By Heidi Reyst, Ph.D., CBIST

Annually, 1.7 million people incur a traumatic brain injury (TBI); (Faul, Xu, Wald and Coronado; 2010) and over 795,000 people sustain a stroke in the U.S. alone (Roger et al., 2012). Collectively, nearly 2.5 million individuals sustain an acquired brain injury (ABI) annually. The annual incidence rate of TBI from 2002 to 2006 was 579 people per 100,000 (Faul, Xu, Wald and Coronado; 2010). The corresponding annual incidence rate for stroke was 189 persons per 100,000 based on a standardized sampling schema (Kleindorfer et al., 2010). Taken together, the annual incidence rate for TBI and Stroke combined is 768 persons per 100,000.

Comparing this number to all cancers combined at 463 persons per 100,000 highlights the significant prevalence of acquired brain injury (Howlader, 2012). See Figure 1. In light of these numbers, it is critical that the processes underlying ABI injury as well as the processes modulating recovery are understood. Only then can treatment and rehabilitation be further refined to enhance recovery.

![Figure 1. Number of persons affected per 100,000 (CDC)](image)

Brain injury cascade

When a traumatic brain injury occurs, there are two distinct phases of injury. The first is the primary insult or injury, where the injury etiology is direct mechanical damage. The second is the secondary insult or injury, following mechanical damage, with the etiology being a cascade of pathophysiological processes. Because the “cure” for the primary phase is prevention, research has focused on improvement of the second phase processes in hopes for increasing outcomes post injury (Shlosberg, Benfia, Kaufer and Friedman, 2010). It is also important to note that depending on the mechanism of injury (for example closed versus penetrating injuries, etc.), the process can differ, as it can depending on other factors like age, location of primary injury etc. Figure 2 outlines the general process of the TBI cascade.

![Figure 2. Injury cascade](image)
Phase One

In the primary phase, injuries typically include direct tissue damage, impaired cerebral blood flow, and impaired metabolic activity, leading to edema formation and cytoarchitecture changes like membrane permeability (Werner and Engelhard, 2007). There are contact forces which cause contusion, hemorrhage and lacerations throughout, and inertial forces which cause shearing and/or compression of brain tissue (Werner and Engelhard, 2007). These forces cause multifocal injuries (usually termed diffuse axonal injury) affecting axons, blood vessels, junctions between white and gray matter, and other select focal areas like the corpus callosum and junctions between the frontal and parietal lobes (McAllister, 2011). As a result of direct damage, a cascade of pathological processes begins.

Phase Two

After the initial injury, neurons are disrupted resulting in depolarization and then a substantive release of excitatory neurotransmitters (McAllister, 2011; Werner & Engelhard, 2007). This results in release of Ca++ (calcium) and Na+ (sodium) ions, which lead to intracellular breakdowns. This sets in motion the release of caspases and calpains, both of which initiate processes leading to cell death. The release of calpains quickly leads to necrosis where cells die as a response to mechanical or hypoxic damage and metabolic failure. This leads to an inflammatory response with the cells being removed (Werner & Engelhard, 2007; McAllister, 2011). The release of caspases initiates the process of apoptosis (programmed cell death), which can take hours to weeks to progress. Apoptosis, contrary to necrosis, is an active process, whereby initially intact cells cause cell membrane disintegration, disruption of cell transport and ultimately cell death (McAllister, 2011).

Throughout the injury processes, there are other critical factors in the injury process affecting outcome. One is the breakdown of the blood brain barrier (BBB). There can be direct injury to the BBB in the primary phase and in injury to the endothelium of the BBB in the secondary phase. This increases permeability of the blood vessels and results in vascular pathology (Shlosberg, Benifla, Kaufer and Friedman, 2010). Breakdown of the BBB is implicated in the formation of edema (causing fluid accumulation within the brain), excitotoxicity, inflammation, and cell death. When the BBB breaks down, an inflammatory response begins, where injured tissue (and tissue adjacent to it) is eliminated, further impacting functional outcomes (Werner & Engelhard, 2007). While inflammation is generally thought to be primarily maladaptive, it is now known that a limited amount of inflammation plays an essential role for repair after injury (Ziebell and Morganti-Kossmann, 2010).

The processes after stroke are similar to those in TBI. For example, the pathophysiological cascade (secondary phase) after ischemic stroke includes loss of cell homeostasis, calcium ion release, neurotransmitter release, excitotoxicity, disruption of the BBB, reduced cerebral blood flow, inflammation, necrosis, and apoptosis. Thus, after acquired brain injury, both primary and secondary injuries can lead to significant deficits and functional problems for individuals. While researchers attempt to find treatments that ameliorate the secondary injury factors (e.g., progesterone, t-PA, etc.), the main recourse after brain injury is neuroplasticity.

Neuroplasticity and brain function after acquired brain injury

Probably the easiest way to conceptualize neuroplasticity after injury to the brain is to view it simply as re-learning (Plowman and Kleim, 2010; Warraich and Kleim, 2010). As Kleim (2011) noted, “the brain will rely on the same fundamental neurobiological process it used to acquire those behaviors initially. The basic rules governing how neural circuits adapt to encode new behaviors do not change after injury” (p. 522). For example, the changes seen in the motor cortex after brain injury in response to motor re-learning are the same motor changes seen in the motor cortex during development of those motor functions.

While we can view re-establishing function as a re-learning process, there are two conceptual differences when it occurs after a brain injury.
First, because neural circuits for a particular function were previously established during the brain’s neurodevelopmental process, it may be possible to take advantage of those learned behaviors should they persist in residual areas of the brain during the rehabilitation (Kleim, 2011). This presents as a potentially adaptive circumstance.

Second, a more maladaptive consequence which occurs post injury relates to the concept of learned non-use. Just as increasing dexterity of motor function leads to increased motor cortex representation of neural circuitry (and therefore improved function), non-use can lead to decreased motor cortex representation, and therefore decreased function (Plowman and Kleim, 2010). Post stroke, research indicates that learned non-use of a paretic limb, combined with an increased reliance on the unaffected limb can result in major brain reorganization.

**Learned non-use**

This occurs when, post stroke, a paretic limb is not used due to the infarct affecting the area of the *primary motor area* (M1) controlling that limb. Consequently, the individual relies heavily on the intact (unaffected) limb. Holding to the maxim of “use it or lose it,” in the acute phase after stroke, if the affected limb goes unused, the motor map size decreases (see previous article titled *Neuroplasticity in the intact brain*). At the same time, the unaffected limb is substantially utilized, and the motor map for that area increases in size. Thus, experience (or lack thereof) impacts the cortical representations of M1 during the stage of spontaneous recovery, but learned non-use in particular may also be implicated in a more nefarious manner, as it may be a contributing factor to interhemispheric imbalance (Takeuchi & Izumi, 2012).

**Interhemispheric imbalance**

Studies have found that in the affected hemisphere where the infarct or lesion occurred (termed the ipsilesional hemisphere) there is decreased excitability leading to a reduction in the likelihood of neurons generating an action potential (which is the precipitant in neuron-to-neuron ‘firing’). The overall result of decreased excitability is a reduction in neuronal communications within that hemisphere. On the contrary, in the unaffected hemisphere (termed the contralesional hemisphere) there is increased excitability.

Studies have shown that the over-excitability of the unaffected hemisphere inhibits the excitability of the affected hemisphere, resulting in decreased motor functioning (Corl et al., 2011). Learned non-use has been theorized as a contributing factor in interhemispheric imbalance additionally by the attenuated neuronal activity in the affected hemisphere, coupled with the greatly increased use of the intact limb driving neuronal activity higher in the unaffected hemisphere (Takeuchi & Izumi, 2012). Credence is given to this idea, in that research has shown that if the unaffected hemisphere is artificially inhibited, this leads to excitability of the affected hemisphere, impacting motor movements positively (Pascual-Leone, Amedi, Fregni & Merabet, 2005).

As noted above, there is substantial biological change to the brain after focal injury (e.g., stroke) and diffuse injury (e.g., TBI). The effect of this biological change is profound. There can be damage to the tissue directly, due to the loss of oxygen resulting from a stroke, or due to inert forces like in a traumatic injury. In addition to these direct effects, additional, and potentially equally damaging biological changes occur at sites of the brain both distant and close to the lesioned areas. This includes the inflammatory process, attenuated blood flow, changes to metabolic processes, edema, and neuronal excitability (Kleim, 2011). These cascade processes result in disruption to intact areas of the brain particularly those areas with connectivity to the injured regions, and has been termed diaschisis.

Diaschisis is in essence a disturbance or loss of function in one part of the brain due to a localized injury in another part of the brain, and these areas can be of considerable distance from the lesioned area including the opposite hemisphere (Stein, 2012). One effect post stroke that affects function within the brain considerably is hyper-excitability in the opposite hemisphere. This, coupled with under-excitability in the damaged hemisphere results overall in a disrupted neural network (Pascual-Leone, Amedi, Fregni and Merabet, 2005). Research has shown that these changes can occur up to 12 months after the initial injury (Cramer and Riley, 2008). With the likelihood of widespread neural dysfunction after injury, what then are the mechanisms for recovery?

**Mechanisms of recovery**
After injury to the brain, there are two mechanisms whereby functional improvement may occur. These are recovery and compensation (Kleim, 2007). Using World Health Organization definitions,

**Recovery** relates to:

1. Restoration of neural tissue initially perturbed after the injury (neural level)
2. Restoration of movement exactly as it was performed prior (behavioral level)
3. Restoration of activity exactly as it was performed prior (activity level)

**Compensation** refers to:

1. Recruitment of new neural circuits (neural level)
2. Training of new movement sequences (behavioral level)
3. Training of activity in a new way after injury (activity level)

Recovery therefore relates to lost functions being restored, and compensation relates to the acquisition of new functions or behaviors to replace those lost after injury (Kleim, 2011). Research has shown that after a stroke, for motor deficits, notable recovery takes place within 30 days for mild, moderate, and moderate-severe severity with additional recovery up to 90 days for severe strokes (Duncan, P., Goldstein, L., Matchar, D., Divine, G. and Feussner, J., 1992). These times frames are similar with other areas of dysfunction where the final level of language function was achieved within six weeks post stroke for 95% of patients (with mild, moderate and severe aphasia; Pedersen, Jorgenson, Nakayama, Raaschou and Olsen, 1995). The level of recovery from spatial neglect was maximized within nine weeks (Hier, Mondlock and Caplan, 1983, cited in Cramer and Riley, 2008). With these types of findings, what is the neurobiological explanation of these changes early on post-injury?

**Neurobiological plasticity changes during recovery**

**Figure 3** displays a model that incorporates a two-stage process of recovery, and within those two stages, provides the neural strategies utilized within the central nervous system.

The first stage is **Spontaneous Recovery**, and the second stage is **Training Induced Recovery** (Chen, Epstein and Stern, 2010). Depending on the stage of recovery, different neural mechanisms are at work to either initiate recovery strategies or in response to changes in experience in the form of training or rehabilitation. Each aspect of the model is described below.

![Figure 3. Two-stage model of recovery with corresponding neurological strategies and recovery vs. compensation distinctions.](image)

**STAGE ONE: Spontaneous Recovery**
With spontaneous recovery, even in the absence of training or rehabilitation, there is resolution of injury and functional change in close time proximity after injury which plateaus within three months for focal injury and six months for diffuse injury (Chen, Epstein and Stern, 2010). Within that time frame three processes have been theorized to explain this early recovery after injury when specific intervention has not ensued (Dancause and Nudo; 2011). They are:

1. Diaschisis reversal
2. Changes in kinematics.
3. Cortical reorganization.

Diaschisis Reversal

Diaschisis as previously described begins to resolve, whereby the inflammatory process, blood flow changes, metabolic changes, edema, and neuronal excitability begin to subside (Warraich and Kleim, 2010). The result of diaschisis reversal is improved function due to intact brain areas that were previously disrupted now being restored. Restoration is therefore a crucial neural strategy after injury. From a purely neurobiological level, this may be thought of as the only true level of recovery in the strictest sense of the word, in that the same brain circuits are facilitating function post injury as they were pre injury. Restoration has been found in both cognitive (e.g., language and attention) and physical (e.g., motor movement) domains (Kleim, 2011).

Changes in Kinematics

The second aspect of early recovery relates to changes in kinematic (movement) patterns where compensatory patterns are utilized. The individual intrinsically begins to complete motor movements in a different manner, resulting in improved function, sometimes in drastically different ways than prior to injury. While these new movements likely contribute to functional improvement, these compensatory strategies have the potential to be maladaptive.

Cortical Reorganization

The third strategy identified as spontaneous recovery is that the nervous system undergoes within-area and between-area reorganization or rewiring. For example, many researchers have found elements of neuroplasticity near the infarct area after stroke, including cortical reorganization, neurogenesis, axonal sprouting, dendritic plasticity, new blood vessel formation (Kerr, Cheng and Jones, 2011), as well as excitability changes (Nudo, 2011). Chen, Epstein and Stern (2010) outlined neural shifts in recruitment of brain areas in the spontaneous recovery period. Soon after stroke, in homologus (similar) areas, the opposite side of the brain is recruited. Later on during spontaneous recovery, there is a shift in activation back to the injury side. An example would be if the left-sided language area (Broca’s area) was damaged, the right-sided equivalent Broca’s area would be recruited. After a period of time, it would then shift back to the left side.

Another key change in brain function relates to activation of learning networks in the early phase, where plasticity similar to when the brain was developing is induced. This includes motor control and task-learning networks (Chen, Epstein and Stern, 2010).

Overall, cortical reorganization during spontaneous recovery is thought to be compensatory as different circuits or networks of neurons are utilized post injury than those utilized pre injury. While spontaneous recovery occurs in the absence of rehabilitation, there is certainly the opportunity for overlap of training induced recovery while spontaneous recovery takes its course.

STAGE TWO: Training-induced recovery

Training in the form of rehabilitation can induce plasticity post injury, but is not necessarily time limited like spontaneous recovery processes demonstrate (Chen, Epstein and Stern, 2010). Recovery in this stage involves compensation, in that either new brain areas or neural networks are enlisted to complete previous functions. Through the process of training, neuroplasticity is induced. Chen, Epstein and Stern (2010) note that adaptive changes after injury are the outcome of new patterns of activation which include
plasticity in areas surrounding the damaged cortex, reorganization of existing networks or recruitment of new cortical areas or networks.

Recruitment

During training-induced recovery, areas which did not make a significant contribution to that particular function pre-injury now contribute to function post-injury (Kleim, 2011). Often times this may be in the form of recruitment of neural areas from the undamaged hemisphere. From a physical perspective, this may include changes in motor maps where the non-injured hemisphere motor cortex can play a distinct role in producing motor movements in an impaired limb, which was previously controlled by the injured motor cortex. From a cognitive perspective, neural recruitment may entail the enlistment of the right side homologue (similar) to Broca’s area to improve language function if Broca’s area (left frontal lobe) is damaged. Rehabilitation to induce such changes may involve constraint induced manual therapy or completion of cognitive tasks while using complex hand movements in the opposite hemisphere which promotes a shift to the uninjured hemisphere.

Retraining

Retraining involves the training of residual brain areas, resulting in reorganization within the cortex and compensation for lost function (Kleim, 2007). This often comes in the forms of reorganization within the damaged hemisphere. In the case of motor function, if tissue is lost which controlled finger movements, other cortical tissue nearby can reorganize to control that lost movement.

Ultimately, recruitment and retraining involve rewiring or reorganization of neural networks. What then are the properties of the brain which, after injury, provide the mechanisms for recovery? Two basic properties provide us the answer:

1. The first is that our brains have a tremendous amount of redundancy. There is internal redundancy in areas like the primary visual cortex, the somatosensory areas, the primary auditory cortex and the primary motor cortex (Warraich and Kleim, 2010). So within primary cortex areas there may be multiple areas that respond to the same or similar stimuli. External redundancy refers to similar functionality being processed across different areas of the brain (Warraich and Kleim, 2010). Both of these redundancies allow for better information integration, but they also provide a pathway to improved function after brain injury.

2. The second property relates to a concept discussed in the previous article, that of experience dependent plasticity. This is where changes in behavior or experience result in changes at a neurobiological level.

Neurobiological Changes after Acquired Brain Injury

After injury to the brain, the processes of neuroplasticity are thought to be the underpinnings of recovery (Carmichael, 2010). To begin, research has found a variety of neuroplastic changes which occur after injury, including:

1. Increases or changes to synapses:
   - This includes synaptogenesis and synaptic plasticity (Chen, Epstein and Stern; 2010; Nudo, 2011)• Dendrite changes including increased arborization, dendritic growth and spine growth (Nudo, 2011)• Axonal changes including axonal sprouting (Nudo, 2011; Carmichael, 2010)

2. Increased neuron growth:
   - Neurogenesis in specific brain areas like the hippocampus subgranular zone of the dentate gyrus and subventricular zone in some areas (Schoch, Madathil and Saatman, 2012), substantia nigra and perinflarcted areas (Font, Arboix & Krupinski, 2010).

3. Angiogenesis
   - Angiogenesis is the process through which new blood vessels form from pre-existing vessels.

4. Excitability changes:
   • Excitability refers to the ability of a neuron to generate action potentials, which is a short-term change in the electrical

potential on the surface of a cell. It is an all or nothing proposition as it either fires or does not fire depending on the strength of the potential.

The first two items on the list above relate to increases in either the number of neurons (this occurs in a very limited sense) or the numbers of synapses or increased strength of existing synapses (this far more prevalent). These changes seen post injury mirror changes seen in the intact brain in the form of experience dependent learning. But instead of it being a learning process, it is a relearning process, aided substantially by rehabilitation.

With experience dependent learning, new synapses form (synaptogenesis) or strengthen through changes in dendrites (new dendritic spine formation), axonal sprouting and long term potentiation (synaptic plasticity). Both synaptogenesis and synaptic plasticity are the main underpinnings of cortical reorganization, recruitment and retraining as identified in Mechanisms of Recovery above. For a general overview of experience dependent learning see the side bar on page 35. For a detailed overview of both synaptogenesis and synaptic plasticity, see the previous article titled Neuroplasticity in the Intact Brain: Experience-Dependent Learning and Neurobiological Substrates.

The third and fourth items on the list relate to changes in excitability homeostasis within the brain (electrophysiological balance across the two hemispheres) and new blood vessel formation. These are described further in the next section.

Figure 4. Dendritic Arbor Expansion and Retraction.

Findings Related to Neurobiological Changes

Synaptic, Dendritic and Axonal Related Changes

Perederiy and Westbrook (2013) reported post injury that researchers found when an area of the brain stops receiving inputs from the body via afferent nerves, the dendritic arbor retracts (Figure 4). This results in the loss of synapses with other neurons. On the other hand they also reported that in areas of the brain not affected after injury, dendritic arbors increased (Figure 4). This former finding indicates a maladaptive response after injury, while the latter finding reflects the brain’s response post injury to increase synapses in intact areas, thereby providing cortical reorganization or rewiring, which is an adaptive response.

Axonal sprouting and reorganization occurs post injury. This sprouting has adaptive consequences in that increased axonal growth leads to greater levels of synapses allowing reinnervation (Perederiy & Westbrook, 2013). Re-innervation can then lead to adaptive changes. However, there are issues with axonal regeneration in that glial scars can prevent axons from reaching their target, and for patients with temporal lobe epilepsy, specific axonal sprouts can synapse onto granule cells which may relate to the recurrence of seizures (Perederiy & Westbrook, 2013).
Research has found that there may be changes within the damaged hemisphere. For example in motor areas, topographical map changes occur, where different areas controlling motor movements compensate for the damaged areas. The neurobiological foundation of motor map changes is synaptic change. This includes synaptogenesis where new synapses form through dendritic growth and axonal sprouting, and synaptic plasticity which strengthens existing synapses through the process of long-term potentiation (see previous article for a description).

Nudo, Wise, SiFuentes and Milliken (1996) mapped the motor areas of monkeys to determine the areas of the brain which controlled hand motor movements. After training on a skilled-hand task, infarcts were induced in the monkey’s mapped motor area. The monkeys were then retrained on the same skilled task. Initially, the monkeys demonstrated significant deficits on the skilled-hand task. After retraining, however, their skills substantially improved, and this related to significant changes to their motor maps. Specifically the hand and digit areas increased significantly during spontaneous recovery between the injured monkeys and a control group. In addition, for monkeys who received re-training, there was no loss of spared hand motor map in nearby intact areas, suggesting that therapy prevented further loss of hand areas representation.

Angiogenesis

Angiogenesis is the process through which new blood vessels form from pre-existing vessels. In ischemic stroke, which is loss of blood flow leading to neuronal death, increased vasculature relates to increase circulation (Font, Arboix, Krupinski, 2010). The benefit is return of blood flow to previously damaged areas, which is assists in establishing metabolic support (Krum, Mani, & Rosenstein, 2008).

In a review assessing research on neurovascular response after stroke, Arai, Jin, Navaratna & Lo (2009) examined the role of angiogenesis. The authors distinguish injury in the acute phase where neurovascular damage causes the primary disruption of the blood brain barrier. After stroke, it is now widely held that the penumbra (which is an area around the infarct affected by vascular compromise) is more than just dying cells – it may be a precursor of neuroplasticity. In the delayed phase after acute stroke, angiogenesis and neurogenesis, which are closely tied together, are primary responses post stroke. One cytokine of note relating to angiogenesis is vascular endothelial growth factor (VEGF), which in its endogenous form relates to brain neuroprotection. Krum, Mani and Rosenstein (2008), found that VEGF is an important factor in post-injury recovery. In particular, by blocking VEGF receptors, preventing them from upregulating, they found that vascular proliferation decreased. By blocking VEGF, and showing a clear decrease in positive vascular changes, they were able to isolate its effect – vascular remodeling (i.e., angiogenesis).

Changes to Network Organization

While reorganization of neural networks has been found post injury, the amount of reorganization depends on the size of the injured area. For example, with areas of smaller damage, reorganization tends to occur close to the injury area. For larger areas of damage, reorganization or recruitment is more widespread to other areas of the brain (Chen, Epstein and Stern, 2010).

Schlaug, Marchina and Norton (2009), using melodic intonation therapy to treat aphasia found that after intensive treatment, significant white matter changes occurred. In particular, through use of diffusion tensor imaging (which detects functionality of white matter tracts) they found increases in the right arcuate fasciculus, which is a white matter tract connecting Wernicke’s area and Broca’s area. Key to this finding is that the right arcuate fasciculus is not typically well developed, indicating that the right hemisphere reorganized to improve function. Another important factor in this finding is that increases in the number of fibers in the arcuate fasciculus correlated with measurable improvement in conversational skills.

Activation and Excitatory Changes

After injury, changes in the excitability of the damaged and intact hemispheres can impact cortical functioning. Excitatory changes across hemispheres can occur quickly after brain injury, where cortical excitability in the affected areas is generally decreased. A model of interhemispheric rivalry has been suggested, where there are distinct differences in the excitability of analogous areas, with a focus on the right hemisphere (Bogen et al., 2001).
between hemispheres (e.g., motor areas). For example in the damaged hemisphere there is hyperpolarization (inhibition of neurons) and in the intact hemisphere there is depolarization (excitation of neurons; Bolognini, Pascual-Leone & Fregni, 2009). Calautti & Baron (2003) reported that in the chronic phase after stroke, researchers found that better recovery was found if activation of the affected-side is more predominant than the unaffected hemisphere over time. This shift of activation to the unaffected side is “the sign of a distressed system” (Cramer et al., 2011, p. 1593). So from a long term perspective if the damaged side was more involved in function, that related to better outcomes. However, if the patient had to rely on the unaffected side more for function, that related to poorer outcomes.

In a study on memory and attention deficits after damage to the prefrontal cortex (PFC) by Voytek, Davis, Yago, Barcelo, Vogel and Knight (2010) they found evidence that the PFC in the undamaged hemisphere compensates for the damaged PFC areas in the opposite hemisphere “on a trial by trial basis dependent on cognitive load” (p. 401). In other words, the undamaged hemisphere dynamically compensates for the damaged hemisphere depending on the level of challenge the damaged hemisphere must deal with. This demonstrates that the intact hemisphere can adapt rapidly and that it is not an all or nothing proposition, where function is relegated to either the intact or damaged hemisphere post injury.

Collectively, this research highlights processes post injury which are similar to those neuroplastic changes in the intact brain. Namely, that when experience in the form of changes to nerve inputs or motor outputs occurs, cortical changes like those of experience dependent learning occurs where synaptogenesis, synaptic plasticity, and axonal sprouting take place. Furthermore, after injury, through aspects of the injury cascade, certain adaptive processes initiate, resulting in changes like angiogenesis, and network reorganization changes. Neuroplasticity is a remarkable tool in our cortical toolbox. And, like many other adaptive tools, it too can have maladaptive consequences.

The maladaptive side of neuroplasticity

While there is huge upside to neuroplasticity, we cannot afford to overlook the downside. While beyond the scope of this article to go into any depth there are plenty of examples to point out that neuroplasticity has its dark side, too. Just a few examples include addictions to alcohol, elicit substances or prescription drugs, pornography addictions (Doidge, 2007), seizure disorders post injury (Cramer et al., 2011), phantom limb pain (Doidge, 2007), hand dystonias in musicians (Candia, Rossset-LLobet, Eibert and Pascual-Leone, 2005), learning and memory interference (Carmichael, 2010) and chronic pain (Cramer et al., 2011). Thus, while we search for adaptive examples of neuroplasticity and ways to promote it both in the intact brain and after injury, we must also seek to prevent these brain changes which can have profound impacts on function, not to mention societal implications.

Final thoughts

![Figure 5. Synapses](image)
In an article put together by 27 leading neuroscientists from the National Institutes of Health Blueprint for Neuroscience Research (Cramer et al., 2011), they noted that "[n]europlasticity occurs with many variations, in many forms, and in many contexts" (p. 1952). This reminds us that brain injury in all of its forms is quite heterogeneous. The host of variables which affect outcomes after acquired injury are vast and varied (e.g., age, lesion area, pre-injury characteristics, genetic profile, etc.).

Yet with all of this heterogeneity, there are similar neuroplastic processes after injury. Cramer et al. (2011) write that "common themes in plasticity that emerge across diverse central nervous system conditions include experience dependence, time sensitivity and the importance of motivation and attention" (p. 1952). Thus it is important that neuroscience and its practitioners continue to identify at the key factors which contribute to neuroplastic changes be it at the molecular, cellular, architectural, behavioral or network level.

As we better understand the neurobiological level of neuroplasticity, we can then begin to better understand how to harness treatments that enhance the recovery process and ultimately patient function. There is currently a tremendous amount of research addressing neuroplasticity at both a basic and applied level. Both are needed to continue to learn more about effective treatments. Some are pharmacologic and focus on drugs or molecules that may impact the secondary phase of injury, or that "prime" the central nervous system in preparation of traditional neurorehabilitation in the form of occupational therapy, physical therapy, and speech & language pathology. Such priming includes non-invasive brain stimulation (e.g., transcranial magnetic stimulation, transcranial direct simulation), deep brain stimulation, and neuropharmacology. Others focus on the timing of rehabilitation efforts, in order to maximize plastic states where the opportunity for recovery is at its highest. Still others focus on the principles of Hebbian learning wherein understanding how experience shapes the brain can best be utilized in any form of treatment.

In closing, neuroplasticity is not an idea, it is a state. This state exists from our earliest years of neurodevelopment (prenatal and postnatal), to our ongoing changing brains as a result of experience, to changes after injuries to our most precious resource, our brain. Our transformative experiences shape and mold our neurochemicals, axons, dendritic arbors and spines, motor maps, cortical networks—in other words, our very essence. And likewise, when our very essence is transformed via injury, the change to our networks and synapses then shape our experiences. How we can best reclaim those experiences by harnessing neuroplasticity is the focus of an article in the next issue of RainbowVisions® Magazine.

**Overview of Experience-Dependent Learning**

For neurons or networks of neurons to communicate they need to have extensive connections with one another (or, quite literally hundreds to thousands of connections for each neuron.) These extraordinarily complex connections require junctions or connections termed synapses.

For example, neuron A connects via its axon terminal to neuron B at its dendrite (see **Figure 5**). The space between the axon and dendrite is the synapse. In a basic sense, the greater the number of synapses, the greater and stronger the connections between neurons. Likewise, the more synapses, dendrites and axons that develop, the greater the opportunity to connect more neurons together and strengthen the existing connections.

As our experiences change, at a neurobiological level, we either increase or decrease the numbers of synapses, dendrites and axons. If we stop a function, we lose synapses, etc., and if we increase an activity we proliferate synapses, etc., resulting in experience-dependent learning.
References


