

The interaction between training and plasticity in the poststroke brain

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Purpose of review

Recovery after stroke can occur either via reductions in impairment or through compensation. Studies in humans and nonhuman animal models show that most recovery from impairment occurs in the first 1–3 months after stroke as a result of both spontaneous reorganization and increased responsiveness to enriched environments and training. Improvement from impairment is attributable to a short-lived sensitive period of postischemic plasticity defined by unique genetic, molecular, physiological, and structural events. In contrast, compensation can occur at any time after stroke. Here, we address both the biology of the brain's postischemic sensitive period and the difficult question of what kind of training (task-specific vs. a stimulating environment for self-initiated exploration of various natural behaviors) best exploits this period.

Recent findings

Data suggest that three important variables determine the degree of motor recovery from impairment: the timing, intensity, and approach to training with respect to stroke onset; the unique postischemic plasticity milieu; and the extent of cortical reorganization.

Summary

Future work will need to further characterize the unique interaction between types of training and postischemic plasticity, and find ways to augment and prolong the sensitive period using pharmacological agents or noninvasive brain stimulation.

Keywords

ischemia, motor learning, motor recovery, neurological rehabilitation, spontaneous recovery

INTRODUCTION

Motor deficits after stroke can improve via two separate mechanisms: true recovery and compensation. Although it is convenient to refer to post-stroke performance gains as recovery, it is important to distinguish between true recovery and compensatory responses. True recovery means that the same or close to the same prestroke movement patterns are regained poststroke (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)[1^a,2,3].

Discussion of rehabilitation after stroke often emphasizes motor training; motor training, however, is a much more ambiguous notion than is generally appreciated. For a healthy individual, motor training usually means extended practice at a goal-directed task, which leads to motor learning with subsequent task-specific improvements. Motor training after stroke can promote either recovery or compensation. In both cases, as in healthy

individuals, the goal of the training is task-specific. In contrast to task-specific learning, spontaneous recovery can lead to a return of all behaviors to varying degrees. This leaves a paradox that to the best of our knowledge does not get much of a mention in the extant literature: spontaneous biological recovery (SBR) is general [4,5] but motor learning is task-specific [6,7]. In this review, rather than being exhaustive we will instead argue for a more explicit conceptual framework for considering the interaction between training protocols and endogenous plasticity mechanisms triggered by ischemia.

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KEY POINTS

- The poststroke sensitive period is a unique, time-limited plasticity environment that mediates SBR and falls off as a function of time and distance from the infarct.
- Plasticity mechanisms in the sensitive period are qualitatively and quantitatively different from those in normal brain and interact with motor training.
- It remains unclear whether rehabilitation in the post-stroke period should emphasize task-specific training or patient-driven exploration of movement in an immersive environment.
- True recovery (i.e. reduction of impairment) will require augmentation of the generalizing effects of SBR.

In both healthy and poststroke brains, motor training can lead to motor learning, defined as better selection of actions and improved execution of these actions for a particular task. Thus, motor training is externally imposed, and motor learning occurs as a consequence. Motor training induces central nervous system (CNS) plasticity [8–11], which we define here as the sum of molecular, physiological, and structural changes that alter motor output for a given sensory input. Two critical points need to be made from the outset: first, CNS plasticity can be triggered by ischemia in the absence of training and still mediate recovery. Data show that both rodents and primates exhibit spontaneous, nontraining-associated recovery after stroke [4,12–19]. Second, and conversely, behavioral changes that improve function can happen in the absence of plasticity. For example, a patient can ‘learn’ within seconds to use their nonparetic arm as a substitute for their paretic arm after stroke. This quick strategic adjustment does not itself come about through practice and motor learning in the usual sense.

There are three observations about poststroke motor recovery in human and nonhuman animal models that suggest that there is a ‘sensitive period’ poststroke. First, almost all recovery from impairment occurs in the first 3 months after stroke in humans [5,20–22,23[¶]] and in the first month after stroke in rodent models [12,23[¶],24]. Secondly, the effectiveness of poststroke training with respect to impairment for both natural and pretrained behaviors diminishes as a function of time after stroke in primates [23[¶],25] and in rodents [12,23[¶],26]. Thus, there is a general concordance between animal and human studies that rehabilitation in the sensitive period is essential for significant recovery from impairment [3,12,23[¶],25,27,28]. Throughout the

remainder of this review, we refer to poststroke brains as being either inside or outside this sensitive period. Thirdly, improvement beyond the sensitive period is mediated almost entirely by compensation.

Here, we posit a unique, time-limited poststroke plasticity environment that falls off as a function of time and distance from the infarct, and which interacts with motor training. Plasticity mechanisms in the sensitive period are quantitatively and qualitatively different from those seen outside the sensitive period or in the normal brain during task-specific learning.

TRAINING-INDUCED PLASTICITY IN HEALTHY BRAIN IN THE ABSENCE OF STROKE

Environmental experiences have diverse structural and functional effects on the CNS. Perhaps the best-studied consequences of environmental-induced plasticity are in the visual system in which specific visual stimuli can alter gene expression, dendritic spine dynamics, neuronal tuning, and circuit connections [29]. Similarly, a large number of studies in rodents and primates have revealed a series of plastic events in motor cortical areas that are associated with improvements in task performance [10,11,30].

The most common task-specific motor training in animal models consists of skilled prehension in which the animal must reach for and grasp a food pellet with subsequent delivery of the pellet to its mouth; success can be quantified not only by successful food delivery but also by quantification of kinematics [31,32]. Although different researchers make modifications, the basic task remains similar. Within 1 day of beginning prehension training in rodents, there are changes in gene expression in primary motor cortex [33]. Between the first and fifth days of motor training, genes influencing synaptic efficacy, synaptogenesis, and cytoskeletal dynamics are upregulated [34[¶],35]. Subsequent to this increased expression, in some studies as early as 3 days, there are increases in evoked field potentials in the primary motor cortex of the trained hemisphere [36]. Over time, the amount of long-term potentiation (LTP) that can be induced in the trained hemisphere increases so that a given stimulus produces excitatory postsynaptic potentials of higher amplitude and with a greater dynamic range [37]. Between days 1 and 5, prehension training alters dendritic spine dynamics leading to both increased formation and elimination of laminar-specific spines [38]. By profiling dendritic spine dynamics *in vivo*, Fu *et al.* [39[¶]] showed that prehension training is associated with the formation of new

dendritic spines and that these spines form in clusters, a phenomenon associated with persistent stability and not seen with motor activity alone.

By days 8–14 of prehension training, there is an expansion of forelimb movement representations (evoked with intracortical microstimulation) in the rodent caudal forelimb area (the rodent equivalent of primary motor cortex) [40–42]. Similar expansions of motor maps have been documented in nonhuman primates [43] as well as in humans [44–46] after training on specific tasks. Although motor map expansion seems to be necessary for acquisition of a particular skill, persistence of the expanded state is not necessary for maintenance of the skill [47,48] and may represent a transient stage in the long-term reorganization of the motor cortex. The changes in gene expression, neurotransmission, spine dynamics, and motor maps outlined here are not seen with use alone, that is, movement repetition in the absence of learning [9,33,39]. It is notable that in all the studies cited, the changes in the brain were documented with respect to learning of a specific single task. The neural correlates of generalization were not examined, which makes the applicability of these learning effects to recovery from stroke unclear unless rehabilitation is viewed as training a patient one task at a time. We will return to this issue later in the review.

MOTOR RECOVERY AND PLASTICITY AFTER STROKE

Ischemic stroke leads to tissue loss at the site of primary injury with a subsequent clinical phenotype that depends on the location of damage. 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).

Plastic milieu during the poststroke sensitive period

There is increasing evidence that there are qualitative and not only quantitative differences in the molecules and genes expressed, the physiological responses manifested (including levels of inhibition), and structural changes observed, when training combines with the postischemic cortical environment as compared to similar training in the normal brain or in chronic stroke.

Gene expression changes

During the poststroke sensitive period, there are widespread gene activations in peri-infarct cortex

and surrounding areas that are independent of behavior [24,49–54]. Notably, these genes are very similar to those important for neuronal growth, dendritic spine development, and synaptogenesis during early brain development. Transcription analyses in peri-infarct somatomotor cortex [50,51,53] reveal that different genes are up-regulated in response to ischemia compared with uninjured motor cortex after motor training [34]. For example, synapsin, PSD-95, and GFAP are regulated differently by motor training compared with ischemia [55]. Furthermore, recent work by Li *et al.* [50] has shown that during the poststroke sensitive period, peri-infarct neurons express an age-related growth-associated genetic program that controls axonal sprouting and mediates the formation of new patterns of connections within the motor system [53]. For example, ischemia induces a time-dependent increase in semaphorin 6A [51,56], expression of extracellular matrix molecules [50], and sequential waves of neuronal growth-promoting genes [53] that have not been documented with motor training in the absence of ischemia. In addition to qualitative changes in the gene expression profile, there is also an overlap in those genes that are upregulated in response to ischemia and motor learning. For example, brain derived neurotrophic factor is upregulated in response to both ischemia and motor learning [57–59]. These data suggest that the heightened plasticity of the postischemic brain is attributable to both unique gene products and increased expression of genes related to normal motor learning.

Electrophysiological changes

Accumulating data suggest that ischemia rapidly changes the physiology of the remaining nervous tissue in both affected and unaffected hemispheres. For example, beginning quickly after damage, LTP is enhanced [60,61]. Some have used the term *ischemic LTP* to refer to the temporal association with stroke [62]. Also, in-vivo imaging has revealed that preserved and unique sensorimotor pathways become active after focal strokes but not after other forms of injury such as tumor and trauma [63,64].

One of the more striking physiological changes in the poststroke brain is an alteration of excitatory/inhibitory balance. The importance of excitatory/inhibitory balance and the requirement for a specific amount (not too much and not too little) on plasticity has been elegantly demonstrated in the developing visual system. Weak inhibition early in life prevents visual experience-dependent plasticity, likely due to both excitatory synapse over-activation and a loss of temporal and spatial specificity [65]. During a critical period of visual cortical

development, maturation of inhibitory interneurons leads to an intermediate level of inhibition that provides the optimal balance between sensitivity and specificity to inputs on a given neuron for the robust experience-dependent plasticity seen only during the development of adult cortical circuitry. Once formed, increasing amounts of inhibition maintain these adult circuits [65] and shut down the robust plasticity seen only during the critical period.

Poststroke investigations using physiological measures, assays of neurotransmitter expression, magnetoencephalography, and functional MRI have demonstrated either an increase in excitation [66–68] or a decrease of inhibition [67,69,70] (especially synaptic/phasic inhibition) [13,71^{***}] particularly in the peri-infarct cortex. This increase in the excitation/inhibition ratio happens within days after stroke and has been noted to resolve outside of the sensitive period. Such increases in the excitation/inhibition ratio may help to either recreate an environment similar to that seen during a developmental critical period and/or unmask latent cortico-cortical connections [42,72,73]. Interestingly, in contrast to the above data, Clarkson *et al.* [13] have demonstrated an increase in a specific kind of peri-infarct inhibition known as tonic inhibition, which controls the overall excitability of a neuron (as opposed to the excitability of a given synapse). Tonic inhibition is also regulated as a function of time and may serve to limit acute excitotoxic injury as well as be part of a negative feedback loop to limit plastic changes.

Structural changes

Immediately after ischemia, peri-infarct dendritic spine numbers are decreased; however, within days, there is a dramatic increase in the rate of spine formation that is maximal at 1–2 weeks and still evident at least 1 month after stroke [74]. These data agree with studies showing significantly increased axonal sprouting in the peri-infarct cortex during the first 2–4 weeks poststroke [75,76^{***}]. Notably, ischemia results in new axon growth and path-finding associated with the remapping of both local and long-distance connections linked to regions of injury (e.g., premotor as well as sub-cortical areas) [50,77^{***},78^{***}]. These data show ischemia leads to increased neuronal plasticity to a degree not seen with motor training alone. In summary, gene expression, neurotransmission, inhibitory/excitatory balance, and synapse formation, are transiently altered in the poststroke sensitive period, creating a short-lived unique milieu of enhanced plasticity.

The relationship of the sensitive period to spontaneous biological recovery and enriched environments

Despite the critical role of the poststroke sensitive period in motor recovery [23^{***}], there is little investigation specifically linking behavior in the sensitive period to recovery. SBR is often used to describe recovery that occurs as a result of endogenous repair processes rather than behavioral interventions [4,19]. This is a murky area, however, because the animal is always doing *something* behaviorally after a stroke. Here, we will operationally define SBR as motor recovery that occurs in the absence of post-stroke training on the task that is used to test for recovery (the potential pitfalls and risks of circularity when testing with the same task that was trained on merits a longer discussion than we are able to provide here). Although some SBR is likely related to resolution of inflammation and decreased edema, a large component is attributable to reorganization over weeks. Specifically, in both human and nonhuman animal models, motor recovery can occur with either a minimum or even a lack of task-directed motor training [4,19]. As mentioned in the introduction, animal models of poststroke motor recovery are dominated by a task-specific pretraining/posttraining behavioral paradigm. Importantly, however, every assessment with a task that was not specifically trained has shown some degree of improvement, suggesting that SBR generalizes [12–18]. Generalized recovery from impairment because of SBR is observed early after stroke in humans, for example, increases on the Fugl–Meyer scale [5].

Accumulating data suggest that the environment within which behavior occurs is very important for recovery. Environmental enrichment, defined as a more stimulating environment with respect to novelty, variety, and reward, enhances SBR in rodents even in the absence of specific training [12,79,80]. Ongoing research characterizing the molecular, cellular, and behavioral mechanisms that mediate the effects of environmental enrichment [81] suggests that it augments the processes that occur in the sensitive period, and thereby amplifies SBR. Another not mutually exclusive possibility is that an animal in an enriched environment engages in a broader range of more natural premorbid behaviors and that this is preferable to directed task-specific training.

The relationship of the sensitive period to task-specific training

Another mechanism linking the poststroke sensitive period and motor recovery is an enhanced response

to task-specific training. We would venture that it is the task-specific aspects of neurorehabilitation training that have led to the tendency to too readily equate recovery after stroke with motor learning. Recovery of task-specific motor behavior during the poststroke sensitive period can be dramatic, especially if the damage is subtotal and residual motor cortical areas are spared [23^{82–84}]. For example, Nudo *et al.* [18] demonstrated that training monkeys on skilled digital manipulation of food pellets in small wells after an infarct involving the hand area of the primary motor cortex resulted in prevention of the loss of hand territory in the peri-infarct cortex. However, withholding motor training led to decreased digit representations by more than 50% [85]. Thus, during the sensitive period, motor training directs functional reorganization in the peri-infarct motor cortex presumably enabled by the unique poststroke plasticity milieu.

Data suggest that the interaction between training and the poststroke sensitive period can extend plastic changes beyond just peri-infarct cortex. For example, Frost *et al.* [86] have shown that ischemic damage to primary motor cortex leads to reorganization in remote cortical areas beyond peri-infarct cortex and that the greater the damage, the greater these remote changes. Other more recent data show reorganization beyond peri-infarct cortex in premotor areas [87,88]. These findings have led to the suggestion of an ordered sequence of reorganization from peri-infarct cortex to ipsilesional cortex to contra-lesional areas [24,89].

An important point, which is perhaps underappreciated, is that compensation also occurs during the poststroke sensitive period and is also mediated by plastic changes in peri-infarct cortex [84,90] and in other cortical areas [91]. Thus, true recovery and compensation can happen simultaneously during the sensitive period, which raises the possibility that these compete for available plasticity. A variant on this concern would be that even an over-emphasis on particular tasks may be detrimental to more general learning.

The enhanced plasticity milieu in the sensitive period amplifies the effects of motor training on motor recovery, but motor training also sculpts the poststroke sensitive period plastic milieu. Not all conditions during the poststroke sensitive period are permissive to plasticity and recovery. Poststroke, there is also increased expression of genes inhibitory to plasticity. For example, ischemia leads to increased expression of myelin-associated proteins [50,92] and ephrins [50,76⁹³], both of which are inhibitory to axonal outgrowth. Importantly, there are hints that prehension motor training can reduce the effects of these molecules and increase

axonal sprouting [93,94]. Additionally, within 3 days after stroke, tonic inhibitory activity is increased. In contrast to phasic inhibition, tonic inhibition is extra-synaptic, controls the overall inhibitory state of a neuronal circuit [71⁹⁴], and is indirectly related to motor recovery after stroke [13]. In a recent study, task-specific motor training, and not just ischemia alone, led to reduced inhibitory markers in a premotor area that mediated recovery [87]. Thus, there is two-way causal traffic between motor training and plasticity during the poststroke sensitive period.

It remains an open question as to what kind of training to emphasize in the sensitive period. We are not aware of any studies directly comparing task-specific training and enrichment. In an intriguing study by Biernaskie *et al.* [12], rats were pretrained to perform multiple task-specific behaviors including prehension, spontaneous forelimb use, and beam walking followed by poststroke retraining at various times in the setting of an enriched environment. The results suggested that the combination of task-specific training coupled with an enriched environment enhanced recovery compared with just an enriched environment. There are caveats, however. First, task-specific training without an enriched environment was never directly compared with free behavior in an enriched environment alone. Second, and perhaps more importantly, animals were trained and then evaluated with the same task. If task-specific training is to be compared with self-exploration across a wider task space then the test used for comparison cannot be the trained task.

Training-induced plasticity in the poststroke brain beyond the sensitive period

Although the poststroke sensitive period seems to wane at 1 month in rodents and 3 months in humans [23⁹⁵], there are no definitive studies characterizing the plasticity milieu outside of the poststroke sensitive period. Nevertheless, observations suggest the following: first, motor training's ability to induce true recovery is reduced outside of the poststroke sensitive period [23⁹⁶]. 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. Thus, we suggest that the plasticity milieu in the poststroke brain outside the sensitive period resembles (or is perhaps identical to) the plasticity milieu in the uninjured brain. That is to say, poststroke plasticity normalizes with the passage of time. It is very likely that the task-specificity of both

compensatory responses in chronic stroke and skill learning in healthy individuals can be attributed to this more limited plasticity that does not allow for reorganization.

CONCLUSION

There is a unique milieu of enhanced plasticity for 1–3 months after ischemic stroke, and that within this time window both spontaneous and intervention-mediated recovery from impairment is maximal. The interaction between this milieu and training is distinct from equivalent training in a healthy person or in patients with chronic stroke. The crucial question that remains is how to best take advantage of this limited time window. What should not be done, in our view, is to simply allow SBR to run its course with respect to impairment and focus rehabilitation efforts on behavioral compensation, that is, current practice. We say this because data suggest that impairment could be reduced further with behavioral and pharmacological interventions (e.g., fluoxetine) [95] and that training compensation early on may reduce the chance of impairment reduction ('use it or lose it').

The current state of knowledge makes it much harder to state what should be done early after stroke. It is probably safe to say that the ideal would be to augment the generalizing effects of SBR but to attempt this with task-specific training alone is a contradiction. Thus the human equivalent of enrichment is needed, perhaps a video game arcade-like space that allows more general movement exploration [96]. Task-specific training could be added if focused on tasks with the greatest chance of generalization (e.g., reaching and grasping). Both enrichment and the task-specific training need to be at doses and intensities of exposure much greater than is currently provided [97]. Future approaches should enhance plasticity both during and after the sensitive period. Two promising therapies include pharmacological manipulation (e.g., fluoxetine) and noninvasive brain stimulation, as both might augment, prolong, or mimic the poststroke sensitive period [95,98–104].

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Conflicts of interest

There are no conflicts of interest.

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