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The interaction between training and plasticity in the post-stroke brain

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Abstract

Purpose of review—Recovery after stroke can occur either via reductions in impairment or through compensation. Studies in humans and non-human animal models show that most recovery from impairment occurs in the first 1 to 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 post-ischemic 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 post-ischemic 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: (i) the timing, intensity, and approach to training with respect to stroke onset, (ii) the unique post-ischemic plasticity milieu, and (iii) the extent of cortical reorganization.

Summary—Future work will need to further characterize the unique interaction between types of training and post-ischemic plasticity, and find ways to augment and prolong the sensitive period using pharmacological agents or non-invasive brain stimulation.

Keywords

Motor recovery; spontaneous recovery; motor learning; ischemia; neurological rehabilitation

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 pre-stroke movement patterns are regained post-stroke (i.e. a reduction of impairment) whereas compensation means using

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alternative movements to accomplish a motor task (i.e. using different muscle groups, joints, or effectors) [1-3].

Discussion of rehabilitation after stroke often emphasizes motor training, however, motor training is a much more ambiguous notion that is generally appreciated. For a healthy subject 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 subjects, 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.

In both healthy and post-stroke 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: (1) 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, non-training associated recovery after stroke [4,12-19]. (2) Conversely, behavioral changes that improve function can happen in the absence of plasticity. For example, a patient can “learn” within seconds to use their non-paretic 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 post-stroke motor recovery in human and non-human animal models that suggest that there is a “sensitive period” (SP) post-stroke. First, almost all recovery from impairment occurs in the first three months after stroke in humans [5,20-23] and in the first month after stroke in rodent models [12,23,24]. Second the effectiveness of post-stroke training with respect to impairment for both natural and pre-trained 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 SP is essential for significant recovery from impairment [3,12,23,25,27,28]. Throughout the remainder of this review we refer to post-stroke brains as either being inside or outside this SP. Third, improvement beyond the SP is mediated almost entirely by compensation.

Here we posit a unique, time-limited post-stroke 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 SP are quantitatively and qualitatively different from those seen outside the SP 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 where 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 one 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 up regulated [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 EPSPs 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 clustered groups, a phenomenon associated with persistent stability and not seen with motor activity alone.

By days 8-14 of prehension training, there is expansion of forelimb movement representations (evoked with intra-cortical micro-stimulation) in the rodent caudal forelimb area (the rodent equivalent of primary motor cortex) [40-42]. Similar expansions of motor maps have been documented in non-human 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, i.e., 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 post-stroke 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 post-ischemic cortical environment as compared to similar training in the normal brain or in chronic stroke.

Gene expression changes—During the post-stroke SP, 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 to uninjured motor cortex after motor training [34]. For example, synapsin, PSD-95, and GFAP are regulated differently by motor training compared to ischemia [55]. Furthermore, recent work by Li and colleagues have shown that during the post-stroke SP, 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 [50,53]. For example, ischemia induces a time-dependent increase in semaphorin 6A [51,56], 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 up regulated in response to ischemia and motor learning. For example, brain derived neurotrophic factor (BDNF) is up regulated in response to both ischemia and motor learning [57-59]. These data suggest that the heightened plasticity of the post-ischemic brain is attributable both to unique gene products and increased expression of genes related to normal motor learning.

Electrophysiological changes—Accumulating data suggest that ischemia rapidly changes the electrophysiology of the remaining nervous tissue in both affected and unaffected hemisphere. For example, beginning quickly after damage, long-term potentiation (LTP) is enhanced [60,61]. Some have used the term ischemic LTP (iLTP) 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 post-stroke brain is an alteration of the excitatory/inhibitory balance. The importance of excitatory/inhibitory balance and the requirement for a specific amount (not too much, 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 only seen 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.

Post-stroke investigations measuring currents, neurotransmitter receptor expression, MEG recordings, and fMRI signals 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 SP. 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 and colleagues [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 was also temporally regulated relative to the infarct 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 one 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 post-stroke [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 (for example premotor as well as subcortical 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 altered in the post-stoke SP are transiently altered, 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 post-stroke SP in motor recovery [23], there is little investigation specifically linking behavior in the SP 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 can 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 non-human 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 post-stroke motor recovery are dominated by a task-specific pre-training/post-training 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 due to SBR is observed early after stroke in humans, for example increases on the Fugl-Meyer scale [5].

Accumulating data suggests 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] suggest that it augments the processes we have described that are seen in the SP 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 pre-morbid 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 post-stroke SP and motor recovery is 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 post-stroke SP can be dramatic, especially if the damage is subtotal and residual motor cortical areas are spared [23,82-84]. For example, Nudo and colleagues 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% [18,85]. Thus, during the SP, motor training directs functional reorganization in the peri-infarct motor cortex presumably enabled by the unique post-stroke plasticity milieu.

Data suggest that the interaction between training and the post-stroke SP can extend plastic changes beyond just peri-infarct cortex. For example, Frost and colleagues 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 [86]. 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 under-appreciated, is that compensation also occurs during the post-stroke SP 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 SP, which raises the possibility that they compete for plasticity

mechanisms in the SP. 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 SP amplifies the effects of motor training on motor recovery but motor training also sculpts the post-stroke SP plastic milieu. Not all conditions during the post-stroke SP are permissive to plasticity and recovery. Post-stroke, 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 [50,76], 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 [71], 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 post-stroke SP.

It remains an open question as to what kind of training to emphasize in the SP. We are not aware of any studies directly comparing task-specific training and enrichment. In an intriguing study by Biernaskie and colleagues, rats were pre-trained to perform multiple task-specific behaviors including prehension, spontaneous forelimb use, and beam walking followed by post-stroke 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 to just an enriched environment [12]. There are caveats, however. First, task-specific training without an enriched environment was never directly compared to 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 to self-exploration across a wider task space then the test used for comparison has to be on a *different* task.

Training-induced plasticity in the post-stroke brain beyond the sensitive period

Although the post-stroke SP seems to wane at 1 month in rodents and 3 months in humans [23], there are no definitive studies characterizing the plasticity milieu outside of the post-stroke SP. Nevertheless, observations suggest the following: First, motor training's ability to induce true recovery is reduced outside of the post-stroke SP [23]. 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 post-stroke brain outside the SP resembles (or is perhaps identical to) the plasticity milieu in the uninjured brain. That is to say, post-stroke 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 subjects can be attributed to this more limited plasticity that does not allow for reorganization.

Conclusions

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 spontaneous biological recovery to run its course with respect to impairment and focus rehabilitation efforts on behavioral compensation, i.e., current practice. Data suggest that impairment could be reduced further with behavioral and pharmacological interventions (for example, fluoxetine) [95] and because 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 do so only with task-specific training is a contradiction. Thus the human equivalent of enrichment is needed, perhaps a videogame 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 SP. Two promising therapies include pharmacological manipulation (e.g., fluoxetine) and non-invasive brain stimulation as both might augment, prolong, or mimic the post-stroke SP [95,98-104].

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Key points

1. The post-stroke sensitive period (SP) is a unique, time-limited plasticity environment that mediates spontaneous biological recovery (SBR) and falls off as a function of time and distance from the infarct.
2. Plasticity mechanisms in the SP are qualitatively and quantitatively different from normal brain and interact with motor training.
3. Training can either be task specific or encourage more general exploration in an immersive environment
4. True recovery (i.e. reduction of impairment) will require augmentation of the generalizing effects of SBR.