g., brain-derived neurotrophic factor, synapsin I), and certain neurotransmitters, but also expression of inhibitory factors occurs in the central nervous system [20, 21]. These modifications probably lead to morphological changes, e.g., synaptic plasticity and sprouting, especially in the first weeks after stroke [22]:

- *Synaptic plasticity* refers to the altered synaptic function when cells are communicating, leading to plastic changes, stated as "cells that fire together, wire together" by Hebb [6]. Changes in synaptic activity can be measured by alterations in the number of, e.g., *N*-methyl-D-aspartate (NMDA) receptors and are morphologically seen as "spines" between two neurons.
- *Sprouting of axons and dendrites* occurs in cortical regions ipsi- and contralateral to the stroke lesion, as demonstrated in animal model [23, 24]. Further results from research in human recovery can be expected by the use of MR diffusion-tensor tractography imaging (DTI), which has been regarded as a useful method in showing the relationship between structural corticospinal tract damage and motor task-related cortical activity in chronic hemiparetic stroke patients [25] as well as in quantification of connectivity [26]. However, no longitudinal studies of larger sample size in the course of recovery are published. Sprouting of dendrites is more common than sprouting of axons or neurogenesis. Collateral sprouting can lead to a change of function in neurons in a damaged network by receiving new synaptic input from dendrites of nonlesioned sprouting neurons.
- *Diaschisis* is a term used by Von Monakow [27] to describe the phenomenon that a focal lesion may also lead to changes in brain functioning of areas located far away. An example demonstrated by several recent neuroimaging studies is enhanced contralesional cerebellar activity after cortical infarction.
- Furthermore, *enriched environment* as a driver of neuroplasticity has been demonstrated in animal models [13]: rats with ischemic lesions due to middle cerebral artery occlusion showed much better recovery when held in an enriched environment with free access to physical activity and social interactions [28].

Recent *connectivity studies* reviewed by [29] address functional network interactions and changes in neural networks after stroke, increasingly offering implications for better understanding of neural plasticity and findings of functional imaging during recovery as well as intervention effects on connectivity. Especially primary M1, dorsal and ventral premotor cortex, supplementary motor area, parietal cortex, secondary somatosensory cortex, and prefrontal cortex were considered in *connectivity models*. A major finding is enhanced interhemispheric coupling between homotopical areas as a common feature of reorganized resting-state networks after stroke, which is, however, often paralleled by a reduced network efficiency in these patients [29].

Inducing and promoting neural plasticity

There are many parallels between postlesional neuroplasticity (relearning) and human learning as part of personal development, education, or training leading to changes of behavior and abilities or knowledge, e.g., by repetitive interactions with the social environment. In clinical neurorehabilitation, the main effect of the multidisciplinary teamwork and applied therapies is to create repetitive specified learning conditions and a stimulating learning atmosphere in a defined way and considering interdisciplinary treatment goals that match the patient's individual needs and deficits. This is achieved by therapeutic sessions (see below) and methods as well as in everyday life on the neurorehabilitation ward in interactions with physicians, nursing team, therapists, and others, in which the patient is guided to the highest meaningful degree of mental and physical activity. A valuable didactical principle to force the individual to learn is the use of constraint-induced therapies (CIT), which, however, cannot be used in the treatment of the majority of stroke patients (see below). In addition, other stimulation techniques and enhancement by use of medications are under evaluation, as overviewed in the following section.

Supporting neural plasticity by peripheral and noninvasive electromagnetic brain stimulation techniques

Although not yet recommended for clinical routine, several trials have been undertaken and are currently ongoing to evaluate noninvasive cortical stimulation techniques with the purpose of enhancing neuroplasticity and recovery, using clinical outcome measures or fMRI. The main techniques are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (TDCS), which can be used for both cortical enhancement and inhibition, depending on the setup parameters. Furthermore, epidural electrical stimulation (EES) is an invasive approach using a grid of electrodes implanted neurosurgically. Therefore, its practical use in stroke patients is limited.

Beside therapeutically modifying cortical activity in certain cortex regions (e.g., motor or language-related areas), which might be altered by damage or indirectly due to mechanisms of neuroplasticity (see above), another important theory behind influencing cortical activity is the hypothesis of contralesional hemisphere overexcitability [17–19]. To simplify, due to interhemispheric imbalance after damage caused by overfunction of the nonlesioned hemisphere, further negative functional effects with considerations for recovery can occur. The main approaches to brain stimulation are to increase the excitability of the cortex in the ipsilesional hemisphere and/or suppression of the contralesional hemisphere. This can be achieved noninvasively in conscious humans using rTMS and TDCS.

In rTMS, an electric current is induced in the underlying cortex by a magnetic field, which then activates the axons of cortical neurons. Low-frequency rTMS around 1 Hz results in decreased cortical excitability (which persists after the application of rTMS) and is therefore used on the contralesional hemisphere for downregulation. Higher frequencies of more than 5 Hz increase cortical excitability and can be applied to stimulate the cortex on the ipsilesional hemisphere. Special patterns of rTMS (theta bursts) have also been established and are reported to have longer-lasting modulatory capacity [30–33].

In TDCS, two electrodes (one active and one reference) are placed on the skin, delivering weak polarizing electrical current leading to different effects in the cortex, depending on the polarity: anodal TDCS has an excitatory effect, cathodal TDCS induces inhibition via presumed hyperpolarization. Usually 10–20 min of TDCS at 1–2 mA is regarded as safe and painless.

With the application of these newer treatment methods in stroke patients, recent findings suggest a 10% functional improvement in single sessions, and about 20% (up to 30%) in multiple sessions has been reported. Long-term effects are widely unknown. As far as is known now, cortical stimulation appears to be a safe and promising intervention for stroke patients; however, more trials are needed to assess the long-term benefit and to optimize protocols [34, 35]. In a consensus paper [36], standards for practical application in research and clinical practice for diagnostic and therapeutic TMS are suggested. Main potential (although rare overall) side-effects include seizure induction, possible syncope, transient headache or local pain, transient hearing changes, transient cognitive or neuropsychological changes, burns from scalp electrodes, and others. Also, a standard screening questionnaire for rTMS candidates is provided, and ethical and regulatory issues are discussed as well as protocols, with a supplementation [37] according to a theta-bursts protocol. However, many questions remain to be solved, including patient selection, optimal stimulation parameters, and localization, as well as the combination with other types of interventions.

Furthermore, peripheral sensorimotor techniques to improve voluntary movement control as well as functional motor ability by indirectly influencing cortical activity have been evaluated [38]. In a recent Cochrane review it is, however, concluded that there is still insufficient robust data to suggest clinical use of electrostimulation for neuromuscular retraining [39] (Fig. 1).

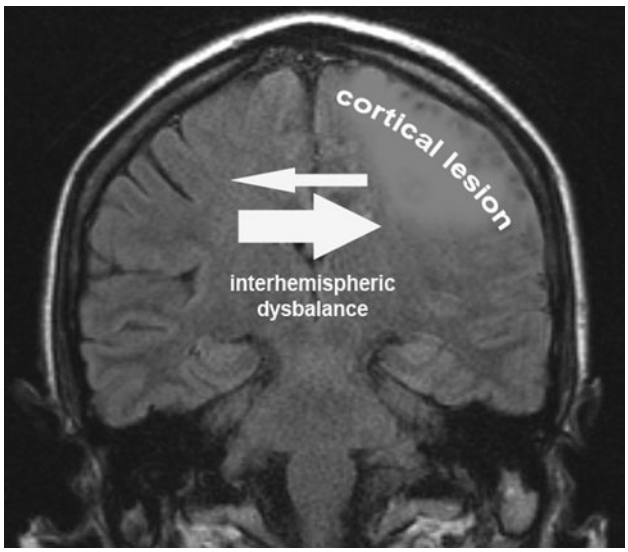

Fig. 1 Stroke-related hemispheric imbalance (see text) is a target of brain stimulation techniques. Repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (TDCS) as the main noninvasive brain stimulation techniques in stroke recovery research can be used for cortical enhancement as well as inhibition, depending on the setup parameters used:

Unaffected hemisphere	Affected hemisphere
Decrease excitability	*Increase excitability*
- cathodal TDCS	- anodal TDCS
- inhibitory low-frequency rTMS (including theta burst protocols)	- excitatory rTMS > 5Hz

Supporting neural plasticity by pharmacological interventions

Pharmacological interventions can address several brain neurotransmitter systems that have been identified to be related to motor learning, e.g., glutamate, acetylcholine, 5-hydroxy-tryptophane, noradrenaline, and dopamine. Drugs have been studied in animal models, healthy volunteers, and stroke patients in single or multiple dosages, with and without additional therapeutic tasks. No single medication evaluated for its beneficial effect of modulating plasticity in the human M1 in stroke patients has reached class I evidence so far. Several studies using this approach have been conducted for motor learning as well as aphasia therapy, but the results of some studies are contradictory. Especially levodopa, D-amphetamine, methylphenidate, donepezil, reboxetine, and fluoxetine are found to be beneficial in trials evaluating motor and/or aphasia recovery after stroke, but in one study D-amphetamine was found to have no effect [40–45]. In a recent study including 118 patients in a multicenter setting, fluoxetine was found to be beneficial (initiated 5–10 days after onset of stroke) in addition to standard inpatient rehabilitation in terms of promoting motor recovery and independence, demonstrated by significantly better scores using Fugl–Meyer and Rankin scales than in the placebo group [46]. The noradrenergic enhancement of reboxetine was found to be beneficial in reduction of cortical hyperactivity, especially in the ipsilesional ventral premotor cortex and supplementary motor area, as well in improvements of pathological hypoconnectivity of ipsilesional supplementary motor area with the primary M1 [45], leading to functional improvements. For further description of models of functional network interactions and changes in neural networks after stroke, refer to [29].

However, still larger controlled trials are needed, and findings need to be replicated and patient selection criteria reapproved before pharmacological augmentation can be generally recommended; some trials are ongoing.

Meanwhile patients presenting reduced ability to take part in therapies due to diminished alertness and drive should be carefully evaluated for poststroke depression first. If treatment with stimulating antidepressants is not successful or not possible, use of levodopa or a central stimulating agent may be an alternative treatment option, considering regulative issues of "off-label" use. In a single-center observational study with various drugs, pharmacological augmentation was regarded as relatively safe [48].

Negative effects on outcome were noted for benzodiazepines, haloperidol, prazosine, and clonidine [47], leading to the advice to rather avoid these drugs during rehabilitation.

Structured multidisciplinary neurorehabilitation

Importance of multidisciplinary teamwork for stroke recovery

According to a large meta-analysis ($n = 1{,}437$), the benefit of postacute treatment in organized inpatient multidisciplinary rehabilitation (as compared with treatment on a general ward and other nonspecific rehabilitation clinics) is associated with reduced odds for death, institutionalization, and dependency. According to differences in place of stay with respect to independence after poststroke rehabilitation, of 100 patients treated by organized multidisciplinary neurorehabilitation (as compared with general medical treatment), an extra 5 returned home in an independent state [49].

The amount of rehabilitation treatment in the acute phase may vary widely, as a multicenter study examining physical activity within the first 14 days of acute stroke unit care has shown: in the daytime, patients spent more than 50% of the time resting in bed, 28% sitting out of bed, and only 13% engaged in activities with the potential to prevent complications and improve recovery of mobility. Furthermore patients were alone for 60% of the time [50]. The best timing for transferring a patient after initial treatment to a specialized neurorehabilitation ward or clinic is still under discussion, and concerns regarding optimal timing and intensity might also contribute to the problem.

After acute stroke treatment, medically stable patients with relevant neurological deficits should be treated in a specialized neurorehabilitation clinic or stroke unit in an in- or outpatient setting to take advantage of the impact of the work of a specialized multidisciplinary team with structured organization and processes: the patient takes part in a multimodal, intensive treatment program which must be adapted to the individual goals of rehabilitation with regular interdisciplinary reevaluation.

A short and useful definition for organized inpatient multidisciplinary rehabilitation includes [49]: (a) interdisciplinary goal-setting; (b) input from a multidisciplinary team of medical, nursing, and therapy staff with expertise in stroke and rehabilitation whose work is coordinated through regular weekly meetings; (c) involvement of patients and family in the rehabilitation process; and (d) a program of staff training (Fig. 2).

This approach should be centered on the individual patient and family/caregivers, interacting closely with a multidisciplinary team consisting mainly of physicians, nursing experts, physical and occupational therapists, kinesiotherapists, speech and language pathologists (SLP), psychologists, recreational therapists, and social workers [2]. The required equipment in a neurorehabilitation department must be defined in detail to ensure structural

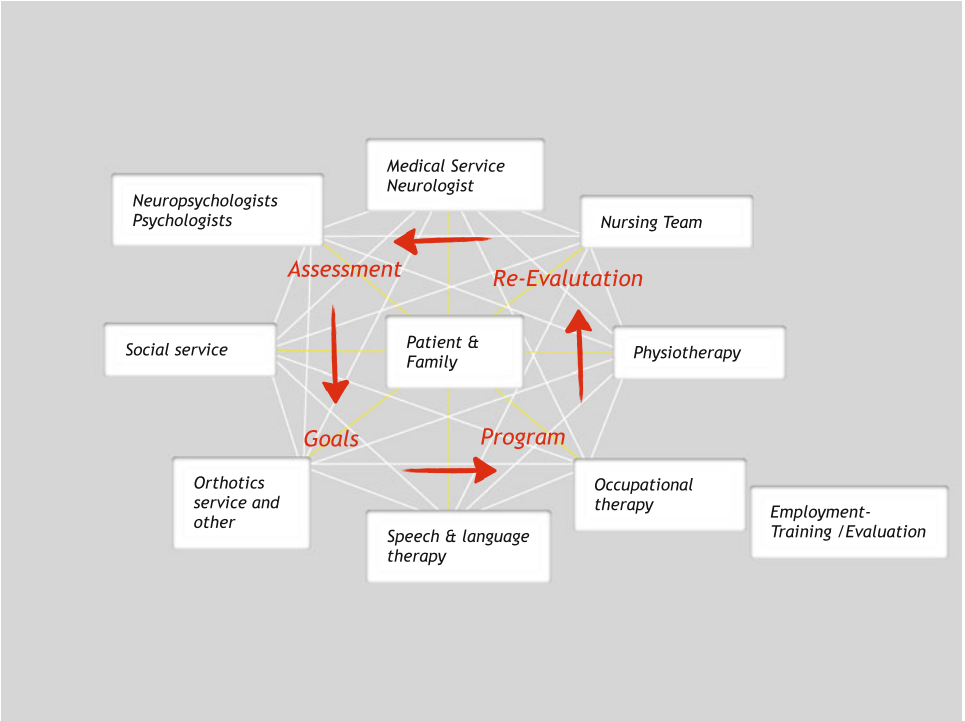

Fig. 2 The patient-centered model of multidisciplinary specialized neurorehabilitation includes assessment, individual goal-setting, multimodal therapies, and reevaluation. The work of the multidisciplinary team of medical, nursing, and therapy staff with expertise in stroke rehabilitation is coordinated through regular weekly meetings with involvement of patients and family in the rehabilitation process

quality. A description of medical and organizational processes using a quality management system and "learning from mistakes," e.g., using a critical incidence reporting system (CIRS), is also important for rehabilitation centers.

At the onset of the rehabilitation process, a multidisciplinary assessment of deficits and resources is mandatory, including clinical neurological examination, assessment of functional performance, activities of daily living (ADL), social and personal background, and coping strategies. To achieve recovery of physical and psychological functions and to reintegrate the patient into his/her social environment, therapies and other interventions must be adopted to the individual abilities and stroke-related deficits. In the course of rehabilitation, the patient's progress and abilities are critically discussed and reevaluated in the multidisciplinary team in at least weekly sessions, with adaptation and reconsideration of treatment strategies and goals (see below) if necessary [51].

Early mobilization, initiation, and intensity of therapies

In addition to thrombolysis, the multidisciplinary management in a stroke unit or by a stroke team has been shown to improve outcome significantly by reducing death rates and dependency [number needed to treat (NNT) 7 for thrombolysis versus NNT 9 for stroke unit treatment] [1]. The positive effect of stroke units is achieved by structural organization and interdisciplinary management, but also by early use of elements of neurorehabilitation. In a recent study, early mobilization within 24 h after onset of stroke of the medically stable patient led to better and faster walking ability, and the group with later mobilization could not catch up during study monitoring [52].

Clinical studies indicate that early start and high intensity of therapies are decisive for favorable long-term outcome. On the basis of pathophysiological data, the first 3 weeks after stroke are considered as a particularly promising period: in animal models, active training leads to better functional recovery and sprouting, whereas inactivity results in additional loss of ability [10, 22, 24]. However, some experimental studies in rats show that very early (starting within 24 h) and intense forced activity could lead to an enlargement of lesion areas. The occurrence of these negative consequences is explained by cytotoxic effects of glutamate, metabolic collapse of the penumbra region, inhibition of upregulation of signal proteins, focal hyperthermia, and other factors [53–55]. The transfer of some results of animal studies to human stroke recovery seems questionable, as some animals were forced to action during their whole wake-time. Other recent animal studies, however, support early initiation of appropriate activation. Early motor activation after focal ischemia starting at day 5 had a superior outcome (functional measures and more dendritic sprouting) as compared with a later beginning (at days 14 and 30) [22] with similar results replicated in other studies [56].

Clinical data are consistent with these findings. In humans, however, other factors should be taken into account: immobilization increases the rate of complications after acute stroke, including thrombosis, infections,

deconditioning, and ulcers. Early mobilization in the first days and structured training at an early stage on a stroke unit enhances the rate of discharges to the home with a lower degree of disabilities, as compared with later activation on a medical ward [57]. Better long-term outcome is reported in stroke patients with early start of an organized inpatient multidisciplinary rehabilitation within 7 days in a multicenter study ($n = 1{,}760$) with reduction of disability and better quality-of-life measures [58]. In another large study ($n = 969$) specifically examining the impact of timing of initiation of neurorehabilitation and functional recovery, a highly significant correlation of early treatment start and functional outcome was detected [59]. Not only early initiation of treatment but also the intensity of rehabilitative therapies is of significant importance, as shown in a meta-analysis [60] with higher mobility, autonomy, and improved executive functions when different therapeutic modalities are performed with increased intensity. Therapy intensity was also related to shorter lengths of stay and to improvements in patients' functional independence. A higher intensity of therapies can also be achieved by additional use of rehabilitation robotics in the multidisciplinary approach, as established for arm functioning and walking (see below).

To summarize:

- Standard immobilization after stroke for several days is counterproductive (and should be reserved for specific rare situations, e.g., in the case of unstable brain perfusion due to arterial stenosis);
- An appropriate amount of activity should take place very early after onset of stroke;
- This should include the initiation of specific and intense, individually adapted neurorehabilitation of the medically stable patient, ideally within the first days after stroke, with clinical monitoring of the event of mobilization;
- The course of treatment should include a high proportion of multimodal therapies.

Goal-setting and assessment in stroke rehabilitation

Most widely accepted is the International Classification of Functioning, Disability, and Health (ICF) proposed by the World Health Organization (WHO) in 2001. In determining treatment goals, the medical model is extended by adding a social perspective and defining participation as an important objective. Treatment goals measure the physical and psychological status, examining the impact of deficits on social aspects such as everyday life, social communication, or ability to work. Even if some somatic functions cannot be regained directly, higher social goals can be reached by establishing compensatory strategies. Interdisciplinary goal-setting is crucial for determining the exact treatment schedule, for estimating the duration of neurorehabilitation, and for evaluating rehabilitative potential (Fig. 3).

Assessment in stroke is crucial to demonstrate the course of recovery and benefit of neurorehabilitation, and also to deliver instruments for research purposes. It adds evaluation of quality of life to activity as an outcome parameter. Activity can be assessed by activity scales and scales of activities of daily living. Activity scales evaluate abilities and have their value in detailed measurement of aspects of specific therapies

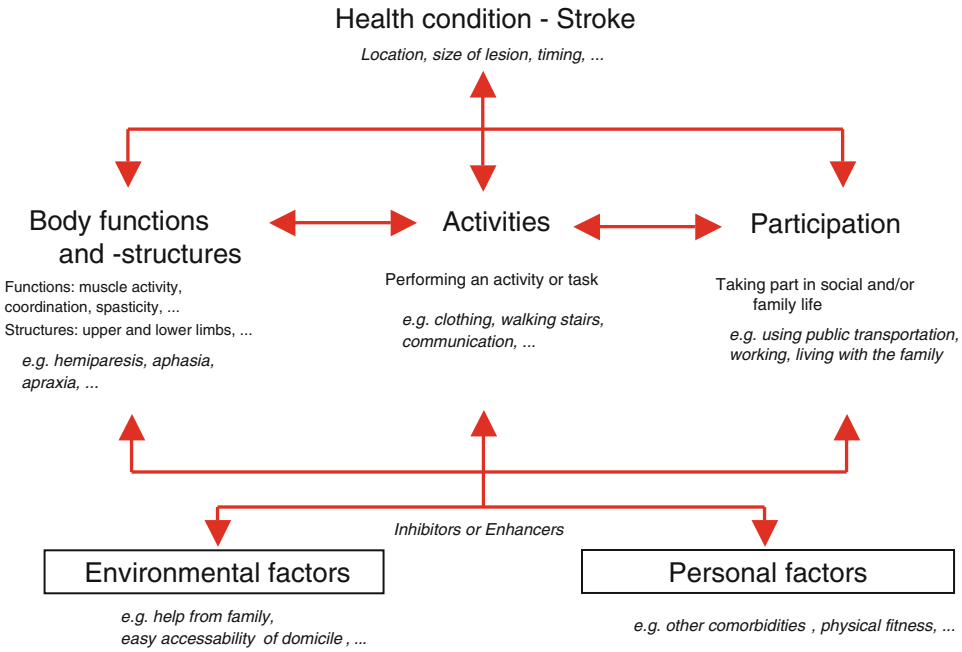

Fig. 3 The International Classification of Functioning, Disability, and Health (ICF) proposed by the WHO transforms "disability" of the former WHO concept to "activity" and stresses the interrelation of several components (activity, body functions, and structures), as well as participation, with interrelation to two context factors: environmental and personal factors, which might have an enhancing or inhibiting effect (figure adapted and examples added from the International Classification of Functioning, Disability, and Health, World Health Organization, 2001)

or in motor function research. For a description of the scales refer to [61] or for a shorter overview to [62]. Stroke-specific instruments include the Stroke Impact Scale (SIS) [63], which is a self-report (patient and caregiver) health status measure to assess multidimensional stroke outcomes.

Methods and subtopics

Concepts of physiotherapy

The predominant common concepts of physiotherapy, i.e., the Bobath, Brunnstrom, proprioceptive neuromuscular facilitation (PNF), Vojta, and other methods, have in common that they claim to have a neurophysiological basis in which, e.g., facilitation and inhibition play a basic role. From an evidence-based point of view there is no doubt about the benefits of physiotherapy, but there are not sufficient data available to identify one of these special concepts as superior to another, as reviewed by [64]. Those authors concluded that patients treated with physiotherapy benefit from an intense training program with complex functional tasks and early application after onset of stroke, but not from programs that mainly focus on the impairment itself.

Motor rehabilitation

Motor impairment is the most common deficit in stroke, often resulting in reduced independence and mobility. Beside the concepts of physical, occupational, and other therapies, the following methods are aimed especially at motor recovery.

Treadmill training and gait machines

Walking is an important objective in stroke rehabilitation, conventional gait training programs on the floor being routine practice. With the aim of enhancing efficacy of gait training and also of easing the burden on the therapists, three groups of treadmill training concepts have been developed and evaluated:

- Body-weight supported treadmill training (BWSTT): partial body-weight support can be used to gain better stepping kinematics in stroke patients unable to walk;
- Treadmill training without body-weight support;
- Robotic-assisted gait training (RAGT) using "gait machines," such as the Lokomat or Gait Trainer GTI, in addition to BWSTT can provide a "gait pattern" even for seriously paretic limbs.

In rehabilitation practice these methods are used in addition to conventional modalities, leaving no doubt about the benefit in terms of easing the burden on therapists and overall being regarded as useful for certain patients. In addition, measurement of gait indicators such as velocity and distance can be easily monitored. Several studies have investigated the efficacy on different outcome parameters of gait [65–69]. Some of the studies can be criticized for low treatment contrast, since control groups also received intense conventional training, and in addition different outcome parameters and intensities make comparison of the results harder. However, a meta-analysis [70] concludes thatthere is weak evidence for overall effectiveness in improvement of gait endurance. The authors recommend that currently BWSTT should be reserved for patients whose physical condition is too weak to tolerate intense training.

Gait training devices in stroke rehabilitation (their benefit having already been shown in neurorehabilitation of multiple sclerosis [71]) are currently being investigated regarding the potential benefit for walking training as well as for certain subgroups of stroke patients. It has been assumed that there might be an additional benefit for patients with neglect or pusher syndrome. In a recent study, patients took part either in conventional training or in robotic-assisted gait training, and the participants of the conventional group had better benefits, e.g., in improving their walking speed. The authors conclude that, for subacute stroke participants with moderate to severe gait impairments, the diversity of conventional gait training interventions appears to be more effective than robotic-assisted gait training for facilitating returns to walking ability [72]. However, benefits were found when integrating treadmill training with structured speed dependence as a complementary tool in gait rehabilitation of stroke patients including physiotherapy, resulting in better gait speed and cadence after a 2-week training program for hemiparetic outpatients. These findings were recently reproduced [73]: at the end of a 6-week trial including 67 patients in the first 3 months after subacute stroke, the subgroup that received locomotor therapy with the use of RAGT combined with regular physiotherapy showed promising effects on functional and motor outcomes as compared with regular physiotherapy alone, as expressed by a greater functional ambulatory capacity score and in their neurological status according to the National Institutes of Health Stroke Scale (NIHSS). However, for the primary outcome point (ability to walk independently) there were nonsignificant differences between the groups.

It is therefore concluded [74] that patients who receive robot-assisted training in combination with physiotherapy after stroke are more likely to achieve better motor function than patients trained without these devices, or only with these devices. Further data need to be collected.

Gait training with rhythmical acoustical pacing was found to be useful with or without further technical support. Auditory stimulation was successfully combined with

Fig. 4 A stroke patient using a "gait machine" in robotic-assisted gait training (RAGT) under supervision of a physiotherapist

treadmill training [75], resulting in gait symmetry improved with acoustic pacing. Nonblinded studies illustrate the positive effect of conventional gait training with rhythmic cueing by a metronome or embedded in music, resulting in better stride length and walking speed [76, 77] (Fig. 4).

Constraint-induced therapy (CIT)

The principles of constraint-induced therapy (CIT) or constraint-induced movement therapy (CIMT) were described by Taub in 1993 [78], who argued that, after stroke patients try unsuccessfully to use the affected side, discouragement due to initial failure leads to "learned nonuse." However, the relevance of CIT to practical neurorehabilitation and experimental neuroscience came later as three principles for this kind of therapy were formulated, consisting of constraining the unaffected limb, forcing use of the affected limb, and intensive practice. Using this method for motor rehabilitation of the upper limb is possible, if a selective function for the paretic wrist and fingers is present before initiation of treatment with CIMT. Therefore, its use as a general treatment method in stroke is limited. A placebo-controlled study applying CIMT over a 2-week period in patients with stroke onset at 3–9 months before therapies showed highly significantly greater improvements than in the control group in motor and functional improvement [79], still detectable at 2-year follow-up [80]. In a recent review including further studies, it was stated that the performed trials according to CIMT delivered a large effect size and showed robust effects on arm function, but not on hand function [81].

Repetitive training, aerobic exercises, and specific muscle strength training

According to learning theories and knowledge derived from studies of neuronal plasticity, repetition of tasks in rehabilitation to achieve better functional outcome is mandatory. A review of repetitive task training after stroke, however, revealed modest improvement in lower limb function only, not in upper limb function [82].

Stroke patients do not only suffer from neurological deficits but also to varying extents from physical deconditioning and sometimes also from cardiac comorbidity. Several studies address the possible benefit of general strengthening and aerobic exercises. In a retrospective analysis, whole-body intensive rehabilitation was found to be feasible and effective in chronic stroke survivors [83]. In an observational study, aerobic capacity and walking capacity were found to be decreased in hemiplegic stroke patients but were directly correlated with each other [84]. Adding physical fitness programs, e.g., by water-based exercise for cardiovascular fitness in stroke patients [85] or task-related circuit training [86, 87], was found to be useful, leading to better outcome not only in physical fitness but also in various secondary measures such as walking speed and endurance, muscle strength, and others.

One concern in specific muscle strength training is increasing abnormal tone, leading to worsening of functional recovery. However, current opinions based on acquired data have changed; e.g., an observational study [88] showed that targeted strength training significantly increased muscle power in patients with muscle weakness of central origin without any negative effects on spasticity. Instead, it was beneficial for functional outcome, showing that strength is related statistically to functional and walking performance.

Robotics for upper limb rehabilitation with/without elements of virtual reality

It has been stated that an estimated 30–60% of adult patients after stroke do not achieve satisfactory motor recovery of the upper limb despite intensive rehabilitation [89, 90]. Therefore, robotics for upper limb rehabilitation and elements of virtual reality (VR) have been combined in several technical devices and used for therapy and studies. In a recent meta-analysis of robot-assisted therapy of upper limb recovery after stroke, only a subsequent sensitivity analysis showed a significant improvement in upper limb motor function. No significant improvements were found in ADL function [91]. It has been concluded that larger samples, adequately controlled study design and follow-up, greater homogeneity in selection criteria, and parameters measuring severity of stroke, motor impairment, and recovery are necessary [89]. For an overview of different available robotics refer to [92]. Comparable to gait machines, some devices provide training programs even for severely paretic limbs.

Virtual reality (VR) is a relatively recent approach that (in combination with robotics or interfaces) may enable

simulated practice of functional tasks at a higher dosage than traditional therapies and therefore enhance the effect of repetitive task training as described above [93]. VR uses computer technology to create environments that appear similar to real-world objects and situations, and furthermore VR technology has the capability of creating an interactive, motivating environment in which practice intensity and feedback can be manipulated to create individualized treatments to retrain movement [89, 93].

Beside the development of robotics and VR devices for rehabilitation purposes, there has been rising interest in the use of available "off-the-shelf" gaming consoles, as models with sensors are available that enable participants to interact with games while performing wrist, arm, and hand movements [94, 95], but more data need to be collected. As there is a demand for cost-effective therapies and augmentation of therapies, also having in mind the worldwide burden of stroke in countries with lesser capacities to spend money on medical devices, further studies are regarded as valuable.

Mirror therapy

In mirror therapy a mirror is placed at 90° close to the midline of the patient and the affected limb is positioned behind the mirror. Using this arrangement, the patient is instructed to watch the nonaffected limb in the mirror with both eyes and perform exercises. Thereby, he receives the visual impression that the limb in the mirror—attributed as the affected limb—is now fully functioning. The role of mirror therapy in motor rehabilitation is not yet clear, but recently, after methodologically weak publications, a promising randomized controlled trial ($n = 40$) has been published for upper limb rehabilitation of subacute stroke patients with severe motor affection without aphasia or apraxia [96]: approximately 1 h of mirror therapy daily in addition to a conventional rehabilitation program was more beneficial in terms of motor recovery and hand-related functioning than a similar treatment without mirroring. The beneficial effect on hand functioning started posttreatment and continued during the 6-month follow-up evaluation, as rated by Functional Independence Measure subscales. Several underlying mechanisms have been discussed, e.g., substitution of mirror illusions of normal movement of the affected hand for decreased proprioceptive information, thereby helping to activate the premotor cortex and promoting rehabilitation by enhancing connections between visual input and premotor areas [97]. Contralateral activation of visual fields was also shown using fMRI [98], with the result that healthy subjects view their hand as their opposite hand by mirroring, activating the visual cortex opposite to the seen hand. Mirror therapy could be an additional option for rehabilitation of severely paretic limbs, but more data need to be collected.

Mental practice

Several studies examined the additional use of mental practice with motor imagery in stroke patients, especially of the upper limb. While some studies reported promising results with improvements of motor functions, e.g., [99–101], there have also been reports of no benefit [102]. Although the results of several publications suggest that mental practice can be a promising addition in motor rehabilitation of the severely affected limb, the role of mental practice for clinical routine remains unclear by now, and well-designed studies with sufficient numbers of patients are needed [103]. There is also a lack of a current meta-analysis of existing data, which is in preparation by the Cochrane Collaboration.

Treatment of spasticity

Although spasticity as a consequence of stroke might also have certain beneficial compensatory aspects, it can in many cases also lead to increased disability, loss of function, diminished voluntary movements in paretic limbs, pain, and hindered care, and also carries the risk of secondary complications. The treatment of spasticity requires mainly physiotherapy, nursing care, occupational therapy, and in many cases orthotic management. However, if physical treatment reaches a limit, for generalized symptoms of spasticity one might want to consider the option of oral agents and intrathecal baclofen, although in most cases orally given medication such as baclofen in cortical or subcortical stroke has a disappointing effect versus side-effect ratio. In focal or sometimes multifocal spasticity, botulinum toxin as part of a longer-term strategy is often a successful treatment option, requiring patient assessment and selection, with definition of the goals of treatment [104]. As several products of botulinum toxin A and B with different rates of effectiveness per unit are available, documentation of the product used is indispensable. In a recent European consensus paper, it is stated that there is evidence from about 20 randomized controlled trials that the treatment leads to a decrease in muscle tone and improved passive functions, including reduced impairment and improved participation, and also growing evidence to show that decreasing spasticity results in active functional improvements [105]. In general, patient selection for this treatment is very important, leading to cost-effectiveness of the treatment of poststroke spasticity with botulinum toxin as part of general management. If multimodal treatment of spasticity (maybe also considering serial casting) fails, surgical therapy in some cases may finally be a therapeutic option.

Rehabilitation of speech disorders

Aphasia with its affection of different modalities, including speech, comprehension, reading, and writing, is a common consequence of stroke, mainly of the left hemisphere. Because of its enormous impact on patients' lives, rehabilitative therapy is mandatory [106]. Even more than in other therapeutic modalities, the importance of high treatment intensity has been demonstrated: a meta-analysis [107] shows that studies which demonstrated a significant treatment effect of speech therapy on average provided 8.8 h of therapy per week for about 11 weeks. In contrast, the negative studies only provided an average of 2 h per week for about 23 weeks. Furthermore the total number of hours of aphasia therapy applied were directly related to outcome, as measured by the Token Test, for example.

In the acute stage, intense daily therapies are recommended. While spontaneous recovery can also be expected to some extent within the first year, only a minimal effect size is reported after 1 year post onset [106]. Therefore, there is a need for therapy in chronic aphasia and an appeal for episodic concentration of therapies has been made, as positive effects were found after intensive (3 h/day) short-term (10 consecutive days) intervention using communication language games in a group-therapy setting [108]. For transfer of results from the therapeutic situation to the patients' environments, there is also an indication for lower-frequency therapies of long duration. The effect of aphasia therapy was also demonstrated using PET [109]. From functional imaging it is known that clinical aphasia syndromes in practice are not strictly linked to anatomical regions and furthermore, with these methods, the courses of recovery and less successful progress can be revealed [110, 111], showing that successful regeneration from poststroke aphasia depends more on the integration of available language-related brain regions than on recruiting new brain regions. Using PET and rTMS interference, restoration (for the right-handed patient) of the left hemisphere network seems to be more effective, although in some cases right hemisphere areas are integrated successfully. As summarized by [112], responses due to tasks and therapies in the right superior temporal gyrus especially in Wernicke's patients and in the inferior frontal gyrus are seen, but restoration of language is usually achieved only if left temporal areas are preserved and can be reintegrated into the functional network. Furthermore, the existence of a dual-pathway network for language and recovery with different functions for repetition and comprehension has been described, showing that the "classic" connection between motor and sensory speech center, the arcuate fascicle, is active during language repetition, even of pseudowords [113], whereas the function of language comprehension is linked to the integrity of the ventral pathway through the extreme capsule, providing therefore a different anatomical course (implicating a potentially different location of damage) of these routes. These elaborated findings of contemporary neuroscience can be linked to already similar historical concepts of the scientists Wernicke, Lichtheim, Freud, and Geschwind [114, 115].

Several studies examined the additional benefit from brain stimulation techniques [116] and medication [42] on recovery from aphasia with positive results. However, it is premature to deduce a recommendation for clinical routine, as for aphasic patients there is currently not enough evidence that these task-specific improvements are persistent or have any impact on real-life communication abilities [117]. *Dysarthria* is an impairment of speech intelligibility, which in about half of cases is due to lacunar syndromes, and although severe persistence exists, this symptom is supposed to have a rather good prognosis under standard rehabilitation [118].

Dysphagia

Dysphagia is a potentially life-threatening complication, and stroke is the most common cause of neurogenic swallowing disorder. Dysphagia occurs in the acute state of stroke in more than 50% of patients, probably leading to aspiration in more than about 20% of them. In a meta-analysis of more than 15 studies using techniques such as fiber-optic endoscopic examination of swallowing (FEES), dysphagia rates between 30% and 78% were found [119, 120].

The main dangers of dysphagia are (a) bolus, leading to acute blockage of airways, (b) pneumonia due to aspiration, and (c) malnutrition and/or dehydration.

On the other hand, swallowing and food intake are important for quality of life and autonomy of patients and will for many patients be considered an important goal of rehabilitation. If a stroke patient presents with warning signs and/or has failed a bedside test, at least three main targets should be considered: (a) avoiding aspiration: mandatorily discontinue oral food/fluid intake until a detailed treatment plan is set up; (b) nutrition and hydration: choose an alternative pathway, e.g., nasogastric tube or in many cases percutaneous endoscopic gastrostomy; and (c) quality of life, regaining autonomy: continuing diagnosis and description of the swallowing problems previous to individual therapy during the process of rehabilitation, which in most cases will include technical evaluation. For a further overview refer to [62] and for a description of screening protocols to [121, 122].

Cognitive recovery of stroke

Besides defined neuropsychological syndromes, cognitive impairment after a stroke is very common and may persist

in the postacute and also the chronic phase. Individual assessment includes evaluation of several aspects of attention, intelligence, memory, executive functions, and personality prior to devising an individual treatment schedule, which can be neuropsychologically specific but should also be interdisciplinary, as the impairment usually has an impact on several aspects of the rehabilitation progress and the ability to cope with the activities of daily living. Depending on treatment goals, a more practical evaluation including out-of-hospital observations can also be useful. For detailed guidelines on cognitive rehabilitation refer to [123].

Spatial neglect

Spatial neglect is a common syndrome following stroke, most frequently of the right hemisphere, predominantly but not exclusively of the parietal lobe. It is a complex deficit in attention and awareness which can affect extrapersonal space and/or personal perception. Elements of spatial neglect may be seen also with infarctions of the left hemisphere; however, symptoms are clinically less consistent than in right hemispheric neglect [124].

The therapeutic process is often prolonged. In multidisciplinary neurorehabilitation, perception via the affected side is enforced as much as possible, and additional alertness training as well as visual, proprioceptive, and vestibular stimulation techniques are used [125]. In addition to focal disturbances, in this condition an interhemispheric imbalance is supposed to be of clinical relevance. Therefore, several pilot studies have been published to evaluate the benefit of cortical stimulation techniques in neglect therapy, addressing the contralesional hemisphere overexcitability as a central pathophysiological mechanism in hemispatial neglect. Using a special rTMS protocol with theta burst, improvements were described in a pilot study even after a single session [126]. For a review on available data refer to [127].

Other neuropsychological syndromes

Hemianopia can be combined with neglect syndromes and has in any event a large impact on daily activities that appears in problems in reading, orientation, and safety in traffic. Basic rehabilitative management includes stimulation from the hemianopic side (e.g., positioning of the bed, talking to the patient) and tasks with exploration to the hemianopic side. While spontaneous recovery might occur at least up to several months, treatment options such as visual field training are discussed controversial. Using compensatory visual field training, compared with a control group no formal change of visual defect was reported by [128], although the training improved detection of and reaction to visual stimuli. Other groups recently reported improvements of the visual field of up to 5% for ischemic lesions and up to 10% benefit for stroke after hemorrhage, using reaction perimetry treatment [129].

Space perception disorders can lead to spatial disorientation (affecting a person's topographical orientation), well known in right hemisphere infarction. A misperception of the body's orientation in the coronal plane is seen in stroke patients with a "pusher syndrome." They experience their body as oriented upright when it is in fact tilted to one side, and therefore use the unaffected arm or leg to actively push away from the unparalyzed side and typically try to resist any attempt to passively correct their body posture. The syndrome is a distinctive clinical disorder after unilateral left or right brain lesions in the posterior thalamus or in the insula and postcentral gyrus [130]. Recovery under physical therapy, e.g., by trying to enhance sensorimotor input from the contralateral side, is often prolonged.

Apraxia is a syndrome of left hemisphere infarction. It often severely hinders ADL independence (apart from contributing to speech disorders as speech apraxia), and treatment of apraxia should definitely be part of the overall neurorehabilitation program [123]. Although the literature on recovery and treatment is limited, apraxia has been shown to be improved by occupational therapy. For a review of apraxia treatment and also on other aspects of occupational therapy, refer to [131].

Outlook

As robust data clearly show, the overall effectiveness of neurorehabilitation in stroke medicine, and the identification of useful elements and methods to further enhance recovery, lie at the center of research nowadays. Despite growing evidence of the usefulness of the above-described emerging methods, there is still a long way to go before, hopefully, many of them can be integrated into routine clinical practice. However, until now, for many methods there is a need for further randomized controlled trials with assessment of long-term benefits. The main problems are: (a) the time window: many intervention studies take place in the "chronic phase" (even with promising results), although we know from basic science that neuroplasticity is most likely to occur in an early stage after stroke; (b) low intervention contrast, as the "controls" also receive conventional therapies, however, facing the dilemma that on the other hand it is likely that (c) many of the emerging techniques can deliver improvements only when combined with active learning; (d) difficulties to identify the "dosage" of the interventions; (e) heterogeneity of studies: different patient criteria as well as heterogeneous types of stroke and outcome measures that also make meta-analysis difficult; and (f) lack of funding for nonpharmacological methods and therefore multicenter

organization. Further studies of interventions need careful selection of patient groups which, for some methods, might make a combination with imaging methods essential.

In spite of these obstacles to research, in many places, neurorehabilitation of stroke continues to enhance its benefit for stroke patients, because of improvements in the organization of its application, proliferation of knowledge of clinical practice, and closer interconnection to acute stroke treatment.

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