

The Neuroscience of Recovery and Rehabilitation: What Have We Learned From Animal Research?

Lyn S. Turkstra, PhD, Audrey L. Holland, PhD, Gina A. Bays, MS

ABSTRACT. Turkstra LS, Holland AL, Bays GA. The neuroscience of recovery and rehabilitation: what have we learned from animal research? *Arch Phys Med Rehabil* 2003; 84:604-12.

Objectives: To encourage rehabilitation specialists to develop a critical approach to the animal research literature that is relevant to human neurorehabilitation and to encourage clinicians to lend their perspectives to basic research.

Data Sources: Scientific publications cited in MEDLINE, PubMed, and PsychInfo, and professional presentations of leading neuroscience researchers. The focus was on current publications to 2001, with historical works included when appropriate.

Study Selection: Studies were selected based on their relevance to the objectives.

Data Extraction: Reviewed study methodology and findings and extracted key principles relevant to rehabilitation.

Data Synthesis: Many themes emerging from neuroscience research are relevant to human rehabilitation, including issues related to timing of intervention and recovery, and characteristics of nervous system plasticity.

Conclusions: Although animal research has many limitations, it provides a unique window on nervous system recovery and has generated important directions for future human research. Clinician involvement in basic animal research will improve the extent to which results are relevant to human rehabilitation and recovery.

Key Words: Communication disorders; Neurosciences; Recovery of function; Rehabilitation; Review [publication type].

© 2003 by the American Congress of Rehabilitation Medicine and the American Academy of Physical Medicine and Rehabilitation

DURING THE PAST SEVERAL years, there has been an explosion of knowledge about neurologic injury and recovery. The primary vehicle for acquiring this knowledge has been animal research, from *in vitro* studies of single cells to the study of complex behaviors in whole organisms. Clearly, there are limits to the application of these results to humans. Nevertheless, animal studies have revealed principles that are critical to human study and provide directions for the study of

human recovery and rehabilitation. In this article, we summarize several of these principles and directions and discuss potential limitations in their application to humans, particularly to human recovery from language and cognitive deficits. This information is intended to help readers become critical consumers of the animal research literature in neuroscience. The study focuses on the adult central nervous system (CNS) in the subacute and chronic phase postinjury, when most rehabilitation occurs. This article is an update and extension of an earlier review of animal research that was relevant to aphasia.¹ We include more recent developments and broaden the scope of the article to include consideration of cognitive recovery in general. Findings on recovery of sensory and motor function are included when the underlying principles are relevant to recovery of cognitive function.

WHAT WE HAVE LEARNED FROM ANIMAL RESEARCH

Experience Changes the Brain at Any Age

In the introduction to his text on brain plasticity, Kolb² described the life of a fictitious woman. When born, she “can neither walk, nor talk, nor use a toilet” and “does not seem to know anything.”^{2(p3)} As a young adult, after years of training, she becomes a professional dancer and several years later retires to raise children. In midlife, she returns to dance, and resumes professional training and performing. Then she is struck by a car and must relearn lost skills and knowledge. Kolb’s description illustrates what he refers to as “one of the most intriguing important properties of the human brain”^{2(p4)}—its capacity to change throughout the lifespan. Because of plasticity, the human brain may respond to both external stimuli (eg, a dance instructor’s guidance) and internal stimuli (eg, the cellular and molecular effects of injury).²

Kolb² pointed out 3 further key aspects of brain plasticity. First, it permits us to maintain, and even improve, function in the face of a gradual loss of neurons that begins prenatally. Second, any single mechanism of plasticity is likely to underlie more than 1 form of behavioral change so that, for example, mechanisms such as cell migration and dendritic sprouting that are involved in normal development may also be involved in recovery after injury. Similarly, the mechanisms underlying change in humans are likely to be similar to those in animals. This latter assumption is the basis for extrapolating results from animal research to humans. Third, as the brain changes, behavior may also change. The refinement of behavior brings changes in experiences, which in turn alter the brain. Frontal lobe development permits self-regulation, which enhances learning, which in turn changes the structure and function of the brain. Motor development permits a child to explore the world and to be exposed to stimuli that affect further brain development. Thus, there is an ongoing process of modification in both directions: experience to brain and brain to experience. This complex interaction challenges our understanding of the process of recovery and rehabilitation, and it underscores the importance of considering behavioral experience (eg, therapy) in any study of injury and recovery.

From the Department of Communication Sciences, Case Western Reserve University, Cleveland, OH (Turkstra); and the Department of Speech and Hearing Sciences, University of Arizona, Tucson, AZ (Holland, Bays).

Supported in part by the National Institute on Deafness and Other Communication Disorders (grant no. DC-00163) and the National Multipurpose Research and Training Center, National Institute on Deafness and Other Communication Disorders (grant no. DC-01409).

Presented in part at the American Congress on Rehabilitation Medicine’s annual assembly, October 25, 2001, Tucson, AZ.

No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit upon the author(s) or upon any organization with which the author(s) is/are associated.

Reprint requests to Lyn S. Turkstra, PhD, Dept of Communication Sciences, Case Western Reserve University, 11206 Euclid Ave, Cleveland, OH 44106-7154, e-mail: LST2@po.cwru.edu.

0003-9993/03/8404-7468\$30.00/0

doi:10.1053/apmr.2003.50146

Our knowledge of how, where, and when plasticity occurs has been largely derived from animal research. Although the notion that experience results in brain changes was suggested as early as the beginning of the 20th century, it was not until 1948 that Konorski³ proposed a mechanism that would explain the changes. He postulated that sensory stimulation could alter neurons and their connections, and that this alteration could be brief or long lasting. Hebb⁴ identified the synapse as the site of this plasticity. He proposed that the use of a synapse strengthens that synapse selectively—that is, that there is activity-dependent synaptic plasticity—but only when both the pre- and postsynaptic neurons are simultaneously activated. Thus, the strength of synaptic contacts is increased for simultaneously active neurons but not for randomly firing neurons. It is now thought that neural repair is dependent on both pre- and postsynaptic activity. Repair requires not only regrowth and other changes in the injured presynaptic neuron, but also factors secreted in a retrograde fashion from the target postsynaptic neuron (eg, trophic factors) and factors present in the cellular environment (eg, glial cells).⁵

Brain Design Permits Plasticity

Humans have larger brains than mammals of comparable size and also are capable of more complex brain functions. This is not because human brains have more neurons per kilogram than other animals. Rockel et al⁶ compared the number and density of cortical neurons in human, macaque, cat, rat, and mouse brains. The measures were taken between the pial layer and the white matter, in sections corresponding to the typical width of functional columns in the cerebral cortex. They found that, with the exception of the visual cortex, the number of neurons in each section was the same through the thickness of the cortex and across species, although the total surface area was greatest in humans. The numbers and proportions of cell types also were relatively constant. The major difference was the pattern of afferent and efferent fiber connections among regions. Rockel hypothesized that the greater thickness of cortex in larger animals such as humans was “due largely to the more numerous and extensive dendritic and axonal ramifications, because with an increase in area of cortex by one square centimeter there will be several million more cells with axons.”^{6(p238)}

There are 2 major implications in these findings. One is that functional connections, rather than raw numbers of neurons, determine computational power. The ability to modify these connections is the basis for learning throughout the lifespan. The second implication is that, at least in theory, many sections of the brain possess the basic cell types to perform the functions of other sections, although the distribution and organization of cell types may differ. What is required for functional substitution to occur is the establishment of connections. The connections existing at the time of injury develop over a lifetime of genetic programming and experience, and thus are likely to be resistant to change. However, as many researchers have shown, both functional and anatomic changes are possible.

Plasticity in the normal CNS. There are several mechanisms by which the brain is modified in normal animals. Many experiments, beginning with those of Hebb⁴ (see Kolb²) have shown that experience increases the number and density of synapses on dendrites (synaptogenesis), dendritic length, and synapse size. These changes may make it possible for animals to adapt to tasks other than those chosen for training. That is, improvements in 1 task may generalize to novel, related tasks. For example, Kolb et al (unpublished data, 1995) found that rats trained on a task with 1 paw showed increased dendritic

materials in homologous regions in both hemispheres, which did not differ from the changes found in rats trained with 2 paws. Thus, experience may “prime” the brain to improve future learning.

Another mechanism of plasticity in the normal nervous system is long-term potentiation (LTP), which was proposed by Bliss and Lomo.⁷ Through repeated stimulation of input pathways to the hippocampus in rabbits, they discovered that a rapid, brief sequence of excitatory pulses enhanced synaptic efficacy that could last for hours. The mechanism by which synapses were strengthened was related to Hebb's⁴ original hypothesis, that is, “neurons that fire together wire together.”^{8(p731)} In other words, when a presynaptic neuron is active and at the same time a postsynaptic neuron is stimulated by other inputs, the synapse formed by these 2 neurons is strengthened. LTP may be an important mechanism underlying the plastic changes that occur during acquisition of new learning and memory. When a presynaptic neuron is strongly active, and a postsynaptic neuron is only weakly activated by other inputs, the strength of the synapse between the 2 neurons is weakened. This phenomenon is referred to as long-term depression, that is, “neurons that fire out of sync lose their link.”^{8(p731)} A discussion of the molecular mechanisms of LTP and long-term depression is beyond the scope of this article. In brief, these long-term changes may be related to factors such as insertion of new receptors into the synaptic membrane,⁸ and the release of chemicals such as nitric oxide (NO) after binding of glutamate to its *N*-methyl-D-aspartate (NMDA) receptor.⁹

Recently, through the use of imaging techniques, plasticity has been shown in developing humans. For example, Pascual-Leone et al¹⁰ showed that the finger representations in the dominant primary motor cortex of blind individuals who had read braille from childhood or young adulthood differed significantly from those of individuals who were blinded in adulthood and were not proficient braille readers. Blind braille readers also have superior tactile spatial ability, corresponding with an increased size of the cortical representation for fingers of the reading hand.¹¹ Imaging studies comparing children and adults have shown plasticity in the course of normal development. For example, children who perform verbal fluency tasks recruit more widespread areas of cortex than do adults, including greater frontal activation that may relate to the process of establishing semantic networks.¹²

Plasticity after injury. Evidence of functional reorganization after injury was first presented in 1950 by Glees and Cole.¹³ Using electric stimulation techniques, they showed that somatotopic maps in the primary motor cortex changed after unilateral cortical stroke in the macaque monkey. More recently, Nudo et al¹⁴ used the technique of intracranial microstimulation in adult nonhuman primates to demonstrate somatotopic reorganization after focal lesions and retraining. They trained 4 monkeys on a pellet retrieval task, mapped the primary motor cortex (M1) somatotopic representation, then infarcted the hand area of M1 by using a microcoagulation technique. They then remapped the area after 3 to 4 weeks of training on the pellet task. The resulting maps were compared with those of monkeys that had not received “rehabilitation.” The group found that training increased the size of the hand representation in the perilesional region of M1, whereas monkeys that had no training showed a decrease. The researchers concluded that “in the absence of postinjury rehabilitative therapy, the surrounding tissue undergoes a further territorial loss in the functional representation of the affected body part.”^{14(p1794)} In other words, “use it or lose it.”

The Nature of Experience Influences the Nature of Change

Kilgard and Merzenich¹⁵ proposed that experience is necessary but not sufficient to induce plasticity. They noted that learning was as related to the behavioral importance of the stimulus as it was to its frequency of occurrence, so that a stimulus that is relevant to the organism (like the scent of a potential mate or the location of food) may be learned in a single trial. They argued that for functional reorganization to occur, it is necessary to “mark” the importance of a stimulus with input from limbic and paralimbic structures. Kilgard and Merzenich¹⁵ tested this hypothesis by examining the effect of nucleus basalis stimulation on learning. One third of the nucleus basalis projections to the cerebral cortex are cholinergic and, based on evidence that acetylcholine is important in learning, Kilgard and Merzenich predicted that this cholinergic input would mark the importance of the stimuli. The researchers paired electric stimulation of the nucleus basalis with auditory stimuli in adult rats and measured the resulting changes in the tonotopic representation of the auditory cortex. The tone-stimulation pairing occurred every 8 to 40 seconds, 300 to 400 times a day for 20 to 25 days. They observed significant reorganization of tonotopic maps, with an increase in the number of cells responding to the training stimulus. Reorganization was significantly greater than when stimuli were presented without the cholinergic stimulation.

Kilgard and Merzenich¹⁵ suggested that their findings represented the type of plasticity that permits adults to recover from CNS injury. The results also suggest that rehabilitation may be more successful if the tasks and stimuli are important to the person. This is another example of how experience changes the brain (ie, so that some things have more behavioral importance than others), which in turn changes the effects of experience.

Many animal studies have shown that the extent and direction of recovery depends on the environment and the nature of the training stimuli. Hamm et al¹⁶ studied the effects of an enriched environment on recovery from lateral fluid percussion injury in the rat. This injury is a common animal model of traumatic brain injury (TBI) and replicates characteristics of TBI such as diffuse axonal injury.¹⁷ In this study, rats that received either a sham injury (ie, surgery and anesthesia without injury) or lateral fluid percussion injury were randomized to either an enriched environment or a standard cage environment. The enriched environment included features such as toys, group housing, and a variety of food (including cookies). After about 2 weeks, all animals were tested in the Morris water maze, a test of spatial memory that requires the animal to find a platform submerged in opaque water, by using visual cues located around the perimeter of the water maze. The injured rats that recovered in an enriched environment performed no differently than the sham-injured rats and significantly better than the injured rats in the standard cage group. The enriched environment did not affect the performance of sham-injured rats. In other words, environmental enrichment had an effect specifically on rats with an impaired nervous system. Hamm et al concluded that, “Although generalization of these results to human TBI must be approached with caution, it seems that appropriate environmental stimulation during rehabilitation may have a positive influence on the recovery of function after injury.”^{16(p44)} They also commented that behavioral interventions, unlike pharmacologic interventions, did not have negative side effects.

Animal research has shown that failure to participate in rehabilitation may have adverse effects on recovery. Taub et

al^{18,19} tested the hypothesis that nonhuman primates learn to avoid using an injured limb, based on negative experiences in the early phase after an injury, and that this early “learned nonuse” prohibited later functional recovery of the affected limb. In these early studies, Taub et al deafferented the limbs of nonhuman primates, an injury that leads to transient weakness of a limb. They found that although the potential for motor behavior improved over time, the animals permanently ceased to attempt to use the injured limb. However, if the animal’s intact limb was restrained during the chronic period postinjury and a shaping technique was used to teach functional movements, the animal learned to use the injured limb in its normal activities. Taub et al replicated these findings in studies of hemiparetic human stroke patients,^{18,20} and recently reported in an interview that they had used the techniques of limb restraint, forced use, and shaping therapy in more than 200 stroke patients in rehabilitation.²¹ The benefits of forced use are significantly greater than the benefits of a similarly intensive intervention that was based on neurodevelopmental therapy in a blinded, randomized clinical trial of 66 chronic stroke patients.²² Thus, the effects are unlikely to be attributable to intensity of rehabilitation alone.

Recently, the model of Taub was applied to the rehabilitation of individuals with aphasia. Pulvermuller et al²³ treated individuals with chronic aphasia with intensive massed practice of oral language stimuli over a 2-week period, restricting responses to spoken language only in several interactive communication tasks. This intensive training was associated with significant improvements on standard tests and self-ratings as well as other ratings of communication in daily living. It is not clear whether the observed changes resulted from the forced use of spoken speech (as opposed to training word-finding strategies), or to the intensity of the treatment itself. Nonetheless, it is an interesting (and testable) attempt to provide a linguistic analog to the motor work described above.

The negative effects of nonuse also have been documented²⁴⁻²⁷ in a series of studies by Feeney et al beginning in the 1980s. These researchers observed severe delays in recovery in animals that were either physically or chemically restrained (via Haldol [haloperidol]) in the acute phase after unilateral middle cerebral artery occlusion. Restrained animals were significantly delayed in recovery relative to animals that participated in “rehabilitation,” with the greatest delays seen in animals that were both chemically and physically restrained. This research and Taub’s previously cited research show the successful transfer of knowledge from the animal laboratory to the human clinic.

Timing Is Everything

The research of Taub et al¹⁸⁻²⁰ suggests that intervention in the chronic stage postinjury may be most effective if it is delivered with high intensity over a relatively brief period. Other temporal factors also influence the effects of experience. These include the age or developmental stage of the animal, and how soon after injury the experience occurs.

Age effects. There is evidence that an enriched environment is beneficial to adult animals that are recovering from injury; however, the same may not be true in the case of injury to developing nervous systems. Shieh et al²⁸ studied the effects of rearing in an enriched environment on recovery from lateral fluid percussion injury in young rats. They found that the occipital cortex of injured rats from the enriched environment showed increased dendritic density (ie, greater length and number of dendrites) but no increase in dendritic branching. In other words, the increase in neural outgrowth was not accompanied by an increase in functional connections. There also was

no significant improvement in behavior. The authors noted that lateral fluid percussion injury had induced NMDA-receptor dysfunction, and that NMDA-receptor activation is involved in the process of pruning in the CNS during development. Thus, they speculated that the combination of lateral fluid percussion injury and environmental enrichment early in life could stimulate dendritic outgrowth without appropriate pruning.

The fact that environmental enrichment did not enhance recovery in young animals may appear to contradict current thinking that early intervention improves outcome in acquired neurogenic communication disorders in children. It must be remembered, however, that the human analog of the Hamm paradigm is probably intensive sensory stimulation in the acute stage after a traumatic injury, which likewise is not associated with improved outcome in humans.²⁹

Age effects on recovery may reflect normal changes in the CNS throughout the lifespan. For example, research in animal models has shown that, in the developing nervous system, neurotransmitters play a qualitatively different role in addition to the role of the classical synaptic transmission seen in adult nervous systems.³⁰ During development, these chemicals act over greater distances and are involved in the formation of different regions of the brain.³⁰ Thus, models of injury and recovery, including those that address catecholamine and excitatory amino acid effects, may fail to capture essential processes in developing systems. Further, treatments that are effective in adult animals (eg, glutamate antagonism) may, in fact, interfere with normal neural development.³¹

At the other end of the age spectrum, factors that have no influence on young, healthy nervous systems may have adverse effects on the aging brain. To illustrate, Stuntz et al³² reported that administering aspartame in the drinking water of aged rats had detrimental effects on their recovery from sensorimotor functions after cortical lesions. In young, healthy rats, the neurotoxic effects of aspartame are mitigated by the blood-brain barrier. Stuntz suggested that age-related changes in the blood-brain barrier reduced the brain's ability to buffer those effects.

Effects of time postinjury. Schallert et al³³ reported adverse effects of intervention in the early stage after injury. Schallert stated that 2 opposing processes occur during recovery: neural compensation mechanisms, which improve function, and secondary, injury-initiated, neurodegenerative processes that interfere with recovery. These secondary processes are biochemical and physiologic changes that are initiated by the injury and may continue for hours or days afterward.^{34,35} Schallert suggested that behavioral strategies aimed at improving compensation may exacerbate secondary injury. They found that lesions of the rat sensorimotor cortex induced increased growth and complexity of dendritic connections in the contralateral homotopic somatosensory cortex, if the animal was free to use both the affected and unaffected limbs. This is an example of neural compensation. However, if the unaffected limb was restrained and the animal was forced to use the affected limb, there was an "overuse" injury. That is, there was no growth of dendrites and the lesion size increased, an example of secondary neurodegenerative injury.

Neither dendritic outgrowth nor lesions occurred in intact animals, leading Schallert to hypothesize that the injury sensitized the brain to both secondary injury and use-dependent compensatory neural growth. In fact, others have shown that a lesion to the nervous system sensitizes it to both compensatory and degenerative influences. For example, if a spinal cord injury (SCI) is preceded by a peripheral nerve injury, the latter injury acts as a "conditioning" lesion, increasing axonal regeneration and the expression of growth factors when the spinal

cord is later injured³⁶ and increasing the proportion of regenerating fibers in a spinal cord graft.³⁷ These early factors do not appear to be present in the chronic stage after injury, because Schallert found no effect of overuse if the uninjured limb was restrained after the first 7 days, suggesting that these use-dependent mechanisms are transient. This explains the apparent inconsistency between the benefits of forced use reported by Taub et al,¹⁸⁻²⁰ who studied animals and humans in the chronic stage, and the adverse effects of forced use reported by Schallert,³³ who studied humans and animals in the acute stage.

In a subsequent study, Humm et al³⁸ showed that the damaging effects of early overuse were mediated by NMDA-receptor activity. They further proposed that the neurotransmitter, glutamate, which binds to and activates the NMDA receptor, might be involved in this secondary exaggeration of injury. Although glutamate is critical to normal cell function, excessive release of glutamate is known to occur after injury, with neurotoxic effects (see reviews by Seisjo³⁴ and Kochanek³⁹). Humm³⁸ hypothesized that high glutamate levels were induced in the perilesional area, leading to the destruction of nonfunctioning but still viable cells. In support of this hypothesis, animals that were given an NMDA antagonist, MK-801, showed no increase in lesion size. In fact, animals that were restrained and given MK-801 in the acute stage postinjury had the best outcome because they were forced to use the injured limb but avoided adverse effects on lesion size or dendritic growth. From a clinical perspective, Schallert concluded that, in the acute stage after injury, "behavior, including neurological assessment, might affect neural events . . . [as] the behavioral tests themselves might alter the process of recovery."^{33(p236)} This is further evidence that behavioral intervention may have a powerful influence on outcome—in either a positive or a negative direction.

Effects of preinjury training. In research on SCI in the cat, Tillakaratne et al,⁴⁰ Edgerton et al,⁴¹ and de Leon et al⁴² have shown that preinjury skill level interacts with the effects of rehabilitation on recovery. In a series of related studies, these researchers showed recovery of stepping after spinal cord transection, when cats were provided with appropriate sensory stimulation and weight-bearing opportunities. They found, however, that drugs such as strychnine (a glycine agonist) improved stepping only of nontrained or poorly stepping cats, and had no effect on performance of cats that were trained in the stepping task preinjury. Although there are critical differences between spinal cord and brain structure and function, the results suggest an important characteristic to consider in animal models of brain injury and recovery. That is, as the saying goes: "It's not just the brain injury, but the brain you bring to the injury." The effects of premorbid cognitive function have been documented in human studies,^{43,44} but often are not modeled in animal studies of recovery and rehabilitation, because animals are trained to homogeneous criteria preinjury.

Neurogenesis as a Possible Experience-Dependent Change in the CNS

In the last decade, neuroscientists have revised the long-held notion that adult mammalian neurons do not divide and reproduce. Animal research across several species has now shown that events such as neurogenesis and cellular migration, previously considered unique to embryonic developmental phases, persist in specific regions of the adult mammalian brain, primarily in the olfactory system and the hippocampus.⁴⁵ Neuroblasts, the precursors to neurons, divide in the subventricular zone in the adult rat, and these progenitor cells migrate to the olfactory bulb and differentiate into neurons with functional connections.⁴⁶ Also in the adult rat, new granule cell neurons

are generated in the hippocampal dentate gyrus.⁴⁷ This generation of hippocampal granule cells in adulthood has recently been shown in primates and in humans.⁴⁸ The functional significance of neurogenesis in the adult is still hotly debated (eg, see discussion in Rakic⁴⁹).

Research with animals has begun to suggest factors that may induce or enhance adult mammalian neurogenesis and promote cell survival. Factors identified to date include exposure to enriched environments,^{50,51} physical activity,⁵¹ associative learning,⁵² and stimulation sufficient to induce long-term potentiation.⁴⁵ Lesions to the hippocampus also have been found to stimulate the production of precursor cells in the lesioned area.⁵³

NO, a cellular messenger and unconventional neurotransmitter, is currently the leading candidate to be the messenger molecule involved in long-term potentiation, the mechanism believed to underlie hippocampal learning and memory. As a gaseous, diffusible neurotransmitter, NO is not bound by the synaptic pathways that other neurotransmitters must follow and is able to coordinate cellular signaling among populations of neurons.⁵⁴ In addition to its role as a possible mediator of synaptic plasticity, it has been recently proposed that NO is active in neurogenesis.⁵⁵ In preliminary support of this hypothesis, neurons that express the neuronal isoform NO synthase have been located in areas where neurogenesis occurs in the adult mouse brain. Thus, possible sources of NO have been identified in the vicinity of neuronal progenitor cells in an animal model.

For neurogenesis to occur in a mature nervous system, several steps are necessary: the cell must survive, the axon must regrow, and the axon must remyelinate and form functional synaptic connections.⁵ The characterization of factors that could influence each of these steps has been a major focus of recent research on nervous system recovery. Through studies in whole animal models, as well as through cell culture and molecular models, key strategies for regeneration have been identified. These strategies include neurotrophic factor delivery, removal of growth inhibitors, manipulation of intracellular signaling, and manipulation of the nervous system immune response.⁵ This research has considerable promise; however, there is currently little direct evidence that neurogenesis plays a significant role in either experience-dependent changes in behavior or behavioral recovery after CNS injury.

The recent identification of factors that inhibit the regeneration of injured axons may eventually allow increased neural recovery after injury to the CNS. Researchers have recently, through molecular cloning, identified a protein in the myelin cells of the CNS that may actually inhibit axonal regeneration after CNS injury.⁵⁶⁻⁵⁸ This protein, known as Nogo, is notably absent from the peripheral nervous system in which axonal regeneration and functional recovery occur naturally after injury.⁵⁹ An antibody known as IN-1 was created to recognize and disrupt the Nogo inhibitory protein, and it has allowed axonal regrowth and some functional recovery when applied to CNS lesions in animals.⁶⁰ In related research, Huang et al⁶¹ created an antiserum to CNS myelin by injecting mice with a CNS myelin preparation. This antiserum decreased myelin inhibition and increased axon growth *in vitro* and also allowed extensive regrowth of injured corticospinal tract axons when used as a "myelin vaccine" in mice. As inhibitory factors such as Nogo are identified, their receptors found, and their roles in inhibition of axonal regrowth understood, it may become possible to therapeutically promote recovery of injury in the CNS through disruption of this myelin-dependent inhibition of recovery.⁵⁹

Animal research also has led the way in the area of neural tissue transplantation. Gage et al⁶² transplanted basal forebrain neurons, known to degenerate in Alzheimer's disease, into near-senile, aging rats. These rats had a significant increase in spatial memory after transplantation. Freed et al⁶³ and Olson⁶⁴ showed a similar effect with transplantation of catecholaminergic cells into rats with experimentally induced Parkinson's disease. This transplantation treatment largely eliminated the rigidity, tremor, and paucity of movement that was exhibited by the rats before cellular therapy. Progress in this area has been remarkable, and discoveries are beginning to be applied to humans in a limited fashion. For example, the immune response to fetal tissue transplants has been studied in humans with Parkinson's disease who received fetal nigral cell implants,⁶⁵ and fetal cell implants and clones from nonfetal cell lines have been considered for the treatment of ischemic hippocampal injury in humans, based on positive results in rats and other animal models.⁶⁶

Plastic Changes Require Repetition and Maintenance

The work of Nudo et al,¹⁴ Kilgard and Merzenich,¹⁵ and others has shown the importance of repetition in inducing brain changes. Repetition also is important in maintaining such changes. This principle is illustrated by the work of Pascual-Leone et al.⁶⁷ Pascual-Leone used transcranial magnetic stimulation (TMS) to generate cortical maps of the hand muscles in blind people who were proficient braille readers and used braille in their work. Pascual-Leone found that the maps changed in size, depending on whether the subjects had been working for a 6-hour period or had taken the day off from work. This result may be intuitive for those who have taken music or dance lessons, but who have then not practiced for a period of time. From a clinical perspective, it suggests a source of evidence to support the need for consistent practice to maintain gains in therapy.

The "Recovered" Brain Remains Sensitive to Drug and Other Effects

Dixon et al⁶⁸ studied the effect of drugs on the recovery of memory after lateral fluid percussion injury in adult rats. The rats initially showed severe impairments in performance on the Morris water maze task, but recovered over a period of several weeks until their performance did not differ significantly from that of sham-injured rats. At 35 days postinjury, the rats were administered scopolamine, a muscarinic cholinergic receptor antagonist, to test the hypothesis that a deficit in acetylcholine has a role in the memory impairments commonly observed after TBI. Scopolamine decreased maze performance to the levels observed immediately postinjury, although there was no effect on the performance of sham-injured rats. In other words, the injured rats appeared to be functioning normally, yet were vulnerable to drug effects.

In a related experiment, Kozlowski et al⁶⁹ examined the effects of ethanol, a known NMDA-receptor antagonist, on recovery after brain injury in adult rats. They made lesions in the area of the forelimb representation of the rat sensorimotor cortex, causing significant postural and sensorimotor deficits. When the rats had recovered physical function, the researchers introduced ethanol into their diets, which caused a chronic reinstatement of previous lesion-induced deficits. In addition, ethanol ingestion prevented the pruning of sprouting dendrites, a process that typically is observed during recovery in the hemisphere contralateral to the lesion. Lesion-induced dendritic pruning may be important in the recovery process and is mediated by NMDA-receptor activity, as discussed in relation

to lateral fluid percussion injury in developing rats. Kozłowski⁶⁹ suggested that the antagonistic action of ethanol at NMDA receptors may prevent normal postlesion dendritic pruning, contributing to the reinstatement of physical deficits. This is an important finding, given the frequency with which humans are intoxicated at the time they sustain a TBI.

A FEW CAVEATS IN THE APPLICATION OF ANIMAL RESEARCH TO HUMANS

Animal Injury Models Versus Human Injury

In general, patterns of neural development and cell structure found in animals such as rats parallel those found in humans. Nevertheless, there are a few key differences that limit the extent to which nonprimate animal research may be extrapolated to humans. First, the time course of neural and other development varies across species. For example, although humans and rats both have neural proliferation and migration, cell differentiation, synaptogenesis, gliogenesis, and myelination into adulthood, the proportion of neurogenesis that is complete by birth is greater in humans.³⁰ The gestational period for a rat is approximately 3 weeks, and rat adolescence is reached between postnatal days 35 and 45. This time scale differs substantially from the human time scale, and must be considered in any discussion of processes such as recovery and response to rehabilitation. Few studies have explicitly addressed these differences in developmental time course relative to recovery from CNS injury, although the information is critical for the application of animal findings to humans.

A second key difference is that although the gross regional development of the brains of rats and humans is similar, there are differences in the development of specific regions.³⁰ For example, rats have a larger olfactory system, consistent with their environmental needs, and humans have a relatively larger proportion of the brain dedicated to neocortex and the visual system. The proportion of the brain allocated to association cortex, particularly in the frontal and temporal lobes, increases across species from smaller animals to humans.⁷⁰ The importance of the limbic system and hindbrain decrease accordingly. Rats also have a lissencephalic (smooth) brain, which may not respond to mechanical injury in the same way as the gyrencephalic (convoluted) human brain. The most appropriate animal model is the nonhuman primate, which is highly similar to the human in brain structure and function. However, because of political pressure and the expense and care required, research on recovery from acquired CNS lesions in nonhuman primates is relatively rare.

Other factors limit the ability to extrapolate animal data to humans. Animal studies are done in a highly controlled environment, with relative homogeneity in lesion characteristics, animal characteristics (genotypes, phenotypes), and experiences. Typically, premorbid measures are taken, and premorbid environments also are controlled. Animals may undergo hundreds or thousands of repetitions of a task, as in the study by Kilgard and Merzenich,¹⁵ without intervening activities that may influence the treatment outcome. Thus, the animal situation is usually highly dissimilar to that encountered by human patients.

Recently, Kochanek⁷¹ noted that animal research on TBI had modeled only the clinical situation of the young male construction worker (ie, drop-weight models are popular, animals tend to be young males). Kochanek also argued that current models fail to capture most of the complexity of human TBI, including premorbid genetics and experience, the effects of injury in women, the relatively short laboratory time course compared with the typical rehabilitation time course, and secondary com-

plications like herniation (see discussion in Meythaler et al⁷²). The same may be said of research on other CNS disorders. Experimental tasks used in animal research also may fail to replicate important behavioral outcomes from CNS injury. Tasks such as the Morris water maze have limited resemblance to activities of humans (with the possible exception of sailors who are swept overboard), and do not address cognitive impairments that are most handicapping after human injury, including impairments in language, declarative memory, and executive function.

A major element of human clinical recovery that is not addressed in most animal studies is rehabilitation. Although even the earliest research on plasticity in the CNS considers the role of experience, animal research on recovery has just begun to consider rehabilitation in any detail. When retraining has been considered, the results are unequivocal: experience, particularly specific experience related to the injured systems, may have a significant positive impact on recovery.⁷³ The comments of Barker and Dunnett,⁷³ regarding motor function after neurotransplantation, may be applied in general to animal research:

We need to consider not only the anatomic connectivity needed to reconstruct the damaged circuitry, but also the relearning and retraining of the normal adult's rich repertoire of motor skills and habits. This is the realm of the rehabilitation specialists, who have to this point not been active participants in existing transplantation programs. We might expect, though, that they (you) have much to offer, and the marriage of rehabilitation and neurobiological disciplines may pave the way to marked improvements in present strategies for therapy.^{73(p245)}

Thus, clinicians may have an important role in the direction of animal research. Although animal studies currently may not replicate important aspects of human rehabilitation and recovery, they do suggest directions for human study and offer opportunities for fruitful collaboration.

Plasticity Does Not Equal Improvement in Functional Outcome

In many studies of injury and recovery, it is difficult to document physiologic or functional benefits associated with anatomic changes. It is possible to demonstrate such benefits conclusively in animal research by correlating behavioral change with anatomic evidence, using techniques such as staining or labeling of neurons, or re-injury. For example, Ramer et al⁷⁴ studied the effect of intrathecal neurotrophic factor administration on sensory axon regrowth in the CNS. They judged outcome by measuring specific behaviors that were linked to the functions of the lesioned axons, followed by re-injury to show reinstatement of impairments related to those behaviors. In this way, they showed both physical regrowth of sensory axons and the importance of this regrowth to the whole organism.

In a review of current research on injury and recovery, Horner and Gage⁵ emphasized the need to tie cellular events to behavioral recovery, and noted that functional benefits had not been shown in many studies that showed positive effects at the cellular and system level. Examples included studies of cell replacement (eg, fetal tissue implants), neurotrophic factor stimulation, and manipulation of intracellular signaling (eg, blocking glutamate or calcium after injury). Treatments that are effective for *in vitro* or animal models may have adverse or even lethal consequences for humans. For example, the high-affinity glutamate antagonist MK-801 has psychomimetic effects in humans and has caused vacuolization of the cingulate gyrus and retrosplenial cortex in rats,⁷⁵ and administration of the most effective calcium channel antagonist probably would

result in death. Other treatments may be safe for humans but show no significant benefit in clinical trials. Thus, many potential treatments have yet to demonstrate functional benefits in clinical populations.

Imaging the Live Human Versus Animal Research

The major resurgence of interest in plasticity and recovery has been prompted in part by the availability of techniques to study these processes in live humans with and without injuries. Techniques such as TMS, functional magnetic resonance imaging, and positron emission tomography have permitted researchers to ask questions in human research that cannot be asked in animal research, particularly questions related to language. As Small stated, "By their very nature, language functions have qualitatively different brain representations than sensorimotor functions . . . (and do not) map straightforwardly to the environment."^{76(p228)} Thus, the results of studies of sensory and motor function in animals may have limited relevance to the processes involved in language rehabilitation and recovery. This is probably also true of processes involved in the rehabilitation of other higher cognitive functions.

By using human *in vivo* imaging, it is possible to study changes in brain organization over time in populations such as persons with aphasia who are in rehabilitation^{77,78} or patients who are dysphagic after having unilateral stroke.⁷⁹ Such studies provide insights into mechanisms of recovery (eg, ipsilateral vs contralateral compensation vs "unmasking" of new cortical networks).

Given the possibility of studying live humans, one might ask what role animal studies will play in the future of rehabilitation and recovery research. Animal research remains critical to our understanding of the basic mechanisms of injury and recovery. Animal research may occur at a level of analysis that is not possible in an *in vivo* human model, and methods such as reinjury and randomization of treatment are not ethically acceptable for human research. This is particularly relevant for rehabilitation studies that involve drug treatments. It may seem odd to await animal studies to confirm what we have been observing for centuries in humans, but the use of animal models permits tight control of factors that may confound the outcomes in human studies. The control that is routinely obtained in animal studies may never be achieved in human research, given the complexities inherent in working with people who are active participants in the recovery process. Thus, animal research is likely to remain a major influence on the development of rehabilitation science, and it is in our best interests to remain current with advances in this area.

CONCLUSION

We have presented basic neuroscience concepts in terms understandable to rehabilitation specialists; however, collaboration between rehabilitation specialists and basic neuroscientists is rapidly becoming a 2-way street. As rehabilitation specialists, we are well positioned to contribute to the evolution of clinical neuroscience research, particularly with regard to the construction of rehabilitation paradigms and the measurement of functional outcome. Given the rapid pace of developments, this contribution requires that we stay current with major themes and results in animal research, and appreciate the possibilities and challenges in their application to human recovery and rehabilitation.

Clinicians are well positioned to test concepts derived from animal studies in clinical practice, with the ultimate goal of maximizing the potential benefits of rehabilitation and eliminating interventions that may have no results or negative consequences for the individual. Animal research has shown that

the brain is a flexible, plastic system that is highly sensitive to experience after injury, and that changes in brain circuitry require maintenance if an individual is to achieve lasting benefits. These findings are compelling and should guide clinical decision making in the future.

Acknowledgments: We thank Drs. Leslie Gonzalez-Rothi and Leslie Tolbert for their inspiration and support of neuroscience research in communication disorders.

References

1. Keefe KA. Applying basic neuroscience to aphasia therapy: what the animals are telling us. *Am J Speech Lang Pathol* 1995;4:88-93.
2. Kolb B. Brain plasticity and behavior. Mahwah: Lawrence Erlbaum Associates; 1995.
3. Konorski J. Conditioned reflexes and neural organization. Cambridge: Cambridge Univ Pr; 1948.
4. Hebb D. Organization of behavior. New York: John Wiley & Sons; 1949.
5. Horner PJ, Gage FH. Regenerating the damaged central nervous system. *Nature* 2000;407:963-9.
6. Rockel A, Hiorns R, Powell T. The basic uniformity in structure of the neocortex. *Brain* 1980;103:221-44.
7. Bliss TV, Lomo T. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J Physiol* 1973;232:331-56.
8. Bear MF, Connors BW, Paradiso MA. Neuroscience: exploring the brain. 2nd ed. Baltimore: Lippincott Williams & Wilkins; 2001.
9. Schuman EM, Madison DV. A requirement for the intracellular messenger nitric oxide in long-term potentiation. *Science* 1991; 254:1504-6.
10. Pascual-Leone A, Cammarota A, Wassermann EM, Brasil-Neto JP, Cohen LH, Hallett M. Modulation of motor cortical outputs to the reading hand of braille readers. *Ann Neurol* 1993;34:33-7.
11. Van Boven RW, Hamilton RH, Kauffman T, Keenan JP, Pascual-Leone A. Tactile spatial resolution in blind braille readers. *Neurology* 2000;54:2230-6.
12. Gaillard WD, Hertz-Pannier L, Mott SH, Barnett AS, LiBihan D, Theodore WH. Functional anatomy of cognitive development: fMRI of verbal fluency in children and adults. *Neurology* 2000; 54:180-5.
13. Gleebs P, Cole J. Recovery of skilled motor functions after small repeated lesions of motor cortex in macaque. *J Neurophysiol* 1950;13:137-48.
14. Nudo RJ, Wise BM, SiFuentes F, Milliken GW. Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. *Science* 1996;272:1791-4.
15. Kilgard MP, Merzenich MM. Cortical map reorganization enabled by nucleus basalis activity. *Science* 1998;279:1714-8.
16. Hamm RJ, Temple MD, O'Dell DM, Pike BR, Lyeth BG. Exposure to environmental complexity promotes recovery of cognitive function after traumatic brain injury. *J Neurotrauma* 1996;13:41-7.
17. Gennarelli T. Animate models of human head injury. *J Neurotrauma* 1994;11:357-68.
18. Taub E, Crago JE, Burgio LD, et al. An operant approach to rehabilitation medicine: overcoming learned nonuse by shaping. *J Exp Anal Behav* 1994;61:281-93.
19. Taub E, Uswatte G, Elbert T. New treatments in neurorehabilitation research. *Nat Rev Neurosci* 2002;3:228-36.
20. Taub E, Miller NE, Novack TA, et al. Technique to improve chronic motor deficit after stroke. *Arch Phys Med Rehabil* 1993; 74:347-54.
21. Huelskamp S. Breakthroughs in stroke rehabilitation. *Adv Directors Rehabil* 2000;9(10):33-8.
22. van der Lee JH, Wagenaar RC, Lankhorst GJ, Wogelaar TW, Deville WL, Bouter LM. Forced use of upper extremity in chronic stroke patients. *Stroke* 1999;30:2369-75.
23. Pulvermuller F, Benkinger B, Elbert TR, Mohr B, Rockstroh BS, Taub E. Constraint-induced therapy of chronic aphasia following stroke [abstract]. *Soc Neurosci Abstracts* 2000;26:2295.

24. Feeney D, Gonzalez A, Law W. Amphetamine, haloperidol, and experience interact to affect rate of recovery after motor cortex injury. *Science* 1982;217:855-7.
25. Feeney DM, Sutton RL. Pharmacotherapy for recovery of function after brain injury. *CRC Crit Rev Neurobiol* 1987;3:135-97.
26. Feeney D, Sutton R. Catecholamines and recovery of function after brain injury. In: Stein D, Sabel B, editors. *Pharmacological approaches to the treatment of brain and spinal cord injury*. New York: Plenum Pr; 1988. p 121-42.
27. Sutton R, Weaver M, Feeney D. Drug-induced modifications of behavioral recovery following cortical trauma. *J Head Trauma Rehabil* 1987;2:50-8.
28. Shieh EY, Giza CG, Griesbach GS, Hovda DA. Lateral fluid percussion injury followed by rearing in enriched environment increases cortical dendritic density [abstract]. *J Neurotrauma* 2000;17:986.
29. Wood RL. Critical analysis of the concept of sensory stimulation for patients in vegetative states. *Brain Inj* 1991;5:401-9.
30. Rice D, Barone S. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. *Environ Health Perspect* 2000;108:511-33.
31. Jenkins LW. Injury to the developing brain. Paper presented at: National Neurotrauma Society Annual Meeting Symposium; 2000 Nov 4; New Orleans (LA).
32. Stuntz PM, Hart CL, Barth TM. Detrimental effects of aspartame on behavioral function in "at risk" populations [abstract]. *J Neurotrauma* 2000;17:973.
33. Schallert T, Kozlowski DA, Humm JL, Cocke RR. Use-dependent structural events in recovery of function. *Adv Neurol* 1997;73:229-38.
34. Seisjo BK. Pathophysiology and treatment of focal cerebral ischemia. Part I: Pathophysiology. *J Neurosurg* 1992;77:169-84.
35. Seisjo BK. Pathophysiology and treatment of focal cerebral ischemia. Part II: Mechanisms of damage and treatment. *J Neurosurg* 1992;77:337-54.
36. Chong MS, Woolf CJ, Haque NS, Anderson PN. Axonal regeneration from injured dorsal roots into the spinal cord of adult rats. *J Comp Neurol* 1999;410:42-54.
37. Oudega M, Varon S, Hagg T. Regeneration of adult rat sensory axons into intraspinal nerve grafts: promoting effects of conditioning lesion and graft predegeneration. *Exp Neurol* 1994;129:194-206.
38. Humm JL, Kozlowski DA, Bland ST, James DC, Schallert T. Use-dependent exaggeration of brain injury: is glutamate involved? *Exp Neurol* 1999;157:349-58.
39. Kochanek PM. Ischemic and traumatic brain injury: pathobiology and cellular mechanisms. *Crit Care Med* 1993;21(9 Suppl):S333-5.
40. Tillakaratne NJ, de Leon RD, Hoang TX, Roy RR, Edgerton VR, Tobin AJ. Use-dependent modulation of inhibitory capacity in the feline lumbar spinal cord. *J Neurosci* 2002;22:3130-43.
41. Edgerton VR, de Leon RD, Tillakaratne NJ, Recktenwald MR, Hodgson JA, Roy RR. Use-dependent plasticity in spinal stepping and standing. *Adv Neurol* 1997;72:233-47.
42. de Leon RD, Tamaki H, Hodgson J, Roy RR, Edgerton VR. Hindlimb locomotor and postural training modulates glycinergic inhibition in the spinal cord of the adult spinal cat. *J Neurophysiol* 1999;82:359-69.
43. Dickerson-Mayes S, Pelco LE, Campbell CJ. Relationships among pre- and post-injury intelligence, length of coma and age in individuals with severe closed head injuries. *Brain Inj* 1989;3:310-3.
44. Donders J, Strom D. The effect of traumatic brain injury on children with learning disability. *Pediatr Rehabil* 1997;1:179-84.
45. Derrick BE, York A, Martinez JL. Increased granule cell neurogenesis in the adult dentate gyrus following mossy fiber stimulation sufficient to induce long-term potentiation. *Brain Res* 2000;857:300-7.
46. Lois C, Alvarez-Buyalla A. Proliferating subventricular zone cells in the adult mammalian forebrain can differentiate into neurons and glia. *Proc Natl Acad Sci U S A* 1993;90:2074-7.
47. Kuhn HG, Dickenson-Anson H, Gage FH. Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. *J Neurosci* 1996;16:2027-33.
48. Eriksson PS, Perfilieva E, Bjork-Eriksson T, et al. Neurogenesis in the adult human hippocampus. *Nat Med* 1998;4:1313-7.
49. Rakic P. Adult neurogenesis in mammals: an identity crisis. *J Neurosci* 2002;22:614-8.
50. York A, Breedlove SM, Diamond MA. Increase in granule cell neurogenesis following exposure to enriched environments [abstract]. *Soc Neurosci Abstracts* 1989;15:602.
51. Kempermann G, van Praag H, Gage FH. Activity-dependent regulation of neuronal plasticity and self repair. *Progr Brain Res* 2000;127:35-48.
52. Gould E, Beylin A, Tanapat P, Reeves A, Shors TJ. Learning enhances adult neurogenesis in the hippocampal formation. *Nat Neurosci* 1999;2:203-5.
53. Gould E, Tanapat P. Lesion-induced proliferation of neuronal progenitors in the dentate gyrus of the adult rat. *Neuroscience* 1997;80:427-36.
54. Contestabile A. Roles of NMDA receptor activity and nitric oxide production in brain development. *Brain Res Rev* 2000;32:476-509.
55. Moreno-Lopez B, Noval JA, Gonzalez-Bonet LG, Estrada C. Morphological bases for a role of nitric oxide in adult neurogenesis. *Brain Res* 2000;869:244-50.
56. GrandPre T, Nakamura F, Vartanian T, Strittmatter SM. Identification of the Nogo inhibitor of axon regeneration as a Reticulon protein. *Nature* 2000;403:439-44.
57. Chen MS, Huber AB, van der Haar ME, et al. Nogo-A is a myelin-associated neurite outgrowth inhibitor and an antigen for monoclonal antibody IN-1. *Nature* 2000;403:434-9.
58. Prinjha R, Moore SE, Vinson M, et al. Inhibitor of neurite outgrowth in humans. *Nature* 2000;403:383-4.
59. Fournier AE, Strittmatter SM. Repulsive factors and axon regeneration in the CNS. *Curr Opin Neurobiol* 2001;11:89-94.
60. Caroni P, Schwab ME. Antibody against myelin-associated inhibitor of neurite growth neutralizes non-permissive substrate properties of CNS white matter. *Neuron* 1988;1:85-96.
61. Huang DW, McKerracher L, Braun PE, David S. A therapeutic vaccine approach to stimulate axon regeneration in the adult mammalian spinal cord. *Neuron* 1999;24:639-47.
62. Gage F, Bjorkland A, Stenevi U, Dunnett SB, Kelly PA. Intra-hippocampal septal grafts ameliorate learning impairments in aged rats. *Science* 1984;225:533-6.
63. Freed WJ, Morihisa JM, Spoor E, et al. Transplanted adrenal chromaffin cells in rat brain reduce lesion-induced rotational behavior. *Nature* 1981;292:351-2.
64. Olson L. On the use of transplants to counteract the symptoms of Parkinson's disease: background, experimental models, and possible clinical applications. In: Cotman CW, editor. *Synaptic plasticity and remodeling*. New York: Guilford Pr; 1985. p 485-505.
65. Kordower JH, Styren S, Clarke M, DeKosky ST, Olanow CW, Freeman TB. Fetal grafting for Parkinson's disease: expression of immune markers in two patients with functional fetal nigral implants. *Cell Transplant* 1997;6:213-9.
66. Hodges H, Nelson A, Virley D, Kershaw TR, Sinden JD. Cognitive deficits induced by global cerebral ischaemia: prospects for transplant therapy. *Pharmacol Biochem Behav* 1997;56:763-80.
67. Pascual-Leone A, Wassermann E, Sadato N, Hallett M. The role of reading activity on the modulation of motor cortical outputs to the reading hand in braille readers. *Ann Neurol* 1995;38:910-5.
68. Dixon CE, Hamm RF, Taft WC, Hayes RL. Increased anticholinergic sensitivity following closed skull impact and controlled cortical impact traumatic brain injury in the rat. *J Neurotrauma* 1994;11:275-87.
69. Kozlowski DA, Hilliard S, Schallert T. Ethanol consumption following recovery from unilateral damage to the forelimb area of the sensorimotor cortex: reinstatement of deficits an prevention of dendritic pruning. *Brain Res* 1997;763:159-66.
70. Nolte J. *The human brain: an introduction to its functional anatomy*. 4th ed. St. Louis: Mosby-Year Book; 1999.

71. Kochanek P. The simple model vs. the supermodel. Paper presented at: National Neurotrauma Society Annual Meeting; 2000 Nov 4; New Orleans (LA).
72. Meythaler JM, Peduzzi JD, Eleftheriou E, Novack TA. Current concepts: diffuse axonal injury-associated traumatic brain injury. *Arch Phys Med Rehabil* 2001;82:1461-71.
73. Barker RA, Dunnett SB. Neural repair, transplantation and rehabilitation. East Sussex: Psychology Pr; 1999.
74. Ramer MS, Priestley JV, McMahon SB. Functional regeneration of sensory axons into the adult spinal cord. *Nature* 2000;403:312-6. Comment in: *Nature* 2000;403:257, 259-60.
75. Muir K, Lees KR. Clinical experience with excitatory amino acid antagonist drugs. *Stroke* 1995;26:503-13.
76. Small SL. The future of aphasia treatment. *Brain Lang* 2000;71:227-32.
77. Musso M, Weiller C, Kiebel S, Muller S, Bulau P, Rijntjes M. Training-induced brain plasticity in aphasia. *Brain* 1999;122:1781-90.
78. Beeson PM, Rapcsak SZ, Plante E, Ramage A, Hirsch F, Trouard T. Broca's aphasia from the right hemisphere: a functional neuroimaging study [abstract]. Paper presented at: American Speech-Language-Hearing Association Convention; 1999 Nov 18-21; San Francisco (CA). p 144.
79. Hamdy S, Rothwell JC, Aziz Q, Thompson DG. Organization and reorganization of human swallowing motor cortex: implications for recovery after stroke. *Clin Sci* 2000;98:151-7.