Principles of Experience-Dependent Neural Plasticity: Implications for Rehabilitation After Brain Damage

SUPPLEMENT

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Purpose: This paper reviews 10 principles of experience-dependent neural plasticity and considerations in applying them to the damaged brain.
Method: Neuroscience research using a variety of models of learning, neurological disease, and trauma are reviewed from the perspective of basic neuroscientists but in a manner intended to be useful for the development of more effective clinical rehabilitation interventions.
Results: Neural plasticity is believed to be the basis for both learning in the intact brain and relearning in the damaged brain that occurs through physical rehabilitation. Neuroscience research has made significant advances in understanding experience-dependent neural plasticity, and these findings are beginning to be integrated with research on the degenerative and regenerative effects of brain damage. The qualities and constraints of experience-dependent neural plasticity are likely to be of major relevance to rehabilitation efforts in humans with brain damage. However, some research topics need much more attention in order to enhance the translation of this area of neuroscience to clinical research and practice.
Conclusion: The growing understanding of the nature of brain plasticity raises optimism that this knowledge can be capitalized upon to improve rehabilitation efforts and to optimize functional outcome.

KEY WORDS: rehabilitation, recovery, plasticity

Neuroscientists studying rehabilitation are often asked questions about the specific therapies that should be included in clinical treatment programs. Unfortunately, findings from animal models of neurological disorders do not automatically translate to specific recommendations for the clinic. Rather, our role is to study neurobiological phenomenon related to functional recovery and to identify fundamental principles that may help to guide the optimization of rehabilitation. Over the last several decades, neuroscience research has begun to characterize the adaptive capacity of the central nervous system *(plasticity)*. The existing data strongly suggest that neurons, among other brain cells, possess the remarkable ability to alter their structure and function in response to a variety of internal and external pressures, including behavioral training. We will go so far as to say that neural plasticity is the mechanism by which the brain encodes experience and learns new behaviors. It is also the mechanism by which the damaged brain relearns lost behavior in response to rehabilitation. By understanding the basic principles of neural plasticity that govern learning in both the intact and damaged brain, identification of the critical behavioral and neurobiological signals that drive recovery can

begin. The goal of the present article is to provide a review of some principles of neural plasticity that we hope will be useful for clinical research and, ultimately, treatment. Companion articles in this issue discuss the translation of these principles to the treatment of aphasia (Raymer et al., 2007) and impairments in motor speech (Ludlow et al., 2007) and swallowing (Robbins et al., 2007).

Part 1: Relearning After Brain Damage—Why Learning Matters
Currently, Learning Is Our Best Hope for Remodeling the Damaged Brain

In neuroscience research, the approaches to improving function after brain damage fall into two major categories: (a) efforts to limit the severity of the initial injury to minimize loss of function and (b) efforts to reorganize the brain to restore and compensate for function that has already been compromised or lost. The first approach is obviously important; however, even in those benefiting from early treatment, many will go on to have severe long-term disabilities. Thus, there is a critical need to understand how brain structure and function can be driven to remodel in the days, months, and years after brain damage. Neuroscience research has made major advances in understanding the brain, but we are far from understanding brain circuitry at the level needed to place new neurons and neural connections in just the right places to restore a lost function. Fortunately, there is another way to create functionally appropriate neural connections. We can capitalize upon the way the brain normally does this—that is, via learning. There is overwhelming evidence to indicate that the brain continuously remodels its neural circuitry in order to encode new experiences and enable behavioral change (Black, Jones, Nelson, & Greenough, 1997; Grossman, Churchill, Bates, Kleim, & Greenough, 2002). Research on the neurobiology of learning and memory suggests that, for each new learning event, there is some necessary and sufficient change in the nervous system that supports the learning (Cooper, 2005; Donegan & Thompson, 1991; Hebb, 1949; Kandel, 2001; Rose, 1991). This neuroplasticity is, itself, driven by changes in behavioral, sensory, and cognitive experiences. In our view, this endogenous process of functionally appropriate reorganization in healthy brains is also the key to promoting reorganization of remaining tissue in the damaged brain. This approach of using the process of learning, alone and in combination with other therapies, to promote adaptive neural plasticity is a growing focus of research in animal models of brain damage (Johansson, 2000, 2003; Jones et al., 2003; Jones, Hawrylak, Klintsova, & Greenough, 1998; Monfils, Plautz, & Kleim, 2005). Translation of this research to humans is likely to be enhanced by consideration of principles of experience-dependent neural plasticity, as overviewed in Part 2 of this article.

Learning Reorganizes the Damaged Brain Even in the Absence of Rehabilitation

Learning is an essential component of brain adaptation to brain damage even when there are no overt rehabilitation efforts. One of the most reliable behavioral consequences of brain damage is that individuals develop compensatory behavioral strategies to perform daily activities in the presence of lost function (Gazzaniga, 1966; Gentile, Green, Nieburgs, Schmelzer, & Stein, 1978; Kwakkel, Kollen, & Lindeman, 2004). These self-taught behaviors are potentially among the most significant behavioral changes of an individual's adult life. Animal research has indicated that these compensatory behaviors can be key drivers of what is often thought of as the "normal" response to brain damage (Jones et al., 1998; Morgan, Huston, & Pritzel, 1983). For example, reliance on the less-affected limb after unilateral cerebral damage is associated with major restructuring and neuronal growth in the contra-to-lesion hemisphere (Adkins, Voorhies, & Jones, 2004; Jones & Schallert, 1994; Jones, Kleim, & Greenough, 1996). Thus, a brain that one may attempt to reorganize with rehabilitative training is one that is being, and likely already has been, driven to reorganize by compensatory behavioral changes. Such self-taught behavioral changes can be adaptive and major contributors to functional outcome (e.g., Whishaw, 2000). However, they can also be maladaptive and interfering with improvements in function that could be obtained using rehabilitative training. For example, after unilateral brain damage, although reliance on the less-affected body side is associated with major neuroplastic changes in the unaffected hemisphere, this reliance may also limit the propensity of individuals to engage in behaviors that improve function of the impaired body side (Allred, Maldonado, Hsu, & Jones, 2005; Mark & Taub, 2004).

Brain Damage Changes the Way the Brain Responds to Learning

Learning involves changes in genes, synapses, neurons, and neuronal networks within specific brain regions. Brain damage results in many changes in neurons and non-neuronal brain cells that can alter these learning processes. In addition to the loss of tissue at the site of the primary injury, brain damage causes major neurodegenerative and neuroplastic changes in connected regions. When a brain region loses some of its connections, it undergoes a cascade of changes related to the clearance of degenerating debris, the remodeling of

neuronal processes, and the production of new neural connections (synapses) by remaining inputs, a process termed *reactive synaptogenesis* (Kelley & Steward, 1997). Brain damage can also result in both a time-dependent disruption of function (*diaschisis*) and long-lasting functional changes, such as the altered cortical excitability reported after cerebral stroke (Bütefisch, Netz, Wessling, Seitz, & Homberg, 2003; Murase, Duque, Mazzocchio, & Cohen, 2004; Witte, Bidmon, Schiene, Redecker, & Hagemann, 2000). It is not surprising that learning would be dramatically altered when it involves the very neurons and neural connections that are undergoing regenerative and degenerative responses to the injury or that have been chronically altered in excitability. These effects of brain damage may be related to both deficiencies and enhancements in learning that need to be considered when translating rules of learning to individuals with brain damage.

Part 2: Principles of Experience-Dependent Neural Plasticity and Their Translation to the Damaged Brain

Table 1 lists principles of experience-dependent plasticity derived from decades of basic neuroscience research that are likely to be especially relevant to rehabilitation after brain damage. This is hardly a comprehensive list, but it is one that highlights some factors that researchers have found relevant to rehabilitation outcome and to experience-dependent plasticity in models of learning and brain damage recovery. These principles are discussed in the context of their influence on brain plasticity in the intact and damaged brain.

Principle 1: Use It or Lose It

Neural circuits not actively engaged in task performance for an extended period of time begin to degrade.

This was first systematically demonstrated by Hubel and Wiesel in the 1960s in their visual deprivation experiments. They found that depriving a kitten's eye of light reduced the number of neurons in the visual cortex that responded to light (Hubel & Wiesel, 1965). Further work extended the finding to adult cortex and also showed that the reduction in neuronal responses to light was accompanied by a decrease in synapse number (Fifkova, 1969). Similar results were reported in owl monkey somatosensory cortex, where neurons responsive to tactile stimulation of the hand are found. In 2–9 months after removal of a single digit, neurons throughout its entire cortical representation region were now responsive to the adjacent digits and skin surfaces of the palm (Merzenich et al., 1984). Auditory deprivation also causes a loss of sound representation (Reale, Brugge, & Chan, 1987) and a decrease in synapse number (Perier, Buyse, Lechat, & Stenuit, 1986) in the cortex. In developing rats, restriction of movement results in poorly developed Purkinje neurons in the cerebullum (Pascual, Hervias, Toha, Valero, & Figueroa, 1998). It is important to point out that, in many cases, sensory deprivation results not in a total loss of cortical function but rather an apparent reallocation of cortical territory. Deprivation of one sensory modality may cause its corresponding cortical area to be at least partially taken over by another modality. For example, functional magnetic resonance imaging (fMRI) in blind subjects shows activation of visual cortical areas during tactile tasks such as Braille reading (Sadato et al., 1996), whereas deaf subjects show auditory cortical activation to visual stimuli (Finney, Fine, & Dobkins, 2001). This is an important concept for rehabilitation research for two reasons. The first reason is that failing to engage a brain system due to lack of use may lead to further degradation of function. Thus, for example, as proposed by Robbins et al. (2007), tube feeding may permit the disuse of the neural circuitry involved in swallowing, which in turn may lead to a further loss of swallowing function. The second reason is that functional recovery may be

Table 1. Principles of experience-dependent plasticity.

Principle	Description
1. Use It or Lose It	Failure to drive specific brain functions can lead to functional degradation.
2. Use It and Improve It	Training that drives a specific brain function can lead to an enhancement of that function.
3. Specificity	The nature of the training experience dictates the nature of the plasticity.
4. Repetition Matters	Induction of plasticity requires sufficient repetition.
5. Intensity Matters	Induction of plasticity requires sufficient training intensity.
6. Time Matters	Different forms of plasticity occur at different times during training.
7. Salience Matters	The training experience must be sufficiently salient to induce plasticity.
8. Age Matters	Training-induced plasticity occurs more readily in younger brains.
9. Transference	Plasticity in response to one training experience can enhance the acquisition of similar behaviors.
10. Interference	Plasticity in response to one experience can interfere with the acquisition of other behaviors.

supported, at least in part, by shifting novel function to residual brain areas.

Behavioral experiences after brain damage can also protect neurons and networks that would otherwise be lost after the injury. In both rats and monkeys, focal ischemic lesions to the motor cortex result in a loss of the ability to elicit movements in adjacent regions of the cortex (Barbay et al., 2005; Nudo & Milliken, 1996). However, this loss is prevented and functional reorganization is promoted as a result of rehabilitative training in a skilled reaching task (Kleim, Bruneau, et al., 2003; Nudo, Wise, et al., 1996). Combining rehabilitative training with constraint of the ipsilesional arm in humans with unilateral strokes improves the function of the impaired limb and promotes greater movement-associated activation in the remaining cortex of the injured hemisphere (e.g., Liepert et al., 2000; Sterr et al., 2002; Taub, 2000; Taub, Uswatte, & Morris, 2003; Wolf et al., 1989). Mimicking this therapeutic approach in rats (using limb-restricting vests combined with training) beginning 7 days after striatal hemorrhagic injury results in markedly improved function on measures of skilled reaching and postural–motor asymmetries in comparison to either rehabilitative training alone or constraint of one limb alone (DeBow, Davies, Clarke, & Colbourne, 2003; Maclellan, Grams, Adams, & Colbourne, 2005). Constraint plus training was also associated with a reduction in tissue loss in the damaged striatum (DeBow et al., 2003). As discussed in Raymer et al. (2007), several studies support the importance of language use for maintenance and improvements in language abilities. It is also possible to overuse impaired functions, an issue of relevance to timing and intensity of interventions after some types of brain damage, as discussed in the *Principle 5* section.

Principle 2: Use It and Improve It

In contrast to the experiments showing how a lack of use can degrade brain function, several studies in intact animals have shown how plasticity can be induced within specific brain regions through extended training. Monkeys trained to perform fine digit movements by retrieving small food pellets out of a well had an increase in digit representation areas within primary motor cortex (Nudo, Milliken, et al., 1996). Similarly, rats trained to reach outside of their cage to retrieve food rewards had an increase in distal forepaw representations within motor cortex (Kleim, Barbay, & Nudo, 1998). Synaptogenesis (Kleim, Barbay, et al., 2002, 2004) and increased synaptic responses (Monfils & Teskey, 2004) were found within these same cortical areas. Reorganization of representations within auditory (Weinberger & Bakin, 1998) and somatosensory (Recanzone, Merzenich, & Schreiner, 1992) cortex has

also been demonstrated following sensory discrimination training. Thus, the improvements in sensory and motor performance brought about by skill training are accompanied by profound plasticity within the cerebral cortex. It is hypothesized that similar neural changes occur in response to rehabilitation and mediate functional improvement.

A great deal of research indicates that behavioral experience can enhance behavioral performance and optimize restorative brain plasticity after brain damage. It has long been known that housing animals in complex environments pre- and/or postinjury can enhance functional recovery (e.g., Kolb & Gibb, 1991; Xerri & Zennou-Azogui, 2003; reviewed in Will, Galani, Kelche, & Rosenzweig, 2004). In recent years, investigators have focused on the effects of more directed training experience. Motor skill training after unilateral cortical damage has been found to both improve motor function and to drive restorative neural plasticity in remaining cortical regions (Castro-Alamancos & Borrel, 1995; Nudo, Milliken, et al., 1996; Jones, Chu, Grande, & Gregory, 1999; Biernaskie & Corbett, 2001). For example, after unilateral sensorimotor cortex lesions, a several-week period of "acrobatic" training (training rats to traverse an obstacle course) was found to improve behavioral function and increase reactive synaptic plasticity in the contralateral cortex compared with controls receiving simple exercise (Jones, Chu, Grande, & Gregory, 1999; see also Biernaskie & Corbett, 2001). Dendritic growth and synaptogenesis in the cortex contralateral to unilateral cortical damage in rats has been found to be dependent upon postinjury behavioral experiences with the less-affected body side (Jones et al., 1998). Rehabilitative training has also become increasingly viewed as a means of enhancing the potency of other therapeutic approaches, such as grafts of fetal tissue, provision of neuronal precursors, and other treatments intended to promote restorative plasticity (reviewed in Johansson, 2000). Unilateral reach training with the impaired limb, for example, was found to markedly enhance the survival of fetal tissue grafts placed into the site of frontal cortical aspiration lesions in rats (Riolobos et al., 2001). The combination of the training and grafts produced improvements in reaching ability that were not found as a result of either independent manipulation.

Principle 3: Specificity

In research on the neurobiology of learning and memory, a basic distinction is made between the engram itself (the brain changes that are the memory) versus the changes that modulate the strength of the engram (Cahill & McGaugh, 1996). In many studies, learning or skill acquisition, rather than mere use, seem to be required to produce significant changes in patterns of

neural connectivity. For example, motor skill acquisition is associated with the changes in gene expression, dendritic growth, synapse addition,and neuronal activity in the motor cortex and cerebellum (Black, Isaacs, Anderson, Alcantara, & Greenough, 1990; Kleim, Lussnig, Schwarz, Comery, & Greenough, 1996; Monfils et al., 2005; Nudo, 2003). In humans, skill acquisition is associated with changes in activation patterns in the motor cortex as revealed by fMRI (e.g., Karni et al., 1998; Ungerleider, Doyon, & Karni, 2002) and in movement representations as revealed using transcranial magnetic stimulation (TMS; e.g., Muellbacher, Ziemann, Boroojerdi, Cohen, & Hallett, 2001; Pascual-Leone et al., 1995; Perez, Lungholt, Nyborg, & Nielsen, 2004). Repetition of previously acquired motor movements, however, has not been found to result in significant synapse addition or map expansion in motor cortex in animal models (Plautz et al., 2000; Kleim, Cooper, & VandenBerg, 2002). Similarly, human participants who were trained to make skilled ankle movements exhibited enhanced corticospinal excitability, whereas participants who were trained to repeat unskilled movements did not (Perez et al., 2004). In rats with unilateral motor cortical infarcts, several weeks of motor rehabilitation in skilled reaching with the impaired forelimb improved function and resulted in a major increase in the cortical territory in which forelimb movements could be evoked in comparison with controls. However, performance of unskilled movements was not sufficient to reproduce the effects of skilled reach training on motor maps, consistent with findings in intact animals (Kleim, Cooper, & VandenBerg, 2002; Remple, Bruneau, VandenBerg, Goertzen, & Kleim, 2001).

Learning-induced brain changes also show regional specificity. For example, unilateral training in reach-and-grasp tasks in rats causes dendritic growth in the motor cortex contralateral to the trained limb but has only subtle effects on the ipsilateral motor cortex (Greenough, Larson, & Withers, 1985; Withers & Greenough, 1989). The synaptic and motor map changes occurring with training and sensory manipulations are also localized to specific cortical subregions. For example, Kleim et al. (1998) found training-induced changes in motor map topography and synapse number within caudal but not rostral areas of the forelimb motor cortex in rats. Learning to be afraid of a simple auditory stimulus is believed to critically involve synaptic plasticity in the amygdala, but learning to distinguish between closely related auditory stimuli also involves auditory cortex (LeDoux, 2000).

Thus, specific forms of neural plasticity and concomitant behavioral changes are dependent upon specific kinds of experience. The implication for rehabilitation is that training in a specific modality may change a limited subset of the neural circuitry involved in the more general function and, therefore, influence the capacity to acquire behaviors in nontrained modalities (see *Principle 9: Transference* and *Principle 10: Interference* sections). For example, as suggested in the companion article (Ludlow et al., 2007), training in swallowing after stroke may not automatically generalize to training in voice production (Huang, Carr, & Cao, 2002). In aphasia research, several findings support limits in the generalization of trained language abilities (reviewed in Raymer et al., 2007). As previously mentioned, when learning involves a brain region that is undergoing damage-induced remodeling of neuronal circuitry, there are also likely to be major differences in learning effects compared with intact brains. This might provide a special opportunity to guide the restructuring of this brain region with appropriate behaviors, as suggested both in the cortical tissue bordering a lesion (Nudo, Milliken, et al., 1996) and in regions remote from, but connected to, the site of primary injury (Adkins, Bury, & Jones, 2002; Jones et al., 1998).

Principle 4: Repetition Matters

Simply engaging a neural circuit in task performance is not sufficient to drive plasticity (see *Principle 3: Specificity* section). Repetition of a newly learned (or relearned) behavior may be required to induce lasting neural changes. For example, rats trained on a skilled reaching task do not show increases in synaptic strength (Monfils & Teskey, 2004), increases in synapse number, or map reorganization (Kleim et al., 2004) until after several days of training, despite making significant behavioral gains. Thus, some forms of plasticity require not only the acquisition of a skill but also the continued performance of that skill over time. It is hypothesized that the plasticity brought about through repetition represents the instantiation of skill within neural circuitry, making the acquired behavior resistant to decay in the absence of training (Monfils et al., 2005). The same phenomenon has been observed in studies of electrical stimulation–induced increases in synaptic strength within cortex. Racine, Chapman, Trepel, Teskey, & Milgram (1995) examined the effects of daily stimulation on cortical field potentials in rats with chronically implanted electrodes. Enduring long-term potentiation (LTP) of synaptic responses within sensorimotor cortex required 5 days of stimulation and did not reach asymptote until Day 15.

The role of repetition in driving plasticity and concomitant learning may be critical for rehabilitation. Plasticity may represent a surrogate marker of functional recovery indicative of behavioral change that is resistant to decay. We suggest that a sufficient level of rehabilitation is likely to be required in order to get the subject "over the hump"—that is, repetition may be needed to obtain a level of improvement and brain

reorganization sufficient for the patient to continue to use the affected function outside of therapy and to maintain and make further functional gains.

Principle 5: Intensity Matters

In addition to the repetition, the intensity of stimulation or training can also affect the induction of neural plasticity. Animals trained on a skilled reaching task to perform 400 reaches per day had increases in synapse number within motor cortex (Kleim, Barbay, et al., 2001), whereas animals trained to reach 60 times per day did not have such increases (Luke, Allred, & Jones, 2004). Similar effects have been found in stimulation experiments. Low-intensity stimulation can induce a weakening of synaptic responses (long-term depression), whereas higher intensity stimulation will induce long-term potentiation (Lisman & Spruston, 2005). Transcranial magnetic stimulation experiments within human motor cortex have shown that stimulation trains consisting of 1,800 pulses, but not 150 pulses, were sufficient to induce lasting increases in motor-evoked potential amplitudes (Peinemann et al., 2004). Intensity is clearly an important factor in aphasia rehabilitation, as reviewed in Raymer et al. (2007).

One potential negative side effect of training intensity after brain damage is that it is possible to overuse impaired extremities in a manner that worsens function. This seems to require both an extreme amount of use and that the overuse occur during an early vulnerable period. Schallert and others have found that forcing rats to rely on the impaired forelimb (by placing them in limb-restricting vests for 24 hr/day) for the first 7 days after unilateral sensorimotor cortex lesions exaggerated tissue loss and worsened functional outcome compared with rats permitted to use both forelimbs (Humm, Kozlowski, James, Gotts, & Schallert, 1998; Kozlowski, James, & Schallert, 1996; see also DeBow et al., 2004). This effect appears to be due to an exaggeration of excitotoxicity in vulnerable tissue surrounding the primary injury (Humm, Kozlowski, Bland, James, & Schallert, 1999). Griesbach and colleagues (Griesbach, Gomez-Pinilla, & Hovda, 2004; Griesbach, Hovda, Molteni, Wu, & Gomez-Pinilla, 2004) have also found that a voluntary exercise regime (wheel running) provided in the first 6 days after traumatic brain injury reduced the expression of plasticity-related molecules in the hippocampus. In contrast, exercise that was delayed until 2 weeks postlesion enhanced expression of some of the same molecules and improved functional outcome in spatial memory tests. The sensitivity to overuse effects also depends upon the nature of the injury (Woodlee & Schallert, 2006). In unilateral models of Parkinson's disease in rats, the neurotoxin 6-hydroxydopamine is used to produce damage to dopamine producing neurons in one hemisphere. Forced use of the forelimb before or shortly after the neurotoxin infusion has been found to reduce loss of dopamine-producing cells in the substantia nigra and to enhance behavioral function. However, the benefit of forced forelimb use is lost if the manipulation is delayed until a week after the neurotoxin exposure (Cohen, Tillerson, Smith, Schallert, & Zigmond, 2003; Tillerson et al., 2001).

Principle 6: Time Matters

The neural plasticity underlying learning can be best thought of as a process rather than as a single measurable event. Indeed, it is a complex cascade of molecular, cellular, structural, and physiological events (e.g., Kandel, 2001; Rose, 1991). Certain forms of plasticity appear to precede and even depend upon others. Thus, the nature of the plasticity observed and its behavioral relevance may depend on when one looks at the brain. For example, during motor skill training, gene expression precedes synapse formation (Kleim et al., 1996), which in turn precedes motor map reorganization (Kleim et al., 2004). In addition, the stability of the plastic change may also depend upon the time after training. Stimulation experiments have shown that enhanced synaptic responses are more susceptible to degradation during early phases of stimulation than later (Trepel & Racine, 1998). It has long been known that the stable consolidation of memories requires time (Dudai, 2004; Wiltgen, Brown, Talton, & Silva, 2004).

The time factor may be even more critical after brain damage given the dynamic changes in the neural environment that are occurring independent of any rehabilitation. As previously mentioned, there are major cascades of neuronal reactions to brain damage that occur over periods of months or longer (Badan, Platt, et al., 2003; Kelley & Steward, 1997). A consideration in the timing of behavioral treatments may be whether treatment is primarily neuroprotective in nature—that is, sparing of neuron death and loss of neural connections or whether the treatment works primarily by driving reorganization of remaining connections, as typically proposed for rehabilitative training. These are not independent processes because neurons that are driven to form new synaptic connections are likely to receive more signals promoting of survival (e.g., Purves, Snider, & Voyvodic, 1988), but they are likely to vary, temporally, in their sensitivity to behavioral experience effects.

If therapy promotes neural restructuring, then it should work anytime, but there may be time windows in which it is particularly effective in directing the lesion-induced reactive plasticity. Biernaskie, Chernenko, & Corbett (2004) found that a 5-week period of rehabilitation initiated 30 days after cerebral infarcts was far less

effective in improving functional outcome and in promoting growth of cortical dendrites than the same regimen initiated 5 days postinfarct. Norrie, Nevett-Duchcherer, & Gorassini (2005) found that a 3-week period of motor rehabilitative training improved stepping function in rats even when it was delayed until 3 months after a spinal cord injury. Nevertheless, the training was considerably more effective when administered shortly after the injury. Nudo and colleagues previously found that early training in skilled reaching after focal motor cortical infarcts in squirrel monkeys prevents a loss of movement representations in peri-lesion cortex (Nudo, Wise, et al., 1996). Barbay et al. (2005) recently found that training delayed until 1 month after the injury was effective in producing other changes in movement representations and in improving function, but it failed to prevent the loss of movement representations in peri-infarct cortex that was found in monkeys receiving earlier training. As discussed in Raymer et al. (2007), aphasia treatment initiated in the chronic phase can result in major functional improvements, but meta-analysis indicates that the effect sizes are greatest when initiated during the acute postinjury period (Robey, 1998). A better understanding of the neural processes responsible for this time-dependent sensitivity may lead to ways of reinstigating this sensitivity at later time periods.

Time delays may also allow for the greater establishment of self-taught compensatory behaviors, some of which may interfere with rehabilitative training efforts. As mentioned in the previous section, there are also time-dependent vulnerabilities in use-dependent exaggeration of excitotoxicity. Obstacles in translating these rat research results to humans include the need for much more basic information on time-dependent interactions between learning and brain adaptation to brain damage and the need to better understand how time windows in short-lived rodents (rats only live ~2–3 years) may translate to those found in humans recovering from brain damage.

Principle 7: Salience Matters

In order for an organism to effectively function, there must be a system in place to weigh the importance of any given experience such that it can be encoded. Research using auditory tones as classical conditioning stimuli has provided evidence for such a system and demonstrated that plasticity within the auditory cortex is dependent upon the salience of the experience. In this paradigm, animals are trained to recognize a tone of a specific frequency in order to receive a reward. Thus, one tone becomes more salient than the others. Animals trained in such a manner show an increase in the representation of the salient tone within the auditory cortex (Weinberger, 2004). Simply playing the tone without the reward does

not alter the topography of the auditory maps. However, if the tone is paired with stimulation of the basal forebrain cholinergic system, thought to mediate attention, a similar reorganization is observed (Dimyan & Weinberger, 1999; Kilgard & Merzenich, 1998). Furthermore, selective lesions of the cholinergic neurons within the basal forebrain prevents learning and auditory cortex reorganization (Kudoh, Seki, & Shibuki, 2004). Similarly, human subjects trained on a tone discrimination task had reduced activity within auditory cortex in response to the trained tone when given an acetylcholine antagonist (Thiel, Bentley, & Dolan, 2002). Although this phenomenon is more difficult to demonstrate within motor systems, some indirect evidence is available. Stefan, Wycislo, & Classen (2004), using a paired associative stimulation (PAS) consisting of repetitive application of single electric stimulus, delivered to the right median nerve, paired with single-pulse TMS of the right abductor pollicis brevis muscle representation in motor cortex. This protocol leads to an enhancement of motor-evoked potential (MEP) amplitude in the muscle to future stimulation of the cortex. However, PAS failed to induce plasticity when the subject's attention was directed away from the target hand during stimulation. Furthermore, training-dependent cortical plasticity was enhanced when subjects were administered an acetylcholine agonist (Meintzschel & Ziemann, 2006). In rat motor cortex, disruption of the cholinergic system prevented motor map reorganization and impaired skill learning (Conner, Chiba, & Tuszynski, 2005). These experiments demonstrate that there is a neural system that mediates saliency and that engaging this system is critical for driving experience-dependent plasticity.

Saliency is already an important consideration in the treatment of many neurological disorders, including aphasia and motor speech disorders. However, a better understanding of the neural processes underlying the modulation of recovery processes by saliency may be useful for optimizing treatment. Very few studies have directly examined the effects of saliency on recovery of function and associated plasticity, but there is a wealth of evidence showing that acetylcholine is involved, and this may be due, in part, to its contribution to saliency of experiences. Conner et al. (2005) demonstrated that lesions of the basal forebrain cholinergic system prevented reorganization of movement representation within motor cortex after cortical damage and impaired motor recovery. Administration of acetylcholine agonists can also enhance recovery after brain damage (Brown, Gonzalez, & Kolb, 2000). It has long been known that emotions modulate the strength of memory consolidation (reviewed in McGaugh, 2004). Sufficient motivation and attention are also, of course, essential to promoting engagement in the task. For example, rats will voraciously engage in rehabilitative reaching if it earns them palatable food treats. Providing stimulation of a rewarding

circuit in the brain (the ventral tegmental area) has also been found to be extremely effective in promoting performance of rehabilitative reaching tasks in rats (Castro-Alamancos & Borrel, 1995).

Principle 8: Age Matters

It is clear that neuroplastic responses are altered in the aged brain (Nieto-Sampedro & Nieto-Diaz, 2005). Experience-dependent synaptic potentiation (Rosenzweig & Barnes, 2003), synaptogenesis (Greenough, McDonald, Parnisari, & Camel, 1986) and cortical map reorganization (Coq & Xerri, 2001) are all reduced with aging. Normal aging is associated with widespread neuronal and synaptic atrophy (Salat et al., 2004) and physiological degradation (Pitcher, Ogston, & Miles, 2003). Indeed, aging may be analogous to an insidious brain insult, and some have argued that plasticity is the mechanism by which the brain compensates for aging. Cognitive decline may reflect the progressive failure of plasticity processes in compensating for age-related impairments. Nevertheless, the aging brain is also clearly responsive to experience, even though the brain changes may be less profound and/or slower to occur than those observed in younger brains (e.g., Green, Greenough, & Schlumpf, 1983; van Praag, Shubert, Zhao, & Gage, 2005). Furthermore, there is evidence in both humans and animal models that the effects of aging vary with lifespan experiences and are generally better in individuals with greater physical and mental activity (reviewed in Churchill et al., 2002).

The effects of brain damage vary with developmental age in young animals (reviewed in Kolb et al., 2000). The neuroplastic responses to brain damage are also altered in aging animals. In adult rats, lesions that cause loss of connections to subregions of the hippocampus trigger the sprouting of new connections, which takes about 2 months to complete. The onset of sprouting is within 2–4 days after the lesion in young adult rats, but in aged animals, it is initiated in about 20 days (Hoff, Scheff, Benardo, & Cotman, 1982; McWilliams & Lynch, 1979). Reduced expression of plasticity-related molecules, increased accumulation of neurotoxic factors, and altered temporal profiles of these changes have also been found after stroke-like injuries in rats (Badan et al., 2003; Sato et al., 2001). Ischemic injury in young adult rats triggers increases in the production of new neurons (*neurogenesis*). This neurogenic response is greatly reduced in aged rats compared with young adults (Jin et al., 2004). Several studies have also found that the infarct sizes produced by experimental ischemia are much greater in older animals than in young animals (Davis et al., 1997; Kharlamov, Kharlamov, & Armstrong, 2000; Rosen, Dinapoli, Nagamine, & Crocco, 2005), perhaps because of a reduced capacity of old neurons to deal with the metabolic challenge of ischemic insult (e.g.,

Hoyer & Krier, 1986; Davis et al., 1997; Siqueira, Cimarosti, Fochesatto, Salbego, & Netto, 2004). It is not surprising that larger infarcts can lead to greater disability. However, not all studies using animal models have found significant differences in the behavioral and brain effects of damage produced in young adult versus aged animals. Zhao, Puurunen, Schallert, Sivenius, & Jolkkonen (2005), for example, found that recovery of sensorimotor deficits after unilateral cortical infarcts was similar in aged animals and young animals when these groups were compared with age-matched intact control animals (see also Shapira, Sapir, Wengier, Grauer, & Kadar, 2002). Although there has been little research on the effects of rehabilitative training after brain damage in aged animals, healthy old animals clearly benefit from complex motor skills training (Churchill, Stanis, Press, Kushelev, & Greenough, 2003), exercise (Adlard, Perreau, & Cotman, 2005; Fordyce, Starnes, & Farrar, 1991), and exposure to complex and social environments (Green et al., 1983; Greenough et al., 1986).

Principle 9: Transference

Transference refers to the ability of plasticity within one set of neural circuits to promote concurrent or subsequent plasticity. This phenomenon has been recently demonstrated in human motor cortex with skill learning and TMS. Training on a fine digit movement task induces an increase in corticospinal excitability and an expansion of hand muscle representation in primary motor cortex (Pascual-Leone et al., 1995). A similar increase in excitability can be induced through application of repetitive transcranial magnetic stimulation (rTMS) to motor cortex (Peinemann et al., 2004). When TMS was applied to motor cortex synchronously during skill training, it enhanced skill acquisition (Bütefisch, Khurana, Kopylev, & Cohen, 2004). Similar findings have been reported in association with recovery after stroke (Hummel & Cohen, 2006). Anodal transcranial direct current stimulation of the affected hemisphere in humans with unilateral stroke has been found to result in transient improvements in motor function (Hummel et al., 2005). Peripheral stimulation of the pharynx has been found to enlarge its cortical representation and to improve swallowing function in stroke survivors (Fraser et al., 2002; Hamdy, Rothwell, Aziz, Singh, & Thompson, 1998). As noted in the companion article by Robbins et al. (2007), coupling training with peripheral or central stimulation may be necessary to drive the tranference effects into a functionally beneficial direction. Direct electrical stimulation of the motor cortex after ischemic insult enhanced motor recovery (Adkins-Muir & Jones, 2003), enhanced synaptic responses (Teskey, Flynn, Goertzen, Monfils, & Young, 2003), and motor map reorganization (Kleim, Bruneau, et al., 2003; Plautz et al., 2003) when coupled with rehabilitative training. Combining rehabilitative

training with rTMS of the affected hemisphere early after stroke was found to improve motor function (Khedr, Ahmed, Fathy, & Rothwell, 2005). In addition to electrical stimulation, previous behavioral experience can also promote subsequent plasticity. For example, it has long been known that rats housed in complex environments have better functional outcomes after various types of brain damage compared with rats housed in standard laboratory environments (reviewed in Will et al., 2004).

Although learning may be needed to promote the formation of functionally appropriate synaptic connections after brain damage, exercise may be more appropriate for promoting a fertile environment to support these changes. Exercise results in angiogenesis in the motor cortex (Kleim, Cooper, & VandenBerg, 2002; Swain et al., 2003) and cerebellum (Black et al., 1990) and in expression of factors (neurotrophins) that promote neuronal growth and survival of vulnerable neurons in the spinal cord, hippocampus, and other brain regions (reviewed in Cotman & Berchtold, 2002; Kleim et al., 2003; Vaynman & Gomez-Pinilla, 2005). After traumatic brain injury or spinal cord injury in animal models, appropriately timed exercise has been found to robustly elevate neurotrophic factors and other plasticity-related molecules and to improve functional outcome (e.g., Griesbach, Gomez-Pinella, et al., 2004; Molteni, Zheng, Ying, Gomez-Pinilla, & Twiss, 2004; Ying, Roy, Edgerton, & Gomez-Pinilla, 2005).

Principle 10: Interference

Neural plasticity often has a favorable connotation when described in the context of recovery of function. However, plasticity can also serve to impede behavioral change. *Interference* refers to the ability of plasticity within a given neural circuitry to impede the induction of new, or expression of existing, plasticity within that same circuitry. This, in turn, can impair learning. Although some types of noninvasive cortical stimulation applied during or shortly before skill training may enhance motor learning (Bütefisch et al., 2004; Floel & Cohen, 2006), other forms can be disruptive of learning. For example, transcranial direct current stimulation given after training reduced the training-dependent increases in cortical excitability (Rosenkranz, Nitsche, Tergau, & Paulus, 2000). Similarly, swallowing function can be both enhanced (Fraser et al., 2002) and impaired (Power et al., 2004) by peripheral stimulation, as discussed in Robbins et al. (2007). Rodent experiments of spatial learning have shown that saturation of synaptic potentiation within the hippocampus, a brain structure critical for spatial learning, impairs subsequent learning (Moser, Krobert, Moser, & Morris, 1998). Presumably, synchronizing training with stimulation improves performance because the behavioral signals driving plasticity during training are augmented by the presence of the extra

stimulation. When stimulation is applied outside of the training experience, in addition to potentially disrupting the memory consolidation process, it may induce plasticity that is not shaped by behavioral signals and is, therefore, detrimental to performance. This has specific implications for how adjuvant stimulation might be applied to enhance recovery after brain damage.

It is also possible for behavioral experience to drive plasticity within residual brain areas in a direction that will impede optimal behavioral recovery. Brain damage survivors may develop compensatory strategies that are easier to perform ("bad habits") than more difficult but ultimately more effective strategies acquired through rehabilitation. These strategies might be adopted earlier and used with much greater frequency than those guided in therapy. The ease of learning certain compensatory behaviors may also be facilitated after brain damage. After small unilateral sensorimotor cortex lesions, rats have a reduction in apparent aiming errors when learning a new skilled reaching task with the less-affected forelimb compared with intact rats, and this is related to enhanced neuroplastic changes in the contralesional motor cortex (Allred & Jones, 2004; Bury & Jones, 2002, 2004; Hsu & Jones, 2005). In humans, transient virtual lesions of the motor cortex also enhance some function in the ipsilesional hand (Kobayashi, Hutchinson, Theoret, Schlaug, & Pascual-Leone, 2004; see also Takeuchi, Chuma, Matsuo, Watanabe, & Ikoma, 2005). However, over-reliance on less-affected modalities may also exaggerate impairments. Early skill training that was focused on the ipsilesional limb of rats with unilateral infarcts was found to greatly worsen subsequent performance and decreased use of the impaired forelimb (Allred et al., 2005), suggesting that it contributed to learned nonuse (Mark & Taub, 2004; Taub, 2000). When maladaptive, these self-taught compensatory strategies may induce plasticity that will have to be overcome with subsequent rehabilitation and other treatment approaches (see e.g., Celnik & Cohen, 2004; Fregni & Pascual-Leone, 2006; Taub et al., 2003).

Another reason to consider interference effects is that a therapy that benefits one skill may interfere with performance of another. Furthermore, as brain injury may change the neural response during learning, it may also change sensitivities to interference effects. For example, providing explicit instruction on how to perform a motor sequence task was found to improve implicit motor learning in healthy controls, whereas the same instructions interfered with learning in subjects with strokes (Boyd & Winstein, 2006).

Summary

Neuroscience research has yielded a great deal of information on the nature of experience-dependent brain

plasticity, and there is reason for optimism that our understanding of this can be capitalized upon to improve functional outcome after brain damage. This work strongly supports the use of rehabilitative training as a tool to improve brain reorganization and functional outcome. However, many issues that are likely to be critical for optimizing rehabilitation remain poorly understood and require greater attention by neuroscientists. A better understanding is needed of how training experiences interact with neural reactions to the brain damage, with self-taught compensatory behavioral changes, and with age, as well as how to combine rehabilitative training with other treatment approaches. Of particular importance is the need to understand time windows in which training can be optimally and safely applied. Translation of these findings to rehabilitative treatment will also normally require intermediate steps, including experimental research using human subjects and computational models. This may be especially true for disorders that are challenging to model in detail in animals, such as some cognitive and motor disorders of speech and language (see Ludlow et al., 2007; Raymer et al., 2007). Continued momentum in human experimental neuroscience research shows promise for improving the bridge between animal research findings and clinical application (reviewed in Floel & Cohen, 2006). Hopefully, the translational relevance of future research will be improved by greater interaction between basic and clinical researchers and a better awareness, on the part of the neuroscientists, of the problems faced by those in the clinic who are administering and receiving rehabilitation.

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