Getting Neurorehabilitation Right : What Can Be Learned From Animal Models?

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Neurorehabil Neural Repair 2012 26: 923 originally published online 30 March 2012
DOI: 10.1177/1545968312440745

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Neurorehabilitation and
Neural Repair
26(8) 923–931

DOI: 10.1177/1545968312440745
http://nnr.sagepub.com

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Abstract

Animal models suggest that a month of heightened plasticity occurs in the brain after stroke, accompanied by most of the recovery from impairment. This period of peri-infarct and remote plasticity is associated with changes in excitatory/inhibitory balance and the spatial extent and activation of cortical maps and structural remodeling. The best time for experience and training to improve outcome is unclear. In animal models, very early (<5 days from onset) and intense training may lead to increased histological damage. Conversely, late rehabilitation (>30 days) is much less effective both in terms of outcome and morphological changes associated with plasticity. In clinical practice, rehabilitation after disabling stroke involves a relatively brief period of inpatient therapy that does not come close to matching intensity levels investigated in animal models and includes the training of compensatory strategies that have minimal impact on impairment. Current rehabilitation treatments have a disappointingly modest effect on impairment early or late after stroke. Translation from animal models will require the following: (1) substantial increases in the intensity and dosage of treatments offered in the first month after stroke with an emphasis on impairment; (2) combinational approaches such as noninvasive brain stimulation with robotics, based on current understanding of motor learning and brain plasticity; and (3) research that emphasizes mechanistic phase II studies over premature phase III clinical trials.

Keywords

neural plasticity, stroke rehabilitation, physical therapy, dose–response relationship, sensitive period, GABA signaling, neuroimaging

Stroke is the leading cause of disability among adults, and hemiparesis is the most common impairment after stroke.[1] Animal models suggest a time-limited window of heightened plasticity in the brain early after stroke when most recovery from impairment occurs.[2,3] Surprisingly and disappointingly, however, insights from animal models have had few effects on thinking about rehabilitation in humans—a situation that must change. There are 3 fundamental interconnected areas of research that urgently require new and innovative approaches: (1) the time course of spontaneous recovery in the first 3 months after stroke and its underlying mechanisms, (2) the interaction between motor learning and endogenous plasticity mechanisms, and (3) new interventions, including novel learning protocols and noninvasive brain stimulation, to enhance recovery from impairment in the first 3 months after stroke.

Preclinical models of stroke have recently provided important data on the timing and sequence of events for recovery of function during this period. Most of the behavioral recovery seen in animal models of stroke is apparent within the first month after the event. There is a series of events, beginning with changes in cell–cell signaling and other molecular events in the peri-infarct tissue, that lead to recovery of function within motor and sensory cortices.

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Animal Models: Molecular, Cellular, and Physiological Changes in the Peri-infarct Cortex

The timing of poststroke functional and structural reorganization and recovery in preclinical stroke models suggests an early poststroke phase of increased brain plasticity. Supporting this concept is the finding that cortical sensory maps are highly plastic within the first 2 weeks after stroke. Within 3 days after stroke, unilateral sensory stimulation leads to activation of ipsilateral sensory cortex, as opposed to normal contralateral activation. Then, 2 weeks later, the peri-infarct cortex regains responsiveness and there is a diminished response in the cortex contralateral to the stroke.[4,5] Functional MRI measures show that the degree of shift of cortical sensory responsiveness back to the peri-infarct cortex in this 2-week period correlates with the level of sensory recovery.[4] Recent technological advances using optical intrinsic signal and calcium indicator imaging methods have added crucial timing and spatial details to reveal how reorganization occurs in the peri-infarct cortex. At 2 weeks after a small somatosensory cortical stroke, there is loss of forelimb sensory responses, with minimal responsiveness in the surrounding cortex. By 4 weeks poststroke there is a response to forelimb stimulation in peri-infarct tissue, although neurons exhibit atypical responses and cortical map organization includes enlarged and unusual body part representations.[4]

At the cellular level, dendritic spine morphogenesis occurs in parallel with expansion in cortical maps. The first month after stroke is an intense period of reorganization of dendritic spine architecture.[6,7] As dendritic spines are the receiving structures for input onto pyramidal neurons, this change in neuronal structure is likely part of the substrate for restoration of activity in the peri-infarct cortex over the first month after stroke.

In parallel to the imaging data showing a period of decreased responsiveness after stroke, electrophysiological studies of the peri-infarct cortex show that stroke stuns the adjacent peri-infarct cortex, and this process evolves over the first month after the stroke.[8] Neurons in the peri-infarct motor cortex are hypoexcitable for at least several weeks after the infarct. This hypoexcitability impairs their ability to respond to afferent inputs and activate lower motor neurons. The reduced excitability in the peri-infarct motor cortex after stroke is the result of a diminished reuptake of the inhibitory neurotransmitter GABA (γ-aminobutyric acid) by reactive astrocytes. A key translational element to this finding is that the receptors that mediate tonic GABA signaling can be targeted with unique pharmacological agents, such as $GABA_A$ receptor α5 inverse agonists, which restore normal levels of excitability to motor cortical neurons and also improve functional recovery.[9]

Besides increased inhibition, there is evidence of decreased excitation in the peri-infarct cortex during the first month after stroke. The main excitatory neurotransmitter in the brain is glutamate, and it signals through AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA (N-methyl-D-aspartate) receptors. The role of these glutamate receptors in recovery is just being defined. Normal excitatory signaling through the AMPA receptor is an important element in motor recovery after stroke. Low levels of AMPA receptor blockade in the first 2 weeks after stroke, which would not cause behavioral deficits in normal mice, transiently impair motor recovery. Conversely, enhancing AMPA receptor activity in the first weeks after stroke improves motor recovery. Mechanistically, this improvement in motor recovery with AMPA receptor modulation occurs via induction of brain-derived neurotrophic factor (BDNF). Poststroke excitatory signaling in the peri-infarct cortex controls motor recovery through local induction of BDNF in circuits adjacent to the infarct.[10] BDNF may have direct effects on synapses but also affects angiogenesis and other aspects of brain remodeling after stroke[11,12] and, as discussed in the next section, may be induced by a neurorehabilitation paradigm.

Stroke triggers a regeneration molecular program in peri-infarct neurons that is maximally induced 1 week after stroke and then plateaus at 3 weeks.[13] Because axonal sprouting occurs in the same circuits that relate to recovery in human brain imaging studies, and because new patterns of cortical connections are induced in rats, mice, and nonhuman primates, this process of sprouting and formation of new connections appears to contribute to stroke recovery. Stroke stimulates new connections to form within the peri-infarct cortex, including projections from the cortex contralateral to the infarct.

In summary, the first month after stroke is a crucial time for synaptic plasticity in the peri-infarct cortex. Cortical map changes are detected in the opposite hemisphere from the stroke during a period of hypoexcitability in the peri-infarct cortex. Within 2 weeks, the peri-infarct cortex regains responsiveness to cortical afferents and remaps limb responsiveness in locations that were not limb related prior to the stroke. This process is accompanied by the formation of new connections within cortical circuits, both in terms of turnover of dendritic spines and the formation of new axonal connections. A unique regeneration molecular program stimulates this alteration in cortical circuits after stroke and progresses through distinct phases in the first 3 weeks. Therapies that target tonic GABA inhibition or glutamate receptor signaling during this recovery phase promote recovery and serve as viable clinical targets for a stroke repair treatment. In addition, manipulation of growth factor signaling in peri-infarct tissue, such as with BDNF, may be a promising approach.

Timing of Rehabilitation in Animal Models of Stroke

Dendritic spine morphogenesis, axonal sprouting, and neuronal growth factor induction occur both after stroke and

as a result of behavioral experience. For example, housing animals in enriched environments produces dendritic growth, new spine formation, and synaptogenesis.[14,15] It is important to note that these behavioral effects on plasticity are evident in both normal and brain-damaged animals.[16] Thus, the possibility exists for enrichment/rehabilitation to augment the brain's own intrinsic repair capacity and thereby improve functional outcome after stroke. However, the interplay between neuroplasticity processes triggered by injury and by experience is complex, particularly with regard to timing.

How Early, How Late?

Concern about initiating therapy too early following stroke arose from animal studies showing that forced use of the affected limb and forced disuse of the nonaffected limb immediately after injury blocked potentially beneficial plasticity changes and/or exacerbated injury.[17] These results are perhaps not too surprising given the close temporal pairing of highly altered activity with induction of injury. However, animal studies where motor training or exposure to enrichment have been initiated several days after stroke are more revealing, as they bear closer resemblance to clinical practice. In such cases, early intervention (ie, 1-3 days) again was associated with increased cell death but paradoxically improved long-term behavioral outcomes.[18,19] Cell death may reflect a pruning effect, whereby energy-compromised dysfunctional neurons are eliminated early on as a result of use-dependent activation associated with rehabilitation. However, even without rehabilitation, such compromised cells would most likely have died with more extended survival. The overall consensus from animal data is that rehabilitation initiated 5 or more days after stroke has no adverse effects.

When is the best time to start rehabilitation? Stroke triggers changes in gene and protein expression that are characteristic of early brain development, a time of robust axonal growth and synaptic proliferation. The notion that sensitive periods might exist following stroke derives from the classic demonstration by Hubel and Wiesel that visual deprivation during a sensitive period early in life permanently altered the properties of the adult visual cortex. For example, is there an optimal time window beyond which rehabilitation is less effective? Experimental evidence suggests that such a time window does exist.[20,21] Exposing rats to an enriched environment in combination with daily sessions of reach training therapy following middle cerebral artery occlusion resulted in significant gains in the recovery of forelimb reaching ability when the rehabilitation was initiated 5 or 14 but not 30 days after stroke. Recovery was associated with increased dendritic branching of layer V motor cortex neurons—a response not seen when rehabilitation was delayed by 30 days. This behavioral recovery profile relates quite well to the known sequence of neuroplasticity changes that are implicated in stroke recovery. For example, Carmichael and others have identified waves of growth promoting gene changes that begin in the first days after stroke, peak at approximately 7 days after stroke, and then shift into a maintenance phase at later time points.[13,22] In contrast, many molecules that limit inappropriate growth appear to have a delayed induction after stroke, gradually reaching a zenith several weeks after stroke when growth-promoting gene changes have peaked and are beginning to decline. Additionally, as noted, studies have identified a period of GABA-mediated tonic inhibition that is necessary in the first few days after stroke to limit an expansion in infarct size.[9] Rehabilitation initiated in this very early time frame may worsen injury and result in less functional recovery.

Behavioral Changes Associated With Reorganization in the Peri-infarct Cortex: Compensation Versus True Recovery

Although it is convenient to refer to gains in poststroke performance as *recovery*, it is important to distinguish between compensatory responses and true recovery. There has been extensive characterization of skilled forelimb reaching in the rat after stroke, with an emphasis on this distinction between compensation and true recovery. Here, we will briefly describe how these studies are performed and analyzed and then summarize the results to date. The skilled reach task requires that the rat reach through an aperture with its forelimb to grab a pellet off an elevated shelf.[23] The animals are trained on this task before a stroke is induced and then retrained after stroke. Two kinds of measures are used to quantify performance. The first captures global success or the end point of the reaching behavior and comes in 3 variants: total percentage success, percentage success on the first reach, and total number of attempts. The second measure quantifies the kinematics of reach using video-recorded behavior; 12 movement elements and the posture during grasp are scored on a 3-point scale. This kinematic measure allows for a distinction to be made between compensatory movements and true recovery of prestroke movements. A large number of studies using this task or similar variants and the same scoring approach have led to the following consistent observations:

1. Recovery of end point behavior in the first 2 weeks to 1 month after stroke, even after a large cortical lesion, can be dramatic. Specifically, even the percentage success rate on first reach shows large improvements. Indeed, this measure can return to prestroke levels even with large cortical lesions.[24-26]
2. For large strokes, recovered end point measures are not accomplished by a return to prestroke

kinematic patterns but instead by the adoption of new compensatory movement patterns—for example, trunk rotation.[27]

3. For small cortical strokes with a spared peri-infarct forelimb cortex, recovery is mediated by both partial recovery of prestroke kinematics and compensatory movements.[28]
4. Both true recovery and compensatory movements are mediated predominantly by plastic changes in the peri-infarct cortex,[29] albeit likely in different areas.[30]
5. Although never complete, there is always some degree of true recovery. The rat may choose a compensatory strategy over true recovery. There is nothing in these studies that precludes the possibility that more true recovery would have occurred had compensation been restrained. It may be that changes in the peri-infarct cortex can mediate both kinds of recovery in the acute poststroke period and that it is, to some degree, a zero-sum game.
6. Recovery from cortical infarcts is not immediate but instead takes 2 to 3 weeks.[31] This is in contrast to the recovery from partial pyramidal tract lesions, which is maximal the day after the induction of stroke[32] and suggests that peri-infarct reorganization takes time, whereas use of spared descending tracts may not. This time window could be exploited to test interventions that might augment reorganization.
7. The concept of spontaneous biological recovery is not brought up much in animal studies, because the approach is to train and then retrain on a novel task rather than to assess spontaneous reductions in impairment in naturalistic behaviors.

Comparing the Time Courses of Stroke Recovery in Animal Models and Humans

There is a general concordance between animal-model and human studies that earlier intervention is more effective than delayed rehabilitation. Notably, recovery in animal models is maximal 4 weeks after injury even in the presence of continued therapy, and human stroke survivors complete almost all recovery from impairment by 3 months. The reason for the difference between 4 weeks and 3 months is unknown at this time, although it may be a reflection of biological differences or the fact that rehabilitation started early in animal models is much more effective than current rehabilitation approaches used in patients over a comparable time period. Compared with some inpatient rehabilitation settings, rodents provided with a more enriched environment are continuously physically and cognitively challenged in a highly social setting. Furthermore, in many studies, voluntary access to impairment-specific poststroke reach training therapy in animals is not limited to short therapy sessions.[21] These studies suggest an additive effect of environmental and activity-dependent stimulation on recovery in the poststroke brain. Many of these features of enriched rehabilitation could and should be incorporated into current clinical rehabilitation practice. A final point is that in humans the strict time window pertains mainly to recovery from impairment (true recovery) rather than compensation, which can also be learned in the chronic phase.[33,34]

It may well be, however, that like in rodent models, even compensatory movements are learned more quickly early after stroke. Indeed, it seems as though changes in peri-infarct cortex in rodent models may be weighted toward supporting compensatory changes, whereas large reductions in impairment can occur in humans. At present, we do not have an understanding of how compensatory changes that occur in chronic stroke in humans compare to compensatory changes that occur early in rodent models.

Few animal studies have examined recovery in the chronic phase of stroke (ie, 2-6 months—the reverse of the case in human studies), but in 1 report, several brief 2-week periods of rehabilitation or "tune-ups" initiated after the initial recovery phase (ie, first month poststroke) were without benefit.[35] This is consistent with the unimpressive gains seen at the level of impairment in patients receiving rehabilitation in the chronic phase. However, patients can be trained to walk faster and build strength and fitness at any time after stroke, which may improve daily functioning.

Both Timing and Dose Are Important

In most rodent stroke recovery studies that use reaching as part of the rehabilitation protocol, there is often no limit imposed on the amount of reaching allowed; rats will typically reach 300 times in a training session. In studies by Corbett and colleagues, rats were given voluntary access to a reaching chamber for 4 to 6 hours per day, 5 days per week. In a recent experiment, the amount of reaching the animals were permitted was varied, and the result was a reaching threshold above which recovery occurred.[36] Rats that failed to attain this threshold, though still engaging in considerable reaching behavior, did not exhibit significant recovery. It is interesting to note that the group of animals that showed the most recovery also had elevated levels of BDNF in the motor cortex—a significant finding, because this growth factor has been causally linked to poststroke recovery.[10,11] In view of evidence that stroke patients are given far less reaching practice than is usual during comparable animal rehabilitation studies,[37] it is imperative to consider developing more intensive as well as earlier rehabilitation paradigms in the clinical setting. A recent feasibility study found that it is possible to deliver a similar

number of upper-limb repetitions to stroke patients in a 1-hour therapy session as occurs in typical animal rehabilitation studies.[38]

The Human Perspective on Time Course of Gains

When Is Acute, Subacute, or Chronic Stroke?

The designation of time periods after stroke can be confusing. From the point of view of vascular neurologists, the *acute* stroke is within a few hours of onset because that is the time window for acute interventions. After that window has closed, the patient is *subacute*. But when the patient is transferred to a rehabilitation facility, from that perspective, they are *acute*, unless they go to a less intensive setting, in which case they may be considered *subacute*, *chronic*, or *long term*. The terminology depends on the clinical target: acute cell death for vascular neurologists and acute (early) rehabilitation for neurorehabilitation specialists. Most agree that at 6 months the patient is *chronic*. This is the only useful term, so we will refrain from using the other terms, and we refer specifically to the early time periods.

Medical System

In the United States, the current practice of stroke care involves acute interventions within or on the first day, diagnostic tests for about the first 2 days, followed by discharge to a variety of settings, unless complications ensue. There is considerable heterogeneity between institutions, states, and countries. The discharge location can range from home with no therapy to an inpatient rehabilitation facility, a setting that requires at least 3 hours of formal physical, occupational, and speech therapy per day. However, what happens during the 3 hours may not be intensive; time is lost in transportation, setup, and other activities that do not involve task practice, with the result that relatively little functional practice with the affected limb occurs.[39]

In 2009, the average acute rehabilitation stay was about 14 days (the trend is toward ever shorter lengths of stay, driven by the reimbursement system, not scientific evidence). It is tacitly understood that 2 weeks is too little time to train the affected side to any significant degree—that is, the emphasis is not on the reduction of impairment, which would almost certainly take considerably longer, but on the rapid establishment of independence in activities of daily living through compensatory strategies. Some examples are training ambulation with a hemiwalker and self-feeding and toileting using the unaffected arm exclusively.

After discharge, patients may enter an outpatient program, often after some delay, for an hour or less of each type of therapy 2 to 3 times a week. Patients often do not practice much between visits. This outpatient therapy continues until a plateau in several measurable functions is reached. This clinical protocol for extended neurorehabilitation in patients after stroke clearly differs from animal models of stroke rehabilitation and establishes a tempo and an intensity that are suboptimal for recovery, based on the preclinical literature.

Current Approaches to Rehabilitation

The vast majority of studies on neurorehabilitation and recovery in stroke have been conducted in chronic patients (>6 months out). The emphasis on patients with chronic stroke is understandable from a practical standpoint; these patients are much easier to recruit and are thought to have a stable baseline for which any change in performance can be attributed to the experimental treatment. The most impressive gains have been seen with functional outcome measures, and the least impressive ones were for impairment measures. This suggests that rehabilitation techniques applied in chronic stroke, as in subacute stroke, are mainly teaching compensation. The emphases on teaching compensation during acute rehabilitation stays and on conducting research on chronic patients to assess new rehabilitation techniques are both at odds with what basic neuroscience research in animal models is revealing. Currently, this critical period of spontaneous biological change that could improve gains is all but ignored. It has been stated that "in rehabilitation medicine, spontaneous recovery is perceived as one of the most neglected features of the clinical course of stroke."[40]

The Time-Dependent Effects of Constraint-Induced Therapy and Rehabilitation Robotics

The pivotal question raised by the animal model literature is whether intensive rehabilitation will prove more effective than conventional treatment early after stroke. Unfortunately, rehabilitation in existing studies in humans, with few exceptions, has not been intense *and* early. Thus, the human data can be examined for hints of a temporal gradient of effectiveness but not much more because it is simply a fact that studies that adequately mimic the conditions in animal models have yet to be conducted. Interest so far has been focused mostly on constraint-induced movement therapy (CIMT), which is directed at function, and robot-assisted arm therapy, which is directed at the impairment in the affected upper extremity. In the VECTORS study,[41] 52 stroke patients were randomized at about 10 days postonset to 2 levels of intensity of CIMT[42] or standard upper-extremity therapy. It should be stated that *intense* here meant 3 hours versus 2 hours of shaping therapy. The surprising result was that at 90 days, affected upper-extremity motor outcomes, measured with the upper-extremity Fugl-Meyer score (UEFM), were worse for the more intensive

CIMT group. Notably, however, there was no difference at 30 days, so conclusions are uncertain. In addition, longitudinal MRI did not show any enlargement of the brain lesion that could be related to intensity of treatment, so there was no evidence for infarct expansion, which was the putative explanation for intensity-related worsening in a rodent model.[17]

A study similar to VECTORS enrolled 23 patients within 1 week after stroke onset but with only 1 CIMT intensity level. In this case, the trend favored CIMT, although the traditional therapy group was more intensive than usual in order to match the CIMT group.[43] One must be cautious not to generalize from these small samples, but the conclusion appears to be that more impairment-directed training may be better in the first several weeks after stroke. The jury is still out on how early is too early, but this concern has been greatly exaggerated and may reflect negativity bias.

A much larger study, EXCITE, enrolled stroke patients about 6 months out from stroke, and it showed effectiveness of CIMT versus a usual care control (no active treatment) in increasing the speed of standardized, likely compensatory, movements on the impaired side.[44] The usual care group had CIMT 1 year later (ie, at about 1.5 years after stroke) and showed lesser gains. Given the measures used, however, it is unclear whether CIMT has any effect at all on impairment once outside (or even inside) the 3-month window. Some small studies have shown efficacy for a late phase of therapy,[45] but a tune-up after previous therapy is far more likely to affect functioning than impairment.

One of the first studies in robotics demonstrated a 4-point trend on the UEFM for the superiority of added robotic therapy during the 3- to 10-week interval after stroke[46] (there was also statistical significance for a more expanded impairment measure). The large VA Cooperative Study of robotics demonstrated a smaller 3-point gain on the UEFM for intensive therapy applied much later (average 4 years) after stroke.[47] The functional significance of such gains is, however, uncertain.

The conclusion to be drawn from these studies is that CIMT and robotics are most effective within a time window between 1 and 9 months after stroke, a time period most commonly taken up by nonintense outpatient therapy or nothing. Overall, the data may suggest that CIMT is having an effect on function, whereas robotic therapy is having an effect on impairment. It is of interest to consider whether even compensatory improvements benefit from the heightened period of plasticity early after stroke. At the impairment level, CIMT and robotics, with the timing and dosing used thus far, have been unimpressive. A meta-analysis performed several years ago had a similar conclusion for augmented practice schedules in general, demonstrating an effect within 6 months but not in the chronic phase.[48] Another analysis had also concluded that earlier, more intense therapy may be the most beneficial.[49]

Neuromodulators

Research experience with amphetamine as an adjunctive agent in the early rehabilitation period after stroke is sobering. Decades of animal research had suggested a beneficial effect of amphetamine in recovery of motor function.[50] However, more recent studies in both humans[51] and animals[52] are equivocal. It is not entirely clear why there are conflicting data, although it has long been recognized that amphetamine has multiple mechanisms of action, so testing of more pharmacologically specific agents continues. There has not, as of yet, been direct clinical application of the GABA and glutaminergic manipulations performed in preclinical studies, but the effects of modulation of other biogenic amines, such as serotonin, have been tested. Fluoxetine, a serotonin-selective reuptake inhibitor, was started about 9 days after stroke and continued for 3 months.[53] There was an impressive 10-point difference in total Fugl-Meyer score gain with fluoxetine. This study, in our view, is one of the first to look in the proper time window and to show effect sizes at the impairment level that compare with what has been seen in animal models.

Current Rehabilitation Methods Do Not Sufficiently Target Impairment

One could interpret all the research on improving function in chronic stroke as a tacit admission that patients do not get sufficiently intense therapy in the subacute and acute periods. A recent study determined that patients were active only 13% of the time and were alone 60% of the time during inpatient rehabilitation.[54] Lang and colleagues,[37] in a study of how much movement practice is provided during rehabilitation (inpatient and outpatient), found that practice of task-specific, functional upper-extremity movements occurred in only 51% of the rehabilitation sessions that were meant to address upper-limb rehabilitation and that even then the average number of repetitions per session was only 32. Data from the animal literature suggest that this dosage of repetitions is too low; changes in synaptic density in the primary motor cortex occur after 400 but not 60 reaches.[55,56]

We have recently shown that there is a highly predictable relationship, in the majority of patients, between their degree of arm impairment in the first week after stroke and their subsequent recovery at 3 months.[57] It is interesting to note that the relationship is proportional in nature; patients achieve about 70% of their maximal potential recovery, which suggests that spontaneous recovery may obey first-order dynamics. That we see such good prediction at 3 months based on measurements at 1 week has somewhat disturbing implications with regard to the current efficacy of rehabilitation. Three possibilities suggest themselves: (1) patients are actually dosed in direct proportion to their

level of impairment, and thus, current therapeutic approaches create the relationship; (2) some basal rate of rehabilitation is required for spontaneous recovery to express itself; or (3) current rehabilitation has no significant impact on recovery from impairment over what can be expected from spontaneous recovery. It is unlikely that 1 is correct, whereas if either 2 or 3 are correct, and it is very difficult to posit otherwise, then we need to do far better than we are doing now.

Rehabilitation of Impairment

An ideal poststroke therapy scheme would include a ramped intensity increase over the first few weeks after stroke, continued high-intensity therapy for several weeks, and a transition to a program of similar intensity in the outpatient setting, supplemented by a home exercise program with measureable practice parameters and outcomes.

Thus, we suggest the following new rules for both research and treatment of patients after stroke. The research focus needs to be on impairment—not on function, not on activities of daily living, and not on quality of life. This is because it is impairment that will most accurately reflect true biological repair mechanisms. To properly understand these mechanisms, we therefore need to be able to distinguish true recovery from compensation,[34,58] which will require quantitative movement analysis methods—not crude clinical scales that fail to inform as to how patients are improving. It will be important to conduct parallel analytic studies of recovery versus compensation in animal models. Those few laboratories that have conducted careful quantitative analysis have shown that it is critical to distinguish between mechanisms of these 2 quite distinct forms of recovery.[24,27,31] Distinguishing between recovery and compensatory motor patterns requires kinematic analyses of prestroke and poststroke reaching. Because these outcome measures are so time-consuming, they are not practical to implement in all proof-of-principle stroke recovery studies. However, when an intervention is identified that appears to enhance poststroke recovery in animal models using end-point measures, these interventions should be subjected to kinematic analysis to reveal whether the improved performance is a result of true recovery or compensation. The attraction of this serial approach—end-point measures then kinematics—is that it can be duplicated in human studies.

In terms of treatment, there needs to be a large increase in dosage and intensity of treatment in the first 4 weeks (and up to 3 months) with a focus exclusively on impairment. A recent study has shown that intensity can be markedly increased in this time period.[38] Training of compensatory strategies should be forbidden, with the possible exception of patients who remain hemiplegic at 2 weeks. Only at the 3-month mark, or after impairment starts to level off, should a training program be started to encourage optimal compensation. That is to say, the goal should be training that is specifically geared toward generalizing from reductions in impairment to functional gains. Development of methods that take advantage of the regional poststroke plasticity identified in animal models may help optimize that training. Such methods may include combinations of cortical stimulation, robotic training, CIMT, and other interventions.[59,60]

These suggestions will require a change in how rehabilitation research is funded and a change in emphasis. Scientists working on animal models, systems-level neuroscientists, and clinicians need to work together at the inception of projects and not simply pass knowledge along serially in 1 direction—the translational cliché. Funding should be geared toward longer term projects that emphasize mechanism, multidisciplinary teams, infrastructure, and phase II trials. We need to avoid expensive and premature mechanism-blind phase III trials, which have largely been, unsurprisingly in our opinion, negative.

Acknowledgments

This article arose out of the first American Society of Neurorehabilitation satellite meeting at the Society for Neuroscience Annual Meeting in San Diego, California, on November 12, 2010. Other speakers included Drs Carolee Winstein and Alexander Thiel, whose contributions to this topic are appreciated.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The authors acknowledge funding for projects related to this manuscript from multiple agencies, including NINDS, NICHD/NCMRR, The Department of Veterans Affairs, Canadian Institutes of Health Research, Canada Research Chairs Program, and the Heart and Stroke Foundation of Canada.

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