Published in final edited form as:

Neurosci Biobehav Rev. 2008 ; 32(4): 657–674. doi:10.1016/j.neubiorev.2007.10.004.

Is Exposure To Enriched Environment Beneficial For Functional Post-Lesional Recovery In Temporal Lobe Epilepsy?

Anandh Dhanushkodi and Ashok K. Shetty*

Department of Surgery (Neurosurgery) Duke University Medical Center, Durham, NC 27710.

Medical Research and Surgery Services, Veterans Affairs Medical Center, Durham, NC 27705.

Abstract

Exposure to environmental enrichment has been shown to induce robust neuronal plasticity in both intact and injured adult central nervous system, including up-regulation of multiple neurotrophic factors, enhanced neurogenesis in the dentate gyrus of the hippocampus, and improved spatial learning and memory function. Neuronal plasticity, though mostly adaptive and abnormal, also occurs during certain neurodegenerative conditions such as the temporal lobe epilepsy (TLE). The TLE is characterized by hippocampal neurodegeneration, aberrant mossy fiber sprouting, spontaneous recurrent motor seizures, cognitive deficits, and abnormally enhanced neurogenesis during the early phase and dramatically declined neurogenesis during the chronic phase of the disease. As enrichment has been found to be beneficial for treating animal models of Alzheimer's, Parkinson's, and Huntington's diseases, there is considerable interest in determining the efficacy of this strategy for preventing or treating chronic TLE after the initial precipitating brain injury. This review first discusses the proof of principle behind the potential application of the environmental enrichment strategy for preventing or treating TLE after brain injury. The subsequent chapters confer the portrayed beneficial effects of enrichment for functional post-lesional recovery in TLE and the possible complications which may arise from housing epilepsy-prone or epileptic rats in enriched environmental conditions. The final segment discusses studies that are essential for further understanding the efficacy of this approach for preventing or treating TLE.

Keywords

Neuronal plasticity; Epilepsy; Enriched environment; Neuroprotection; Dentate neurogenesis; Seizures

1. Introduction

Epilepsy is a neurodegenerative disease that interrupts the normal electrical activity of the brain and promotes abnormal wiring in the brain. From time to time, multiple groups of neurons fire simultaneously in people with epilepsy, which triggers an electrical tempest within the brain culminating in seizures. The temporal lobe epilepsy (TLE) with hippocampal sclerosis, one of the most frequent kinds of human epilepsy, is typified by a progressive development of spontaneous recurrent motor seizures (SRMS). Although the precise cause of TLE is unknown

*Correspondence should be addressed to: Ashok K. Shetty, M.Sc., Ph.D., Professor, Division of Neurosurgery, Box 3807, Duke University Medical Center, Durham NC 27710, Phone: 919-286-0411, Ext. 7096, E-mail: Ashok.Shetty@Duke.Edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

in most cases, it is typically seen after an initial precipitating injury (IPI) such as the brain injury, tumors, meningitis, encephalitis, status epilepticus (SE), and febrile seizures during childhood in other cases (Engel et al., 1989; French et al., 1993; Mathern et al., 1995; Mathern et al., 1996; Wieser, 2004; Lewis, 2005). A classic sequence of seizures in TLE encompasses an aura followed by arrest of motor behavior, blank stare, and automatisms. Furthermore, patients with TLE often show impairments in attention, memory, mental processing speed, executive functions, mood, personality and interictal depression (Devinsky, 2004). Although not perfect, the SE and hippocampal injury models serve as useful animal prototypes of TLE for both understanding the pathophysiology and developing potential treatment strategies. Besides, these models are valuable for developing therapies that have the potential to prevent chronic epilepsy and learning and memory impairments after the SE and/or brain injury (Ben-Ari et al., 1986; Hellier et al., 1999; Gorter et al., 2001; Gorter et al., 2003; Shetty and Turner, 1996, 2000; Turner and Shetty, 2003; Shetty et al., 2005; Rao et al., 2006).

It is widely believed that the hippocampus is the site of origin of SRMS in most cases of TLE. Indeed, multiple hippocampal changes are apparent in both TLE and animal models of TLE (Sloviter, 2005). The structural changes in the hippocampus comprise partial degeneration of CA1 and CA3 pyramidal neurons and dentate hilar neurons (Fig. 1; Rao et al., 2006), reductions in gamma-amino butyric acid positive (GABA-ergic) interneurons (Shetty and Turner, 2000, 2001), loss of the calcium binding protein calbindin in dentate granule cells (Nagerl et al., 2000; Shetty and Hattiangady, 2007), and abnormal sprouting of dentate granule cell, entorhinal, and CA3 axons (Shetty and Turner, 1997; Shetty, 2002; Shetty et al., 2005; Siddiqui and Joseph, 2005; Wozny et al., 2005). The axons of dentate granule cells (hippocampal mossy fibers) branch out of the dentate hilus and abnormally innervate the dentate inner molecular layer in TLE, a phenomenon known as aberrant mossy fiber sprouting (Tauck and Nadler, 1985; Sutula et al., 1989; Okazaki et al., 1995; Shetty and Turner, 1997; Shetty et al., 2003; Koyama and Ikegaya, 2004, 2005). It appears that the aberrant mossy fiber sprouting contributes to the increased seizure susceptibility of the dentate gyrus, as the extent of aberrant mossy fiber sprouting positively correlates with both antidromically evoked burst firing and spontaneous seizures in kainic acid (KA) models of TLE (Cronin and Dudek, 1988; Masukawa et al., 1989; Mathern et al., 1993; Dudek et al., 1994; Okazaki et al., 1995; Buhl et al., 1996; Lynch and Sutula, 2000; Wuarin and Dudek, 2001). Therefore, strategies that prevent or reverse abnormal mossy fiber sprouting in the dentate gyrus have received considerable attention as a treatment for TLE (Shetty and Turner, 1997; Shetty et al., 2005; Hattiangady et al., 2006). Furthermore, many studies suggest that anomalous migration of newly developed granule cells from the subgranular zone into the dentate hilus is another key feature of TLE (Houser, 1990; Parent and Lowenstein, 1997; Parent et al., 1997; Scharfman et al., 2000; Scharfman et al., 2002b; Scharfman et al., 2003; McCloskey et al., 2006; Parent et al., 2006; Gong et al., 2007; Scharfman et al., 2007). In comparison to granule cells located in the granule cell layer, the ectopically migrated granule cells exhibit abnormal dendritic orientation (Shapiro et al., 2005; Shapiro and Ribak, 2005, 2006), aberrant synaptic connectivity (Pierce et al., 2005; Jessberger et al., 2007), spontaneous epileptiform activity (Scharfman et al., 2000). Further studies imply that these cells contribute to a lower seizure threshold in the epileptic hippocampus and are likely involved in inducing SRMS in epileptic rats (Scharfman, 2002b; Scharfman et al., 2003; McCloskey et al., 2006). Thus, involvement of the hippocampus in the pathophysiology of TLE is substantial.

Antiepileptic drug therapy is ineffective to control seizures in a significant fraction of people (~25%) afflicted with epilepsy (Litt et al., 2001; McKeown and McNamara, 2001). Besides, antiepileptic drugs have side effects and do not influence the course of the disease. Although surgical resection of the epileptic hippocampus is efficacious for controlling seizures in many cases of drug-resistant TLE (Clusmann et al., 2002; Engel, 2003), this approach is associated with significant cognitive deficits (Nunn et al., 1999; Martin et al., 2002; Richardson et al.,

2004). Therefore, developing alternative therapeutic approaches that prevent or restrain epileptogenic changes and SRMS after an IPI have considerable significance. Classically, a latent period of several years is observed between the IPI and the onset of chronic TLE and learning and memory impairments. This provides a window for intervention using strategies that have the potential to prevent chronic epilepsy and long-term learning and memory impairments after an IPI. In recent years, exposure to enriched environment has shown to be a promising approach to mitigate neurological deficits in animals models of Alzheimer's, Parkinson's and Huntington's diseases (Nithianantharajah and Hannan, 2006). Similar approach may be useful for preventing or restraining chronic TLE and learning and memory deficits that ensue after an IPI. The primary goal of this review is to discuss and assess the current information regarding the beneficial effects of enriched housing conditions for functional post-lesional recovery in TLE. Additionally, future prospects and potential complications of environmental enrichment intervention when applied either before or after the onset of chronic epilepsy are also discussed. Although other brain structures such as the amygdala and the entorhinal cortex are also involved in the epileptogenic processes and TLE (McIntyre and Kelly, 2000; Jutila et al., 2002), the hippocampus receives much of the attention for understanding the pathophysiology and treatment of TLE because of multiple changes as summarized in the preceding paragraph of this section. Therefore, the present review focuses on the potential impact of environmental enrichment on various aspects of epileptogenesis in the hippocampus.

2. Definition of environmental enrichment to laboratory animals

Almost half a century ago, Donald Hebb (1949) hypothesized that when one cell excites another repeatedly, a change takes place in one or both cells in such a way that one cell becomes more efficient at firing the other. He suggested that environmental influence during the critical period of development determines their physiological and behavioral processes in adulthood. In late 1940s, the perception of enriched environment for improving the quality of life occurred to Hebb following his observation that rats he carried home as pets exhibited much superior behavioral performance over their littermates housed in the laboratory (Hebb, 1947). Following this, Rosenzweig and colleagues developed models for the standardized enriched environmental conditions that are classically used today (Rosenzweig et al., 1969; Rosenzweig and Bennett, 1972; Rosenzweig and Barnes, 2003). Environmental enrichment to laboratory animals means exposure to housing conditions that offer an enhanced stimulation of sensory, cognitive and motor systems of the brain, in comparison to standard housing conditions that are considered impoverished (Rosenzweig and Bennett, 1972; Murphy et al., 2004; Nithianantharajah et al., 2004; Nithianantharajah and Hannan, 2006; Pang et al., 2006). In most experimental paradigms, the enrichment also comprises increased social interaction, as larger numbers of animals are usually housed together in bigger and wider cages with exploratory chambers. In most enriched environmental conditions described in the published studies, 8–12 rats are housed together in larger cages containing a variety of objects that are changed daily. This arrangement bestows environmental novelty, which in turn provides different cognitive stimulation every day with respect to the formation of spatial mapping and social interaction. The objects typically comprise toys of different color and shapes for visual stimulation, wooden objects of different texture for sensory perception, tunnels of different shapes for spatial navigations, and running wheels for motor activity. Figure 2 illustrates some of the inanimate objects that are classically used in laboratory studies for enrichment of rodents (Fig. 2). However, currently, there is no consensus on which environmental enrichment paradigms are ideal for maximal beneficial effects on brain and behavior (Nithianantharajah and Hannan, 2006).

3. Extent of plasticity in the normal brain with exposure to environmental enrichment

The phrase, “neural plasticity”, is commonly referred to modifications that arise in the cytoarchitecture, connectivity and function of the brain because of experience. Experience-dependent neural plasticity occurs in the nervous system all through life. It encompasses changes such as dendritic pruning (Hickmott and Ethell, 2006), loss or addition of spines in dendrites (Segal, 2001), and increased participation of new neurons in the circuitry of critical learning centers of the brain such as the hippocampus and the olfactory bulb (Gould, 2007). Environmental enrichment has been shown to induce neural plasticity at several levels in the brain, which include modifications in structure and circuitry, improvements in cognitive function, and mostly favorable alterations in brain chemistry. The following section briefly discusses studies pertaining to these issues.

3.1. Modifications in structure and neurogenesis

Environmental enrichment induces multiple structural changes in the brain. The anatomical changes comprise increases in the brain weight, the thickness of the cerebral cortex, the size of neuronal soma, and numbers of dendritic spines, synapses and non neuronal cells (Rosenzweig et al., 1962a, b; Greenough et al., 1973; Greenough and Volkmar, 1973; Mohammed et al., 1990; Mohammed et al., 1993; Moser et al., 1997; Rampon and Tsien, 2000; Johansson and Belichenko, 2002; Nilsson and Pekny, 2007). Furthermore, environmental enrichment increases the proliferation of neural stem/progenitor cells resulting in an enhanced neurogenesis in the hippocampus (Kempermann et al., 1997; Olson et al., 2006). Neurogenesis occurs throughout life in the hippocampus, which is mediated by stem/progenitor cells residing in the subgranular zone of the dentate gyrus (Kaplan and Hinds, 1977; Gage, 2002; Gould, 2007). The different steps of neurogenesis include proliferation of neural stem/progenitor cells and production of new cells, neuronal fate-choice decision of newly born cells, dendritic and axonal growth of newly differentiated neurons, afferent and efferent connectivity of newly added neurons to the granule cell layer (Kempermann et al., 2004; Abrous et al., 2005; Rao et al., 2005; Ge et al., 2007). There is considerable interest in applying environmental enrichment strategy to improve cognitive function through increased neurogenesis in neurodegenerative disorders. This is because; it is possible to improve virtually all steps of neurogenesis via exposure to environmental enrichment (Olson et al., 2006), and increased dentate neurogenesis is associated with better learning and memory functions (Aimone et al., 2006; Leuner et al., 2006; Drapeau et al., 2003, 2007). An increased dentate neurogenesis is also considered important for mediating some of the behavioral effects of antidepressants in major depressive disorders (Sahay and Hen, 2007). Studies have so far shown environmental enrichment induced association between increased dentate neurogenesis and improved functional outcome in aged mice (Kempermann et al., 2002), animals that underwent traumatic brain injury (Gaulke et al., 2005), transgenic mice exhibiting characteristics of Huntington's and Alzheimer's diseases (Lazic et al., 2006; Levi and Michaelson, 2007), and animals that underwent cranial irradiation (Fan et al., 2007).

3.2. Changes in cognitive function

Environmental enrichment induced alterations at the physiological level include enhanced synaptic strength (Foster and Dumas, 2001) and increased excitatory glutamatergic synaptic transmission (Nichols et al., 2007). However, the most conspicuous result of environmental enrichment in rats and mice has been the enhanced cognitive performance. For instance, exposure to enriched environment improves spatial learning and memory performance in the Morris water maze task (Mohammed et al., 1990; Kempermann et al., 1997; Moser et al., 1997; Nilsson et al., 1999; Pham et al., 1999a; Williams et al., 2001; Pham et al., 2002), the

radial arm maze task (Bindu et al., 2005; Dhanushkodi et al., 2007) and hippocampal-independent learning tasks (Rampon et al., 2000b). In the Morris water maze test, enriched mice exhibited faster learning, better adaptation during exploration and greater locomotor skills, in comparison to mice housed in standard conditions (Kempermann et al., 2002). Furthermore, rats with hippocampal damage demonstrated better cognitive performance in eight arm radial maze task but not in Morris water maze task (Dhanushkodi et al., 2007; Bindu et al., 2005) suggesting that the effects of enriched environment on distinct aspects of cognitive function may differ between intact rats and rats with hippocampal damage. Moreover, electrophysiological recordings from acute hippocampal slices of rats housed in enriched environment demonstrated enhanced long term potentiation (LTP) (Duffy et al., 2001; Tang and Zou, 2002). The LTP is characterized by a continual increase in the chemical strength of synapses for extended periods, which is considered one of the major mechanisms underlying learning and memory formation in the brain (Jeffery, 1997; Abraham et al., 2002). A study by Tang et al (2001) demonstrated that mice housed in enriched conditions display better performance in contextual and cued conditioning, fear extinctions, and novel object recognition tasks. These changes were also associated with increased protein levels of GluR1, NR2B, and NR2A subunits of glutamate receptors. Likewise, Tang and Zou (2002) demonstrated that the LTP of population spikes and the LTP of excitatory post-synaptic potentials increase in animals experiencing neonatal novelty exposure. Moreover, animals enriched in cages equipped with running wheels or animals subjected to forced running on treadmill exhibited increased neurogenesis and gliogenesis, and better motor and cognitive performance (van Praag et al., 1999; Ehninger and Kempermann, 2003). Additionally, studies suggest beneficial effects of the environmental enrichment for mitigating age-associated cognitive deficits (Kobayashi et al., 2002; Huang et al., 2007) and augmenting hippocampal information processing (Irvine et al., 2006).

3.3. Alterations in brain chemistry

The underlying molecular cause for the structural and behavioral plasticity following enrichment was partially attributed to the up-regulation of neurotrophic factors and essential genes and proteins involved in the neuronal plasticity (Rampon et al., 2000a; Mora et al., 2007). Studies have shown that exposure to enriched environment induces increases in the concentration of glial-derived neurotrophic factor (GDNF; Young et al., 2000), brain-derived neurotrophic factor (BDNF; Rossi et al., 2006; Zhu et al., 2006; Branchi et al., 2004, 2006; Bindu et al., 2007); nerve growth factor (NGF; Zhu et al., 2006; Branchi et al., 2004; Pham et al., 1999a, b, 2002), neurotrophin-3 (NT-3; Mohammed et al., 1993; Torasdotter et al., 1996, 1998), insulin-like growth factor (IGF-1; Mohammed et al., 2002), and vascular endothelial growth factor (VEGF; During and Cao, 2006). The above changes are considered important because of the various functions of these neurotrophic factors in the brain (Thoenen, 1995; Poo, 2001; Huang and Reichardt, 2001; Carro et al., 2003; Binder et al., 2004; Brockington et al., 2004). First, the neurotrophic factors support the development, survival, and differentiation of neurons. Second, the neurotrophic factors synthesized by neuronal and non neuronal cells interact with the target cells and such neurochemical communication is essential for the survival of both synthesizing cells as well as target neurons. Third, the neurotrophic factors have neuroprotective action in various neurodegenerative diseases and after brain injury. Thus, through increased levels of various neurotrophic factors, environmental enrichment likely decreases the vulnerability of the brain to neurodegeneration following environmental insults and injury. Furthermore, environmental enrichment modulates cholinergic (Rosenzweig and Bennett, 1996; Del Arco et al., 2007; van Praag et al., 2000), serotonin-ergic (Rasmuson et al., 1998), dopaminergic (Bezard et al., 2003; Bowling et al., 1993; Del Arco et al., 2007) and glutamatergic neurotransmission (Foster et al., 1996; Bredy et al., 2004; Naka et al., 2005; Mlynarik et al., 2004). Moreover, adult rats placed in an enriched environment demonstrated increased levels of proteins involved in learning and memory function. These include increases

in immediate early genes like NGFI-A, Zif/268, Arc (Wallace et al., 1995; Pinaud et al., 2001) and phosphorylation of cyclic AMP response element binding protein (CREB) (Young et al., 1999; Faverjon et al., 2002). A study by Nithianantharajah et al. (2004) demonstrated increased levels of post-synaptic density-95 protein in several brain regions after one month of housing in enriched environmental conditions.

4. Benefits of exposure to enriched environment for treating neurological disorders

A pioneer study by Schwartz (1964) demonstrated that exposure to enriched environment early after injury reverses the cortical lesion-induced deficits in neonatal rats (Schwartz, 1964; Will et al., 2004). Since then, interest in ascertaining the effects of exposure to environmental enrichment in distinct animal models of neurodegenerative disorders has snowballed. Interestingly, most studies available in the literature demonstrate beneficial effects through environmental enrichment, regardless of the site of brain damage.

4.1 Effectiveness for alleviating depression and mental retardation

Pertaining to depression, a recent study demonstrates that mice housed in enriched conditions exhibit decreased immobility in the forced swim test (i.e. a test typically employed to assess the extent of depression in laboratory animals) and an enhanced neurogenesis in the hippocampus (Hattori et al., 2007). As these effects are similar to results obtained with antidepressant administration (Santarelli et al., 2003; Sahay and Hen, 2007), it appears that exposure to enriched environment mimics the effects of antidepressant therapy. In this context, an earlier study in humans is very relevant. Specifically, Raine and associates (2003) investigated the effects of nutritional, educational and physical exercise enrichment program at ages 3–5 years on the development of schizophrenia personality at adulthood. Fascinatingly, children participating in the enrichment program exhibited lower scores for schizophrenia personality, antisocial and criminal behaviors at adulthood. Thus, an enriched, stimulating environment during childhood can induce beneficial psychological and behavioral outcomes at adulthood. In the same vein, a study by Restivo and colleagues (2005) demonstrates that enriched housing conditions can alleviate the morphological and behavioral deficits in transgenic mice exhibiting characteristics of fragile X syndrome, an inherited mental retardation syndrome exhibiting dendritic spine abnormalities (Comery et al., 1997).

4.2. Usefulness for treating cognitive dysfunction in Alzheimer's and aging models

The efficacy of environmental enrichment for easing cognitive dysfunction has been demonstrated in animal models of Alzheimer's disease. Studies reveal that mice with Alzheimer's pathology exhibit improved cognitive performance following exposure to enriched environment (Arendash et al., 2004; Jankowsky et al., 2005). However, this improvement was associated with increased amyloid plaque formation, suggesting that mice housed in enriched conditions have the ability to withstand a greater degree of pathological insults than their counterparts housed in standard conditions. Furthermore, studies examining the effects of environmental enrichment on normal aging also suggest an improved performance in maze learning (Cummins and Livesey, 1979), and maintenance of synaptophysin (a protein associated with synapses) in several regions of the aged brain at levels found in the young brain (Saito et al., 1994). Thus, exposure to enriched environmental conditions has the potential to prevent the loss of synapses associated with aging, and to delay the cognitive dysfunction associated with Alzheimer's disease. This is consistent with the suggestions that lack of cognitive stimulation is a risk factor in the etiology of Alzheimer's disease, and education, social interaction and advanced occupational attainment can reduce the risk of age-associated dementia and the onset of Alzheimer's disease (Terry et al., 2006).

4.3. Efficiency for improving functional recovery in other neurodegenerative diseases

The usefulness of enriched environment for improving functional recovery has been demonstrated in several animal models of neurodegenerative disorders. To begin with, in animal models of Huntington's disease, exposure to environmental enrichment was efficient for preventing the degeneration of motor and striatal neurons as well as for mediating motor functional recovery (Hockly et al., 2002; Bezard et al., 2003; Glass et al., 2004; Spires et al., 2004). This is believed to be mediated through up-regulation of neurotrophic factors such as the BDNF, NGF and GDNF, and cannabinoid receptors (Glass et al., 2004; Spires et al., 2004; Hockly et al., 2002). Second, studies in animal models of Parkinson's disease have suggested that exposure to enriched environment can diminish the progression and severity of symptoms, and improve the motor function in unilateral dopamine-depleted rats (Jadavji et al., 2006). Third, in animal models of stroke and traumatic brain injury, enhanced motor and cognitive performances have been observed with exposure to enriched environment (Biernaskie and Corbett, 2001; Gobbo and O'Mara, 2004; Farrell et al., 2001; Belayev et al., 2003; Passineau et al., 2001). Interestingly, these improvements were associated with greater dendritic arbors in the undamaged contralateral motor cortex, suggesting that enrichment mediates functional recovery through increased neural plasticity in the remaining neurons (Biernaskie and Corbett, 2001). Moreover, recent studies suggest that the beneficial effects of enrichment on motor skill recovery following stroke may be linked to increased number of oligodendrocytes and the oligodendrocyte progenitors expressing the proteoglycan, neuron-glia 2 (NG2) (Komitova et al., 2002; Komitova et al., 2005a, b, 2006). Third, in animal models of autism, environmental enrichment has been shown to reverse some of the behavioral abnormalities associated with autism (Turner et al., 2002; Turner et al., 2003; Schneider et al., 2006). These include higher sensitivity to pain, lower sensitivity to non-painful stimuli, diminished locomotor and stereotypic activity, enhanced explorative behavior, decreased anxiety, increased incidence of social behavior, and shorter latency to social explorations. These changes were also associated with enhanced neuronal activity and increased levels of neurotrophic factors (Turner et al., 2002, 2003), suggesting that environmental enrichment related improvements are associated with increased metabolic activity and elevated neurotrophic factors. Thus, the efficacy of exposure to environmental enrichment for improving functional recovery has been demonstrated in animal models of multiple neurodegenerative diseases.

5. Efficacy of enrichment strategy for functional post-lesional recovery in temporal lobe epilepsy

Although a large body of literature is available on various positive effects of environmental enrichment and social stimulation for inducing functional brain recovery in conditions such as stroke, Alzheimer's, Huntington's and Parkinson's diseases, information on the effects of environmental enrichment for restraining acute and chronic seizures has been limited. However, studies on animal models of epilepsy so far report two important observations. First, animals reared in environmentally enriched conditions exhibit decreased susceptibility to seizures and hippocampal neurodegeneration when challenged with chemoconvulsants such as the KA or the pilocarpine. Second, housing animals in environmentally enriched conditions after the induction of the SE improves learning and memory abilities and minimizes the probability for developing behavioral abnormalities and depression. We discuss these and other studies pertaining to enrichment and epilepsy in the following sections.

5.1. Capacity for restraining the frequency and intensity of seizures

A seminal report by Young and colleagues (Young et al., 1999) gave initial insights about the utility of exposure to enriched environment for restraining seizures in epileptic conditions. In this study, the effects of standard or enriched housing conditions on seizures induced by KA

were examined in rats. Kainic acid is an excitotoxin, which activates kainate receptors (a subtype of glutamate receptors) and induces a seizure syndrome with associated excitotoxic neurodegeneration in rodents characteristic of TLE (Shetty and Turner, 1996, 1997, 2000; Shetty et al., 2000, 2005; Rao et al., 2006b). Rats housed in standard housing conditions displayed seizures that are typical for KA administration (at a dose of 8mg/Kg b.w.), which comprised wet dog shakes in ~67% of rats during the first hour after KA, and bilateral forelimb clonus and rearing in ~50% of rats during the second hour which lead to SE in 17% rats. In contrast, only 17% of rats housed in enriched housing conditions for 3 weeks prior to the KA administration exhibited wet dog shakes and none displayed motor seizures. Interestingly, when all rats were given a second dose (10 mg/Kg b.w.) of KA the next day, 33% of rats housed in standard conditions developed the SE, whereas no enriched rat demonstrated wet dog shakes or motor seizures. Thus, rats housed in environmentally enriched conditions exhibit considerably diminished response to the excitotoxin KA, suggesting that environmental enrichment increases the resistance of the brain to acute seizures and excitotoxic injury. Consistent with this idea, Auvergne and associates (2002) demonstrate that prior housing of adult rats in enriched environment increases their threshold for amygdala kindling induced seizures, in comparison to their counterparts housed in standard conditions.

Nevertheless, it is vital to examine whether exposure to enriched environment after the induction of acute seizures or SE is efficacious for preventing chronic epilepsy. Rutten and colleagues (2002) have tried to examine this issue by housing postnatal day 20 rats that underwent lithium-pilocarpine induced SE in enriched conditions for 30 days after the SE. The electroencephalographic recordings performed after the completion of enrichment however revealed no differences between enriched and non-enriched groups. In both groups, spectral power analyses (for assessing epileptiform discharges following the SE) of spikes revealed greater power in comparison to that observed in saline treated controls (i.e. non-SE rats). However, the results were not conclusive (as also noted by the authors) because this study comprised a limited number of animals with significant inter-animal variations and the progression into the chronic epilepsy phase (characterized by SRMS) was not assessed at extended time-points after the SE in these immature rats. Furthermore, it is important to note that the consequences of the SE in immature rats are different from adult rats in many ways. In comparison to adult rats, the immature rats undergoing the SE typically exhibit diminished: (i) mortality rate; (ii) hippocampal and non-hippocampal neurodegeneration; (iii) aberrant mossy fiber sprouting in the dentate gyrus; and (iv) propensity for developing chronic epilepsy (see the review by Scantlebury et al., 2007 for details). Considering these, it remains unknown whether exposure to enriched environment after the induction of SE is efficacious for preventing or reducing the intensity of chronic epilepsy in adult rats. In this context, an investigation in a genetic model of absences seizures is relevant, where enriched housing for 60 days worsened the incidence and expression of spike wave discharges (Schridde and van Luijckelaar, 2004). Thus, currently, there is no evidence to suggest that application of environmental enrichment after the induction of SE or an IPI prevents or restrains the development of chronic epilepsy. Additionally, no studies are currently available regarding the effects of environmental enrichment on the frequency or intensity of SRMS during chronic epilepsy.

5.2 Ability for preventing neurodegeneration

Examination of brain tissues from KA treated rats housed in standard or enriched conditions revealed significant neuroprotection with enrichment, as only rats that were housed in standard conditions exhibited hippocampal neurodegeneration following KA administration (Young et al., 1999). Since none of the enriched rats exhibited SE after KA administration, the hippocampal neurodegeneration was not apparent in these rats. In contrast, the SE in rats housed in standard conditions induced significant cell loss in CA1 and CA3 subfields of the

hippocampus. These results imply that exposure to environmental enrichment not only provides resistance to seizures induced by excitotoxins but also prevents the excitotoxin-induced hippocampal neurodegeneration. Interestingly, neuroprotection was evident even when suprathreshold dose (12 mg/Kg b.w.) of KA was administered to enriched rats (Young et al., 1999). Assessment of the apoptosis using the TUNEL method for labeling fragmented DNA demonstrated 45% decrease in naturally occurring cell death after SE in rats housed in enriched conditions, in comparison to the SE induced cell death in rats housed in standard conditions. Thus, exposure to enriched environment provides considerable neuroprotection against excitotoxins in adult rats.

5.3. Capability for improving cognitive function

Studies suggest that housing rats in enriched conditions is beneficial for minimizing learning and memory deficits that typically ensue at various time points after the SE (Faverjon et al., 2002; Rutten et al., 2002). The enriched paradigm applied in this study comprised an aluminum tank housing that had running treadmills, tunnels for rats to hide and play, wooden objects for climbing and auditory stimuli via music from Mozart's piano concerts. The objects in the enriched cage were changed every third day to provide novel stimulation. Overall, rats housed in enriched conditions following the SE demonstrated behavioral performance that was comparable to normal rats housed in standard conditions. In these studies, the SE was induced in postnatal day 20 (P20) rats using lithium-pilocarpine, a widely accepted animal model for childhood epilepsy. In standard housing conditions, rats that underwent SE displayed cognitive impairments at all time-points assessed between P22 and P50 (Rutten et al., 2002). However, enriched housing of rats for 4 hours everyday during the first 28–30 days after the SE, improved their cognitive performance in water maze task (Faverjon et al., 2002; Rutten et al., 2002). Thus, enrichment commencing after the SE is efficacious for improving cognitive function in immature rats. However, it remains to be tested whether similar recovery in cognitive function is achievable with environmental enrichment of adult rats after the SE.

The finding that exposure of immature rats to enriched environment after the SE improved their cognitive performance to levels observed in age-matched normal rats despite significant loss of CA1 and CA3 pyramidal neurons (Faverjon et al., 2002; Rutten et al., 2002) is intriguing. This is because considerable loss of CA1 and CA3 pyramidal neurons is typically associated with impairments in spatial learning task. However, the immature rats that underwent SE and housed in enriched environment exhibited increased neurogenesis in the dentate gyrus (Faverjon et al., 2002). From this perspective, it is tempting to conclude that enrichment induced improvements in learning and memory performance in rats that underwent SE is due to increased dentate neurogenesis, as this neurogenesis is considered important for hippocampal-dependent spatial memory functions (Kee et al., 2007). A similar increase in dentate neurogenesis has been observed in adult amygdala kindled rats with environmental enrichment (Auvergne et al., 2002). However, increased dentate neurogenesis at early time-points (2–4 weeks) after the SE is a normal phenomenon observed in rats that undergo SE and housed in standard conditions (Hattiangady et al., 2004; Jessberger et al., 2007). Thus, it is unknown whether or not the increased dentate neurogenesis is the substrate underlying the enrichment-induced improved cognitive performance in rats that underwent SE. Another reason for better cognitive performance of immature rats housed in enriched conditions following the SE is the increased pCREB expression, as this protein is linked to learning and memory (Mayr and Montminy, 2001; Mayr et al., 2001; Hattiangady et al., 2005; Mayr et al., 2005; Moncada and Viola, 2006). A recent study suggests that enrichment improves spatial memory in rats subjected to early life SE though increased phosphorylation of extracellular signal-regulated kinase 2 (ERK2) in the hippocampus (Wang et al., 2007). Alternatively, it is possible that beneficial effects of environmental enrichment on cognitive performance and neuroprotection are global phenomenon and have likely comprised an enhanced function of other brain regions.

Indeed, enrichment is characteristically associated with up-regulation of the expression of multiple genes, neurotrophic factors and other proteins essential for learning and memory in cortical as well as subcortical regions (Nithianantharajah and Hannan, 2006; McNair et al., 2007). Such positive influence of enrichment likely helps animals to cope with the cognitive demand during any given task in spite of having considerable hippocampal damage. Better memory performance in rats following stroke or ischemia with enriched housing also supports the above possibility (Johansson, 1996a, b; Johansson and Ohlsson, 1996; van Rijzingen et al., 1997; Briones et al., 2000).

5.4. Ability for preventing seizure-related behavioral abnormalities and depression

Behavioral problems, school failure, and memory impairment are common among children with epilepsy. Koh and colleagues investigated the efficacy of environmental enrichment in reversing early life seizure-induced changes in exploratory behavior and gene expression (Koh et al., 2005). They employed a KA model of childhood epilepsy in rats and placed them in either standard or enriched housing conditions for 7–10 days. In rats housed in standard conditions after KA treatment, the exploratory behavior was decreased in open field while rats housed in enriched conditions after KA exhibited behavior that was similar to control rats. In addition to behavioral improvement, rats housed in enriched conditions after KA displayed increased levels of genes involved in synaptic plasticity and memory consolidation such as Arc, Homer1a and Egr1 (Koh et al., 2005). These results support the idea that promoting enriching education programs for children with epilepsy might diminish their behavioral problems. Likewise, a recent report by Koh and associates (Koh et al., 2007) suggests beneficial effects of enrichment for minimizing depression that typically ensues after the SE. These results are important, as depression is the most common psychiatric co-morbidity in epilepsy. In this study, Porsolt forced swim test revealed decreased mobility (indicative of depression) in juvenile rats reared in standard conditions after KA-induced seizures, and this depressive behavior was associated with down-regulation of serotonin receptor 5B. However, neither depressive behavior nor changes in serotonin receptor 5B were evident in juvenile rats reared in enriched conditions after KA-induced seizures (Koh et al., 2007). These results imply that increased susceptibility to depression that typically occurs after seizures or SE via transcriptional regulation may be prevented by exposure to enriched environment. It has been proposed that environment interacts with gene expression and influences the behavioral outcome of epilepsy (Koh et al., 2007).

5.5. Competence for influencing the dentate neurogenesis

Increased production of new granule cells after the SE typically results in abnormal migration of a substantial fraction of newly differentiated granule cells into the dentate hilus. Studies by Scharfman and colleagues suggest that the granule cells that migrate into the dentate hilus get integrated abnormally into the CA3 network despite retaining intrinsic properties of granule cells (Scharfman et al., 2000). The hilar granule cells get activated when animals display spontaneous seizures during the chronic epilepsy (Scharfman et al., 2002b; Jessberger et al., 2007). With perforant path stimulation, the ectopic granule cells display an unusually long latency to onset of evoked responses, suggesting polysynaptic activation of these cells (Scharfman et al., 2003). Analysis of dendrites of hilar dentate granule cells confirms mossy fiber terminals as their source of afferent input (Pierce et al., 2005). Further characterization implies that the synaptic connectivity of hilar granule cells predisposes them to discharge in epileptiform bursts. For instance, physiological recordings in hippocampal slices demonstrate spontaneous bursts of action potentials in ectopic granule cells. Because these spontaneous discharges are synchronized with area CA3 pyramidal cell population discharges, it suggests an abnormal activity (Scharfman et al., 2000). Because of the above connectivity and behavior, it is believed that the hilar granule cells contribute to spontaneous recurrent seizures occurring in chronically epileptic animals. Indeed, a study by McCloskey et al (2006) reports that the

frequency of behavioral seizures in animals treated with pilocarpine is directly proportional to the size of the ectopic granule cell population in the dentate hilus. Additionally, Jung et al (2004) demonstrate that inhibition of dentate neurogenesis after the SE via intracerebroventricular infusions of the mitotic inhibitor cytosine- β -D-arabinofuranoside reduces the frequency of chronic seizures, suggesting the involvement of ectopically integrated newly born neurons in the generation of spontaneous seizures. Thus, if exposure to enriched environment after the SE increases the proportion of hilar granule cells, the consequences will likely be detrimental. Instead of restraining seizures, it may actually exacerbate the frequency and intensity of seizures. However, it is unknown currently whether the enrichment induced increases in dentate neurogenesis after the SE also increases the proportion of hilar granule cells.

On the other hand, if exposure to enriched environment after the SE selectively increases the proportion of granule cells in the granule cell layer, the consequences may be beneficial. This is because an electrophysiological study in an electrical stimulation model of epilepsy reports that new granule cells that are added into the granule cell layer at delayed time-points after acute seizures integrate functionally in such a way that they exhibit reduced excitability, which may act to mitigate pathological brain function (Jakubs et al., 2006). However, it is unknown whether the phenomenon of reduced excitability of newly added granule cells is specific to the model investigated by Jakubs et al (2006) or applicable to all SE models of epilepsy. Furthermore, it is also likely that enhanced addition of new dentate granule cells into the granule cell layer after the SE may result in an increased aberrant mossy fiber sprouting into the inner molecular layer of the dentate gyrus (Parent et al., 1997). Although most of the aberrant mossy fiber sprouting after seizures or injury occurs from the mature dentate granule cells (Parent et al., 1999), a dramatically increased addition of new granule cells into the granule cell layer might further enhance this aberrant plasticity. The aberrant axonal sprouting response of granule cells after hippocampal injury is likely a consequence of the degeneration of their post-synaptic target cells (CA3-pyramidal neurons) and/or afferent neurons (hilar mossy cells) and is conspicuously observed in animal models of TLE as well as in human TLE (Tauck and Nadler, 1985; Sutula et al., 1989; Okazaki et al., 1995; Shetty and Turner, 1997, 1999; Shetty et al., 2005; Rao et al., 2006). A greatly increased aberrant mossy fiber sprouting is considered detrimental because many studies imply that the extent of aberrant dentate mossy fiber sprouting positively correlates with both antidromically evoked burst firing and the degree of SRMS in animal models of TLE (Cronin and Dudek, 1988; Masukawa et al., 1989, 1992; Mathern et al., 1993; Dudek et al., 1994; Okazaki et al., 1995; Buhl et al., 1996; Lynch and Sutula, 2000; Wuarin and Dudek, 2001; Cavazos et al., 2003). Thus, if enrichment after the SE greatly increases the dentate neurogenesis, this may be counterproductive. Rather than facilitating recovery, this may aggravate the different components of chronic epilepsy. Additional studies, examining the links between the extent of dentate neurogenesis, cognitive function and degree of spontaneous seizures, are needed in animals housed in enriched conditions after the SE.

5.5 Proficiency for apt modulation of neurotrophic factors and other proteins

The mechanisms that restrain seizures and neurodegeneration in animals reared in enriched housing conditions are unknown. However, it is believed that processes such as activation of specific signal transduction pathways and increases in multiple growth factors including BDNF and GDNF are involved (Young et al., 1999). Although increased levels of neurotrophic factors are beneficial for providing neuroprotection in animals reared in enriched housing conditions, a dramatic increase in the concentration of neurotrophic factors after the induction of SE through enrichment may be detrimental. This is because acute seizures induced by excitotoxins result in multiple epileptogenic changes in the hippocampus such as upregulation of several neurotrophic factors, neurogenesis, aberrant mossy fiber sprouting in the dentate gyrus (Rao

et al., 2006) and abnormal sprouting of CA1, CA3 and entorhinal axons (Perez et al., 1995; Avoli et al., 2002; Shetty, 2002; Bausch and McNamara, 2004; Siddiqui and Joseph, 2005). As these events progress during the so-called "quiescent phase" after the KA-induced SE, application of enrichment strategy during this phase may exacerbate these processes through increased concentration of certain neurotrophic factors like BDNF (Young et al., 1999). This is because BDNF can influence the above types of synaptic reorganizations in the injured hippocampus (Scharfman et al., 1999; Binder et al., 2001; Scharfman et al., 2002a; Shetty et al., 2003; Koyama et al., 2004; Scharfman, 2005). Rigorous studies examining the links between the levels of neurotrophic factors and the extent of epileptogenic processes are needed in animals housed in enriched conditions after the SE.

6. Overall conclusions and future directions

From the studies available so far, the following conclusions emerge regarding the efficacy of enrichment for functional post-lesional recovery in TLE. First, prior enrichment decreases seizure susceptibility and hippocampal neurodegeneration in adult rats when exposed to chemoconvulsants. Second, application of the enrichment paradigm following the SE in immature rats improves learning and memory abilities and minimizes the probability for developing behavioral abnormalities and depression. However, multiple other questions remain unanswered regarding the efficacy of environmental enrichment approach for treating epileptic conditions.

Figure 3 illustrates the potential windows after an IPI at which enrichment strategy may be applied for addressing various issues (Fig. 3). The first issue is, will the application of the enrichment strategy immediately after the initial brain injury (e.g. 24 hrs after the SE) or during the silent period (e.g. ~2 weeks after the SE but before the onset of chronic epilepsy) be useful for restraining chronic epilepsy development and preventing learning and memory impairments? (Fig. 3). If the answer is yes, it is important to determine whether the beneficial effects of enrichment are enduring or transient. Although some of the studies investigated the effects of pre-exposure to enriched environment on excitotoxin-induced SE, no long-term studies are available to comprehend the role of pre-enrichment on onset and severity of SRMS, which may ensue at delayed time-points after the chemoconvulsant treatment. The second issue is whether epileptic rats housed in enriched conditions exhibiting improved performance in certain spatial tasks have the ability to display enhanced performance in more complex cognitive tasks. Furthermore, whether or not the outcome of enrichment on behavioral performance depends on the severity of hippocampal damage needs to be determined. This is because several studies imply that the outcome of the enriched housing condition on spatial task depends on both the type of task employed and the lesion locus (Will et al., 2004). For instance, positive influence of enriched condition was observed in rats with dorsal hippocampal lesions but not with entorhinal cortex lesions (Will et al., 2004). Likewise, Galani and colleagues (Galani et al., 1997) reported beneficial effects of enrichment in rats with hippocampal lesions for performing Hebb-Williams maze task. However, the positive effects were not evident when rats were examined with novelty test or Morris water maze task. Furthermore, rats with fimbria-fornix lesions perform badly in radial arm maze task despite their housing in enriched conditions (Kelche et al., 1987) but exhibit improved performance in Morris water maze task (van Rijzingen et al., 1997). Collectively, the above results suggest that enriched housing of rats with hippocampal lesions is helpful for improving certain behavioral tasks and the extent of improvements seem to be dependent upon the lesion size and locus. These findings also highlight that exposure to enriched environment will not have positive influence on all behavioral tasks.

The third issue is whether introduction of enrichment shortly after the SE would increase the dispersion of granule cells into the dentate hilus (Fig. 3). As this phenomenon is already

observed in epileptic rats at early time-points after the SE and is believed to be important for the development of chronic epilepsy, any further increase following exposure to enriched environment may be detrimental. Rather than restraining seizures and improving cognitive function, it may actually exacerbate the frequency and intensity of spontaneous seizures. The fourth issue is whether exposure to enriched environment during chronic epilepsy is efficacious for decreasing the severity and intensity of SRMS, improving the learning and memory function, increasing the extent of appropriate dentate neurogenesis and alleviating the chronic epilepsy associated depression (Fig. 3).

Finally, it is important to determine the time-frame that is suitable for obtaining maximal beneficial effects through enrichment. This is important, as acute seizures or the SE induced by chemoconvulsants result in multiple epileptogenic changes in the hippocampus. These include hippocampal neurodegeneration, loss of functional inhibition, enhanced neurogenesis in the dentate gyrus and inappropriate migration of newly born granule cells into the dentate hilus, all of which likely contribute to the development of chronic epilepsy. As these epileptogenic changes progress during the so-called "quiescent phase" after the SE, application of enrichment strategy during this phase may exacerbate these processes through increased concentration of critical neurotrophic factors that influence these processes in the injured hippocampus. Therefore, long-term studies that determine both time-frame and duration of enrichment for obtaining the most beneficial effects after the induction of SE are critical.

Acknowledgements

This work was supported by grants from the National Institute of Neurological Disorders and Stroke (NS054780 & NS 043507 to A.K.S.), National Institute for Aging (AG20924 to A.K.S.) and the Department of Veterans Affairs (VA Merit Review Award to A.K.S.).

References

- Abraham WC, Logan B, Greenwood JM, Dragunow M. Induction and experience-dependent consolidation of stable long-term potentiation lasting months in the hippocampus. *J Neurosci* 2002;22:9626–9634. [PubMed: 12417688]
- Abrous DN, Koehl M, Le Moal M. Adult neurogenesis: from precursors to network and physiology. *Physiol Rev* 2005;85:523–569. [PubMed: 15788705]
- Aimone JB, Wiles J, Gage FH. Potential role for adult neurogenesis in the encoding of time in new memories. *Nat Neurosci* 2006;9:723–727. [PubMed: 16732202]
- Arendash GW, Garcia MF, Costa DA, Cracchiolo JR, Wefes IM, Potter H. Environmental enrichment improves cognition in aged Alzheimer's transgenic mice despite stable beta-amyloid deposition. *Neuroreport* 2004;15:1751–1754. [PubMed: 15257141]
- Auvergne R, Lere C, El Bahh B, Arthaud S, Lespinet V, Rougier A, Le Gal La Salle G. Delayed kindling epileptogenesis and increased neurogenesis in adult rats housed in an enriched environment. *Brain Res* 2002;954:277–285. [PubMed: 12414110]
- Avoli M, D'Antuono M, Louvel J, Kohling R, Biagini G, Pumain R, D'Arcangelo G, Tancredi V. Network and pharmacological mechanisms leading to epileptiform synchronization in the limbic system in vitro. *Prog Neurobiol* 2002;68:167–207. [PubMed: 12450487]
- Bausch SB, McNamara JO. Contributions of mossy fiber and CA1 pyramidal cell sprouting to dentate granule cell hyperexcitability in kainic acid-treated hippocampal slice cultures. *J Neurophysiol* 2004;92:3582–3595. [PubMed: 15269228]
- Belayev A, Saul I, Liu Y, Zhao W, Ginsberg MD, Valdes MA, Busto R, Belayev L. Enriched environment delays the onset of hippocampal damage after global cerebral ischemia in rats. *Brain Res* 2003;964:121–127. [PubMed: 12573520]
- Ben-Ari Y, Repressa A, Tremblay E, Nitecka L. Selective and non-selective seizure related brain damage produced by kainic acid. *Adv Exp Med Biol* 1986;203:647–657. [PubMed: 3024465]

- Bezard E, Dovero S, Belin D, Duconger S, Jackson-Lewis V, Przedborski S, Piazza PV, Gross CE, Jaber M. Enriched environment confers resistance to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and cocaine: involvement of dopamine transporter and trophic factors. *J Neurosci* 2003;23:10999–11007. [PubMed: 14657156]
- Biernaskie J, Corbett D. Enriched rehabilitative training promotes improved forelimb motor function and enhanced dendritic growth after focal ischemic injury. *J Neurosci* 2001;21:5272–5280. [PubMed: 11438602]
- Binder DK, Croll SD, Gall CM, Scharfman HE. BDNF and epilepsy: too much of a good thing? *Trends Neurosci* 2001;24:47–53. [PubMed: 11163887]
- Binder DK, Scharfman HE. Brain-derived neurotrophic factor. *Growth Factors* 2004;22:123–131. [PubMed: 15518235]
- Bindu B, Alladi PA, Mansooralikhan BM, Srikumar BN, Raju TR, Kutty BM. Short-term exposure to an enriched environment enhances dendritic branching but not brain-derived neurotrophic factor expression in the hippocampus of rats with ventral subicular lesions. *Neuroscience* 2007;144:412–423. [PubMed: 17097239]
- Bindu B, Rekha J, Kutty BM. Post insult enriched housing improves the 8-arm radial maze performance but not the Morris water maze task in ventral subicular lesioned rats. *Brain Res* 2005;1063:121–131. [PubMed: 16324686]
- Bowling SL, Rowlett JK, Bardo MT. The effect of environmental enrichment on amphetamine-stimulated locomotor activity, dopamine synthesis and dopamine release. *Neuropharmacology* 1993;32:885–893. [PubMed: 8232791]
- Branchi I, D'Andrea I, Fiore M, Di Fausto V, Aloe L, Alleva E. Early social enrichment shapes social behavior and nerve growth factor and brain-derived neurotrophic factor levels in the adult mouse brain. *Biol Psychiatry* 2006;60:690–696. [PubMed: 16533499]
- Branchi I, Francia N, Alleva E. Epigenetic control of neurobehavioural plasticity: the role of neurotrophins. *Behav Pharmacol* 2004;15:353–362. [PubMed: 15343058]
- Bredy TW, Zhang TY, Grant RJ, Diorio J, Meaney MJ. Peripubertal environmental enrichment reverses the effects of maternal care on hippocampal development and glutamate receptor subunit expression. *Eur J Neurosci* 2004;20:1355–1362. [PubMed: 15341607]
- Briones TL, Therrien B, Metzger B. Effects of environment on enhancing functional plasticity following cerebral ischemia. *Biol Res Nurs* 2000;1:299–309. [PubMed: 11232208]
- Brockington A, Lewis C, Wharton S, Shaw PJ. Vascular endothelial growth factor and the nervous system. *Neuropathol Appl Neurobiol* 2004;30:427–446. [PubMed: 15488020]
- Buhl EH, Otis TS, Mody I. Zinc-induced collapse of augmented inhibition by GABA in a temporal lobe epilepsy model. *Science* 271:369–373.
- Carro E, Trejo JL, Nunez A, Torres-Aleman I. Brain repair and neuroprotection by serum insulin-like growth factor I. *Mol Neurobiol* 2003;27:153–162. [PubMed: 12777685]
- Cavazos JE, Zhang P, Qazi R, Sutula TP. Ultrastructural features of sprouted mossy fiber synapses in kindled and kainic acid-treated rats. *J Comp Neurol* 2003;458:272–292. [PubMed: 12619081]
- Clusmann H, Schramm J, Kral T, Helmstaedter C, Ostertun B, Fimmers R, Haun D, Elger CE. Prognostic factors and outcome after different types of resection for temporal lobe epilepsy. *J Neurosurg* 2002;97:1131–1141. [PubMed: 12450036]
- Comery TA, Harris JB, Willems PJ, Oostra BA, Irwin SA, Weiler IJ, Greenough WT. Abnormal dendritic spines in fragile X knockout mice: maturation and pruning deficits. *Proc Natl Acad Sci U S A* 1997;94:5401–5404. [PubMed: 9144249]
- Cronin J, Dudek FE. Chronic seizures and collateral sprouting of dentate mossy fibers after kainic acid treatment in rats. *Brain Res* 1988;474:181–184. [PubMed: 3214710]
- Cummins RA, Livesey PJ. Enrichment-isolation, cortex length and the rank order effect. *Brain Res* 1979;178:89–98. [PubMed: 497866]
- Del Arco A, Segovia G, Canales JJ, Garrido P, de Blas M, Garcia-Verdugo JM, Mora F. Environmental enrichment reduces the function of D1 dopamine receptors in the prefrontal cortex of the rat. *J Neural Transm* 2007;114:43–48. [PubMed: 16955373]
- Devinsky O. Diagnosis and treatment of temporal lobe epilepsy. *Rev Neurol Dis* 2004;1:2–9. [PubMed: 16397445]

- Dhanushkodi A, Bindu B, Raju TR, Kutty BM. Exposure to enriched environment improves spatial learning performances and enhances cell density but not choline acetyltransferase activity in the hippocampus of ventral subicular-lesioned rats. *Behav Neurosci* 2007;121:494–500.
- Drapeau E, Mayo W, Aurousseau C, Le Moal M, Piazza PV, Abrous DN. Spatial memory performances of aged rats in the water maze predict levels of hippocampal neurogenesis. *Proc Natl Acad Sci U S A* 2003;100:14385–14390. [PubMed: 14614143]
- Drapeau E, Montaron MF, Aguerre S, Abrous DN. Learning-induced survival of new neurons depends on the cognitive status of aged rats. *J Neurosci* 2007;27:6037–6044. [PubMed: 17537975]
- Dudek FE, Obenaus A, Schweitzer JS, Wuarin JP. Functional significance of hippocampal plasticity in epileptic brain: electrophysiological changes of the dentate granule cells associated with mossy fiber sprouting. *Hippocampus* 1994;4:259–265. [PubMed: 7842047]
- Duffy SN, Craddock KJ, Abel T, Nguyen PV. Environmental enrichment modifies the PKA-dependence of hippocampal LTP and improves hippocampus-dependent memory. *Learn Mem* 2001;8:26–34. [PubMed: 11160761]
- During MJ, Cao L. VEGF, a mediator of the effect of experience on hippocampal neurogenesis. *Curr Alzheimer Res* 2006;3:29–33. [PubMed: 16472200]
- Ehninger D, Kempermann G. Regional effects of wheel running and environmental enrichment on cell genesis and microglia proliferation in the adult murine neocortex. *Cereb Cortex* 2003;13:845–851. [PubMed: 12853371]
- Engel J Jr, Babb TL, Crandall PH. Surgical treatment of epilepsy: opportunities for research into basic mechanisms of human brain function. *Acta Neurochir Suppl (Wien)* 1989;46:3–8. [PubMed: 2672711]
- Engel J Jr. A Greater Role for Surgical Treatment of Epilepsy: Why and When? *Epilepsy Curr* 2003;3:37–40. [PubMed: 15309078]
- Fan Y, Liu Z, Weinstein PR, Fike JR, Liu J. Environmental enrichment enhances neurogenesis and improves functional outcome after cranial irradiation. *Eur J Neurosci* 2007;25:38–46. [PubMed: 17241265]
- Farrell R, Evans S, Corbett D. Environmental enrichment enhances recovery of function but exacerbates ischemic cell death. *Neuroscience* 2001;107:585–592. [PubMed: 11720782]
- Faverjon S, Silveira DC, Fu DD, Cha BH, Akman C, Hu Y, Holmes GL. Beneficial effects of enriched environment following status epilepticus in immature rats. *Neurology* 2002;59:1356–1364. [PubMed: 12427884]
- Foster TC, Dumas TC. Mechanism for increased hippocampal synaptic strength following differential experience. *J Neurophysiol* 2001;85:1377–1383. [PubMed: 11287462]
- Foster TC, Gagne J, Massicotte G. Mechanism of altered synaptic strength due to experience: relation to long-term potentiation. *Brain Res* 1996;736:243–250. [PubMed: 8930330]
- French JA, Williamson PD, Thadani VM, Darcey TM, Mattson RH, Spencer SS, Spencer DD. Characteristics of medial temporal lobe epilepsy: I. Results of history and physical examination. *Ann Neurol* 1993;34:774–780. [PubMed: 8250525]
- Gage FH. Neurogenesis in the adult brain. *J Neurosci* 2002;22:612–613. [PubMed: 11826087]
- Galani R, Jarrard LE, Will BE, Kelche C. Effects of postoperative housing conditions on functional recovery in rats with lesions of the hippocampus, subiculum, or entorhinal cortex. *Neurobiol Learn Mem* 1997;67:43–56. [PubMed: 9013500]
- Gaulke LJ, Horner PJ, Fink AJ, McNamara CL, Hicks RR. Environmental enrichment increases progenitor cell survival in the dentate gyrus following lateral fluid percussion injury. *Brain Res Mol Brain Res* 2005;141:138–150. [PubMed: 16171896]
- Ge S, Pradhan DA, Ming GL, Song H. GABA sets the tempo for activity-dependent adult neurogenesis. *Trends Neurosci* 2007;30:1–8. [PubMed: 17116335]
- Glass M, van Dellen A, Blakemore C, Hannan AJ, Faull RL. Delayed onset of Huntington's disease in mice in an enriched environment correlates with delayed loss of cannabinoid CB1 receptors. *Neuroscience* 2004;123:207–212. [PubMed: 14667455]
- Gobbo OL, O'Mara SM. Impact of enriched-environment housing on brain-derived neurotrophic factor and on cognitive performance after a transient global ischemia. *Behav Brain Res* 2004;152:231–241. [PubMed: 15196790]

- Gong C, Wang TW, Huang HS, Parent JM. Reelin regulates neuronal progenitor migration in intact and epileptic hippocampus. *J Neurosci* 2007;27:1803–1811. [PubMed: 17314278]
- Gorter JA, Goncalves Pereira PM, van Vliet EA, Aronica E, Lopes da Silva FH, Lucassen PJ. Neuronal cell death in a rat model for mesial temporal lobe epilepsy is induced by the initial status epilepticus and not by later repeated spontaneous seizures. *Epilepsia* 2003;44:647–658. [PubMed: 12752463]
- Gorter JA, van Vliet EA, Aronica E, Lopes da Silva FH. Progression of spontaneous seizures after status epilepticus is associated with mossy fibre sprouting and extensive bilateral loss of hilar parvalbumin and somatostatin-immunoreactive neurons. *Eur J Neurosci* 2001;13:657–669. [PubMed: 11207801]
- Gould E. How widespread is adult neurogenesis in mammals? *Nat Rev Neurosci* 2007;8:481–488. [PubMed: 17514200]
- Greenough WT, Volkmar FR. Pattern of dendritic branching in occipital cortex of rats reared in complex environments. *Exp Neurol* 1973;40:491–504. [PubMed: 4730268]
- Greenough WT, Volkmar FR, Juraska JM. Effects of rearing complexity on dendritic branching in frontolateral and temporal cortex of the rat. *Exp Neurol* 1973;41:371–378. [PubMed: 4126876]
- Hattiangady B, Rao MS, Shetty AK. Chronic temporal lobe epilepsy is associated with severely declined dentate neurogenesis in the adult hippocampus. *Neurobiol Dis* 2004;17:473–490. [PubMed: 15571983]
- Hattiangady B, Rao MS, Shetty GA, Shetty AK. Brain-derived neurotrophic factor, phosphorylated cyclic AMP response element binding protein and neuropeptide Y decline as early as middle age in the dentate gyrus and CA1 and CA3 subfields of the hippocampus. *Exp Neurol* 2005;195:353–371. [PubMed: 16002067]
- Hattiangady B, Rao MS, Zaman V, Shetty AK. Incorporation of embryonic CA3 cell grafts into the adult hippocampus at 4-months after injury: effects of combined neurotrophic supplementation and caspase inhibition. *Neuroscience* 2006;139:1369–1383. [PubMed: 16580143]
- Hattori S, Hashimoto R, Miyakawa T, Yamanaka H, Maeno H, Wada K, Kunugi H. Enriched environments influence depression-related behavior in adult mice and the survival of newborn cells in their hippocampi. *Behav Brain Res* 2007;180:69–76. [PubMed: 17397941]
- Hebb DO. The effects of early experience on problem-solving at maturity. *Am Psychol* 1947;2:306–307.
- Hellier JL, Patrylo PR, Dou P, Nett M, Rose GM, Dudek FE. Assessment of inhibition and epileptiform activity in the septal dentate gyrus of freely behaving rats during the first week after kainate treatment. *J Neurosci* 1999;19:10053–10064. [PubMed: 10559413]
- Hickmott PW, Ethell IM. Dendritic plasticity in the adult neocortex. *Neuroscientist* 2006;12:16–28. [PubMed: 16394190]
- Hockly E, Cordery PM, Woodman B, Mahal A, van Dellen A, Blakemore C, Lewis CM, Hannan AJ, Bates GP. Environmental enrichment slows disease progression in R6/2 Huntington's disease mice. *Ann Neurol* 2002;51:235–242. [PubMed: 11835380]
- Houser CR. Granule cell dispersion in the dentate gyrus of humans with temporal lobe epilepsy. *Brain Res* 1990;535:195–204. [PubMed: 1705855]
- Huang FL, Huang KP, Boucheron C. Long-term enrichment enhances the cognitive behavior of the aging neurogranin null mice without affecting their hippocampal LTP. *Learn Mem* 2007;14:512–519. [PubMed: 17671107]
- Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. *Annu Rev Neurosci* 2001;24:677–736. [PubMed: 11520916]
- Irvine GI, Logan B, Eckert M, Abraham WC. Enriched environment exposure regulates excitability, synaptic transmission, and LTP in the dentate gyrus of freely moving rats. *Hippocampus* 2006;16:149–160. [PubMed: 16261558]
- Jadavji NM, Kolb B, Metz GA. Enriched environment improves motor function in intact and unilateral dopamine-depleted rats. *Neuroscience* 2006;140:1127–1138. [PubMed: 16678972]
- Jakubs K, Nanobashvili A, Bonde S, Ekdahl CT, Kokaia Z, Kokaia M, Lindvall O. Environment matters: synaptic properties of neurons born in the epileptic adult brain develop to reduce excitability. *Neuron* 2006;52:1047–1059. [PubMed: 17178407]
- Jankowsky JL, Melnikova T, Fadale DJ, Xu GM, Slunt HH, Gonzales V, Younkin LH, Younkin SG, Borchelt DR, Savonenko AV. Environmental enrichment mitigates cognitive deficits in a mouse model of Alzheimer's disease. *J Neurosci* 2005;25:5217–5224. [PubMed: 15917461]

- Jankowsky JL, Xu G, Fromholt D, Gonzales V, Borchelt DR. Environmental enrichment exacerbates amyloid plaque formation in a transgenic mouse model of Alzheimer disease. *J Neuropathol Exp Neurol* 2003;62:1220–1227. [PubMed: 14692698]
- Jeffery KJ. LTP and spatial learning--where to next? *Hippocampus* 1997;7:95–110. [PubMed: 9138673]
- Jessberger S, Zhao C, Toni N, Clemenson GD Jr, Li Y, Gage FH. Seizure-associated, aberrant neurogenesis in adult rats characterized with retrovirus-mediated cell labeling. *J Neurosci* 2007;27:9400–9407. [PubMed: 17728453]
- Johansson BB. Environmental influence on outcome after experiment brain infarction. *Acta Neurochir* 1996a;63–67.
- Johansson BB. Functional outcome in rats transferred to an enriched environment 15 days after focal brain ischemia. *Stroke* 1996b;27:324–326. [PubMed: 8571431]
- Johansson BB, Belichenko PV. Neuronal plasticity and dendritic spines: effect of environmental enrichment on intact and postischemic rat brain. *J Cereb Blood Flow Metab* 2002;22:89–96. [PubMed: 11807398]
- Johansson BB, Ohlsson AL. Environment, social interaction, and physical activity as determinants of functional outcome after cerebral infarction in the rat. *Exp Neurol* 1996;139:322–327. [PubMed: 8654535]
- Jung KH, Chu K, Kim M, Jeong SW, Song YM, Lee ST, Kim JY, Lee SK, Roh JK. Continuous cytosine-b-D-arabinofuranoside infusion reduces ectopic granule cells in adult rat hippocampus with attenuation of spontaneous recurrent seizures following pilocarpine-induced status epilepticus. *Eur J Neurosci* 2004;19:3219–3226. [PubMed: 15217378]
- Jutila L, Immonen A, Partanen K, Partanen J, Mervaala E, Ylinen A, Alafuzoff I, Paljarvi L, Karkola K, Vapalahti M, Pitkanen A. Neurobiology of epileptogenesis in the temporal lobe. *Adv Tech Stand Neurosurg* 2002;27:5–22. [PubMed: 11887582]
- Kaplan MS, Hinds JW. Neurogenesis in the adult rat: electron microscopic analysis of light radioautographs. *Science* 1977;197:1092–1094. [PubMed: 887941]
- Kee N, Teixeira CM, Wang AH, Frankland PW. Preferential incorporation of adult-generated granule cells into spatial memory networks in the dentate gyrus. *Nat Neurosci* 2007;10:355–362. [PubMed: 17277773]
- Kelche C, Dalrymple-Alford J, Will B. Effects of postoperative environment on recovery of function after fimbria-fornix transection in the rat. *Physiol Behav* 1987;40:731–736. [PubMed: 3671543]
- Kempermann G, Gast D, Gage FH. Neuroplasticity in old age: sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment. *Ann Neurol* 2002;52:135–143. [PubMed: 12210782]
- Kempermann G, Kuhn HG, Gage FH. More hippocampal neurons in adult mice living in an enriched environment. *Nature* 1997;386:493–495. [PubMed: 9087407]
- Kempermann G, Wiskott L, Gage FH. Functional significance of adult neurogenesis. *Curr Opin Neurobiol* 2004;14:186–191. [PubMed: 15082323]
- Kobayashi K, Ikeda Y, Suzuki H. Locomotor activity correlates with modifications of hippocampal mossy fibre synaptic transmission. *Eur J Neurosci* 2006;24:1867–1873. [PubMed: 17040477]
- Kobayashi S, Ohashi Y, Ando S. Effects of enriched environments with different durations and starting times on learning capacity during aging in rats assessed by a refined procedure of the Hebb-Williams maze task. *J Neurosci Res* 2002;70:340–346. [PubMed: 12391594]
- Koh S, Chung H, Xia H, Mahadevia A, Song Y. Environmental enrichment reverses the impaired exploratory behavior and altered gene expression induced by early-life seizures. *J Child Neurol* 2005;20:796–802. [PubMed: 16417873]
- Koh S, Magid R, Chung H, Stine CD, Wilson DN. Depressive behavior and selective downregulation of serotonin receptor expression after early-life seizures: Reversal by environmental enrichment. *Epilepsy Behav* 2007;10:26–31. [PubMed: 17196883]
- Komitova M, Mattsson B, Johansson BB, Eriksson PS. Enriched environment increases neural stem/progenitor cell proliferation and neurogenesis in the subventricular zone of stroke-lesioned adult rats. *Stroke* 2005a;36:1278–1282. [PubMed: 15879324]

- Komitova M, Perfilieva E, Mattsson B, Eriksson PS, Johansson BB. Effects of cortical ischemia and postischemic environmental enrichment on hippocampal cell genesis and differentiation in the adult rat. *J Cereb Blood Flow Metab* 2002;22:852–860. [PubMed: 12142570]
- Komitova M, Perfilieva E, Mattsson B, Eriksson PS, Johansson BB. Enriched environment after focal cortical ischemia enhances the generation of astroglia and NG2 positive polydendrocytes in adult rat neocortex. *Exp Neurol* 2006;199:113–121. [PubMed: 16427625]
- Komitova M, Zhao LR, Gido G, Johansson BB, Eriksson P. Postischemic exercise attenuates whereas enriched environment has certain enhancing effects on lesion-induced subventricular zone activation in the adult rat. *Eur J Neurosci* 2005b;21:2397–2405. [PubMed: 15932598]
- Koyama R, Ikegaya Y. Mossy fiber sprouting as a potential therapeutic target for epilepsy. *Curr Neurovasc Res* 2004;1:3–10. [PubMed: 16181061]
- Koyama R, Ikegaya Y. To BDNF or not to BDNF: that is the epileptic hippocampus. *Neuroscientist* 2005;11:282–287. [PubMed: 16061515]
- Koyama R, Yamada MK, Fujisawa S, Katoh-Semba R, Matsuki N, Ikegaya Y. Brain-derived neurotrophic factor induces hyperexcitable reentrant circuits in the dentate gyrus. *J Neurosci* 2004;24:7215–7224. [PubMed: 15317847]
- Lazic SE, Grote HE, Blakemore C, Hannan AJ, van Dellen A, Phillips W, Barker RA. Neurogenesis in the R6/1 transgenic mouse model of Huntington's disease: effects of environmental enrichment. *Eur J Neurosci* 2006;23:1829–1838. [PubMed: 16623840]
- Leuner B, Gould E, Shors TJ. Is there a link between adult neurogenesis and learning? *Hippocampus* 2006;16:216–224. [PubMed: 16421862]
- Levi O, Michaelson DM. Environmental enrichment stimulates neurogenesis in apolipoprotein E3 and neuronal apoptosis in apolipoprotein E4 transgenic mice. *J Neurochem* 2007;100:202–210. [PubMed: 17074063]
- Lewis DV. Losing neurons: selective vulnerability and mesial temporal sclerosis. *Epilepsia* 2005;46:39–44. [PubMed: 16201994]
- Litt B, Esteller R, Echaz J, D'Alessandro M, Shor R, Henry T, Pennell P, Epstein C, Bakay R, Dichter M, Vachtsevanos G. Epileptic seizures may begin hours in advance of clinical onset: a report of five patients. *Neuron* 2001;30:51–64. [PubMed: 11343644]
- Lynch M, Sutula T. Recurrent excitatory connectivity in the dentate gyrus of kindled and kainic acid-treated rats. *J Neurophysiol* 2000;83:693–704. [PubMed: 10669485]
- Martin R, Sawrie S, Gilliam F, Mackey M, Faught E, Knowlton R, Kuzniecky R. Determining reliable cognitive change after epilepsy surgery: development of reliable change indices and standardized regression-based change norms for the WMS-III and WAIS-III. *Epilepsia* 2002;43:1551–1558. [PubMed: 12460258]
- Masukawa LM, Uruno K, Sperling M, O'Connor MJ, Burdette LJ. The functional relationship between antidromically evoked field responses of the dentate gyrus and mossy fiber reorganization in temporal lobe epileptic patients. *Brain Res* 1992;579:119–127. [PubMed: 1623399]
- Masukawa LM, Higashima M, Kim JH, Spencer DD. Epileptiform discharges evoked in hippocampal brain slices from epileptic patients. *Brain Res* 1989;493:168–174. [PubMed: 2776004]
- Mathern GW, Cifuentes F, Leite JP, Pretorius JK, Babb TL. Hippocampal EEG excitability and chronic spontaneous seizures are associated with aberrant synaptic reorganization in the rat intrahippocampal kainate model. *Electroencephalogr Clin Neurophysiol* 1993;87:326–339. [PubMed: 7693444]
- Mathern GW, Babb TL, Pretorius JK, Leite JP. Reactive synaptogenesis and neuron densities for neuropeptide Y, somatostatin, and glutamate decarboxylase immunoreactivity in the epileptogenic human fascia dentata. *J Neurosci* 1995;15:3990–4004. [PubMed: 7751960]
- Mathern GW, Leite JP, Pretorius JK, Quinn B, Peacock WJ, Babb TL. Severe seizures in young children are associated with hippocampal neuron losses and aberrant mossy fiber sprouting during fascia dentata postnatal development. *Epilepsy Res* 1996;33–43.
- Mayr B, Montminy M. Transcriptional regulation by the phosphorylation-dependent factor CREB. *Nat Rev Mol Cell Biol* 2001;2:599–609. [PubMed: 11483993]

- Mayr BM, Canettieri G, Montminy MR. Distinct effects of cAMP and mitogenic signals on CREB-binding protein recruitment impart specificity to target gene activation via CREB. *Proc Natl Acad Sci U S A* 2001;98:10936–10941. [PubMed: 11535812]
- Mayr BM, Guzman E, Montminy M. Glutamine rich and basic region/leucine zipper (bZIP) domains stabilize cAMP-response element-binding protein (CREB) binding to chromatin. *J Biol Chem* 2005;280:15103–15110. [PubMed: 15703171]
- McCloskey DP, Hintz TM, Pierce JP, Scharfman HE. Stereological methods reveal the robust size and stability of ectopic hilar granule cells after pilocarpine-induced status epilepticus in the adult rat. *Eur J Neurosci* 2006;24:2203–2210. [PubMed: 17042797]
- McIntyre DC, Kelly ME. The parahippocampal cortices and kindling. *Ann N Y Acad Sci* 2000;911:343–354. [PubMed: 10911884]
- McKeown MJ, McNamara JO. When do epileptic seizures really begin? *Neuron* 2001;30:1–3. [PubMed: 11343635]
- McNair K, Broad J, Riedel G, Davies CH, Cobb SR. Global changes in the hippocampal proteome following exposure to an enriched environment. *Neuroscience* 2007;145:413–422. [PubMed: 17261355]
- Mlynarik M, Johansson BB, Jezova D. Enriched environment influences adrenocortical response to immune challenge and glutamate receptor gene expression in rat hippocampus. *Ann N Y Acad Sci* 2004;1018:273–280. [PubMed: 15240378]
- Mohammed AH, Henriksson BG, Soderstrom S, Ebendal T, Olsson T, Seckl JR. Environmental influences on the central nervous system and their implications for the aging rat. *Behav Brain Res* 1993;57:183–191. [PubMed: 8117423]
- Mohammed AH, Zhu SW, Darmopil S, Hjerling-Leffler J, Ernfors P, Winblad B, Diamond MC, Eriksson PS, Bogdanovic N. Environmental enrichment and the brain. *Prog Brain Res* 2002;138:109–133. [PubMed: 12432766]
- Mohammed AK, Winblad B, Ebendal T, Larkfors L. Environmental influence on behaviour and nerve growth factor in the brain. *Brain Res* 1990;528:62–72. [PubMed: 2245339]
- Moncada D, Viola H. Phosphorylation state of CREB in the rat hippocampus: a molecular switch between spatial novelty and spatial familiarity? *Neurobiol Learn Mem* 2006;86:9–18. [PubMed: 16426870]
- Mora F, Segovia G, Del Arco A. Aging, plasticity and environmental enrichment: Structural changes and neurotransmitter dynamics in several areas of the brain. *Brain Res Rev* 2007;55:78–88. [PubMed: 17561265]
- Moser MB, Trommald M, Egeland T, Andersen P. Spatial training in a complex environment and isolation alter the spine distribution differently in rat CA1 pyramidal cells. *J Comp Neurol* 1997;380:373–381. [PubMed: 9087519]
- Murphy M, Greferath U, Nag N, Nithianantharajah J, Wilson YM. Tracing functional circuits using c-Fos regulated expression of marker genes targeted to neuronal projections. *Front Biosci* 2004;9:40–47. [PubMed: 14766342]
- Nagerl UV, Mody I, Jeub M, Lie AA, Elger CE, Beck H. Surviving granule cells of the sclerotic human hippocampus have reduced Ca(2+) influx because of a loss of calbindin-D(28k) in temporal lobe epilepsy. *J Neurosci* 2000;20:1831–1836. [PubMed: 10684884]
- Naka F, Narita N, Okado N, Narita M. Modification of AMPA receptor properties following environmental enrichment. *Brain Dev* 2005;27:275–278. [PubMed: 15862190]
- Nichols JA, Jakkamsetti VP, Salgado H, Dinh L, Kilgard MP, Atzori M. Environmental enrichment selectively increases glutamatergic responses in layer II/III of the auditory cortex of the rat. *Neuroscience* 2007;145:832–840. [PubMed: 17291690]
- Nilsson M, Pekny M. Enriched environment and astrocytes in central nervous system regeneration. *J Rehabil Med* 2007;39:345–352. [PubMed: 17549323]
- Nilsson M, Perfilieva E, Johansson U, Orwar O, Eriksson PS. Enriched environment increases neurogenesis in the adult rat dentate gyrus and improves spatial memory. *J Neurobiol* 1999;39:569–578. [PubMed: 10380078]
- Nishiyama A, Watanabe M, Yang Z, Bu J. Identity, distribution, and development of polydendrocytes: NG2-expressing glial cells. *J Neurocytol* 2002;31:437–455. [PubMed: 14501215]

- Nithianantharajah J, Hannan AJ. Enriched environments, experience-dependent plasticity and disorders of the nervous system. *Nat Rev Neurosci* 2006;7:697–709. [PubMed: 16924259]
- Nithianantharajah J, Levis H, Murphy M. Environmental enrichment results in cortical and subcortical changes in levels of synaptophysin and PSD-95 proteins. *Neurobiol Learn Mem* 2004;81:200–210. [PubMed: 15082021]
- Nunn JA, Graydon FJ, Polkey CE, Morris RG. Differential spatial memory impairment after right temporal lobectomy demonstrated using temporal titration. *Brain* 1999;122:47–59. [PubMed: 10050894]
- Okazaki MM, Evenson DA, Nadler JV. Hippocampal mossy fiber sprouting and synapse formation after status epilepticus in rats: visualization after retrograde transport of biocytin. *J Comp Neurol* 1995;352:515–534. [PubMed: 7721998]
- Olson AK, Eadie BD, Ernst C, Christie BR. Environmental enrichment and voluntary exercise massively increase neurogenesis in the adult hippocampus via dissociable pathways. *Hippocampus* 2006;16:250–260. [PubMed: 16411242]
- Pang TY, Stam NC, Nithianantharajah J, Howard ML, Hannan AJ. Differential effects of voluntary physical exercise on behavioral and brain-derived neurotrophic factor expression deficits in Huntington's disease transgenic mice. *Neuroscience* 2006;141:569–584. [PubMed: 16716524]
- Parent JM, Lowenstein DH. Mossy fiber reorganization in the epileptic hippocampus. *Curr Opin Neurol* 1997;10:103–109. [PubMed: 9146991]
- Parent JM, von dem Bussche N, Lowenstein DH. Prolonged seizures recruit caudal subventricular zone glial progenitors into the injured hippocampus. *Hippocampus* 2006;16:321–328. [PubMed: 16435310]
- Parent JM, Yu TW, Leibowitz RT, Geschwind DH, Sloviter RS, Lowenstein DH. Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus. *J Neurosci* 1997;17:3727–3738. [PubMed: 9133393]
- Parent JM, Tada E, Fike JR, Lowenstein DH. Inhibition of dentate granule cell neurogenesis with brain irradiation does not prevent seizure-induced mossy fiber synaptic reorganization in the rat. *J Neurosci* 1999;19:4508–4519. [PubMed: 10341251]
- Passineau MJ, Green EJ, Dietrich WD. Therapeutic effects of environmental enrichment on cognitive function and tissue integrity following severe traumatic brain injury in rats. *Exp Neurol* 2001;168:373–384. [PubMed: 11259125]
- Perez J, Vezzani A, Civenni G, Tutka P, Rizzi M, Schupbach E, Hoyer D. Functional effects of D-Phe-c[Cys-Tyr-D-Trp-Lys-Val-Cys]-Trp-NH₂ and differential changes in somatostatin receptor messenger RNAs, binding sites and somatostatin release in kainic acid-treated rats. *Neuroscience* 1995;65:1087–1097. [PubMed: 7617164]
- Pham TM, Ickes B, Albeck D, Soderstrom S, Granholm AC, Mohammed AH. Changes in brain nerve growth factor levels and nerve growth factor receptors in rats exposed to environmental enrichment for one year. *Neuroscience* 1999b;94:279–286. [PubMed: 10613518]
- Pham TM, Soderstrom S, Winblad B, Mohammed AH. Effects of environmental enrichment on cognitive function and hippocampal NGF in the non-handled rats. *Behav Brain Res* 1999a;103:63–70. [PubMed: 10475165]
- Pham TM, Winblad B, Granholm AC, Mohammed AH. Environmental influences on brain neurotrophins in rats. *Pharmacol Biochem Behav* 2002;73:167–175. [PubMed: 12076736]
- Pierce JP, Melton J, Punsoni M, McCloskey DP, Scharfman HE. Mossy fibers are the primary source of afferent input to ectopic granule cells that are born after pilocarpine-induced seizures. *Exp Neurol* 2005;196:316–331. [PubMed: 16342370]
- Pinaud R, Penner MR, Robertson HA, Currie RW. Upregulation of the immediate early gene arc in the brains of rats exposed to environmental enrichment: implications for molecular plasticity. *Brain Res Mol Brain Res* 2001;91:50–56. [PubMed: 11457492]
- Poo MM. Neurotrophins as synaptic modulators. *Nat Rev Neurosci* 2001;2:24–32. [PubMed: 11253356]
- Raine A, Mellingen K, Liu J, Venables P, Mednick SA. Effects of environmental enrichment at ages 3–5 years on schizotypal personality and antisocial behavior at ages 17 and 23 years. *Am J Psychiatry* 2003;160:1627–1635. [PubMed: 12944338]

- Rampon C, Jiang CH, Dong H, Tang YP, Lockhart DJ, Schultz PG, Tsien JZ, Hu Y. Effects of environmental enrichment on gene expression in the brain. *Proc Natl Acad Sci U S A* 2000a; 97:12880–12884. [PubMed: 11070096]
- Rampon C, Tang YP, Goodhouse J, Shimizu E, Kyin M, Tsien JZ. Enrichment induces structural changes and recovery from nonspatial memory deficits in CA1 NMDAR1-knockout mice. *Nat Neurosci* 2000b;3:238–244. [PubMed: 10700255]
- Rampon C, Tsien JZ. Genetic analysis of learning behavior-induced structural plasticity. *Hippocampus* 2000;10:605–609. [PubMed: 11075831]
- Rao MS, Hattiangady B, Abdel-Rahman A, Stanley DP, Shetty AK. Newly born cells in the ageing dentate gyrus display normal migration, survival and neuronal fate choice but endure retarded early maturation. *Eur J Neurosci* 2005;21:464–476. [PubMed: 15673445]
- Rao MS, Hattiangady B, Reddy DS, Shetty AK. Hippocampal neurodegeneration, spontaneous seizures, and mossy fiber sprouting in the F344 rat model of temporal lobe epilepsy. *J Neurosci Res* 2006;83:1088–1105. [PubMed: 16493685]
- Rasmuson S, Olsson T, Henriksson BG, Kelly PA, Holmes MC, Seckl JR, Mohammed AH. Environmental enrichment selectively increases 5-HT1A receptor mRNA expression and binding in the rat hippocampus. *Brain Res Mol Brain Res* 1998;53:285–290. [PubMed: 9473697]
- Restivo L, Ferrari F, Passino E, Sgobio C, Bock J, Oostra BA, Bagni C, Ammassari-Teule M. Enriched environment promotes behavioral and morphological recovery in a mouse model for the fragile X syndrome. *Proc Natl Acad Sci U S A* 2005;102:11557–11562. [PubMed: 16076950]
- Richardson MP, Strange BA, Thompson PJ, Baxendale SA, Duncan JS, Dolan RJ. Pre-operative verbal memory fMRI predicts post-operative memory decline after left temporal lobe resection. *Brain* 2004;127:2419–2426. [PubMed: 15459025]
- Rosenzweig ES, Barnes CA. Impact of aging on hippocampal function: plasticity, network dynamics, and cognition. *Prog Neurobiol* 2003;69:143–179. [PubMed: 12758108]
- Rosenzweig MR, Bennett EL. Cerebral changes in rats exposed individually to an enriched environment. *J Comp Physiol Psychol* 1972;80:304–313. [PubMed: 5047833]
- Rosenzweig MR, Bennett EL. Psychobiology of plasticity: effects of training and experience on brain and behavior. *Behav Brain Res* 1996;78:57–65. [PubMed: 8793038]
- Rosenzweig MR, Bennett EL, Diamond MC, Wu SY, Slagle RW, Saffran E. Influences of environmental complexity and visual stimulation on development of occipital cortex in rat. *Brain Res* 1969;14:427–445. [PubMed: 5794917]
- Rosenzweig MR, Krech D, Bennett EL, Diamond MC. Effects of environmental complexity and training on brain chemistry and anatomy: a replication and extension. *J Comp Physiol Psychol* 1962a; 55:429–437. [PubMed: 14494091]
- Rosenzweig MR, Krech D, Bennett EL, Zolman JF. Variation in environmental complexity and brain measures. *J Comp Physiol Psychol* 1962b;55:1092–1095. [PubMed: 13975016]
- Rossi C, Angelucci A, Costantin L, Braschi C, Mazzantini M, Babbini F, Fabbri ME, Tessarollo L, Maffei L, Berardi N, Caleo M. Brain-derived neurotrophic factor (BDNF) is required for the enhancement of hippocampal neurogenesis following environmental enrichment. *Eur J Neurosci* 2006;24:1850–1856. [PubMed: 17040481]
- Rutten A, van Albada M, Silveira DC, Cha BH, Liu X, Hu YN, Cilio MR, Holmes GL. Memory impairment following status epilepticus in immature rats: time-course and environmental effects. *Eur J Neurosci* 2002;16:501–513. [PubMed: 12193194]
- Sahay A, Hen R. Adult hippocampal neurogenesis in depression. *Nat Neurosci* 2007;10:1110–1115. [PubMed: 17726477]
- Saito S, Kobayashi S, Ohashi Y, Igarashi M, Komiya Y, Ando S. Decreased synaptic density in aged brains and its prevention by rearing under enriched environment as revealed by synaptophysin contents. *J Neurosci Res* 1994;39:57–62. [PubMed: 7807593]
- Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C, Hen R. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* 2003;301:805–809. [PubMed: 12907793]

- Scantlebury MH, Heida JG, Hasson HJ, Veliskova J, Velisek L, Galanopoulou AS, Moshe SL. Age-dependent consequences of status epilepticus: animal models. *Epilepsia* 2007;48:75–82. [PubMed: 17571355]
- Scharfman H, Goodman J, McCloskey D. Ectopic granule cells of the rat dentate gyrus. *Dev Neurosci* 2007;29:14–27. [PubMed: 17148946]
- Scharfman HE. Brain-derived Neurotrophic Factor and Epilepsy-A Missing Link? *Epilepsy Curr* 2005;5:83–88. [PubMed: 16145610]
- Scharfman HE, Goodman JH, Sollas AL. Actions of brain-derived neurotrophic factor in slices from rats with spontaneous seizures and mossy fiber sprouting in the dentate gyrus. *J Neurosci* 1999;19:5619–5631. [PubMed: 10377368]
- Scharfman HE, Goodman JH, Sollas AL. Granule-like neurons at the hilar/CA3 border after status epilepticus and their synchrony with area CA3 pyramidal cells: functional implications of seizure-induced neurogenesis. *J Neurosci* 2000;20:6144–6158. [PubMed: 10934264]
- Scharfman HE, Goodman JH, Sollas AL, Croll SD. Spontaneous limbic seizures after intrahippocampal infusion of brain-derived neurotrophic factor. *Exp Neurol* 2002a Apr;174(2):201–214. [PubMed: 11922662]
- Scharfman HE, Sollas AL, Goodman JH. Spontaneous recurrent seizures after pilocarpine-induced status epilepticus activate calbindin-immunoreactive hilar cells of the rat dentate gyrus. *Neuroscience* 2002b;111:71–81. [PubMed: 11955713]
- Scharfman HE, Sollas AE, Berger RE, Goodman JH, Pierce JP. Perforant path activation of ectopic granule cells that are born after pilocarpine-induced seizures. *Neuroscience* 2003;121:1017–1029. [PubMed: 14580952]
- Schneider T, Turczak J, Przewlocki R. Environmental enrichment reverses behavioral alterations in rats prenatally exposed to valproic acid: issues for a therapeutic approach in autism. *Neuropsychopharmacology* 2006;31:36–46. [PubMed: 15920505]
- Schridde U, van Luijtelaar G. The influence of strain and housing on two types of spike-wave discharges in rats. *Genes Brain Behav* 2004;3:1–7. [PubMed: 14960010]
- Schwartz S. Effect of Neonatal Cortical Lesions and Early Environmental Factors on Adult Rat Behavior. *J Comp Physiol Psychol* 1964;57:72–77. [PubMed: 14125092]
- Segal M. New building blocks for the dendritic spine. *Neuron* 2001;31:169–171. [PubMed: 11502247]
- Shapiro LA, Ribak CE. Integration of newly born dentate granule cells into adult brains: hypotheses based on normal and epileptic rodents. *Brain Res Brain Res Rev* 2005;48:43–56. [PubMed: 15708627]
- Shapiro LA, Ribak CE. Newly born dentate granule neurons after pilocarpine-induced epilepsy have hilar basal dendrites with immature synapses. *Epilepsy Res* 2006;69:53–66. [PubMed: 16480853]
- Shapiro LA, Korn MJ, Ribak CE. Newly generated dentate granule cells from epileptic rats exhibit elongated hilar basal dendrites that align along GFAP-immunolabeled processes. *Neuroscience* 2005;136:823–831. [PubMed: 16344154]
- Shetty AK. Entorhinal axons exhibit sprouting in CA1 subfield of the adult hippocampus in a rat model of temporal lobe epilepsy. *Hippocampus* 2002;12:534–542. [PubMed: 12201638]
- Shetty AK, Hattiangady B. Restoration of calbindin after fetal hippocampal CA3 cell grafting into the injured hippocampus in a rat model of temporal lobe epilepsy. *Hippocampus* 2007;17:943–956. [PubMed: 17604349]
- Shetty AK, Turner DA. Development of fetal hippocampal grafts in intact and lesioned hippocampus. *Prog Neurobiol* 1996;50:597–653. [PubMed: 9015829]
- Shetty AK, Turner DA. Fetal hippocampal cells grafted to kainate-lesioned CA3 region of adult hippocampus suppress aberrant supragranular sprouting of host mossy fibers. *Exp Neurol* 1997;143:231–245. [PubMed: 9056386]
- Shetty AK, Turner DA. Aging impairs axonal sprouting response of dentate granule cells following target loss and partial deafferentation. *J Comp Neurol* 1999;414:238–254. [PubMed: 10516594]
- Shetty AK, Turner DA. Fetal hippocampal grafts containing CA3 cells restore host hippocampal glutamate decarboxylase-positive interneuron numbers in a rat model of temporal lobe epilepsy. *J Neurosci* 2000;20:8788–8801. [PubMed: 11102487]

- Shetty AK, Turner DA. Glutamic acid decarboxylase-67-positive hippocampal interneurons undergo a permanent reduction in number following kainic acid-induced degeneration of ca3 pyramidal neurons. *Exp Neurol* 2001;169:276–297. [PubMed: 11358442]
- Shetty AK, Zaman V, Hattiangady B. Repair of the injured adult hippocampus through graft-mediated modulation of the plasticity of the dentate gyrus in a rat model of temporal lobe epilepsy. *J Neurosci* 2005;25:8391–8401. [PubMed: 16162921]
- Shetty AK, Zaman V, Shetty GA. Hippocampal neurotrophin levels in a kainate model of temporal lobe epilepsy: a lack of correlation between brain-derived neurotrophic factor content and progression of aberrant dentate mossy fiber sprouting. *J Neurochem* 2003;87:147–159. [PubMed: 12969262]
- Shetty AK, Zaman V, Turner DA. Pattern of long-distance projections from fetal hippocampal field CA3 and CA1 cell grafts in lesioned CA3 of adult hippocampus follows intrinsic character of respective donor cells. *Neuroscience* 2000;99:243–255. [PubMed: 10938430]
- Siddiqui AH, Joseph SA. CA3 axonal sprouting in kainate-induced chronic epilepsy. *Brain Res* 2005;1066:129–146. [PubMed: 16359649]
- Sloviter RS. The neurobiology of temporal lobe epilepsy: too much information, not enough knowledge. *C R Biol* 2005;328:143–153. [PubMed: 15771000]
- Spires TL, Grote HE, Varshney NK, Cordery PM, van Dellen A, Blakemore C, Hannan AJ. Environmental enrichment rescues protein deficits in a mouse model of Huntington's disease, indicating a possible disease mechanism. *J Neurosci* 2004;24:2270–2276. [PubMed: 14999077]
- Sutula T, Cascino G, Cavazos J, Parada I, Ramirez L. Mossy fiber synaptic reorganization in the epileptic human temporal lobe. *Ann Neurol* 1989;26:321–330. [PubMed: 2508534]
- Tang YP, Wang H, Feng R, Kyin M, Tsien JZ. Differential effects of enrichment on learning and memory function in NR2B transgenic mice. *Neuropharmacology* 2001;41:779–790. [PubMed: 11640933]
- Tang AC, Zou B. Neonatal exposure to novelty enhances long-term potentiation in CA1 of the rat hippocampus. *Hippocampus* 2002;12:398–404. [PubMed: 12099490]
- Tauk DL, Nadler JV. Evidence of functional mossy fiber sprouting in hippocampal formation of kainic acid-treated rats. *J Neurosci* 1985;5:1016–1022. [PubMed: 3981241]
- Terry RD. Alzheimer's disease and the aging brain. *J Geriatr Psychiatry Neurol* 2006;19:125–128. [PubMed: 16880353]
- Thoenen H. Neurotrophins and neuronal plasticity. *Science* 1995;270:593–598. [PubMed: 7570017]
- Torasdotter M, Metsis M, Henriksson BG, Winblad B, Mohammed AH. Expression of neurotrophin-3 mRNA in the rat visual cortex and hippocampus is influenced by environmental conditions. *Neurosci Lett* 1996;218:107–110. [PubMed: 8945739]
- Torasdotter M, Metsis M, Henriksson BG, Winblad B, Mohammed AH. Environmental enrichment results in higher levels of nerve growth factor mRNA in the rat visual cortex and hippocampus. *Behav Brain Res* 1998;93:83–90. [PubMed: 9659990]
- Turner CA, Yang MC, Lewis MH. Environmental enrichment: effects on stereotyped behavior and regional neuronal metabolic activity. *Brain Res* 2002;938:15–21. [PubMed: 12031530]
- Turner DA, Shetty AK. Clinical prospects for neural grafting therapy for hippocampal lesions and epilepsy. *Neurosurgery* 2003;52:632–644. [PubMed: 12590689]discussion 641–634
- van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat Neurosci* 1999;2:266–270. [PubMed: 10195220]
- van Praag H, Kempermann G, Gage FH. Neural consequences of environmental enrichment. *Nat Rev Neurosci* 2000;1:191–198. [PubMed: 11257907]
- Wozny C, Gabriel S, Jandova K, Schulze K, Heinemann U, Behr J. Entorhinal cortex entrains epileptiform activity in CA1 in pilocarpine-treated rats. *Neurobiol Dis* 2005;19:451–460. [PubMed: 16023587]
- van Rijzingen IM, Gispen WH, Spruijt BM. Postoperative environmental enrichment attenuates fimbria-fornix lesion-induced impairments in Morris maze performance. *Neurobiol Learn Mem* 1997;67:21–28. [PubMed: 9013497]
- Wallace CS, Withers GS, Weiler IJ, George JM, Clayton DF, Greenough WT. Correspondence between sites of NGFI-A induction and sites of morphological plasticity following exposure to environmental complexity. *Brain Res Mol Brain Res* 1995;32:211–220. [PubMed: 7500832]

- Wang CA, Lai MC, Lui CC, Yang SN, Tiao MM, Hsieh CS, Lin HH, Huang LT. An enriched environment improves cognitive performance after early-life status epilepticus accompanied by an increase in phosphorylation of extracellular signal-regulated kinase 2. *Epilepsy Behav.* 2007[Epub ahead of print], PMID: 17826356
- Wieser HG. ILAE Commission Report. Mesial temporal lobe epilepsy with hippocampal sclerosis. *Epilepsia* 2004;45:695–714. [PubMed: 15144438]
- Will B, Galani R, Kelche C, Rosenzweig MR. Recovery from brain injury in animals: relative efficacy of environmental enrichment, physical exercise or formal training (1990–2002). *Prog Neurobiol* 2004;72:167–182. [PubMed: 15130708]2004
- Williams BM, Luo Y, Ward C, Redd K, Gibson R, Kuczaj SA, McCoy JG. Environmental enrichment: effects on spatial memory and hippocampal CREB immunoreactivity. *Physiol Behav* 2001;73:649–658. [PubMed: 11495671]
- Wuarin JP, Dudek FE. Excitatory synaptic input to granule cells increases with time after kainate treatment. *J Neurophysiol* 2001;85:1067–1077. [PubMed: 11247977]
- Young D, Lawlor PA, Leone P, Dragunow M, During MJ. Environmental enrichment inhibits spontaneous apoptosis, prevents seizures and is neuroprotective. *Nat Med* 1999;5:448–453. [PubMed: 10202938]
- Zhu SW, Yee BK, Nyffeler M, Winblad B, Feldon J, Mohammed AH. Influence of differential housing on emotional behaviour and neurotrophin levels in mice. *Behav Brain Res* 2006;169:10–20. [PubMed: 16406106]

Glossary

List of abbreviations

BDNF	brain derived neurotrophic factor
CREB	cyclic AMP response element binding protein
GABA	gamma-amino butyric acid
GDNF	glial cell derived neurotrophic factor
GluR1	glutamate receptor 1
IGF-1	insulin-like growth factor-1
IPI	initial precipitating injury
KA	kainic acid
LTP	long-term potentiation
MAP-4	Microtubule associated protein-4
NGF	nerve growth factor

NMDA	n-methyl-d-aspartate
NR2B	NMDA receptor 2B
NR2A	NMDA receptor 2A
NT-3	neurotrophin-3
SE	status epilepticus
SRMS	spontaneous recurrent motor seizures
TLE	temporal lobe epilepsy
VEGF	vascular endothelial growth factor

Figure 1.

Extent of neurodegeneration and aberrant mossy fiber sprouting in the hippocampus of a chronically epileptic rat. Figure A1–Figure C3 show the distribution of neuron-specific nuclear antigen (NeuN) immunopositive neurons in the hippocampus. A1 and A3 show anterior and posterior regions of the hippocampus from a vehicle-treated control rat. B1 and B3 show anterior and posterior regions of the hippocampus from a KA-treated rat showing moderate hippocampal injury at 5 months post-status epilepticus. C1 and C3 show hippocampal regions from a KA treated rat showing severe hippocampal injury at 5 months post-status epilepticus. A2, B2 and C2 are magnified views of dentate hilar regions from A1, B1 and C1. Note that, in the moderate injury group (B1–B3), the loss of neurons is particularly prominent in the CA1

region but moderate in the CA3 region (B1). In contrast, in the severe injury group (C1–C3) the loss of neurons is very conspicuous in both the CA1 and CA3 (C1 and C3) regions and the dentate hilus (C2). Figure D1–Figure E2 compares the distribution of mossy fibers between a control intact hippocampus (D1) and a KA-treated rat at 4 months post-status epilepticus (E1). D2 and E2 are magnified views of regions from the upper blade of the dentate gyrus in D1 and E1 respectively. Note that the KA-induced status epilepticus induces robust aberrant mossy fiber sprouting into the dentate supragranular layer (DSGL). DG, dentate gyrus; DH, dentate hilus; GCL, granule cell layer. Scale bar, A1, B1, C1, and D1 = 500 μm ; A2, B2, C2 and D2 = 100 μm .

Figure 2.

An example of environmental enrichment typically provided to laboratory rats. Note that the inanimate objects placed inside the exploratory chamber provide cognitive, visual, somatosensory and motor stimulations. The music stimulates auditory system whereas the large chamber and housing of multiple rats allows social interaction between rats.

Figure 3.

Schematic diagram to illustrate pathophysiological changes that follow the initial precipitating injury such as the status epilepticus (SE) or acute seizures. Hyperexcitability of the hippocampus during SE leads to multiple pathological changes, which include hippocampal neurodegeneration, loss of functional inhibition, enhanced neurogenesis in the dentate gyrus and inappropriate migration of newly born granule cells into the dentate hilus, all of which likely contribute to the development of chronic epilepsy. Furthermore, aberrant mossy fiber sprouting into the dentate supragranular layer, and sprouting of CA1 and entorhinal axons can also contribute to hyperexcitability in the dentate gyrus and CA1 subfield. These abnormal sprouting may also be enhanced by up-regulation of multiple neurotrophic factors shortly after SE. Collectively, these pathophysiological changes eventually lead to the development of spontaneous recurrent motor seizures (SRMS) and learning and memory impairments. The pathological changes following an initial brain insult (i.e. SE) are represented in red color whereas yellow colored boxes reflect various changes that contribute to aberrant synaptic reorganization and chronic epilepsy development. Potential windows for applying enrichment intervention for preventing pathological changes after the SE or after the onset of SRMS are mentioned in cyan colored boxes. Note that the enrichment may be applied immediately after the initial brain injury (24 hrs after SE) or during the silent period (i.e. ~2 weeks after the SE but before the onset of chronic epilepsy) to ascertain its effects on chronic epilepsy development and learning and memory impairments. In addition, it is of interest to investigate the effects of

enriched housing conditions on the outcome of SRMS, dentate neurogenesis and learning and memory function in chronically epileptic rats.