Towards Effective Neurorehabilitation for Stroke Patients

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Abstract

Despite global and regional health crises, global life expectancy has increased continuously and substantially over the past 40 years. This is associated with an increase in incidence of age-related diseases, such as ischemic stroke and has an important socio-economic impact. There is a growing demand to have more effective treatments to reduce disability and improve the outcome of stroke patients. We reviewed the latest advances on neurorehabilitation and the new trends in this field. We provide practicing neurology and rehabilitation clinicians with a review of concepts of neuroplasticity, engagement, enriched environments, smart robotics, neuroelectronic devices and explain how they could be linked and applied in daily practice. Also, we review pharmacological interventions with a direct effect in neurorehabilitation. We conclude that there is some degree of evidence suggesting a possible positive co-adjuvant effect of citicoline in the rehabilitation phase of patients after stroke.

Keywords: Stroke; Rehabilitation; Neuroplasticity; Robotics; Pharmacological therapy; Citicoline

Introduction

Each year during the world stroke awareness day we recall that 1 in 6 people worldwide will have a stroke in their lifetime. This makes stroke the first cause of disability worldwide with 30% survivors having long-term sequelae and in 50% residual disability requires assistance for basic activities of daily living (ADL) [1]. It has an important socio-economic impact with estimated costs of 27,314 euro per person/year [2,3], exceeds any pharmacological interventions and call for better, and more effective recovery approaches. XXI century neurorehabilitation is a very young field with an evolving concepts and important literature supporting its impact on outcomes. This article provides an overview of the field and summarises the most recent and continuously evolving paradigms of current and modern neurorehabilitation. We examine concept of teacher, or neurotherapist crucial for successfull neurorehabilitation [4]. We provide practicing neurology and rehabilitation clinicians with a review of concepts of neuroplasticity, engagement, enriched environments, smart robotics and neuroelectronic devices and explain how they could be linked and applied in daily practise. For the purpose of the following review, we selected literature based on the most recent publications in the field and international guidelines.

Changing Paradigms of Current Neurorehabilitation Concepts

What is a modern neurorehabilitation? It is all about recovery of functional skills after injury through evidence-based interventions that operate to manipulate the sensorimotor environment of the patient. This involves patient engagement for greater neuroplastic changes and functional outcomes. Engagement is motivation, passion, desire, dedication, trust, attitude about treatment, and active participation of the subject.

One of the biggest discoveries in XX century in neuroscience was neuroplasticity [5,6]. It is a capacity for reorganization and adaptation throughout the lifespan, including post-injury adaptive capacities of the nervous system to change following deprivation of input or overstimulation, increased or decreased usage or learning of new skills. These changes are engendered by creating new neural pathways or through modification of existing ones. Studies show that post-injury, neural reorganization occurs without any clinical intervention based on use and functional compensation. The theoretical foundation of initial and older concepts concentrated on motor recovery was usually based on spinal reflex physiology and hierarchical concepts of motor development going back to the beginning of the 20th century [4]. Much of the knowledge of modern neurophysiology and psychology is not embedded in previous theoretical frameworks. Currently, it is recommended that we move away from intuitive purely motor rehabilitation strategies to knowledge-based selection of therapeutic regimes.

So, How Should We Work Neuroplasticity Post Injury in Hard-Wired Brain?

We can increase neuroplasticity by enriched environments, mental practice, attention and motivation, building trust and rapport, motivational interviewing, enhancing the client education process. Interventions that empower client’s therapeutic relationship with clinicians is essential. We should even shift further from the traditional neurological model (focused on intervention and neuroplasticity) to a neuropsychological perspective of a teacher concept. Therefore, XXI century definition of neuroplasticity includes the concept of...
neurotherapist. The later should guide the patient through the rehabilitation process [7].

We Can Obtain Positive Effects in Rehabilitation When CNS is Challenged and Engaged?

Multimodal factors that influence plasticity can be manipulated in clinical settings to help guide reorganization, such as attention (enhances stimulus driven plasticity via neuromodulator release), spatial patterning (determines the form of plasticity), temporal patterning (by long-term potentiation, LTP), and adequate duration of training. It has been demonstrated that LTP and neurogenesis are neural processes that are enhanced by enriched environments [8]. Engagement may increase activity in several cortical regions and networks, including the orbitofrontal regions facilitating neurorehabilitation (integrates information from sensory and motivational pathways to generate pleasure), ventral striatal dopaminergic systems (appetitive system, behavioral reinforcement), and the anterior cingulated cortex (supports attention to demanding tasks) [9]. In most of the hospitals, we have a limited time available for individual patient. Engagement principles require reconceptualizing "time" in rehabilitation to diminish feelings of not having enough time to complete interventions. Enriched environment is enriched interaction: LTP and neurogenesis are neural processes that are enhanced by enriched environments. Mental practise and motor imagery practice is recommended. Mental practice improves arm function post-stroke [10] and alters the cortical map post-stroke [11]. Actual movements and imagined movements may activate common neural substrates. In positron emission tomography (PET) studies, researchers found that imagining the letter "a" activates the primary visual cortex, much the same as if seeing the letter "a" [12]. Meditation practice is suggested to result in cortical thinning of the right insula, somatosensory, and inferior parietal lobule cortices [13].

Active participation is better than passive [14,15]. Passive tasks can contribute to inattentiveness and lead to decreased engagement [16], whereas increased attention increases cortical neuronal firing rates [17,18]. Attention means active participation-action, to a task at hand and will yield greater neuroplastic changes. The neurophysiological link between motivation and action lies in the connections of the hypothalamus and limbic system to the motor areas. Dopaminergic pathways are further important for behavior reinforcement [12].

Clinical interaction is a critical component of the therapeutic process. Any strategies to promote engagement and therapeutic relationship will help in better recovery. Our strategies should include those that build rapport and trust. We need to spend time with the patient, develop a deeper understanding of the patient beyond, carefully ask "what are your symptoms and signs", use a sense of humor, when appropriate, show compassion, empathy, and respect. We should use motivational interviewing, including use of reflective listening skills, understand the client's goals and aspirations. Patients educational process is of great importance is equally important. We should allow patient to be an active participant in education, use models, not just a brochure or handout, use appropriate language to convey information, encourage questions and take the time to answer them, explain how each intervention works toward the patient's and family goals. Empowerment strategies may encourage self-efficacy, provide choices in interventions and strategies when possible and use client-centered goals [7].

Increase functional neuroplasticity post stroke by:

- Engagement
- Mental practise and motor imagery
- Meditation practice
- Attention, motivation and action
- Neurotherapist build rapport and trust
- Empowerment strategies

Cognitive Rehabilitation after Stroke

Cerebrovascular dysfunction plays an important role both in vascular dementia (VaD) and Alzheimer dementia (AD). Stroke doubles the risk of dementia independently of demographic data or presence of vascular risk factors as was demonstrated from Framingham study [19]. Transient ischaemic attacks and silent infarcts may unmask neurodegenerative processes characterized by primary pathologies such as those found in AD. Vascular risk factors induce stroke, which increase risk of dementia up to 5-fold in the elderly. Poststroke VaD affects 30% of survivors, and the incidence of new-onset dementia increases from 7% 1 year after stroke to 48% after 25 years. Poststroke cognitive decline is more common than stroke recurrence: 6 months after stroke, 44% to 74% of patients present some degree of cognitive disturbance. Vascular Cognitive Impairment (VCI) with no dementia is twice as common as VaD. 50% of the patients with VCI develop dementia within 5 years [20]. All people after stroke should be screened for cognitive difficulties in attention, concentration, memory, perception, and other areas of cognition. Once a cognitive deficit is identified, carry out a detailed assessment using tools that are valid, reliable, and responsive before designing a treatment programme [21].

Interventions for memory and cognitive functions after stroke can include:

- Increasing awareness of the memory deficit
- Enhancing learning by means of errorless learning and elaborative techniques (making associations, use of mnemonics, internal strategies related to encoding information such as "preview, question, read, state, test")
- External aids (such as diaries, lists, calendars, and alarms)
- Environmental strategies (routines and environmental prompts).

How to Organize Successful Neurorehabilitation?

There are three major areas which should be covered: neurorehabilitation general aspects (Who?, How? and When?), -care settings (Where?) and -psychosocial reintegration (early discharge, rehabilitation institutions, social support). Rehabilitation programme, a process time-limited and goal-oriented, which aims to treat disability is essential for maximum functional capacity in each case, facilitate independence and reintegration into the family, social and work. Multidisciplinary team is essential and should include: rehabilitation specialist-physiotherapist, speech therapist, occupational therapy, neuropsychologist and social worker [22]. Basic principles underlying successful functional recovery are summarized in some controlled trials and show that the main factors affecting outcome are individual adaptation of therapy, the intensity and frequency of training [23]. Timing is of major issue and early rehabilitation post-stroke is essential. All patients should be evaluated in the first 24h after stroke.
In the ideal situation, rehabilitation specialist should see the patient as soon as multidisciplinary acute stroke team finished with acute stroke procedures, the diagnosis is established and secured control of vital status. This clearly is related with less immediate complications. It is well tolerated with no major adverse effects. It also provides less disability and better quality of life in the long term [24].

Stepwise (phase) model of rehabilitation is excellent to achieve these goals including immediately post-acute period. In the initial phases, patients with severe neurological deficits are treated with intensive care interventions available. Patients who do not require intensive care and cooperate with rehabilitation to some extent should be attended in different modules most suitable for their needs. Early mobilization phase should be linked to post hospital curative treatments, later followed by occupational reintegration, continuing measures to support, maintain, or improve function. The primary target group for rehabilitation should include patients with Barthel Index (BI) on discharge no higher than 65 points and patient must have lived independently at home before the stroke [25, 26]. Within stepwise phase model of successful rehabilitation continuity is equally important. Hospital rehabilitation services and community must be highly coordinated in each country to ensure rehabilitation program continuity, regardless of the location of patient. Coordination across different care settings must be provided to avoid fragmenting the rehabilitation program, avoid areas unsuitable and no unnecessary treatments restart. The intensity of the rehabilitation treatment should be the maximum that the patient can tolerate and is willing to follow. High intensity improves functional outcome [27], there is less disability at discharge and shorter hospital stay [28] and average better independence and ability to walk at 6 months [29]. Minimum sessions of at least 45 minutes of each relevant stroke rehabilitation therapy for a minimum of five days a week to people who are able to participate, and where functional goals can be achieved are recommended by some guidelines [21]. Duration of the rehabilitation is an open issue. Rehabilitation treatment must cease when new functional targets are not identified or when the patient does not want to continue. During the 1st year (if objective is a functional state) disability improves [30]. However, after the first 6 months of stroke, in the patients with activity limitation, further rehabilitation should be assessed with clearly planned objectives. Routine rehabilitation programs beyond one year evolution are generally ineffective [31]. In the chronic phase, however, patients must have access to rehabilitation services to review long-term needs, treat spasticity and pain. Patient should be periodically evaluated in order to measure the deficit, establish limitation of disability, plan discharge destination and evaluate the quality of life. Commonly used are activity limitation scales, valid, reliable and broad consensus as the BI. Besides the functional global scales, it is recommended to use outcome measures, ADL including implemented and advanced mobility (gait, balance, etc.).

Patients and their caregivers must have early and active involvement in the process rehabilitation. It is recommended to establish programs of systematic education and training for patients and families at the early phase post stroke. In our centre, it is organized every two weeks for families of all inpatients. This leads to less institutionalization. Further, specific training for caregivers lowers cost and burden of care, gives a better quality of life for patients and caregivers at one year after stroke [32]. Requirement of appropriate level of care settings should be established by rehabilitation specialist physician for all patients who have had a stroke. Type of patient, intensity and type of therapy, necessity of medical/nursery attention and family and social support should be evaluated [33].

Patients with acute stroke admitted to a stroke unit should receive coordinated multidisciplinary rehabilitation. There is a major survival and minor dependency by combined acute attention and rehabilitation [24, 34] in patients attended within acute neurological units. Rehabilitation intensive care units are of interest with a short stay (3-4 weeks) and high intensity (more than 3 hours/day). These units should include multidisciplinary team, adequate technology, and early hospital discharge (patient selection for community, social and medical support) [35]. They should be limited to patients with first acute stroke, prior independent for ADL, require hospitalization, with moderate-to-severe discapacity in ≥2 functional areas (mobility, ADL, swallowing, communication, etc.), medical and cognitive capacity to follow therapy. Less severed patients with minor strokes may benefit with low intensity rehabilitation unit prior to discharge.

Outpatient rehabilitation and Day Hospital should be limited to patients with low-to-moderate discapacity in stable phase within the first year. From the first year after stroke, focal functional impairment, can be derived to outpatient rehabilitation services and raise short-term treatment. It requires necessary family/social support, patient medical and cognitive capacity to follow therapy. Above should apply to home rehabilitation with specific therapeutic program coordinated by rehabilitation.

Community reinserction and early hospital discharge programs are effective in mild to moderate stroke (less dependence and institutionalization on follow-up. They should include discharge planning (medical needs, rehabilitation, social), optimal treatment pre discharge rating, social support: evaluation of moderating impact of disability on quality of life of stroke patients and better social support for moderate/severe strokes. Other aspects should be covered like limiting participation in working life, occupational and recreational possibilities, driving vehicles, adapted transport access and contact with patients associations [36].

Patients selection for intensive rehabilitation:
- prior independent for ADL
- require hospitalization
- moderate-to-severe discapacity in ≥2 functional areas
- medical and cognitive capacity to follow therapy

Modular Approach (Therapies)

The treatment time available for an individual patient is limited because of economic constraints in many countries. Therefore modular design helps to ensure that every patient is exposed to a variety of treatment approaches. Based on patient’s evolution and response to each module this approach should be more or less flexible.

Milestones of successful rehabilitation care programs:
- early rehabilitation
- intensity
- care units
- coordination
- multidisciplinary team
- patients and caregivers technology
New Therapies of Brain Damage

Motor training for upper and lower extremity

They include biological, pharmacological, nanomolecules, electrostimulation and intensive physiotherapy. In XXI modern medicine any of the new approaches should be tested and reach level of scientific evidence. However, when it comes to rehabilitation direct application of evidence-based medicine (EBM) roles is a real challenge. Indeed, EBM was invented and validated for pharmacological interventions. This is why only some rehabilitation procedures are recommended based on classical EBM recommendations. Motor therapeutic techniques with higher levels of evidence include: treadmill training with partial body weight support (Ib), constraint-induced movement therapy (“forced use”) (Ib), functional electrical stimulation (Ib), “robot assisted training” upper extremity (Ib), rhythmic acoustic stimulation (II), mental imagery: observation and imagination (II), acupuncture as adjunct treatment (pain and spasticity) (Ia), modulation of sensory inputs e.g., plexus anesthesia (II), transcutaneous electrical nerve stimulation (II) [4].

Levels of evidence:
I a) Meta-analysis of RCTs
I b) At least 1 RCT
II a) At least 1 controlled study – no randomization
II b) At least 1 other type of good experimental study
III) Good descriptive nonexperimental studies (comparative, correlation, case)
IV) Experts’ reports, authoritative opinions

There are important advances in knowledge about ‘motor learning’ [4]. In near future, it will help to design effective approaches to patients after stroke based on current findings of modern neurophysiology. One of the most important findings from animal experimental studies that is likely to have considerable influence on motor therapies was the discovery of so-called “mirror neurons” in the monkey prefrontal cortex [37]. These groups of neurons are active even when animal is not moving but is observing the experimenter moving in a similar way to a target. The “mirror neuron system” is also active in normal humans when similar motor observation tasks are applied [38] and can also be activated in patients [39]. In humans, it corresponds to Brodman’s area 44, Broca’s speech area, suggesting the “mirror neuron system” may also be involved in the acquisition of language by understanding motor acts as semantic gestures. Further, human studies have also shown that motor learning is possible by pure imagination. This is supported by the fact that the same brain areas in parietal and premotor cortical areas are active both during active performance and during imagination of the same movements [40]. Motor learning by imagery may be effective in optimizing motor activities in normal subjects [41], but also in patients with neurological disorders as demonstrated by an increasing number of studies [42-45]. The so-called “mirror therapy” is another example of motor therapy based on learning by imagination and imitation [46]. Above have direct implications in upper extremity rehabilitation. Repetitive training of goal-directed active movements for 60 minutes/day over 2 weeks resulted in an improvement of reaching function in patients with chronic hemiparesis [4]. In subacute stroke patients repetitive sensory motor stimulation applied in the form of self-initiated training 30 minutes daily for 6 weeks resulted in long-term improvements of arm function, especially in more affected patients [47]. Mirror therapy has been successful in several studies. It was shown that mirror therapy applied for 25 minutes 6 days a week for 4 weeks in chronic stroke patients with mild to severe hemiparesis resulted in improved movement abilities of the arm [48]. In subacute to chronic stroke patients with severe to moderate hemiparesis, mirror training for wrist and finger extension/flexion movements for 30 minutes daily over 4 weeks, in addition to conventional treatment, resulted in more improvement compared to a control group with similar intensive training without a mirror [49]. Similar principle applies to mental training when patient is not practicing active movements but is trying to perform movements by mental imagery. Further movement observation may be beneficial in some patients [50].

Another type of training involve impairment-oriented training (IOT) and can be subdivided into arm ability training for patients with mild to moderate paresis and arm basis training (ABT) for patients with severe paresis. In ABT movement-related brain activity is differentially altered in patients with different impairments. The IOT concept intends to characterise the resulting sensorimotor control deficits for each impairment (paresis, apraxia or somatosensory deficits). Specificity of active training seemed more important for motor recovery than intensity (therapy time). The comprehensive modular IOT approach promoted motor recovery in patients with either severe or mild arm paresis [51].

Additional task-oriented therapy in comparison to additional force training was used in moderately affected subacute stroke patients and resulted in better improvement compared to standard therapy alone [4]. In a recent clinical trial neurorehabilitation therapy included task-oriented training with an exoskeleton robot that can enhance improvement of motor function in a chronically impaired paretic arm after stroke more effectively than conventional therapy. However, the absolute difference between effects of robotic and conventional therapy in this study was small and of weak significance, which leaves the clinical relevance in question [52]. In patients with residual arm function but still severe functional impairments (i.e., moderate paresis), treatment with constraint-induced movement therapy (CIMT) should be strongly considered [4]. Human and animal studies using a variety of methods provide evidence that CIMT therapy produces marked neuroplastic changes in the structure and function of the CNS. Moreover, these changes appear to be important for the intervention’s therapeutic effect [53]. Constraint-Induced Movement Therapy (CIMT) is an evidence-based rehabilitation intervention for stroke. Functional electrical stimulation” (FES) is reserved for electrical stimulations embedded into a functional movement context, for instance lifting up the foot in a patient with central foot drop at the beginning of the swing phase of the gait cycle. In patients with severe paresis, cyclical electrical stimulation with or without EMG triggers may be a useful way to facilitate movement. EMG alone has no evidence, acupuncture can be used only for pain and spasticity. In the future it may be possible to embed electrical stimulation into daily activities. For neuromodulation it has been shown in a randomized controlled study that anodal transcranial direct current stimulation (tDCS) applied over the affected hemisphere improves motor function in chronic stroke patients [54,55]. It appears that more severely affected patients receive a bigger benefit than moderately affected patients. Repetitive transcranial magnetic stimulation (rTMS) is a promising technique for promoting rehabilitation of arm function after stroke. The feasibility and impact of rTMS as an adjunct to traditional task-oriented training to improve arm function have not...
yet been demonstrated. Preliminary evidence suggests that an rTMS protocol potent enough to induce transient increases in cortical excitability of the lesioned hemisphere is feasible but did not show promising results as an adjunct to task-specific training [56].

There is more evidence for upper extremity. Arm movements are discrete, goal-directed, and under cortical control. Recommended procedures for upper extremity include: repetitive training, impairment-oriented training (IOT), task-oriented training, constraint-induced movement therapy, mirror neurons and therapy, mental training, movement observation, neuromuscular electrical stimulation, functional electrical stimulation, electromyographic (EMG) biofeedback, and acupuncture.

Leg movements usually are rhythmic, not really goal-directed (except for football players), and are primarily under subcortical control by spinal and supraspinal pattern generators. Early rehabilitation of lower extremity includes rehabilitation of walking. This usually starts with initial out of bed verticalization. Patients who have had a stroke should be mobilized as soon as possible. The rehabilitation of walking includes the bedridden patient is mobilized out of bed, followed by the patient, having been mobilized into a wheelchair, learns to walk again. Further, the patient, having regained the ability to walk, learns to do so rapidly and steadily, also under the prevailing conditions of everyday life. New systems enable early verticalization of the patient and an early start of gait training, with a continuous transition from mainly robot-initiated to increasingly independent movement. Early out of bed verticalization should adopt to individual patient tolerance but is essential in circulatory training, prevention of pneumonia and venous thrombosis, stimulation of the autonomic nervous system and sensory activation through standing. Treadmill training with partial body-weight support is used for lower extremity recovery. Treadmill training is different from conventional gait training in the sense that it induces locomotor activity biomechanically and does not require the patient to initiate locomotion "voluntarily." This (treadmill) treatment originated from studies of patients with incomplete spinal cord injury and is commonly used for locomotor retraining, at least in an early phase after stroke and in incomplete paraplegia. Rhythmic acoustic stimulation (RAS) is another therapeutic principle used in lower extremity rehabilitation. RAS, a repetitive rhythmical sensory (mostly auditory) signal can facilitate rhythmic movements. Neuroimaging studies have recently shown that clearly defined parietal, frontal, and cerebellar areas are involved in the processing of rhythmicity [4,57].

Upper and lower extremity motor recovery:

- repetitive training
- mirror therapy
- impairment-oriented training (IOT)
- task-oriented therapy
- constraint-induced movement therapy (CIMT)
- mental training and movement observation
- functional electrical stimulation
- neuro modulation
- treadmill training and rhythmic acoustic stimulation (RAS) for lower extremity

Robotics and Other Electronic Prosthetics

The last 100 years of rehabilitation therapy practice and research have delivered few actual answers to ameliorate and maximize favorable outcomes in stroke survivors. In the last 30 years, the contingent of seniors in many countries is expected to double. Mechanical devices equipped with motors should be on national roadmap [58]. Rehabilitation robotics are tools to assist the clinician in promoting rehabilitation of an individual so that he or she can interact with the environment unassisted [59]. A variety of therapy “robots” exist at the moment which can be subdivided according to technical criteria, e.g., “exoskeleton robots” versus “end-point robots.” Many of these devices may be programmed to sense the force exerted by the patient in order to provide additional support according to the patient’s motor ability. Examples of end-effector device are G-E-O-System, the Lokohelp, the Haptic Walker and the Gait Trainer GT1. In end-effector device patient’s feet are placed on foot-plates, whose trajectories simulate the stance and swing phases during gait training. Examples of the exoskeleton device are the LOPES and the Lokomat. Such exoskeletons are outfitted with programmable drives or passive elements, which move the knees and hips during the phases of gait. Among the most know orthotics, passive or powered external devices for the neck, upper limb, trunk, and lower limb that are designed to guide motion, bear weight, align body structures, protect joints, or correct deformities are Myomo e100, which employs a surface EMG system to command its electrical actuator to flex or extend the elbow [60], or the Tybion, which measures forces to command movement at the knee and ARGO, a gait orthotics involves powered exoskeletons. Examples of other rehabilitation robots are: (A) The Lokomat TM (Hocoma, Switzerland), which is an exoskeletal robot to manipulate patient’s hip and knee. (B) The Gait Trainer I and (C) the G-E-O System (Reha-Stim, Germany), which are end-effector robots that manipulate the patient’s foot. (D) The BimanuTrack for bimanual training of wrist and forearm (Reha-Stim, Germany). (E) Osaka University’s shoulder and elbow robot (Asahi Chemical Industry) and (F) the Amadeo to manipulate the individual fingers (Tyromotion, Austria).

The use of robots to enhance motor recovery is an area of very active research. Mechanical devices have also been used for the lower extremity such as the exoskeleton based LocomatTM [61] or the electromechanical gait trainer GTITM [62]. Studies have shown that gait supporting devices can be effective also in comparison to classical physiotherapy, including patients not yet able to walk after stroke. The results demonstrated small but statistically significant improvements due to robot- assisted therapy, even when compared like-for-like with conventional therapy in stroke [63,64]. American Heart Association” recommends: "Robot-assisted therapy offers the amount of motor practice needed to relearn motor skills with less therapist assistance. Most robots for motor rehabilitation not only allow for robot assistance in movement initiation and guidance but also provide accurate feedback; some robots additionally provide movement resistance. Most trials of robot-assisted motor rehabilitation concern the upper extremity (UE), with robotics for the lower extremity (LE) still in its infancy. Robot-assisted UE therapy, however, can improve motor function during the inpatient period after stroke." The AHA suggested that robot-assisted therapy for the upper extremity has already achieved Class I, Level of Evidence A for Stroke Care in the Outpatient Setting and Care in Chronic Care Settings. It suggested that robot-assisted therapy for the lower extremity has achieved Class IIa, Level of Evidence A for Stroke Care in the Inpatient Setting [34,65]. In a recent clinical trial robot-assisted group therapy (RAGT) in combination with individual arm therapy (IAT) was equally effective.
as a double session of IAT regarding the restoration of upper limb motor functions in moderate to severely affected subacute patients with stroke. The treatment costs for RAGT were less [66].

The latest revolution in future neurorehabilitation is field of neural prosthetics. This type of research has seen rapid progress, two examples of which are the development of brain–machine interfaces (BMIs) that enable patients to control assistive devices—such as robotic limbs—by using neural signals recorded directly from the brain, and the use of functional electrical stimulation (FES) to reanimate paralysed limbs. Brain–machine interfaces (BMIs) that record and decode signals from the brain in real-time enable volitional control of assistive devices, and modify patterns of cortical activity through the process of neurofeedback. First, neurofeedback will shape patterns of volitional brain activity as users learn how to exploit the prosthesis more efficiently. Feedback could involve residual sensory modalities such as vision, or perhaps include artificial sensory pathways provided by electrical stimulation. Second, repetitive stimulation might induce long-term changes that increase the excitability of spinal circuitry and enhance the efficacy with which movements can be evoked. Third, co-activation of the brain and spinal cord may strengthen surviving connections between the two sites through Hebbian mechanisms. The later can be summarized in statement: cells that fire together wire together. Importantly, these three changes are complementary in acting to potentiate precisely the same sensorimotor loop that is augmented by the prosthesis. The concept is highly based on repetitive training again and Hebbian plasticity for CNS. Thus, co-activation of the brain and spinal cord may strengthen surviving connections between the two sites. Remodelling of such surviving pathways and their spinal targets may help to support some functional recovery [67].

Key points to manipulate plasticity by neural prosthetics:
- brain–machine interfaces (BMIs)
- functional electrical stimulation (FES)
- neuromodulatory stimulation
- the importance of encouraging volitional supraspinal activity in combination with electrical stimulation
- reduction in chronic pain and spasticity

**Indicators of Effective Neurorehabilitation**

There number of established indicators and outcome measures to evaluate patients impairments, functional activity limitations (disabilities), and restriction in participation. Diagnosis, functional activity score on admission, and length of stay are significant predictors of function. Systematic collection, analysis, and interpretation of standardised clinical outcomes data are feasible within routine clinical practice, and provide evidence that inpatient rehabilitation is effective in improving functional level in neurologically impaired patients. Patient are scored prior to current event and on daily or weekly base, at discharge, 3 months after index event and on year follow-up. Limitations in functional activities of daily living are measured by the widely used Barthel Index (BI) and Functional Independence Measure (FIM). Both have proved psychometric properties of reliability, validity, and responsiveness within this and similar rehabilitation settings. Neurological outcome is measured by NIH Stroke Scale. Patient’s perception of rehabilitation are scored by visual analogue scales (VAS) at the end of the first week of admission and within 24 hours prior to discharge. In addition, in partnership with the patient, the team defines measurable short and long term goals that are regularly monitored by the team throughout the inpatient stay. VAS ratings are collected for the main problem as identified by the patient on admission and the benefit gained from inpatient rehabilitation. These are self-rated by patients in the presence of their keyworkers. VAS is commonly used in routine clinical practice [68].

Other indices may be used for more detailed purpose or for clinical trial approach. Studies on sensory-motor performance have identified a multitude of indices to quantify smoothness and coordination for investigating the effect of age, disease, or therapeutic intervention. Feasible measures proposed in the literature on neurorehabilitation of the upper limb to characterize movement smoothness, movement accuracy, and tracking rapidity are: (i) the speed metric (SM), calculated as the mean of the speed divided by the peak speed (between zero and one); (ii) the number of submovements (NSM), obtained by segmenting the movement on the basis of local maxima of the speed exceeding a set threshold value (iii) the deviation (D), defined as the ratio of the area between the actual and the target path and the actual path length (expressed in pixels) (iv) the normalized path length (NPL), defined as the ratio of the actual and the desired path; and (v) the time duration of the trial (T) (expressed in seconds). SM and NSM are selected to measure the movement smoothness (low values of SM and NSM indicate smooth movements); D and NPL are used to quantify the movement accuracy (low values of D indicate accurate movements and low values of NPL identify a nearly rectilinear trajectory from the start to the end points); and T is utilized to measure the tracking speed (low values of T represent rapidly executed tasks). The onset and the termination of a movement were detected by processing the hand speed off-line and a threshold value of 0.05 m/s (1.97 in/s) was used to partition the individual trajectory of a participant in submovements. The indices are computed over a time window starting with the cursor departing from the start point and ending when reaching the final target [69]. Sensory loss is common after stroke, with negative impact on exploration of the immediate environment, hand function, and return to daily activities. To measure the effectiveness of a perceptual-learning based sensory discrimination program composite standardized somatosensory deficit (SSD) index can be useful in rehabilitation of sensory deficits after stroke [70]. Although above mentioned scores have recognised limitations there is evidence that they provide clinically useful information and have reasonable psychometric properties in a range of settings.

**Neuroimaging for Neurorehabilitation Outcome**

Another important issue for the future will be to exploit longitudinal non-invasive functional and morphological imaging to help us select proper treatment strategies in particular patients. Key to understanding the role of advanced neuroimaging analysis techniques is that lesions/abnormalities evolve over time post-onset of stroke in the patient. Therefore, the type of scan performed, its sensitivities for detecting abnormalities, and time post-onset, all become critical variables in understanding the relevance of neuroimaging findings to neurorehabilitation outcome. Techniques used include noninvasive functional and morphological imaging by quantitative MRI analyses, diffusion tensor imaging (DTI) and functional MRI to better understand the neurologically impaired patient. DTI, has already permitted a specific analysis of actual tracts in the living brain. Resting state fMRI (rs-fMRI) provides a tool to examine a harmonic of the blood oxygen-dependent level (BOLD). MRI signal with the
assumption that, at rest, connected regions would exhibit the same harmonic. This provides the framework to establish functional connectivity (fc) maps from rs-fMRI. This enables follow on imaging how these functional networks are being reorganized after lesion [71].

Pharmacological interventions in neurorehabilitation, citicoline after stroke

Lipids are known to play an important role in brain injury and neurological diseases; they are involved in cell signalling and tissue physiology, and alterations in lipid metabolism play an integral role in neuronal death in cerebral ischemia [72,73]. Citicoline, a drug with an effect on phospholipid metabolism in the brain and on some neurotransmitters, has proven neuroprotective and neurorestorative properties in brain ischemia [74]. Citicoline is a drug with several effects at different levels of the ischemic cascade, with actions also promoting neuroplasticity [75].

Hurtado et al. [76] studied the effect of chronic treatment with citicoline on functional outcome and neuromorphological changes after stroke. Treatment with citicoline, started 24 hours after the middle cerebral artery occlusion (MCAO) and maintained during 28 days, improved the functional outcome in both the staircase test and the elevated body swing test. In addition, the animals treated with CDP-choline showed enhanced dendritic complexity and spine density compared with the saline-treated group. Their results suggest that chronic treatment with CDP-choline started 24 hours after the insult is able to increase the neuronal plasticity within uninjured and functionally connected brain regions as well as to promote functional recovery.

Bramanti et al. [77] studied the effects of acetylcholine and the cholinergic precursors choline, citicoline and alpha-glycerophosphorylcholine on transglutaminase and cyclin D1 expression in primary astrocyte cultures by confocal laser microscopy with monodansyl-cadaverine uptake as a marker of enzyme activity and by immunocytochemistry (Western blotting). The authors conclude that the administration of these kinds of compounds may also be considered therapeutically very useful and particularly effective in the recovery from some important neurological diseases, such as stroke.

One of the consequences of brain ischemia is the development of white matter lesions in the brain that are correlated with cognitive impairment. Thus, Lee et al. [78] demonstrated that citicoline can prevent white matter damage and aid cognitive improvement, even after a certain extent of disease progression.

Gutiérrez et al. [79] reported that citicoline and mesenchymal stem cell administration have the same efficacy for neurological recovery, decreasing neuronal death and increasing brain repair, but the combination does not increase the benefit. A similar proangiogenic effect has been described by Krupinski et al. [80]. Diederich et al. [81] demonstrated that citicoline also possesses a substantial neuroregenerative potential. Thanks to its multimodal effects, easy applicability, and history as a well-tolerated drug, promising possibilities of neurological treatment including chronic stroke open up.

Taking into account that citicoline has been extensively investigated in studies in healthy volunteers and patients that have shown it is a well tolerated and safe drug [74]; all such results may have important implications for the management of stroke patients because they could enhance therapeutic options for rehabilitation and reduce suffering.

Citicoline might be useful in patients with acute ischemic stroke as well as in chronic stroke associated with cognitive impairment.

Citicoline has been studied in several patients with various neurological diseases without safety concerns [74]. The efficacy in the treatment of acute stroke has been shown by a pooled-data analysis of patients with acute ischemic stroke [82] and by a study-based meta-analysis [83]. Similar effects have been demonstrated in traumatic brain injury [84].

It has also been reported that treatment with citicoline improves functional recovery in humans with acute ischemic stroke through an increment in circulating endothelial progenitor cells, an effect that has been related to the neuroreparative properties of the compound [85].

Also, in a Cochrane review [86], the positive effects of citicoline on the cognitive and behavioural disturbances associated with chronic cerebral disorders, especially ischemic disorders, in the elderly have been demonstrated.

Regarding the effects of citicoline on the cognitive consequences of an ischemic stroke, Álvarez-Sabín et al. [87] reported that citicoline treatment in patients with a first ischemic stroke event treated for a 12-month period is safe and effective in improving neurocognitive impairment; they explain such an effect by the neuroreparative properties of citicoline and its effects on the cholinergic system.

Regarding the effects of citicoline on the motor deficits after stroke there are 2 studies on the effects of the drug on functional recovery of hemiplegia [88,89], suggesting that citicoline promotes natural recovery in hemiplegic patients, specially in upper limbs. The meta-analysis of these two studies [75], ratified the efficacy of the treatment with citicoline (1g/d/8 weeks) on the improvement of at least one degree in the Hemiplegia Function Test in upper limbs (OR = 1.863; 95% CI = 1.218-2.851; p = 0.004), whereas the effect is not significant in lower limbs (OR = 1.036; 95% CI = 0.681-1.563; p = 0.864).

Irmankanesh and Vakilian [90] carried out a double-blind, placebo-controlled and randomized clinical trial with 32 patients with non-traumatic cerebral hemorrhage, showing that muscular strength in patients with cerebral hemorrhage receiving citicoline increased, and they suggested that citicoline may be effective in the treatment of patients with cerebral hemorrhage.

Based on the reported data, we can conclude that there is some degree of evidence suggesting a possible positive coadyuvant effect of citicoline in the rehabilitation phase of patients with stroke [91].

Conclusions

Over the last years we have seen progress in the scientific evaluation of neurorehabilitation treatments, which is reflected in the increasing number of randomized controlled trials. However, it is essential to keep in mind that direct application of clinical trial rules, initially designed for drug evaluation, may be complicated in the field of neurorehabilitation. In many instances the correct approach should be a non fixed ‘cook-book’ procedure giving some freedom to patients and their families to engage in the process. A primary goal of neurorehabilitation is to guide recovery of functional skills after injury and enhance neuroplasticity. Initial planning, discussion of the objectives and modular approach is essential. Rigid rules of evidence-based medicine should be sometimes removed and the patient allowed to use different devices and techniques if these are particular preferences. The future challenge is to focus on the multitude of
variables that may influence functional outcome, and to determine the interaction or independence among these variables and their actual impact on outcomes. Ultimately the goal should be to determine how to best tailor the treatment protocol to meet each individual patient’s needs. Sufficient training given to the multidisciplinary team, family, and carers on the particular needs of an individual with stroke and ways to support the person would also facilitate the rehabilitation processes since these needs are often poorly addressed. Mechanical assistive devices (robots) and techniques based on motor learning by observation and imitation followed by longitudinal noninvasive functional and morphological imaging are hot spots of modern rehabilitation. In many clinical trials scales used to evaluate robots failed to adequately reflect patients recovery. Further, substantial challenges remain for the development of neural prostheses as tools to promote neurorehabilitation could, therefore, have more-general applications in restoration of function after stroke. Finally, the regenerative potential of the human brain is probably preserved far beyond what we initially thought. It has recently been shown that the human brain can respond to stroke with increased progenitor proliferation in aged patients opening the possibilities to utilize this intrinsic attempt for neuroregeneration of the human brain as a potential pharmacological therapy for stroke.

References


