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Should We Care About Early Post-Stroke Rehabilitation? Not Yet, but Soon

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Abstract

Purpose of Review Studies in humans and animal models show that most recovery from impairment occurs in the first 1–3 months after stroke as a result of both spontaneous recovery as well as increased responsiveness to enriched environments and training. Improvement from impairment is attributable to a short-lived "sensitive period" of post-stroke plasticity defined by unique genetic, physiological, and structural events. Unfortunately, rehabilitative interventions in humans have not been able to exploit this sensitive period similar to that seen in animal models. Here, we review these data and suggest a path forward.

Recent Findings Pre-clinical data reveal underlying mechanisms that define the post-stroke sensitive period. These data are then discussed in the context of the spontaneous post-stroke recovery described in humans.

Summary Future work will need to capitalize on unique interactions between the sensitive period, spontaneous recovery, and novel types of rehabilitative interventions.

Keywords Stroke · Motor recovery · Enriched environment · Sensitive period · Neurological rehabilitation · Spontaneous recovery

Introduction

"Time is brain" has been inculcated into the collective mindset of cerebrovascular practitioners. This colloquialism intimates that acting sooner will more likely lead to a better outcome. Although normally applied to emergent reperfusion therapies, similar sentiments are shared by many interested in improving post-stroke recovery—namely, earlier rehabilitation, by which I mean interventions designed to restore lost function, are more likely to lead to better recovery. To wit, early commencement of rehabilitation after stroke is now recommended in many clinical practice guidelines [3]. The implicit assumption is that there is an early time period after stroke that is sensitive to rehabilitative intervention and such intervention-related gains dissipate over time (I refer to this period as the "sensitive period"). Nevertheless, the debate regarding the timing of rehabilitation after stroke continues and is fueled by data from pre-clinical and clinical studies. Here, I review this data and discuss a path forward. Since the majority of pre-clinical and clinical data focus on motor recovery, so too will this review; where relevant, I mention the recovery of language and visual-spatial neglect.

The term "rehabilitation" refers to post-stroke therapy-based interventions designed to improve recovery; "recovery" refers to the extent to which body structure and function have returned to their pre-stroke state [4••].When discussing motor recovery, it is convenient to refer to post-stroke performance gains as "recovery"; however, it is important to distinguish between true recovery and compensatory responses. True recovery refers to the biological process that leads to the same or close to the same pre-stroke movement patterns regained post-stroke (i.e., a reduction of impairment), whereas compensation means using alternative movements to accomplish a motor task (i.e., using different muscle groups, joints, or effectors). Unless otherwise stated, I will use "recovery" to mean a reduction in impairment (i.e. true recovery).

Discussions of rehabilitation influencing recovery after stroke emphasize current rehabilitation models, which focus on motor training and/or mobilization. Motor training usually means extended practice at a goal-directed task, which leads to

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motor learning and subsequent task-specific improvements. In contrast to task-specific improvement, spontaneous recovery (the most efficacious form of post-stroke recovery; further discussed below) leads to true recovery of all behaviors to varying degrees. It is worth clarifying that true recovery, and therefore a return to pre-stroke function, is the presumed clinical goal of rehabilitation. To the best of my knowledge, the extant literature does not discuss an intervention (including current rehabilitation models) that convincingly impacts spontaneous recovery, or a return of all behaviors. Thus, with the current state of knowledge, it is difficult to state with certainty what should be done after stroke—either early or later. That is to say, discussing clinically relevant sensitive periods is difficult since we do not have a "gold-standard" intervention that significantly enhances recovery, be it early or late after stroke.

Evidence for Sensitive Periods: Pre-Clinical Studies

In 1917, Ogden and Franz recorded the results of recovery from extensive motor cortical lesions in rhesus monkeys. They noted that monkeys' affected arms recovered back to normal by 3 weeks but only if the unaffected arm was constrained and the affected arm actively trained [59]. This century old result served to introduce the idea that early intervention after a cortical injury is important.

This idea has been confirmed in both primate and non-primate mammals. In the 1990s, Randy Nudo and colleagues showed that squirrel monkeys with smaller, subtotal strokes affecting the hand recovered twice as quick if training was offered early after stroke. In the 2000s, Corbett and colleagues demonstrated that exposure to an enriched environment (see below), which encouraged training trials on a particular task, led to larger gains if offered earlier compared to later after stroke [6]. There were significant gains in reach-to-grasp performance (known as prehension) when exposure was initiated within 5 or 14 but not 30 days after stroke. Further, exposure to an enriched environment, at a level even more intense than the initial session, beginning about 3 months post-stroke, provided no additional benefit even though there still was room for improvement [14]. My group has shown that mice receiving a subtotal infarction of the mouse equivalent of primary motor cortex (caudal forelimb area, CFA) will fully recover prehension performance to pre-stroke levels, but only if prehension training is provided prior to 7 days post-stroke [57, 81]. A counter-intuitive implication of such an ischemia-induced sensitive period is that it should be possible to re-open it with a second stroke and thereby trigger recovery from a first stroke. We tested this hypothesis directly by inducing a second focal stroke in a medial pre-motor area of mice that had only partially recovered prehension after a first CFA stroke because training had been delayed. Initially, the second stroke worsened the initial deficit; however, training initiated within 48 h of the second stroke (i.e., within the sensitive period) allowed prehension to return to normal levels [82]. In other words, taking advantage of the sensitive period after a second stroke fully rehabilitated the first stroke.

Recent studies recapitulate the importance of early rehabilitative intervention [25, 29]. The study by Heredia et al., which showed that early growth hormone administration paired with rehabilitative training in rats led to improved recovery after large cortical aspiration injuries (which likely employs overlapping yet distinct recovery mechanisms compared to ischemic injury), bears special consideration [29]. Surprisingly, this study shows that giving growth hormone paired with rehabilitation at 7 days or at 35 days after the lesion, but not at 14 days, led to recovery of the affected paw as assayed by prehension testing. The authors suggest the possibility that waves of "positive" and "negative" signals are differentially timed after stroke. That is to say, there may be "peaks" of recovery upon which we may capitalize.

Preclinical Evidence of an Early Hyper-Plastic Post-Stroke Milieu

The above mentioned pre-clinical studies strongly indicate the existence of a time-limited sensitive period during which there is increased responsiveness to training. The implication is that such responsiveness is mediated by a unique post-stroke plasticity milieu. After ischemic stroke, there is a subsequent cascade of degeneration, neurotoxicity, inflammation, and apoptosis in the ischemic core and penumbra, with consequences for neuronal and synaptic survival in the peri-infarct region and connected areas (e.g., via diaschisis). This cascade of stroke-induced changes has been associated with changes in gene expression, changes in physiology, and altered structure of the surviving tissues—many of which promote recovery over the ensuing days post-stroke. These changes have been previously reviewed [83]. I will make mention of certain recent advances here.

During the post-stroke sensitive period, there are widespread gene activations in peri-infarct cortex [5, 11, 12, 18, 24, 43, 48, 53–55, 61, 66, 71, 84]. Many of these genes are associated with growth-associated genetic programs that control axonal sprouting, dendritic spine formation, and mediate the formation of new patterns of connections within the brain. Recent work has suggested the importance of two master-regulators of gene expression and their effects on recovery: (1) CREB (cAMP response element-binding protein) and (2) epigenetic regulation. CREB binds to cAMP response element (CRE) and thereby increases the transcription of many genes. Ischemia leads to rapid and robust CREB-based signaling and transcriptional responses [39]. Such signaling is involved in structural plasticity and associated with

behavioral recovery and rehabilitative interventions early post-stroke [26, 63]. Further, motor recovery early after stroke can be enhanced or diminished directly by modulating CREB signaling [10•].

Epigenetic mechanisms including DNA methylation, histone deacetylase inhibitors (HDACis), and miRNAs are potent modulators of gene regulation on a grand scale. That is to say, rather than controlling one signaling pathway, these effectors have wide-reaching effects on multiple pathways. Accumulating evidence suggests that such epigenetic mechanisms play a pivotal role in regulating brain remodeling and recovery early after stroke [23, 37, 38, 46].

These genetic effects are thought to have robust effects on electrophysiological plasticity early after stroke [83]. The precise balance of excitation/inhibition plays a permissive (perhaps instructive) role in plasticity throughout the brain (both in health and in disease states). Too much excitation leads to loss of synaptic temporal and spatial specificity; too much inhibition leads to maintenance of synapses and reduced plasticity. The last many years have seen significant shifts in the understanding of the excitation/inhibition balance early after stroke. The notion that the peri-infarct cortex is hyper-excitable may be in part from experiments showing that artificial stimulation evokes hyper-excitable responses (e.g., stimulating cortical connections with TMS or other electrodes). However, recent data obtained measuring neuron excitability at resting state suggests that that the actual physiological responsiveness of peri-infarct cortex is reduced for many weeks after stroke [15, 16, 19, 49]. Nevertheless, there is an important rejoinder to the reduced excitation/inhibition balance early after stroke: the excitation/inhibition balance is robustly enhanced by behavioral training. First, training after stroke reduces the activity of certain inhibitory interneurons (not seen in non-stroke brain) [81], as well as their "insulation" (peri-neuronal nets) [64]. Second, CREB expression, which is a master regulator of neuronal excitation [10•], is upregulated by behavior [63]. Thus, it seems that early after stroke, a maladaptive excitation/inhibition balance can be "balanced" by rehabilitative input.

These genetic and physiological effects are thought to direct structural changes early after stroke [83]. Axonal sprouting extends from neurons in the ipsilesional (especially the peri-infarct) cortex indicating the potential to form new connections in the adult brain and construct new circuits that can potentiate recovery of lost function. Axonal sprouting is profound in the adult brain and not otherwise a normal event. The molecular programs directing axonal sprouting are uniquely seen early post-stroke [47, 48] with the first triggers present as early as days after stroke. Further, not all forms of axonal sprouting are reparative (e.g., [16]) and there is a suggestion that motor training can help direct axonal inputs important for recovery [32, 60, 74].

Recently, Winship and colleagues have demonstrated that spinal cord axonal sprouting is likely to play a role in post-stroke motor recovery and is also time-limited. Chondroitin sulfate proteoglycans are an important component of extracellular matrix and are potent inhibitors of axonal growth and dendritic rearrangement. Injection of chondroitinase, which enzymatically "loosens" the extracellular matrix, can augment the rewiring of circuits connecting the brain to the spinal cord. Moreover, this plasticity can be harnessed by rehabilitative training to significantly promote sensorimotor recovery—a process normally not seen 28 days post-stroke in the rodent [75]. These results suggest that time-dependent plasticity mechanisms throughout the central nervous system, and not just the in neocortex, can shape recovery.

Although the post-stroke sensitive period seems to close at 1 month in rodents, there are no definitive studies characterizing the plasticity milieu outside of the post-stroke sensitive period. That is to say, we know very little about the gene expression profile, physiology, and dendritic spine plasticity and how these variables interact with motor training and recovery months to years after a stroke. Nevertheless, the plasticity milieu in the post-stroke brain outside the sensitive period resembles (or is perhaps identical to) the plasticity milieu in the uninjured brain [83]. First, motor training's ability to induce true recovery is reduced outside of the post-stroke sensitive period. Second, studies detailing gene expression suggest that ischemia-induced alteration of gene expression is maximal in the weeks after the stroke. Third, dendritic spines are maximally plastic in the first month after stroke. Finally, levels of phasic inhibitory neurotransmission seem to nadir soon after stroke.

Overall, the genetic, physiological, and structural changes brought about by ischemia are thought to create a post-stroke plasticity environment that falls off as a function of time and distance from the infarct. Further, this plasticity environment interacts with motor training so as to augment the effects of training. It is this interaction between a post-stroke induced hyper-plasticity environment and training that defines the sensitive period.

Sensitive Period in Humans: Spontaneous Recovery Vs Current Rehabilitative Interventions

The behavioral and mechanistic data supporting the existence of a sensitive period in pre-clinical models is overwhelming. The concern with pre-clinical sensitive period experiments is their relevance to human stroke recovery. To wit, current post-stroke rehabilitation interventions in humans do not convincingly impact true recovery [62, 72, 79]. It is not surprising, therefore, that current post-stroke rehabilitation methods in humans do not drive recovery when applied early after

stroke [20, 44••, 62, 72, 76, 79]. Thus, a "sensitive period" in humans, and the implied interaction between motor training and recovery, is not currently supported by the data.

Regardless of the interaction between motor training and recovery in humans, the early post-stroke period is important. The largest amount of upper extremity motor recovery in humans at both the impairment and functional levels occurs in the first 4 weeks and reaches asymptotic recovery by approximately 3 months post-stroke [21, 27, 36, 62]. This recovery is often referred to as spontaneous biological recovery as it occurs based on endogenous repair processes rather than on rehabilitative interventions. Remarkably, such recovery follows a fixed proportional-recovery approximating 70% of each patient's maximum possible improvement [62, 79]. This 70% proportional-recovery rule alludes to a fundamental biological mechanism given that it holds true for patients regardless of stroke location, age, gender, and type of post-stroke rehabilitation service [9••, 42, 79]. In support of a fundamental biological mechanism, proportional, time-limited recovery has similarly been described for the lower extremity [73], for aphasia [30, 45], as well as for neglect [78]. Therefore, even without direct evidence that rehabilitative input directly influences motor recovery early post-stroke in humans, it is safe to say that the early time period after stroke is unique in humans.

The precise time course of recovery depends upon the outcome measured. This is an important consideration as debate about the importance of early recovery should not be derailed by misunderstandings of timing between different outcome measurements. Perhaps the greatest disparity between time-courses comes when comparing different cortical functions. For example, aphasia recovery is hypothesized to continue for months longer than upper extremity motor recovery (reviewed in [28]); also, finger recovery is more protracted than upper extremity recovery [77, 80]. Even when focusing on upper extremity motor recovery, different measurements reveal different time courses. For example, improvements in paretic arm motor control plateau at 5 weeks, with no significant improvements seen beyond this time point; however, improvements in the upper extremity Fugl-Meyer (FMA-UE), Action Research Arm Test (ARAT), and biceps dynamometry continued beyond 5 weeks (even out to 54 weeks) [17]. Thus, the time window for spontaneous biological recovery is not the same for different aspects of recovery. Nevertheless, a time window exists for every aspect of recovery that has been studied and likely represents similar repair processes/mechanisms.

Recent work by Jeffers and Corbett et al. have demonstrated proportional recovery in the rodent [34••, 35••]. Their team retrospectively assessed biomarkers of stroke recovery in 593 rats and found that (1) the amount of rat proportional recovery (62–70%) was similar to that seen in humans, (2) biomarkers similar to that seen in humans (including initial level of post-stroke impairment as well as infarct volume) predicted recovery, and (3) the intensity of rehabilitation was an additional predictor of functional recovery [35••]. This last point is of particular interest and again underscores the difference between the animal and human post-stroke sensitive period.

What is it about rat rehabilitation that influences proportional recovery—a phenomenon heretofore not seen in humans? Perhaps, the different neuroanatomy between rodent and primate can account for this difference. For example, rodent reticulo- and vestibulospinal tracts are larger in size and play a bigger role in motor control (e.g., voluntary locomotion and grooming); also, there is not enough evidence to conclude whether secondary motor areas in rodents are true homologs of the primate pre-motor cortex, supplementary motor cortex, or a combination of the two. These anatomical nuances raise the possibility that rodent neuroanatomical pathways may be better suited to respond to rehabilitative input early post-stroke. The main problem with this hypothesis is that non-human primate studies have also demonstrated responses to rehabilitation (e.g., [56]).

A non-mutually exclusive alternative as to why rat rehabilitation influences proportional recovery is that rodent rehabilitation is better suited to take advantage of the sensitive period. Notably, in the Corbett studies, rodent rehabilitation consisted of a combination of enriched environmental housing (large cages that encouraged exploration, provided toys, and increased use of the impaired limb) as well as access to equipment that encouraged task-specific reaching movements (the measured outcome). The aforementioned non-human primate studies utilized a large number of motor repetitions of increasing difficulty [56]. That is to say, animal studies offer different and more intense rehabilitative interventions, ideas which I will explore more fully in the next section.

In summary, spontaneous biological recovery has a limited time window. Although animal studies suggest a positive interaction between spontaneous biological recovery and rehabilitative interventions, similar data do not exist in the human. Nevertheless, similar biological mechanisms between animals and humans, as well as the ubiquity of spontaneous recovery cross-species and modalities, suggest that there is hope for systematically enhancing spontaneous recovery during the sensitive period in human patients.

Rehabilitative Interventions and Recovery

Rehabilitation is, of course, a broad concept, and there are many targeted interventions that may be applied early post-stroke. As such, we must resist the possibility that no post-stroke intervention in humans will improve upon spontaneous recovery. Rather, we should use extant data from pre-clinical and clinical models to build an intervention that will reduce impairment.

One potential solution is to find the right timing and dosage of current interventions, which employ motor training and mobilization, so as to augment what is expected from spontaneous recovery. As suggested by rodent [1, 2, 7, 51] and non-human primate studies [56], increased dose is likely to be important and will need to be titrated to a correct level (see next section). However, increased dose will not be the panacea [76], likely because current interventions are based on motor training and fail to target impairment on a global level [41].

Notably, motor training refers to extended practice at a goal-directed task, which leads to motor learning with subsequent task-specific improvements; after stroke, motor training can promote either recovery or compensation [83]. In contrast to task-specific learning, spontaneous recovery leads to a return of all behaviors to varying degrees. This leads to a paradox: how does one train general recovery when training is always of a particular task? Should we quilt together the training of the hundreds of tasks in which a human engages on a daily basis? Even if we had the number of therapists needed for such a heroic endeavor, the sensitive period may close before we could accomplish all of the needed training. Alternatively, I suggest that we should explore new kinds of rehabilitative interventions.

Preclinical work has shown the importance of enriched environments. Enriched environments are designed to enhance sensory, motor, and cognitive stimulation by providing equipment, stimulation, open spaces, and a desire to want to engage in rehabilitative interventions [58]. In rodent experiments, enriched environments include toys, ramps, tubes, mirrors, ropes, and the ability to interact with other rats. Rodents exposed to enriched environments early (but not late) post-stroke showed improved motor performance even on tasks for which they did not receive specific training [6]. Further, there was a synergy between combined motor training and exposure to enriched environments [33•]. The proposed mechanisms of action are plethoric and may relate to multiple molecular pathways [50, 58]. Translating an enriched environment to human patients may take several forms [52]. In a recent study, Brauer and colleagues created open communal areas with access to equipment including iPads, books, puzzles, newspapers, games, music, and interaction with other patients/therapists. These environments were associated with increased patient activity and fewer adverse events [67]. Additionally, one could imagine enrichment using virtual/augmented environments with video games and other technology [69, 70] that would not only increase dose but also enhance enjoyment.

Another option is to take advantage of technological advances in robotics. Although robotics can be used to increase dosage, robotics can also modify and aid with patient movement. During most normal tasks, arms are confined to a small volume of space around the body and movements are predominantly in the vertical plane across many varied tasks [31]. Thus, robotics could be used to assist the hemiparetic limb regain access to its normal "volume-of-space" so as to complete daily tasks.

The use of pharmacological agents to enhance behavioral interventions should also be considered. For example, fluoxetine [13, 57] and Cerebrolysin [8•] can enhance recovery when given early post-stroke. Such agents should likely be used as "add-ons" to enhance any behavioral intervention.

Finally, despite any advances that may occur, behavioral intervention/motor training should always be a part of post-stroke rehabilitation. As mentioned early, motor training is important in directing axonal plasticity, and balancing excitation/inhibition early post-stroke. The sensitive period amplifies the effects of motor training on motor recovery, but motor training also sculpts the post-stroke sensitive period plastic milieu. Thus, to exclude behavioral intervention/motor training, post-stroke may be like expecting a tennis player to improve without ever picking up her racket.

Early Interventions Associated with Harm

Medical interventions have a threshold dose, frequency, and/or timing beyond which they may be ineffective and/or harmful. Honest discussions of the post-stroke sensitive period must acknowledge that pre-clinical and clinical studies suggest that intervening too early post-stroke can be maladaptive. The first suggestion of harm came 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 injury [40]. Similarly, a more recent study showed that exercise (rota-rod running) initiated within 24 h increased markers of glycolysis and was associated with increased apoptosis [68]. Even animal studies where motor training, exposure to fluoxetine, or exposure to enrichment was initiated several days after stroke (and, therefore, more resemble clinical practice), there was increased cell death [22, 57, 65].

However, a closer look at these pre-clinical studies reveals that those animals exposed to early intervention showed improved long-term behavioral outcomes (when measured), despite larger stroke volume. There is a suggestion that early intervention may engage a pruning effect, whereby dysfunctional neurons are eliminated early on as a result of use-dependent activation. The dissociation between stroke-volume and behavioral recovery is important to keep in mind when choosing outcome measures.

Human trials looking at very-early intervention have similarly suggested possible harm. I mention two recent studies here. VECTORS (Very Early Constraint-Induced Movement during Stroke Rehabilitation) enrolled 52 patients with stroke randomized approximately 10 days post-stroke to two levels of intensity of constraint-induced movement therapy (CIMT;

the high CIMT group received an extra hour per day of CIMT) versus standard upper extremity. At 90 days, the ARAT (primary outcome measure) was worse for the high CIMT group [20]. In the AVERT trial (A Very Early Rehabilitation Trial after stroke), 2104 patients were enrolled and received either a median time to mobilization of 18.5 h with a median of 31 min spent daily out-of-bed (early group) versus a median time to mobilization of 22.4 h with a median of 10 min spent daily out-of-bed (usual care group) [44••]. The main and only significant result was that 46% of the early group had a favorable modified Rankin Scale outcome, whereas 50% did in the usual care group.

VECTORS and AVERT suggest that early and more intense intervention may be harmful in humans—a concerning suggestion especially since there is no good evidence that rehabilitative interventions early after stroke help recovery. However, I caution interpreting these trials as a de facto warning against early (and intense) intervention. First, it can be hard to interpret VECTORS and AVERT since they provided no measure of impairment recovery (e.g., there was no FM-UE or kinematic analysis). Reduction of impairment is arguably the key measurement when considering the interaction between rehabilitative input and recovery early post-stroke. Second, in the AVERT trial, a key early rehabilitative intervention distinguishing the experimental from the control group was time-to-mobilization. The early mobilization was associated with a non-significant increased death-rate in the early group (31 patients) compared to the usual care group (19 patients). As such, one must consider that the employed rehabilitative intervention may have potentiated stroke pathology (for example, worsening already impaired auto-regulation, increasing stroke size, increasing risk of hemorrhagic conversion) instead of directly impairing recovery mechanisms. This is a subtle, but important distinction. To say this another way, early mobilization may play a direct role in worsening ischemia and ischemia's immediate downstream effects rather than impairing the genetic, physiological, and/or structural repair mechanisms important in recovery.

VECTORS and AVERT suggest that nuance is needed when implementing early post-stroke rehabilitation. For example, perhaps in patients with vessel stenoses and/or large infarcts, there is a need to limit time out-of-bedtime in the first few days after stroke. Additionally, these studies suggest that understanding the dose-response curve for a given intervention is important.

Conclusion

There is a unique milieu of enhanced plasticity for 1–3 months post-stroke, and that within this time window, both spontaneous and intervention-mediated recovery from impairment is maximal. Nevertheless, rehabilitative interventions in humans fail to capitalize on the sensitive period.

It remains an open question as to what type of rehabilitative intervention to emphasize in the sensitive period. Answering this question has been hampered by a lack of studies that have tried to significantly change either the dose, frequency, or type of rehabilitative intervention early post-stroke (likely because of logistics, economics, and a scientific concern that "earlier = worse"). As such, I suggest that we need to advocate for (1) earlier intervention and (2) research into novel types of interventions that are based on sound scientific theory addressing mechanisms of action and marked by relevant outcome measures.

Compliance with Ethical Standards

Conflict of Interest Steven R. Zeiler reports grants from Everpharma, outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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