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Experience--a double edged sword for restorative neural plasticity after brain damage

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Summary

During the time period following damage, the brain undergoes widespread reorganizational processes. Manipulations of behavioral experience can be potent therapeutic interventions for shaping this reorganization and enhancing long-term functional outcome. Recovery of function is a major concern for survivors of central nervous system damage and management of post-injury rehabilitation is increasingly becoming a topic of chief importance. Animal research, the focus of this review, suggests that, in the absence of behavioral manipulations, the brain is unlikely to realize its full potential for supporting function. However, experiences also have the capacity to be maladaptive for brain and behavioral function. From a treatment perspective, it may be unwise to adopt the canon of “first, do no harm” because maladaptive experiences include behaviors that individuals learn to do on their own. A better understanding of how behavioral experience interacts with brain reorganization could result in rehabilitative therapies, individually tailored and optimized for functional outcome.

Keywords

activity-dependent plasticity; regeneration; synaptogenesis; neurorehabilitation; behavioral compensation; motor skill learning; ischemia; traumatic brain injury; animal models

We live immersed within environments of sensory, cognitive and emotional experiences that are constantly changing in small ways on a moment-by-moment basis and in large ways over time and during dramatic events and life junctures. The brain has long been considered an organ of adaptation that permits animals, including humans, to encode and profit by experiences and to adapt to continuously and sometimes profoundly changing environments. Though there is much to learn about the precise cellular processes underlying the capacity to adapt, it clearly involves changes in the structure and function of neural and glial connections and these take place on a regular, daily basis throughout the lifespan of animals [1].

Behavioral experience also plays a major role in recovery after brain damage. However, in this case, experience interacts with the cellular reactions instigated by the injury. Brain injury, even relatively small injury, causes widespread degenerative, inflammatory and neurotoxic reactions. This in turn initiates a series of plastic responses in regions connected to the damage, including cortical, sub-cortical and spinal cord regions [2,3]. This includes major increases in growth and proliferation factors that support the remodeling of neural connections, glia and

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vasculature as well as the generation and migration of cells [2,4-5]. We refer to this as the degenerative-regenerative cascade. During this time the brain is highly receptive to behavioral experiences. This particularly dynamic and experience-sensitive state has been suggested by some to resemble that found during brain development [6].

This review focuses on how post-injury behavioral experiences can alter the brain's response to injury. This is presented from the perspective of those studying animal models of the recovery process. Functional outcome following CNS damage in rodents and other animals is well-documented to be influenced by manipulations of the environment and by "rehabilitative" training [7-9]. It is also shaped by "self-taught" behavioral changes, i.e., those that individuals spontaneously develop on their own to compensate for the loss of function. A recurring theme is that experiences that are generally beneficial for functional outcome, such as exercise and rehabilitative training, sometimes have maladaptive consequences if administered excessively or during the wrong times after certain types of injuries. Other experiences have mixed effects, as can be the case for self taught behavioral change.

"Self taught" behavioral changes after brain damage

Significant brain damage is a dramatic juncture for the brain because, just as it undergoes degenerative-regenerative cascades, it simultaneously must respond to the behavioral demands of lost function. It is common following brain injury to develop ways of compensating for deficits in function. Many brain injuries are lateralized such that there are major deficits in the contralesional body side and less impairment in the body side ipsilesional to the injury. For the purpose of this review, the body side contralesional to brain damage will be referred to as "impaired" and the body side ipsilesional to the damage will be referred to as "intact", with the understanding that this is relative. Unilateral ischemic or electrolytic lesions to the sensorimotor cortex in rats cause major impairments in the contralesional forelimb (Fig. 1A). These impairments are manifested as significant reductions in the use of this forelimb in measures of food handling behavior [10-11], and postural support [12-15] and deficits in coordinated forelimb use [13,16], responsivity to sensory stimulation [12] and in performance of skillful motor movements, including performance of reaching tasks [17-18]; see also [19]. Although some of these impairments recover partially or can be improved with rehabilitative training (discussed below) many of the behavioral deficits appear to be permanent as measured in sensitive species-appropriate measures [20]. In the presence of this loss of function in one body side, rats, like humans, begin to rely more and in different ways on the intact body side. A right handed human that sustains a left hemisphere stroke may learn to write, type, dress, etc., mostly using the left hand. A rat with a left hemisphere infarct learns to explore its environment and manipulate food and other objects by increasing reliance on the left forepaw.

The increased reliance on the intact body side after unilateral brain damage is an example of self-taught behavioral change that strongly impacts brain reorganization. Unilateral cortical lesions instigate a degenerative-regenerative cascade in the contralesional cortex that makes the neurons here exceptionally responsive to changes in the use of the intact forepaw. The sensorimotor cortex of either hemisphere is interconnected via transcallosal axonal fibers. The lesions cause some of the projections to degenerate and this is associated with increased neurotrophic factor expression [21-22], glial reactivity, dendritic and synaptic structural alterations [13,23-25] and excitability changes [26-27]. The highly plastic environment may increase the ability of the intact body side to carry out tasks. Compared to a healthy rat that learns to use one limb more, a rat learning to use the intact forepaw early after unilateral brain damage has a much greater neuroplastic response (growth of dendrites and synapses) in the contralesional cortex, apparently because this learning capitalizes on a more dynamic neural environment [23,25,28-29]. For example, electrolytic and ischemic damage to the forelimb representation area of the SMC in rats better enables these animals to learn skilled reaching

tasks with their intact forelimb compared with healthy controls [14-16,25,27], despite subtle impairments in this forepaw. In contrast, skilled reaching function that was acquired prior to the injury is impaired in the ipsilesional forelimb, suggesting that the lesions may simultaneously disrupt pre-existing motor engrams and facilitate the formation of new ones [27,30-31]. This effect is somewhat sensitive to time, with more robust enhancements in the intact forelimb learning found earlier after the lesion [27]. In humans, transient virtual lesions of the motor cortex of one hemisphere improve function in the ipsilateral hand [32]. Anesthetization of one limb improves motor and sensory functions in the other limb in humans and rats [30,33-35]. Furthermore, removal of ipsilateral whiskers in rats enhance experience-dependent plasticity in the somatosensory cortex [36]. Together, these findings suggest that there are competitive interactions between the hemispheres that influence experience-dependent plasticity and that these interactions can become unbalanced by unilateral lesions.

Compensatory use of the intact body side is an effective strategy for rapidly regaining the capacity to carry out daily activities. Indeed, it is common to focus early rehabilitation efforts in humans on compensation with the intact body side [37]. The fact that this compensatory strategy can be enhanced by unilateral brain damage initially led us to view this as a generally functionally beneficial effect of behavioral interactions with the degenerative-regenerative cascade. But it appears to be a double-edged sword. We recently investigated how experiences with the intact forelimb affect recovery of function in the *impaired* body side. Rats trained early after unilateral ischemic sensorimotor cortex lesions on a skilled reaching task with their intact forelimb had worsened behavioral outcome and slowed motor “re-learning” with their impaired forelimb compared to rats without the intact forelimb experience [38]. Behavioral training focused on the intact forelimb also decreased expression of FosB/ Δ FosB, a marker of cumulative neuronal activity, in remaining regions of the sensorimotor cortex near the lesion [38;Fig. 1B]. These findings suggest that peri-lesion cortex is highly sensitive to the maladaptive behavioral effects of intact forelimb experience and it may be especially sensitive to the effects of learning *new* skills with the intact forelimb [39]. This creates a conundrum. If there is no capacity to improve function in the impaired limb, then it may be best to focus on compensating with the intact body side and to do this early after ischemic injury to capitalize on time-dependent neuronal growth promoting processes. However, early compensatory use of the intact body side may have detrimental effects for any residual capacity in the impaired body side, including that which might be eventually realized with appropriate rehabilitative training.

Neurorehabilitation

After brain damage, the first line of attack is to minimize tissue loss, and this has been appropriately the focus of much research on neuroprotection for stroke and traumatic brain injury. However, even in those individuals fortunate enough to benefit from early neuroprotective therapies, many can be expected to have long-term loss of function. Thus, it is critical to also develop a second line of attack to minimize the functional consequences of the tissue lost. The goal of neurorehabilitation is to do this by optimizing reorganization of the remaining brain and there is much research to support that this may be accomplished using principles of experience-dependent neural plasticity [40]. Decades of research on the neurobiology of learning and memory support that forming memories and learning new skills and habits involve changes in relevant neural circuits in the brain. The term “neurorehabilitation” reflects that physical therapy and rehabilitative training accomplish changes in behavioral function by changing the brain. Animal models of neurorehabilitation strongly support that behavioral training can be used to reorganize the brain in a functionally beneficial manner after brain damage.

Motor Skill Training

Following cerebral ischemic injuries, there are widespread synaptic and functional effects including changes in neuronal excitability in cortex [26] and in striatum [41]. This reorganization can be influenced with motor skill training. After cortical ischemia, neuroplastic changes in peri-infarct cortex and improvement in function occur with focused training of impaired extremities in motor tasks. For example, after unilateral motor cortical infarcts, skilled use of the impaired forepaw is improved in rats and monkeys as a result of extensive practice in skilled reaching [9,42-43]. The functional improvements are linked to the reorganization of motor representations in remaining regions of the peri-infarct cortex. Skilled reaching (a.k.a. “reach-to-grasp”) tasks have been used extensively as a post-injury rehabilitative therapeutic model in rats and monkeys in part because the movements used in these tasks closely mimic movements made by humans when reaching and grasping objects [44-45]. In healthy animals, training in skilled reaching results in extensive neuroplastic changes in the trained hemisphere [3]. Following unilateral motor cortex damage, squirrel monkeys trained in skilled reaching for 25 days, had improvements in reaching function and expansion of motor maps into remaining peri-infarct cortex [42]. Similarly, following unilateral forelimb area SMC lesions, rats trained in skilled reaching had improvements in impaired forelimb function and reorganization of motor maps in remaining cortex [46-48]. Disruption of motor cortical plasticity and functional integrity, by depletion of cholinergic projections [47] or infusions of protein synthesis inhibitors [49] disrupts the beneficial effects of motor rehabilitative training.

Timing of training onset is a notable factor in the effectiveness of rehabilitative training. In monkeys, if skilled reach training is delayed too long after motor cortex damage (one month), hand movement representations are not spared compared to earlier training onset [50] and in rats it is less effective in promoting functional recovery in the impaired forelimb and dendritic growth in remaining cortex compared to training onset five days after injury [51].

Although motor skill training improves function after brain damage, much of the improvement is a result of compensatory movement strategies. For example, monkeys and rats use compensatory ways of moving the impaired forelimb, as well as the head and trunk, to successfully complete skilled reach-to-grasp sequences [17,52]. Furthermore, extensive training may be required to improve function [43]. Experience-dependent plasticity can be impaired near ischemic lesions [53] and it may be that adjunct therapies are needed to overcome this. An emerging topic of research involves strategies for further improving the effects of rehabilitative training. One promising approach for the treatment of motor deficits is to couple motor rehabilitative training with concurrent motor cortical stimulation. Rats and monkeys with unilateral sensorimotor cortical infarcts that received motor cortical stimulation via implanted electrodes during reach training had improved performance of the impaired forelimb in comparison to animals receiving rehabilitation training alone [54-56]. This effect was linked to increased dendritic and synaptic density [54,57], enlargement of movement representations [55-56] and increases in the polysynaptic component of evoked responses [58]. Transcranial direct current and magnetic stimulation also show promise for facilitating motor and sensory recovery [59]. For a more in depth review on the importance of transcranial magnetic stimulation as an emerging field of post-stroke therapy see Reis et. al [60]. There are also many investigations of pharmacological adjuncts to rehabilitative training, as reviewed elsewhere [61-62].

As discussed above, animals spontaneously increase reliance on the intact body side after unilateral injury. Taub and colleagues have long proposed that this leads to a learned non-use of the impaired body side which further limits its functional recovery [63]. A prominent adjunct to training has been to restrict the use of the intact arm to counter these effects. Constraint-induced movement therapy (CIMT) is a post-stroke rehabilitation protocol in which the intact hand and arm are restricted for many hours each day thereby forcing patients to use their

impaired hand and arm to carry out daily activities [64]. This is coupled with focused training of the impaired arm. CIMT has proven beneficial in improving function of the impaired upper extremity in stroke survivors [65] and enhancing activation in the stroke hemisphere [63]. A similar protocol to CIMT in rats improved forelimb function and reduced tissue loss following striatal hemorrhagic injury [66-67].

It is possible to overuse impaired extremities. Early overuse of the impaired forelimb in rats following unilateral SMC damage was found to exacerbate lesion size and further impede functional recovery [68-70]. This involved extreme use (rats wore vests restricting the intact forelimb 24h/day) and that the forced use occur during an early vulnerable window [69]. The exaggeration of injury was linked to increased excitotoxicity in the peri-lesion cortex. Others have found that early overuse of the intact body side is detrimental to functional recovery following brain trauma [71] and middle cerebral artery occlusion [72]. However, a similar protocol of forced use was found to spare dopaminergic neurons in the substantia nigra from neurotoxic lesions [70,73]. Thus, this overuse effect is dependent upon time, injury type and location.

Physical Activity

The effects of exercise as a rehabilitative approach have been well studied. Running is associated with increased neurotrophic factor expression, angiogenesis, and other neuroplastic changes in neocortex, cerebellum, and hippocampus, as reviewed in more detail elsewhere [74-75]. Voluntary exercise is beneficial to recovery of spatial learning tasks following traumatic brain damage [76]. There is a positive correlation between the amount of running and the neurotrophic factors expressed in hippocampus [77]). However, there was a failure to find a benefit of voluntary running after ischemic sensorimotor cortex lesions on recovery of forepaw motor function, in contrast to the effects of motor skill training [43]. Furthermore, if access to running wheels is provided too soon after a traumatic brain injury, rats do not show improvements and have decreased brain derived neurotrophic factor (BDNF) levels in hippocampus [76] and this effect is dependent upon injury severity [78]. The effectiveness of exercise on recovery from brain trauma therefore appears to depend upon many factors including type and severity of injury and time of exercise onset.

Environmental Complexity

Profound neuroplastic changes occur in the brains of laboratory animals exposed to complex environments and such exposure generally improves function after brain injury [79-80]. Typically, in studies of complex environment exposure, rats live in large groups in large cages with many items to manipulate and explore. This is in contrast to standard housing conditions where the rats are housed alone or in small groups in simple laboratory cages. In animals, complex environments have long been known to support superior cognitive and perceptual functions. Rats housed in these environments have significantly more dendrites, synapses, glial processes and vasculature in the neocortex and other brain regions [81]. They also have greater neurogenesis as adults [82]. Following middle cerebral artery stroke, rats with complex environment exposure have improved recovery in measures of cognitive function (spatial learning; [83-84] and motor and sensory function [85]). Following unilateral cerebral damage, enriched environment housing promotes dendritic process and dendritic spine growth in the contralesional motor cortex [80,86] and, sometimes, enhances post-injury neurogenesis [87]. Complex environment housing initiated early (3 days) after ischemia was found to increase cell death, but the animals were nevertheless improved in function compared to those with less cell death housed in standard laboratory cages [88]. Most studies of complex environments have not found that it affects the size of the injury.

We are often asked about the translational relevance of this research on complex environments in rats, a cogent question given that humans can be said to normally live in complex environments. The relatively poorer outcome of rats in standard housing suggests that impoverishment of experience, such as can occur with the loss of functionality after brain damage, can be maladaptive for functional outcome. Furthermore, these findings suggest that enhancement in the physical, social and cognitive activities of brain injury survivors might be an important strategy for optimizing functional outcome.

Conclusion

Behavioral experience provides a target and potent therapy for enhancing restorative neural plasticity after brain damage. Experiences after brain damage interact with injury-induced degenerative and regenerative changes to shape brain reorganization. There are limitations to animal models of neurorehabilitation in their translational implications for human post-stroke recovery, including the relatively short life-span and the difficulty of modeling certain types of stroke impairments, such as aphasia, in rodents. Nevertheless, these animal models are valuable for uncovering principles of experience-dependent plasticity that contribute to functional recovery following brain damage [40]. Animal research supports that manipulations of experience, including focused training, physical activity and enhancement of cognitive and social experience can have major effects on behavioral recovery and neural plasticity after brain damage. As with many treatments, there is the capacity for maladaptive side-effects. In animal models, there have been many findings that behavioral experiences thought to be generally beneficial sometimes have negative consequences. This is true for exercise, forelimb constraint and self-taught compensatory behavioral changes. These contrasting results most likely reflect that experience effects vary with different types and loci of brain injury and with time, because experience interacts with time-dependent neural degenerative-regenerative processes.

Future Perspective

These findings from animal models provide much basis for optimism regarding the use of behavioral manipulations to optimize functional reorganization of the damaged brain. The greatest potential of rehabilitative therapies is likely to be realized by their combination with other treatments. A recent and growing field of neurorehabilitation research treats behavioral manipulation as a core strategy to be positively modulated by other therapies, including cortical stimulation and pharmacological treatment. Advances in brain imaging technologies are likely to facilitate the translation of the animal research findings to human brain function following brain injury (for reviews see [89-91]).

The findings of bidirectional effects of behavioral manipulations also highlight how little we truly understand the interactions between brain injury and experience. It is not enough to know that experience matters. We need to learn precisely how it interacts with identified degenerative and regenerative changes, as well as how these effects vary with different types of injuries, experiences, ages and other individual characteristics. Such an understanding is likely to be crucial to our ability to use manipulations of experience to optimize functional outcome in survivors of stroke and traumatic brain injury.

Executive Summary

Introduction

- Injury-induced degenerative and regenerative cascades interact with behavioral experiences to shape brain reorganization. Optimization of functional outcome is likely to be critically dependent upon these interactions.

Self-taught behavioral change

- One of the most reliable consequences of survivable brain injury is that animals change their behavior to compensate for lost function.
- These “self-taught” behavioral changes interact with degenerative and regenerative processes instigated by the injury.
- This interaction was found to simultaneously facilitate learning of new skills with the intact forelimb while worsening function in the impaired forelimb in a rat model of unilateral cortical stroke-like injury,

Neurorehabilitation

- An emerging research direction is the reorganization of neural connectivity and activity in the damaged brain using principles of experience-dependent plasticity gleaned from research on the neurobiology of learning and memory.

Motor rehabilitation

- Motor training after cortical stroke-like injury results in functionally beneficial reorganization and greater synaptic connectivity in the peri-infarct cortex.
- Training focused on the impaired upper extremity improves function, but movements remain abnormal and there is room for greater improvement using adjuvant therapies.
- Motor cortical stimulation has shown promise for facilitating the effects of rehabilitative training in both animal models and in humans.
- Extreme overuse of impaired extremities during early vulnerable periods after cortical damage can exaggerate injury extent and sensorimotor impairment in rats; however, these effects vary with injury type and locus.

Physical activity

- Running elevates neurotrophic factors and plasticity-related proteins in the hippocampus and other brain regions and also improves cognitive performance and recovery in animal models.
- The effects of exercise are injury-type and time-dependent. Voluntary running too early after traumatic brain injury reduces neurotrophic factor expression and limits functional recovery

Environmental complexity

- Housing animals in complex environments after brain injury improves behavioral function and promotes plasticity of neurons, glia and vasculature.
- This suggests that enhancing the cognitive and social experiences of brain injury survivors may be a strategy for improving functional outcome.

Future perspective

- Manipulation of behavioral experience is a core strategy for promoting functionally beneficial neural plasticity in the damaged brain. It is critical that we better understand the nature of experience-injury interactions so that experiences can be tailored and facilitated by their combination with other treatments

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Figure 1. Bilateral effects of unilateral ischemic lesions

A, Rats use their forelimbs in dexterous ways to manipulate and reach for food. Unilateral ischemic lesions of the sensorimotor cortex result in deficits in the forelimb contralateral to the lesion (asterisks) and the animals develop compensatory ways of relying on the less-affected (“intact”) forelimb. Plasticity of motor maps and addition of synapses in the cortex near the lesion are strongly implicated in functional outcome and these changes are promoted by motor rehabilitative training focused on the impaired limb. However, the training may need to overcome injury-related changes that impair experience-dependent plasticity near the lesion [53]. In contrast, the cortex contralateral to the lesion has an enhancement in some aspects of experience-dependent plasticity. Training focused on the intact forelimb (PriorT) can worsen function in the impaired forelimb and reduce neuronal activation in the peri-infarct cortex.

B, Light micrographs of the motor cortex near the lesions showing FosB/ Δ FosB labeling, which is sensitive to cumulative neuronal activation. Scale bars = 50 μ m. **C**, Layer V motor cortical synapses as imaged using transmission electron microscopy (image courtesy of S. Y. Kim). Scale bar = 100 nm.