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Neurobiology of Rehabilitation

Bruce H. Dobkin, MD
Department of Neurology, Director, Neurologic Rehabilitation and Research Program, Geffen School of Medicine, University of California Los Angeles, Reed Neurologic Research Center, Los Angeles, California 90095-1769, USA

Abstract

Rehabilitation aims to lessen the physical and cognitive impairments and disabilities of patients with stroke, multiple sclerosis, spinal cord or brain injury, and other neurologic diseases. Conventional approaches beyond compensatory adjustments to disability may be augmented by applying some of the myriad experimental results about mechanisms of intrinsic biological changes after injury and the effects of extrinsic manipulations on spared neuronal assemblies. The organization and inherent adaptability of the anatomical nodes within distributed pathways of the central nervous system offer a flexible substrate for treatment strategies that drive activity-dependent plasticity. Opportunities for a new generation of approaches are manifested by rodent and non-human primate studies that reveal morphologic and physiologic adaptations induced by injury, by learning-associated practice, by the effects of pharmacologic neuromodulators, by the behavioral and molecular bases for enhancing activity-dependent synaptic plasticity, and by cell replacement, gene therapy, and regenerative biologic strategies. Techniques such as functional magnetic resonance imaging and transcranial magnetic stimulation will help determine the most optimal physiologic effects of interventions in patients as the cortical representations for skilled movements and cognitive processes are modified by the combination of conventional and biologic therapies. As clinicians digest the finer details of the neurobiology of rehabilitation, they will translate laboratory data into controlled clinical trials. By determining how much they can influence neural reorganization, clinicians will extend the opportunities for neurorestoration.

Keywords

neurologic rehabilitation; neuroimaging; plasticity; neural regeneration

Neurologic rehabilitation has been a peculiar undertaking for modern medicine. More a clinical art than science since formal programs started about 60 years ago, diagnostic and treatment options have lagged behind other medical specialties. Care for the victims of war and of polio in the 1950s was organized around lengthy hospitalizations, because the burden of care was too great for families. The theories of educators, psychologists, and social scientists, along with highly selected data drawn from physiologists such as Sherrington,

Address for correspondence: Bruce H. Dobkin, MD, Department of Neurology, Director, Neurologic Rehabilitation and Research Program, Geffen School of Medicine, University of California Los Angeles, Reed Neurologic Research Center, 710 Westwood Plaza Los Angeles, California 90095-1769, USA.Voice: 310-206-6500; fax: 310-794-9486. bdobkin@mednet.ucla.edu.

served as an untested conceptual basis for rehabilitation services.[1] In the past 15 years, an infusion of studies from neuroscience on mechanisms of cell and neural network injury, development, activity-dependent synaptic plasticity, and motor control offer interesting hypotheses to be tested.[1] When added to new information about the induction of neurogenesis and axonal regeneration, a neurobiology for rehabilitation practices comes into focus.[2] The resources for neurorestoration include both intrinsic and extrinsic signals (TABLE 1). Success in applying these new approaches and demonstrating robust enough improvements in outcomes to warrant their potential risks will take thoughtful planning and execution of clinical trials. This review emphasizes the bases for enhancing motor skills.

Anatomical Reorganization

Cerebral Sensorimotor System

The cortex in humans contributes to reaching, grasping, individuated finger movements, and walking-related motor control. At least six motor projections, in addition to the dominant ones from the primary motor cortex (M1), excite the motor pools. Descending fibers from the primary sensory cortex (S1) also project within the corticospinal tract to the dorsal horns.[3] Axons from M1 pass through the posterior limb of the internal capsule, dorsal and ventral premotor neurons project through the knee, and the supplementary motor area (SMA) fibers pass through the anterior limb of the internal capsule. Dorsal and ventral cingulate fibers are distributed among the latter regions. For example, the macaque's L-6–S-1 neurons, which contribute to hindlimb stepping, receive descending corticospinal tract projections from about 24,000 neurons in M1, 6000 from SMA, 6200 from dorsal and ventral cingulate, 5000 from dorsal premotor, and 10 from ventral premotor cortices.[4] Each of these cortical regions interacts with visual, vestibular, aural, proprioceptive, cutaneous and other inputs to help plan, select, initiate, and maintain unilateral and bilateral skilled movements. Thus, the corticospinal tract, which includes some uncrossed fibers within the lateral and ventral funiculi, draws from neurons that are distributed and separated by somewhat different vascular territories. One assembly of neurons may partially compensate for loss of another when subjects find a strategy to activate spared neurons.

The neurons within M1 and other somatotopically organized sensorimotor regions are also mutable controllers of muscles and movements. Clusters of neurons connected by horizontal fibers alter their relative ability to represent a shoulder, wrist and finger movement depending on how much the practice of a skilled movement fires these neurons together.[5] Electrical stimulation of clusters of neurons in M1 in trains lasting 500 ms reveals cells within adjacent sites that conduct rather stereotyped, but commonly employed movements, such as elbow flexion or extension that depends on the initial position of the arm, a hand-to-mouth pattern for feeding, and defensive postures.[6] These homuncular organizations increase the flexibility of M1 in guiding complex actions. In addition, an injury that disrupts one assembly of neurons that participate in a movement may have nearby neurons come to represent aspects of that movement with motor skills retraining,[7] although some of the improvement in behavior may arise from other portions of the cortical, sub-cortical, or spinal motor network.[8]

Rapid representational plasticity has been demonstrated using transcranial magnetic stimulation (TMS) of motor cortex by the practice of simple directional finger movements, which can be augmented by neuromodulators such as amphetamine.[9,10] One correlate of learning-induced plasticity is the synaptic expression of long-term potentiation (LTP) and long-term depression (LTD) in neocortex[11] as well as in the hippocampus. LTP is associated with the proliferation of dendritic spines.[12] This morphologic change has been found in homologous cortex opposite from the site of an experimental sensorimotor cortical lesion when the unaffected limb works to compensate for the paretic one.[13]

Corticostriatal neurons from primary and secondary motor areas are distinct from those within the corticospinal tract and respond especially to sensory inputs associated with the direction and force of movements. Uninjured cortical descending tracts from crossed and uncrossed projections may play a greater role during rehabilitation based on their inherent connectivity, perhaps especially if sensory feedback to the sensorimotor cortices is as typical of the desired movement as feasible. Cues from therapists to evoke cognitive strategies that bring these regions into greater play during training may increase the level of descending drive on motoneurons of the spinal cord. For example, ventral premotor neurons are most active during shaping and grasping the hand to hold an object. A visual cue, such as an object, may engage these neurons to enable a subject with a hemiparetic hand to reach and grasp, a movement that cannot otherwise be initiated when no object is present. Imagining a movement and watching a movement will activate many of the nodes in the sensorimotor network that are also active when a person carries out the actual movement.[14,15] Thus, visual practice could produce the cerebral reiterations that increase synaptic efficacy for learning a skill.

Brain Stem Nodes

The brain stem contains centers that contribute to the initiation of rhythmic flexion and extension for walking. The basal ganglia and cerebellum project to these locomotor regions. The dorsal mesencephalic locomotor center and the mesopontine locomotor center with its cholinergic and glutaminergic cells activate the lumbar spinal central pattern generators (CPGs) when stimulated electrically or with certain drugs. These brain stem regions project to reticulospinal nuclei that pass bilaterally into the ventral funciuli, providing another route for spared cortical and brain stem drives to activate motoneurons for movements. This pathway provides a slower and less precise control for flexor movements than the direct descending corticospinal tract. Several brain stem pathways have been shown in animal models to generate new dendrites after being damaged. For example, the corticorubrospinal fibers, which participate in distal more than proximal upper extremity movements for grasping, show spontaneous collateral sprouting[16] from the intact hemisphere and functional reorganization[17] that includes the corticospinal tract. Of interest, atrophic rubrospinal neurons can be coaxed with neurotrophins to regenerate axons after a chronic SCI.[18] This pathway, with its connections to the cerebellum, can potentially substitute for corticospinal fibers for making fine hand movements.

The cerebellum monitors the outcome of every movement using proprioceptive inputs from the dorsal and ventral spinocerebellar tract. These inputs are also copied to the thalamus and

motor cortex, as well as the brain stem locomotor centers. The timing of coordinated movement sequences, as well as computations on the position, velocity, acceleration, and inherent viscous forces of the moving limbs, is partly orchestrated by the cerebellar nuclei and Purkinje cells. The great interest in these afferent signals within cortical regions for motor control suggests that motor skills training during rehabilitation should aim to optimize kinematic and kinetic inputs that are associated with normal walking, reaching, grasping, and pinching.

Spinal Cord Systems

The spinal cord of humans probably includes CPGs for locomotor movements. These neural circuits produce oscillating patterns of flexion and extension, independent of sensory input or supraspinal commands. Elemental CPGs may control different muscles around each joint. These oscillators are interlocked by intrinsic connections and by their responses to segmental afferents and descending command centers.

Evidence for pattern generation comes from experiments in vertebrates, including non-human primates, in which the spinal cord is transected in the low thoracic region and deafferented from all dorsal root inputs below that level. Electrical stimulation and monamines placed on the isolated lumbar cord produce alternating electrical activity in the ventral roots of limb flexors and extensors.[19] When cats and rats undergo spinal transection, their paraplegic hindlimbs lose the ability to step on a treadmill. With practice that emphasizes hindlimb loading and treadmill-induced hip extension, they regain alternating stepping movements, though the paws do not readily clear the surface. Noradrenergic agents may help initiate stepping and the training has lasting effects.[20,21] The cats and rats generally cannot step very well over ground with their hindlimbs, however. Animals trained to stand, rather than to step, walk poorly on the treadmill, pointing to the specificity of the type of practice on spinal cord learning.[22] These findings suggest that a CPG is at work. Evidence for a CPG in humans has been found in both the spontaneous rhythmic movements made by some patients after SCI[23,24] and from the evolution of EMG activity in the legs of patients with paraplegia who are manually stepped on a treadmill[25] or undergo electrical stimulation of the dorsal horns at L-2.[26]

Modulation of the CPG involves the organization of several neurotransmitters that seem to be conserved from lampreys to mammals[27–29] For example, glutaminergic reticulospinal neurons excite ipsilateral spinal motoneurons and interneurons and contralateral glycinergic inhibitory neurons. Glycinergic neurons also have axons that cross to the opposite half of the spinal cord CPG. Other amines and peptides modulate the initiation, maintenance, and termination of cell bursts. Metabotropic receptors for serotonin (5-HT), gamma-aminobutyric acid (GABA), and glutamate are also activated within the CPG network during locomotion. These neurotransmitters could be restored to the lumbar cord after a brain or SCI by systemic or intrathecal drugs, by implanted cells that release a neurotransmitter, or by regeneration of specific axons.

Other intrinsic systems may contribute to the flexibility of spinal control for reaching and for walking. A small set of modules appear to store components of flexor and extensor synergistic movements within the typical workspace of the extremities.[30] The modules may

be activated in chains to achieve functional movements. This synaptic organization probably shares connections with the CPG and responds to segmental sensory inputs and descending controllers of the kinematics for reaching into space and walking.[31] In addition, interconnections among columns of motor pools via propriospinal pathways aid postural adjustments and movement during reaching and ambulation, as do spinal reflex pathways and vestibulospinal inputs.

Sensory inputs provide a powerful source for functional modulation of the CPG, as well as for positive and negative force feedback during walking.[32] In studies of higher vertebrates and human subjects, cutaneous inputs from the sole and Ia and Ib inputs to the hips and ankles are especially important drives for walking.[32,33] For example, the spinal cord responds to varying levels of weight bearing on the legs in patients with clinically complete SCI, reflected in changes in the amplitude and timing of electromyographic bursts from lower extremity muscles.[34] Studies of cats and humans reveal the impact of the timing of hip extension at the end of stance of one leg and simultaneous loading of the opposite leg for successful initiation of the swing phase.[35,36] These sensory inputs presumably contribute to the internal models the brain possesses about the properties of limbs and limb mechanics.[37]

Neurobiologically Based Interventions for Patients

Exercise and practice are the *sine qua non* in rehabilitation for regaining the ability to walk, reach, grasp, and carry out self-care and community activities. Greater intensity of task-specific practice tends to improve motor[38–44] and cognitive[45,46] outcomes for what patients practice. The optimal style, intensity, duration, and feedback needed to relearn most skills have not yet been established. Practice does induce activity-dependent adaptations within the distributed neural networks needed for skilled movement and produces cortical representational plasticity.[47,48]

Motor Control

Theories about motor control and the acquisition and recall of motor skills are beginning to play an important role in the development of more sophisticated rehabilitation strategies. M1 is involved in the initial phase of learning a motor skill, as well as in early consolidation from an unstable to a stable state.[49] Lasting learning of a simple, but novel motor skill in non-human primate studies requires a considerable number of practice repetitions, from 300–1500, to reveal behavioral and neuronal reorganization changes.[50,51] After a brain or spinal cord lesion, the nervous system has less information about how to select, initiate, and correct movements, and even the mechanical properties of the joints and muscles may change, so both attempted actions and the process for relearning functional movements may suffer. Even greater intensity and duration of practice become necessary.

Many parameters for an internal model of interactions with the environment have been investigated. At the neuronal level, for example, firing rates during learning to reach to a target at a specific angle within the body's workspace increase within the subpopulation of cells that are preferentially tuned to the direction of the target. This activity seems most related to a modification in the internal model of movement kinematics for computation of a visuomotor transformation, rather than to movement dynamics.[52] One especially relevant

theory of motor control suggests that enough feedback control for movement can be obtained from optimal estimates of the state of a limb, using parameters such as joint angles or muscle lengths.[37,53,54] The system controls the global goal of a task from low-level signals, each concerned with a portion of the system. Errors that influence motor performance are corrected and signals that are not relevant are ignored. This theory suggests that spared neural nodes may be able to act as controllers by optimally selecting afferent feedback.

Another theory suggests that neural signals may explicitly encode the endpoint of the limb, such as the cat's paw during walking, and that the dorsal spinocerebellar tract provides this kinematic information.[31] Translating models built upon studies in cats with their bi-articular hindlimb muscles into humans may be misleading, however, since these muscles may naturally reflect end-points more than joint angles. Another point of view is that the brain may issue motor commands based on a prediction of the forces for an upcoming movement. An internal model of experienced forces also generalizes to upper extremity parameters such as velocity and position in space.[55,56] Activation of the N-methyl-D-aspartate (NMDA) receptor and inhibition by GABA were shown to be involved in the acquisition, but not the recall of a new internal model of the dynamics for reaching.[57] These theories are important to the neurobiology of rehabilitation, because they help set the tone for styles of practice, the sensorimotor parameters to be monitored to optimize training, the neural pathways that need to be engaged for skills learning, and the potential for pharmacologic interventions to augment motor learning.

Massed Practice of Task-Oriented Motor Skills

The essence of therapy for any disability is *practice*. A practice session can have a powerful, but only temporary effect. A positive effect on performance during a training session by repeatedly practicing the same movement may not lead to long-term learning. Studies of interventions should include a doseresponse curve to establish how much practice is needed to achieve a retraining goal. During practice, contextual interference from intermixing other related tasks may enhance learning, unless cognitive impairment impedes attention or procedural learning.

Treadmill Training

Body weight-supported treadmill training (BWSTT) was derived from the treadmill training approach for cats after complete spinal cord transection in studies of CPG activity. BWSTT, in theory, allows the spinal cord and supraspinal locomotor regions to experience sensory inputs that are more like ordinary stepping compared to the atypical locomotor inputs created by compensatory gait deviations and difficulty loading a paretic limb.[58,59] More typical proprioceptive and cutaneous input, as noted earlier, may improve the timing and increase the activation of residual descending locomotor outputs on the motor pools. Most important, BWSTT allows massed practice at different walking speeds and levels of limb loading with repetitions guided by the cues of the therapist. Randomized clinical trials for patients with hemiparetic stroke have produced mixed results,[60,61] but treadmill speeds have not been optimized.[44] A multi-center trial of patients with acute incomplete SCI tried to optimize training at high treadmill and overground walking speeds for 12 weeks with best-

of-possible kinematics and kinetics, but demonstrated no significant differences from the conventionally trained subjects.[62] The trial established a reproducible retraining approach that can serve as an experimental control for the style and intensity of locomotor rehabilitation in future clinical trials of pharmacologic and biologic interventions.

Constraint-Induced Movement Therapy (CIMT)

Rehabilitation practice-induced neuroplasticity and behavioral gains have been repeatedly demonstrated for the upper extremity in patients who retain at least modest motor control.[63] In the most common paradigm, subjects practice with a therapist for at least six hours a day for two weeks on a variety of tasks with the affected arm plus restraint of the normal hand for most of the day. These patients can, at onset, dorsiflex the wrist at least 10 degrees and partially extend the fingers of the paretic hand.[64,65] Less intensity may work as well.[66] The most important aspect of this approach is massed practice and feedback about movement skills that are important to the subject, rather than the type of restraint. Animal models of forced use early after an ablative or traumatic focal cortical injury suggest an increase in the volume of the lesion and behavioral deficits, probably on the basis of glutaminergic toxicity.[67] The intensity of use of the limb, however, was far greater than any clinical situation could allow. Forced nonuse of the limb affected by experimental damage restricted to the striatonigral dopamine projections, in contrast, augmented dopamine loss and Parkinsonian symptoms.[68] One acute clinical trial of the approach showed positive results[64] and data from a multicenter trial for hemiparetic patients who are 3–9 months post-stroke are pending.[69]

Biofeedback and Automated Robot-Assisted Devices

Biofeedback (BFB) includes a variety of instrumented techniques that try to make the treated subject aware of physiologic information that can be used to better train an activity. Electromyographic BFB to increase the amplitude of muscle contractile bursts, decrease co-contraction of muscles, improve the timing of a contraction, can enhance skilled movements.[70] Robotic devices aim to maximize practice with only intermittent therapist oversight.[1] One robotic exoskeleton manipulates a patient's paretic elbow and shoulder by a two-degrees-of-freedom impedance controller system, much as a therapist might provide hand-over-hand therapy for reaching in a plane across a table. Motor power and control improved at the shoulder and elbow with this form of robotic training, consistent with the greater intensity of practice with those muscle groups.[71] Active participation improves function more than passive movement, as might be expected during motor learning.[72] By providing data on the intensity, duration, and accuracy of practice, these devices allow future studies of parallels between therapy-induced behavioral gains and activitydependent reorganization, perhaps monitored by functional neuroimaging techniques.

Pharmacologic Augmentation

Any neurobiology of rehabilitation must consider the potential to augment training strategies with medications that act on neurotransmitters, neuromodulators, and intracellular second messengers. The goals include strengthening synaptic efficacy within perilesional neurons and other nodes of the motor network during task learning, replenishing neurotransmitter

projections that have been disconnected to reverse diaschisis, and preventing transsynaptic degeneration of neurons.

Among these drugs, dextroamphetamine increases the cortical signal-tonoise ratio.[73] Cholinergic projections serve as a gate for behaviorally relevant sensory information.[74] Human and animal studies have provided preliminary evidence that a variety of medications, such as dopaminergic and noradrenergic,[75–78] cholinergic,[79] and serotonergic[80] agents, may facilitate the rate or degree of motor recovery. Drugs, along with other neurostimulatory approaches, may augment gains in slow learners more than in subjects who can quickly learn a skill.[73,81] Drugs may also activate or inhibit subcomponents of the distributed sensorimotor system, such as the CPG.[21] Blockers of dopamine and norepinephrine may inhibit skilled motor gains,[82] perhaps depending on the time of use in relation to the injury.[83] A few studies suggest that intensive speech therapy combined with a drug that enhances vigilance or learning may benefit patients who have adequate language comprehension.[84,85] The rapid growth in knowledge about the molecules that modulate learning, such as agonists of the NMDA receptor, cyclic nucleotide adenosine monophosphate (cAMP), and cAMP response element binding protein (CREB), is leading to the possibility of new lines of drugs to augment rehabilitation strategies.[86,87]

Controlled trials of anti-spasticity agents have varied widely in the target symptoms managed and the outcome assessments employed.[88–91] Functional gains related to walking and use of the upper limbs are often marginal. However, a medication that prevents disabling spasms may improve quality of life. Continued basic studies of the neurobiology of spasticity, such as the windup of flexion reflexes and other physiologic changes induced in the cord by loss of supraspinal input, are needed.[92–94]

Randomized trials that compare a rehabilitation intervention combined with an experimental drug versus a placebo require considerable thought. For example, both the dose of medication and the dose of the rehabilitation strategy need to be optimized and adverse effects need to be minimized. Outcome measures should be sensitive to important changes in function and relevant to the intervention. The choice of pharmacologic augmenting agent, at least for sensorimotor studies, may be developed from TMS, positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) studies that reveal a drug-induced increase in cortical excitability, rapidly induced plasticity in M1, or change in neurotransmitter levels in patients.[95–97]

Neurostimulators and Neuroprostheses

Regional electrical stimulation of the cortex, deep nuclei, spinal cord, and motor unit could augment retraining. Phasic electrical stimulation of nervemuscle can stimulate genes to increase muscle fiber volume. When optimal afferent stimulation parameters are employed, peripheral electrical stimulation can augment cortical excitability and reorganization to enhance motor skills,[98] especially if coordinated with retraining. Deep brain and vagal nerve electrical stimulators and subdural or implanted cortical arrays may drive excitatory and inhibitory outflow to the forebrain and brain stem.[99] In theory, finding the optimal parameters for stimulation could modulate attentional drives and frontal lobe executive functions[100] and augment the acquisition of procedural or declarative learning. Repetitive

TMS is another potential tool to excite or inhibit cortical pathways for sensorimotor[81] or affective and cognitive processes such as hemi-attention.[101,102]

Neuroprostheses have used local cortical potentials to control an electrical stimulator for anticipated movements.[103] Brain-computer interfaces that employ a variety of brain signals to communicate or to control a prosthesis without muscle stimulation[104] and neuroelectronic chips implanted into the brain to make a circuit[105] may both add to our understanding of the neurobiology of the brain and enhance functional outcomes for highly impaired patients.

Plasticity Induced by Therapies for Patients

Functional neuroimaging using PET, fMRI, TMS, and other modalities reveals cerebral synaptic activity that accompanies normal motor and cognitive processing and learning, evolving changes induced by an injury, and reorganization associated with a rehabilitative intervention. These techniques, despite their individual limitations,[1,106] provide a microscopic view of trainingrelated experience-dependent plasticity.

After an experimental sensorimotor cortical stroke in rats, improved neurologic function correlates with the amount of shift of activation from the initial contralesional homologous cortex back to the ipsilesional cortex. Thus, functional gains are most readily associated with sparing of tissue or restoration of synaptic activity by intrinsic and extrinsic mechanisms (Table 1).[107] Studies of stroke in patients, mostly assessing upper extremity distal movements, reveal similar findings.[108] Using PET and fMRI, correlations of regions of activation with the amount of recovery have been found for the ipsilesional cerebellum,[109] contralateral premotor and secondary sensory cortices,[110] perilesional activity, and an overall decrease in activity over the course of behavioral gains within the sensorimotor network.[111] Regions associated with working memory, attention, and planning are often more active compared to healthy subjects. Behavioral gains for finer motor skills may run more in parallel to the relative sparing of the corticospinal tract, determined by less wallerian degeneration, than to the balance of activation in ipsilateral compared to contralateral M1.[112]

Insights into relationships between activity in the nodes of the distributed motor system after brain or spinal cord injury and gains in task-related motor skills may be pursued with greater correlative power by associated with a defined rehabilitation strategy and repeated over predefined intervals until no further changes in behavior or representational plasticity are found. The therapy should promote intensive practice of functionally important movements, then employ an activation paradigm that directly uses some portion of the skilled movements that were practiced. A few interventional studies do reveal reorganization within M1[63] and related nodes for upper limb movements[110,113] and for walking.[114] Other specific rehabilitation approaches have revealed associations between behavioral gains and reorganization.[45,115] The relationships, however, between specific motor, language, and other cognitive improvements and the size and location of cortical and subcortical activations are still uncertain.

Functional neuroimaging holds promise for serving as a physiologic marker for whether a physical, cognitive, pharmacologic, or biologic intervention engages regions of interest in a

functional network, activates mechanisms of reorganizational plasticity, and leads to adaptations in parallel to the intensity, duration, and efficacy of a therapy. If relationships between cortical maps and important behavioral outcomes can be made for subjects with differing lesions and impairments, then functional imaging protocols may come to have early predictive abilities about whether a treatment is likely to work and how much of a defined rehabilitation therapy is enough.

Augmentation of Rehabilitation by Neural Repair

A variety of models of stroke, TBI, and SCI provide insights into approaches for neural repair–mediated rehabilitation.[1] Axonal sprouting[116,117] and neurogenesis[118] shortly after stroke depend upon signals from the environment that may differ from within the lesion itself, its penumbral periphery, and adjacent normal tissue.[119] Ischemia appears to facilitate LTP, in part by reducing perilesional GABAergic inhibition and increasing glutamate receptor stimulation.[120] Thus, the penumbra is potentially a field for activity-dependent plasticity. The migration and differentiation of neural progenitor cells and regenerating axons and their incorporation into a functional matrix will depend in part on their responsiveness to evolving environmental cues and gene expression.[121]

Experimental interventions to stimulate functional recovery include intralesional grafts of fetal cortex, stem cells, and progenitor cells,[122] as well as intravenous injection of marrow stromal cells.[123] Behavioral gains in animal models have been modest, but increase with exercise and an enriched environment.[124] Such gains may be related more to trophic or other effects of the cells, rather than to new synaptic connections. Near future trials in patients will test the therapeutic potential for targeting myelin-associated inhibitory substances produced by oligodendrocytes, such as myelin-associated glycoprotein (MAG), oligodendrocyte-myelin glycoprotein (OMGP), and Nogo-A. Neurite growth inhibition is caused by their Nogo-66 and amino-Nogo domains when oligodendrocytes, periaxonal CNS myelin, and myelin debris are exposed by an injury. When the receptor complex is signaled by one of these inhibitory substances, a small guanosine triphosphotase (GT-Pase) called Rho and other cascades of intracellular activity stop support for the growth cone. For example, neurite and axonal outgrowth increased in the adult rat's uninjured cortex associated with improved control of the affected forepaw 6 weeks after an antibody to Nogo-A was injected.[125]

Axonal regeneration after experimental SCI is also increased by injecting antibodies to Nogo and MAG, as well as by blocking the Nogo receptor or its intracellular pathways.[126–130] Partial reversal of this inhibition has been accomplished using an intrathecal infusion of the small peptide NEP1–40, which inhibits binding of Nogo-66 to the Nogo receptor.[128] The inhibition of Rho using small antagonist molecules such as C3-05, which is an ADP ribose transferase, may eventually accomplish the same effect in patients.[130] In addition, inactivation of Rho may lessen delayed cell death, which could be of clinical value in patients with gray matter involvement from a cervical or conus SCI.[131] A related approach is to increase the amount of the second messenger cAMP, which induces genes to activate protein kinase A and to synthesize polyamines.[132] An increasing number of

signaling interactions are being found between cAMP, Rho, and neurotrophins for axonal regeneration.

Other animal studies in SCI have aimed to dissolve glycoproteins that inhibit growth cones by local injection of chondroitinase; provide a gradient of neurotrophins or other axon guidance molecules to attract the growth cone; turn on genes that produce growth-, microtubule-, and neurofilament-associated proteins; bridge a cystic cavity with nerve filaments, biopolymers that contain regenerative substances, and neural cells within a nurturing biologic scaffold; implant embryonic neural tissue, stem cells, or neural progenitor cells that may integrate; inject Schwann cells or olfactory ensheathing glia derived from olfactory epithelium that can myelinate axons; implant cells such as fibroblasts genetically modified to secrete neurotrophins; stimulate intrinsic neurogenesis; and reimplant ventral roots from below to above a lesion.[133–135] Human studies have begun to build upon one or more of these approaches.

The first published reports of implantation of a human neuronal cell line into the cavity left by an infarct near the basal ganglia and internal capsule in human subjects demonstrated relative safety[136] and survival of the cells.[137] Efficacy studies are pending. The strategy seems even less likely to reveal functional gains than the slowly emerging human experiments with cell implants for Parkinson's disease, however.[138] In theory, human implants into the brain after stroke may replenish some portion of trophic and other neurohumoral or neurotransmitter substances, provide a bridge for regeneration of host axons, make local synaptic connections, or replace damaged neural elements, but seem unlikely to be incorporated into a complex neural network such as the striatum. Verbal reports describe safety studies of cell implants in patients with multiple sclerosis to remyelinate axons in patients. Unpublished reports from Asia and other regions outside North America tell of transplantation of fetal tissue, olfactory ensheathing cells, and construction of peripheral nerve bridges in humans after SCI (<www.carecure.atinfopop.com>).

Relevance of Animal Models

Much of the neurobiology of rehabilitation is drawn from animal models of injury and repair.[1] The translation of these experiments into rehabilitation interventions is not likely to proceed without discouraging setbacks, if the experience with acute neuroprotective interventions in patients with stroke, SCI and cerebral trauma holds.[139–142]

Type of induced injury, timing of the intervention, location of lesion, relative volume, natural history of recovery, co-morbid conditions, sex and age, levels of activity, and other factors are controlled in laboratory experiments, but not in patients.[140,142–145] Laboratory animals are bred and maintained in relatively unchallenging, impoverished and stressful circumstances, which may make their biologic responses to an injury different from wild rodents and humans.[146,147] Highly inbred rodent strains and transgenic mice allow the study of particular processes of injury and repair, but the cascades of gene expression over time and cellular and molecular changes in the milieu may not unfold in another strain or species, or in humans. Even sensorimotor, locomotor, and cognitive abilities vary between laboratory animal strains,[148] which may confound outcome measurements.

The pathways taken by neural cells and axons during development span distances of a few mm under the outer surface of the neural tube. The paths to targets are both short and sweet —multiple guidance signals that constrain and beckon appear in an orderly sequence within a highly organized, canallike matrix of capillaries and glia. For neural repair in adults, the distances that cells may have to migrate or axons regenerate differ dramatically between humans and rodents. The surface area of a mouse brain is 1/1000th that of the human brain. About 20 cross-sections of the rat lumbar cord can be superimposed within the cross-sectional area of the human cord.[134] Regenerating axons and collateral sprouts in experiments usually extend only 10–15 mm below a spinal cord lesion. Successful biologic interventions in animal studies reveal only modest numbers of short-lived, regenerating cells in models of stroke[118] and modest numbers of regenerating axons after manipulations for SCI.[149–152] As with transplanted cells, the axons must operate within an environment that lacks the ideal ratio of signaling substances and targets that made survival, migration, and functional connectivity over tiny distances an evolutionary wonder that is the study of developmental neurobiology.

Still, if 10% of a supraspinal pathway can be restored,[153,154] then aumented by collateral sprouting, enough connections for rebuilding simple skills may be in place, even if the new inputs only reach propriospinal pathways below a spinal cord injury. Rehabilitation strategies that make use of the neurobiology underlying skills learning within a flexible, distributed motor system can then incorporate newly connected nodes into the motor controllers that lessen the disability of patients.

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Table 1
Potential biological mechanisms for neurorestoration

Intrinsic
Restore excitation, inhibition, and modulation by neurotransmitter projections to reverse diaschisis
Alter ion channel changes to reverse conduction block
Activate neuronal intracellular signaling for trophic functions
Increase synaptic efficacy
Denervation hypersensitivity of postsynaptic receptors
Activity-dependent unmasking of synapses
Hebbian experience–dependent long-term potentiation
Modulate basal synaptic transmission by changes in membrane- or neurotransmitter-mediated excitability
Upregulate number or type of receptors, e.g., AMPA receptors
Axonal and dendritic collateral sprouting
Axonal regeneration
Remyelination
Neurogenesis
Extrinsic
Rehabilitation training-induced plasticity
Preserve neurons and axons by acute neuroprotection: block glutamate and free radical toxicity
Prevent apoptosis and transsynaptic degeneration: neurotrophins, caspase inhibitors
Prevent glial scar: modulate immune response and extracellular matrix molecules
Replace neurotransmitters or activate second messenger cascades: norepinephrine, dopamine, serotonin, acetylcholine, cAMP
Improve axon conduction: 4-aminopyridine potassium channel blockade
Sprout uninjured axons and dendrites: neurotrophins
Regenerate axons: increase intracellular signaling for actin and cytoskeletal proteins: neurotrophins BDNF, NT-3, GDNF; NCAMs; inhibit Rho or block Nogo receptor; chondroitinase to inhibit proteoglycans
Guide axons to targets: gradient of neurotrophins and laminin; modulate chemoattractants and repellants (netrins, semaphorins)
Remyelinate axons: implant olfactory ensheathing cells, oligodendrocyte precursors
Replace neurons and glia: implant stem cells, neural precursors
Reimplant ventral roots to key muscles or bladder
Prevent muscle atrophy; resistance exercise; drugs that alter myosin proteins
Replace a neural network: silicon biochips, microstimulators, neuroprosthetic brain-to-muscle bypass

Abbreviations: AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic; cAMP, cyclic adenosine monophosphate; BNDF, brain-derived neurotrophic factor; NT-3, neurotrophin-3; GDNF, glial-derived neurotrophic factor; NCAM, neural cell adhesion molecule.

Adapted from Dobkin.[1]