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Review Article

Regeneration and plasticity in the brain and spinal cord

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The concept of brain plasticity covers all the mechanisms involved in the capacity of the brain to adjust and remodel itself in response to environmental requirements, experience, skill acquisition, and new challenges including brain lesions. Advances in neuroimaging and neurophysiologic techniques have increased our knowledge of task-related changes in cortical representation areas in the intact and injured human brain. The recognition that neuronal progenitor cells proliferate and differentiate in the subventricular zone and dentate gyrus in the adult mammalian brain has raised the hope that regeneration may be possible after brain lesions. Regeneration will require that new cells differentiate, survive, and integrate into existing neural networks and that axons regenerate. To what extent this will be possible is difficult to predict. Current research explores the possibilities to modify endogenous neurogenesis and facilitate axonal regeneration using myelin inhibitory factors. After apoptotic damage in mice new cortical neurons can form long-distance connections. Progenitor cells from the subventricular zone migrate to cortical and subcortical regions after ischemic brain lesions, apparently directed by signals from the damaged region. Postmortem studies on human brains suggest that neurogenesis may be altered in degenerative diseases. Functional and anatomic data indicate that myelin inhibitory factors, cell implantation, and modification of extracellular matrix may be beneficial after spinal cord lesions. Neurophysiologic data demonstrating that new connections are functioning are needed to prove regeneration. Even if not achieving the goal, methods aimed at regeneration can be beneficial by enhancing plasticity in intact brain regions.
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Brain plasticity

The concept of brain plasticity is not new. In 1890 William James proposed in his book 'Principles of Psychology' that the habits in living beings are because of the plasticity of the brain, defining plasticity as the possession of a structure weak enough to yield to an influence, but strong enough not to yield all at once. Detailed discussions on brain plasticity together with experimental data and beautiful drawings can be found in the papers by Ramon y Cajal. In 'Textura del sistema nervioso del hombre y de los vertebrados' (Textbook on the nervous system of man and the vertebrates 1897–1899), he wrote thatr to explain skill acquisition is necessary to assume formation of new pathways through ramification and progressive growth of dendrite arborization and nervous terminals. In contrast to the worldwide recognition for his contributions to the neuron doctrine, Cajal's pioneering observations on brain plasticity and the impact they have on science even today have not attained much attention (DeFelipe, 2006). Another pioneer was Ernesto Lugaro in Italy who in 1906 wrote about psychic plasticity, plasticity of neurons, and plasticity of neurofibrils. He proposed that the chemotropic activities responsible for the prenatal organization of the nervous system can continue to some extent throughout life to establish fresh, adaptive anatomic-functional connections between neurons (Berlucchi, 2004). Half a century later, Donald Hebb's fundamental studies on how neuronal cortical connections are strengthened and remodeled by experience initiated a wide interest in neuronal plasticity in the intact and injured brain (Hebb, 1949; Rosenzweig, 1960; Johansson, 2004*a*; Pascual-Leone *et al*, 2005; Seitz *et al*, 2005; Will *et al*, 2004).

Dendritic spines are the primary postsynaptic targets of excitatory glutaminergic synapses in the mature brain. The dendritic tree is covered with a

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variety of excitable synaptic channels operating on different timescales and with activity-dependent sensitivity enabling a sophisticated neuronal plasticity (Hickmott and Merzenich, 2002; Segal, 2005). With two- or multiphoton microscopy, individual cells and cortical networks can be studied *in vivo* at depths of up to 1 mm in the mouse cortex, enabling direct visualization of the behavior of cells in their natural environment and their response to manipulations over long periods of time (Kerr *et al*, 2005). The introduction of transgenic mice models expressing high levels of fluorescent proteins in neurons or glia cells has further facilitated studies on how single cells respond to stimuli in the intact and injured brain (Misgeld and Kerschensteiner, 2006).

In addition, training, sensory input, and brain lesions can modify cortical representation areas and subcortical structures (Merzenich and Kaas, 1982; Jenkins and Merzenich, 1987; Johansson, 2004*b*; Kaas *et al*, 1999; Pascual-Leone *et al*, 2005). Rapid and transient alteration of cortical representation areas occur during learning tasks, most likely as a result of decreased inhibition and increased synaptic efficacy in existing neuronal circuits (Pascual-Leone *et al*, 1994). Flexible short-term modulations are important in the acquisition of new skills, and can lead to structural changes in the intracortical and subcortical networks as the skill becomes more established and automatic (Petersen *et al*, 1998). Focal brain lesions lead to extensive neurophysiologic and anatomic changes in the peri-infarct region, in other areas in the injured and intact hemispheres as well as in subcortical structures, in a complex, lesion, and time-related way. Specific aim-related training can influence the process, and the training effect can be enhanced by neurophysiologic and pharmacologic manipulations (Dancause *et al*, 2005; Floel and Cohen, 2006; Nudo, 2006; Seitz *et al*, 2005; Ward and Cohen, 2004).

Regeneration can be considered the optimal example of plasticity in the central nervous system (CNS). The recognition of neurogenesis in some regions in the healthy adult brain together with the identification of myelin inhibitory factors has raised the hope that regeneration may be possible after brain lesions. Regeneration of the CNS will require new neurons, either through proliferation of endogenous stem/progenitor cells or by administration of exogenous cells with potential to substitute for lost tissue, and that the cells differentiate, survive, and integrate into existing neural networks. For that to occur, a permissive extracellular matrix that allows cell integration and axonal proliferation is needed. Regeneration in the brain and spinal cord are dealt with separately. Cell implantation will be discussed in connection with spinal cord lesion but cell implantation in brain disorders is a too large of a research area to be covered here.

Neuronal regeneration in the brain

Endogenous Neurogenesis in the Intact Brain

In the adult mammalian brain neurogenesis persists in two distinct regions, the subgranular zone of the dentate gyrus (DG) in the hippocampus, and in the forebrain subventricular zone (SVZ). These regions maintain the neurogeneic potential in a subset of radial glial fibrillary acidic protein-positive astrocytes (Doetsch *et al*, 1999; Garcia *et al*, 2004). Neurogenesis was demonstrated in the hippocampus and in the subependymal layer in the adult rat brain already four decades ago (Altman and Das, 1965; Lewis, 1968) and has also been shown to occur in the adult human brain (Eriksson *et al*, 1998). According to the definition, stem cells are proliferative, self-renewing, and multipotent for the different neuroectodermal lineages. There is still no way to identify stem cells prospectively *in vivo* or *in vitro* (Berninger *et al*, 2006). Because of the difficulty to separate clearly the stage of the neural stem cells and neuroblasts they are often referred to as precursors or progenitor cells (Emsley *et al*, 2005). Evidence of the multipotency of subventricular stem cells has been obtained *in vitro* using the neurosphere assay system. Many regions of the CNS without any apparent adult neurogenesis can give rise to neurosphere-forming cells and the potential to form neurospheres does not necessarily reflect the presence of stem cells or their behavior *in vivo* (Berninger *et al*, 2006). In the DG newly born granule cells exhibit enhanced synaptic plasticity, and they participate in activity-induced activation during some learning and memory tasks (Bruel-Jungerman *et al*, 2005; Jessberger and Kempermann, 2003) although the link between adult hippocampal neurogenesis, memory and learning is still debated (Leuner *et al*, 2006).

The olfactory sensory system has a unique ability to renew (Lledo *et al*, 2005). It is the only part of the nervous system where nerve cells are continually replaced throughout adult life. In the intact brain, cells generated in the SVZ migrate to the olfactory bulb where the majority of the cells disperse through the granule cell layer to develop into GABAergic granule cells, and a small percentage differentiate into periglomerular cells expressing GABA and/or the dopamine-synthesizing enzyme tyrosine hydroxylase. Sensory input from sensory neurons in the olfactory epithelium is critical for the survival of granular cells. Enriched odor exposure increases the number of newborn neurons in the adult olfactory bulb and improves odor memory (Rochefort *et al*, 2002). Multiple stages in the maturation of newborn neurons in the adult olfactory bulb may serve as a substrate for structural and physiologic plasticity and enable better response to changes in the environment, allowing a continuous adjustment of information in response to the changing external world (Lledo and Saghatelyan, 2005; Magavi *et al*,

2005). Furthermore, mature sensory neurons in the olfactory epithelium have a limited life span that is tightly regulated by environmental factors (Lledo *et al*, 2005), and new olfactory receptor neurons are continuously generated from basal cells in the olfactory epithelium (Beites *et al*, 2005). The olfactory receptor neurons project to the olfactory bulb via the olfactory nerve. The olfactory epithelium ensheathing cell (OEC) is a specialized glia that is essential for the olfactory nerve regeneration and its ability to enter the brain. The unique characteristics of the OEC will be discussed in connection with axonal regeneration after spinal cord trauma.

Mechanisms that specify the fate of embryonic neuronal precursors might at least in part be recapitulated in the adult brain. Multipotent neural stem cells/progenitor cells can be isolated from many regions of the adult CNS, yet neurogenesis is restricted *in vivo* to the DG and SVZ. Primary astrocytes in the hippocampus and the SVZ promote neuronal differentiation of adult progenitor cells, whereas astrocytes in other regions inhibit neural differentiation. There is evidence that cytokines and chemokines in astrocytes in the permissive areas are part of the explanation (Barkho *et al*, 2006). Key questions in current stem cell research are as follows: (1) What makes the environment in neurogenic areas permissive for cell proliferation? (2) What determines whether the stem cells undergo self-renewal or cellular differentiation? (3) How can extrinsic factors interact with the intrinsic mechanisms in the progenitor cells? (4) What is the optimal growth-permissive environment.

In the SVZ, the stem cells make close contact with the ependyma and the cerebrospinal fluid. It has been proposed that substances in the cerebrospinal fluid, or secreted by the choroid plexus, participate in the regulation of new cells. There is an intimate relationship of neural precursors with microcapillaries both in the SVZ and DG (Palmer *et al*, 2000). By secreting vascular endothelial growth factor and other factors that maintain CNS stem cell self-renewal and neurogenetic potential, the endothelial cells are critical components of the neural stem cell niche. Thus endothelial cells cultured above neural progenitors enhance proliferation and maintain the new cells in an undifferentiated stage. After removal of endothelial cells, the neuroblasts generate neurons as well as astrocytes and oligodendrocytes (Shen *et al*, 2004). Erythropoietin, a cytokine that plays a critical role in hemotopoiesis, plays an essential role in regulating embryonic and adult neuronal development and function. Brain-specific deletion of the erythropoietin receptor *EpoR* reduces cell proliferation in the SVZ and impairs migration of neuroblasts to the peri-infarct cortex (Tsai *et al*, 2006). *In vitro* neurosphere formation depends on epidermal growth factor (EGF) and fibroblast growth factor 2 in the media. A large number of cellular and extracellular components have been proposed to promote or inhibit adult neurogenesis (see Berninger *et al*, 2006; Emsley *et al*, 2005; Jagasia *et al*, 2006).

Whether neurogenesis can be induced in the intact neocortex is a controversial issue. An early *in vivo* study indicated the presence of dormant progenitor cells in the rodent cortex that could be activated by fibroblast growth factor 2 in intact animals (Palmer *et al*, 1995). Although neuroblasts migrate to cortical areas surrounding an infarct, there is no convincing evidence for the formation of mature neurons in the cortex. No BrdU-labeled neurons were detected in a systematic analysis of cell turnover in the major areas of the human neocortex from cancer patients that had been given BrdU *in vivo* for diagnostic purposes. The neocortical neurons had ^{14}C levels corresponding to the atmospheric levels at the time of birth of the individual indicating that the neurons studied were not born after that time (Bhardwaj *et al*, 2006). The analysis was performed on brain samples from undamaged brains, and the finding does not rule out that neurogenesis might occur under pathologic conditions as will be discussed in the next section.

The current knowledge of adult mammalian neurogenesis in the intact and injured brain and how it may be modified by external and endogenous factors have been extensively reviewed elsewhere (Berninger *et al*, 2006; Emsley *et al*, 2005; Komitova *et al*, 2006*a*; Lledo *et al*, 2006). The discussion on neurogenesis of clinical interest in this review will be limited to (a) ischemia-induced neurogenesis and (b) transgenic models of degenerative disorders and how result obtained in those models relate to recent data obtained on brains from patients with corresponding degenerative human diseases.

Endogenous Neurogenesis after Ischemic Brain Lesions

That transient global ischemia induces neurogenesis in the DG was demonstrated almost a decade ago (Liu *et al*, 1998). Intraventricular infusion of EGF and fibroblast growth factor 2 has been shown to increase regeneration of hippocampal pyramidal neurons after a brief episode of transient global ischemia that selectively damages hippocampal pyramidal neurons (Nakatomi *et al*, 2002). Electrophysiologic evidence indicated that the neurons may have been integrated into the existing brain circuitry and contributed to amelioration of neurologic deficits.

Focal cerebral ischemia enhances neurogenesis in the DG and the SVZ (Jin *et al*, 2001; Zhang *et al*, 2001). Apparently, ischemic and traumatic brain lesions induce still largely unknown signals that enhance stem cell proliferation in the DG and SVZ and change direction of the migration of new cells from the SVZ. After focal ischemic lesions involving striatum, cells from the SVZ migrate to the ischemic striatum and some of the new cells

develop into striatal medium spiny projection neurons (Arvidsson *et al*, 2002; Parent *et al*, 2002). Neuroblasts that migrate from the SVZ form chain-like aggregates closely associated with astrocytic processes and blood vessels, differentiate and may form synaptic contacts with neighboring striatal cells (Yamashita *et al*, 2006).

Lesion-induced neurogenesis may also occur in older rats. Although the basal neurogenesis was reduced in aged rats, neurogenesis still took place both in the DG and SVZ, and the number of new neuroblasts or mature neurons in the striatum did not differ between 3-month old and 15-month-old female Wistar rats (Darsalia *et al*, 2005). In 24-month-old male Fischer rats, ischemia induced neurogenesis persisted but was reduced in the SVZ, whereas no ischemia-induced cell proliferation was observed in the DG (Jin *et al*, 2004). Because of strain and gender differences in rodent neurogenesis (Kempermann *et al*, 2006; Perfilieva *et al*, 2001), it is difficult to know whether the divergent results regarding the DG are related to gender, strain, or age.

Apparently injury-induced cell proliferation can last for a considerable time, and under what conditions that occur is clearly of clinical interest. In an early study on rats subjected to traumatic brain injury at the age of 4 months, a sixfold proliferation of neuroblasts and glia persisted in the SVZ 1 year after the trauma in contrast to a decrease with aging in noninjured control rats (Chen *et al*, 2003). Daily intraventricular infusions of a caspase inhibitor cocktail during 12 days after focal ischemia generated striatal neuroblasts without decline for at least 4 months (Thored *et al*, 2006).

Epidermal growth factor amplifies the replacement of striatal interneurons after focal ischemia (Teremoto *et al*, 2003). The number of EGF receptor-positive cells in the SVZ increases after an ischemic insult. Postischemic EGF-infusion expands these cells, and after discontinuation of the infusion the number of neuroblasts increased both in the SVZ and the injured striatum (Ninomiya *et al*, 2006). As extensively reviewed by Lichtenwalner and parent (2006), several other trophic factors have been proposed to play a role in neurogenesis after brain ischemia. Increased production of endogenous neurotrophins may be one possible explanation to the observation that postischemic housing in an enriched environment increases progenitor cell proliferation and neuroblasts in the subventricular zone after focal cortical ischemia (Komitova *et al*, 2005).

Whether cortical neurogenesis can be induced in the ischemic cortex remains a controversial question. Using a variety of neuronal markers, most experimental studies have failed to show mature neurons in the ischemic cortex (see Kokaia *et al*, 2006). It was recently reported that cells that expressed markers associated with newborn neurons were noted in the ischemic penumbra in specimens obtained at biopsy performed for 'diagnostic purposes' in patients with cortical infarcts (Jin *et al*, 2006). Whether these cells that were preferentially localized in the vicinity of blood vessels originated locally or had migrated from a neuroproliferative region could not be evaluated on the available specimens. Intraventricular infusion of EGF and erythropoietin, but neither of them alone, has been reported to induce new cortical tissue including neurons after small frontal cortical devascularization lesions in rats (Kolb *et al*, 2006).

Olig2, a transcription factor required for oligodendrocyte lineage specification, has been identified as a possible key inhibitor of cortical neurogenesis in three mouse models of acute and chronic brain lesions, that is stab wound, focal ischemia, and chronic amyloid deposition. A strong upregulation of Olig2 was a common feature in all the models, and by antagonizing Olig2 function some degree of endogenous neurogenesis could be evoked in the injured cortex (Buffo *et al*, 2005).

Neurogenesis in Degenerative Brain Disorders

In a model of selective apoptotic death of cortical pyramidal neurons in the mouse it has been demonstrated that endogenous neural precursors can be induced to differentiate into mature neurons and form long-distance cortico-thalamic and cortico-spinal connections (Magavi *et al*, 2000; Chen *et al*, 2004). Apparently, some signal in the environment can stimulate proliferation of 'dormant' progenitor cells in the cortex in this model of apoptotic cell death that has been proposed to be a relevant experimental model for human degenerative disorders.

Dopaminergic denervation reduces proliferation in the SVZ and DG and neurogenesis in the olfactory bulb in experimental animals, and a reduction of precursor cell proliferation has been observed in brains from patients with Parkinson's disease (Höglinger *et al*, 2004). Whether the impaired generation of neural precursors is of clinical significance is not known. However, because olfactory dysfunction is common in patients with Parkinson's disease and olfactory neurogenesis is implicated in memorization of odors (Rochefort *et al*, 2002), it has been speculated that the reduction of precursor proliferation in the SVZ might contribute to the olfactory impairment in the disease (Höglinger *et al*, 2004).

An enhanced hippocampal neurogenesis has been observed in brains from patients with Alzheimer's disease (AD) as well as in a transgenic mouse model of the disease (Jin *et al*, 2004*a*,*b*). In the mice the increase was observed before any neuronal loss and amyloid deposition was noted, and the authors suggested that it might be a compensatory mechanism triggered by more subtle disease manifestation such as impaired neurotransmission (Jin *et al*, 2004*a*). Studies on other transgenic mouse AD

models have not demonstrated any change in SVZ neurogenesis but have indicated a decreased hippocampal neurogenesis (see Donovan *et al* (2006)). To investigate possible explanations to the controversy, the volume, cell number, and heterogeneity of the granule cell layer were evaluated in the PDAPP mouse, a model of AD with age-dependent AD-like neuropathology and cognitive deficits that has been extensively studied with regard to therapeutic interventions for AD. A 50% reduction in neurogenesis was found in the old but not in the young mice. Interestingly, the decreased neurogenesis was not associated with an age-dependent loss of dentate granule neurons because of a reduced apoptosis. Furthermore, the mice had increased birth of immature neurons in the outer portion of the granule cell layer. These ectopic immature neurons did not survive to maturity, and compared with the subgranular zone proliferating cells the number of ectopic cells were rare, emphasizing that the primary characteristic in these mice was a decreased neurogenesis (Donovan *et al*, 2006).

An increase in the number of proliferating cells in the subependymal layer of the lateral ventricle adjacent to the caudate nucleus has been observed in brains from individuals with late-stage Huntington's disease (Curtis *et al*, 2003, 2005). In transgenic Huntington's disease mice with an increased background neurogenesis in the SVZ, daily subcutaneous administration of FGF2, starting before the animals had developed any symptoms, prolonged survival, and increased the number of proliferating cells in the SVZ, and induced recruitment of new cells from the SVZ into the neostriatum (Jin *et al*, 2005). In another Huntington's disease transgenic mouse model, changes have been noted in the hippocampus but not in the SVZ cell proliferation (Lazic *et al*, 2004, 2006). In 5-week-old transgenic mice, the proliferation in DG was similar as in wild-type controls, but in 20-week-old mice the neurogenesis was significantly reduced, mainly the result of decreased proliferation and survival of neural progenitor cells. The decrease in hippocampal neurogenesis preceded Huntington's disease-induced cell death. The immature neurons had an altered cell morphology, that is smaller and irregular-shaped somas, shorter neuritis, and shorter migration distance than control mice (Lazic *et al*, 2004). Housing the mice in an enriched environment delayed the onset of motor symptoms, improved life expectancy, increased the number of proliferating cells, and improved the morphology of the neuroblasts (Lazic *et al*, 2006), results that are in agreement with other studies demonstrating environmental and gene interactions in plasticity and regeneration.

Studies of brains from patients with bipolar affective disorder, depression, schizophrenia and controls have so far not supported the hypothesis based on animal data that depression is associated with reduced hippocampal neurogenesis in humans (Malberg and Schlechter, 2005), nor has it suggested that cell proliferation is modified by antidepressant drug treatment in humans (Reif *et al*, 2006). However, the number of newborn cells was reduced in schizophrenia.

Neurogenesis in rodents can be stimulated by epileptic activity and lead to abnormal integration of newborn cells in the DG (Parent *et al*, 1997, 2006). Granular cell dispersion in the DG is a frequent feature of Ammon's horn sclerosis in patients with epilepsy, and it has been hypothesized to be caused by an abnormal migration of newly born granule cells. However, a recent study on 41 surgically removed hippocampal specimens from patients with temporal lobe epilepsy indicated that granule cell dispersion is not accompanied by enhanced neurogenesis; rather it is the result of an abnormal migration of mature granule cells along a radial glial scaffold (Fahrner *et al*, 2007).

There are genetic differences between transgenic mouse models, and there are limitations to what can be shown in postmortem studies of human brains. Hopefully, future progress in molecular genetics can give us some clues why transgenic mouse strains give divergent results and to how these animal models relate to the corresponding human disease.

Neutralizing Myelin Inhibiting Factors in the Brain

Many cortical and subcortical lesions affect the corticospinal and corticobulbar tracts and thus lead to disconnection between cell bodies and their axons. A main obstacle to regeneration of neural tracts is thought to be the presence of myelin inhibitors. The understanding of the cellular and molecular processes involved in myelin repair after lesions is incomplete, and to what extent the mechanisms differ from those involved in myelination during development is debated (Harel and Strittmatter, 2006). The myelin protein Nogo-A has been proposed to be the main factor for the lack of axonal regeneration (Chen *et al*, 2000). Nogo-A has two separate domains that can inhibit axon regeneration, one of which, Nogo-66, is common to all Nogo isoforms. The functional receptor for Nogo-66, NgR links the protein to the outer surface of the cell membrane. Two other myelin-associated proteins, myelin-associated glycoprotein and oligodendrocyte-myelin glycoprotein, share the NgR receptor.

Intracerebral injection of the monoclonal antibody IN-1 in adult rats directly after a middle cerebral artery occlusion resulted in functional recovery in a forelimb-reaching task and new corticorubral connections were observed from the opposite, intact hemisphere (Papadopoulos *et al*, 2002). The corticorubral pathway is mainly an ipsilateral projection that controls fine hand movements, and the corticorubral-spinal system is also implicated in precise limb movements. Even if delayed for 1 week,

anti-Nogo antibody treatment enhanced recovery of skilled forelimb function and increased corticorubral fibers in the deafferented red nucleus after middle cerebral artery occlusion in both young and 25-month-old rats, although the time course for recovery was more prolonged in the old rats (Seymour *et al*, 2005; Markus *et al*, 2005). Mutant mice lacking NgR recovered complex motor function better than control animals after a phototrombotic infarct, and a greater number of axons emanating from the undamaged cortex crossed the midline to innervate the contralateral red nucleus and the ipsilateral cervical spinal cord (Lee *et al*, 2004). Application of an IN-1 antibody immediately after a middle cerebral artery occlusion increased dendrite arborization and spine density in the contralateral hemisphere but had little effect in intact rats (Papadopoulos *et al*, 2006).

The studies on the effect of myelin inhibitors after brain lesions have thus so far demonstrated effects on brain plasticity rather than regeneration.

Some data have suggested that axonal sprouting might be induced after brain lesions also in untreated control animals. In a study on traumatic brain injury, a significantly induced axonal sprouting was observed from the contralateral corticospinal tract independent of inhibition of Nogo-A (Lentzlinger *et al*, 2005). Continuous infusion of the purine nucleoside inosine, a naturally occurring metabolite, into the lateral ventricle on the undamaged side after a partial middle cerebral artery occlusion, induced axonal rewiring and promoted behavioral outcome in rats (Chen *et al*, 2002). Neurons on the undamaged side extended new projections to denervated areas of the midbrain and spinal cord. The number of crossing corticorubral fibers was low in normal control animals and increased significantly after the lesion, even in animals treated with saline alone, with a further two- to threefold increase after inosine infusion. Thus, it seems that some lesion-induced signal can stimulate the crossing of fibers from the intact side to the lesion side independent of treatment. This is an interesting observation that needs further exploration and if confirmed, identification of possible signaling mechanisms.

Regeneration after spinal cord injury

Although nerve fibers do not grow to their original destinations after spinal cord trauma, the severed ends sprout in the region of the lesion, and neurons that have lost their incoming connections are spontaneously reinnervated by sprouting adjacent undamaged nerve fibers (Li and Raisman, 1995; Bareyre *et al*, 2004). Glial scars, presence of myelin inhibitory factors, and loss of support from the extracellular environment are some of the factors proposed for the lack of axonal regeneration after spinal cord injury.

Endogenous Cell Proliferation

Proliferation and differentiation of glial progenitor cells that give rise to astrocytes and oligodendrocytes have been demonstrated throughout the intact adult rat spinal cord (Horner *et al*, 2000). In a rat contusion model, the cell proliferation was highest during the first week after injury and declined to an insignificant level by 4 weeks (McTigue *et al*, 2001; Zai and Wrathall, 2005*).* Using a fluorescence protein hematopoietic chimeric mouse it was found that 90% of the dividing cells in the early proliferation phase originated from the spinal cord and only 10% from the bone marrow (Horky *et al*, 2006). A marked increase of newly divided cells have been observed in adult rhesus monkeys with hemisection of the cervical spinal cord studied 7 weeks to 7 months after the lesions. The proportion of macrophages/migroglia diminished over time and 7 months after injury 15% of the new cells expressed mature markers of oligodendrocytes and 12% expressed mature astrocytic markers. Newly born oligodendrocytes were present in zones of injury-induced demyelination and appeared to ensheath or remyelinate host axons (Yang *et al*, 2006*a*).

A population of progenitor cells present in the spinal cord ependyma proliferates many times more rapidly in spinal cord-injured animals 24 h after injury than in uninjured animals They differentiate into astrocytes that migrate toward the injury site and contribute to the formation of scar tissue over a period of several weeks (Johansson *et al*, 1999). These ependyma progenitor cells proliferate even after a minimal lesion that does not involve the central canal (Mothe and Tator, 2005).

Cell Transplantation after Spinal Cord Lesions

On the basis of the observation that regeneration is possible in peripheral nerves, Ramon y Cajal was the first to suggest that Schwann cells might be beneficial after spinal cord trauma. As extensively reviewed by Reier (2004) and Thuret *et al*. (2006) many neural and nonneural sources of cells have been used later. Human neural stem cells and the OECs, the specialized glia cells that enable the olfactory nerve to regenerate, are currently attracting much attention and will be the only cells discussed here. They illustrate two different approaches. Human stem cells, like other progenitor cells, are used with the hope that they will integrate with the host neural system. In contrast, the proposed action of OECs is that they form bridges to enable the axons in the host spinal cord to find its target.

Human fetal neural stem cells grown as microspheres can migrate and express markers for differentiation of neurons and oligodendrocytes after long-term engraftment in spinal cord injured mice. Remyelination and electron microscopic evidence consistent with synapse formation between

transplanted and mouse host neurons were observed in the spinal cord injury model as well as in myelin-deficient shiverer mice (Cummings *et al*, 2005). An associated improvement of locomotor function was abolished by selective ablation of the engrafted cells by diphtheria toxin. Human embryonic stem cell-derived oligodendrocyte progenitor cells have also been reported to remyelinate and restore locomotion after spinal cord injury (Keirstead *et al*, 2005). Adult neural stem cells grafted into a rat spinal cord injury improved motor recovery but had the negative side effects of aberrant axonal sprouting associated with allodynia-like hypersensitivity of the forepaws (Hofstetter *et al*, 2005). Transduction of the neural stem cells with neurogenein-2 before transplantation suppressed astrocytic differentiation and prevented graft-induced sprouting and hypersensitivity. It also increased the amounts of myelin in the injured area and improved the recovery of hindlimb locomotor function and sensory responses.

The normal pathways of nerve fibers in the white matter consist of different types of glial and others cells arranged with great regularity (Levine *et al*, 2001; Suzuki and Raisman, 1992). The longitudinal axis of the tracts in which the long nerve fibers travel in the spinal cord is a dense parallel array of very fine elongated astrocytic processes. OECs can be obtained either from the olfactory bulb or from the olfactory epithelium in lamina propria thus making it possible to use autologous cells. A proposed action is that the OECs reestablish a route along which sprouting axons can elongate and reach useful targets by the door-opening ability of the OECs that has been demonstrated in the capacity of the olfactory nerve to enter the brain (Li *et al*, 2005*b*, *c*). Transplanted to the injured spinal cord, OECs have been reported to induce regeneration and functional recovery after partial or complete spinal cord transection (Li *et al*, 1997; Moreno-Flores *et al*, 2006; Ramon-Cueto *et al*, 1998), as well as to restore breathing after high dorsal cord lesions (Li *et al*, 2003). Corticospinal axons may cross the bridge of transplanted cells and reenter the distal part of the corticospinal tracts, where they become myelinated by host oligodendrocytes from adjacent fiber tracts. Partial recovery of function, including return of motor-evoked potentials, and histologic evidence of long axonal outgrowth of corticospinal, raphespinal, and coerulospinal tracts within the caudal cord stump, have been observed even after transplantation 1 week after the lesion although early transplantation gave the best result (Lopez-Vales *et al*, 2006).

Not all studies have supported the success reported above. Some studies have shown that highly purified OECs are less potent (Takami *et al*, 2002), It has been suggested that fibroblasts contained in nonpurified cell cultures prepared form the olfactory bulb are crucial to their regenerative properties. Reinstating of breathing after hemisection of the cervical cord was obtained with a technique in which OECs were transplanted together with the matrix in which they had been grown, which prevented both diffusion of the cells away from the transplant and loss of cells (Li *et al*, 2003). Comparing the gene expression profiles of three OECs populations that differ in their capacity to promote adult axonal regeneration *in vitro* and *in vivo* after spinal cord injury in adult rats indicated that metalloproteinase 2 stimulated axonal regeneration, possibly by its known effect of inhibiting a neurite-inhibiting chondroidin sulfate proteoglycan (Pastrana *et al*, 2006). Metalloproteinase activity has also been implicated in axonal guidance during development.

Myelin Inhibitors and Spinal Cord Lesions

Administration of a Nogo receptor antagonist peptide to rodents and monkeys with mid-thoracic spinal cord hemisection resulted in significant axon growth of the corticospinal tract and improved functional recovery (GrandPre *et al*, 2002; Li *et al*, 2004; Fouad *et al*, 2004). With functional magnetic resonance imaging, a significant increase in activation was observed within the thalamus during stimulation of the impaired hindpaw in rats that had received intrathecal anti-Nogo-A therapy after a unilateral spinal cord trauma (Liebscher *et al*, 2005). Enhanced corticospinal axonal sprouting into the lumbar spinal cord and improved locomotion has been observed after transgenic inhibition of the Nogo-6 receptor function in mice (Li *et al*, 2005*a*). However, a marked strain difference in axonal regeneration and a conspicuous difference in the recruitment of macrophages have been seen after corticospinal injury in two strains of Nogo-A deficient mice. Fewer macrophages were observed in the strain with best neurite outgrowth. In both strains, more microglia/microphages were observed in the Nogo-A knockouts than in the wild-type mice. No behavioral or neurophysiologic data were reported (Dimou *et al*, 2006).

Raisman (2004) has argued that the proposal that myelin is inhibitory to axon growth is not consistent with the fact that myelinated fiber tracts are a widely conserved anatomic device through which axons travel in the adult brain and spinal cord, and that it is at odds with the requirements of functional plasticity that is the basis of adaptation. Referring to the extraordinary accuracy with which developing axons are guided to specific targets, he proposes that the purpose of the 'inhibitory' molecules is to direct and facilitate long-distance growth of axons along myelinated tracts and that the failure of remyelination is mainly because of a combination of molecular and anatomic changes in the astrocytic pathways as described in the section on cell regeneration in the spinal cord above (Li *et al*, 2005*b, c*). There is substantial evidence that astrocytes have a

dual role in regeneration with facilitating and inhibiting components that vary with characteristics of the astrocytes, the type of lesion, and post-lesion time (Okada *et al*, 2006; Silver and Miller, 2004, Yiu and He, 2006).

Combined Therapies and the Role of Extracellular Matrix

Heterogeneous composition of transplants might be preferable in enhancing the level of repair using OECs and other progenitor cells. The injury-induced glial scar contains proteoglycans and chondroitin sulfate proteoglycans, components that inhibit axon growth. Chondroitinase ABC promotes functional recovery after spinal cord injury (Bradbury *et al*, 2002), including bladder function (Caggiano *et al*, 2005). Combined with neural progenitor cells transplantation it enhances cell migration and outgrowth of growth-associated protein-43-positive fibers after rat spinal cord injury (Ikegami *et al*, 2005). In a rat model of brachial plexus avulsion, in which nerve roots are torn from the spinal cord, both chondroitinase ABC and sialidase, an enzyme that cleaves a different class of axonal receptors for myelin-associated glycoprotein, enhanced spinal axon outgrowth of implanted peripheral nerve grafts (Yang *et al*, 2006*a*). Combining Schwann cell bridges and OEC grafts with chondroitinase ABC promoted locomotor recovery after complete transection of the spinal cord more than grafts alone (Fouad *et al*, 2005). Cocultivation of adult neural progenitor cells with fibroblasts enhanced the effect of progenitor cells and axonal regeneration (Pfeifer *et al*, 2004).

Adult oligodendrocyte precursor cells make up approximately 5% to 8% of the glial cell population in the CNS. Their function in the undamaged CNS is largely unknown but they have been proposed to contribute to CNS remyelination but inhibit axonal regeneration by the chondroitin sulfate proteoglycan NG2 expressed on the surface. NG2 is accumulated in the glial scar after spinal cord trauma and it has been proposed to participate in the creation of a growth-inhibitory environment (Tan *et al,* 2005). Antibodies against NG2 have been reported to promote the regeneration of sensory axons within the dorsal columns of the spinal cord (Tan *et al*, 2006). However, in the presence of a bridge of cellular fibroblasts genetically modified to secrete NGF, axonal growth was observed in sensory, rubrospinal, and nociceptive axons, suggesting that regeneration can be successful when local permissive signals balance and exceed inhibitory signals (Jones *et al*, 2003). The source of NG2 containing cells at the lesion site appears to be different from that in the surrounding spared tissue, and a substantial part of the cells may be nonmyelinating Schwann cells (McTigue *et al*, 2006). The role of NG2 after brain lesions is controversial. Some data indicate that NG2-positive polydendrocytes possess multipotent neural stem cell and neurogenic properties as well as neuron-supporting trophic functions (Komitova *et al*, 2006*b*; Yang *et al*, 2006*c*).

Another new strategy for inducing neurons to overcome inhibitory signals in the environment is to activate cAMP signaling. After spinal cord injury cAMP levels decrease in the rostral spinal cord, sensory motor cortex, and brain stem. Inhibition of cAMP hydrolysis combined with Schwann cell grafts have been reported to promote supraspinal and proprioceptive axon sparing and myelination (Pearse *et al*, 2004).

Functional Improvement after Spinal Cord Injury and Clinical Aspects

Studies using cell therapy, neutralizing myelin inhibitor factors, and modification of the extracellular matrix have all been reported to improve functional recovery. The question is why. Is it because of a common mechanism, is it a nonspecific effect, and is it related to regeneration or plasticity? Most experimental studies have been carried out on partial spinal cord lesions that usually are followed by some spontaneous recovery. Bareyre and coworkers have demonstrated that spontaneous recovery of function after a dorsal hemisection injury involves extensive reorganization of spinal circuits. Some of the transected hindlimb corticospinal tract axons sprouted into the cervical cord and innervated propriospinal neurons. The axons innervating long propriospinal neurons that bridged the lesion were maintained, and the propriospinal neurons arborized on lumbar motor neurons, creating a new intraspinal circuit relaying cortical input to its original spinal target. The functionality of the circuit was confirmed by electrophysiologic and behavioral testing before and after relesion of the corticospinal tract, and retrograde trans-synaptic tracing revealed changes of cortical representation (Bareyre *et al*, 2004). With a transgenic mouse model, in which corticospinal fibers are specifically and completely labeled by fluorescent proteins, it was shown that lesions of the main dorsal corticospinal cord axons lead to extension of new collaterals, and that some of the new collaterals form additional direct synapses into motoneurons (Bareyre *et al*, 2005). This is an elegant model that may be useful to evaluate specificity and differences between test animals and controls in future studies on spinal cord regeneration. Functional and anatomica data are not sufficient as evidence of regeneration, and neurophysiologic data are necessary to prove that new connections are indeed functioning when claiming regeneration in the spinal cord.

Human spinal cord lesions are heterogeneous and differ considerably from the experimental animal models (Schwab *et al*, 2006). Although moderate success in gaining axonal regeneration has been demonstrated in experimental studies, to be

clinically successful, the neuropathology and neurophysiology of human spinal cord injury must be taken into account.

Several distinct mechanisms can underlie functional recovery in spinal cord repair strategies (Bradbury and McMahon, 2006). Input from the brain and sensory information derived from muscle, joints, and skin converge on the spinal cord for final integration and processing. After a complete injury all sources of control will come from the peripheral sensory receptors. Immediately and for months after a spinal cord injury, there are continued changes in the spinal cord at the anatomic, biochemical, and physiologic levels that provide an extensive potential for plasticity within the spinal neural circuitry, and new spinal circuits can develop functional characteristics that enable it to use pathways that is utilized normally. Thus the combination of cell therapy with motor training and pharmacologic modulation of the excitability of spinal neural networks can have a stronger effect than one strategy alone (see Edgerton *et al*, 2006).

Some of the therapies tried in animals have reached or are approaching clinical trials and OECs have been used after spinal cord lesions in many patients in China, Portugal, and Columbia, mostly without controls and under conditions that do not meet international standards for clinical trials. Several other therapies have also been tried (Thuret *et al*, 2006). Recommended guidelines for studies of human subjects with spinal cord injury, as well as protocols enabling comparisons between the results from experimental studies in different research laboratories are available on the web (see Thuret *et al*, 2006).

Concluding remarks

The possibility of obtaining regeneration by stimulation of endogenous cell proliferation and differentiation is an attractive idea. The observation that new pyramidal neurons can substitute for a dying cell population after apoptotic damage and form long-distance cortico-thalamic and cortico-spinal connections (Magavi *et al*, 2000; Chen *et al*, 2004) may be a relevant for degenerative disorders providing that the right cellular and environmental molecular signals can be induced. Future progress in molecular genetics may contribute to answer questions related to the divergent results in transgenic mouse models and postmortem studies on human brains. That new striatal neurons are formed after ischemic lesions in the rat shows that neurogenesis can be induced in an area where it does not normally occur.

Restoration of lost tissue after ischemic and traumatic brain lesions in the complex CNS is a formidable task. Current experimental research raises some hope that at least a partial regeneration may be possible some time in the future. However, the step from rodents to primates, and from primates to humans is considerable (Kaas, 2005). There is an extraordinary diversity within the neuronal population and between the individual cells in the human brain, highlighting the importance of single neurons in a network (Muotri and Gage, 2006). A combined approach of stimulation of endogenous resources and exogenous administration of well-defined cell populations, implanted in a permissive extracellular matrix might be needed to regenerate tissue lost in human adult brain injury. Functional and anatomic data are not sufficient to prove regeneration. Neurophysiologic data are necessary to show that new connections are indeed functioning in the brain and spinal cord.

Two aspects on neural stem cells of clinical relevance that are not discussed in this review are the possible role of stem cells as origin of glioblastoma and medulloblastoma (Sanai *et al*, 2005; Singh *et al*, 2004) and the potential use of neural stem cells as delivery vehicles for tumor-toxic molecules to target tumor cells (Ziu *et al*, 2006; Yip *et al*, 2006). The major reason for the bad prognosis of glioblastoma is the highly infiltrative nature of glioma cells. Tumor-produced extracellular matrix is permissive for stem-cell migration, and neural stem cells are able to target disseminated glioma cells and serve as therapeutic delivery vehicles. Understanding the mechanisms that govern the cell migration toward invasive tumor cells, and clarification of the genesis of glioblastoma, are likely to have an impact on future development of cell therapy after brain lesions.

References

Altman J, Das GD (1965) Auroradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. *J Comp Neurol* 124:319–35

Arvidsson A, Collin T, Kirik D, Kokaia Z, Lindvall O (2002) Neuronal replacement from endogenous precursors in the adult brain after stroke. *Nat Med* 8:963–70

Bareyre FM, Kerschensteiner M, Misgeld T, Sanes JR (2005) Transgenic labeling of the corticospinal tract for monitoring axonal responses to spinal cord injury. *Nat Med* 11:1355–60

Bareyre FM, Kerschensteiner M, Raineteau O, Mettenleiter TC, Weinmann O, Schwab ME (2004) The injured spinal cord spontaneously forms a new intraspinal circuit in adult rats. *Nat Neurosci* 7:269–77

Barkho BZ, Song H, Aimone JB, Smrt RD, Kuwabara T, Nakashima K, Gage FH, Zhao X (2006) Identification of astrocyte-expressed factors that modulate neural stem/progenitor cell differentiation. *Stem Cells Dev* 15: 407–21

Beites CL, Kawauchi S, Crocker CE, Calof AL (2005) Identification and molecular regulation of neural stem cells in the olfactory epithelium. *Exp Cell Res* 306: 309–16

Berlucchi G (2004) The origin of the term plasticity in the neurosciences: Ernesto Lugaro and chemical synaptic transmission. *J Hist Neurosci* 11:305–9

Berninger B, Hack MA, Gotz M (2006) Neural stem cells: on where they hide, in which disguise, and how we may lure them out. *Handb Exp Pharmacol* 174:319–60

Bhardwaj RD, Curtis MA, Spalding KJ, Buchholz BA, Find D, Björk-Eriksson T, Nordborg C, Gabe FH, Druid H, Eriksson PS, Frisén J (2006) Neocortical neurogenesis in humans is restricted to development. *Proc Natl Acad Sci USA* 103:12564–8

Bradbury EJ, McMahon SB (2006) Spinal cord repair strategies: why do they work? *Nat Rev Neurosci* 7: 644–53

Bradbury EJ, Moon LDF, Popat RJ, King VR, Bennett GS, Patel PN, Fawcett JW, McMahon SB (2002) Chondroitinase ABC promotes functional recovery after spinal cord injury. *Nature* 416:636–40

Bruel-Jungerman E, Laroch S, Rampon C (2005) New neurons in the dentate gyrus are involved in the expression of enhanced long-term memory following environmental enrichment. *Eur J Neurosci* 21:513–21

Buffo A, Vosko MR, Erturk D, Hamann GF, Juncker M, Rowitch D, Gort M (2005) Expression pattern of the transcription factor Olig2 in response to brain injuries: implications for neuronal repair. *Proc Natl Acad Sci USA* 102:18183–8

Caggiano AO, Zimber MP, Ganguly A, Blight AR, Gruskin EA (2005) Chondroitinase ABCI improves locomotion and bladder function following contusion injury of the rat spinal cord. *J Neurotrauma* 22:226–9

Chen J, Magavi SS, Macklis JD (2004) Neurogenesis of corticospinal motor neurons extending spinal projections in the adult mice. *Proc Natl Acad Sci USA* 101:16357–62

Chen M, Huber AB, van der Haar ME, Frank M, Schnell L, Spillmann AA, Christ F, Schwab ME (2000) Nogo-A is a myelin-associated neurite outgrowth inhibitor and an antigen for monoclonal antibody IN-1. *Nature* 403: 369–70

Chen P, Goldberg DE, Kolb B, Lanser M, Benowitz L I (2002) Inosine induces axonal rewiring and improves behavioral outcome after stroke. *Proc Natl Acad Sci USA* 99:9031–6

Chen XH, Iwata A, Nonaka M, Browne KD, Smith DH (2003) Neurogenesis and glial proliferation persist for at least one year in the subventricular zone following-brain trauma in rats. *J Neurotrauma* 20:623–31

Cummings BJ, Uchida N, Tamaki SJ, Salazar DL, Hooshmand M, Summers R, Gage F, Anderson AJ (2005) Human neural stem cells differentiate and promote locomotor recovery in spinal cord-injured mice. *Proc Natl Acad Sci* 102:14069–74

Curtis MA, Penny EB, Pearson J, Dragunov M, Connor B, Faull RL (2005) The distribution of progenitor cells in the subependymal layer of the lateral ventricle in the normaland Huntington's disease human brain. *Neuroscience* 132:777–88

Curtis MA, Penney EB, Pearson J, van Roon-Mom, Butterworth NJ, Dragunov M, Connor B, Faull RLM (2003) Increased cell proliferation and neurogenesis in the adult human Huntington's disease brain. *Proc Natl Acad Sci* 100:9023–7

Dancause N, Barbay S, Frost SB, Plautz EJ, Chen D, Zoubina EV, Stowe AM, Nudo RJ (2005) Extensive cortical rewiring after brain injury. *J Neurosci* 25: 10167–79

Darsalia V, Heldmann U, Lindvall O, Kokaia Z (2005) Stroke-induced neurogenesis in aged brain. *Stroke* 36:1780–5

DeFelipe J (2006) Brain plasticity and mental processes: Cajal again. *Nat Rev Neurosci* 7:811–7

Dimou L, Schnell L, Montani L, Duncan C, Simonen M, Schneider R, Liebscher T, Gullo M, Schwab ME (2006) Nogo-A deficient mice reveal strain-dependent differences in axonal regeneration. *J Neurosci* 26:5591–603

Doetsch E, Caille I, Lim DA, Garcia-Verdugo JM, Alvarez-Buylla A (1999) Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. *Cell* 97:703–16

Donovan MH, Yazdani U, Norris RD, Games DC, German DC, Eisch AJ (2006) Decreased adult hippocampal neurogenesis in the PDAPP mouse model of Alzheimer's disease. *J Comp Neurol* 495:70–83

Edgerton VR, Kim SJ, Ichiyama RM, Gerasimenko YP, Roy RR (2006) Rehabilitative therapies after spinal cord injury. *J Neurotrauma* 23:560–70

Emsley JG, Mitchell BD, Kempermann G, Macklis JD (2005) Adult neurogenesis and repair of the adult CNS with neural progenitors, precursors, and stem cells. *Prog Neurobiol* 75:321–41

Eriksson PS, Perfilieva E, Björk-Eriksson T, Alborn AM, Nordborg C, Peterson DA, Gage FH (1998) Neurogenesis in the adult human hippocampus. *Nat Med* 4: 1313–7

Fahrner A, Kann G, Flubacher A, Heinrich C, Freiman TM, Zentner J, Frotscher M, Haas CA (2007) Granule cell dispersion is not accompanied by enhanced neurogenesis in temporal lobe epilepsy patients. *Exp Neurol* 203:320–33

Floel A, Cohen LG (2006) Translational studies in neurorehabilitation: from bench to bedside. *Cogn Behav Neurol* 16:1–10

Fouad K, Klusman I, Schwab ME (2004) Regenerating corticospinal fibers in the Marmose (*Callitrix jacchus*) after spinal cord lesion and treatment with the anti-Nogo-A antibody IN-1. *Eur J Neurosci* 20:2479–82

Fouad K, Schnell L, Bunge MB, Schwab ME, Liebscher T, Pearse DD (2005) Combining Schwann cell bridges and olfactory-ensheathing glia grafts with chondroitinase promotes locomotor recovery after complete transection of the spinal cord. *J Neurosci* 25:1169–78

Garcia AD, Doan NB, Imura T, Bush TG, Sofroniew MW (2004) GFAP-expressing progenitors are the principal source of constitutive neurogenesis in adult mouse forebrain. *Nat Neurosci* 7:1233–41

GrandPre, Li S, Strittmatter SM (2002) Nogo-66 receptor antagonist peptide promotes axonal regeneration. *Nature* 417:547–51

Harel NY, Strittmatter SM (2006) Can regenerating axons recapitulate developmental guidance during recovery from spinal cord injury? *Nat Rev Neurosci* 7: 603–16

Hebb DO (1949) *The organization of Behavior*. New York, NY.: John Wiley Sons Inc.

Hickmott PW, Merzenich MM (2002) Local circuit properties underlying cortical reorganization. *J Neurophysiol* 88:1288–301

Hofstetter CP, Holmström NAV, Lilja JA, Schweinhardt P, Hao J, Spenger C, Wiesenfeld-Hallin ÄZ, Kurpad SN, Frisén J, Olson L (2005) Allodynia limits the usefulness of intraspinal neural stem cell grafts; directed differentiation improves outcome. *Nat Neurosci* 8:346–53

Höglinger GU, Rizk P, Muriel MP, Duyckaerts C, Oertel WH, Caille I, Hirsch EG (2004) Dopamine depletion impairs precursor cell proliferation in Parkinson disease. *Nat Neurosci* 7:726–35

Horky LL, Galimi F, Gage FH, Horner PJ (2006) Fate of endogenous stem/progenitor cells following spinal cord injury. *J Comp Neurol* 498:525–38

Horner PJ, Power AE, Kempermann G, Kuhn HG, Palmer TD, Winkler J, Thal LJ, Gage FH (2000) Proliferation and differentiation of progenitor cells throughout the intact adult rat spinal cord. *J Neurosci* 20:2218–28

Ikegami T, Nakamura M, Yamane J, Katoh H, Okada S, Iwanami A, Watanabe K, Ishii K, Kato F, Fujita H, Takahashi T, Okano HJ, Toyama Y, Okano H (2005) Chondroitinase ABC combined with neural stem/progenitor cell transplantation enhances graft cell migration and outgrowth of growth-associated protein-43-positive fibers after rat spinal cord injury. *Eur J Neurosci* 22:3036–46

Jagasia R, Song H, Gage FH, Lie DC (2006) New regulators in adult neurogenesis and their potential role for repair. *Trends Mol Med* 12:400–5

Jenkins WM, Merzenich MM (1987) Reorganization of neocorticl representations after brain injury: a neurophyiological model of the bases of recovery from stroke. *Prog Brain Res* 71:249–66

Jessberger S, Kempermann G (2003) Adult-born hippocampal neurons mature into activity-dependent responsiveness. *Eur J Neurosci* 18:2707–12

Jin K, Galvan V, Xie L, Mao XO, Gorostiza OF, Bredesen DE, Greenberg DA (2004*a*) Enhanced neurogenesis in Alzheimer's disease transgenic (PDGF-APPSv,Ind) mice. *Proc Natl Acad Sci USA* 101:13363–7

Jin K, LaFevre-Berndt M, Sun Y, Chen S, Gafrni J, Crippen D, Logvinova A, Ross CA, Greenberg DA (2005) FGF-2 promotes neurogenesis and neuroprotection and prolongs survival in a transgenic mouse model of Huntington's disease. *Proc Natl Acad Sci USA* 102: 18189–94

Jin K, Minami M, Lan JQ, Mao XO, Batteur S, Simon R, Greenberg DA (2001) Neurogenesis in dentate subgranular zone after focal cerebral ischemia in the rat. *Proc Natl Acad Sci USA* 98:4710–5

Jin K, Minami M, Xie L, Sun Y, Mao XO, Wang Y, Simon RP, Greenberg DA (2004) Ischemia-induced neurogenesis is preserved but reduced in the aged rodent brain. *Aging Cell* 3:373–7

Jin K, Peel AL, Mao XO, Xie L, Cottrell BA, Henshall DC, Greenberg DA (2004*b*) Increased hippocampal neurogenesis in Alzheimer's disease. *Proc Natl Acad Sci USA* 101:343–7

Jin K, Wang X, Xie L, Mao XO, Zhu W, Wang Y, Shen J, Ying M, Banwait S, Greenberg DA (2006) Evidence for stroke-induced neurogenesis in the human brain. *Proc Natl Acad Sci USA* 103:13198–202

Johansson BB (2004*a*) Functional and cellular effects of environmental enrichment after experimental brain infarcts. *Rest Neurol Neurosci* 22:163–74

Johansson BB (2004*b*) Brain plasticity in health and disease. *Keio J Med* 53:231–46

Johansson CB, Momma S, Clarke DL, Risling M, Lendahl U, Frisen J (1999) Identification of a neural stem cell in the adult mammalian central nervous system. *Cell* 96:25–34

Jones LL, Sajed D, Tuszynski MH (2003) Axonal regeneration through regions of chondroitin sulfate proteoglycan deposition after spinal cord injury: a balance of permissiveness and inhibition. *J Neurosci* 23:9276–88

Kaas JH (2005) From mice to men: the evolution of the large, complex human brain. *J Biosci* 30:155–65

Kaas JH, Florence SL, Jain N (1999) Subcortical contribution to massive cortical reorganization. *Neuron* 22: 657–60

Keirstead HS, Nistor G, Bernal G, Totoiu M, Cloutier F, Sharp K, Steward O (2005) Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants remyelinate and restore locomotion after spinal cord injury. *J Neurosci* 25:4694–705

Kempermann G, Chesler EJ, Lu L, Williams RW, Gage FM (2006) Natural variation and genetic covariance in adult hippocampal neurogenesis. *Proc Natl Acad Sci USA* 103:780–5

Kerr JND, Greenberg D, Helmchen F (2005) Imaging input and output of neocortical networks *in vivo*. *Proc Natl Acad Sci* 102:14063–8

Kokaia Z, Thored P, Arvidsson A, Lindvall O (2006) Regulation of stroke-induced neurogenesis in adult brain – recent scientific progress. *Cereb Cortex* 16: 162–7

Kolb B, Morshead C, Gonzalez C, Kim M, Gregg C, Shigo T, Weiss S (2006) Growth factor- stimulated generation of new cortical tissue and functional recovery after stroke damage to the motor cortex of rats. *J Cereb Blood Flow Metab* . Epub ahead of print.

Komitova M, Johansson BB, Eriksson PS (2006*a*) On neural plasticity, new neurons and the postischemic milieu: an integrated view on experimental rehabilitation. *Exp Neurol* 199:42–55

Komitova M, Mattsson B, Johansson BB, Eriksson PS (2005) Enriched environment increases neural strem/progenitor cell proliferation and neurogenesis in the subventricular zone of stroke-lesioned adult rats. *Stroke* 36:1278–82

Komitova M, Perfilieva E, Mattsson B, Eriksson PS, Johansson BB (2006*b*) Enriched environment after focal brain ischemia enhances the generation of astroglia and NG2 positive polydendrocytes in adult neocortex. *Exp Neurol* 199:113–21

Lazic SE, Grote HE, Armstrong RJ, Blakemore C, Hannan AJ, van Dellen A, Barker RA (2004) Decreased hippocampal cell proliferation in R6/1 Huntington's mice. *Neuroreport* 15:811–3

Lazic SE, Grote HE, Blakemore C, Hannan AJ, van Dellen A, Phillips W, Barker RA (2006) Neurogenesis in the R6/1 transgenic mouse model of Huntington's disease: effects of environmental enrichment. *Eur J Neurosci* 23:1829–38

Lee J-K, Kim J-E, Sivula M, Strittmatter SM (2004) Nogo receptor antagonism promotes stroke recovery by enhancing axonal plasticity. *J Neurosci* 24:6209–17

Lentzlinger PM, Shimizu S, Marklund N, Thompson HJ, Schwab ME, Saatman KE, Hoover RC, Bareyre FM, Motta M, Luginbuhl A, Pape R, Clouse AK, Morganti-Kossmann C, McIntosh TK (2005) Delayed inhibition of Nogo-A does not alter injury-induced axonal sprouting but enhances recovery of cognitive function following experimental traumatic brain injury in rats. *Neuroscience* 134:1047–56

Leuner B, Gould E, Shors TJ (2006) Is there a link between adult neurogenesis and learning? *Hippocampus* 16: 216–24

Levine JM, Reynolds R, Fawcett JW (2001) The oligodendrocyte precursor cell in health and disease. *Trends Neurosci* 24:39–47

Lewis PD (1968) A quantitative study of cell proliferation in the subependymal layer of the adult rat brain. *Exp Neurol* 20:203–7

Li S, Kim JE, Budel S, Hampton TG, Strittmatter SM (2005*a*) Transgenic inhibition of Nogo-66 receptor function allows sprouting and improved locomotion after spinal cord injury. *Mol Cell Neurosci* 29:26–39

Li S, Liu BP, Budel S, Li M, Ji B, Walus L, Li W, Jirik A, Rabacchi S, Choi E, Worley D, Sah DW, Pepinsky B, Lee D, Relton J, Strittmatter SM (2004) Blockade of Nogo-66, myelin-associated glycoprotein, and oligodendrocyte myelin glycoprotein by soluble Nogo-66 receptor promotes axonal sprouting and recovery after spinal cord injury. *J Neurosci* 24:10511–20

Li Y, Decherchi P, Raisman G (2003) Transplantation of olfactory ensheathing cells into spinal cord lesions restores breathing and climbing. *J Neurosci* 23:727–31

Li Y, Field PM, Raisman G (1997) Repair of adult rat corticospinal tract by transplants of olfactory ensheathing cells. *Science* 277:2000–2

Li Y, Field PM, Raisman G (2005b) Olfactory ensheathing cells and olfactory nerve fibroblasts maintain continuous open channels for regrowth of olfactory nerve fibres. *Glia* 52:245–51

Li Y, Li D, Raisman G (2005c) Interaction of olfactory ensheathing cells with astrocytes may be the key to repair of tract injuries in the spinal cord: The pathway hypothesis. *J Neurocytol* 34:343–51

Li Y, Raisman G (1995) Sprouts from cut corticospinal axons persist in the presence of astrocytic scarring in long-term lesions of the adult rat spinal cord. *Exp Neurol* 134:102–11

Lichtenwalner RJ, Parent JM (2006) Adult neurogenesis and the ischemic forebrain. *J Cereb Blood Flow Metab* 26:1–20

Liebscher T, Schnell L, Schnell M, Scholl J, Schneider R, Gullo M, Fouad K, Mir A, Rausch M, Kindler D, Hamers FPT, Schwab ME (2005) Nogo-A antibody improves regeneration and locomotion of spinal cord-injured rats. *Ann Neurol* 58:706–19

Liu J, Solway 2, Messing RO, Sharp FR (1998) Increased neurogenesis in the dentate gyrus after transient global ischemia in gerbils. *J Neurosci* 18:7768–78

Lledo PM, Alonso M, Grubb MS (2006) Adult neurogenesis and functional plasticity in neuronal circuits. *Nat Rev Neurosci* 7:179–93

Lledo PM, Gheusi G, Vincent JD (2005) Information processing in the mammalian olfactory system. *Physiol Rev* 85:281–317

Lledo PM, Saghatelyan A (2005) Integrating new neurons into the adult olfactory bulb: joining the network, life-death decisions, and the effects of sensory experience. *Trends Neurosci* 28:248–54

Lopez-Vales R, Fores J, Verdu E, Navarro X (2006) Acute and delayed transplantation of olfactory ensheathing cells promote partial recovery after complete transection of the spinal cord. *Neurobiol Dis* 21:57–68

Magavi SS, Leavitt BR, Macklis JD (2000) Induction of neurogenesis in the neocortex of adult mice. *Nature* 405:951–5

Magavi SS, Mitchell BD, Szentirmai O, Carter BS, Macklis JD (2005) Adult-born and preexisting olfactory granule neurons undergo distinct experience-dependent modifications of their olfactory responses *in vivo*. *J Neurosci* 25:10729–39

Malberg JE, Schlechter LE (2005) Increasing hippocampal neurogenesis: a novel mechanism for antidepressant drugs. *Curr Pharm Des* 11:145–55

Markus TM, Tsai SY, Bollnow MR, Farrer RG, ÓBrien TE, Kindler-Baumann DR, Rausch M, Rudin M, Wiessner C, Mir AK, Schwab ME, Kartje GL (2005) Recovery and brain organization after stroke in adult and aged rats. *Ann Neurol* 58:950–3

McTigue DM, Tripathi R, Wei P (2006) NG2 colocalizes with axons and is expressed in a mixed cell population in spinal cord lesions. *J Neuropathol Exp Neurol* 65: 406–20

McTigue DM, Wei P, Stokes BT (2001) Proliferation of NG2-positiv cells and altered oligodendrocyte numbers in the contused rat spinal cord. *J Neurosci* 21:3392–400

Merzenich MM, Kaas JH (1982) Reorganization of mammalian somatosensory cortex following peripheral nerve injury. *Trends Neurosci* 5:434–6

Misgeld T, Kerschensteiner M (2006) *In vivo* imaging of the diseased nervous system. *Nat Rev Neurosci* 7: 449–63

Moreno-Flores MT, Bradbury E, Martín-Bermejo MJ, Agudo M, Lim F, Pastrana E, Avila J, Díaz-Nido J, McMahon SB, Wandosell F (2006) A clonal cell line from immortalized olfactory ensheathing glia promotes functional recovery in the injured spinal cord. *Mol Ther* 13:598–608

Mothe AL, Tator CH (2005) Proliferation, migration and differentiation of endogenous ependymal region stem/progenitor cells following minimal spinal cord injury in the adult rat. *Neuroscience* 131:177–87

Muotri AR, Gage FH (2006) Generation of neuronal variability and complexity. *Nature* 441:1087–93

Nakatomi H, Kuriu T, Okabe S, Yamamoto S, Hatano O, Kawahara N, Tamura A, Kirino T, Nakafuku M (2002) Regeneration of hippocampal pyramidal neurons after ischemic brain injury by recruitment of endogenous neural progenitors. *Cell* 110:429–41

Ninomiya M, Yamashita T, Araki N, Okano H, Sawamoto K (2006) Enhanced neurogenesis in the ischemic striatum following EGF-induced expansion of transit-amplifying cells in the subventricular zone. *Neurosci Lett* 403:63–7

Nudo RJ (2006) Mechanisms for recovery of motor function following cortical damage. *Curr Opin Neurobiol* 16:1–7

Okada S, Nakamura M, Katoh H, Miyao T, Shimazaki T, Ishii K, Yamane J, Yoshimura A, Iwamoto Y, Toyama Y, Okano H (2006) Conditional ablation of Stat3 or Socs3 discloses a dual role for reactive astrocytes after spinal cord injury. *Nat Med* 12:829–34

Palmer TD, Ray J, Gage FH (1995) FGF-2-responsive neuronal progenitors reside in proliferative and quiescent regions of the adult rodent brain. *Mol Cell Neurosci* 6:474–86

Palmer TD, Willhoite AR, Gage FH (2000) Vascular niche for adult hippocampal neurogenesis. *J Comp Neurol* 425:479–94

Papadopoulos CM, Tsai SY, Alsbiei T, ÓBrien TE, Schwab ME, Kartje GL (2002) Functional recovery and neuroanatomial plasticity following middle cerebral artery occlusion and IN-1 antibody treatment in the adult rat. *Ann Neurol* 51:433–44

Papadopoulos CM, Tsai SY, Cheatwood JL, Bollnow MR, Kolb BE, Schwab ME, Kartje GL (2006) Dendritic plasticity in the adult rat following middle cerebral artery occlusion and Nogo-A administration. *Cereb Cortex* 16:529–36

Parent JM, Elliott RC, Pleasure SJ, Nicholas MB, Lowenstein DH (2006) Aberrant seizure-induced neurogenesis in experimental temporal lobe epilepsy. *Ann Neurol* 59:81–91

Parent JM, Vexlaer ZS, Gong C, Derugin N, Ferriero DM (2002) Rat forebrain neurogenesis and striatal neuron replacement after focal stroke. *Ann Neurol* 52:802–13

Parent JM, Yu TW, Leibowitz RT, Geschwind DH, Sloviter RS, Lowenstein DH (1997) Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus. *J Neurosci* 17:3727–38

Pascual-Leone A, Amedi A, Fregni F, Merabet LB (2005) The plastic human brain cortex. *Annu Rev Neurosci* 28: 377–401

Pascual-Leone A, Grafman J, Hallett M (1994) Modulation of cortical motor output maps during development of implicit and explicit knowledge. *Science* 263:1287–9

Pastrana E, Moreno-Flores MT, Gurzov EN, Avila J, Wandosell F, Díaz-Nido J (2006) Genes associated with adult axon regeneration promoted by olfactory ensheathing cells: new role for matrix metalloproteinase 2. *J Neurosci* 26:5347–59

Pearse DD, Pereira FC, Marcillo AE, Bates ML, Berrocal YA, Filbin MT, Bunge MB (2004) cAMP and Schwann Cells promote axonal growth and functional recovery after spinal cord injury. *Nat Med* 10:610–6

Perfilieva E, Risedal A, Nyberg J, Johansson BB, Eriksson PS (2001) Gender and strain influence on neurogenesis in dentate gyrus of young rats. *J Cerebr Blood Flow Metab* 21:211–7

Petersen SE, van Mier H, Fiez JA, Raichle ME (1998) The effect of practice on the functional anatomy of task performance. *Proc Natl Acad Sci USA* 95:853–60

Pfeifer K, Vroemen M, Blesch A, Weidner N (2004) Adult neural progenitor cells provide a permissive guiding substrate for corticospinal axon growth following spinal cord injury. *Eur J Neurosci* 20:1695–704

Raisman G (2004) Myelin inhibitors: does NO mean GO? *Nat Rev Neurosci* 5:157–61

Ramon-Cueto A, Plant GW, Avila J, Bunge MB (1998) Long-distance axonal regeneration in the transected adult rat spinal cord is promoted by olfactory ensheathing glia transplants. *J Neurosci* 18:3803–15

Reier PJ (2004) Cellular transplantation strategies for spinal cord injury and translational neurobiology. *NeuroRx* 1:424–51

Reif A, Fritzen S, Finger M, Strobel A, Lauer M, Schmitt A, Lesch K-P (2006) Neural stem cell proliferation is decreased in schizophrenia, but not in depression. *Mol Psychiatry* 11:514–22

Rochefort C, Gheusi G, Vincent JD, Lledo PM (2002) Enriched odor exposure increases the number of newborn neurons in the adult olfactory bulb and improves odor memory. *J Neurosci* 22:2679–87

Rosenzweig MR (1960) Environmental complexity, cerebral change, and behavior. *Am Psychol* 21:321–32

Sanai N, Alvarez-Buylla A, Berger MS (2005) Neural stem cells and the origin of gliomas. *N Engl J Med* 353: 811–22

Schwab JM, Brechtel K, Mueller C-A. Failli V, Kaps H-P, Tuli SK, Schluesener HJ (2006) Experimental strategies to promote spinal cord regeneration – an integrative perspective. *Prog Neurobiol* 78:91–116

Schwab ME (2002) Repairing the injured spinal cord. *Science* 295:1029–31

Segal M (2005) Dendritic spines and long term plasticity. *Nat Rev Neurosci* 6:277–84

Seitz RJ, Butefisch CM, Kleiser R, Homberg V (2005) Reorganisation of cerebral circuits in human ischemic brain disease. *Rest Neurol Neurosci* 22:207–29

Seymour AB, Andrews EM, Tsai SY, Marcus TM, Bollnow MR, Brenneman MM, OBrien TE, Castro AJ, Schwab ME, Kartje GL (2005) Delayed treatment with monoclonal antibody IN-1 1 week after stroke results in recovery of function and corticorubral plasticity in adult rats. *Cerebr Blood Flow Metab* 25:1366–76

Shen Q, Goderie SK, Jin I, Karanth N, Sun Y, Abramova N, Vincent P, Pumiglia K, Temple S (2004) Endothelial cells stimulate selfrenewal and expand neuroenesis of neural stem cells. *Science* 304:1338–40

Silver J, Miller JH (2004) Regeneration beyond the glial scar. *Nat Neurosci Rev* 5:146–56

Singh SK, Hawkins C, Clarke ID, Squire JA, Bayani J, Hide T, Henkelman RM, Cusimano MD, Dirks PB (2004) Identification of human brain tumour initiating cells. *Nature* 432:396–401

Suzuki M, Raisman G (1992) The glial framework of central white matter tracts: segmented rows of contiguous interfascicular oligodendrocytes and solitary astrocytes give rise to a continuous meshwork of transverse and longitudinal processes in the adult rat fimbria. *Glia* 6:222–35

Takami T, Oudega M, Bates ML, Wood PM, Kleitman N, Bunge MB (2002) Schwann cell but not olfactory ensheathing glia transplants improve hindlimb locomotor performance in the moderately contused adult rat thoracic spinal cord. *J Neurosci* 22:6670–81

Tan AM, Colletti M, Rorai AT, Skene JH, Levine JM (2006) Antibodies against the NG proteoglycan promote the regeneration of sensory axons within the dorsal columns of the spinal cord. *J Neurosci* 26:4729–39

Tan AM, Zhang W, Levine JM (2005) NG2: a component of the glial scar that inhibits axon growth. *J Anat* 207: 717–25

Teremoto T, Qui J, Plumier JC, Moskowitz MA (2003) EGF amplifies the replacement of parvalbumin-expressing striatal interneurons after ischemia. *J Clin Invest* 111: 1125–32

Thored P, Andreasson A, Cacci E, Ahlenius H, Kallur T, Darsalia V, Ekdahl CT, Kokaia Z, Lindvall O (2006) Persistent production of neurons from adult brain stem cells during recovery after stroke. *Stem Cells* 24:739–47

Thuret S, Moon LDF, Gage FH (2006) Therapeutic interventions after spinal cord injury. *Nat Rev Neurosci* 7:628–43

Tsai PT, Ohab JJ, Kertesz N, Groszner M, Matter C, Gao J, Liu X, Hong W, Carmichel ST (2006) A critical role of erythropoietin receptor in neurogenesis and post-stroke recovery. *J Neurosci* 26:1269–74

Ward NS, Cohen LG (2004) Mechanisms underlying recovery of motor function after stroke. *Arch Neurol* 61: 1844–8

Will B, Galani R, Kelche C, Rosenzweig MR (2004) Recovery from brain injury in animals: relative efficacy of environmental enrichment, physical exercise or formal training (1990–2002). *Prog Neurobiol* 72:167–82

Yamashita T, Ninomiya M, Acosta PH, García-Verdugo JM, Sunabori T, Sakaguchi M, Adachi K, Kojima T, Hirota Y, Kawase T, Araki N, Abe K, Okano H, Sawamoto K (2006) Subventricular zone-derived neuroblasts migrate and differentiate into mature neurons in the post-stroke adult striatum. *J Neurosci* 26:6627–36

Yang H, Lu P, McKay HM, Bernot T, Keirstead H, Steward O, Gage FH, Edgerton VR, Tuszynski MH (2006*b*) Endogenous neurogenesis replaces oligodendrocytes and astrocytes after primate spinal cord injury. *J Neurosci* 26:2157–66

Yang LJS, Lorenzini L, Vajn K, Mountney A, Schramm LP, Schnaar RL (2006*a*) Sialidase enhances spinal axon outgrowh *in vivo*. *Proc Natl Acad Sci USA* 103:11057–62

Yang Z, Suzuki R, Daniels SB, Brunquell CB, Sala CJ, Nishiyama A (2006*c*) NG2 glial cells provide a favorable substrate for growing axons. *J Neurosci* 26:3829–39

Yip S, Sabetrasekh R, Sidman RL, Snyder EY (2006) Neural stem cells as novel cancer therapeutic vehicles. *Eur J Cancer* 42:1298–308

Yiu G, He Z (2006) Glial inhibition of CNS axon regeneration. *Nat Rev Neurosci* 7:617–27

Zai LJ, Wrathall JR (2005) Cell proliferation and replacement following contusive spinal cord injury. *Glia* 50: 247–57

Zhang RL, Zhang ZG, Zhang L, Chopp M (2001) Proliferation and differentiation of progenitor cells in the cortex and the subventricular zone in the adult rat after focal cerebral ischemia. *Neuroscience* 105:33–41

Ziu M, Schmidt NO, Cargioli TG, Aboody KS, Black PM, Carroll RS (2006) Glioma-produced extracellular matrix influences brain tumor tropism of human neural stem cells. *J Neurooncol* 79:125–33