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How to gain evidence in neurorehabilitation: a personal view

Abstract: Neurorehabilitation is an emerging field driven by developments in neuroscience and biomedical engineering. Most patients that require neurorehabilitation have had a stroke, but other diseases of the brain, spinal cord, or nerves can also be alleviated. Modern therapies in neurorehabilitation focus on reducing impairment and improving function in daily life. As compared with acute care medicine, the clinical evidence for most neurorehabilitative treatments (modern or conventional) is sparse. Clinical trials support constraint-induced movement therapy for the arm and aerobic treadmill training for walking, both high-intensity interventions requiring therapist time (i.e., cost) and patient motivation. Promising approaches for the future include robotic training, telerehabilitation at the patient's home, and supportive therapies that promote motivation and compliance. It is argued that a better understanding of the neuroscience of recovery together with results from small-scale and well-focused clinical experiments are necessary to design optimal interventions for specific target groups of patients.

Keywords: learning; recovery; rehabilitation; robotics; stroke.

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Introduction

In the conventional view, rehabilitation starts when and where acute care medicine has left the patient with a disability. The aim of rehabilitation is to reintegrate the patient into his or her professional life, social life, and home environment. This aim can be achieved by different approaches: by providing assistive devices, making adjustments to life or home, or by reducing individual impairments. Neurorehabilitation treats patients with brain disorders – most often stroke because it is frequent and usually has neurological sequelae. After a stroke, a patient typically recovers unless another stroke interferes. This is in contrast to diseases with a slowly progressive (e.g., Parkinson disease) or undulating time course (e.g., multiple sclerosis). Recovery from stroke is a slow process, lasting months or years.

If one aims at fast reintegration and wants to minimize rehabilitation costs, assisting (nursing), modifying the environment, or training the patient to compensate for disability (e.g., training to eat or dress with the good arm when the other one is impaired) is often chosen. This leaves the patient with an impairment that reduces his or her quality of life (QoL). Also, cost reduction is short sighted – in the long-run, functional impairments put the patient at a higher risk for complications that may cost much more then the rehabilitation up front.

Modern neurorehabilitation aims at reducing impairments and gaining function. This requires time and training of sufficient intensity [25, 51, 55, 62]. If performed intensely, most treatments that involve active training provide similar benefits across groups [26, 50, 54, 57]. However, the response of individual patients varies largely. Little is known about the factors that determine therapy response. Although small-scale studies show the effects of a lesion's location, side, or the timing of therapy relative to the stroke [27], larger trials are necessary to confirm these findings.

Although many decisions in acute care medicine can be based on scientifically sound evidence from clinical trials, only few trials exist for stroke rehabilitation. Those that are available were conducted in small patient groups, with only a few hundred subjects at most [29]. This level of evidence compares poorly with trials testing, for example, the use of thrombolysis for acute stroke. These trials recruited several hundreds to thousands of patients [15, 44].

This article does not aim at providing a complete overview of stroke rehabilitation but formulates an opinion about how the field can develop in the coming years.

Evidence of benefit

Training interventions without technical assistance

Despite these difficulties, there is sufficient evidence to assume that a few treatments are effective. Two examples are constraint-induced movement therapy (CIMT) and aerobic treadmill exercise. CIMT is based on the neuroscientific observation that immobility leads to functional deficits [53]. If a stroke survivor does not use the arm due to weakness, the arm will deteriorate further. Therefore, CIMT forces stroke survivors to use the weak arm by immobilizing the intact arm. This, of course, only works if the subjects have good residual arm function. If one cannot move the arm at all, immobilizing the other arm will be frustrating. In addition, CIMT includes an intensive (usually 2 h/day) physical therapy protocol that trains movements by reinforcing goal-directed behavior in a stepwise fashion (shaping). The latter component – or the fact that it is delivered in an intensity higher than standard physical therapy protocols – may be more important than immobilization itself [3]. CIMT has been shown to be more effective in reducing impairment and improving arm function than standard rehabilitation protocols [49, 60]. However, one must consider that comparing an intervention to “standard rehabilitation” carries the disadvantage of poor generalizability because the “standard” greatly differs among institutions, countries, and continents. Also, the standard is often insufficiently described in study reports to arrive at generalizable conclusions.

Another form of effective motor therapy is treadmill training. Walking on a treadmill is a task-oriented, highly repetitive form of training that carries over to better walking over ground [18]. Treadmill training with body weight support can be performed early after the stroke and seems to be equally effective as a home-based physical therapy program [9]. Treadmill training works by inducing changes in brain activation related to knee movement [31], an indication of reorganization within CNS circuits. It also changes the composition of skeletal muscle, thereby potentially improving insulin resistance and type II diabetes [16, 22]. If performed at a sufficient intensity to increase heart rate, aerobic treadmill training also has a conditioning effect, thereby improving cardiorespiratory fitness even in patients with very low fitness levels [13, 31, 32]. Thus, this form of training serves several objectives: it not only trains walking but equips the patients with better fitness to effectively walk in daily life and reduces diabetes as a major risk factor for future strokes [14].

Training interventions with technical assistance

Neurorehabilitation engineering is an expanding field and has produced many interesting devices to aid rehabilitative training. However, few have been tested in larger groups of patients. Weight-supported treadmill training uses a harness to reduce the body weight while the patient walks on a treadmill [18]. Several clinical trials were conducted after stroke; a Cochrane meta-analysis of trials shows no superiority of weight-supported treadmill over other gait interventions, although individual trails have suggested added benefits [38]. Results in patients after spinal cord injury are conflicting because studies are too heterogeneous to be compared [7, 30]. The widespread use of these interventions remains disputed [6].

Promising technical developments

Sensors and monitoring

Neurorehabilitation science needs to improve its methods, specifically, how to optimally and reliably measure therapy effects. First, researchers have to agree on the purpose of therapy. The international classification of function proposes a trichotomy of therapy goals: (1) to reduce impairment, (2) to regain functional use, (3) to enable participation in life. From 1 to 3, these objectives become more difficult to achieve because a multitude of cofactors intervene. If an impairment, e.g., spasticity is reduced, it does not necessarily mean that the patient can use the arm to eat. If the patient is trained to use the fork with the weak arm, it does not mean that she/he will actually do so in daily life, i.e., participate. It will be interesting to measure the effects of therapy on participation. Participation is difficult to measure because it requires patient monitoring in the natural environment (home, work, etc.). Sensor technologies measuring location, acceleration, rotation, altitude, heart rate, muscle activity, interaction forces, etc. combined with storage and analytical capabilities may be able to deliver this information. Simple accelerometry is useful for activity monitoring in stroke survivors [12]. Combining accelerometers and gyroscopes can classify activities at least into broad categories of standing, sitting, lying, and walking [23, 58]. Gait and balance can be monitored using accelerometry sensors on the pelvis [63] or inertial sensors and force sensors in the shoes [34, 35]. For the upper extremity, sensing of reaching movements have been performed using textile-integrated sensing systems [55]. These data can then be used to optimize a therapy for the individual patient.

Robots

Robotic devices have originally been developed to assist physical and occupational therapists in movement training [19], and highly repetitive training like walking on a treadmill with the therapist moving the weak leg is facilitated by a robot. However, theoretically, robots can do more. By precisely monitoring the patient's movement, they can interfere with it at the right time and place. This robot-human interaction can be in the form of assistance, that is, to complete a movement that the patient cannot fully perform. Assistance or guidance has been shown to improve motor skill acquisition [33] but may also impair the acquisition of tasks that highly depend on error-based learning [8, 59]. The devices include end-effector-based robotic manipulanda [24, 28] or exoskeletons [39]. The assist-as-needed robotic training has been tested in a clinical trial and has not been found to be superior to conventional physical therapy [29]. In spinal cord injury, the efficacy of assist-as-needed training has been suggested by animal models [4] and human studies [1, 52]. Robot-human interaction can also mean that the robot perturbs the patients movement, e.g., by applying a force that deviates from the desired movement path [40, 48]. Because perturbation renders a movement more difficult, it delivers a stronger learning stimulus that may support recovery [36, 41]. Both elements of robotic training, assistance and perturbation, have not been fully tested in humans after stroke. Based on motor learning theory, one would expect more benefit from perturbation than from assistance [21].

Another element of robotic arm therapy is proximal support. Proximal support of the arm facilitates distal movements [10]. This concept – part of the Brunnstrom stages of motor recovery – has been successfully integrated into robotic training. Stepwise loading of the arm proximally helps to increase the range of motion across the elbow [10]. The range of motion increases the work area of the arm, thereby helping to overcome thresholds necessary for daily life tasks [42].

Another element of robotic training is to stimulate strength and muscle force. Strength training is beneficial for motor recovery after stroke [17]. Although simpler, non-robotic devices are available to enable muscle training, robots may be specifically useful for the integration of strength into task-oriented training.

Rehabilitation at home

Training can be more efficient if delivered at a high intensity (long duration and greater complexity of motor exercises) as long as it is not limited by motivation or fatigue [2, 25, 61]. High-intensity training is costly and often not feasible because the patient needs be admitted as inpatient or is required to travel to a rehabilitation center frequently for outpatient training. Therefore, new approaches to rehabilitation at home are needed. Training at home by a rehabilitation therapist is often practiced and useful [51, 62]. Computer-assisted gaming can provide assistance, supervision, and motivational feedback to enable effective training at home. Commercially available products have been used and found feasible and safe for stroke survivors at home [11, 45]. Even video-based training has been proposed [43]. The potential problems are the price of the equipment, malcompliance, poor ergonomics of use, and the lack of immediate expert feedback if training is conducted in the wrong way. Depending on the system and on the focus of rehabilitation (e.g., arm, leg), the patient's home needs to fulfill certain requirements (e.g., minimum space, Internet connection). However, modern computer technology provides low-cost and high-quality equipment to render home rehabilitation a realistic option for the future.

Motivational therapy

Motivation is a prerequisite to successful therapy. Therapists need to engage and motivate the patient to be successful. One factor that stimulates motivation is positive feedback and reward. Reward is in part encoded within the dopaminergic networks of basal brain regions, such as substantia nigra and ventral tegmental area [47]. These regions also send projections to the primary motor cortex where dopamine supports the acquisition of a motor skill as well as the formation of synaptic plasticity, that is, a cellular mechanism of learning [20, 37]. It is therefore likely that reward signals are directly fed into motor cortex networks to support learning. It remains to be shown that the effects of specific rehabilitative training can be augmented by emphasizing rewards or by medications that facilitate dopamine actions. Preliminary evidence suggests a role of levodopa in supporting physiotherapy in stroke survivors [46]. Training schemes may pay specific attention to being rewarding and motivational. Promising approaches are music therapy [57] and virtual reality training [45] or rehabilitation gaming [5]. Further research is necessary to elucidate the neuroscience and potential clinical applications behind motivation-enhancing strategies as an add-on to movement training.

Why is there little evidence in neurorehabilitation?

There are many reasons why the evidence level in stroke neurorehabilitation is poor.

The problem is complex. The stroke survivor faces a plethora of problems: deficits of movement, language and communication, mobility and fitness, cognition, and emotion as well as social issues. It is obvious that each of these require different and likely individualized treatment approaches. However, single treatments need to be developed and tested separately in smaller trials before they can be combined into multimodal rehabilitative programs. An alternative solution is to carefully select a homogeneous sample of patients with specific deficits or lesions to be included in trials. However, this carries the disadvantage that results are unlikely to generalize to larger populations and that the study cannot address questions about correlations between therapy response and, e.g., lesion location of deficit severity.

Although the overall aim of all therapies taken together is to improve the patient’s functioning and independence, it is unclear which specific outcome measure to use to prove that a single therapy works. A therapy aiming, for example, at improving elbow movement can only be expected to do exactly that, i.e., improving the elbow [56]. It cannot be expected to increase QoL or independence because more than elbow function is needed to achieve this goal. Using elbow movement as an end-point measure of a trial investigating elbow therapy – even there is debate what should actually be measured – is often criticized as being meaningless for the patient. Although this is true from a global perspective, substituting the elbow measure with a more global assessment will render the trial negative. As a consequence, the therapy is no longer investigated or utilized. Therapies aiming to improve QoL will have to consist of different interventions addressing all functional domains that are impaired in an individual patient. A collection of single interventions is extremely difficult or impossible to standardize between cases.

It is difficult to formulate valid comparisons for randomized trials. A pill can be compared with a placebo pill using a double-blinded design. Blinding is difficult in neurorehabilitation. Comparisons of two treatments, e.g., a new therapy robot with conventional therapy, can be criticized: patients may be more impressed by expensive robotic equipment than by a conventional physical therapist or they may like the therapist more than the non-human robot – both settings that will induce large placebo effects. Valid comparisons are needed to identify training strategies that work better than others and in whom, i.e., in which population of patients.

Neurorehabilitative treatment in most cases involves many hours of training, requiring high compliance of patients and therapists alike. This translates into cost. On the one hand, clinical trials are expensive and are even more so if the investigational therapy is costly. On the other hand, funding for neurorehabilitation trials is scarce because there are few large companies – like the pharmaceutical industry – with an interest in neurorehabilitative interventions. Public funding for neurorehabilitation trials is insufficient.

There is too little basic understanding of recovery mechanisms. Before a drug is tested in a clinical trial, an exact knowledge exists about its mode of action, dosage, pharmacokinetics, etc. In neurorehabilitation, the threshold dosage (intensity) of a treatment that are required to produce an effect is seldom known, let alone how the treatment works. More studies in neuroscience are required to pave the way for successful neurorehabilitative interventions.

Summary

Technical developments not only show the way toward novel therapeutic approaches but also provide excellent research tools to test a hypothesis relevant for therapy development and optimization. The important hypotheses

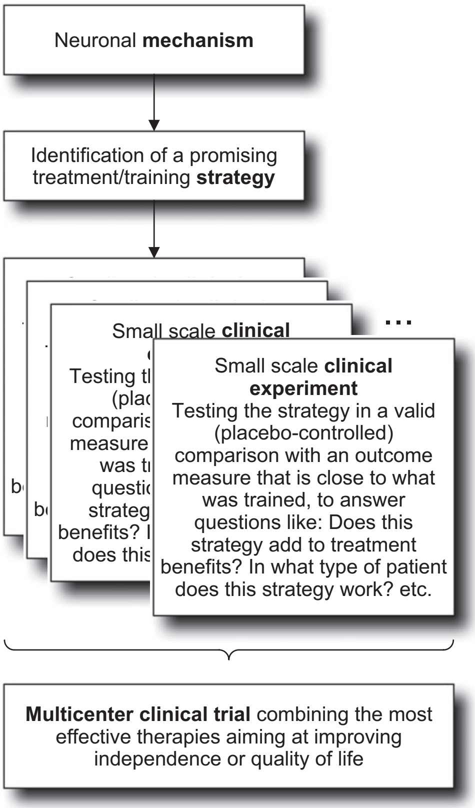

Figure 1 Potential conceptual framework for achieving well-founded evidence in neurorehabilitation.

to be tested are the following: What strategies of training, e.g., perturbation, motivation, assistance, repetition, are more beneficial than others? What strategies work best in which patient population? At what time after the stroke should these therapies be applied and which dose?

In neurorehabilitation, there is little evidence on the efficacy of interventions. Versatile treatment options are available, but they all seem to provide similar benefits if delivered at a sufficient intensity. Nevertheless, the treatment response varies greatly between individuals. It seems likely that certain (unknown) factors predispose a patient to treatment success, that different individuals will require different therapies, and that treatment plans need to be tailored to optimize the individual's response. A well-characterized therapeutic instrumentarium will therefore be necessary. Novel sensor technologies can provide powerful assessment instruments to measure not only motor impairment and function but also how the patient moves in daily life. Neurorehabilitation technology to improve training carries a great potential but probably is still used in suboptimal ways and, therefore, cannot demonstrate superiority to conventional approaches. Optimal strategies can only be developed if a thorough understanding of the neuroscience of recovery is achieved. Based on this knowledge, therapeutic concepts can be derived that require testing in smaller clinical experiments before large-scale clinical trials can yield interpretable results (Figure 1).

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