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Review Article

Current trends in stroke rehabilitation. A review with focus on brain plasticity

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Current understanding of brain plasticity has lead to new approaches in ischemic stroke rehabilitation. Stroke units that combine good medical and nursing care with task-oriented intense training in an environment that provides confidence, stimulation and motivation significantly improve outcome. Repetitive trans-cranial magnetic stimulation (rTMS), and trans-cranial direct current stimulation (tDCS) are applied in rehabilitation of motor function. The long-term effect, optimal way of stimulation and possibly efficacy in cognitive rehabilitation need evaluation. Methods based on multisensory integration of motor, cognitive, and perceptual processes including action observation, mental training, and virtual reality are being tested. Different approaches of intensive aphasia training are described. Recent data on intensive melodic intonation therapy indicate that even patients with very severe non-fluent aphasia can regain speech through homotopic white matter tract plasticity. Music therapy is applied in motor and cognitive rehabilitation. To avoid the confounding effect of spontaneous improvement, most trials are preformed ≥3 months post stroke. Randomized controlled trials starting earlier after strokes are needed. More attention should be given to stroke heterogeneity, cognitive rehabilitation, and social adjustment and to genetic differences, including the role of BDNF polymorphism in brain plasticity.

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Introduction

Brain plasticity is a broad term for the property of the human brain to adapt to environmental pressure, experiences, and challenges including brain damage (1–5). It occurs at many levels from molecules to cortical reorganization. The advances in technologies enabling non-invasive exploration of the human brain have increased our understanding of brain reorganization after ischemic stroke (6–13). The time after stroke, the lesion location, and the integrity of cortico-spinal tracts and cortical and subcortical connections are factors that influence outcome. Diffusion tensor imaging tractography is a recent technique that enables non-invasive visualization of fiber tracts in the human brain *in vivo* (14–17), which is likely to have an impact on future design and choice of rehabilitation methods for individual patients.

The value of stroke units

Key principles of stroke rehabilitation include a functional approach targeted at specific activities, frequent and intense practice, and start in the first days or weeks after stroke (18). These general principles are applied in stroke units where multidisciplinary teams stress the importance of active participation of the patients in the rehabilitation process. Stroke unit care is the only treatment that has so far been shown to have a major impact on the outcome after stroke (19). More patients can return home early, and the need for institutional care is reduced. It is highly cost-effective when compared with general medical ward care (20–22). Also cognitively impaired stroke patients do benefit from admission to an acute stroke unit (23). These data have been supported by a large study including 105,043 patients with acute stroke reported to the Swedish Stroke Register during the years 2001 through 2005 that were followed until January 2007 (24). Stroke unit care was associated with reduced risk for death and institutional living at 3 months after stroke onset, and with better long-term survival in all subgroups (age, sex, stroke subtypes, and level of consciousness). The benefit of stroke units compared to general wards is most likely a combination of optimal medical and nursing care, task oriented, and for the individual meaningful training in an environment that gives them confidence, stimulation, and motivation (25). Mere admittance to a stroke unit with specially trained staff encouraging active participation in the rehabilitation process and more information to patients and relatives may increase the motivation and expectation of the patients. Animal studies have demonstrated that environmental enrichment has many functional and biological effects and significantly enhance the effect of other interventions (2, 5, 26, 27).

Motor rehabilitation

Tactile sensibility of the hand is essential for identifying objects and for motor performance. When sensory perception is affected in stroke, rehabilitation of motor skills is more difficult to achieve (28). Aging is associated with reduced tactile discrimination and deterioration of fine manipulative movements and handling of tools. Sensory stimulation by means of tactile coactivation of fingertips successfully improves tactile acuity in elderly individuals and, in contrast to motor training, it does not require active participation or attention of the subjects. This lead to the suggesting that it might be a useful therapeutic intervention to improve the activity of daily living in stroke patients with impaired sensory motor abilities (29, 30). A preliminary study on four individual post-stroke showed that all improved in sensory tasks and motor performance, effects that remained 4 weeks post treatment (31). If those data can be confirmed in larger studies, it may have a considerable impact in stroke rehabilitation.

Constraint-induced movement therapy (CIMT) is a method in which a splint is applied to the intact hand 90% of the day to force the use of the paretic hand, and combined with "shaping" by which the tasks are made progressively more difficult (32). It has attained much media interest after a significant effect was obtained in a randomized study with a 2-week program of CIMT applied to 222 stroke patients mostly with mild to moderate impairment 3–9 months after stroke (33). A follow-up 24 months after the ischemic event showed a persistent benefit (34). Some limitations with the study include that the controls received "usual and customary care" that involved less motor training than that delivered to the CIMT group. Furthermore, the separate effects of higher dose of motor training and immobilization cannot be evaluated. The study included rather few patients with severe impairments, and the participating patients may have represented a minority of patients with chronic stroke (35). A remaining question is whether it is superior to other treatment of comparable intensity.

There is no evidence that CIMT is of benefit in early stroke rehabilitation. No significant differences were noted in patients randomized within 2 weeks after stroke either to 2 weeks of CIMT or to traditional therapy at an equal frequency of up to 3 h/day. The groups were well balanced for frequency, duration, and intensity of the treatment, and the results did not show any significant differences between the groups (36). In another study, patients were randomized within 28 days of admission into three groups. Control treatment consisted of 1 h of activity of daily living retraining and 1 h of bilateral training 5 days a week during 2 weeks, The standard CIMT group received 2 h of shaping therapy and wore a mitten 6 h a day; and high intensity CIMT underwent 3 h of shaping therapy and mitten 90% of waking hours. Standard CIMT was equally effective but not superior to an equal dose of traditional therapy (37), and the higher intensity CIMT resulted in less improvement at 90 days. These two studies on early CIMT emphasize the need for control groups that match therapy intensity and dose in clinical trials.

A meta-analysis based on 10 studies of robot-assisted therapy on motor and functional recovery in patients with stroke involving 218 patients showed a significant effect on motor recovery of the upper paretic limb but no significant effect on functional ability. The recommendation was that future research on the effect should distinguish between upper and lower robotics arm training and concentrate on kinematic analysis to differentiate between genuine upper limb motor recovery and functional recovery owing to compensation strategies by proximal control of the trunk and upper limb (38). Similarly, a Cochrane report based on 11 trials with 328 participants found no significant improvement in activities of daily although arm motor function and arm motor strength improved (39). Rehabilitation program may require different therapy protocols and equipment in acute and chronic stages of recovery (40, 41). Adding virtual reality to robot-based gate training (42) and arm (43) training may have beneficial effects as will be discussed later.

Bilateral coordination is important in daily life. Bilateral arm training (BAT) may be of value particular for stroke patients with severe functional deficits (44). In a randomized controlled trial 6–67 months after stroke onset, BAT improved the spatiotemporal control of the affected arm in both bilateral and unilateral tasks and reduced motor impairment (45). Comparing CIMT, BAT, and a control intervention of equally intense but less specific therapy for 2 hours a day 5 days a week for 3 weeks, both CIMT and bilateral arm training resulted in better performance than the control intervention. BAT exhibited greater gains in the proximal upper limb than the other two groups on motor performance, and CIMT produced greater functional gains in hand functions in patients with mild to moderate chronic hemiparesis (46). It has been proposed that bilateral training is a necessary adjunct to unilateral training and that individuals at all level of severity can benefit from bilateral training although not all approaches are effective at all severity levels (47). Specific training approaches need to be matched to the individual case characteristics. To achieve bilateral skills important in daily life training should not be either unilateral or bilateral but both. In a systematic review based on 56 studies 1979–2008, the authors concluded that the current evaluation scales are not optimal for exploring changes in real life of the patients and that there is a need for the development of direct measures of arm use in real-life environments (48).

Electrical brain stimulation

After a cortical lesion, the surrounding intact tissue has an inhibitory action on the damaged area, an intra-hemispheric inhibition. Most patients with stroke have better function in the upper arm than in the hand, and it was postulated that intracortical competition from surrounding areas had an inhibitory effect on the hand muscles. When the upper part of the brachial plexus was anaesthetized, intense training of the paretic hand significantly enhanced motor function, and the improvement was associated with an increase in TMS-evoked motor output to the practiced hand muscles. The effect remained at follow-up 2 weeks later (49). However, the anesthetic procedure is not easy, which explains why this intervention has not been much used.

Another approach is based on the concept of interhemispheric inhibition. The cortical sensory and motor representation of the hand exerts inhibitory influences on the homonymous representation in the opposite hemisphere (50), an interhemispheric inhibition that is thought to contribute to skilled motor performance. Short-term ischemic nerve block to the hand leads to functional reorganization in the de-afferented motor cortex, and also to functional changes in homotopic motor regions in the contra-lateral cortex (51, 52). Based on the observation of an abnormally high interhemispheric inhibitory drive from the motor cortex of the intact hemisphere to the injured hemisphere during a voluntary movement of the paretic hand in patients with subcortical infarcts, it was hypothesized that this abnormality might adversely influence motor recovery (53). Different neurophysiologic strategies to increase the activity of the injured area have been proposed mainly using transcranial magnetic stimulation, TMS (54, 55), and transcranial direct current stimulation, tDCS (56). Lower frequencies of repetitive TMS (rTMS = a train of TMS pulses of the same intensity) in the range 1 Hz range suppress excitability of the motor cortex, while 20 Hz lead to a temporary increase in cortical excitability (57). With tDCS, a weak polarizing electrical current is delivered to the cortex, and the effect depends on the polarity (56). An excitatory effect is obtained with the anode placed over the motor cortex, and inhibition is induced with the cathode over motor cortex. tDCS is easier to apply and less expensive than TMS, and a feasibility study demonstrated that the participants could not distinguish tDCS from sham stimulation, making it suitable for larger double-blinded, sham-controlled randomized trials (58).

Two main approaches to alter the hemispheric dominance have been used in clinical studies. 1) Reducing the cortical activity on the intact side by low frequency rTMS (59–61) or by reducing the somatosensory input to the intact hemisphere (62, 63); 2) Enhancing the activity in the damaged hemisphere by high-frequency rTMS (64), anodal tDCS (58, 65), or increasing the sensory input by electrical stimulation of the peripheral nerves in the paretic hand (66–68). These manipulations have shown 10–30% significant effects in behavioral test in these pilot studies. Combining peripheral nerve stimulation with tDCS can facilitate the beneficial effects motor performance beyond levels reached with each intervention alone with 41% increase compared to sham (69). The differences were maintained 6 days after the end of the training with no further follow-up.

Most of the above-mentioned studies have been performed on patients with chronic stroke from several months up to 4 years after stroke. However, in one study patients were randomized 5–7 days after stroke to receive high-frequency rTMS to enhance neuronal activity on the lesion side once a day for 10 days or to a standard treatment group (64). Compared to the standard therapy group, the study group had better scores in all tests used, and the gains remained at 10 days after the end of treatment. The same group has reported beneficial effects of rTMS on dysphagia in the subacute stage (70). The first study on long-term follow-up of patients treated 5–15 days after stroke with 5 daily stimulations and followed for 1 year demonstrated a lasting benefit (71). Although stroke leads to changes in the brain tissue that potentially could alter the electrical response properties, no adverse effects have been reported in the studies with rTMS and tDCS after stroke. Thirty-six authorities in the field have published a consensus statement on safety and ethical considerations together with an application guideline for the use of TMS in clinical practice and research (72).

Epidural cortical stimulation is an invasive technique that improves motor rehabilitation in experimental animals. In a preliminary report from a planned multi-center non-blinded trial, patients with stroke were randomized to surgery or to a control group at least 4 months after stroke. Subdural electrodes were implanted in the cortex of the treatment groups, and both groups underwent rehabilitation for 3 weeks after which the electrodes in the treatment group were removed. Stimulation plus rehabilitation improved function in the upper extremity significantly more then rehabilitation alone, and the effect remained at 12 weeks after the stimulation (73). A multicenter feasibility study of safety and efficacy was also promising (74). However, in a phase III study based on 146 patients with hemispheric stroke, the outcome of the stimulated group was not better than in the group that received only rehabilitation (75).

Considering many reports on the importance of cortico-spinal tract integrity for functional recovery (7, 8, 10, 17) future studies on motor outcome after stroke should take that into consideration. A recent study indicates different effects of rTMS on the ipsi-lesional primary motor cortex in cortical and subcortical chronic middle cerebral artery stroke (76).

Hemispheric subspecialization in motor activities

Studies on motor lateralization have revealed a consistent difference in the control strategies of the dominant and non-dominant hand; the performance with the dominant arm/hand is most accurate when reaching from one fixed starting position to multiple targets, whereas performance with the non-dominant hand is most accurate when reaching toward a single target from multiple start locations (77). Studies on patients with stroke have demonstrated deficiencies that reflect these distinctions (78), data that may help to explain why patients with stroke may have some difficulties also with the hand corresponding to the intact hemisphere. The subspecialization and function of the ipsilateral hand may be of importance particularly for patients with severe motor dysfunction that must relay on the ipsilateral intact hand for some activities of daily living (79). The side of lesion influences the degree of bilateral activation in chronic post-stroke hemiparesis (80). In healthy individuals, the interhemispheric inhibition is stronger from the dominant to the non-dominant side than in the opposite direction (81). Simultaneously applying cathodal tDCS over the dominant motor cortex and anodal tDCS over the non-dominant motor cortex produced an additive effect that facilitates motor performance in the non-dominant hand (82). Modulation of excitability in the dominant motor cortex significantly affected performance for the contra-lateral and ipsi-lateral hands, whereas modulating excitability in the non-dominant motor cortex only had a significant impact for the contra-lateral hand (83). The evidence for a hemispheric asymmetry in the ipsilateral effect of modulating excitability in the motor cortex may be important for clinical research on motor recovery. The arm use after left or right hemiparesis is influenced by hand preference. Although both groups used their ipsi-lesional intact arm more than the contra-lesional paretic arm, the right hemisphere-damaged group used the intact arm four times more frequently and the left hemisphere damaged two times more frequently than their paretic arm (84). If this observation was related to the frequency of hemi-neglect after right-hemisphere lesions was not studied. Recent data that successful recovery of motor skills after hemiparetic stroke involves participation of contra-lesional cortical networks support that we need to pay attention to both hemispheres (85). Whether the hemispheric subspecialization is of the magnitude that it could significantly influence the rehabilitation strategies in left and right hemispheric stroke remains to be investigated.

Multisensory interaction; Training with a mirror, action observation, motor imagery or mental practice, virtual reality

Perception, attention, memory, language and other cognitive functions consist of distributed interactive and overlapping networks. The healthy human brain has a large capacity for automatic simultaneous processing and integration of sensory information, and multisensory influences are integral to primary as well as higher-order cortical operations. Multisensory-training protocols can better approximate natural settings and are more effective for learning in healthy individuals (86, 87).

Cortical lesions interrupt cortical and cortico-subcortical networks, and the capacity for automatic and simultaneous processing of incoming stimuli is reduced. Current data indicate that relearning and compensation for lost functions benefit from multisensory stimulation. Multisensory approaches to motor, somatosensory, and cognitive rehabilitation include action observation, mental training, and training in a virtual reality and music-related therapies.

In training with a mirror, the patient's affected arm is hidden behind a mirror. While moving the unaffected arm, the patient watches its mirror image as if it were the affected arm (88). Some pilot studies have been published, indicting that it might be useful in patients with stroke, and two randomized controlled trials have been published with positive results lasting at least 6 months after training (89, 90). The mirror-training patients regained more distal hand function than control patients. Interestingly, across all patients, mirror training patients improved recovery of surface sensibility, and it stimulated recovery from hemineglect, suggesting that training with a mirror may induce multisensory interactions and be related to action observation that activates motor and premotor areas (91). Neurons in the regions that discharge both in association with performance of a motor task and with observation of another individual performing the same action are named mirror neuron and are thought to contribute to imitation and to be important for our understanding of other individuals intensions (92–94). Four weeks of action observation significantly enhanced motor function with a significant rise in activity in the bilateral ventral premotor cortex, the supplementary motor area, bilateral superior temporal gyrus, and some other areas in fMRI. The functional improvement remained at 8 weeks after the end of the intervention (95). Combining observation of daily actions concomitant with physical training of the same movements significantly enhanced the effect of training alone on rehabilitation of motor deficits (96). Broca's area is one of the cortical areas activated by hand/mouth action observation, and it has been reported that patients with frontal aphasia are specifically impaired in their capability to correctly encode observed human actions (97).

Imaging performance of a motor action requires conscious activation of brain regions involved in movement preparation and execution. Mental training can improve motor function and alter cortical representation areas (4, 91, 98). In a placebo-controlled trial on patients with stroke with a mean post-stroke time of 3.6 years, mental practice induced a significant effect on motor outcome (99). One advantage is that it is not dependent on the ability to execute a movement and can thus start early in rehabilitation even in severely paretic patients with little motor activity and that it can be combined with other treatments. However, some patients with left parietal or left lateral prefrontal lesions may have problem with mental imagery (98).

Virtual reality (VR) technologies provide multimodal, interactive, and realistic 3-D environments with a high level of control of the parameters and applications that can be adjusted for each user (100, 101). VR can enhance velocity and walking distance in robot-based gate training (42), and VR games improves attention, speed, precision, and timing in robot-based hand training (43). A virtual supermarket provides opportunity for practicing functional tasks in everyday life (102). Unilateral spatial neglect that is present in almost 50% of patients with right-hemisphere stroke has a negative impact on functional recovery (103). VR has been successfully used both for assessment and treatment of neglect. (104–107). A three-dimensional virtual street crossing program has been developed for assessment and training extra-personal neglect and enable outdoor mobilization (108). Computerized VR interfaced with robots, movement tracking, and sensing glove systems can further be coupled to fMRI images providing modified visual feedback (109). VR spatial brain processing differs from brain fMRI activation in reality. Thus, in evaluation of possible restoration effects caused by VR training it is important to integrate information about the brain activation networks elicited by the training (110). Tele-rehabilitation that allows a therapist to conduct interactive VE treatment sessions with a patient who is located at home has shown highly significant results in three standard clinical tests after 30 l-h sessions, maintained at 4- month follow-up (111). Data from training activities of daily living in a virtual reality setting are promising. The patients have to be positive to VR training, continued contact with a therapist is essential, and it needs to be further evaluated for long-term gains. A low cost multiple users VR environment system has been developed for rehabilitation of patients with stroke (112).

Speech and language rehabilitation

The brain organization for language involves a combination of cortical structures and white matter tracts, some of which are unilateral and other bilateral. A dorsal stream, ''sound to action'' (non-fluent or Broca′s aphasia), is essentially left oriented in most persons, and a ventral stream, from ''sound to meaning'' (semantic aphasia), is to a considerable extent bilateral (113, 114). The degree of language lateralization determines susceptibility to unilateral brain lesions (115).

Aphasia or dysphasia can be caused by cortical lesions and/or to damage to white matter tracts connecting different language areas. Decreased fMRI activation was observed in the remaining language area during the first days after stroke (acute phase followed 10 days later by an activation of homolog regions in the right hemisphere. In the chronic phase (about a year later), the activity had reappeared in the remaining left language areas in patients with good recovery (116). However, there is a large variability of language recovery after first-ever stroke, and a follow-up study 90 days after stroke onset failed to identify any prognostic factors (117). Several studies indicate that both hemispheres can be involved in the recovery process.

Language and actions are closely linked in the brain (118–120), and Broca′s area, traditionally looked upon an exclusive language area, is now thought to detect and represent complex hierarchical dependencies regardless of modalities and use including gesture, action and music (121–124). Listening to speech specifically modulates the tongue muscles (125) and language perception activates the hand motor cortex (126). Integrating observed facial movements into the speech perception process involves a network of multimodal brain regions associated with speech production that contribute less to speech perception when only auditory signals are present (127). Gestures may facilitate word retrieval in aphasia (128).

There is a bihemispheric network for vocal production regardless of whether the words/phrases are intoned or spoken (129), and words and melody are intertwined in singing (130), which may explain why some patients with aphasia are able to sing the text of a song while they are unable to speak the same text. When allowed to sing and speak along with an auditory model, aphasics repeat and recall more words when singing than when speaking (131). The intelligibility and naturalness of the speech improved after vocal exercises and singing training in patients with non-fluent aphasia after stroke or trauma (132).

Intensive melodic intonation therapy for aphasia is an old method that has been systematically applied and evaluated in recent years (133, 134). The method includes three important components: melodic intonation, intense training 1.5 h/d 5 days a week, and simultaneous tapping with the left hand to prime the sensorimotor and premotor cortices on the right side for articulation. Melodic intonation therapy delivered at high intensity to patients with chronic severe Broca′s aphasia leads to remodeling of the right arcuate fasciculus, a fiber bundle that combines the anterior and posterior language area in the left hemisphere demonstrating that plasticity can be induced in the contra-lateral homolog tract (135).

Constraint-induced aphasia therapy (CIAT) is a different approach. Based on the concept of constraint-induced therapy for motor therapy, it was hypothesized that gestures and other types of non-speech communication should be prevented, and patients forced to use speech while a therapist is playing language games with two or three aphasic patients. The picture cards and the hands are hidden for other players to prevent visual input, and all communication, mainly questions and answers, have to be performed by spoken words and sentences. The game is getting more difficult in small steps and reinforcement is provided. Extensive training 3 h a day resulted in significant effect compared to standard training one hour a day during an extended period adding up to the same total amount of training, thus the same training time spread over a longer time (136). In a study when all aphasia patients were trained with CIAT over a 2-week period 1–9 years after stroke, half of the patients received additional training in everyday communication with the assistance of family members. Language tests improved after training in both CIAT groups. No alterative treatment group was included. However, only the patients who were encouraged by their relatives to be more active verbally during the 2- week training period exhibited more communicative activity than before treatment when re-examined after 6 months (137), demonstrating that environmental encouragement is essential for transforming the effects observed in language tests into useful verbal communication. For en extensive review on the theory and practice of CIAT, see review by Pulvermuller and Berthier (138).

Using MEG (magneto-encephalography) before, direct after and 3 months after the training, three patterns of behavioral and neurophysiologic response to constraint-induced language therapy, not described in detail, were observed (139). Patients with initial response who maintained the gains at 3 months exhibited an increase in left temporal activation (responders, $n = 8$). Patients with initial significant response to the therapy but no effect at 3- month follow-up had greater right-hemisphere activation than other patients at all MEG sessions (lost-response, $n = 4$). Those who did not improve at any time had increased activation in left parietal areas (non-responders, $n = 11$).

Deficits in auditory single word and sentence comprehension correlate with the degree of disruption of left-right anterior-lateral superior temporal cortical connectivity and with local activation in the superior temporal cortex (118). Voxel-based lesion-symptom mapping has confirmed the necessary role for the left anterior temporal lobe in mapping concepts to words (140). Also aphasia related to frontal lesions can include semantic components. More studies that specify the location and extension of the lesions and the related language problems as to speech fluency and understanding in daily life situations are needed.

Rehabilitation of other cognitive deficits

Post-stroke cognitive impairment interferes with recovery and is a major problem for social rehabilitation and post-stroke quality of life at all ages (141–143). Cognitive activation is clearly involved in several examples of multisensory interactions already referred to including the effect on neglect in VR training. Although early bedside cognitive assessment is possible in most cases (144), specific cognitive rehabilitation is often neglected in the early stage after stroke. Two week after a first-ever ischemic infarct, 91.5% of 177 patients (mean age 50 ± 16 years) failed in at least one cognitive domain, predominantly in working memory, episodic memory, and executive functions, compared with education and age-matched control subjects (145). Cognitive dysfunction was associated with age, low level of education, NIHSS score at day 15, and middle cerebral artery infarcts, suggesting that simple criteria may be a useful tool for designing clinical trials. (146). In another study on 149 stroke patients 70+ were investigated after 18 months suggested that a composite score based on four subtests of NIHSS was almost as good as the MMSE in detecting severe cognitive impairment (147). Neglect is an important prognostic factor. Among 138 patients with stroke aged 70–91 , visual neglect was present in 15% 20 months after stroke (141). Cognitive impairment was twice as common in patients with neglect and three times as common in those with severe neglect, indicating that early rehabilitation of neglect might have important long-term effects.

In a review based on 78 published quantitative and qualitative studies reporting social consequences after stroke in patients <65 years of age, the proportions for return to work ranged from 0% to 100%. A negative impact on family relationships ranged from 5% to 79% and for deterioration in leisure activities from 15% to 79%. The review highlights the need for robust and consistent methodologies in future studies on the prevalence of social problems and of the effect of interventions to address them (148).

Attention is closely related to cognition and is also important for motor skill training. A significant reduction in the attention deficit was observed at 5 weeks and 6 months in a recent randomized controlled trial with an attention-training program starting within 2 weeks after stroke onset (149). The study included 78 patients with stroke identified via neuropsychological assessment as having attention deficit. If these results can be confirmed in further studies, they are likely to have effects both on motor and cognitive rehabilitation and may improve quality of life after stroke.

Whether rTMS and tDCS can influence cognitive deficits after stroke has so far been little explored. In healthy individuals, tDCS may improve language learning (150–152) and enhance planning activity (153). There is some evidence that it may improve naming in aphasia (154, 155), working memory (156), and attention (157) in patients with stroke. These are all small studies with no long-term follow-up.

Music therapy

Listening to rhythm activates motor and premotor cortices (158–160). Rhythmic auditory stimulation and musical motor feedback can improve gait (161–163) and arm training after stroke (164, 165). Music-supported finger and arm training that significantly improved function was accompanied by electrophysiological changes, indicating better cortical connectivity and improved activation of the motor cortex (166).

Music is a multimodal stimulus with a well-established role in cultural and social communication and emotional well-being. During the last years, a number of studies have demonstrated that music listening activates many brain structures related to sensory processing, attention, and memory and can stimulate complex cognition and multisensory integration (158, 167). To what extent these effects can be transferred to therapeutic interventions in patients with stroke is currently investigated. Patients with neglect show enhanced visual awareness associated with increased fMRI activation of regions related to emotion and attention while they listen to music they like but not to un-preferred music or silence (168). Music therapy improves executive function and emotional adjustment in traumatic brain injury rehabilitation (169). It has been reported to improve attention and verbal memory in patients with stroke (170). However, the statistical analyses of the data were not adequate, and further studies are needed. Merely listening to music and speech after stroke starting 1 week after stroke onset induced long-term plastic changes in early sensory processing that correlated with the improvement in verbal memory and focused attention both in music and in speech listening (171). A community-based intervention program combining rhythmic music and a specialized rehabilitation program during 8 weeks resulted in a wider range of motion and flexibility, more positive moods as well as an increased frequency and quality of interpersonal relationships compared to the control group (172).

Genetic polymorphism

Genetic polymorphism is one factor that may influence the response of the brain to injury and disease. Brain-derived growth factor (BDNF) has a critical role in activity-dependent modulation of synaptic plasticity in human motor cortex. A common single nucleotide polymorphism (BDNF val66met), which results in reduced secretion of BDNF, reduces the activity-related cortical plasticity in response to motor training in healthy individuals (173) and is associated with greater error and poorer retention in short-term motor learning (174). In a cohort of 722 elderly individuals, the presence of the polymorphism was associated with significantly reduced cognitive performance on processing speed, delayed recall, and general intelligence (175). It modulates the response to rTMS, which may explain some of the individual differences in the effect of stimulation (176). It has also been proposed to be a predictor for poor outcome among survivors of aneurismal subarachnoid hemorrhage (177). There are likely to be other genetic differences that can influence outcome.

Concluding remarks

Progress of time is an independent covariate that reflects spontaneous recovery of functions that occur during the first months after a stroke. To avoid the confounding effect of time (178), most studies testing new rehabilitation methods involve patients with chronic stroke several months after stroke onset. Optimal benefits for the patients and the society would supposedly be obtained by successful interventions in the subacute phase of stroke as indicated by the beneficial effect on motor outcome in stroke units. Rehabilitation program may require different therapy protocols in acute and chronic stages of recovery, and we need to know the optimal time for specific interventions. More homogenous groups of patients need to be studied. Although it has been repeatedly shown that the integrity of the corticospinal tracts is of main importance for a favorable outcome after stroke (7–11), the information is lacking in most studies. Cognitive rehabilitation programs starting early after stroke are essential to establish whether attention-training, music, and other cognitive interventions can lead to better social adjustment and quality of life post stroke.

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