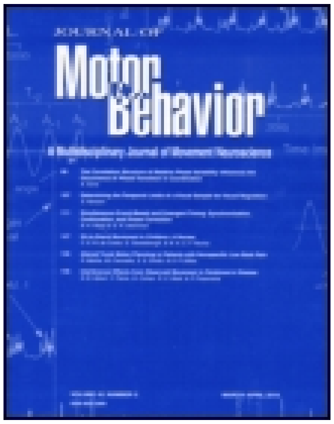

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REVIEW ARTICLE

Science-Based Neurorehabilitation: Recommendations for Neurorehabilitation From Basic Science

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ABSTRACT. Neuroscience has fundamentally changed the understanding of learning and memory within recent years. Here, the authors discuss a number of specific areas where they believe new understanding of the CNS from basic science is having a fundamental impact on neurorehabilitation and is leading to new therapeutic approaches. These areas have constituted a basis for development of some basic principles for neurorehabilitation: Optimal rehabilitation should involve (a) active (patient) participation in the training, (b) training that does not only involve many repetitions, but also continues to challenge the skill of the training person, (c) motivation and reward, (d) intensive training and practice over a long time, (e) careful organization of the training in relation to other activities, and (f) incorporation of other potentially beneficial parameters such as sleep and diet. It should in this relation also be pointed out that albeit neurorehabilitation may be predicted to have the most optimal effect early in life and as soon after injury as possible, there is no reason to believe that beneficial effects of training may not be obtained late in life or several years after injury.

Keywords: neurorehabilitation, clinical practice guidelines, science-based rehabilitation, motor learning, nutrition

There is an increasing worldwide political and economic pressure to provide solid evidence of the efficiency of neurorehabilitation in order to enable the most optimal treatment to be provided by the health care systems. The past few decades have thus witnessed a gradual movement away from physical interventions based on outdated theoretical concepts toward physiotherapy based on scientific evidence provided by randomized clinical trials (Health Quality Ontario, 2011; Pak & Patten, 2008; Tansey, 2012). Although this development is very sound, it also poses challenges that need to be considered. Foremost, it should be realized that it is not possible to apply the strict criteria that are required in clinical trials of new drugs in a clinical study of a physical intervention. Double-blinding is naturally not possible and placebo treatments are difficult if not impossible to design. Furthermore, although matched control groups receiving no treatment or conventional treatment are naturally desirable in these studies, it is not straightforward to deny a group of patients treatment that is believed to be efficient. Crossover designs do not solve this problem because the timing of intervention in relation to injury (and in children in relation to developmental stage) may be crucial. Finally, physical interventions require far more (expensive) human resources than any drug trial both because of the necessity of supervision and the long duration of the intervention. For all of these reasons consistent evidence of the efficiency of interventions in neurorehabilitation is likely to be slow in the coming and in a number of cases it must be feared that we will never be able to obtain satisfying evidence. While not denying the importance of evidence-based neurorehabilitation, we would therefore like to emphasize in this review the equal importance of science-based neurorehabilitation. First, there is in our opinion no reason to instigate a costly and potentially nonconclusive clinical evaluation of an intervention for which there is no clear scientific basis to expect that it would have an effect. In our view it makes sense to concentrate the available resources on those interventions for which there is a solid scientific framework and where we can expect a clear effect based on all the knowledge that we have available regarding neuroplastic processes in the nervous system in relation to motor learning and memory (Carr & Shepherd, 2011; Shepherd & Carr, 2005, 2006). Second, in those cases where we may not be able to obtain sufficiently consistent evidence of the efficiency of a given intervention, knowledge of the underlying neural processes must take over and provide the necessary arguments for the instigation of one intervention rather than another (Carr & Shepherd, 2011; Shepherd & Carr, 2005, 2006). It is the purpose of this review to highlight a number of areas where we believe that knowledge regarding the neuroplastic processes underlying learning and memory in the CNS provides a useful framework from which specific recommendations of what may and what may not work in practical neurorehabilitation can be made. This science-based neurorehabilitation may help to guide the selection of interventions to be evaluated, but may also in some cases be used alone as a valid scientific argument for the potential efficiency of one or the other intervention. In this review we cover 12 main topics that we consider important for the enhancement of motor skills in a practical neurorehabilitation setting.

Active Patient Participation Is Necessary

In the past physical therapy has focused on passive handling techniques where the therapist moves the affected limb of the subject in the belief that activation of sensory feedback may help to activate and train the neural circuitries responsible for the movement and thereby help the subject to regain function quicker and more efficiently (Kollen

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et al., 2009). Robotic training where a robot moves either the arm (Armeo; Colomer et al., 2013) or the legs of the patient (locomat; Harkema et al., 2012) is an attempt at automatizing this type of training. Such an approach makes sense from the point of view that passive manipulation may be one of the only means of ′training′ a paralyzed, very paretic or unconscious patient.

There are however, a number of problems with these approaches. First, sensory feedback provided by passive manipulation of a limb is not similar to that evoked when the same limb is moved actively by the owner of the limb. One very significant difference is that active contraction of a muscle involves activation of gamma motor neurons which will cause significant deviations in the activity of muscle spindle afferents as compared to that produced by passive movement of the limb (Prochazka & Gorassini, 1998). Active contraction also produces a significant load on muscle tendon, which is the required stimulus for activation of Golgi tendon organ afferents (Jami, Petit, Proske, & Zytnicki, 1985). Such activity is likely only elicited to a limited extent during passive manipulation. Joint afferents will be activated during passive movements, but cutaneous feedback is inevitably highly different from what is obtained during active movements given the way passive movements can be elicited. To this may be added that the activity of the spinal motoneurones themselves influence the spinal neural networks involved in their activation through Renshaw cell inhibition (Katz & Pierrot-Deseilligny, 1999). This influence will also be lacking during passive manipulation and the input to the central neural networks elicited by passive manipulation is therefore very different from that elicited during active movement.

A second problem for the idea of providing sensory feedback through passive manipulation is that the central processing of sensory input is very different depending on whether the sensory feedback is produced as part of an active or passive movement (Blakemore, Wolpert, & Frith, 1998, 2000; Shergill, Bays, Frith, & Wolpert, 2003). Presynaptic inhibition efficiently gates the access of sensory input to the spinal networks involved in activation of spinal motoneurones and is strongly regulated in relation to voluntary movement (Hultborn, Meunier, Pierrot-Deseilligny, & Shindo, 1987). Some reflex pathways are thus facilitated through removal of presynaptic inhibition at onset of movement, while transmission in others is blocked (Crone & Nielsen, 1989; Hultborn et al., 1987). The profile of sensory activation of the neural networks produced by sensory feedback during passive manipulation is therefore fundamentally different from that produced during active movement. This also applies to the sensory information transmitted to the brain through ascending sensory pathways. It has thus been known for quite some time that our perception of a sensory stimulus is strongly reduced (gated) when we perform an active movement at the same time (Blakemore et al., 1998). This observation has been incorporated in newer models of the basic principles of motor skill learning (Wolpert, Diedrichsen, & Flanagan, 2011). The idea is that the reduction in perception of a sensory stimulus reflects that the brain may disregard sensory information that can be predicted from the motor program that was responsible for the active movement. What the brain does according to this theory is monitor discrepancies between the actual sensory feedback and the predicted sensory feedback in order to optimize the model or central motor program (Wolpert et al., 2011). Deviations between the predicted and the actual sensory feedback are thus error signals that inform the brain that the existing motor program is not optimal and requires updating. From this point of view, improvements in motor function thus require active probing of the motor program and a comparison of the efficiency or outcome of that program in the form of actual elicited feedback and that predicted from the program itself. From this point of view providing external sensory input without activation of a central motor program at the same time as will be the case if the subject is not actively participating in the movement is not optimal for updating of the motor program and thus for learning to take place. There is indeed evidence from healthy subjects that passive movement does not induce plastic changes in the motor cortex similar to those observed in relation to the acquisition of a new motor task, even though the movements produced are kinetically and functionally identical (Perez, Lungholt, Nyborg, & Nielsen, 2004). Systematic reviews have also failed to demonstrate convincing evidence of a treatment effect of rehabilitation programs involving passive manipulation (Katalinic, Harvey, & Herbert, 2011; Kollen et al., 2009).

Whenever possible, active patient participation should therefore be a central part of the therapy. For patients where this is not possible due to the severity of the lesion, there is hope in the finding that mental training and imagination of movements may activate the same areas of the brain that are activated as part of active voluntary movements (Hetu et al., 2013). Clinical effects of motor imagery have not been convincing (Barclay-Goddard, Stevenson, Poluha, & Thalaman, 2011; Malouin, Jackson, & Richards, 2013), which may be at least partly explained by a general lack of experience with mental practice techniques in the average neurological patients. Mental practice and imagination have been shown to be effective in subjects such as elite athletes or musicians who have practiced their mental training skills for years (Isaac & Marks, 1994; Keller, 2012; Lotze & Halsband, 2006), but cannot be expected to work as well also in the general population without prior experience. Techniques that can help the patient to obtain an illusion of movement and thereby more vividly get engaged mentally in the training, such as virtual reality training (Laver, George, Thomas, Deutsch, & Crotty, 2012; Moreira, de Amorim Lima, Ferraz, & Benedetti Rodrigues, 2013) and mirror therapy (Thieme, Mehrholz, Pohl, Behrens, & Dohle, 2013), have in line with this shown promising results in controlled trials.

Physical Aids Should Only Be Given When Really Necessary

Although it may sound harsh, it should be realized that we do not necessarily do the patients a favor by providing them with aids that help them to accomplish tasks that they cannot manage on their own. Wheelchairs are efficient aids for people who cannot walk—and have no hope of walking, but we need to remember that time spent in a wheelchair is time taken away from gait training. The decision to offer a patient the aid of a wheelchair should therefore always be balanced by the prospect of recovery through the training that the patient would be given the opportunity to do without the wheelchair. Similarly, splints and other supportive devices may be efficient in stabilizing joints and helping patients to move around, but they also prevent the patients from adequately activating the muscles acting on the stabilized joints and therefore may prevent recovery of function. These aids should therefore only be instigated when there is little hope of recovery of function. We fear that aids are often implemented much too early due to economic considerations and misconceptions of what is the best for the patient.

Knowledge from motor learning theory also makes us concerned that robotic devices that are designed to train and provide neurorehabilitation may not live up to current hopes (Colomer et al., 2013; Harkema et al., 2012). As already pointed out, providing passive movement without active participation from the patient is unlikely to have any major benefits. In addition, providing external sensory feedback to a patient who is attempting to (re)learn a given skill may confuse the establishment of a solid internal model/motor program. There is indeed evidence from healthy subjects that external sensory feedback such as that provided through passive manipulation may interfere with learning or disrupt consolidation of a newly learned skill (Lundbye-Jensen, Petersen, Rothwell, & Nielsen, 2011). We do not know to what an extent this is also a problem in patients with a limited capacity to perform unassisted movements, but it seems evident that the motor program that the patient develops when trained in a robotic device may be different from and even interfere with the program required for production of unassisted movements under normal conditions.

Partly to take this problem into account newer robotic devices allow the patient to contribute to an increasing extent to the movement as functional recovery progresses. There is, however, a caveat to this. We should be careful that the brain of the patient does not outsmart the robots or the therapists so that the robotic device ends up being a handy helper for the patient rather than a training device. In that case the smart device that helps the patient to function better in the short term may end up limiting the functional recovery in the long term.

Provide Challenges That Can Support Learning

In terms of inducing plastic changes in the nervous system, improving the performance of a given task and achieving new skills, it is important that simple repetition of the task has only limited efficiency. Following a single bout of training a new task or a new skill increased representation of the muscles involved in the task is seen in the primary motor cortex (Pascual-Leone, Amedi, Fregni, & Merabet, 2005; Perez, Lundbye-Jensen, & Nielsen, 2006; Perez et al., 2004). This increased representation, is, however, short-lived and disappears again within minutes to hours. With repeated training that leads to improved performance of the task more long lasting changes in cortical representation are seen (Jensen, Marstrand, & Nielsen, 2005; Pascual-Leone et al., 2005). These changes, however, reach a plateau around the time where the performance of the task also begins to improve less with each training bout and the cortical representation may even begin to decrease. Continued expansion of the cortical representation will only be observed if the level of difficulty is increased or if learning of a new task is started (Perez et al., 2006). Once a task has been learned to a certain level of performance further practice of the task will thus not be accompanied by any induction of plasticity and little is therefore gained by continuation of practicing the task (at least in terms of changes in plasticity). Training is thus not about simple repetition of a task, and as many repetitions as possible. It is about setting specific goals for the tasks and skills that are to be acquired. Deliberate training with these goals in mind appears to be the key to improved performance (Ericsson, 2004, 2008, 2013; Ericsson, Krampe, & Heizmann, 1993). Translated into neurorehabilitation this means that the therapist has to help the patient setting realistic goals that are sufficiently above the current level of performance, but not more than can be achieved with practice within a reasonable time period.

Training Should Be the Responsibility of the Patient—the Therapist as a Personal Coach?

It has been a general finding in studies of neuroplasticity in both animals and humans that training needs to be much more intensive and of a much longer duration than what is normally the case in clinical studies on neurorehabilitation or is possible through centralized physiotherapy offered through the public health service (Lang et al., 2009). This point was made clear by Lang et al.; they compared the number of arm or leg movements made by animals in laboratory settings where lasting functional effects have been demonstrated to the number of movements made by patients in physical therapy sessions. On average the patients performed less than 10% of the movements that were performed by the animals in the published studies. Although, this is certainly a crude measure, it does indicate that the amount of training that can be offered through centralized physical therapy is very little as compared to that necessary to induce lasting plastic changes in the nervous system. Another calculation that gives more or less the same answer comes from studies on skill acquisition and what it takes to become an expert. Although it is naturally a gross measure, these studies have indicated that it takes approximately 10.000 hr of practice to become an expert more or less regardless of the exact skill (Ericsson, 2004, 2008, 2013; Ericsson et al., 1993). To give an idea of what this involves, 10,000 hr corresponds to 3 hr of training every day for 10 years. This is not to say that this amount of training is necessary for every single patient, but it helps to give an idea of how far away we are from providing the amount of training—both in the health system and in so-called highly intensive training studies—which is required in order to be able to say with certainty that the patient has achieved his or her full potential for recovery. With the training that we can offer through traditional public health services we are very far away from this, which is something that should be kept in mind when evaluating the efficiency of physical therapy.

This realization has two important implications. One is that we need to emphasize for the patients (and the politicians) that rehabilitation does not take weeks or months, but years. The patients need to be prepared that daily training is going to be part of the rest of their lives, but that functional gains may still be achieved even years after the lesion. The other implication is that it is unrealistic to imagine that we will be able to afford training with the necessary intensity and duration if we rely only on physical therapy as it is organized in most countries today. Offering 1–2 hr of centralized physical therapy sessions per week at the most is a very small drop in the sea. Hands-on and direct therapist–patient interaction is probably of value, but far too expensive and inefficient for training at the large scale, which is necessary for full recovery (or at least better recovery than at the present time) to be achieved. The logical implication of this is that we have to find better and less expensive ways of helping the patients to train in a noncentralized setting, in their own homes or in their local community (e.g., fitness centers). The role of the therapist should be changed from being the one who performs hands-on therapy to being someone who helps the patient to plan the training, set goals and stay motivated. This can be organized in a variety of ways, but the internet and the smartphone technologies offer obvious possibilities of communication with the patient, organizing and communicating training plans, evaluating the effect of training and adjusting accordingly if necessary and setting goals for the training (Bilde et al., 2011; Nielsen, 2013). These technologies also offer opportunities for creating social communities of patients with similar ailments and training needs who can meet (virtually or in real life) through the internet and with smartphones as a central node for communication and contact. The role of the therapist will in this way become more that of a personal coach, who helps the patient to perform as much training with the highest possible quality in their own home or fitness center with the use of internet and smartphones as central means of communication, evaluation, and motivation. This will be a fundamental change in the way that therapists interact with patients and it will also require fundamental changes in the education of therapists to fulfill these goals.

Train Every Day for as Long as Possible

How much do I need to train? This is usually the first question a patient about to start a training program will be asking. The answer should be something similar to "the more you put into it, the more you get out of it," in line with the previous section. However, because it is a point that is of natural concern it is necessary to try and provide some directions and guidelines that can give the patient a good idea of what will be required. Studies on neuroplastic changes in healthy humans have usually involved training either every day or every second day and the amount of training has usually been for at least 30 min. The minimal time of training required has not been specifically investigated but Perez et al. (2004) reported that they observed no plastic changes with a 15-min training bout in pilot experiments and consequently chose to use at least 20 min of training in their study. We also have evidence from computer-based training of stroke patients and children with cerebral palsy that division of training into three bouts of 10 min daily training was as effective as 30 min of daily training (unpublished observations). For training that requires intense physical activity, development of fatigue and muscle pain is a concern that has to be taken into account. A similar concern does not seem to be required in relation to induction of neuroplastic changes and training every day and even several times per day appears to be possible and even to some extent desirable.

Ensure Motivation and Reward

Reinforcement learning is one of the most powerful ways (albeit not the only one) of learning new skills. The simple and widely known example of reinforcement learning is rats, who receive a reward (food pellet or water) when they accidentally press a lever (Schachter, Gilbert, & Wegner, 2010). With repeated reward of the behavior the rats will soon end up pressing the lever deliberately whenever they require food or water. Reinforcement learning is similarly the basis for training of any animal from dogs to dolphins using whistles, commands or biscuits as rewards. And it also works in humans. When subjects are provided with a (monetary or otherwise) reward every time they improve the performance of a task they learn to master the task much more quickly than if they receive no reward. Interestingly they do not even need to be aware that they received any reward (Pessiglione et al., 2007). Release of dopamine in key areas of the brain is at the center of this (Pessiglione et al., 2007; Wickens, Reynolds, & Hyland, 2003). Release of dopamine when the reward is provided leads to improved consolidation of the motor program responsible for the behavior in the motor cortex and basal ganglia to a large extent through facilitation of the late part of long-term potentiation (Sajikumar & Frey, 2004). At the same time release of dopamine also influences prefrontal areas where it acts to facilitate the decision to perform similar behavior in the long term (Rogers, 2011). Reward-based dopamine release thus plays a dual role in facilitating consolidation of motor memory and in strengthening the motivation for specific behaviors (Bromberg-Martin, Matsumoto, & Hikosaka, 2010; Phillips, Vacca, & Ahn, 2008). From a neurorehabilitation point of view this is of great interest. One of the biggest challenges in any attempt to train patients with or without a brain lesion is to maintain motivation over the long periods of time necessary to achieve significant and lasting functional improvements.

This is even more challenging when training has to be performed at home by the patient themselves in order to achieve the necessary frequency and intensity of training. Clear goals that are accompanied by rewards when achieved are indispensable in this situation, but difficult to administer if the therapist is not present during the actual training. For optimal effect feedback about the performance of the task and subsequent reward should be provided as soon as possible. This calls for frequent measurement of the performance of the patients on one hand to ensure that the improved performance is detected, but it also requires that clear goals and achievements are set for the patient during the training program and that the feedback and reward is provided relatively immediately during the training. This is difficult to achieve with current rehabilitation programs. It is in this relation of interest that reinforcement learning and the associated reward of the ´correct´ behavior is at the heart of computer games, which may explain much of the addiction to computer games that at least some young people may experience (Granic, Lobel, & Engels, 2014). It seems obvious to make use of the available computer game technology with this in mind and there are consequently also a number of studies that have started to address the possibilities that have become available with these new technologies (Lee, 2013; Levac & Miller, 2013; Neil, Ens, Pelletier, Jarus, & Rand, 2013).

Structure Practice to Optimize Acquisition and Retention

During recent years, behavioral research has provided evidence for an important distinction between the immediate performance gains that accompany practice and long-term changes in motor performance that reflect retention and thus more permanent changes in the capability for the practiced skills (i.e. learning; Kantak & Winstein, 2012). This learning–performance distinction is particularly important when assessing the effects of rehabilitation training or physiotherapy. Improved in-session performance is naturally desirable—not least for motivation—but long-term retention of motor skills and transfer to real life is essential. A review of motor learning studies with a specific focus on comparing differences in performance between the end of practice and at delayed retention suggests that the delayed retention or transfer performance is a better indicator of motor learning than the performance during or at the end of practice (Kantak & Winstein, 2012; Winstein, 1991). In other words, it is important both that the learner knows both what was effective during practice and "look, weeks later and I can still do it."

Many factors may influence retention of learning, but one important aspect is practice structure (Kantak, Sullivan, Fisher, Knowlton, & Winstein, 2010, 2011; Robertson, 2004). In general it has been found that practice of a single skill during constant conditions is accompanied by the largest improvements in motor performance during the practice session. When learning is assessed in delayed retention tests, it does, however, often turn out that retention is poorer than if compared to subjects who practiced during varied conditions (Gentile, 2000; Kantak et al., 2011, 2012). When considering acquisition of multiple motor skills a similar principle seems to hold for the concepts of blocked practice versus random or interleaved practice (Robertson, 2004). If subjects practice a block of task A, then a block of task B, and so on, this practice is associated with significantly higher gains in motor performance during practice. If learning is assessed in delayed retention tests, it does however often turn out that random or interleaved practice is accompanied by better retention effects (Robertson et al., 2004).

While it thus seems that variable practice (within skills) and interleaved or random practice (between skills) is preferable in order to promote retention effects, care should be taken when structuring practice particularly for patients. Although slow performance improvements during random practice may ultimately lead to better retention effects, it may not be well appreciated by the patient (or therapist) and the performance gains observed with constant, blocked practice may also carry motivation, which may reinforce learning. Though large parts of the literature on motor learning mechanisms and principles is based on findings in able-bodied subjects, it should be recognized that an important effort has been made to make the research findings on able-bodied populations relevant to those with disabilities (e.g., Carr & Shepherd, 2011; Winstein, 1991; for a textbook, see Carr & Shepherd, 2000). During recent years, researchers have worked on implementing practice structures leading to adaptive practice schedules (Choi, Qi, Gordon, & Schweighofer, 2008). An example of this is the "win, shift; lose, stay" principle, which allows repeated (blocked) practice of a skill until the patient reaches a specified (individual) criterion level of success (Salter, Wishart, Lee, & Simon, 2004; Simon, Lee, & Cullen, 2008). Once this level of performance is reached, the patient switches to practice another task. Thus switching between tasks is beneficial for retention possibly through an effect on retrieval and problem-solving and this practice schedule seeks to combine the beneficial effect of blocked and interleaved practice (Kantak & Winstein, 2012). It is however necessary to consider the resources and needs of the individual patient. What remains to be investigated is the manner in which these adaptive practice schedules influence the motor memory processes and related neural substrates. This information will improve practical application of motor learning principles for rehabilitation (Kantak & Winstein, 2012). Structuring a practice session that may enhance both performance and delayed retention thus requires a thorough understanding of performance and learning effects at a behavioral and neural level but also understanding of psychological factors such as motivation.

Improved Function Requires Optimal Consolidation

Studies on motor learning have revealed that lasting improved function does not only depend on the actual training, but also on off-line learning and stabilization of (motor) memory after the training and optimal consolidation of what was learned during the training period (Krakauer, 2009; Krakauer & Shadmehr, 2006; Robertson & Cohen, 2006). Following training there is thus a period of time where the learned material has not yet been consolidated as structural changes in the neural circuitries underlying learning and where the improved motor ability obtained during the training may therefore be completely lost (Brashers-Krug, Shadmehr, & Bizzi, 1996; Krakauer & Shadmehr, 2006; Lundbye-Jensen et al., 2011; Muellbacher et al., 2002). This happens if the subject starts learning another task or is subjected to external stimuli which activate the neural circuitries in which the learned task is about to be stored within 3–4 hr following the training period (Brashers-Krug et al., 1996; Lundbye-Jensen et al., 2011; Muellbacher et al., 2002). Translated into neurorehabilitation, this means that therapists should be concerned about what happens to the patient in the time following a session of therapy. All the efforts and all the gain in function obtained during the therapy session may be lost if care is not made to prevent interference with the learned material during the time period immediately afterward. Conversely, the consolidation of the learned material may also be facilitated in various ways. Amphetamine, which increases the level of monoamines (e.g., adrenaline, noradrenaline, dopamine), causes a general facilitation of the consolidation process in both humans and animals (Leri et al., 2013; Soetens, D'Hooge, & Hueting, 1993). One possible mechanism for this is that dopamine has been shown to be essential for the late phase of long-term potentiation, which is related to the process of consolidation and the induction of structural network changes (Sajikumar & Frey, 2004). Stimuli that increase dopamine in the brain during the consolidation period may therefore facilitate consolidation. Generally, this would involve stimuli that are interpreted by the brain as a reward, but increased dopamine may also explain the improved memory of a learned motor task when healthy subjects perform a bout of aerobic exercise during the consolidation period (Roig, Skriver, Lundbye-Jensen, Kiens, & Nielsen, 2012). Although it is too early to say anything with certainty, such findings may indicate that it could be beneficial to let patients perform aerobic exercise at the close of a therapy session to ensure optimal consolidation of the learned material. Based on the hypothesis that stimuli or instruments that increase dopamine during the consolidation period would facilitate retention of the learning many other beneficial interventions could be suggested and explored.

As mentioned, it has been a repeated finding that gains in performance are seen within the next day and even one week following a training bout (Robertson, 2004; Roig et al., 2012). A significant part of this gain in performance has been demonstrated to be related to sleep (Diekelmann & Born, 2010; Rasch & Born, 2013). It appears as if different phases of sleep influence the consolidation of different forms of learning and memory differently (Rasch & Born, 2013). The exact mechanisms involved have not been clarified but one theory is that the brain replays and rehearses the learned material in the different phases of sleep and that this strengthens the connectivity within the network (Fogel & Smith, 2011; Gorgoni et al., 2013). A good night's sleep is therefore also essential for the outcome of neurorehabilitation, but probably even more relevant, it has been found that sleep during the day following a training session may efficiently consolidate the learned material and protect it from interference from other learning processes and other influences (Doyon et al., 2009; Korman et al., 2007). This may suggest that neurorehabilitation should be planned in such a way that the patient can sleep as soon after the training session as possible. Whether sleep, exercise or some combination of the two facilitate consolidation most efficiently is an open question and may depend on specific circumstances for the individual subject.

Less Emphasis on Spasticity—Focus on the Paresis

Spasticity is a prime example of how new understanding from basic science gradually changes the understanding of the disorder and as a consequence of this also the therapeutic approaches in the clinic—although somewhat slowly. Dating back to the original description of reflexes by Sherrington (1906) increased stretch reflex activity has been seen as the hallmark of spasticity most clearly expressed by Lance (1980):

> Spasticity is a motor disorder characterised by a velocity dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from

> hyper-excitability of the stretch reflexes, as one component of the upper motor neuron syndrome. (p. 485)

It has been assumed that this pathologically increased reflex stiffness also significantly impairs the ability of the affected patients to perform voluntary movements and considerable clinical efforts have therefore been and are still to a large extent directed at finding ways of diminishing spasticity. It has been pointed out that fear of increasing spasticity has also until recently led to warnings against physical activity and especially strength training as pointed out by several authors (Damiano, Dodd, & Taylor, 2002; Damiano, Quinlivan, Owen, Shaffrey, & Abel, 2001; Dodd, Taylor, & Damiano, 2002). However, it has proven very difficult to demonstrate that spasticity has any negative impact on the functional abilities of spastic patients (Dietz & Sinkjaer, 2007, 2012; Willerslev-Olsen, Andersen, Sinkjaer, & Nielsen, 2013). A number of studies have demonstrated that stretch reflexes are only exaggerated in the resting state but not during movement (Dietz & Sinkjaer, 2007, 2012; Ibrahim, Berger, Trippel, & Dietz, 1993; Sinkjaer, Toft, Larsen, Andreassen, & Hansen, 1993). The limitation in functional ability is rather explained mainly by paresis and secondary structural changes in the muscles leading to increased resistance against movement and reduced joint mobility (Alhusaini, Crosbie, Shepherd, Dean, & Scheinberg, 2010; Willerslev-Olsen, Andersen, et al., 2013; Willerslev-Olsen, Lorentzen, Sinkjaer, & Nielsen, 2013). Based on the past 20–30 years of basic research, which has demonstrated that reflexes are an integrated part of voluntary movement, spasticity is now seen as an adaptive, plastic change in the spinal neural circuitries aimed at maintaining a functional output from the spinal cord to the muscle in the face of diminished descending drive (Burke & Pierrot-Deseilligny, 2012). Rather than being a pathological condition by necessity, spasticity could also be seen as a therapeutic opportunity. After all, the main problem for the patients (and the therapist) is to activate the muscles and the increased sensory drive to the spinal motoneurones that spasticity reflects provides an opportunity for providing such activation. What is required is that we find a way of teaching the patients how to integrate the sensory feedback optimally into the central motor programs in order to optimize movements. Simply reducing or even getting rid of the sensory feedback that is the aim of antispastic therapy at least seems not a sensible choice. This is also the experience which is gradually coming out of the clinic (Dietz, 2003; Dietz & Sinkjaer, 2007, 2012): Many patients use their spasticity to stand and walk—and removing this useful access to the spinal motoneurones through antispastic medication may cause more problems than it solves. Therapy directed at taking opportunity of the plastic potential of the spinal circuitries and their remaining supraspinal control makes more sense with our current understanding.

Other Factors That Influence Learning and Memory

Brains require fuel in order to work appropriately and it is therefore not surprising that studies have repeatedly demonstrated that subjects learn better when a high blood glucose level is ensured by providing them with sugar intake prior to learning (Korol, 2002; Messier, 2004). It is less clear whether this also applies for motor learning and neurorehabilitation, but it could still seem reasonable to assume that patients undergoing neurorehabilitation would benefit from having a sufficiently high blood glucose level throughout the training session. This could easily be ensured if an energy bar was offered as a natural part of the training session—albeit it should naturally be taken into account whether the patient suffers from diabetes or other diseases that require dietary restrictions.

The structural changes in the neural circuitries related to learning and memory, however, also require other substances in order to establish new spines and synapses (Cansev, Wurtman, Sakamoto, & Ulus, 2008; Gomez-Pinilla, 2008; Gomez-Pinilla & Gomez, 2011). The neural membrane consists to a large extent of phosphatidylcholines that are derived from three key substances docosahexaenoic acid (DHA), choline, and uridine (Cansev et al., 2008; Wurtman, Cansev, Skamoto, & Ulus, 2010). Dietary supplementation of these three substances in rodents has been demonstrated to result in an increased number of spines and improved learning in a number of tasks (Wurtman et al., 2009, 2010). There is some evidence that DHA may have similar effects in humans (Kim et al., 2010; Osendarp et al., 2007; Stonehouse et al., 2013), but not all studies have shown convincing results (Jackson, Deary, Reay, Scholey, & Kennedy, 2012; Kennedy et al., 2009), and it is therefore too early to conclude whether dietary supplementation of one or the other nutrient will be of value in a practical neurorehabilitation setting. However, the emergence of this research field within recent years will help to increase our awareness of the significance of dietary influences on brain function especially in relation to rehabilitation of the lesioned brain. Exercise has been subjected to a growing interest also relating to learning during recent years and it is highly relevant to focus on the potential interaction. Indeed it has been demonstrated that disuse as seen during immobilization is accompanied by plastic changes at multiple levels within the CNS (Lundbye-Jensen & Nielsen, 2008a, 2008b). This implies that disuse in itself may represent an obstacle for rehabilitation. It is in other words necessary to consider multiple factors. After all, diet and exercise goes hand in hand in sports and general health promotion so why not also in neurorehabilitation?

Individualization Is Necessary

We are all born with a different genetic profile and the wiring of neurons in our neuronal circuitries probably varies considerably (Sporns, 2013). Lesions also vary between subjects as do the compensatory and plastic responses to the lesion. If we add to this that subjects react differently to reward and are motivated by different things, we are faced with the problem that a considerable tailoring of the rehabilitation program to the individual person is necessary (Pearson-Fuhrhop, Burke, & Cramer, 2012; Pearson-Fuhrhop & Cramer, 2013). Although the principles mentioned in the previous sections thus apply across a broad spectrum of patients with various brain lesions at different times in their life, the details of the practical implementation of these principles have to be adjusted according to the needs and abilities of the individual subject. Some patients may require little encouragement in order to train for several hours per day, whereas others may require daily goals and rewards. Some patients may show large improvements in function with relatively little effort, where others may require much longer training. The achievements obtained by the individual patient in a training program to a large extent depend on such inter-individual variables. We may be able to predict these outcomes based on genetic and other information in the future (Pearson-Fuhrhop et al., 2012; Pearson-Fuhrhop & Cramer, 2013; Sporns, 2013), but at the present time we have to rely on the experience of the therapists and their ability to adjust the training program to the individual patient. This is unfortunate because not all therapists may be equally adept at this task and because the exact parameters to use for the individualization are likely to vary considerably between therapists. This is not only a problem for any attempt to guarantee all patients an optimal rehabilitation program, but also for attempts at providing evidence for the efficacy of rehabilitation. Demonstration that one intervention produces larger gains in function than another intervention may only show that those therapists who administered the interventions were better at tailoring the intervention to the patients, but this may not necessarily be the case for other therapists who lack similar experience with that particular intervention.

Neurorehabilitation Has Effects Late in Life and Long After the Primary Injury

It has been suggested over the years that the plastic potential of the immature newborn brain is much larger than the adult and old brain (S. N. Burke & Barnes, 2006; Nieto-Sampedro & Nieto-Diaz, 2005). During the critical periods for neurodevelopment early in life, interventions directed at facilitating developmental adaptations and plastic compensations following injury must be expected to have the most optimal effects (Kolb & Teskey, 2012; Michel, 2012; Vida, Vingilis-Jaremko, Butler, Gibson, & Monteiro, 2012). However, this does not preclude that plastic changes may also be induced later in life and that neurorehabilitation may have very significant effects even in old age. Although learning, consolidation of memory and especially recall of memory is affected in elderly people, studies have repeatedly demonstrated that old brains retain a considerable plastic potential (S. N. Burke & Barnes, 2006; Kolb & Teskey, 2012). Motor learning and consolidation in particular appear to proceed at rates that are only slightly diminished as compared to younger brains (Bock & Schneider, 2002). There is thus no reason that neurorehabilitation should not have an effect also in elderly people.

There is also no reason that neurorehabilitation would not have an effect several years after a primary lesion. There is certainly every reason to start neurorehabilitation as soon after lesion as possible and there is evidence from animal experiments that there is a period of increased plasticity within the initial weeks after injury (Kitago & Krakauer, 2013). It is also a general observation in humans that the main part of recovery occurs in the initial 3–4 months after injury (Kitago & Krakauer, 2013). However, this is not a reason to argue that efforts should not be made to promote functional recovery at later times following injury. The injured nervous system certainly retains its capacity for plastic changes at least at the same level as the healthy nervous system and there is therefore every reason to believe that functional gains may be obtained long after the primary lesion. The additional functional recovery that may be obtained certainly diminishes as the patient gradually recovers and it is certainly a relevant discussion whether the additional functional gain that can be expected at some point becomes so small that it does not make sense for the general health system to support the training. For the individual patient the message is, however, that there is no reason not to continue training for the rest of life. This is necessary not only to retain functional capacity, but also to potentially achieve improved function.

Concluding Remarks

Our understanding of the neural processes responsible for learning and memory has increased significantly in recent years and it is now established that the ability to change functionally and structurally is a fundamental essence of the nervous system. This understanding creates a unique basis for a biological framework for neurorehabilitation. We have highlighted 12 different areas in this review where knowledge from basic neuroscience and related fields can be used to make specific recommendations for neurorehabilitation. Translation of this knowledge into clinical rehabilitation is essential for optimization of our approaches to neurorehabilitation in the future. We believe that a science-based neurorehabilitation will guarantee the best possible rehabilitation at the lowest possible cost in a future where an increased elderly population will put increasing demands on our health systems.

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