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Experience-dependent neural plasticity in the adult damaged brain

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Abstract

Behavioral experience is at work modifying the structure and function of the brain throughout the lifespan, but it has a particularly dramatic influence after brain injury. This review summarizes recent findings on the role of experience in reorganizing the adult damaged brain, with a focus on findings from rodent stroke models of chronic upper extremity (hand and arm) impairments. A prolonged and widespread process of repair and reorganization of surviving neural circuits is instigated by injury to the adult brain. When experience impacts these same neural circuits, it interacts with degenerative and regenerative cascades to shape neural reorganization and functional outcome. This is evident in the cortical plasticity resulting from compensatory reliance on the "good" forelimb in rats with unilateral sensorimotor cortical infarcts. Behavioral interventions (e.g., rehabilitative training) can drive functionally beneficial neural reorganization in the injured hemisphere. However, experience can have both behaviorally beneficial and detrimental effects. The interactions between experience-dependent and injury-induced neural plasticity are complex, time-dependent, and varied with age and other factors. A better understanding of these interactions is needed to understand how to optimize brain remodeling and functional outcome.

Learning outcomes—Readers will be able to describe (a) experience effects that are maladaptive for behavioral outcome after brain damage, (b) manipulations of experience that drive functionally beneficial neural plasticity, and (c) reasons why rehabilitative training effects can be expected to vary with age, training duration and timing.

Keywords

neurorehabilitation; cortical plasticity; learned non-use; skill learning; stroke; animal models

1. Introduction

Throughout the lifespan, behavioral experiences are constantly shaping nervous system function and structure. Experience can change neuronal structure and synaptic efficacy, remodel vasculature and glial processes, and alter the rate of neurogenesis (Kleim & Jones, 2008). This experience-driven plasticity is needed to respond to, and learn from, an ever-changing environment: It is the mechanism of behavioral change. Behavioral experience is also important for function following neural insult, such as stroke and traumatic brain injury

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(TBI). In fact, manipulations of behavioral experience, (e.g., in the form of physical and occupational therapy), are the primary tools currently available for treatment of chronic functional deficits after brain injury. However, we lack a secure knowledge of how behavioral experience interacts with the brain's response to injury, and this is needed to learn how to optimize behavioral interventions.

Aspects of human post-stroke impairments, recovery, and CNS plasticity can be modeled in rodents (rats and mice) (Levy, Nichols, Schmalbrock, Keller, & Chakeres, 2001; Liepert et al., 2000; Nudo, 2003; Taub & Morris, 2001), making rodent models useful for exploring mechanisms of functional recovery and rehabilitation efficacy following central nervous system (CNS) insult. This review covers findings on how experience interacts with the post-stroke CNS environment to promote restorative plasticity, with a particular focus on rodent models of upper extremity (hand and arm) impairments. Behavioral experiences, including rehabilitative interventions and self-taught compensatory strategies, have a powerful impact on post-stroke brain remodeling and functional outcome. However, not all plasticity is good plasticity. Experience interacts with injury-induced brain changes in ways that can be both functionally beneficial and detrimental.

2. Examples of experience-dependent plasticity in intact adult brains

Behavioral experiences have diverse structural and functional effects on the CNS. Various changes in behavioral experience have been found to induce synaptic turnover, modulate synaptic strength, alter glial-neuronal interactions, instigate vascular remodeling, and influence cell proliferative events, including neurogenesis (Grossman, Churchill, Bates, Kleim & Greenough, 2002; Kleim & Jones, 2008). The type and site of CNS change varies with different types of experience. For instance, aerobic exercise drives angiogenesis in the cerebellum and hippocampus, as well as hippocampal neurogenesis (Black, Isaacs, Anderson, Alcantara, & Greenough, 1990; Kerr & Swain, 2011; Swain et al., 2003; van Praag, Shubert, Zhao, & Gage, 2005). Motor skill learning is associated with synaptogenesis and dendritic spine plasticity in motor cortex and cerebellum, as well as motor map plasticity (Anderson, Alcantara, & Greenough, 1996; Black et al., 1990; Kleim, Barbay, & Nudo, 1998; Kleim et al., 2003; Kleim, Cooper, & VandenBerg, 2002; Monfils & Teskey, 2004; Nudo, Milliken, Jenkins, & Merzenich, 1996; Tennant, Adkins, Scalco, et al., 2010; Xu et al., 2009). Fear conditioning (learning to be afraid of tone paired with footshock), results in synaptic changes in the amygdala (Helmstetter, Parsons, & Gafford, 2008; Ostroff, Cain, Bedont, Monfils, & Ledoux, 2010). Experience in an enriched (or “complex”) environment, in which animals are socially housed in a large cage with many objects that can be explored and manipulated, results in dendritic growth, synaptogenesis, and angiogenesis in visual cortex and other areas (Black, Zelanzny, & Greenough, 1991; van Praag, Kempermann, & Gage, 2000), as well as hippocampal neurogenesis (Grossman et al., 2002; Johansson & Belichenko, 2002; Kempermann, Kuhn, & Gage, 1997).

Learning a new motor skill is associated with plasticity of motor cortex. This is evident at the level of synapses, neuronal architecture, and across neural networks in the organization of movement representations (Adkins, Boychuk, Remple, & Kleim, 2006; Bury & Jones, 2002; Greenough, Larson, & Withers, 1985; Jones, Chu, Grande, & Gregory 1999; Jones et al., 2009; Kleim et al., 1998, 2002; Kleim, Lussnig, Schwartz, Comery, & Greenough, 1996; Monfils, Plautz, & Kleim, 2005). Rats and mice are useful for investigations of the neurobiology of manual skill learning because of their intrinsic manual dexterity (Fig. 1) and homologies with primates in forelimb movements (e.g., in reach-to-grasp tasks) and motor system organization (Tennant, Adkins, Donlan, et al., 2010; Whisaw & Coles, 1996; Wishaw & Gorny, 1994). This includes a remarkably large territory of motor cortex devoted to forelimb representations (Fig. 2). In mice, it is also becoming increasingly feasible to

view neural changes on a microanatomical level over time in individual animals using *in vivo* imaging approaches (e.g., Estrada & Dunn, 2010; Estrada, Ponticorvo, Ford, & Dunn, 2008; Sigler & Murphy, 2010). This has revealed sequential changes in motor cortical dendritic spines (the sites of synaptic contacts) during the establishment of a new motor skill (Xu et al., 2009). As mice first practice a new manual skill (skilled reaching), there is a rapid turn over of dendritic spines in the motor cortex, and the new spines created during this period endure long after the skill is established. Months later, when the same mice learn a different manual skill (pasta handling), the turnover process is repeated, and a new population of long lasting spines is created without a loss of those established during the first task. These synaptic effects help explain the endurance of well-learned motor skills, as well as the ability to learn many different skills over a lifetime. Manual skill learning also reorganizes movement representations in the motor cortex, as has been found in monkeys (Nudo, Milliken, et al., 1996), rats (Kleim et al., 1998) and mice (Tennant, Adkins, Scalco, et al., 2010a).

These are just a few examples, out of a wealth of findings, on how experience can change the brain. The major point is that it is likely that experiences are continuously changing the nervous system throughout the lifespan and, for good reason, because these changes enable behavioral change. It may be that day-to-day adult brain plasticity is usually more subtle than that often observed in many of the animal studies, because especially salient (e.g., fear learning), significant (e.g., new skill learning), or even dramatic (e.g., environmental enrichment) types of experiences tend to be investigated. This is nevertheless quite relevant to stroke, which is (too) often accompanied by dramatic life changes. There is also growing evidence that experience-induced plasticity interacts with the post-stroke neural environment to shape CNS reorganization following injury.

3. Brain and behavioral changes after stroke

Ischemic stroke results in degeneration, neurotoxicity, inflammation, and apoptosis that impact not only the ischemic core, but also neuronal and synaptic survival in the peri-infarct region and connected areas (Doyle, Simon, & Sentzel-Poore, 2008). In addition, stroke increases growth promoting factors and results in diverse glial responses. Over time, there is dendritic growth, axonal sprouting, synaptogenesis, vascular remodeling, and migration of newly generated cells to the ischemic region (Brown, Aminoltejarl, Erb, Winship, & Murphy, 2009; Brown & Murphy, 2008; Carmichael, 2006; Cheatwood, Emerick, & Kartje, 2008; Jones & Adkins, 2010; Wieloch & Nikolich, 2006). Many of these processes, including dendritic and vascular plasticity, are likely to contribute to behavioral outcome (e.g., Gibb, Gonzaleez, Wegenast, & Kolb, 2010; Kerr, Steuer, Pochtarev, & Swain, 2010; Ohab, Fleming, Biesch, & Carmichael, 2006). The degenerative and regenerative cascades create both neuronal growth-permissive (Barbay et al., 2005; Biernaskie, Chernenko, & Corbett, 2004; Hsu & Jones, 2005; Johansson, 2000; Kelly & Steward, 1997; Norrie, Nevett-Duchcherer, & Gorassini, 2005) and neuronal death-vulnerable (Woodlee & Schallert, 2004) environments that can be influenced by behavioral experiences.

Some level of spontaneous recovery occurs following stroke in both humans and animal models (Nudo, 2007). This behavioral improvement may be mediated by recovery from diaschesis and CNS plasticity in regions near or connected to the infarct. For example, in peri-infarct cortex, cortical reorganization, neurogenesis, axonal sprouting, dendritic plasticity, and angiogenesis have been linked with spontaneous recovery (Biernaskie & Corbett, 2001; Castro-Almancos & Borrel, 1995; Conner, Chiba & Tuszynski, 2005; Nudo, 2007; Nudo & Milliken, 1996; Paris, 2007; Ramanathan, Conner, & Tuszynski, 2006). Behavioral experience can further facilitate functional outcome and support additional CNS plasticity in humans and non-human animals (Johansson, 2000; Liepert et al., 2000; Levy, et

al., 2001; Maldonado, Allred, Felthauser, & Jones, 2008; Nudo, Wise, SiFuentes, & Milliken, 1996), as described below (section 4.1).

Because degenerative and regenerative cascades unfold over time, the manner in which experience interacts with them must be time-dependent. Furthermore, *both* degenerative and regenerative responses can be influenced by experience in bidirectional ways. That is, it is possible to both reduce and increase degenerative responses as well as regenerative responses. As a result, it is possible for experience to both enhance and impair behavioral outcome. There are many examples of these bidirectional effects in the animal research literature (reviewed in Jones & Adkins, 2010), but we still do not understand experience-injury interactions well enough to predict the exact brain effects of most behavioral manipulations after most injuries. This is made challenging by the nature of the brain's multifaceted response to stroke, which evolves over long time periods and large areas and varies with injury severity and locus, and many other factors (Carmichael, 2006; Murphy & Corbett, 2009).

4. Experience-dependent plasticity after stroke

4.1 Behavioral interventions

There is a growing body of evidence indicating that behavioral interventions can improve functional outcome by promoting adaptive functional and structural plasticity in the CNS. One such behavioral intervention is enriched environment housing, mentioned above, which has a mixture of social, sensory, cognitive and motor experiences. Following stroke, enriched environment exposure can attenuate cell death (Griesbach, Gomez-Pinilla, & Hovda, 2004), increase astrocytic reactivity (Briones, Woods, Wadowska, Rogozinska, & Ngyen, 2006), and stimulate dendritic growth, synaptogenesis (Briones, Suh, Jozsa, & Woods, 2006), and, sometimes, neurogenesis (Komitova, Zhao, Gido, Johansson, & Eriksson, 2005). Enriched environment housing also typically improves functional outcome following insult (Johansson & Belichenko, 2002; Will, Galani, Kelche, & Rosenzweig, 2004).

Upper extremity (hand and arm) impairments are leading long-term disabilities after stroke. Just as rodents' intrinsic manual dexterity and homologies with primate motor systems make them useful for studying manual skill learning, it also makes it possible to use them to model some aspects of upper extremity impairments and their recovery. In rodent models, unilateral stroke-like damage that involves sensorimotor cortex results in impaired use of the contralateral-to-lesion forelimb. This includes deficits in dexterous food handling (e.g., Allred et al., 2008; Castro, 1972; Tennant, Asay, et al, 2010; Whishaw & Coles, 1996), postural support (e.g., Adkins, Voorhies, & Jones, 2004; Tennant & Jones, 2009), deficits in coordinated forelimb use (e.g., Bouet et al., 2007; Metz & Whishaw, 2002), and skilled reaching (e.g., Farr & Whishaw, 2002; Peterson & McGiboney, 1951; Tennant & Jones, 2009; Whishaw 2000). Focused rehabilitative training of the paretic limb can improve motor function and drive functional plasticity in residual regions of motor cortex (Castro-Alamancos & Borrel, 1995; Maldonado et al., 2008; Nudo, 2007; Nudo, Milliken et al., 1996; Nudo, Wise, et al., 1996; Ramanthan et al., 2006). In addition, this training results in neuroanatomical plasticity in remaining motor cortex. It increases synaptic densities overall and especially increases efficacious synapse subtypes (e.g., perforated synapses) (Adkins, Hsu, & Jones 2008; Hsu, Donlan, Kleim, & Jones, 2007). This synaptic structural plasticity is coordinated with plasticity of peri-synaptic astrocytic processes (Kim, Hsu, & Jones, 2009).

These effects rely on the mechanisms of experience-dependent plasticity, just as they do in intact animals, but they can occur at a time when the neural environment is dramatically

different and also dynamic as it undergoes degenerative and regenerative cascades. As a result, the neural response to rehabilitative training can reflect, at least in part, its interactions with these cascades. For example, in response to cortical ischemia, there is a dramatic increase in cell proliferation and migration of the newly generated cells to the ischemic region (e.g., Ohab et al., 2006). Rehabilitative training focused on the paretic limb increases the survival of cells generated early in the course of the training and then reduces cell proliferation thereafter (Maldonado & Jones, 2009; see also Keiner, Wurn, Kunze, Witte, & Redecker, 2008). This might reflect a training-induced enhancement in health and functional activity of the residual cortex, which in turn reduces the degenerative signals for further proliferation.

4.2. Behavioral compensation and plasticity

We tend to learn what works and to stop doing what does not. A natural response to loss of some function is to develop alternative strategies, or tricks, to circumvent the problem. In humans and rodent models of stroke, this is very evident in an increased reliance on the "good" hand and arm to deal with stroke-induced impairments in the other arm (Jones & Schallert, 1994; Taub, Uswatte, Mark, & Morris, 2006; Whishaw, 2000). (Note that this side is referred to as the "unaffected", "less-affected", "nonparetic", or "contralateral" side, in reference to peripheral impairments, and "ipsilateral", in reference to injury side. We use the term "good" to compensate for the confusion.) The good limb is used more and in different ways and, in rats, this results in major synaptogenesis and dendritic growth in the cortex contralateral to the injury. This is a consequence of experience-driven plasticity interacting with reactive neural plasticity, the latter of which is instigated by moderate degeneration (of transcallosal projections) (Bury et al., 2000; Jones, 1999; Jones & Schallert, 1992; Jones, Kleim, & Greenough, 1996; Luke, Allred, & Jones, 2004). The growth-permissive environment in the contralesional cortex makes it more sensitive to the behavioral experiences of the good limb and this, in turn, facilitates learning new ways of using it, even when it shows subtle impairments (Allred & Jones, 2008b; Bury & Jones, 2002; Hsu & Jones, 2006; Luke et al., 2004).

The increased reliance on the good limb is an example of a self-taught behavioral change that induces major brain reorganization as a result of its co-occurrence with an injury-induced growth permissive environment. This indicates that the ability to learn compensatory strategies for coping with impairments can sometimes be enhanced as a result of CNS damage. This might enable the stroke survivor to more quickly resume some daily activities, but it is not necessarily optimal for returning more normal function.

Learning with the good limb also worsens disuse of the paretic limb and reduces the beneficial effects of later rehabilitative training focused on the paretic limb (Allred & Jones, 2008b; Allred, Maldonado, Hsu, & Jones, 2005). It also decreases neuronal activation (Allred & Jones, 2008a) and results in a further reduction in forelimb movement representations in the motor cortex of the injured hemisphere (Allred et al., 2009). This is the very region implicated in the efficacy of rehabilitative training focused on the paretic limb, as described above.

These findings suggest that the phenomenon of learned non-use (Mark & Taub, 2004) may result, in part, because learning with the good limb somehow fouls the potential of the residual cortex to mediate better function in the paretic limb. In human stroke survivors, the intact hemisphere can develop disruptive influences over the injured hemisphere and over movements of the paretic side (Murase, Duque, Mazzocchio, & Cohen, 2004; Rushmore, Valero-Cabre, Lomber, Hilgetag, & Payne, 2006; Talelli, Waddingham, Ewas, Rothwell, & Ward, 2008; Ward & Cohen, 2004). Because the maladaptive impact of good limb training

is dependent upon interhemispheric connections (Allred, Cappellini, & Jones, 2010), it may be that learning to compensate with this limb exaggerates this interhemispheric disruption.

Rehabilitative training focused on the paretic limb may need to overcome limitations in experience-dependent plasticity imposed by disruptive interhemispheric activity and prior experiences with the good limb. Anesthetization of the good limb results in a transient functional improvement in the paretic limb in both rat stroke models (O'Bryant, Berneir, & Jones, 2007) and in humans (Werhahn, Mortensen, Van Boven, Zeuner, & Cohen, 2002). Furthermore, combining a rehabilitative training regime with constraint of the good arm improves function of the paretic limb in both species (DeBow, Davies, Clarke, & Colbourne, 2003; Liepert et al., 2000; Maclellan, Grams, Adams, & Colbourne, 2005; Sterr et al., 2002; Taub et al., 2006; Taub, Uswatte, & Morris, 2003). In rats, constraint-like therapy not only improves skilled reaching performance, but also improves postural-motor asymmetries compared with either rehabilitative training or constraint therapy alone (DeBow et al., 2003; Maclellan et al., 2005). Another approach is to facilitate the plasticity in the injured hemisphere to help it change in response to rehabilitative training of the paretic limb. For example, pairing rehabilitative training with cortical stimulation of peri-infarct cortex results in faster and more enduring performance improvements (Nowak, Grefkes, Ameli, & Fink, 2009; Plow, Carey, Nudo, & Pascual-Leone, 2009) and greater structural and functional plasticity in peri-lesion motor cortex (Adkins-Muir & Jones, 2003; Adkins et al., 2008; Kleim et al., 2003; Nowak, Grefkes, Ameli & Fink, 2009; Teskey, Flynn, Goertzen, Monfils, & Young, 2003) compared with animals receiving reach training or stimulation alone.

With a better understanding of bilateral and interhemispheric interactions after stroke, we may be able to find ways to capitalize upon growth promoting environments to optimize compensation without thwarting the potential for the injured hemisphere to change in a manner that restores function in paretic extremities. These findings also reveal that experience can be expected to shape the course of brain remodeling even when there are no overt manipulations of it, other than those that stroke survivors develop on their own.

5. Factors that impact rehabilitation efficacy

Behavioral interventions can capitalize on the process of experience-dependent plasticity to improve functional outcome following brain injury, but there are several factors that are likely to impact the efficacy of this approach, as reviewed in more detail previously (Kleim & Jones, 2008). Here we briefly consider how age, practice, and timing may affect rehabilitative training approaches.

5.1. Aging brains learn differently

Neuroplasticity occurs over the lifetime, but the neuroplasticity associated with behavioral change varies with age. There are many reports that the neural plasticity observed in young adults takes longer to occur and occurs at a lessened magnitude in older animals. For example, aged animals experience decreased synaptic potentiation, synaptogenesis, and cortical map reorganization in response to manipulations of experience compared to younger animals (Churchill et al., 2002; Coq & Xerri, 2001; Greenough, McDonald, Parnisari, & Camel, 1986; Rosenzweig & Barnes, 2003).

The aging brain also responds differently to insult than does the young adult brain. Neurogenesis occurs in response to stroke in both young and aged animals, though this response is significantly reduced with age (Jin et al., 2004). The synaptogenesis found in contralesional cortex (discussed above) is not found in aged rats sustaining similar cortical ischemic damage, possibly because the growth-permissive responses to ischemic damage at

this age are more limited (Kim & Jones, 2010) and because interhemispheric interactions also change with age (Talelli et al., 2007). Axonal sprouting and synapse formation in older animals can occur, but it takes much longer (Anderson, Scheff, & DeKosky, 1986). Stroke also results in greater infarct size in aged animals (Davis, Whitely, Turnbull, & Mendelow, 1997; Kharlamov, Kharlamov, & Armstrong, 2000; Rosen, Dinapoli, Nagamine, & Crocco, 2005), likely in part because mature neurons have a reduced capacity to accommodate the metabolic challenge of ischemia (e.g., Anderson, Greenwood, & McCloskey, 2010; Davis, Whitely, Turnbull, & Mendelow, 1997; Hoyer & Krier, 1986; Siqueira, Cimarosti, Fochesatto, Salbego, & Netto, 2004).

Nevertheless, the aging brain is hardly inflexible. Although somewhat slower and less profound, the aged brain does respond to experience (Green, Greenough, & Schlumpf, 1983; Kronenberg et al., 2006; van Praag, Schubert, Zhao, & Gage, 2005). For instance, experience-dependent plasticity occurs in aged animals in response to complex motor skill training (Churchill, Stanis, Press, Kushelev, & Greenough, 2003), exercise (Adlard, Perreau, & Cotman, 2005; Fordyce, Starnes, & Farrar, 1991; van Praag et al., 2005), and enriched environment exposure (Green et al., 1983; Greenough et al., 1986). Furthermore, substantial improvements in paretic limb function can be found with rehabilitative motor training in older animals (Maldonado et al., 2008).

When examining age dependencies in experience effects, one must consider that the accumulation of experiences over a lifespan, as well as age-related cellular, structural, and functional brain changes, result in a “baseline” brain that is different in an older animal compared to a younger one (e.g., Ward, 2006). For example, aged mice learn a novel motor skill (skilled reaching) about as fast and as well as young mice. However there are age-related changes in the organization of the forelimb representation region in untrained mice, and motor skill training reorganizes the maps of aged mice in a different manner than found in younger adults. This reorganization also requires a *longer* period of daily training in older mice than in young adults (Tennant et al., 2009; Tennant, Adkins, Scalco, et al., 2010). Thus, the training parameters effective for driving brain plasticity after brain injury can be expected to vary with age.

5.2. Practice makes perfect

There are many variables that impact the likelihood that a new behavior will be learned and will be long lasting (Kleim & Jones, 2008). In motor skill learning, training intensity impacts both the rate of behavioral gains and the neural changes associated with skill acquisition. For example, rats permitted 400 reaches per day on a skilled reaching task increase synapse numbers in motor cortex (Kleim, Barbay, et al., 2002), but this is not found in those practicing only 60 reaches a day for a similar number of days (Luke et al., 2004).

Repeated practice of a new skill over time also enhances the likelihood that the skill will be well established and enduring. This is clearly a factor in motor rehabilitative training efficacy. In rats with unilateral stroke-like injuries to sensorimotor cortex, a few days of practice on a motor rehabilitative training task using the paretic limb results in little improvement, whereas several weeks of daily practice results in major functional gains (e.g., Maldonado et al., 2008). However, if the practice is then ended, the functional gains may gradually decline over time (Adkins & Jones, 2005; O'Bryant, Sitko, & Jones, 2007). One must consider that laboratory rodents are not given many opportunities to practice fine motor skills in their home cage. It may be most important for the rehabilitative training to be sufficient to effectively translate into the use of the regained functions in activities of daily living, so that they continue to be practiced after the end of treatment.

5.3. Timing

Timing is everything in experience-dependent brain development, and it also is a major factor in experience effects on the injured brain. There is an early vulnerable period following insult, during which excessive activity can impede behavioral recovery and exacerbate neural damage. Schallert and colleagues found that forced use of the paretic forelimb during the first seven days following a cortical injury increased lesion size and worsened functional outcome compared with rats free to use either forelimb (Humm, Kozlowski, James, Gotts, & Schallert, 1998; Kozlowski, James, & Schallert, 1996; Woodlee & Schallert, 2004). Excessive exercise, even when it is performed voluntarily, can also have negative consequences. Voluntary wheel running beginning just after traumatic brain injury in rats reduces neuroplasticity-related molecules in the hippocampus. However, if the exercise opportunity is delayed by two weeks, the same plasticity molecules are upregulated and spatial memory is improved (Griesbach, Gomez-Pinilla, et al., 2004; Griesbach, Hovda, Molteni, Wu, & Gomez-Pinilla, 2004). This is also true in ischemic stroke models in which too early intense exercise can increase apoptosis and impair learning performance (Sim, Kim, Kim, Shin, & Kim 2004; Sim et al., 2005).

Skilled motor rehabilitation is most effective when initiated early, but not immediately, after insult. Biernaskie and colleagues (2004) report that a five-week rehabilitative training period is more effective when initiated five days after cerebral infarct as opposed to thirty days after insult. Norrie and colleagues (2005) also report that, although a three week motor rehabilitative program improves stepping function in rats when initiated after a three month delay period following insult, it is far more effective when initiated soon after injury. Motor map changes in response to rehabilitative training also vary with time. In monkeys, training that is delayed until a month after cortical infarcts was less effective in sparing movement representations in the motor cortex than early onset training (Barbay et al., 2005).

Though its effects vary with time, rehabilitative training continues to be effective in improving function of the paretic limb when delayed well into the chronic period of recovery (O'Bryant & Jones, 2008). However, an earlier onset has the potential to capitalize upon, and to shape, the reactive plasticity instigated by the injury and, therefore, the potential to speed and enhance training effects. Treatment strategies *merely* need to avoid the types of extreme activity associated with exaggeration of the degenerative effects of the injury. The problem, of course, is that we do not have a sufficient understanding of the exact nature and timing of degenerative and regenerative responses after any given injury and the ways that experience interact with them to know precisely how to do this. Advances in non-invasive *in vivo* imaging of brain structural and functional states, combined with the use of transgenic mouse strains, should help us to more precisely identify the ways experience influences post-injury cellular responses and to predict the consequences for functional outcome.

6. Conclusion

Experience interacts with the neural environment to influence and shape CNS structure and function. Functional outcome following stroke is heavily dependent upon a combination of regenerative and degenerative processes that interact with behavioral experience. In both humans and animal models of upper extremity impairment, rehabilitative training of the paretic forelimb results in structural and functional plasticity in remaining motor systems. These plastic responses are associated with improved functional outcome. Self-taught compensatory behaviors also shape neural plasticity after brain injury, sometimes in maladaptive ways. However, experience-dependent plasticity after brain injury and its consequences for behavioral outcome continue to be sketchily understood. We need a more precise understanding of this process, and how it varies with time as well as with different

injury types and sites, modalities of impairment, and individual characteristics, such as age, to know how to use manipulations of experience optimally to improve outcomes.

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Appendix A. Continuing education

1. Rehabilitative training of the paretic limb in animal models of unilateral stroke has been found to result in which effects in the remaining motor cortex of the injured hemisphere?
    - **a.** Increased survival of newly generated cells
    - **b.** Increased glial scar formation
    - **c.** Reduced synaptic density
    - **d.** Increased duration of cell proliferation responses
    - **e.** All of the above
2. In rat models of chronic upper extremity impairments after stroke, reliance on the “good” forelimb has been linked with
    - **a.** Dendritic growth in the cortex contralateral to the injury
    - **b.** Greater disuse of the paretic limb
    - **c.** Reduction in rehabilitative training efficacy
    - **d.** Both a & b
    - **e.** All of the above
3. One reason why rehabilitative training effects can vary with age is that, compared with younger adults, the aged brain
    - **a.** shows no neural plasticity in response to training
    - **b.** may require a different duration of training to yield substantial neural plasticity
    - **c.** is unlikely to benefit from most rehabilitative treatments
    - **d.** shows synaptic plasticity but fails to show cortical functional reorganization
4. Experience effects can vary with time after brain injury because
    - **a.** they interact with time-dependent regenerative responses
    - **b.** after a few months, the brain becomes incapable of responding to experience
    - **c.** there are early vulnerable periods in which excessive activity can exaggerate damage
    - **d.** cortical map plasticity can only be driven to remodel in the first few days after injury
    - **e.** Both a & c

5. Practice is an important variable in motor rehabilitative training effects because sufficient practice is needed to
    a. instigate functional improvements
    b. induce synaptic plasticity in motor cortex
    c. result in enduring performance improvements
    d. have skills that translate to activities of daily living
    e. All of the above

Answer key: 1. a; 2. e; 3. b; 4. e; 5. e

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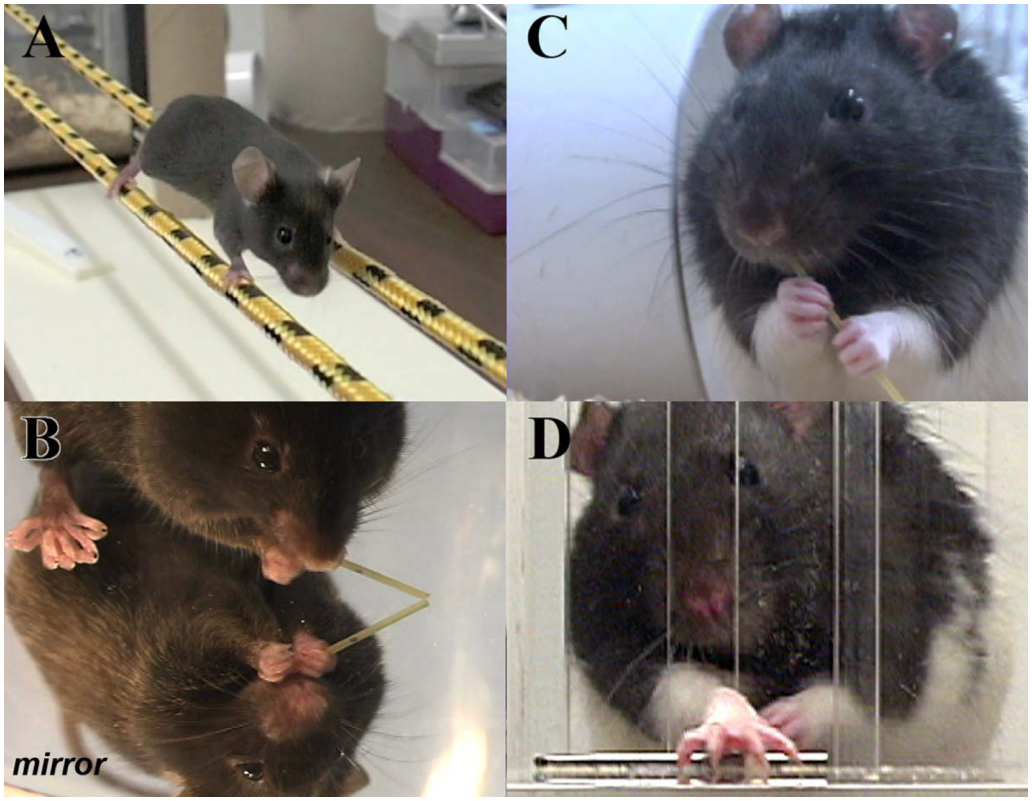

Fig. 1.

Examples of mice (A, B) and rats (C, D) performing motor skills, including an acrobatic task (A) pasta handling tasks (B, C) and a skilled reaching task (D). (The mouse in B is standing on a mirror.) These types of tasks are used to study neurobiology of motor skill learning and recovery from upper extremity impairments.

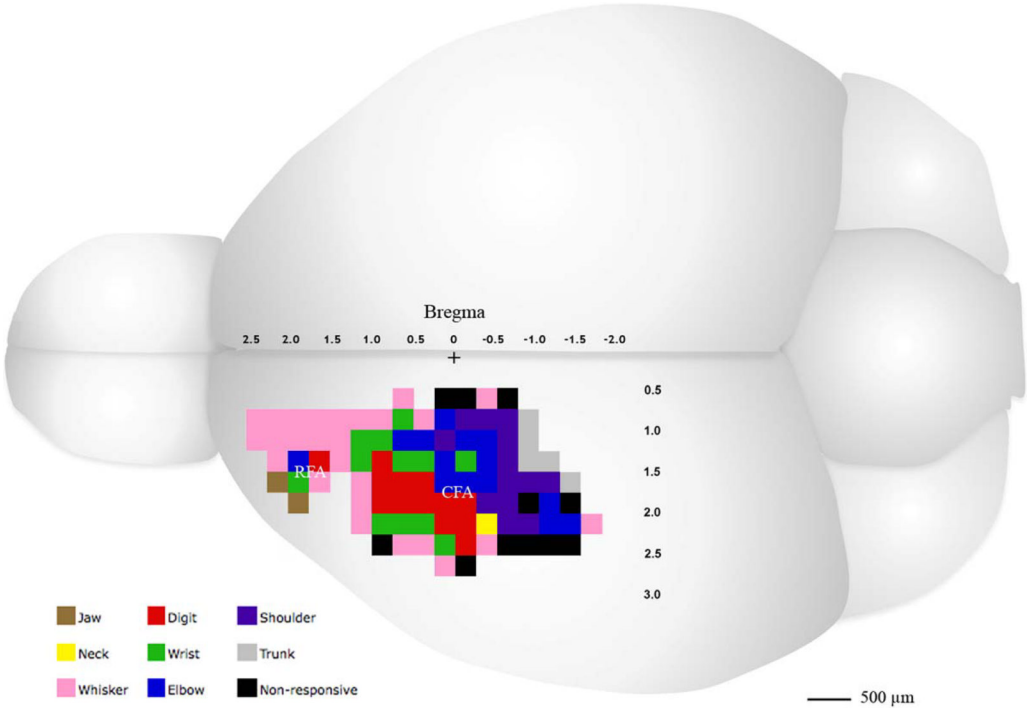

Fig. 2.

An example of a mouse forelimb representation area in the motor cortex, overlaid to scale on a schematic mouse brain. Each square represents a 250 × 250 μm area in which a movement was evoked with micro-current delivery into the center of the square. CFA: caudal forelimb area; RFC: caudal forelimb area.