

**PLASTICITY OF THE CENTRAL NERVOUS SYSTEM AFTER INJURY:
ANALOGOUS THEORY OF RE-CONSTRUCTION**

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Abstract

When considering plasticity, the central nervous system can be viewed as a building block center. Following damage, building components might be lost or loosened; and may be rearranged by renovation, analogous to neuroplasticity that occurs following CNS injury. In both scenarios, the location and severity of damage will determine the efficacy of renovation/rehabilitation, and thus the quality of the adapted structure. Viewing the central nervous system as a set of building components is useful to describe injury-induced neuroplasticity.

Keywords: Plasticity injury; Central nervous system; Brain storm; Synaptic changes

Introduction

The central nervous system (CNS: brain, brainstem and spinal cord) can learn, re-arrange and adapt, a process often referred to as neuroplasticity. Plasticity can occur in the healthy CNS as experienced during learning of new skill or memorization of new information, and following injuries where an even greater extent of plasticity can occur (Brown & Weaver, 2012). A number of research studies examining the effects of injuries to the central and peripheral nervous systems have reported plasticity at various anatomical and physiological levels, including the cortex, brainstem and spinal cord (Onifer, Smith & Fouad, 2011). The mechanisms involved in this plasticity include changes in cortical maps, anatomical changes such as collateral sprouting, synaptic changes and adaptations in neuronal properties (Nudo, 2013; Onifer, Smith & Fouad, 2011). It has to be kept in mind that adaptive processes in the CNS do not only occur in motor systems and are not always beneficial. Quite the contrary, plasticity has frequently been associated with undesirable outcomes including autonomic dysreflexia, neuropathic pain and spasticity (Brown & Weaver, 2012). However, this review will be limited to adaptive changes in CNS (motor system) following injury.

Although various pharmacological approaches to promote plasticity have been reported, intensive training is currently viewed as the most successful treatment to promote functionally meaningful adaptive changes following CNS injuries. One could consider the effect of rehabilitative training as an extension of spontaneous recovery.

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Additionally, in accordance with processes in the developing nervous system, where activity is essential to the establishment of functional circuitry where rehabilitative training (and thereby the activation of neuronal networks in a meaningful pattern) is needed to translate plasticity-promoting effects of drugs into functional recovery (Garcia-Alias, Barkhuysen, Buckle & Fawcett, 2009; Weishaupt, Li, Di Pardo, Sipione & Fouad, 2013).

Considering the multifaceted underlying processes of plasticity and the fact that the use of the term plasticity is often ambiguous, it becomes quite clear that it is, and likely always will be, very difficult to fully comprehend all adaptive changes following injuries of the CNS. This review will define plasticity as the entire spectrum of changes in the intact or injured CNS including structural changes, alterations in synaptic strength and changes in neuronal properties. Thus, despite the analogy introduced in this manuscript, plasticity should not be viewed to be limited to structural changes but should also include functional reorganization of spared elements. Furthermore, predicting the effects of plasticity on particular aspects of recovery and maladaptive side effects is exceedingly difficult. Not surprisingly, investigating the mechanisms of plasticity is currently a pronounced focus of research, in order to develop treatments targeted to promote the beneficial aspects of plasticity following injuries and diseases of the nervous system, and thereby functional recovery. This is a daunting task, especially considering the relatively slow progression of our understanding of how the uninjured CNS functions. On the other hand, from a clinical point of view with an interest in maximizing the positive effects of rehabilitative training, a detailed understanding of the mechanisms of plasticity might not be essential. In this case a simplified view of the changes occurring following CNS injury might be sufficient and could prevent getting lost in details. We propose that the nervous system can be described as a house made of building components, including bricks and mortar. These building components represent neuronal structures of the CNS. The mortar that holds bricks together can be viewed as growth inhibitory components of the CNS such as myelin associated inhibitors or chondroitin sulphate proteoglycans (CSPGs) of the perineuronal net (Akbik, Cafferty & Strittmatter, 2012; Karetko-Sysa, Skangiel-Kramaska & Nowicka, 2011).

We are using the metaphor of a building structure in combination with the restriction that, comparable to the CNS, no additional building components are available following damage. It is important to note that even the uninjured CNS is constantly changing, and these changes can occur at a physiological level (Nudo, 2013). This is comparable to superficial changes to a building. In contrast, more substantial remodeling has to occur after damage to a structure in order to keep the structure functional, similar to the structural plasticity following CNS injury. Viewing the nervous system as a set of building components simplifies the interpretation and illustration of adaptive changes following injury, stimulates creative thinking about neuroplasticity, and may assist with predictions regarding treatment effects such as rehabilitative training. Our proposed analogy is supported by various findings from studies in animal models of, and individuals with, CNS injuries (Akbik, Cafferty & Strittmatter, 2012).

Damage to the CNS enables limited Remodeling and Adjustments

Similar to a natural disaster (e.g., earthquake) that loosens a building by shaking the structure and breaking up the mortar, an injury to the nervous system temporarily enhances plasticity of the CNS. Comparable to the loosened mortar (that allows restructuring of a building), growth inhibitory components like CSPGs in the perineuronal net are down-regulated following injury of the CNS (Karetko-Sysa et al., 2011). This results in heightened structural flexibility (i.e., enhanced neuroplasticity) and thus allows “remodeling” a process utilized and amplified by intensive rehabilitative training (Girgis, Merrett, Kirkland, Metz, Verge & Fouad, 2007; Nudo, 2013). This remodeling conforms to certain rules that match the scenario in a building. For example, building components can be moved, reused, and the structure can be reassembled in an alternative or compensatory fashion. Importantly, like a structure where building components have been damaged and cannot be re-used, the nervous system cannot replace lost “neuronal hardware”. More specifically, there is no general supply of stem cells that can replace lost neurons or the surrounding glia cells. The remodeling process should thus not be viewed as “repair” because it will not restore the original structure, but will instead maximise the use of spared building components. This is mirrored following CNS injuries by functional recovery that mainly consists of compensatory approaches rather than restoration of original functions (McKenna & Whishaw, 1999; Webb & Muir, 2002). Spontaneous recovery can thus be viewed as a “home remodeling” without using any new building materials to rebuild, and plasticity promoting treatments (including rehabilitative training) are comparable to hiring a contractor who has access to special tools (but not building components). Similar to home repair, when remodeling is performed without the assistance of a professional, the end product might not be satisfactory. In fact, if the homeowner attempts to repair their home it may be more difficult to restore it back to normal. This could be compared to spontaneous recovery that is frequently based on functional substitution or the establishment of compensatory movements, whereas targeted rehabilitative training can enforce the training of lost function. Similarly, the immediate approach by a contractor yields a better chance to recreate a functional house. If repairs are delayed, further problems may arise, or there may be further structural damage because weakened areas have not been reinforced. This could be compared to spontaneous recovery that is frequently based on functional substitution or the establishment of compensatory movements, whereas targeted rehabilitative training can enforce the training of lost function. Once a compensatory function has been established, retraining is more challenging.

Furthermore, the phase of injury-induced enhanced neuroplasticity after CNS injury offers a time window of opportunity for rehabilitative training, during which the nervous system can rewire and is particularly responsive to activity-based therapies comparable to “critical periods” during development (Norrie, Nevett-Duchcherer & Gorassini, 2005). The mechanisms that create this critical period or window of opportunity and enhanced neuroplasticity are not completely understood, but the injury-induced transient up-regulation of so called immediate early genes, neurotropic factors,

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and the down-regulation of CSPGs have been included in the speculations (Rickhag, Wieloch, Gido, Elmer, Krogh, Murray, 2006; Sist, Fouad & Winship, 2014).

The Amount of Spared Hardware Determines the Degree of Spontaneous Recovery

Spontaneous functional recovery can be found over a few weeks following CNS injury. The duration of this process and the degree of recovery greatly depend on the severity of the injury (Kitago, Liang, Huang, Hayes, Simon, Tenteromano, Lazar, Marshall, Mazzoni, Lennihan & Krakauer, 2012). For example, it is generally acknowledged that more severe injuries allow a lesser degree of spontaneous recovery and likely reduced efficacy of rehabilitative training. Robust repair mechanisms to replace lost tissue are very limited due to insufficient availability of stem cells and the inability of neurons to regenerate in the adult mammalian CNS (Lu, Kadoya & Tuszyński, 2014). Consequently, beyond the obvious observation that more severe lesions result in more severe deficits, the number of spared neuronal building blocks also determines the degree of plasticity and thus spontaneous and training induced functional recovery. When comparing this to a building, extensive damage to all bricks, analogous to a complete transection of the spinal cord or the ablation of an entire cortical area, results in no pieces remaining for meaningful rebuilding or plasticity. On the other hand, very small injuries to the brain or spinal cord can be immediately compensated for without any obvious effects and are often hardly noticeable in animal models or the clinical setting (Hurd, Weishaupt, & Fouad, 2013; Kitago, Liang, Huang, Hayes, Simon, Tenteromano, Lazar, Marshall, Mazzoni, Lennihan & Krakauer, 2012). This offers a straightforward analogy to a building block structure; the more damage that occurs, the less restructuring without additional building materials is possible. Minor damage can be “patched up” without influencing the overall stability of the building, but when critical load bearing components are destroyed, reconstruction is impossible.

The Non-linear Relationship between Structural Damage and Function

Although severe lesions to the CNS hardly allow spontaneous recovery controlled by descending input from the brain, and small lesions can be immediately compensated for, the relation between functional recovery and tissue loss is generally not linear (Hurd et al., 2013; Loy, Talbott, Onifer, Mills, Burke, Dennison, Fajardo, Magnuson & Whittemore, 2002; Schucht, Raineteau, Schwab & Fouad, 2002). For example, the success rate in a reaching task in an animal model of spinal cord injury remains very high following small lesions; with increasing tissue damage however, a drastic decline in function occurs before a plateau is reached (Kitago, Liang, Huang, Hayes, Simon, Tenteromano, Lazar, Marshall, Mazzoni, Lennihan & Krakauer, 2012). This plateau can be maintained for a surprisingly large increase in the lesion size. Yet, when a critical point in lesion size is exceeded, the ability to reach is abolished even though not all tissue has been injured. This could be interpreted as compensation by using spared previously non-critical components to take on more critical roles when small losses of neuronal hardware occur. Adaptive strategies allow for the maintenance of a

new plateau in motor function after a significant loss of tissue. No functionally meaningful neuronal network can be established once a critical amount of tissue loss has been exceeded. This is comparable to a house where a few building components can be damaged, and if they are essential for the house to be habitable, they can be compensated for by using components less critical for the structural integrity of the house. However, with a continuous increase in damage, a threshold will be reached where the house will have to be remodeled to remain habitable, by downsizing. With further increase in the number of damaged building components, too many pieces will be missing and even the smaller house will become uninhabitable. Although pieces of the structure might still be available it cannot be remodeled to be habitable again. These findings are especially important when attempting to judge and compare the efficacy of treatments including rehabilitative training. Treatment effects may range from significant to non-existent depending on the severity of the lesion.

The Specific use of Building Components Determines the Outcome during Remodeling

Currently, the most successful treatment following injuries to the CNS is rehabilitative training. It has been reported that training effects are often task specific and may even negatively influence untrained motor functions. For example, training to walk forward on a treadmill does not translate into recovery of backward walking or stepping in place in individuals with SCI (Grasso, Ivanenko, Zago, Molinari, Scivoletto & Lacquaniti, 2004). Cats with complete spinal cord injury that were trained to stand have more difficulty relearning to step compared to untrained cats and step-trained cats (Hodgson, Roy, de Leon, Dobkin & Edgerton, 1994). Similarly, step-trained cats are not able to stand as well as stand trained cats. Comparably, rats with SCI trained to grasp for food pellets showed deficits in an untrained task i.e., crossing a horizontal ladder (Girgis, Merrett, Kirkland, Metz, Verge & Fouad, 2007). Additionally, it has been reported that training of one language following stroke in bilingual individuals reduces the ability to re-establish speech in the second language (Abutalebi, Della Rosa, Tettamanti, Green & Cappa, 2009). These findings suggest that spared neuronal hardware can be “remodeled” following an injury to the CNS according to the trained tasks. Similar to the developing nervous system, this process is driven by activity and illustrates an important aspect of post-injury rehabilitative training. Following injury this process will result in compensation, or functional substitution, rather than repair to reach the status quo.

It can be generalized that the available neuronal hardware is dedicated in a competitive manner on a first-come, first-served basis, and tasks that require higher neuronal activity are favoured. This scenario is comparable to a building where, once a structure is damaged, broken components become useless and spared pieces can be reused to recreate certain portions of the original structure. There will be competition for the limited building materials, which will decide the final structure and therefore functional capabilities. For example, the roof will be leaky if building pieces from the roof are used to stabilize the walls. Even though moving building pieces from the nervous

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system is not a realistic option, integrating neurons in different circuitries may result in an alternative utilization for them.

The damaged location can be used to predict functional outcome

Recovery following injury is not only determined by the amount of tissue damage, but also depends on the location of the injury (Chen, Tang, Chen, Chung & Wong, 2000; Loy et al., 2002; Schucht et al., 2002). This is based on the fact that the CNS is built in functional units. The different parts of the body are represented by specific cortical areas, and specific spinal tracts with different functions project in bundles in specific locations within the spinal cord. This can explain why a small lesion in the ventral spinal cord can have more severe effects on locomotor ability than a big lesion in the dorsal cord, because tracts that are involved in initiating locomotion project in the ventro-lateral portion of the spinal cord. Another example is that recovery in reaching function is better when two descending tracts involved in reaching are partly lesioned rather than the complete ablation of one track. Parallels to a building can be drawn, where it would be easier to create a downsized structure when pieces of all the building components are still available.

Effects of spinal lesions staggered in time support the reconstruction idea

We have described a model in which the building blocks of the nervous system, similar to building components of a house, can be re-assembled/rewired in an alternative manner following injury. Furthermore, we discussed that rehabilitative training is a key component to achieve this. Illustrative examples where an injury induces permanent changes to the nervous system are provided by experiments with two lesions staggered in time. This approach has been used with injuries to the spinal cord, where convincing differences in the response to a lesion were found depending on whether a second spinal lesion was induced at the same time as the initial one or later in time. For example, a spinal lesion ablating one side of the cord allows for nearly complete recovery of stepping in rats and cats alike (Ballermann & Fouad, 2006; Martinez, Delivet-Mongrain & Rossignol, 2013). Following our hypothesis, this is due to an activity-based rearrangement of building materials and reinforcing remodeling. When such a lesion is followed by a complete spinal transection caudal to the first lesion a few weeks later, the spinal networks below the lesion are able to recover the same stepping pattern much faster when compared to animals that only received a single transection (Martinez & Rossignol, 2013). This demonstrates that the first injury induced compensatory rewiring within the spared spinal cord network that is maintained even when completely disconnected from the brain. Thus, if a house that was remodeled after a first earthquake had to overcome a second earthquake, the overall damage would not be necessarily comparable to the damage that same house would have had if only a single stronger earthquake had hit it.

Another example demonstrating the “remodeling” of the CNS following injuries comes from an experiment where the recovery of reaching function over weeks following

a cervical lesion of the corticospinal tract in rats was observed. This recovery is paralleled by rewiring of injured CST fibers to alternate targets, a process that is amplified by rehabilitative training (Girgis, Merrett, Kirkland, Metz, Verge & Fouad, 2007). A second lesion of the corticospinal tract rostral to these new connections completely abolishes the observed recovery (Krajacic, Weishaupt, Girgis, Tetzlaff & Fouad, 2010), indicating that this compensatory rewiring is functionally meaningful. These provide strong evidence for the involvement of plasticity in recovery and demonstrate that training is a key concept to enhance it. The spontaneous recovery found after CNS injuries is very likely based on activity and training inadvertently performed during daily life. This has been dramatically demonstrated by the lack of spontaneous recovery in rats with thoracic SCI when the use of the hind limbs were disabled (Caudle, Brown, Shum-Siu, Burke, Magnuson, Voor & Magnuson, 2011).

Building block structure analogy not only applies to common treatment strategies

This review has compared the injured CNS to a structure where new building supplies are unavailable. Obviously, treatments designed to introduce new “building materials” or to minimize damage following CNS injury would be desirable. For example, a much-anticipated approach is the grafting of stem cells into injured areas of the CNS (Lu, Kadoya & Tuszynski, 2014; Reeves & Keirstead, 2012). Theoretically these cells have the ability to develop into various cells types including neurons and glia, thereby replacing damaged building materials. This approach would greatly extend the opportunities to repair an injured structure, however in order to properly integrate new building blocks rehabilitative training will likely be needed to connect the pieces in a functionally meaningful manner.

An alternative and already utilized approach for treating CNS injuries is based on the knowledge that lost neuronal hardware is difficult to replace. These treatments focus on neuroprotection. To be effective, these treatments have to be applied as soon as possible following injury. Following CNS injuries, there are various approaches either in clinical use, in trials or currently tested in animal models ranging from cooling the injured CNS to the application of anti-inflammatory drugs (Onose, Anghelescu, Muresanu, Padure, Haras, Chendreanu, Onose, Mirea, Ciurea, El Masri & Von Wild, 2009; Sutherland, Minnerup, Balami, Arba, Buchan & Kleinschnitz, 2012).

Conclusion

A detailed understanding of the mechanisms of neuronal plasticity is important for optimizing treatments for CNS injury. However, from a more clinical point of view, these intricate details may be unnecessary. Viewing the CNS as a house made out of different component of neuronal hardware that can be reassembled in response to injury is not necessarily a simplified view of injury-induced plasticity, but a metaphor derived from various findings. A more tangible view of injury-induced plasticity in the brain and spinal cord may be helpful in communicating the process of plasticity. This may be a better window in the understanding and use of cognito-training as a means for absolute development and rehabilitation.

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