Restorative Neurology and Neuroscience 22 (2004) 163–174
IOS Press

Functional and cellular effects of environmental enrichment after experimental brain infarcts

Barbro B. Johansson
Division for Experimental Brain Research, Department of Clinical Neuroscience, Lund University, Wallenberg Neuroscience Center, Lund, Sweden
Tel.: 46 46 222 0621; Fax: 46 46 222 0626; E-mail: Barbro.Johansson@neurol.lu.se

Abstract. Our genes interact with environmental stimuli throughout our lives. The attitude and reaction to an acute cerebral trauma or stroke, as well as the pre-lesion life event and activities, can influence functional outcome. Although difficult to separate in adult human beings, genetic and environmental factors can be selectively evaluated in animal studies. Post- ischemic housing in an enriched environment, i.e. larger cages which allow both social interaction and various activities improves functional outcome, modifies gene activation, and increases dendrite branching and number of dendritic spines in pyramidal neurons in layers II-III in the contra-lateral cortex. Furthermore, it alters lesion-induced progenitor cell differentiation and interacts with neocortical transplantation, drug treatment and training. It is proposed that the interaction between environment and specific treatment needs more clinical attention, and that a general stimulating and positive environment is the optimal base for specific interventions in neurological rehabilitation.

Keywords: Brain infarcts, dendritic spines, gene activation, progenitor cell differentiation, neocortical transplantation, plasticity, spontaneously hypertensive rats, stroke

1. Introduction

Half a century ago Donald Hebb demonstrated that laboratory rats allowed to run freely in his house had better memory and learning capacity than rats housed in laboratory cages [39]. This and further studies indicating that neuronal cortical connections can be remodeled by experience [28,40] initiated a number of early studies on behavioral, anatomical and biochemical effects of an enriched environment [3,20,30,42,93, 109], and it is now well established that an activity-stimulating environment can influence the healthy as well as in the lesioned brain in many ways [48–50,62, 86,104,112,115]. Surprisingly little clinical attention has been given to the experimental data on environmental influence on outcome after brain lesions.

2. Environmental effect on functional outcome after focal brain ischemia

Most surviving stroke patients improve with time and a spontaneous functional improvement takes place also in animals with experimental focal brain infarcts [77]. An important question is to what extent the post-ischemic environment, in addition to specific training and interventions, can enhance the spontaneous recovery processes. An early study showed that housing in an enriched environment prior to bilateral cortical lesions had a potent influence on initial deficit and recovery of locomotion, and in rats preoperatively housed in isolation, postoperative enrichment speeded recovery and reduced the deficit [41]. After occlusion of the middle cerebral artery (MCA) in spontaneously hypertensive rats, postoperatively repeatedly tested during 12 weeks, the rats housed in an enriched environment improved significantly more than individually housed rats in a leg

0922-6028/04/$17.00

placement test, beam walking, crossing a rotating pole, and climbing, with no difference in infarct volume and thalamic atrophy [77]. Compared to rats housed 3 or 4 together in cages with no special equipment, a significant effect of enriched housing was seen even when the transfer to an enriched environment was delayed for 15 days after the arterial occlusion [47]. Whereas the correlation between infarct size and functional outcome tend to increase with time in rats with standard laboratory housing, no correlation is seen between lesion size and outcome in rats housed in an enriched environment indicating plastic changes in the remaining intact brain [33].

3. Environment and gene activation

Brain-derived neurotrophic factor (BDNF) is known to play an important role in brain plasticity in intact animals. Contrary to the hypothesis that post-ischemic housing in an enriched environment could lead to an enhanced BDNF gene expression, a marked down-regulation in BDNF gene expression was observed with significant differences with standard rats above and enriched rats below baseline in the peri-infarct region, contra- lateral cortex, and in hippocampus 2 to 12 days after induction of ischemia [118]. The BDNF protein levels 12 days after the MCA occlusion was likewise significantly reduced in the peri-infarct area but not in the contra-lateral hemisphere [119]. An early dampening of the post-ischemic gene expression in rats housed in enriched environment was seen also for NGFI-A mRNA [17]. We have no evident explanation to this observation although we have postulated that it might be beneficial to reduce an initial hyperexcitability [118]. Cortical networks ad jacent to a focal brain ischemia are hyperexcitable because of an imbalance between excitation and inhibition with increased NMDA receptor-mediated excitation and decreased GABAergic inhibition [73,87]. Hyperexcitability has been recorded not only around the infarct but also in the contralateral hemisphere 1 week after a phototrombotic lesion or MCA occlusion. Both a negative role (impaired processing of incoming information) and a beneficial role (adaptation favoring recovery) of the hyperexcitability have been proposed [9,89].

4. Enriched environment, social interaction and physical activity

In the enriched environment used in our laboratory rats have opportunity to climb and use a number of tools that are changed two or three of times a week [77], and video recordings show that rats are very active particularly during the dark period, climbing, swinging and manipulating the tools and objects available to them in rather skilled ways. In addition to physical activities enriched environment stimulates social interactions but social grouping alone cannot explain the beneficial effect of an enriched environment [55,94]. As to physical exercise, wheel running prior to a transient global cerebral ischemia in gerbils can reduce mortality and neuronal damage [102], an effect proposed to be due to an improved post-ischemic recirculation [101]. An early study comparing the effect of pre-lesion exposure to enriched environment versus running prior to bilateral cortical ablation lesions demonstrated that physical activity did not yield the same protective effect fr om post-operative impairment as enriched environment, albeit the former rats recovered somewhat earlier than control rats [29]. Physical exercise in the form of wheel running increases cell proliferation and neuronal survival in healthy mice, and it has been proposed that physical exercise may be the most important component in housing in enriched environment [107,108]. However, no study has shown that wheel running initiated after a lesion is beneficial for functional outcome. A comparison between post-ischemic environmental enrichment, social housing and individual housing with free access to a running wheel in the home cage showed that enriched environment had by far the largest benefit and that social interaction was significantly better than running [55]. When a group of individually housed rats with no access to a running wheel was added in a later study, enriched and social rats were significantly better than runners, which did not differ from individually housed r ats with no access to a running wheel [91]. The transcription factors NGFI-A and NGFI-B, thought to be important in neuronal plasticity, did not differ from sham operated rats for rats housed in enriched or social environment one month after focal cortical ischemia, but were significantly lower in individually housed rats with or without access to a running wheel [18]. The experimental data indicating that running cannot substitute for enriched environment after focal brain ischemia in rats are consistent with the observations that motor learning but not repetitive physical exercise generates new synapses in the cerebellar cortex [6,61], and that strength training alone does not induce cortical reorganization [84,90]. Furthermore, unlimited running, although voluntary, may be stressful for lesioned rats [55, 91].

In a recent study on regional effects of wheel running and environmental enrichment on cell proliferation in the neocortex of adult healthy mice, environmental enrichment led to a significant increase in the number of new astrocytes in layer 1 of the motor cortex whereas voluntary wheel running caused an induction of microglia proliferation in superficial cortical layers of several brain regions [24]. Brain lesions induce microglia activation with complex and at least to a large extent detrimental effects [100]. One might speculate that a further microglia proliferation induced by running might not be beneficial in lesioned rats. The role of astrocytes after brain lesions is also complex [13]. However, astrocytes are important for neural plasticity including synapse formation [1,14,56,105], which might be important in compensatory reactions in the non-damaged part of the brain. Whether the different cellular reactions to wheel running and environmental enrichment in healthy animals have any relevance for the effects on functional outcome after focal brain lesions [17,55,91] remains to be studied.

5. Environmental effects on neuronal morphology and dendritic spines

Dendritic spines, i.e. tiny protrusions that are the primary postsynaptic targets of excitatory glutaminergic synapses in the mature brain, have been proposed as primary sites of synaptic plasticity [25,36]. The dendritic tree is covered with a variety of excitable synaptic channels operating on different time scales and with activity-dependent sensitivity enabling a sophisticated neuronal plasticity [103]. The spine cytoskeleton consists of actin filaments, and video recordings from hippocampal neurons expressing actin tagged with fluorescent protein have shown that the shape of spines can change rapidly [27,69], events that are accompanied by changes in calcium influx and decay [67,116]. Using a technique enabling in vivo images of neurons expressing green fluorescent protein, the lifetime of superficial pyramidal spines in the mouse barrel cortex has been observed to vary greatly [104]. About 20% of spines disappeared between imaging sessions from one day to the next, a loss that was balanced by formation of new spines. About 60% of dendritic spines persisted for at least 8 days, and of those 17% had disappeared one months after the imaging began. Serial - section electron microscopy of imaged dendritic segments revealed retrospectively that spine sprouting and retraction are associated with synapse formation and elimination. Trimming every other whisker, which induced a rapid and robust remodeling of whisker representation, increased the pool of transient spines present for only a day or less in the cortical representation areas of the trimmed whiskers [104]. Thus, experience-depending plasticity of cortical receptive fields was accompanied by increased synapse turnover. There may, however, be regional differences in spinal plasticity. In one study using a similar in vivo-technique on layer V pyramidal neurons in the visual cortex, the majority of spines were more stable [35].

Most studies on environmental influence on dendritic morphology have been performed using modification of Golgi technique or with electron microscopy of thin sections. Because of the small size and highly variable shapes of dendritic spines, those techniques are not optimal for identification and quantification of spines, for which three-dimensional visualization is essential [37]. Microinjection of Lucifer yellow into individual neurons combined with confocal microscopy allows a three-dimensional view of dendritic spines and better quantification. With this technique, pyramidal neurons in cortical layers II/III, which have extensive intra-cortical connections known to play a role in cortical plasticity, had more dendritic branches (Fig. 1) and significantly higher number of dendritic spines [Fig. 2] in the contra-lateral cortex of rats housed in an enriched environment than in rats housed in standard environment 3 weeks after a cortical infarct [51,52]. The immediate early g ene arc, a gene labeling dendrite, is markedly up regulated in the same region after exposure to an enriched environment for one hour daily for 3 weeks in intact animals [83].

6. Environmental interaction with lesion-induced proliferation and differentiation of endogenous progenitor cells

The subventricular zone and the subgranular zone of the dentate gyrus contain neural stem cells or progenitor cells which continuously give rise to new neurons in the adult brain including in humans [26]. Small numbers of progenitor cells are thought to be present in other brain areas including the cerebral cortex in rodents, and cortical neurogenesis has been induced by bFGF in intact rodents [78]. Whether neurogenesis occurs in the adult primate neocortex is controversial [76,88]. The progenitor cell proliferation in subventicular zone and hippocampus can be stimulated by exogenous factors such as trophic factors, hormones, physical activity, drugs, brain trauma, and global [66] and focal brain ischemia [2,46,64,80,120]. As reviewed elsewhere [50],

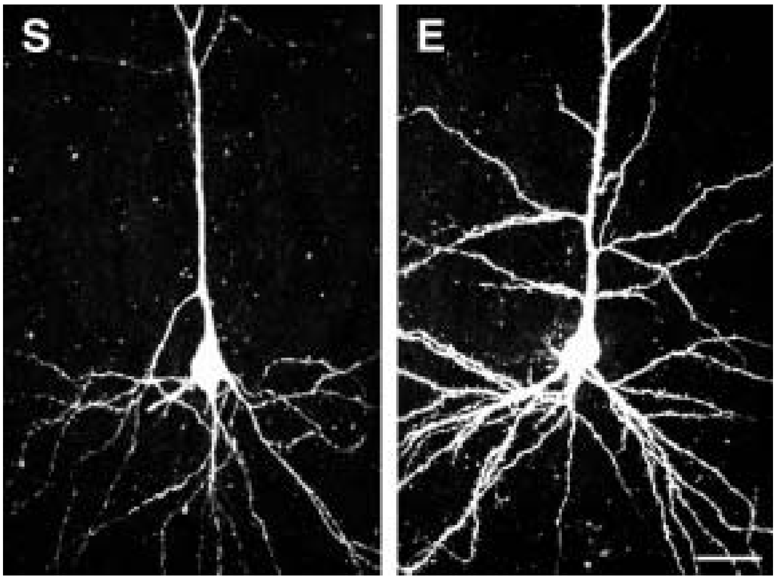

Fig. 1. A pyramidal neuron in cortical layer III in male 4 months' old spontaneously hypertensive rats housed in standard environment (S), or housed in an enriched environment for 3 weeks (E) as viewed in three-dimensional confocal laser scanning microscopy after microinjection of Lucifer yellow into individual neurons. From Johansson and Belichenko [51], with permission, Springer Verlag.

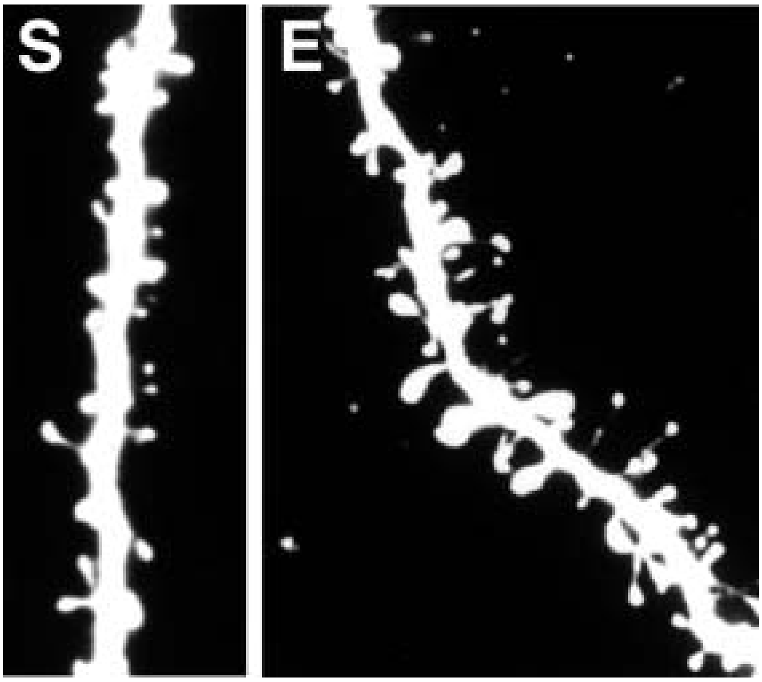

Fig. 2. Dendritic spines from pyramidal neurons in layer III contralateral to a cortical infarcts from a rat housed in standard environment (S) and a rat housed in an enriched environment (E) using the same technique as in Fig. 1.

an acute brain lesion can apparently induce chemotactic signals that stimulate endogenous cell proliferation and migration of endogenous and exogenous immature cells.

A stimulating environment enhances the survival of newly formed neurons in the hippocampus of intact rats and mice [60,75], even in old mice [59], a cellular plasticity that is accompanied by significant improvements of learning parameters and exploratory behavior. The combined effect of cortical ischemia and environmental stimulation on survival on cell proliferation and differentiation in the dentate gyrus has been studied in 6 months old spontaneously hypertensive with cortical infarcts. BrdU, a substance that marks dividing cells, was given daily during the first postoperative week [64]. 5 weeks later, a five- to six-fold ipsilateral increase in BrdU labeled cells compared to sham operated rats was seen in all rats, and about 80% of the new cells were neurons. Whereas there was no group difference in newly formed neurons, a highly significant difference in the number of new astrocytes was observed. In rats housed in standard environment few new astrocytes were forme d resulting in a many-fold increase in the neuron to glia ratio, a ratio that was normalized in rats housed in enriched environment [64]. The clinical relevance of this observation is not clear and we do not know whether lesion-induced neurogenesis and gliogenesis in hippocampus is of any relevance for functional outcome after cortical infarcts. Recent studies indicate significant differences between cellular reaction in the dentate gyrus and the subventricular zone after a cortical infarct [Komitova et al, in preparation]. In any case it seems likely that the low number of astrocytes in the standard group is insufficient to support the newly formed neurons whatever their function. As mentioned above, there is increasing evidence that astrocytes take an active part in neural signaling and in synaptic plasticity [1,14,71,105], and astrocytes increase in number and contact with synaptic elements in rats reared in an enriched environment [20,56,98].

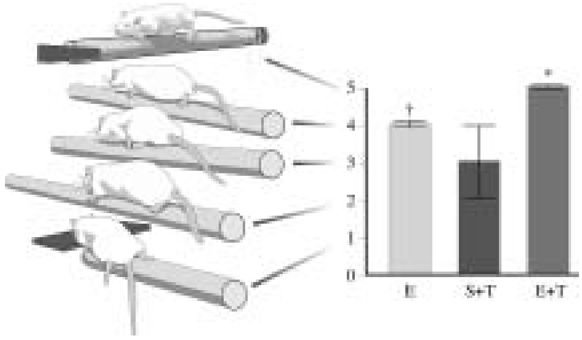

Fig. 3. Combination of fetal neocortical grafting and housing in an enriched environment results in better performance and prevents the lesion-induced deviation of the tail to the contra-lateral side normally seen when rats with cortical lesions cross a rotating pole. The tail effect is associated with significant reduction of the thalamic atrophy, most likely due to growth stimulating factors in grafts. In rats with poor performance the tail touches the rotating pole, in enriched rats without grafts it does not but the tail still deviates. Behavioral data 20 weeks after a distal ligation of the middle cerebral artery followed by grafting in two groups one week later. E = Non-grafted rats housed in an enriched environment; S+T: Transplanted rats housed in standard environment (3 or 4 rats per cage); E + T = transplanted rats housed in enriched environment. Median values and 25% percentiles. Kruskal -Wallis non-parametric ANOVA with a multiple comparison post hoc test at the 95% significance level. *Significantly different from the two other groups; † significantly different from S + T. Based on data published in Mattsson et al., [68].

7. Environmental influence on neocortical transplantation

Fetal neocortical tissue grafted into the infarcted area of adult rats receives ample afferent fibers from the intact host brain [31,97]. Reciprocal connections from the graft to the host brain exist but are sparse [99], presumably due to the presence of myelin preventing proteins in the adult brain [96]. Grafts respond to contralateral sensory stimulation with increased metabolic activity, indicating functional integration between neocortical grafts and host afferent systems [32]. However, improved performance in behavioral tests has been obtained only when grafting is combined with housing in an enriched environment [33,68]. When grafting was performed early, i.e. one week after a cortical infarct, significant improvement both in function and anatomy was obtained in rats housed in enriched environment compared to non-grafted rats in the same environment and to grafted rats housed in standard environment. After a cortical infarct, the tail deviates to the con tralateral side when traversing a rotating pole even in rats housed in enriched environment, which have no problem in crossing the pole. No such deviation was observed in transplanted rats housed in an environmental enrichment (Fig. 3), and the lesion-induced secondary atrophy in posterior thalamus was significantly reduced [68], most likely due to production of growth stimulating factors in the grafts. In another study, zinc-containing glutaminergic terminals from the host brain formed better connections with the grafts in rats reared in an enriched environment [117]. These data on interaction between transplantation and environment are consistent with data from other grafting procedures such as intrastriatal grafting [22,23].

8. Interactions between environment, drugs and training

The beneficial effect of a stimulating environment is likely to be related to release and combined action of various endogenous substances including catecholamines, glutamate and hormones. It is not surprising that environment can interact with the effects of drugs. Selegiline, an irreversible monoamine oxidase B inhibitor, which alone has no beneficial effect after focal cerebral ischemia, reduces behavioral and cognitive deficits when combined with housing in enriched environment [85]. Xerri and Zennou-Azogui have reported a protective effect of the combined treatment with piracepam and enriched environment on the neurophysiological properties and cortical representation areas of cortical neurons after neocortical lesions [113]. Enriched environment may also neutralize a drug effect. Thus, amphetamine, which in other experimental studies has been shown to improve outcome, had no additional effect in rats housed in enriched environment [54]. Likewise, data from our labo ratory suggest that diazepam, which has been reported to reduce functional outcome in individually housed rats [95] has no negative effect on outcome in rats housed in enriched environment [Zhao and Johansson, unpublished observations]. Skilled reach training combined with enriched environment has been shown to increase the performance and the dendritic growth compared to training alone [5]. However, no group housed in enriched with no training was included in the study.

9. Can an enriched environment enhance axonal outgrowth?

CNS myelin inhibits outgrowth of axons after brain lesions [12,96]. Three myelin proteins, Nogo, myelin-associated glycoprotein (MAG) and oligodendrocyte-myelin glycoprotein (OMgp) inhibit regeneration of axons after CNS injury. They share a common receptor, and blockade of this receptor promotes CNS repair and functional recovery [110]. Intrathecal administration of a Nogo receptor antagonist peptide to rats with mid-thoracic spinal cord hemisection resulted in significant axon grow of the corticospinal tract and improved functional recovery [34]. Intracerebral injection of the monoclonal antibody IN-1 in adult rats directly following a MCA occlusion enhanced functional recovery on a forelimb-reaching task. 10 weeks after the lesion new corticorubral connections from the opposite, unlesioned hemisphere could be demonstrated [79]. Continuous intraventricular infusion of an anti-Nogo-A antibody for 2 weeks, starting 24 h after phototrombotic cortical injury in normot ensive rats, and after middle cerebral occlusion in spontaneously hypertensive rats, significantly increased midline crossing of corticospinal fibers originating in the unlesioned sensorimotor cortex with a significant correlation between the number of crossing fibers and forepaw function [111]. Interestingly, a naturally occurring metabolite, the purine nucleoside inosine, likewise induced axonal rewiring and promoted behavioral outcome when infused continuously into the cisterna magna or into the lateral ventricle on the undamaged side after a partial MCA occlusion [11]. Neurons on the undamaged side of the brain extended new projections to denervated areas of the midbrain and spinal cord. The anatomical changes were paralleled by improved performance on several behavioral measures. The number of crossing cortico-rubral fibers was low in normal control animals and increased significantly after stroke, even in animals treated with saline alone, but with a further 2 to 3 fold increase after inosine infusion. Thus it seems that lesion alone, and inosine to a larger extent, can overcome some of the molecular signals that normally inhibit axonal growth. Subcutaneous administration of inosine has earlier been shown to stimulate axonal growth in the rat corticospinal tract after injury [4].

These two approaches to stimulate axonal growth implicate plasticity from the intact hemisphere as a mechanism for recovery in the rat. To what extent blockade of Nogo-A or administration of inosine can influence axonal growth in the lesioned hemisphere, where imaging studies in animals and man have indicated substantial reorganization [10,21] has so far not been reported. Whether addition of post-ischemic environmental enrichment can improve axonal growth corresponding to what has been observed after fetal neocortical transplantation [117] needs to be studied.

10. Can post-ischemic enriched environment have negative effects?

Concerns about early training have been raised based on studies with immobilization of the intact forelimb by casting immediately after an electrolytic lesion to the sensorimotor cortex in order to force the rats to use the weak limb. Seven days of forced overuse caused expansion of the neuronal injury and greatly interfered with restoration of function. When the initiation of forced use was delayed till the second week after the lesion, function was still reduced [44]. 10 days of overuse of the impaired forlimb also interfere with recovery of function after a transient MCA [7,8]. This is an interesting experimental model albeit with no evident clin-

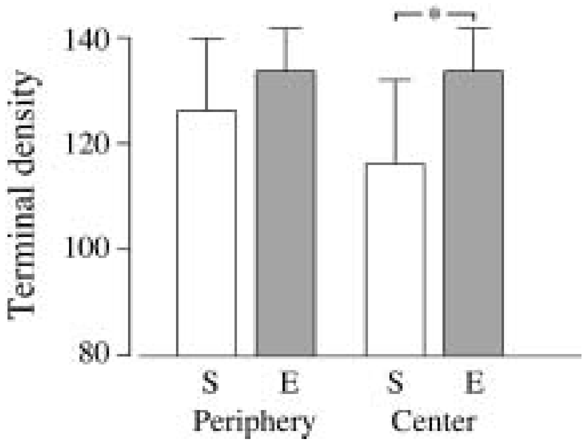

Fig. 4. The density of Zinc-containing glutaminergic terminals in fetal neocortical grafts 15 weeks after grafting 7 days following ligation of the middle cerebral artery distal to the striatal branches in hypertensive rats. Environmental enrichment improved the capacity of terminals entering the graft from the host brain to penetrate into the center of the graft. S = standard environment E = enriched environment. $^{*}p < 0.05$. Based on data published in Zeng et al. [117].

ical counterpart. Although constraint therapy is used in stroke rehabilitation it is usually initiated in a later stage. In contrast to the studies reported above, a study on early and late task-related treadmill training after a transient MCA occlusion indicated that training starting 24 hours, but not 2 weeks, after the ischemic event reduced infarct volume and improved outcome [114].

In the studies on enriched environment after focal ischemic lesions referred to above the animals were placed in an enriched environment not earlier than 24 h after the permanent legation of MCA, and no increase in infarct volume has been observed [47,55,77,91]. The enriched environment does not include any forced training, and the animals can use the intact side all the time together with the weak limbs. If the enriched housing is combined with training in which the rat needs to use both sides but still have the intact side available, no negative effect is found on outcome although the lesion size increases if the training is started 24 h [92] but not 3 days (unpublished data) after the lesion. The use-dependent exaggeration of brain injury has been shown to be glutamate dependent and can be prevented by the NMDA receptor antagonist MK-801 [43]. Thus, in the absence of constrain to use the intact limbs, the possible risk for additional tissue loss after focal brain isc hemia in the rat seems to be restricted to the acute stage before the infarct is manifest. In patients with stroke early mobilization is essential, and shorter time to start mobilization/training has been shown to be an independent factor significantly associated with discharge to home within 6 weeks after stroke onset [45].

11. How relevant are data from experimental animal models for clinical stroke rehabilitation?

Many brain lesion models have been called experimental stroke including transient or permanent vascular occlusions, cortical ablation, electrolytic, excitotoxic and phototrombotic models. The time course of lesion progression, influence on the surrounding tissue, and regenerative capability are likely to differ and could influence the efficacy of interventions. Thus grafting after a cortical infarct gives better host to graft connectivity than grafting to a cortical aspiration lesion [117]. Photothrombotic lesions are associated with an immediate break down of the blood-brain barrier and thus a different edema pattern than the more slowly developing edema after arterial ligations or embolization, and in cortical ablation lesions the surrounding tissue is not exposed to the same environment as in the vascular models. We do not know what influence such factors can have on the restoration processes in the brain. One important difference between rodents and man is that the human brain has a much larger proportion of white matter. The commonly used model of 2-hour transient MCA intraluminal occlusion reduces protein synthesis also in areas outside the MCA territory including ipsilateral thalamus, hypothalamus, hippocampus and substantia nigra, and it has been suggested that it should be referred to as an internal carotid artery occlusion model rather as an MCA occlusion model [57]. A corresponding human lesion might lead to life-threatening brain edema. In a comparison between a 2 h suture occlusion and permanent diathermy occlusion of MCA, the axonal degeneration and oligodendrocyte damage was much more severe in the suture model. The different distribution of axonal pathology in the two models was not a reflection of differences in the size of the neuronal perikarya pathology but rather a consequence of occlusion of additional vessels [72].

Lack of information on age, strain and sex is another problem. Few reports on animal studies give full data on the animals used, and weight rather than age is commonly used. However, weight curves differ between strains, and when the adult weight is reached there may be little further change. Within a strain it can differ with breeders and local food intake. Experience-dependent changes in dendritic arbor and spine density in neocortex have been reported to vary with age and sex [63]. Strain, sex and age differences have been documented in progenitor cell proliferation and survival in mice and rats [38,58,65,81]. We have learned much from experimental models. However, with better-defined models and information about the animals used, the results obtained may better answer clinical relevant questions. Pharmacological interventions may well differ with the models and animals used.

12. What is an enriched environment for a stroke patient? Relevance of animal studies on environmental enrichment for neurorehabilitation?

Regarding the relevance of animal studies on enriched environment for human stroke rehabilitation, two arguments can be raised. One is that standard laboratory housing is a deprived environment not comparable to normal human life, and that an enriched environment for a rat would be at least a little closer to human life. This is a valid argument, which, however, leads to the conclusion that a stimulating environment should be the standard condition in animal recovery studies. An opposite argument would be that some elderly stroke patients might have lived a rather isolated life before stroke onset, also a valid argument considering the fact that half of the first-ever stroke patients in Sweden [53] and probably several other European countries are 75 years or older. In any case, the transfer from home to hospital after an acute stroke involves a drastic change in environment that justifies any attempts to optimize the hospital and rehabilitation environment.

Are stroke units with specially trained medical and nursing staff, co-ordinated multidisciplinary rehabilitation, and education programs for patients and their families an enriched environment compared to general wards? Referral to a stroke unit or rehabilitation unit may increase the expectation of the patient, and a positive surrounding can stimulate them to take a more active part in the training. Recent studies using position emission tomography to address the question of a neuroanatomical correlate to expectation have shown that placebo and opioid analgesia share a neuronal network [82], that systemic injection of saline in patients with Parkinson's disease can induced dopamine release in the brain [19] and that placebo treatment in depressed patients induces some of the effects of antidepressant drugs positively related to dopamine and endorphin [70]. Thus there is no doubt that expectation plays an important role in all treatments.

13. Concluding remarks

The concept that the environment influences our life in health and disease is not new. Ancient and contemporary literature gives ample evidence for this commonly held view. A retrospective small study published 20 years ago proposed that the view through the window influenced recovery after surgery [106]. Individuals have different capabilities to handle crisis including diseases. The patient's own attitude, physical, social and intellectual activities influence functional outcome and quality of life after stroke [15,53]. Previous brain lesions may limit later plasticity processes as suggested from a study demonstrated that penetrating head injury in young adulthood exacerbated cognitive decline in later years [16]. However, the substantial experimental evidence that a post-ischemic stimulating environment can significantly improve functional outcome, influence cellular and molecular events, and interacts with other interventions, emphasizes the importance of general st imulation and activation in neurological and other rehabilitation, as a base to which specific interventions should be added.

References

[1] A. Araque, G. Carmignoto and P.G. Haydon, Dynamic signaling between astrocytes and neurons *Annual Review of Physiology* **63** (2001), 795–813.

[2] A. Arvidsson, Z. Kokaia and O. Lindvall, N-methyl-D-aspartate receptor-mediated increase of neurogenesis in adult rat dentate gyrus following stroke, *European Journal of Neuroscience* **14** (2001), 10–18.

[3] E.L. Bennett, M.C. Diamond, D.D. Krech and M.R. Rosenzweig, Chemical and anatomical plasticity of brain, *Science* **146** (1964), 610–619.

[4] L.I. Benowitz, D.E. Goldberg, J.R. Madsen, D. Soni and N. Irwin, Inosine stimulates extensive axon collateral growth in the rat corticospinal tract after injury, *Proceedings of the National Academy of Sciences USA* **96** (1999), 13486–13490.

[5] J. Biernaskie and D. Corbett, Enriched rehabilitative training promotes improved forelimb motor function and enhanced dendritic growth after focal ischemic injury, *Journal of Neuroscience* **21** (2001), 5272–5278.

[6] J.E. Black, K.R. Isaacs, B.J. Anderson, A.A. Alcantara and W.R. Greenough, Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats, *Proceedings of the National Academy of Sciences USA* **87** (1990), 5568–5572

[7] S.T. Bland, T. Schallert, R. Strong, J. Aronowski, J.C. Grotta and D.M. Feeney, Early exclusive use of the affected forelimb after moderate transient focal ischemia in rats: functional and anatomic outcome, *Stroke* **31** (2000), 1144–1152.

[8] S.T. Bland, R.N. Pillai, J. Aronowski, J.C. Grotta, and T. Schallert, Early overuse and disuse of the affected forelimb after moderately severe intraluminal suture occlusion of the middle cerebral artery in rats, *Behavioral Brain Research* **126** (2001), 33–41.

[9] I. Buchkremer-Ratzmann, M. August, G. Hagemann and O.W. Witte, Electrophysiological transcortical diaschisis after cortical photothrombosis in rat brain, *Stroke* **27** (1996), 1105–1119.

[10] J.R. Carey, T.J. Kimberley, S.M. Lewis, E.J. Auerbach, L. Dorsey, P. Rundquist and K. Ugurbil, Analysis of fMRI and finger tracking training in subjects with chronic stroke, *Brain* **125** (2002), 773–788.

[11] P. Chen, D.E. Goldberg, B. Kolb, M, Lanser and L.I. Benowitz, Inosine induces axonal rewiring and improves behavioral outcome after stroke, *Proceedings of the National Academy of Sciences USA* **99** (2002), 9031–9036.

[12] M.S.Chen, A.B. Huber, M.E. van der Haar, M. Frank, L. Schnell, A.A. Spillmann, F. Christ and M.E. Schwab, Nogo-A is a myelin-associated neurite outgrowth inhibitor and an antigen for monoclonal antibody IN-1, *Nature* **403** (2000), 369–370.

[13] Y. Chen and R.A. Swanson, Astrocytes and brain injury, *Journal of Cerebral Blood Flow and Metabolism* **23** (2003), 137–149.

[14] A. Chvatal and E. Sykova, Glial influence on neuronal signaling, *Progress in Brain Research* **125** (2000), 199–216.

[15] A. Colantonio, S.V. Kasl, A.M. Ostfeld and L.F. Berkman, Prestroke physical function predicts stroke outcomes in the elderly, *Archives of Physical Medicine and Rehabilitation* **77** (1996), 562–566.

[16] S. Corkin, T.J. Rosen, E.V. Sullivan and R.A. Clegg, Penetrating head injury in young adulthood exacerbates cognitive decline in later years, *Journal of Neuroscience* **9** (1989), 3876–3883.

[17] P. Dahlqvist, A, Rönnbäck, A. Risedal, R. Nergrdh, I.M. Johansson, J.R. Seckl, B.B. Johansson and T. Olsson, Effects of postischemic environment on transcription factor and serotonon receptor expression after permanent focal cortical ischemia in rats, *Neuroscience* **119** (2003), 643–652.

[18] P. Dahlqvist, L. Zhao, I.M. Johansson, B. Mattsson, B.B. Johansson, J.R. Seckl and T. Olsson, Environmental enrichment alters NGFI-A and glucocorticoid receptor mRNA expression after MCA occlusion in rats, *Neuroscience* **93** (1999), 527–535.

[19] R. de la Fuente-Fernandez and A.J. Stoessl, The placebo effect in Parkinson's disease, *Trends in Neuroscience* **159** (2002), 728–737.

[20] M. C. Diamond, F. Law, H. Rhodes, B. Lindner, M.R. Rosenzweig, D. Krech and E.L. Bennett, Increases in cortical depth and glia number in rats subjected to enriched environment, *Journal of Comparative Neurology* **128** (1966), 117–126.

[21] R.M. Dijkhuizen, A.B. Singhal, J.B. Mandeville, O. Wu, E.F. Halpern, S.P. Finklestein, B.R. Rosen and E.H. Lo, Correlation between brain reorganization, ischemic damage, and neurologic status after transient focal cerebral ischemia in rats: a functional magnetic resonance imaging study, *Journal of Neuroscience* **23** (2003), 510–517.

[22] M.D. Döbrössy and S.B. Dunnett, The influence of environment and experience on neural grafts, *Nature Neuroscience* **2** (2001), 871–879.

[23] M.D. Döbrössy, M. Le Moal, M.F. Montaron and N. Abrous, Influence of environment on the efficacy of intrastriatal dopaminergic grafts, *Experimental Neurology* **165** (2000), 172–183.

[24] D. Ehninger and G. Kempermann, Regional effects of wheel running and environmental enrichment, *Cerebral Cortex* **13** (2003), 845–851.

[25] J. Eilers and A. Konnerth, Dendritic signal integration, *Current Opinion in Neurobiology* **7** (1997), 385–390.

[26] P.S. Eriksson, E. Perfilieva, T. Björk-Eriksson, A.M. Alborn, C. Nordborg, D.A. Peterson and F.H. Gage, Neurogenesis in the adult human hippocampus, *Nature Medicine* **4** (1998), 1313–1317.

[27] M. Fischer, S. Kaech, D. Knutti and A. Matus, Rapid actin-based plasticity in dendritic spines, *Neuron* **20** (1998), 847–854.

[28] D.C. Forgays and J.W. Forgays, The nature of the effect of free-environmental experience in the rat, *Journal of Comparative Physiology and Psychology* **45** (1952), 322–328.

[29] A.M. Gentile, Z. Beheshti and M.J. Held, Enrichment versus exercise effects on motor impairments following cortical removals in rats, *Behavioral and Neural Biology* **47** (1987), 321–332.

[30] A. Globus, M.R. Rosenzweig, E.L. Bennett and M.C. Diamond, Effect of differential experience on dendritic spines counts in rat cerebral cortex, *Journal of Comparative Physiology and Psychology* **82** (1973), 175–181.

[31] M. Grabowski, P. Brundin and B.B. Johansson, Fetal neocortical grafts implanted in adult hypertensive rats with cortical infarcts following a middle cerebral artery occlusion. Ingrowth of afferent fibers from the host brain, *Experimental Neurology* **116** (1992), 105–121.

[32] M. Grabowski, P. Brundin and B.B. Johansson, Functional integration of cortical grafts placed in brain infarcts of rats, *Annals of Neurology* **34** (1993), 362–368.

[33] M. Grabowski, J.C. Sørensen, B. Mattsson, J. Zimmer and B.B. Johansson, Influence of an enriched environment and cortical grafting on functional outcome in brain infarcts of adult rats, *Experimental Neurology* **133** (1995), 96–102.

[34] T. Grandpre and S.M. Strittmatter, Nono-66 receptor antogonist peptide promotes axonal regeneration, *Nature* **417** (2002), 547–551.

[35] J. Grutzendler, N. Kasthuri and W.B. Gan, Long-term dendritic spine stability in the adult cortex, *Nature* **420** (2002), 751–752.

[36] K.M. Harris, Structure, development, and plasticity of dendritic spines, *Current Opinion in Neurobiology* **9** (1999), 343–348.

[37] K.M. Harris, F.E. Jensen and B. Tsao, Three-dimensional structure of dendritic spines and synapses in rat hippocampus (CA1) at postnatal day 15 and adult ages: implications for the maturation of synaptic physiology and long-term potentiation, *Journal of Neuroscience* **12** (1992), 2685–2705.

[38] N.L. Hayes and R.S. Nowakowski, Dynamics of cell proliferation in the adult dentate gyrus of two inbred strains of mice, *Brain Research Developmental Brain Research* **134** (2002), 77–85.

[39] D.O. Hebb, The effect of early experience on problem solving at maturity, *American Psychology* **2** (1947), 737–745.

[40] D.O. Hebb, *The Organization of Behavior*, Wiley & Sons Inc., New York, 1949.

[41] J. M. Held, J. Gordon and A.M. Gentile, Enrichmental influences on locomotor recovery following cortical lesions in rats, *Behavioral Neuroscience* **99** (1985), 678–690

[42] R.L. Holloway, Dendritic branching: some preliminary results of training and complexity in rat visual cortex, *Brain Research* **2** (1966), 393–396.

[43] J.L. Humm, D.A. Kozlowski, S.T. Bland, D.C. James and T. Schallert, Use-dependent exaggeration of brain injury: is glutamate involved? *Experimental Neurology* **157** (1999), 349–358.

[44] J.L. Humm, D.A. Kozlowski, D.C. James, J.E. Gotts and T. Schallert, Use-dependent exacerbation of brain damage occurs during an early post-lesion vulnerable period, *Brain Research* **783** (1998), 286–292.
[45] B. Indredavik, F. Bakke, S.A. Slördahl, R. Rikseth and L.L. Hheim, Treatment in a combined acute and rehabilitation stroke unit. Which aspects are most important? *Stroke* **30** (1999), 917–923.
[46] K. Jin, M. Minami, J.Q. Lan, X.O. Mao, S. Batteur, R.P. Simon and D.A. Greenberg, Neurogenesis in dentate subgranular zone and rostral subventricular zone after focal cerebral ischemia in the rat, *Proceedings of the National Academy of Sciences USA* **98** (2001), 4710–4715.
[47] B.B. Johansson, Functional outcome in rats transferred to an enriched environment 15 days after focal brain ischemia, *Stroke* **27** (1996), 324–326.
[48] B.B. Johansson, Brain plasticity and stroke rehabilitation, The Willis Lecture, *Stroke* **31** (2000), 223–231.
[49] B.B. Johansson, Environmental influence on recovery after brain lesions – experimental and clinical data, *Journal of Rehabilitation Medicine Supplement* **41** (2003), 11–16.
[50] B.B. Johansson, Regenerative ability in the CNS, in: *Recovery after Stroke*, J. Bogousslavsky, M.P. Barnes and B. Dobkin, eds, Cambridge University Press, in press.
[51] B.B. Johansson and P.V. Belichenko, Environmental influence on neuronal and dendritic spine plasticity after permanent focal brain ischemia, in: *Maturation Phenomenon in Cerebral Ischemia IV*, N.G. Bazan, U. Ito, V.L. Marcheselli, T. Kuroiwa and I. Klatzo, eds, Springer Verlag, Berlin, Heidelberg, 2001, pp. 77–83.
[52] B.B. Johansson and P.V. Belichenko, Neuronal plasticity and dendritic spines: effect of environmental enrichment on intact and postischemic rat brain, *Journal of Cerebral Blood Flow and Metabolism* **22** (2002), 89–96.
[53] B.B. Johansson, G. Jadbäck, B. Norrving and H. Widner, Evaluation of long-term functional status in first-ever stroke patients in a defined population, *Scandinavian Journal of Rehabilitation Medicine Supplement* **26** (1992), 103–114.
[54] B.B. Johansson, B. Mattsson and A.L. Ohlsson, Functional outcome after brain infarction: effect of enriched environment and amphetamine, in: *Maturation phenomenon in cerebral ischemia II*, U. Ito, T. Kirino, T. Kuroiwa and I. Klatzo, eds, Springer-Verlag, Berlin, Heidelberg, 1997, pp. 159–167.
[55] B.B. Johansson, A.L. Ohlsson, Environment, social interaction and physical activity as determinants of functional outcome after cerebral infarction in the rat, *Experimental Neurology* **139** (1996), 322–327.
[56] T.A. Jones and W.T. Greenough, Ultrastructural evidence for increased contact between astrocytes and synapses in rats reared in a complex environment, *Neurobiology of Learning and Memory* **65** (1996), 48–56.
[57] H. Kanemitsu, T. Nakagomi, A. Tamura, T. Tsuchiya, G. Kono and K. Sano, Differences in the extent of primary ischemic damage between middle cerebral artery coagulation and intraluminal occlusion models, *Journal of Cerebral Blood Flow and Metabolism* **22** (2002), 1196–1204.
[58] G. Kempermann and F.H. Gage, Genetic influence on phenotypic differentiation in adult hippocampal neurogenesis, *Brain Research Developmental Brain Research* **134** (2002), 1–12.
[59] G. Kempermann, D. Gast and F.H. Gage, Neuroplasticity in old age: sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment, *Annals of Neurology* **52** (2002), 133–134.
[60] G. Kempermann, H.G. Kuhn and F.H. Gage, More hippocampal neurons in adult mice living in an enriched environment, *Nature* **386** (1997), 493–495.
[61] J.A. Kleim, R.A. Swain, K.A. Armstrong, R.M. Napper, T.A. Jones and W.T. Greenough, Selective synaptic plasticity within the cerebellar cortex following complex motor skill learning, *Neurobiology of Learning and Memory* **69** (1998), 274–189.
[62] B. Kolb, *Brain plasticity and behaviour*, Lawrence Erlboum, Hillsdale, New Jersey, 1995.
[63] B. Kolb, R. Gibb and G. Gorny, Experience-dependent changes in dendritic arbor and spine density in neocortex vary qualitatively with age and sex, *Neurobiology of Learning and Memory* **79** (2003), 1–10.
[64] M. Komitova, E. Perfilieva, B. Mattsson, P.S. Eriksson and B.B. Johansson, Effects of cortical ischemia and postischemic environmental enrichment on hippocampal cell genesis and differentiation in the adult rat, *Journal of Cerebral Blood Flow and Metabolism* **22** (2002), 852–860.
[65] H.G. Kuhn, H. Dickinson-Anson and F.H. Gage, Neurogenesis in the dentate gyrus of the adult rat: Age related decrease of neuronal progenitor population, *Journal of Neuroscience* **16** (1996), 2027–2033.
[66] J. Liu, R. Bernabaeu, L. Aigang and F.R. Sharp, Neurogenesis and gliogenesis in the postischemic brain, *Neuroscientist* **6** (2000), 362–370.
[67] A. Majewska, A. Tashiro and R. Yuste, Regulation of spine calcium dynamics by rapid spine motility, *Journal of Neuroscience* **20** (2000), 8262–8268.
[68] B. Mattsson, J.C. Sørensen, J. Zimmer and B.B. Johansson, Neural grafting to experimental neocortical infarcts improves behavioral outcome and reduces thalamic atrophy in rats housed in an enriched but not in standard environments, *Stroke* **28** (1997), 1225–1232.
[69] A. Matus, Postsynaptic actin and neuronal plasticity, *Current Opinion in Neurobiology* **9** (1999), 561–565.
[70] H.S. Mayberg, J.A. Silva, S.K. Brannan, J.L. Tekell, R.K. Mahurin, S.McGinnis and P.A. Jerabek, The functional neuroanatomy of the placebo effect, *American Journal of Psychiatry* **159** (2002), 728–737.
[71] M. Mazzanti and P.G. Haydon, Astrocytes selectively enhance N-type calcium current in hippocampal neurons, *Glia* **41** (2003), 128–136.
[72] J. McCulloch, K. Komajti, V. Valeriani and D. Dewar, Beyond neuroprotection: the protection of axons and oligodendrocytes in cerebral ischemia, in: *Cerebrovascular disease*, P.H. Chan, ed., 22nd Princeton Conference, Cambridge University Press, Cambridge, 2002, pp 404–415.
[73] T. Mittmann, M. Qu, K. Zilles and H.J. Luhmann, Long-term cellular dysfunction after focal cerebral ischemia: in vitro analyses, *Neuroscience* **85** (1998), 15–27.
[74] C.M. Müller, A role for glial cells in activity-dependent central nervous plasticity? Review and hypothesis, *International Review of Neurobiology* **34** (1992), 215–281.
[75] M. Nilsson, E. Perfilieva, U. Johansson, O. Orwar and P.S. Eriksson, Enriched environment increases neurogenesis in the adult rat dentate gyrus and improves spatial memory, *Journal of Neurobiology* **39** (1999), 569–578.
[76] R.S. Nowakowski and N.L. Hayes, New neurons: extraordinary evidence or extraordinary conclusion? *Science* **288** (2000), 771.
[77] A.L. Ohlsson and B.B. Johansson, Environment influences functional outcome of cerebral infarction in rats, *Stroke* **26** (1995), 644–649.

[78] T.D. Palmer, E.A. Markakis, A.R. Willhoite, F. Safar, and F.H. Gage, Fibroblast Growth Factor-2 activates a latent neurogenic program in neural stem cells from diverse regions of the adult CNS, *Journal of Neuroscience* **19** (1999), 8487–8497.

[79] C.M. Papadopoulos, S.Y. Tsai, T. Alsbiei, T.E. O'Brien, M.E. Schwab and G.L. Kartje, Functional recovery and neuroanatomical plasticity following middle cerebral artery occlusion and IN-1 antibody treatment in the adult rat, *Annals of Neurology* **51** (2002), 433–441.

[80] J.M. Parent, Z.S. Vexler, C. Gong, N. Derugin and D.M. Ferriero, Rat forebrain neurogenesis and striatal neuron replacement after focal stroke, *Annals of Neurology* **52** (2002), 802–813.

[81] E. Perfilieva, A. Risedal, J. Nyberg, B.B. Johansson and P.S. Eriksson, Gender and strain influence on neurogenesis in dentate gyrus of young rats, *Journal of Cerebral Blood Flow and Metabolism* **21** (2001), 211–217.

[82] P. Petrovic, E. Kalso, K.M. Petersson and M. Ingvar, Placebo and opioid analgesia – Imaging a shared neuronal network, *Science* **295** (2002), 1737–1740.

[83] M.R. Pinaud, H.A. Penner, Robertson and R.W. Currie, Upregulation of the immediate early gene arc in the brains of rats exposed to environmental enrichment: implications for molecular plasticity, *Brain Research and Molecular Brain Research* **91** (2001), 50–56.

[84] G.W. Plautz, Millikan and R.J. Nudo, Effect of repetitive motor training on movement prepresentations in adult squirrel monkeys: role of use versus learning, *Neurobiology of Learning and Memory* **74** (2000), 27–55.

[85] K. Puurunen, J. Jolkkonen, J. Sieviö, A. Haapalinna and J. Sivenius, Selegiline combined with enriched-environment housing attenuates spatial learning deficits following focal cerebral ischemia in rats, *Experimental Neurology* **167** (2001), 348–355.

[86] K. Puurunen and J. Sivenius, Influence of enriched environment on spatial learning following cerebral insult, *Rev Neurosci* **13** (2002), 347–364.

[87] M. Qu, T. Mittmann, H.J. Luhmann, A. Schleicher and K. Zillis, Long-term changes of ionotropic glutamate and GABA receptors after unilateral permanent focal cerebral ischemia in the mouse brain, *Neuroscience* **85** (1998), 29–43.

[88] P.Rakic, Neurogenesis in adult primate neocortex: an evaluation of the evidence, *Nature reviews Neurosciences* **3** (2002), 65–71.

[89] S. Reinecke, M. Lutzenburg, G. Hagemann, C. Bruehl, T. Neumann-Haefelin and O.W. Witte, Electrophysiological transcortical diaschisis after middle cerebral artery occlusion (MCAO) in rats, *Neuroscience Letters* **261** (1999), 85–88.

[90] M.S. Remple, R.M. Bruneau, P.M. VandenBerg, C. Coertzen and J.A. Kleim, Sensitivity of cortical movement representations to motor experience: evidence that skill learning but not strength traning induced cortical reorganization, *Behavioral Brain Research* **123** (2001), 133–141.

[91] A. Risedal, B. Mattsson, P. Dahlqvist, C. Nordborg, T. Olsson and B.B. Johansson, Environmental influences on functional outcome after a cortical infarct in the rat, *Brain Research Bulletin* **58** (2002), 315–321.

[92] A. Risedal, J. Zeng and B.B. Johansson, Early training may exacerbate brain damage after focal brain ischemia in the rat, *Journal of Cerebral Blood Flow and Metabolism* **19** (1999), 997–1003.

[93] M.R. Rosenzweig, Environmental complexity, cerebral change, and behavior, *American Psychologist* **21** (1966), 321–332.

[94] M.R. Rosenzweig, E.L. Bennett, M. Herbert and H. Morimoto, Social grouping cannot account for cerebral effects of enriched environments, *Brain Research* **153** (1978), 563–576.

[95] T. Schallert, T.D. Hernandez and T.M. Barth, Recovery of function after brain damage: Severe and chronic disruption by diazepam, *Brain Research* **379** (1986), 104–111.

[96] M.E. Schwab, Myelin-associated inhibitors of neurite growth and regeneration in the CNS, *Trends in Neuroscience* **13** (1990), 452–456.

[97] F.R. Sharp, M.F. Gonzalez and S.M. Sagar, Fetal frontal cortex transplanted to injured motor/sensory cortex of adult rats. II: VIP-, somatostatin, and NPY-immunoreactive neurons, *Journal of Neuroscience* **7** (1987), 3002–3015.

[98] A.M. Sirevaag and W.T. Greenough, Plasticity of GFAP-immunoreactive astrocyte size and number of visual cortex in rats read in complex environments, *Brain Research* **540** (1991), 273–278.

[99] J.C. Sørensen, M. Grabowski, J. Zimmer and B.B. Johansson, Fetal neocortical tissue blocks implanted in brain infarcts of adult rats interconnect with the host brain, *Experimental Neurology* **138** (1996), 227–235.

[100] G. Stoll, S. Jander and M. Schroeter, Detrimental and beneficial effects of injury-induced inflammation and cytokine expression in the nervous system, *Advance in Experimental Medicine and Biology* **513** (2002), 87–113.

[101] W. Stummer, A. Baethmann, R. Murr, L. Schurer and O.S. Kempski, Cerebral protection against ischemia by locomotor activity in gerbils. Underlying mechanisms, *Stroke* **26** (1995), 1423–1429.

[102] W. Stummer, K. Weber, B. Tranmer, A. Baethmann and O. Kempski, Reduced mortality and brain damage after locomotor activity in gerbil forebrain ischemia, *Stroke* **25** (1994), 1862–1869.

[103] K. Svoboda, W. Dent, D. Kleinfeld and D. Tank, In vivo dendritic calcium dynamics in neocortical pyramidal neurons, *Nature* **385** (1997), 161–165.

[104] J.T. Trachtenberg, B.E. Chen, G.W. Knott, G. Feng, J.R. Sanes, E. Welker and K. Svoboda, Long-term in vivo imaging of experience-dependent synaptic plasticity in adult cortex, *Nature* **420** (2002), 788–794.

[105] E.M. Ullian, S.K. Sapperstein, K.S. Christopherson and B.A. Barres, Control of synapse number by glia, *Science* **291** (2001), 657–661.

[106] R. Ulrich, View through a window may influence recovery from surgery, *Science* **224** (1984), 420–421.

[107] H. Van Praag, G. Kempermann and F.H. Gage, Running increases cell proliferaion and neurogenesis in the adult mouse dentate gyrus, *Nature Neuroscience* **2** (1999), 266–270.

[108] H. Van Praag, G. Kempermann and F.H. Gage, Neural consequences of environmental enrichment, *Nature Reviews Neuroscience* **1** (2000), 191–198.

[109] F.R. Volkmar and W.T. Greenough, Rearing complexity affects branching of dendrites in the visual cortex of the rat, *Science* **176** (1972), 1445–1447.

[110] T.A. Watkins and B.A. Barres, Nerve Generation: regrowth stumped by shared receptor, *Current Biology* **12** (2002), R654–656.

[111] C. Wiessner, F.M. Bareyre, P.R. Allegrini, A.K. Mir, S. Frentzel, M. Zurini, L. Schnell, T. Oertle and M.E. Schwab, Anti-Nogo-A antibody infusion 24 hours after experimental stroke improved behavioral outcome and corticospinal plas-

ticity in normotensive and spontaneously hypertensive rats, *Journal of Cerebral Blood Flow and Metabolism* **23** (2003), 154–165.

[112] B. Will and C. Kelche, Environmental approaches to recovery of function from brain damage: a review of animal studies (1981-1991), in: *Recovery frombrain damage*, F.D. Rose and D.A. Johnson, eds, Plenum publishing Corp, New York, NY, 1992, pp. 79–103.

[113] C. Xerri and Y. Zennou-Azogui, Influence of the postlesion environment and chronic piracetam treatment on the organization of the somatotopic map in the rat primary somatosensory cortex after focal cortical injury, *Neuroscience* **118** (2003), 161–177.

[114] Y.R. Yang, R.Y. Wang and P.S. Wang, Early and late treadmill training after focal brain ischemia in rats, *Neuroscience Letters* **339** (2003), 91–94.

[115] D. Young, P.A. Lawlor, P. Leone, M. Dragunow and M.J. During, Environmental enrichment inhibits spontaneous apoptosis, prevents seizures and is neuroprotective, *Nature Medicine* **5** (1999), 448–453.

[116] R. Yuste, A. Majewska and K. Holthoff, From form to function: calcium compartmentalization in dendritic spines, *Nature Neuroscience* **3** (2000), 653–659.

[117] J. Zeng, B. Mattsson, M. Schulz, B.B. Johansson and J.C. Sørensen, Expression of Zink-positive cells and terminals in fetal neocortical homografts to adult rat depends on lesion type and rearing conditions, *Experimental Neurology* **164** (2000), 176–183.

[118] L.R. Zhao, B. Mattsson and B.B. Johansson, Environmental influence on brain-derived neurotrophic factor messenger RNA expression after middle cerebral artery occlusion in spontaneously hypertensive rats, *Neuroscience* **97** (2000), 177–184.

[119] L.R. Zhao, A. Risedal, A. Wojcik, J. Hejzlar, B.B. Johansson and Z. Kokaia, Enriched environment influences brain-derived neurotrophic factor levels in rat forebrain after focal stroke, *Neuroscience Letters* **305** (2001), 169–172.

[120] R.L. Zhang, Z.G. Zhang, L. Zhang and M. Chopp, Proliferation and differentiation of progenitor cells in the cortex and the subventricular zone in the adult rat after focal cerebral ischemia, *Neuroscience* **105** (2001), 33–41.