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Getting Neurorehabilitation Right – What Can We Learn From Animal Models?

John W. Krakauer, MD¹, S. Thomas Carmichael, MD, PhD², Dale Corbett, PhD³, and George F. Wittenberg, MD, PhD⁴

¹Center for the Study of Motor Learning and Brain Repair, Department of Neurology, Johns Hopkins University School of Medicine; and the Department of Neuroscience, Johns Hopkins University

²Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, Los Angeles, CA, USA

³Department of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada

⁴Baltimore VA Medical Center Geriatric Research, Education and Clinical Center (GRECC) and Department of Neurology, University of Maryland, Baltimore, MD, USA

Abstract

Stroke is the leading cause of disability, causing impairments in movement and sensation. Animal models suggest that there is about a month of heightened plasticity in the brain early after stroke when most recovery from impairment occurs. This heightened plasticity occurs against background changes in excitatory/inhibitory balance, is apparent structurally as neurite remodeling, and changes in the extent and responsiveness of cortical maps. The best time for experience to improve outcome is unclear, but in animal models only very early (< 5 days from onset) and intense activities lead to increased histological damage. Conversely, late rehabilitation (>30 days) is much less effective both in terms of outcome and morphological changes. In clinical practice, rehabilitation after disabling strokes involves a relatively brief period of inpatient rehabilitation that does not come close to matching intensity levels investigated in animal models, and it involves training compensatory strategies with minimal impact on impairment. Research on the effect of Constraint-induced and robotic therapy has been conducted almost entirely in chronic stroke but earlier does seem better. Current rehabilitation treatments have a disappointingly modest effect on impairment early or late after stroke. Translation from animal models will require: (1) substantial increases in the intensity and dosage of treatments offered in the first month after stroke with an emphasis on impairment, (2) Treatment combination approaches, for example, non-invasive brain stimulation with robotics, based on current understanding of motor

Corresponding author: George F. Wittenberg, VA Maryland, GRECC, 10 N. Greene St. (BT/18/GR), Baltimore MD 21201-1524, gwittenb@grecc.umaryland.edu, 410-605-7118.

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learning and brain plasticity, and (3) Research that emphasizes mechanistic phase II studies over premature phase III clinical trials.

Keywords

Plasticity; rehabilitation; timing; intensity; dosage; sensitive period; GABA

Stroke is the leading cause of disability among adults and hemiparesis is the most common impairment after stroke¹. As outlined below, animal models suggest that there is 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 three fundamental inter-connected area of research that urgently require new and innovative approaches: (1) The time course of spontaneous recovery in the first three 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 non-invasive brain stimulation, to enhance recovery from impairment in the first three months after stroke.

Pre-clinical 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 leads to recovery of function within motor and sensory cortices.

Animal models: molecular, cellular, and physiological changes in peri-infarct cortex

The timing of post-stroke functional and structural reorganization and recovery in pre-clinical stroke models suggests an early post-stroke phase of increased brain plasticity. Supporting this concept is the finding that cortical sensory maps are highly plastic within the first two weeks after stroke. Within three days after stroke, unilateral sensory stimulation leads to activation of the ipsilateral sensory cortex, as opposed to the normal contralateral activation. Two weeks later, peri-infarct cortex regains responsiveness to the contralateral limb, and there is a diminished response in cortex contralateral to the stroke^{4,5}. Functional MRI measures show that the degree of shift of cortical sensory mapping back to the peri-infarct cortex in this two-week period correlates with the level of sensory recovery⁴. 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 peri-infarct cortex. Two weeks after a small somatosensory cortical stroke there is loss of forelimb sensory responses with minimal responsiveness in surrounding cortex. By four weeks post-stroke 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 representations⁴.

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 peri-infarct cortex over the first month after stroke.

In parallel to the imaging data showing a period of decreased responsiveness after stroke, electrophysiological study of peri-infarct cortex shows that stroke stuns adjacent peri-infarct cortex and this process evolves over the first month after the stroke⁸. Neurons in 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 peri-infarct motor cortex after stroke is due to diminished re-uptake of the inhibitory neurotransmitter GABA by reactive astrocytes. A key translational element to this event is that the receptors that mediate tonic GABA signaling can be targeted with unique pharmacological agents, such as GABA_A receptor $\alpha 5$ inverse agonists, which restore the normal levels of excitability to motor cortical neurons, and also improve functional recovery⁹.

Besides increased inhibition, there is evidence of decreased excitation in peri-infarct cortex during the first month after stroke. The main excitatory neurotransmitter in the brain is glutamate, and it signals through AMPA and NMDA 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 two 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). Post-stroke excitatory signaling in peri-infarct cortex controls motor recovery through local induction of BDNF in circuits adjacent to the infarct¹⁰. 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 neurorehabilitative paradigm.

Stroke triggers a regeneration molecular program in peri-infarct neurons that is maximally induced one week after stroke, and then plateaus at three weeks after stroke¹³. Because new patterns of cortical connections are induced in rats, mice and non-human primates and axonal sprouting occurs in the circuits that correlate with recovery in human brain imaging studies, this process appears to contribute to stroke recovery. Stroke stimulates new connections to form within peri-infarct cortex including projections from cortex contralateral to the infarct.

In summary, the first month after stroke is a crucial time for synaptic plasticity in peri-infarct cortex. Cortical map changes are detected in the opposite hemisphere from the stroke during a period of hypoexcitability in peri-infarct cortex. Within two 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 three 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 are not only seen after stroke but can also be brought about as a result of behavioral experience. For example, housing animals in enriched environments also produces dendritic growth, new spine formation and synaptogenesis^{14,15}. Importantly, these behavioral effects on plasticity are evident in both normal and in brain-damaged animals¹⁶. 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 non-affected limb immediately after injury blocked potentially beneficial plasticity changes and/or exacerbated injury¹⁷. These results are perhaps not too surprising given the close temporal pairing of highly altered activity with induction of injury. More revealing are animal studies where motor training or exposure to enrichment have been initiated several days after stroke, which bears closer resemblance to clinical practice. In such cases, early intervention (i.e. 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? As described in the preceding section, it is now recognized that stroke triggers a number of changes in gene and protein expression that are characteristic of early brain development, a time of robust axonal growth and synaptic proliferation. The classic work of Hubel and Wiesel demonstrating that visual deprivation during a *sensitive period* early in life permanently altered the properties of the adult visual cortex leads to the notion that similar sensitive periods might also exist following stroke. For example, is there an optimal time window beyond which rehabilitation is less effective? Experimental evidence suggests 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 above, recent 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 size⁹. Rehabilitation initiated in this time frame may worsen injury and/or result in less functional recovery.

Behavioral changes associated with reorganization in peri-infarct cortex: compensation versus true recovery

While it is convenient to refer to gains in post-stroke 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 precisely this distinction between compensation and true recovery. Here we will briefly describe how these studies are performed and analyzed, and then summarize and the results to date. The original skilled reached task requires that the rat reach through an aperture with its forelimb to grab a pellet off an elevated shelf²³. The animals are trained on this task before a stroke is induced and then retrained after stroke. Two kinds of measure are used to quantify performance on this task. The first measure captures global success, or the endpoint of the reaching behavior, and comes in three variants: total percent success; percent success on the *first* reach; and total number of attempts. The second kind of measure quantifies the kinematics of reach using video recorded behavior; twelve movement elements and the posture during grasp are scored on a 3-point scale. This second kinematic measure allows for a distinction to be made between compensatory movements and true recovery of pre-stroke movements. A large number of studies using this task, or similar variants, and scoring approach have made the following consistent observations: 1) Recovery of endpoint behavior in the first 2 weeks to one month after stroke, even after a large cortical lesion, can be dramatic. Specifically, even the percent success rate on first reach shows large improvements. Indeed, this measure can return to pre-stroke levels even with large cortical lesions^{24–26}. 2) For large strokes, recovered endpoint measures are not accomplished by a return to pre-stroke kinematic patterns but instead by the adoption of new compensatory movement patterns, e.g., trunk rotation²⁷. 3) For small cortical strokes with spared peri-infarct forelimb cortex, recovery is mediated by both partial recovery of pre-stroke kinematics and compensatory movements²⁸. 4) Both true recovery and compensatory movements are mediated predominantly by plastic changes in peri-infarct cortex²⁹, albeit likely in different areas³⁰.

A number of additional conclusions and interpretations, not necessarily emphasized by the authors of the original studies, can be gleaned from review of this literature and are of direct relevance to the current review: 5) Although not complete, there is always some degree of true recovery. The skilled reaching task is redundant therefore 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 peri-infarct cortex can mediate both kinds of recovery in the acute post-stroke period and that it is, to some degree, a zero-sum game. 6) Recovery from cortical infarcts is not immediate but instead takes 2–3 weeks³¹. This is in contrast to the recovery from partial pyramidal tract lesions, which is maximal the day after the induction of stroke³² 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 four 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 may reflect 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 to some inpatient rehabilitation settings, rodents are 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* post-stroke reach training therapy in animals is not limited to short therapy sessions, e.g.²¹. These studies suggest an additive effect of environmental and activity-dependent stimulation on recovery in the post-stroke 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 towards supporting compensatory changes whereas large reductions in impairment can occur in humans. At the current time we do not have an understanding as to 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 (i.e. 2–6 months – the reverse of the case in human studies) but in one report several brief two-week periods

of rehabilitation or "tune-ups" initiated after the initial recovery phase (i.e. first month post-stroke) were without benefit³⁵. This is consistent with the unimpressive gains seen at the level of impairment in patients receiving rehabilitation in the chronic phase.

Both timing and dose are important

In most rodent stroke recovery studies that employ reaching as part of the rehabilitation protocol there is often no limit imposed on the amount of reaching allowed and rats will typically reach ≈ 300 times in a training session. In studies from Corbett and colleagues rats are given voluntary access to a reaching chamber for 4–6 hours per day, five days per week. In a recent experiment the amount of reaching the animals were permitted was varied and the result was that there was a reaching threshold above which recovery occurred³⁶. Rats that failed to attain this threshold level of reaching, though still engaging in considerable reaching behavior, did not exhibit significant recovery. Interestingly, the group of animals that showed the most recovery also had elevated levels of BDNF in motor cortex, a significant finding since this growth factor has been causally linked to post-stroke recovery^{10,11}. In view of evidence that stroke patients are given far less reaching practice than is conducted during comparable animal rehabilitation studies³⁷ 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 studies³⁸.

The Human Perspective on Time Course of Recovery after Stroke

What is Acute, Subacute, Chronic, in 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. But most agree that at 6 months the patient is *chronic*, from any perspective. This is the only useful term, so we will be careful to specify the earlier time periods relevant to research studies.

Medical system

In the U.S., the current practice of stroke care involves acute interventions in the first day or less, diagnostic tests for about the first two 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 (IRF), a setting that requires at least three hours of formal therapy per day. That therapy is a combination of physical, occupational and speech therapy. However, what happens during the three hours may not be *intensive* therapy; often time is lost in transfers, transportation, set-up, and other activities that do not involve

randomized task practice, with the result that relatively little functional use of the affected limb occurs³⁹.

The number of days allowed in an IRF is limited by third party payers, who mandate discharge to occur near a point when the patient is safe to go home, not at the point where they cease to benefit from intensive therapy. In 2009, the average acute rehabilitation stay was about 14 days (the trend is for ever shorter lengths of stay, driven by the reimbursement system, not scientific evidence). It is tacitly understood that two weeks is too little time to train the affected side to any significant degree, i.e., 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, although it may not start immediately, and it generally consists of an hour or less of each type of therapy three times a week. Few patients practice their rehabilitative techniques between these three times a week outpatient visits. This outpatient therapy continues for a variable period, again affected by third-party payers, but with the end-point defined by a plateau in measurable function. Access to outpatient therapy is very variable, affected by geography, transportation, family support and other factors. Some patients may have home health visits that include therapy, but these are generally less intensive experiences with a similar range of limitations. This clinical protocol for extended neurorehabilitation in patients after stroke clearly differs from animal models of stroke rehabilitation and establishes a tempo and intensity that is suboptimal for recovery based on the pre-clinical 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 have a stable baseline; 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 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. At the current time this critical period of spontaneous biological recovery is all but ignored by modern medicine. It has been stated: “*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 is more effective than conventional treatment early after stroke. Unfortunately, rehabilitation in existing studies in humans, with few exceptions, have 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 study⁴¹ 52 stroke patients were randomized at about 10 days post onset to two levels of intensity of constraint-induced movement therapy (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 of the study was that 90 day 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 the earlier 30 day time point; thus it is very difficult to know what to conclude. 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; the putative explanation for intensity-related worsening in a rodent model¹⁷.

A study similar to VECTORS enrolled 23 patients within one week after stroke onset but with only one 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 group⁴³. 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 for stroke rehabilitation 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 showed effectiveness of CIMT vs. a usual care control in increasing the speed of standardized, likely compensatory, movements on the impaired side⁴⁴. The usual care group had CIMT one year later (i.e. 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 therapy⁴⁵, but the concept of a *tune-up* after previous therapy remains controversial.

One of the first studies in robotics demonstrated a 4-point trend on the UEFM for the superiority of added robotic therapy during the 3–10 week interval after stroke⁴⁶ (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 yrs.) after stroke.⁴⁷.

The conclusion to be drawn from these studies is that CIMT and robotics are most effective within a time window between 1–9 months after stroke, a time period most commonly taken up by non-intense outpatient therapy or nothing. Overall, the data suggest that CIMT is having an effect on function whereas robotic therapy is having an effect on impairment. It is of interest to consider the possibility that even compensatory improvements benefit from the heightened plasticity early after stroke. At the impairment level, CIMT and robotics, with the timing and dosing employed 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 phase⁴⁸. Another analysis had also concluded that earlier, more intense therapy is beneficial⁴⁹.

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 function, e.g.⁵⁰. However, more recent studies in both humans⁵¹ and animals⁵² failed to show a benefit. It is not entirely clear why there is 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 pre-clinical studies but the effects of modulation of other biogenic amines, such as serotonin, have been tested. Fluoxetine, a serotonin-selective reuptake inhibitor, has been tested, starting about 9 days after stroke and continuing for three months⁵³. 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 to 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 on the degree of activity in the first two weeks after stroke was titled *"Inactive and alone: physical activity within the first 14 days of acute stroke unit care"*⁵⁴. The authors reported that patients were active only 13% of the time and were alone 60% of the time. Lang and colleagues, 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/session was only 32³⁷. Data from the animal literature suggest that this dosage of repetitions is too low; changes in synaptic density in primary motor cortex occur after 400 reaches but not 60^{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 months⁵⁷. Interestingly, 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 one week has somewhat disturbing implications with regard to 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 in order 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 post-stroke 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 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. In order 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 two quite distinct forms of recovery^{24,27,31}. Distinguishing between recovery and compensatory motor patterns requires kinematic analyses of pre-and post-stroke 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 post-stroke recovery in animal models using endpoint measures, these interventions should then be subjected to kinematic analysis to reveal whether the improved performance is due to true recovery or compensation. The attraction of this serial approach – endpoint 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 four 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 period³⁸. 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 level 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 towards generalizing from reductions in impairment to functional gains. Development of methods that take advantage of the regional post-stroke plasticity identified in animal models may help optimize that training.

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 one direction – the translational cliché. Funding should be geared towards 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.

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