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Pathophysiology of Stroke Rehabilitation: The Natural Course of Clinical Recovery, Use-Dependent Plasticity and Rehabilitative Outcome

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Abstract
Even though the disruption of motor activity and function caused by stroke is at times severe, recovery is often highly dynamic. Recuperation reflects the ability of the neuronal network to adapt. Next to an unmasking of latent network representations, other adaptive processes, such as excitatory metabolic stress, an imbalance in activating and inhibiting transmission, leading to salient hyperexcitability, or the consolidation of novel connections, prime the plastic capabilities of the system. Rehabilitative interventions may modulate mechanisms of neurofunctional plasticity and influence the natural course after stroke, both positively, but potentially also acting detrimentally. Though routine rehabilitative procedures are an integral part of stroke care, evidence as to their effectiveness remains equivocal. The present review describes the natural course of motor recovery, focusing on ischemic stroke, and discusses use- and training-dependent adaptive effects. It complements a prior article which highlighted the pathophysiology of plasticity. Though the interaction between rehabilitation and plasticity remains elusive, an attempt is made to clarify how and to what extent rehabilitative therapy shapes motor recovery.

The natural course of clinical recovery after stroke reflects the ability of the neuronal network to plastically adapt to injury [1]. Though recuperation is variable, depending primarily on the location and size of the ischemic lesion [2], it is often highly dynamic, especially in the early phases after stroke [3]. Mechanisms that support or modulate recovery are not yet fully understood, though there is surmounting evidence, in large parts coming from animal studies, that highlight the potential of plastic adjustment in cortical and, to a lesser extent, subcortical structures under specific training or behavioral adaptation [4]. The results are less conclusive in humans. Epidemiologic and meta-analytic reviews do support the notion that patients receiving a mix of mostly traditional rehabilitative therapies may fare better than those who remain untreated [5]. Nonetheless, only few prospective trials have attempted to investigate the specific relationship between training and outcome after stroke in respect to efficacy [6]. It must be noted that recent advances in novel therapeutic regimens [7], including neuropharmacological intervention [8], central [9] or peripheral [10] 'electrical' manipulation and machine-aided approaches [11, 12], may prove to be highly effective in the long run. However, their introduction into daily practice is still a way down the road, at present, their domain being small, well-controlled series. Therefore, we focus this review on therapeutic approaches that form the broad basis of rehabilita-

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tion in the routine clinical setting, their mechanisms of action remaining nebulous [13].

A part of the problem in delineating the effects of rehabilitative approaches is the sheer diversity of regimens and the difficulty to quantify subjective therapist-patient interactions [14, 15]. This makes it next to impossible to accurately characterize the type and intensity of physiotherapy or other training provided in the clinical setting [16]. Moreover, traditional rehabilitative interventions are, by and large, empirically deduced and their methods often unrelated to the underlying principles of neurofunctional adaptation (the term used here to summarize the broad spectrum of transmitter-related events, morphological change, and modification in the efficacy of neuronal transmission). As treatment diversity remains unmanageable, any attempt to clarify the interaction between rehabilitation, plasticity and outcome in larger-scale trials will have to rely on an empirical description of therapeutic intensity, duration and continuity, all of which are easier and more reliable to quantify [17].

Simply relating a more demanding therapy of longer duration, continuing well into the chronic phase of stroke, to a better outcome seems intriguing in practice. In fact, it has been demonstrated that learning is dependent on task-oriented repetition and consolidation [18]. However, the lesioned brain may also be more vulnerable to maladaptive processes under focused training [19]. Moreover, neurofunctional adaptation is not static in the temporal domain: rehabilitative interventions may act beneficially in certain phases of recovery, detrimentally in others [20].

In the following, we limit our discussion to the disruption of motor control, representing the larger part of stroke-induced impairments.

Numerous recent reviews have described the mechanisms involved in the recovery of motor competence after stroke and have proposed possible specific strategies promoting an optimal outcome [1, 4, 21–24]. However, the interaction between the natural course of amelioration of stroke-induced motor deficits and function, the magnitude of rehabilitative therapy, vulnerability to positive and negative plasticity and the resulting outcome has only been vaguely delineated [25, 26].

In a preceding companion article [1], we chronologically categorized the neurofunctional processes that underlie recovery after ischemic lesions. Next to an unmasking of latent network representations, other adaptive processes, such as excitatory metabolic stress, an imbalance in activating and inhibiting transmission, leading to salient hyperexcitability, or mechanisms that consolidate novel connections, prime the plastic capabilities of the system. These pathophysiological processes are potentially influenced by rehabilitative interventions. The present review describes the natural course of motor recovery in more detail, discusses use- and training-dependent adaptive effects and evidence that rehabilitation influences outcome. We try to focus on data available for ischemic stroke, which is more common.

Natural Course of Motor Recovery after Stroke

Several principles of motor recovery can be summarized (see fig. 1 for a schematic drawing of 'typical' motor recovery patterns).

- Approximately 90% of all stroke patients show at least some degree of motor impairment at onset, equally divided into groups of severe, moderate or mild paresis.
- Without further stratification, the average of all stroke patients' initial motor deficit lies at about half of the maximum best score of most motor-sensitive scales at onset, improving to three quarters of the scale's maximum at follow-up in the 'chronic' stage (defined as the time after which the direct and secondary consequences of ischemia have subsided and plastic processes tend to become static).
- The most dynamic period of recovery lies beyond the 'hyperacute' phase (up to 48 h after onset, when the direct consequences of ischemia are most prominent), in the 'acute' (up to 4 days after onset, a period in which secondary events reach full force) and 'subacute' stages of recovery (starting anywhere as early as 48 h after ischemia and lasting 2–3 weeks; secondary events subside and plasticity fully unfolds), with patients reaching at least half of their individual maximum best scores within 2 weeks after parenchymal injury.
- Recovery continues into the 'period of consolidation' (beginning after the subacute phase and continuing up to no more than several months after onset, a period when neurofunctional alterations wane and then followed by the chronic stage), slowing dramatically as time passes. In most cases, recovery from paresis levels off substantially 3 months after onset.
- Notwithstanding the fact that motor deficits remain more or less unchanged thereafter, positive (and at times negative) functional compensation may signifi-

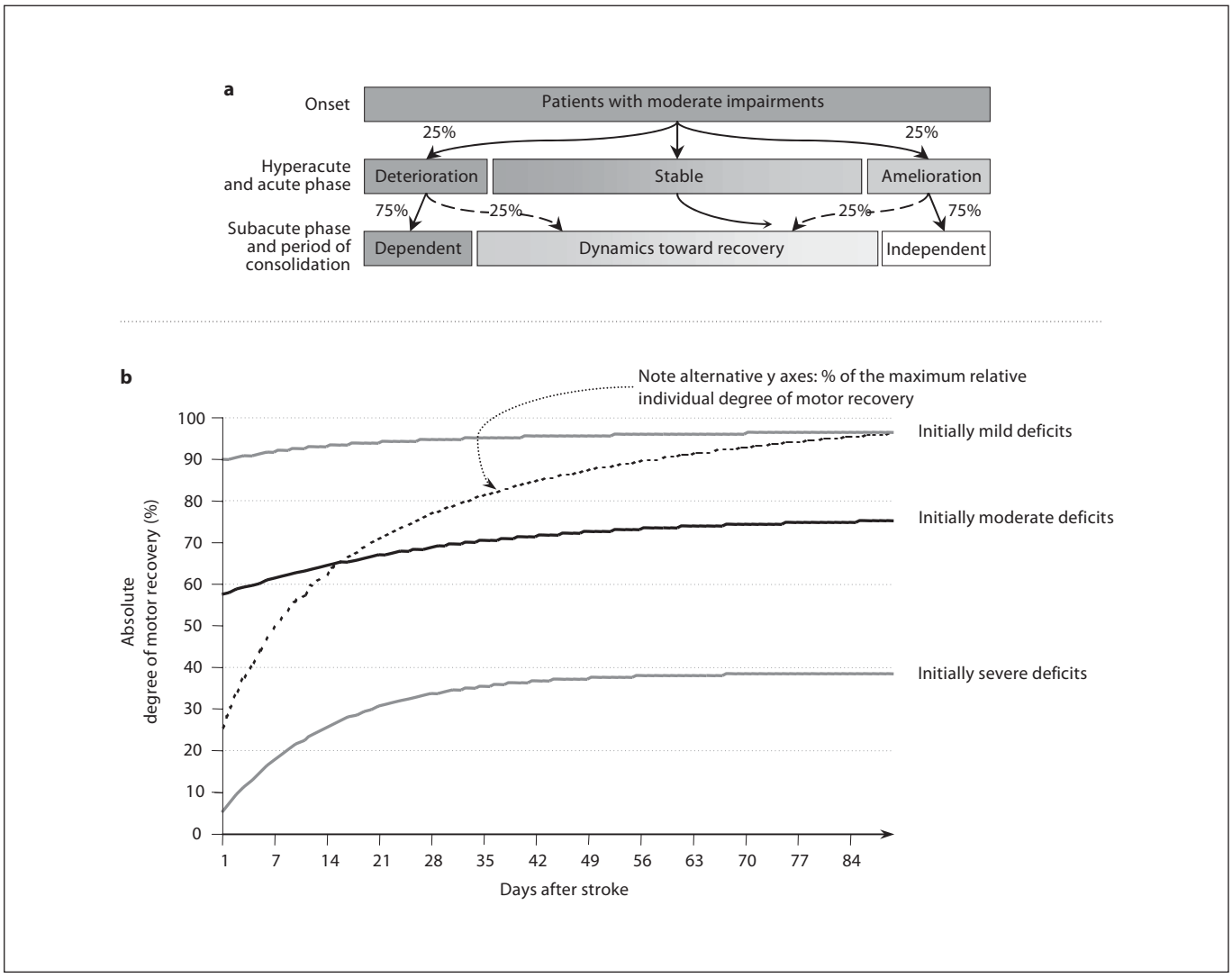

Fig. 1. a Schematically delineated recovery pattern of patients with initially moderate impairments, showing the percentages of those deteriorating or recuperating in each phase of recovery. **b** Recovery from paresis, up to an absolute best (i.e. completely restored innervation = 100% on most motor-sensitive scales), stratified according to onset severity versus the timeline after onset. The dashed curve reflects the relative degree of motor recovery (i.e. 100% = best possible individual recovery), being more or less independently of initial severity. The figure is based on data extracted from two comprehensive studies on the natural course of recovery [3, 32].

cantly influence the degree of handicap even in the long run.

Though a multitude of prognostic variables have been established [27], none are as robust as the initial clinical impression [28]. Clearly, the more severe the initial deficit, the more desolate the outcome will be. However, reflecting the heterogeneity of stroke lesion location and size [29] – next to an individually variable ability of the neuronal network to adapt, owing in part to age, leading to a reduced ability to compensate [30], and perhaps a previous lesion load [31] – patients with mild paresis may recover only incompletely, whereas those with devastating initial impairments can unexpectedly fare better. Nonetheless, an almost certain prognosis can be made at the end of the subacute phase [32].

Timeline of Recovery

The patterns of recovery are illustrated in more detail below, stratified according to initial stroke severity. The discussion is based on the published data of the Copenhagen Stroke Study [3, 33–35], its results being comparable with other studies and epidemiologic summaries [36]. Ischemic and hemorrhagic stroke subtypes were differentiated, though most results were pooled. The authors present a community-based and therefore robust continuous follow-up of the degree of neurological deficits and general disability over a period of approximately half a year. As a note of caution, it is at times difficult to compare outcomes across studies owing to the inconsistent use of measurement tools [37]. Moreover, scales are always prone to floor and ceiling effects, especially prominent in the dynamic early phases of recovery and when change levels off.

General Recovery

The timeline of recovery clearly highlights the fact that the most dynamic period lies within the first weeks after onset. The best individually achievable general neurological outcome is reached in 80% of all patients within 4–5 weeks, showing the same degree of functional disability recovery (i.e. activities of daily living) within 6 weeks after stroke. Virtually no further change (i.e. 95% of patients having reached their best outcome) in either measure is detected starting 3 months after onset.

One day after stroke, three fourth of the cohort are still viable to neurological recovery, one half become better 1 week later, and after 3 weeks, only one fourth show subsequent improvement in the long run. Disability measures improve correspondingly, though reflecting somewhat shallower dynamics: 1 week after stroke, 55% of patients are still open for recovery, and at 3 weeks, one third will continue to improve.

Though the rates of recovery differ between the groups stratified according to initial severity, with the most devastating stroke subtypes reaching 80% of the individual best neurological recovery at 9–10 weeks, those only mildly affected surpassing this point as early as 2.5 weeks after onset follow similar patterns. Early on, there are greater gains, though gradually decreasing in the more chronic stages. Again, improvement in disability slightly lags behind.

Motor Recovery

Initial upper extremity paralysis or severe paresis is found in one third of all patients, the lower extremity being affected to a somewhat lesser extent. Moderate or mild paresis in the upper extremity is seen in a further one third of the group, with approximately the same figure for the leg. However, these deficits translate into different impairments of motor function in the subacute phase. The upper extremity is shown to be completely dysfunctional in only 20% (one quarter with partial function). However, almost half of the group could not walk, a further 10% walking with some help (i.e. partial function). At discharge approximately 5 weeks after stroke, 80% of patients surviving had regained upper extremity function, but only two thirds could walk independently. This discrepancy is reflected by the fact that by the third week, 80% of the individual maximum function is reached for the arm, but slightly later for the leg (by the fifth week).

One must differentiate between recovery through 'true' plastic mechanisms, leading to neurofunctional adaptation in areas directly affected by the ischemic injury, alleviating paresis, and a more broad modification of behavior associated with compensation. Measuring only motor activity as a correlate of the degree of paresis, patients lose on average near half of their normal capabilities at onset [38]. At the end of the acute phase, patients recover to about two thirds of the absolute scale maximum. In the phase of consolidation, further improvement takes place to three quarters of the full motor activity, no longer changing relevantly thereafter.

Improvement in the proximal muscles related to cruder movement patterns tends to be quicker than the reinstatement of distal fine motor control [39]. In part, this may be explained by their greater bilateral innervation [40], complemented by the fact that they receive a larger fraction of noncorticospinal input [41], rendering them less vulnerable to disruption.

Numerous other factors influence motor recovery, for example, neuropsychological deficits [42] such as neglect, which severely reduce the odds for good recovery [43].

Temporal Dynamics

Intriguingly, the rate of motor recovery towards the individual best outcome is almost independent of the initial severity in most patients (fig. 1) [3, 32]. A possible, though highly theoretical, explanation may be that the underlying processes of neuronal adaptation are in fact identical, unfolding at equivalent speeds, differing only in respect to the achievable potential of plasticity defined by the individual pathoanatomy of the ischemic lesion.

There has been some controversy explaining clinical change in the first 48 h after onset. An obvious mecha-

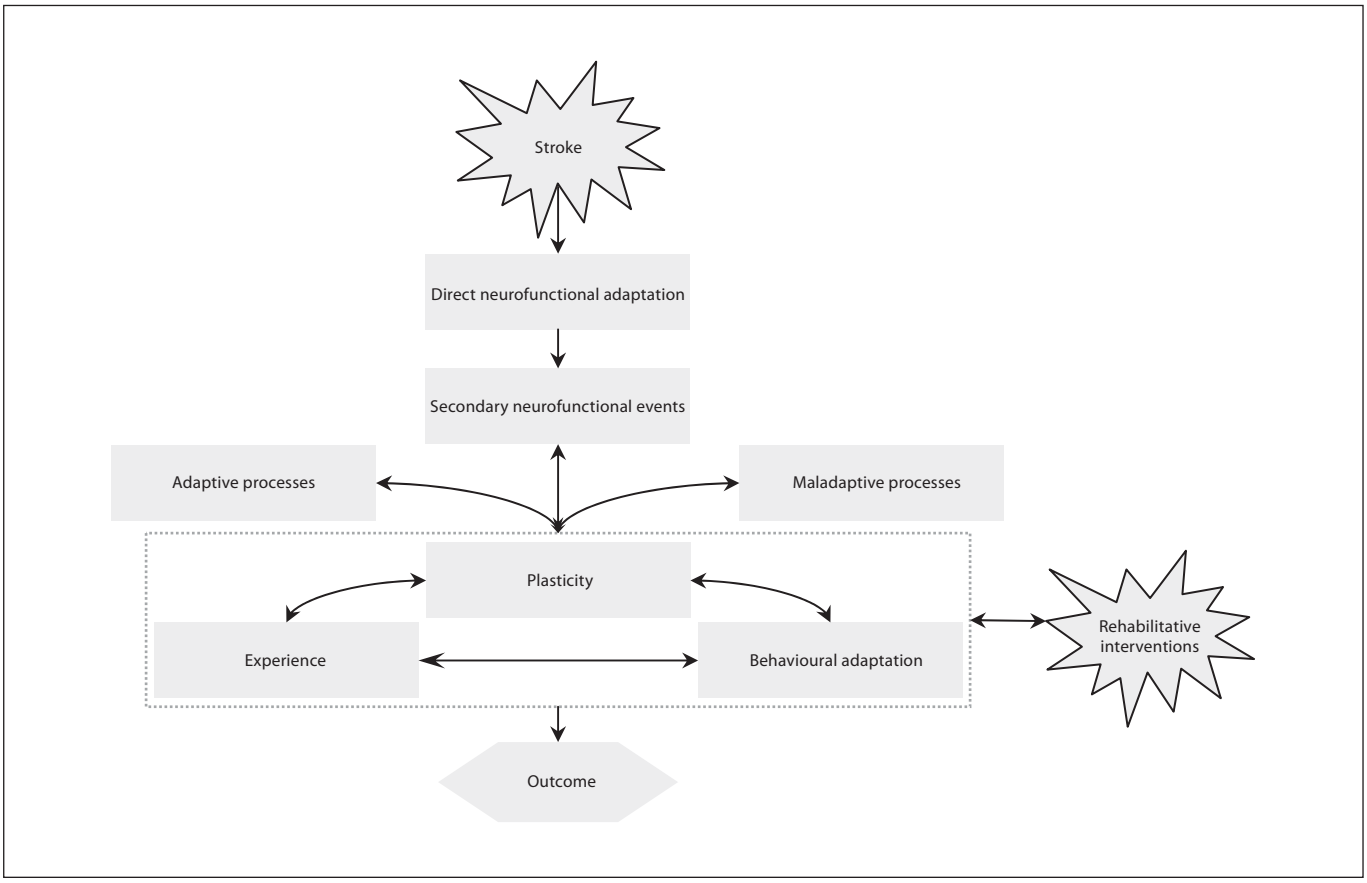

Fig. 2. Flowchart summarizing the interactions between neurofunctional adaptation, behavioral change and rehabilitative interventions towards outcome.

nism for spontaneous quick recovery could be early reperfusion leading to a direct alleviation of ischemic stress and the salvaging of functionally still intact parenchyma [44]. On the contrary, clinical deterioration will be related to such things as lesion core growth or, in large infarctions, rapidly developing edema [45]. Interestingly, however, if these assumptions hold true in all cases, it is difficult to explain the larger portion of patients with smaller, often microangiopathic lesions unsuspicious of any notable reperfusion dynamics experiencing substantial improvement [46]. Here, we may find a very serious indication of 'true' positive neuronal adaptation.

In a similar light, when direct or secondary effects of parenchymal injury have subsided, motor improvement taking place in the later stages of recuperation, though minor on average, provides some evidence substantiating the plastic potential of the neuronal network [47].

Use- and Training-Dependent Plasticity

It has been demonstrated that there is substantial recovery after stroke with clearly delineated dynamics, resulting in a faster recovery in the acute and subacute stages, gradually leveling off as time progresses. In the preceding review, we attempted to describe the temporal pattern of pathophysiological events that drive the adaptation of the system [1]. In the following, we will look at the possibility whether rehabilitative intervention can interact and influence neurofunction (fig. 2).

There are several prerequisites to keep in mind. Experience modulates behavior [48], and consequently, enriching stimulation leads to plastic processes including morphological change [49, 50]. Moreover, specific training leads to specific adaptation [51, 52]. For example, the location and size of representational fields change under movement [53]. However, interventions such as simple repeti-

tive motion alone hardly result in profound plastic change [54]. Skill learning must be present to promote cortical plasticity [55]. Also, subjective connotations promote consolidation [56]. In addition, active participation (i.e. voluntary motor control) is more efficient in eliciting network alterations than passive movement [57]. Though motor training can lead to neurofunctional adaptation within a matter of minutes [58], lasting representational change may take days [59] or weeks of practice [60]. Rapid alternations are bound to be reflected in a less specific remodeling of network activity [61]. More permanent change is reflected in, for example, augmented dendritic branching [62] and synaptogenesis [63], possibly provoked by specific gene induction [64, 65], and cumulates in an increase in the efficacy of synaptic transmission [66].

Positive Plasticity

Direct stimulation of the motor cortex, as an analogy to an increase in cortical activation [67], leads to a change in representation, as does real motor activity [18]. In turn, a 'strengthening' of cortical connections follows [66]. This exemplary physiological cascade is quasi identical to plasticity initiated by injury [68] and subsequent retraining [69]. It results in neuronal change [70] as well as structural response in glial parenchyma [71].

Next to evidence supporting rehabilitative training as a way to at least partially reinstore innervation, a further important argument in its favor must be noted. Without use of the paretic extremity, representational areas undergo further deterioration [72]. Conversely, this negative effect is preventable if specific (i.e. preferential use and further repetition of specific movements of the impaired extremity) and early retraining is initiated, leading to an enlargement of relevant representation perilesionally [73].

Two essential points implied by these results must be discussed further. (1) How specific is the plastic reaction to specific use? (2) Is plasticity dependent on the time after injury?

Specific Effects of Specific Use

Specific effects of specific training after stroke should in theory be reflected by a functional gain in the motor skill being rehabilitated. In turn, this should be accompanied by specific neurofunctional changes. Though there is substantial evidence in favor of such an interrelationship, it has not been conclusively demonstrated in animal studies [74], much less in humans [4].

Additional supportive retraining in primates, in comparison with a regimen of simple preferential use of the affected extremities, is more effective in inducing representational changes [75]. In the same light, completely restricting the use of the impaired extremity suppresses morphologic change perilesionally [76]. On the other hand, if an animal is prevented from using its nonaffected side, morphologic change (here in the contralesional hemisphere) is also inhibited [77].

Interestingly, more complex early acrobatic training, in contrast to simple unilateral motor exercise of the impaired extremity, leads to better recovery accompanied with more profound morphological change [70]. Also, providing an enriching environment leads to significantly better functional change [78]. Combining both strategies further ameliorates the outcome [79].

Inevitably, an ischemic lesion of the motor system will lead to a disruption of motor function, usually contralaterally, and at the same time, provokes compensatory use of the intact side. This 'natural' change in behavior clearly has an impact on the distribution of activity in favor of the unaffected hemisphere. It is therefore not surprising that any plastic reaction reflects a bihemispheric phenomenon and, in fact, may be the best indicator for successful positive use-dependent plasticity [76].

Temporal Vulnerability of Positive Plasticity

Neurofunctional change in reaction to an ischemic injury is likely to depend on the time after the lesion [1]. In experimental rodent and primate studies, one sees a clear negative dependency between time after onset and possible effects of rehabilitative interventions. The longer one waits, the smaller the chance to therapeutically influence outcome. Training initiated after day one is more effective than training started a week after experimentally induced ischemia [80]. If animals are placed in enriched environments and receive rehabilitative training within 5 days after onset, clinical outcome is significantly better compared with those who received specific training starting 14 days after ischemia. In turn, the latter animals performed better than those whose therapy was initiated at 1 month [81]. Importantly, these ameliorations are associated with structural change in the contralesional hemisphere, among other areas [81]. The morphologic adaptation seen may be associated with a time-dependent increase in neurotrophic factors stimulating dendritic modulation (dendritic growth and arborization) and synaptogenesis, both peri- as well as contralesionally [82]. The former process is most prominent at around 1 week after ischemia, the latter within the first several weeks. Possibly associated with or complimentary to these events is a similarly time-dependent hyperexcitability in regions

critical for motor innervation [1]. An experimentally induced downregulation of network overactivation consequently disrupts clinical improvement [83].

Are these animal results similar to what is seen in human recovery under rehabilitation? Again, there is no hard evidence refuting the hypothesis that early training is more effective than late training. On the other hand, positive evidence is insubstantial as well. However, some studies do report a slight benefit if training is started earlier. Patients receiving rehabilitative treatment within the first 20 days, compared with those whose treatment began between day 21 and day 40, have a greater chance of benefiting from therapy. In turn, the latter group performs better than those starting rehabilitation even later [84]. Moreover, there is some evidence that supports a treatment start within the first days [85, 86], though the effects are small. Also, patients receiving a more specialized treatment earlier tend to profit more [87].

Use-Dependent Detrimental Effects

The direct consequences of an ischemic lesion, namely the loss of innervation and the associated imbalance of network activation and inhibition, drive the system to an on average positive adaptation [1]. However, the feedback of altered behavior or therapeutic manipulations also initiates secondary negative effects. In the very early period after stroke, these may be mediated on the basis of an excess release of excitatory transmitters, exacerbating damage to vulnerable perilesional tissue. In the chronic stages of recovery, one often sees a consolidation of functionally ineffective movement patterns, including an overuse of the unaffected extremities, leading to detrimental compensation.

There is convincing animal experimental evidence that the penumbra and perilesional areas in the hyperacute, acute and early subacute phases are negatively vulnerable to external manipulations, such as increased motor activity in the affected extremity. The most probable pathway inducing such change is related to the efflux of glutamate. Glutamate, directly or indirectly, has been associated with exaggerated cell death in ischemia [88]. Intriguingly, it has been shown to be released in the vicinity of innervating neurons under movement [89, 90]. Therefore, it is possible that (excessive) use of the paretic extremity may provoke further damage in the surrounding areas of the lesion [91].

The lesion induces morphological change in the unaffected hemisphere [92]. An underuse of the intact extremity subsequently prevents corresponding contralesional adaptation [77]. Based on these findings, and substantiating the hypothesis of use-dependent detrimental ipsilesional effects, it has analogously been shown that if the paretic extremity is used excessively early, as would be the case under an intense rehabilitation regimen, not only is morphological adaptation inhibited contralesionally, but also a dramatic increase in the size of the lesion is found [19]. This correlates with more severe clinical deficits. Alarmingly, even when training is not unphysiological, as would be the case when forcing the use of the paretic side, applying only moderate rehabilitative training, one finds larger lesion sizes than in control rodents [93]. Interestingly, the resulting clinical deficits, possibly related to a more differentiated therapeutic regimen, are not as profound. Results to this extent have been replicated in numerous other animal studies [94, 95]. Consolidating the proposed link that glutamate is involved, the detrimental perilesional effects can be suppressed if its effect is blocked pharmacologically [91].

However, very early training must not imperatively be detrimental. It has been shown that a mild and more specific rehabilitative therapy of the impaired extremity can provoke positive effects [73]. In fact, it has been demonstrated that restricting the use of the impaired extremity inhibits the expression of relevant growth factors in the surrounding areas of the lesion, implying that motor activation is a prerequisite for any functional improvement in later stages [96].

Though these results are clearly not transferable to the setting of human acute stroke rehabilitation, asking the opposite question – does an intensive therapy very early after stroke enhance outcome? – sheds some light as to possible effects in humans. In fact, it has never been conclusively demonstrated that providing acute, intense rehabilitative therapy actually augments the dynamics towards recovery [97, 98]. Next to denying acute rehabilitation any positive influence on outcome, and remaining speculative, perhaps the therapeutic regimens applied very early actually circumvented positive effects. Later interventions, for example in the second week after onset, forcing the use of the paretic extremity, do provoke some amelioration [99].

Effects of Stroke Rehabilitation in Humans

Subsuming the above discussion, we must ask the following cardinal question: can the evident drive towards reorganization of the motor system provoked by an ischemic lesion, reflected in the clinical dynamics and having a clear temporal pathophysiological profile, be positively

influenced through rehabilitation? There have been numerous attempts to provide an affirmative answer. However, results are at best equivocal, owing in large parts to the heterogeneous nature of the disease. More importantly though, the plethora of intervention strategies makes any sensible synopsis of potential positive effects nearly impossible. Nonetheless, some valuable contributions have been made, evaluating the literature along evidence-based criteria [5, 100, 101]. It is the general conclusion that for a rehabilitative approach to have any chance of being effective, the therapy must be intense and specific. Moreover, it must be started early after stroke, though there is no consensus as to the exact time, and must be continued well into the chronic stage.

Intensity and Specificity of Treatment

The intensity and specificity of rehabilitative regimens reciprocally influence the treatment effect. However, the one does not go without the other. Numerous studies employing traditional physiotherapeutic approaches have failed to demonstrate substantial results, even though therapy was intense [102–104]; however, less severely affected subgroups do tend to profit [105]. Yet interestingly, conventional treatment regimens based on an unspecific peripheral modulation of motor tone can lead to neurofunctional change [106]. Nonetheless, clinical effects remain insubstantial, independent of the time of treatment onset, be it early on [107] or in later stages of recovery [108]. On the other hand, if interventions are more closely related to the 'relearning' of motor functions, a certain superiority to traditional schemes is seen [109]. Henceforth, the intensity of treatment may positively influence the outcome [110], but in order to produce tangible results, it must also be specific. Further highlighting this interrelationship is the fact that if effects are found under a more intense but nonspecific regimen, they tend to be more general, improving disability but not leading to an explicit recuperation of impaired motor activity [111]. Though these interactions had been predictable from early trials [112–114], it has not been until relatively recently that they have been substantiated: intense and specific training of the upper and lower extremity can provoke a gain in motor performance in the target extremity, next to an amelioration of the more general functional status [115].

Though precise information as to the nature of individual patient-therapist interactions is missing in many rehabilitation studies, positive effects are bound to be directly related to the time spent repeating relevant tasks. There is no reason for intense and specific stroke rehabilitation to differ from motor learning schemes in unaffected individuals, though it must be cautioned that the limited potential to recuperate may inevitably necessitate alternative strategies leading to compensation [116]. The essence of an effective intervention strategy is to treat task oriented, subsuming focused and repetitive elements of therapy.

Not without reason are the most effective rehabilitation regimens to date based on repetition, as a correlate of intensity, and use constrained to the paretic extremity, as a correlate of specificity [117]. Next to the already established method of forcing the use of the affected extremity in the chronic phase of stroke, by selectively restraining movement of the intact side [118], there have been some reports that this procedure may also be useful when applied as early as 14 days after the stroke [99, 119]. Substantiating the effectiveness of comparable treatment regimens is the fact that they actually lead to measurable change in neurofunction. It has been shown that with as little as a single session of therapy, representational size increases ipsilesionally, correlating with clinical improvement [120]. Specifically focusing on one part of an impaired extremity, while at the same time suppressing the function of other parts, ameliorates the performance by enhancing representation of the muscles involved in training [10]. In fact, abnormal hemispheric asymmetries, with a predominant activation of the contralesional hemisphere, can be normalized, resulting in a shift towards ipsilesional representation [121], though this conclusion is not without controversy [122].

Notwithstanding these encouraging results, the majority of evidence comes from trials in patients well after stroke onset, when the potential to positively 'shape' plasticity has succumbed [1]. Moreover, the unresolved issue of detrimental effects, especially in the very early phases of recovery [123], may counteract a more general application of these forms of therapy. Also, simply forcing the use of impaired function without supporting motivation directed to the task, associated with a focus on attention, will not lead to sustainable effects [57]. In fact, learning on the network level is in large parts dependent on subjectively connoted sensory stimulation (i.e. salient cues) [56, 124]. Nonetheless, several studies have highlighted the positive effects of simple focused repetitive training [125, 126], though not all with positive results [127]. Moreover, it is noteworthy that more complex bilateral repetitive maneuvers also enhance the outcome [128–130], in line with bihemispheric mechanisms of neurofunctional adaptation.

Continuity

Though practice enhances representation, an engrammation of restored function may be the more difficult task at hand. Some of the effects produced by, for example, forcing the use of the paretic extremity persist for periods of up to 1 year. However, there is evidence that without maintenance of therapy, effects may be reversed as soon as 1 day after discontinuation [120]. In larger clinical trials that showed positive results under therapy within the first several months after onset [115], recovery of those intensely treated initially remained stable, whereas those having undergone conventional treatment and having recovered only partially caught up in the long run, even without further rehabilitation [131]. Late therapy well into the chronic stage may make the difference [132–134], as effects decline once treatment is stopped [135]. Moreover, epidemiologic studies show functional competence continuously dropping in the course of 5 years after stroke, reaching levels equaling those at discharge [136]. However, patients receiving more intense and specific therapies in the subacute phase and the period of consolidation retain their outcome benefits over long periods of time [137]. This substantiates the temporal vulnerability of plasticity and underlines the possibility that intense and specific therapies crucially prime further recovery.

What Is Next?

Any rehabilitative treatment must compete with the natural course of recovery and demonstrate that it substantially influences the dynamics of recovery. This remains a difficult obstacle to surmount. Research into rehabilitation and its effects on the natural course of stroke is only now gaining sufficient momentum to provide an environment in which to address the questions discussed in this review and its companion article [1].

It has been clearly demonstrated that the brain undergoes neurofunctional adaptation after stroke, compensating for lost function. Though the ischemic lesion leads to debilitating impairment, it also primes plasticity, reflected in the otherwise unexplainable clinical dynamics towards recovery. Recuperation follows a clear temporal profile, being most active early on, leveling off to near stagnation in the chronic phase. Rehabilitative interventions in line with neurofunctional adaptation, being intense and specific, support the natural course of recovery. This implies an early start of treatment, but rehabilitation is also effective in later stages. Nonetheless, next to being beneficial, there is some concern that intensive training in the hyperacute and acute phases after stroke may be detrimental.

What then are the major points to be addressed in future research in the routine clinical setting?

- Rehabilitative intervention must be tested in respect to its effect, necessitating far larger trials, satisfying evidence-based criteria.
- In light of the difficulty of quantifying rehabilitative interventions, next to the insurmountable variety of possible treatment regimens and the substantial subjective component innate to therapist-patient interactions, this implies that one should limit the intervening variable to measures of time on task and specificity.
- Trials must document clinical impairments serially, not only limited to onset and outcome scores. Moreover, instruments that rate the breadth of motoric activity, motoric function and disability must be used complementarily.
- Delineating beneficial, but also detrimental, effects of rehabilitative interventions, future studies must look into questions related to the time of treatment onset and the continuity of treatment in later phases of recovery.

Rehabilitation is a major part of comprehensive therapy and care after stroke. However, its effects and mechanisms of action have been taken for granted for far too long. Any contemporary therapeutic option must be impartially tested in respect to its usefulness. If one bases future research on solid ground, there is reason to be optimistic that rehabilitative interventions will prove to show a significant positive influence on patient recovery.

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