

PLASTICITY IN THE DEVELOPING BRAIN: IMPLICATIONS FOR REHABILITATION

Michael V. Johnston*

Departments of Neurology, Pediatrics and Physical Medicine and Rehabilitation, Kennedy Krieger Institute and
Johns Hopkins University School of Medicine, Baltimore, Maryland

Neuronal plasticity allows the central nervous system to learn skills and remember information, to reorganize neuronal networks in response to environmental stimulation, and to recover from brain and spinal cord injuries. Neuronal plasticity is enhanced in the developing brain and it is usually adaptive and beneficial but can also be maladaptive and responsible for neurological disorders in some situations. Basic mechanisms that are involved in plasticity include neurogenesis, programmed cell death, and activity-dependent synaptic plasticity. Repetitive stimulation of synapses can cause long-term potentiation or long-term depression of neurotransmission. These changes are associated with physical changes in dendritic spines and neuronal circuits. Overproduction of synapses during postnatal development in children contributes to enhanced plasticity by providing an excess of synapses that are pruned during early adolescence. Clinical examples of adaptive neuronal plasticity include reorganization of cortical maps of the fingers in response to practice playing a stringed instrument and constraint-induced movement therapy to improve hemiparesis caused by stroke or cerebral palsy. These forms of plasticity are associated with structural and functional changes in the brain that can be detected with magnetic resonance imaging, positron emission tomography, or transcranial magnetic stimulation (TMS). TMS and other forms of brain stimulation are also being used experimentally to enhance brain plasticity and recovery of function. Plasticity is also influenced by genetic factors such as mutations in brain-derived neuronal growth factor. Understanding brain plasticity provides a basis for developing better therapies to improve outcome from acquired brain injuries.

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Plasticity is one of the most prominent features of the central nervous system (CNS) and denotes several capacities including the ability to adapt to changes in the environment and to store information in memory associated with learning [Johnston, 2004]. Children appear to learn more quickly than adults and can easily acquire new languages if exposed early in life. Skills such as playing a musical instrument and the ability to play sports such as golf or baseball are easier to acquire in childhood. It is well known that impaired vision early in life from strabismus or ocular disorders can lead to permanent amblyopia because of reorganization of central visual pathways, and early hearing impairment can lead to impaired central auditory perception. Children also recover from certain brain injuries more readily than adults. For example, older children who undergo surgical removal of one

hemisphere for refractory epilepsy can regain the ability to walk after surgery [Holloway et al., 2000]. Understanding the mechanisms responsible for brain plasticity and how they can be influenced to improve outcomes after brain injuries are areas of knowledge important for all neuroscience clinicians.

MECHANISMS FOR PLASTICITY IN THE CENTRAL NERVOUS SYSTEM

Several mechanisms that involve neuronal plasticity stand out as important contributors to the developing brain's ability to acquire new information, change in response to environmental stimulation, and recover from injury [Johnston et al., 2009]. The processes that control neurogenesis and cell death by apoptosis are carefully controlled in fetal life to assure that proper number of neurons take their places in each region of the brain during the second trimester. Studies in animals indicate that there is a marked overproduction of neurons in the fetus when compared with the final number in the mature brain, and that the final complement is determined by programmed cell death as well as by the programs for neurogenesis [Rakic, 2000]. Mice with mutations in genes for caspase enzymes involved in apoptosis have reduced cell death in fetal life and develop an expanded cerebral cortex that is too large for the skull [Haydar et al., 1999]. Overproduction of neurons could be adaptive for the brain by creating a reservoir that is available to repair injury in the fetus. Recent evidence indicates that neurogenesis persists beyond the fetal period and into adulthood in certain areas of the brain including the subventricular zone of the lateral ventricles and the subgranular zone of the dentate gyrus of the hippocampus [Toni et al., 2008]. In neonatal rats with experimental hypoxic-ischemic injury, sustained neurogenesis persists in the subventricular zone for months after injury and continues to populate the cerebral cortex with new neurons [Yang et al., 2007]. A similar phenomenon has been shown to occur in adult rodents after stroke [Lichtenwalner and Parent, 2006]. Newborn neu-

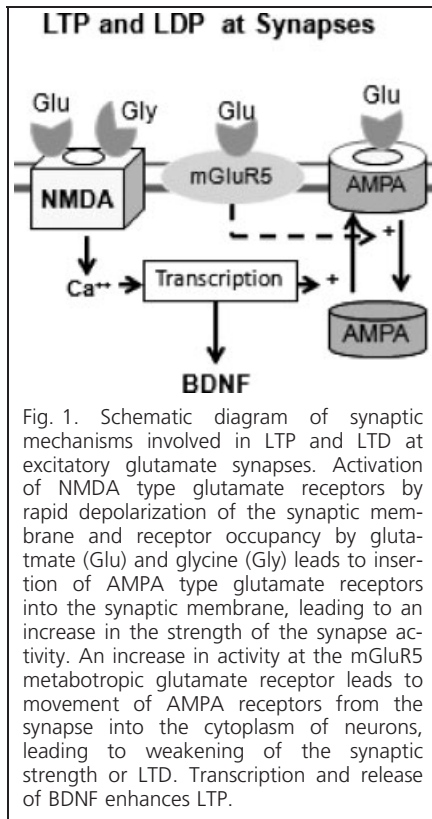
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*Correspondence to: Michael V. Johnston, Kennedy Krieger Institute, 707 North Broadway, Baltimore, MD 21205. E-mail: Johnston@kennedykrieger.org

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rons integrate into existing circuits and could contribute to recovery from injury. In addition to their potential role in replacing damaged neurons, newborn stem cells have been shown to have a protective effect when injected within days after injury, possibly by expressing growth factors [Comi et al., 2008].

ACTIVITY-DEPENDENT NEURONAL PLASTICITY

In addition to modulation of neurogenesis, changes in the strength of synapses and reorganization of neuronal circuits also play important roles in brain plasticity. Synaptic plasticity refers to changes in the strength of neurotransmission induced by activity experienced by the synapse in the past. Changes in the frequency or strength of activation across synapses can result in long-term increases or decreases in their strength, referred to as either long-term potentiation (LTP) or long-term depression (LTD), respectively (Fig. 1) [Citri and Malenka, 2008]. These activity dependent changes occur in all excitatory synapses that use glutamate as their neurotransmitter as well as in some inhibitory GABAergic synapses [Nugent and Kauer, 2008]. They can be mediated by changes in the release of neurotransmitter from presynaptic terminals as well as changes in the number of excitatory receptors on postsynaptic neurons. LTP

can be produced experimentally by rapid repetitive presynaptic stimulation of synapses on pyramidal neurons in the CA1 region of the hippocampus and this is the best studied form of synaptic plasticity. Rapid stimulation of synapses opens NMDA-type glutamate receptors in the postsynaptic membrane leading to an increase in intracellular calcium and insertion of AMPA type glutamate receptors in the postsynaptic membrane. AMPA receptors move into the postsynaptic membrane from a receptor pool located in endosomes within the cytoplasm of dendritic spines through a process called receptor trafficking. Activation of signaling cascades, including calcium calmodulin II (CaMKII), by calcium fluxed through NMDA channels plays an essential role in this process. Release of the neuronal growth factor brain-derived neuronal growth factor (BDNF) from electrically active neurons enhances the formation of LTP, and this process is associated with an enlargement of dendritic spines. [Hartmann et al., 2001] LTP is enhanced in the immature brain as compared to the adult brain [Crair and Malenka, 1995].

In contrast to LTP, LTD is produced by slow repetitive stimulation of excitatory synapses and is related to a reduction in AMPA receptors in the postsynaptic membrane as they move into the cytoplasm into endosomes [Citri and Malenka, 2008]. Another form of LTD is caused by the stimulation of type I metabotropic glutamate receptors that activate phosphoinositide turnover in dendritic spines. This form of plasticity is prominent in the cerebellum. LTP is associated with memory formation in the hippocampus, and LTP and LTD form the basis for activity-dependent reorganization and stabilization of developing neuronal networks in sensory-motor cortex [Feldman et al., 1999]. Prolonged in vivo imaging of neurons in rodent cerebral cortex indicates that sensory experience drives the continuous sprouting and retraction of synapses located on dendritic spines to remodel neural circuits [Trachtenberg et al., 2002]. Similar mechanisms are probably responsible for enhanced excitability in cerebral cortex that has been documented following short periods of motor skill training using the hands or lower legs [Perez et al., 2004].

OVERPRODUCTION AND PRUNING OF SYNAPSES IN THE DEVELOPING BRAIN

Development of the cerebral cortex in children is characterized by an

early postnatal burst in synaptogenesis followed by activity-dependent pruning of excessive synapses later in the postnatal period [Huttenlocher and Dabholkar, 1997]. This phenomenon probably contributes to cortical plasticity by providing an excess of synapses to be selected based on experience during childhood. A burst in synapse production begins in the occipital cortex in the early postnatal period, rising to a density that is approximately twice that in the adult brain by age 2 years, then falling to adult levels by early adolescence [Huttenlocher and de Court, 1987]. Similar waves of synaptogenesis that occur in parietal-temporal and then frontal regions lag behind those in visual areas, peaking at around early adolescence in the case of the frontal lobes. There is a general correlation between behavioral development and temporal periods of dynamic changes in synaptic number in specific cortical regions. For example, patching the eye with good vision to reverse unilateral amblyopia related to strabismus is less effective after age 12, at the same time when synapse number in the occipital lobes is rapidly declining [Holmes et al., 2006]. Synapse counts in frontal lobe postmortem cortex showed that they remained elevated above adult levels well into the teens, consistent with the relatively prolonged period required for development of mature judgment [Huttenlocher, 1990]. Magnetic resonance imaging-based (MRI) measurement of cortical thickness in a longitudinal sample of children aged 7–19 years showed a trajectory of early thickening followed by thinning. Children with superior intelligence have a more plastic cortex with greater initial acceleration and a prolonged phase of increase in cortical thickness compared to average and high intelligence children, especially in the prefrontal cortex [Shaw et al., 2006]. This supports the hypothesis that a prolonged period of overproduction and pruning of synapses in children and young adults contributes to their capacity for plasticity and learning.

VULNERABILITY ASSOCIATED WITH PLASTICITY MECHANISMS IN THE DEVELOPING BRAIN

The enhanced plasticity mechanisms present in the developing nervous system allow it to be influenced more strongly by the environment than the adult brain, but these mechanisms can also create vulnerabilities. On the plus side the developing brain, especially in

rodent models, is positively influenced by environmental enrichment [Nithianantharajah and Hannan, 2006]. Enriched cage environments for rodents and opportunities for exercise lead to increases in neurogenesis, dendritic branching, number of dendritic spines and size of synapses. Enrichment can also lead to increases in neurotrophins, expression of excitatory amino acid receptors, angiogenesis as well as in learning and memory ability. On the other hand, developing neurons are dependent on a stable level of neuronal depolarization and are vulnerable to loss of stimulation by excitatory neurotransmitters. Accordingly, the developing nervous system in children is more vulnerable to sensory deprivation and abuse than adults [McDonald and Johnston, 1990]. For example, infant rodents demonstrate extensive neuronal apoptosis in response to sciatic nerve lesions, leading to more restricted cortical reorganization than adults from similar lesions [Cusick, 1996]. Neonatal rodents are also more prone to apoptosis from trauma and hypoxia-ischemia than adults, probably related to the importance of apoptosis in normal developmental programs [Nakajima et al., 2000]. The developing brain is also more vulnerable to drugs that impair neuronal activity, such as glutamate antagonists and GABA agonist sedatives [Ikonomidou et al., 2001]. The developing brain's enhanced excitability at glutamate synapses, which enhances plasticity, also makes it more vulnerable to seizures and excitotoxicity than the adult brain [Johnston, 2005]. This means that the developing brain's greater plasticity does not always translate into greater recovery from injuries.

STRUCTURAL CHANGES IN BRAIN CIRCUITRY CAUSED BY EXPERIENCE

There is abundant evidence that the structure of certain brain circuits can change in response to environmental stimuli [Chen et al., 2002]. This effect was first established in great detail for the visual system in the experiments of Hubel et al. [1977] on ocular dominance plasticity dating from the late 1950s. The first experiments to demonstrate this effect in the somatosensory cortex used the neonatal mouse after selective surgical removal of whiskers from the animal's snout [Inan and Crair, 2007]. The mouse's whiskers are represented in a spatial map on the surface of the contralateral somatosensory cortex and the map can be visualized in tan-

gential sections using histological markers such as stains for cytochrome oxidase activity. Whiskers in the mouse are represented by a relatively large map on the surface of the cortex in comparison to other areas such as the paws or the visual system because whiskers are important to the mouse for guidance in the dark places where they prefer to live. Removal of a row of whiskers in the neonatal period results in shrinkage of the cortical areas referred to as "barrels" assigned to each extirpated whisker, while the cortex assigned to adjacent intact whiskers expanded. These results show that activity-dependent rearrangement of the receptive field to compensate for loss of whisker input, and the effect is far more robust in the neonatal period than at later ages.

Numerous other experiments have shown activity-dependent changes in somatosensory cortical maps in rodents, primates, and other species [Buonomano and Merzenich, 1998]. In primates and humans, the somatotopic map for the hand and fingers has expanded considerably compared to lower animals in keeping with the importance of refined hand movements in these species compared with rodents. Nudo et al. [1996] showed that retraining of hand skill in an experimental primate model after a focal infarct in motor cortex prevented the shrinkage of the hand area that normally occurred adjacent to the infarct following the injury [Nudo, 2006]. They also found that the hand area sometimes expanded into the area generally occupied by the shoulder and elbow. Froemke et al. [2007] demonstrated that reorganization in the representation of the tonotopic map for sound in rat cerebral cortex occurred in response to a combination of persistent exposure to specific tones in combination with a behavioral paradigm. This behavioral effect was mediated in part by input to the cortex from the cholinergic nucleus basalis in the basal forebrain, and the importance of this input for plasticity has also been demonstrated in the mouse whisker barrel model [Nishimura et al., 2002]. Experimental work over the years has shown a close relationship between the basic mechanisms responsible for synaptic plasticity and cortical map plasticity. Similar to synaptic plasticity, cortical map plasticity appears to be modulated continuously in response to activity. Rapid changes in cortical representation have been observed within minutes in human subjects subjected to transient deafferentation of a limb using a tourni-

quet, probably due to unmasking of latent synapses [Chen et al., 2002].

CLINICAL EXAMPLES OF PLASTICITY AND REORGANIZATION IN CEREBRAL CORTEX

Adaptive plasticity refers to functional and structural changes in the brain that are advantageous in that they help to improve function. Musical practice is a good example of adaptive plasticity, and it is well known that practicing a stringed instrument from early childhood results in greater skill than practice started later in childhood or in adulthood. In a now classic experiment, Taub's group studied the cortical representation of the fingers of the left hand using magnetic source imaging in nine young adult musicians who began practicing their stringed instruments over a range from 5 to 19 years of age [Elbert et al., 1995]. Six nonmusicians served as controls. The left hand is generally used to finger the strings while the right hand is used for bowing. During experimental sessions somatosensory stimulation was applied first to the first digit and then to the fifth digit, and the strength of the response as well as the distance between the responses from the first and fifth digit were calculated. There was a significant linear relationship between age of initiation of practice and strength of the magnetic dipole evoked by finger stimulation and initiation at a younger age was associated with a stronger response. The nonmusician controls had weaker responses than the players who started at the oldest age. The string players also had a larger cortical representation of the fingers of the left hand compared to their right hand. These results show that a longer period of practice was associated with plastic changes in the representation of the fingers in cerebral cortex.

Another example of cortical reorganization in response to early experience has been studied in adult subjects who became blind at an early age. Sadato et al. [1996] used positron emission tomography (PET) to demonstrate that Braille reading in these subjects activated the somatosensory cortex assigned to the Braille reading fingers, as well as the primary visual cortex. They also showed that transient inactivation of the occipital cortex with transcranial magnetic stimulation (TMS) impaired tactile discrimination in the blind subjects but did not affect sensation in nonblind individuals [Cohen et al., 1997]. A case has been reported

in which an individual with early blindness learned to read Braille proficiently but then lost this ability following bilateral occipital stroke although her primary somatosensory perception remained intact [Hamilton et al., 2000]. These studies document the functional relevance of cross-modal plasticity in which cortical areas that are deprived of afferent input are rewired to receive information related to another sensory modality. A similar phenomenon has been described in children with early deafness in which auditory association cortex is appropriated for visual processing [Sadato et al., 2004]. A temporal window for transfer of visual cortex to auditory functionality has been defined up to age 14 years, while the window for reassignment of auditory cortex to the visual system is earlier than 5 years of age [Cohen et al., 1999]. These studies show that cortex that is not receiving afferent stimulation can be rewired to create circuits that provide a functional advantage to reduce the impact of disability.

CORTICAL PLASTICITY ASSOCIATED WITH EPILEPSY SURGERY

Focal epilepsy that is refractory to medical therapy can often respond to focal resection of cortex or more extensive hemispherectomy operations that remove much of the cortex on one side of the brain. Despite the extensive amount of cortex removed, children who have had this surgery often regain the ability to walk and speak although recovery of fine motor function in the contralateral fingers and hand remains problematic. Graveline et al. [1998] used fMRI to demonstrate that cortical activation associated with both motor and sensory function are transferred to motor and sensory association cortices in the opposite hemisphere. Boatman et al. [1999] examined six children who had left hemispherectomy performed for Rasmussen's syndrome at ages 7–14 years and found that receptive functions surpassed presurgical abilities 1 year later, although naming remained impaired and language production was limited to single words. This demonstrated plasticity in the right hemisphere that extended beyond the usual critical period for language acquisition and lateralization. Hertz-Pannier et al. [2002] used serial fMRI to document the ability of the right hemisphere to become activated in association with recovery of expressive language ability following extensive removal of language cortex in

a 9-year-old boy with Rasmussen's syndrome. Additional studies using fMRI, TMS, and PET showed that recovery of motor function in the leg contralateral to hemispherectomy is associated with normal or enhanced activation of the ipsilateral hemisphere, consistent with activation of persistent ipsilateral corticospinal tracts [Shimizu et al., 2000]. de Bode et al. [2005] used fMRI to show that children with surgery for intractable epilepsy due to perinatal strokes showed better recovery of motor skills than those with cortical dysplasia or Rasmussen's syndrome, and there were differences between groups in the cortical areas activated in the remaining hemisphere. Locomotor training that includes weight-supported treadmill exercise has been shown to improve gait in children after hemispherectomy, and

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training is associated with increased volume and intensity of cortical fMRI activation in sensorimotor and somatosensory cortex [de Bode et al., 2007]. These observations demonstrate the capacity of the brain to reorganize after extensive removal of cerebral cortex and subcortical structures late into childhood.

STRUCTURAL CHANGES IN THE BRAIN ASSOCIATED WITH NEURAL PLASTICITY

The advent of advanced MRI techniques has led to the recognition that structural changes occur in the brain in association with neuronal plasticity. One of the first studies to suggest this effect showed that taxi drivers in London had posterior hippocampi that were larger than controls in proportion to the length of their driving experience [Maguire et al., 2000]. This is consistent with the hypothesis that this region stores spatial representations of the environment and enlarges as more information is stored. Interestingly, in a recent study of hippocampal volume

and navigational skills in individuals with blindness, the subjects also had enlarged hippocampi and superior ability to learn new routes, and to perform pointing tasks in a maze and a spatial layout task [Fortin et al., 2008]. Additional studies have shown that limb amputation is associated with decreased gray matter in the thalamus while mathematicians have been reported to have increased gray matter in the parietal cortex [Draganski et al., 2006b; Aydin et al., 2007]. Consistent with early studies on musicians, voxel-based morphometry has also demonstrated changes in gray matter in motor, auditory, and visual-spatial brain regions when comparing professional and amateur musicians with nonmusicians [Bermudez et al., 2008].

In 2004, Draganski et al. [2004] used MRI voxel-based morphometry to examine young adults before and 3 months after they learned a three ball cascade juggling task and showed a transient increase in gray matter regions associated with the processing and storage of complex visual motion. In a follow-up study, this group confirmed their previous results and showed that the increase in gray matter was present within 1 week after training [Driemeyer et al., 2008]. The imaging method cannot distinguish changes in neuronal number or blood vessels from increases in axono-dendritic membranes, but the authors postulate that the time course is most consistent with a change in dendritic spines and synapses. They suggest that learning the new task of juggling is more important than the exercise itself because it is the initial learning period that is associated with the increase in gray matter and further improvement in skill over time does not lead to structural change. Increased gray matter on voxel-based morphometry has also been found in the parietal cortex of medical students after a period of intense learning associated with study for examinations [Draganski et al., 2006a]. These studies demonstrate clearly that practice and learning cause structural neuroplasticity in the brain.

STRUCTURAL NEUROPLASTICITY AFTER THERAPY FOR HEMIPARESIS

Structural neuroplasticity has also been demonstrated in response to neurorehabilitation intervention for adult patients with hemiparesis from stroke. Constraint-induced movement therapy (CIMT) is an intervention for patients with hemiplegia in which they wear a

restraining mitt on the less-affected hand while engaging in repetitive task practice and behavioral shaping with the hemiplegic hand [Gauthier et al., 2008]. The EXCITE (Effect of Constraint-Induced Movement Therapy on Upper Extremity Function) randomized clinical trial of this therapy in adults with stroke in the previous 6–9 months showed that it produced significant and clinically relevant improvement in arm motion that persisted for at least 1 year [Wolf et al., 2007]. The effect of this technique on structural plasticity in the brain has been examined using voxel-based morphometry in a group of 49 patients (26 male, 23 female) with an average age of 65 years who were an average of 3.6 years out from a stroke and had mild to moderate upper extremity hemiparesis [Gauthier et al., 2008]. Patients randomized to the CIMT therapy received 3 hr of therapy for the hemiparetic arm daily for 10 consecutive weekdays and restraint of the less-impaired arm for a target of 90% of waking hours. They also received a set of behavioral techniques designed to facilitate transfer of therapeutic gains to real-world activities including daily monitoring of life situation and use of the hemiparetic arm and problem solving with the therapist to overcome perceived barriers to the use of the extremity. This “transfer package” lasted a half hour per day in addition to the other therapy. Sixteen patients received the complete CIMT treatment while 20 received the comparison therapy which consisted of therapy without the behavioral transfer package, and they were imaged at 1 week before and 1 week after the completion of therapy. Clinical evaluation showed much greater use of the hemiparetic arm in real-world situations using a standardized scale (Quality of Movement scale of the Motor Activity Log) in the CIMT treatment group as opposed to the constraint-induced therapy without the behavioral interventions. The MRI results also showed significant bilateral increases in gray matter in sensory and motor areas as well as in both hippocampi in the CIMT group as compared to the group without the behavioral intervention. Voxel-based comparisons also showed significant changes in the anterior supplementary motor area contralateral to the motor deficit. This is the first study of structural changes in gray matter of cerebral cortex after constraint-based therapy, and the results complement previous data using functional methods (TMS

mapping, PET, and fMRI) to document cortical changes following the procedure [Liepert et al., 2000; Schaechter et al., 2002; Wittenberg et al., 2003]. The results of the study highlight the importance of combining a behavioral intervention with the functional activity task and constraint of the better arm to produce functional improvement and structural change in the brain. They are also consistent with preclinical data cited earlier showing that structured activity combined with behaviorally salient environmental stimulation can enhance adaptive plasticity to improve function.

It is interesting to compare the EXCITE trial of therapy, which focused on the differential use of the upper extremities, with other trials that used bilateral arm training with auditory cues or treadmill training. A randomized

Cortical excitability is controlled by the balance of excitatory (glutamate) and inhibitory (GABA) neurotransmission and greater excitement has been linked to greater plasticity while enhanced inhibition is associated with impaired plasticity.

controlled trial of BATRAC (bilateral arm training with rhythmic auditory cueing) over 6 weeks in older adults with hemiparesis due to stroke did not show overall improvement in function over a control exercise intervention [Luft et al., 2004]. However, fMRI scanning showed that BATRAC therapy was associated with greater activation of the cerebellum, ipsilateral precentral gyrus, and the contralateral hemisphere compared to controls, and there was an association between the fMRI response and clinical improvement. In contrast, another randomized controlled trial of task-related treadmill exercise alone in adult patients with chronic hemiparesis due to stroke showed improved walking and cardiovascular fitness and greater activation in fMRI compared to control therapy in the cerebellum and midbrain only [Luft et al., 2008]. Taken together,

these results indicate that functional and structural imaging is providing objective data to consider alongside functional outcomes in assessing the effects of therapies on brain plasticity.

ENHANCING PLASTICITY WITH BRAIN STIMULATION

Cortical excitability is controlled by the balance of excitatory (glutamate) and inhibitory (GABA) neurotransmission and greater excitement has been linked to greater plasticity while enhanced inhibition is associated with impaired plasticity [Benali et al., 2008]. Drugs such as benzodiazepines and baclofen which enhance inhibition have been linked experimentally to impaired plasticity [McDonnell et al., 2007]. Other drugs have been found to enhance plasticity [Maya Vetencourt et al., 2008]. Interest in modifying cortical excitability to improve recovery from brain injuries has grown with the advent of tools to modify cortical excitability noninvasively using TMS and transcranial direct current stimulation (tDCS) and indirectly through peripheral nerve stimulation [Harris-Love and Cohen, 2006; Alonso-Alonso et al., 2007]. Clinical studies have shown that peripheral nerve stimulation of somatosensory cortex in patients with hemiparesis due to stroke enhances the effects of training for functional hand tasks [Uy and Ridding, 2003; Celnik et al., 2007]. TMS may have this effect because it reverses cortical inhibition that has been detected shortly after strokes in some subjects. It has been hypothesized that excessive inhibition following stroke may be related to a combination of dysregulation of intrinsic GABAergic interneurons and interhemispheric inhibition transmitted through crossed callosal fibers [Fregni and Pascual-Leone, 2007]. Other research showed that repetitive stimulation to somatosensory cortex through the median nerve paired with TMS pulses delivered to motor cortex synergistically enhances the excitability of motor cortex [Stefan et al., 2002]. These results are consistent with a model of synaptic plasticity associated with LTP mediated by NMDA type glutamate receptors as studied in laboratory models.

PLASTICITY IN CHILDREN WITH CEREBRAL PALSY

Activity-dependent neuronal plasticity appears to play a role in the evolution of clinical signs of motor dysfunction in children with cerebral palsy.

Eyre et al. [2007] used TMS to study the development of the corticospinal tracts over the first 2 years of life in 39 infants with either unilateral or bilateral cerebral infarctions related to stroke, hemorrhage or hypoxia-ischemia compared to 32 healthy age-matched controls. They found that TMS stimulation initially evoked responses in the biceps muscle in infants with unilateral lesions but these responses became progressively abnormal and disappeared in seven patients. Imaging studies also documented hypertrophy of the ipsilateral corticospinal tract from the noninfarcted hemisphere. In contrast, infants with bilateral cerebral lesions maintained normal development of the responses from TMS stimulation. Although early TMS responses did not predict motor outcome, progressive loss of TMS responses and ipsilateral hypertrophy of the axons from the noninfarcted hemisphere predicted poor outcome.

These results from infants are consistent with experimental studies in immature cats showing that corticospinal tracts from each side initially project bilaterally into both ventral horns of the spinal cord [Eyre, 2007]. As the animal matures, axons from corticospinal projections are pruned depending on neuronal activity, and there is competition between axons projected from each hemisphere. When one hemisphere is silenced experimentally, its axons are retracted in the contralateral side of the spinal cord ventral horn, and ipsilateral fibers from the normal hemisphere take their place. The active side maintains bilateral terminations at the expense of the silenced side. These experiments found that immobilization of an extremity also reduced innervation of the spinal cord by contralateral corticospinal tracts, suggesting that sensory activity from the limb also was important for plasticity of the developing corticospinal tracts [Martin et al., 2007].

Eyre [2007] have suggested that it is both the progressive loss of the contralateral projections and the persistence of bilateral projections from the ipsilateral hemisphere that are responsible for progressive functional disability after injury. In the case of perinatal injury in the term infant, the persistence of ipsilateral corticospinal projections appears to reflect maladaptive plasticity, although data from infants with cortical malformations or other early fetal lesions suggests that ipsilateral projections may be compatible with preserved function of the arm and hand. Eyre

et al. suggest that TMS or other stimulation techniques might be used to correct the postnatal imbalance in cortical activity and perhaps reduce functional disability. The same principles of activity-based plasticity can be harnessed causing CIMT for children with hemiplegic cerebral palsy. fMRI studies of cerebral activation of children with hemiplegia showed a shift in laterality from the ipsilateral to contralateral hemisphere after CIMT therapy in association with improved function [Eliasson et al., 2005]. Kuhnke et al. [2008] found that children with congenital hemiparesis and preserved contralateral corticospinal tracts from the damaged hemisphere respond differentially to CIMT than children with only ipsilateral responses to TMS. Both groups respond to CIMT with improved function but only those with contralateral corticospinal tracts have improvement in speed of movement. Therapy using a virtual reality environment to stimulate the use of the hemiparetic hand has also been reported to switch cortical motor activation from the ipsilateral to contralateral side [Jang et al., 2005].

MALADAPTIVE PLASTICITY FOLLOWING INJURY

Although neuronal plasticity is usually adaptive in that it supports beneficial responses and behaviors, excessive plasticity has also been implicated in the pathogenesis of neurological disorders. Two examples of maladaptive plasticity are use-dependent dystonia and phantom limb pain. Musicians or writers can develop involuntary dystonic co-contraction of the muscles in the hands and fingers over time after prolonged use [Quartarone et al., 2006]. Physiological studies of somatosensory cortex in these patients indicate that the representation of individual digits is less segregated on both sides of the brain than in control subjects. Studies utilizing TMS also showed that their motor cortex was more easily activated than cortex in controls and the response to focal stimulation of motor responses in the hand muscles was less spatially restricted than in controls. These results suggest that individuals who develop hand dystonia related to overuse have abnormal cortical plasticity that may in some cases be due to some underlying genetic predisposition. Certain cases of phantom limb pain following amputation reflect a similar phenomenon occurring in sensory cortex [Flor, 2008]. Phantom limb pain occurs more commonly after amputation in adults than children and is asso-

ciated with reorganization at multiple levels in the spinal cord, brain stem, thalamus, and cerebral cortex. Studies in individuals with arm amputation indicate that pain is associated with reorganization of sensory cortex so that the representation of the mouth area moves into the area normally occupied by the arm. Patients with phantom pain have also been shown to have enhanced excitability in the sensory cortex.

GENETIC INFLUENCES ON BRAIN PLASTICITY

It follows from what is known about the neurobiology of neuronal development and synaptic plasticity that variations in some of the genes that control basic steps in the process are likely to emerge as clinically determinants of recovery from acquired injuries. At this point, one leading candidate for this type of gene is brain derived neurotrophic factor (BDNF). BDNF is expressed by neurons in response to neuronal activity, and it plays a role in NMDA-dependent LTP and in hippocampal plasticity and memory formation. Egan et al. [2003] reported that individuals with the val66met polymorphism of BDNF had poor episodic memory and low levels of hippocampal *N*-acetyl aspartate (NAA) measured with MR spectroscopy, as well as a defect depolarization induced secretion of BDNF when the variant was transfected into normal neurons in vitro. A follow-up report showed that these individuals also had differences in the anatomy of the hippocampus and frontal lobes compared to individuals with val66val [Pezawas et al., 2004]. Kleim et al. [2006] used a motor training task involving the fingers to show that individuals with val66met had significantly lower training dependent increases in the amplitude of motor evoked potentials and reduced motor map reorganization in cerebral cortex. A recent study also showed that individuals with the met allele had impaired responses to median nerve paired associative stimulation and a probe of cortical plasticity using tDCS and TMS [Cheeran et al., 2008]. This information strengthens the link between the basic science model of neuronal plasticity presented above and clinical plasticity, but there is limited information about this mutation in children or adults with brain injuries.

CONCLUSION

Plasticity mechanisms are enhanced in the developing brain so

that children can recover more fully from brain injuries than adults. Plasticity can have negative as well as positive consequences because in certain situations it can lead to development of movement disorders or chronic pain related to amputation. Results from basic neuroscience, neurophysiology, and neuroimaging are providing greater insight into the mechanisms for efficacy of rehabilitation therapies. Activity-dependent plasticity at synapses combined with reorganization of motor and sensory maps in the brain is one of the major mechanisms for adaptive plasticity after injury. Exercise as well as direct electrical stimulation of the brain can enhance recovery if these interventions are designed to take advantage of the brain's intrinsic plasticity mechanisms. ■

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