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Review

# Effects of enriched environment on animal models of neurodegenerative diseases and psychiatric disorders

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ABSTRACT

Environmental stimulation throughout development adjusts the neurobehavioral systems involved in learning, memory and defensive responses. Environment-mediated phenotypic plasticity can be considered from two different, yet complementary, viewpoints. On one hand, the possibility that environmental interventions protect against the effects of genetic and/or acquired vulnerabilities, offers unprecedented avenues towards the elaboration and refinement of therapeutic strategies. On the other hand, an accurate understanding of the adaptive mechanisms regulating the interaction between an experimental subject and its environment may substantially benefit the quality of experimental data. Here we review experimental evidence showing that enriched environment can be beneficial in several psychiatric and neurodegenerative disorders implicating the monoamine systems where it can (i) compensate for impairments in animal models of schizophrenia, Huntington's, and Parkinson's diseases; (ii) increase resistance to the addictive properties of psychostimulant drugs; (iii) level-out the consequences of prenatal stress in animal models of depression. Additionally we discuss why some of the effects of environmental enrichment question the validity of current animal models of mental disorders.



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## Introduction

While much progress has been made in recent years in understanding how genetic factors and other molecular mediators contribute to various brain disorders, less is known about how environmental factors and associated experience-dependent plasticity modulate pathogenesis and disease progression. The discovery of the relatively low number of genes composing the human genome (Lander et al., 2001) has renewed the debate on the crucial role that environmental factors may play both in determining the phenotype of an individual and in the etiology of diseases. Several recent findings clearly indicate that the etiology of numerous brain diseases is often multifactorial and implicates complex

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interactions between life experiences and genetic background. The complex interactions between life experiences and the pathogenic effects of genetic and epigenetic factors are currently unknown. Indeed, the knowledge in this later domain is often descriptive (Sanchez et al., 2001) and does not take into account the underlying mechanisms. The plastic response of phenotypic traits to environmental change is a common research focus in several disciplines ranging from ecology and evolutionary biology to physiology and molecular genetics (for a review see Callahan et al., 1997). The two-way exchange between reductionist and holist camps has been essential to rapid and sustained progress in simple model systems. However, relatively little research has been done in complex organisms such as mammals to understand how genes and environment interact to produce phenotypic changes. Nevertheless, there is growing evidence that environmental stimulation induces long-term adjustments of neurobehavioral systems involved in learning, memory and defensive responses.

Enriched environments are "a combination of complex inanimate and social stimulation" (Rosenzweig et al., 1978) and are generally constituted by bigger housing cages, with a running wheel and a few toys that are periodically changed to stimulate animal curiosity and exploration (for example, see Rosenzweig and Bennett, 1996 and Bezard et al., 2003). Enriched environments have powerful effects on brain functions and structure, however most studies using enriched environments have focused, at the behavioral level, on learning and memory functions, and, at the cellular and molecular level, on the brain structures such the hippocampus that are involved in memory and learning (see van Praag et al., 2000 for review) (Fig. 1).

This review focuses on the effects of enriched environment on brain disorders involving abnormal monoaminergic neurotransmission such as Parkinson's disease, Huntington's disease, schizophrenia, drug addiction and depression. We will describe experimental and pre-clinical data showing how environment can alter the behavioral and neurochemical responses in animal models of these disorders and we will highlight several concepts and hypotheses as to the implication of the sensorimotor stimulation in brain plasticity and the subsequent behavioral responses.

## Gene–environment interactions mediating experience-dependent plasticity in animal models of neurodegenerative disorders

Reports dated back in 1956 have already described that targeted sensorimotor interventions can be used therapeutically in Parkinson's disease (Bilowit, 1956). Since then, an extensive amount of studies have investigated motor enrichment methods and voluntary exercise as possible treatments for a variety of central nervous system injuries (For a review see Kleim et al., 2003). Indeed, it is now well documented in clinical studies that physical therapy can be beneficial in neurodegenerative disorders (Palmer et al., 1986; Hirsch, 2000). Environmental enrichment studies using transgenic mouse models of the neurodegenerative disorders have provided important new insights into gene–environment interactions and experience-dependent plasticity in brain disease. It has also been demonstrated that environmental enrichment has beneficial effects in animal models of brain injury and neurodevelopmental disorders (reviewed by Nithianantharajah and Hannan, 2006). The effects of environmental enrichment on models of brain disorders can provide information critical to develop novel clinical approaches to the prevention and treatment of brain disorders. Furthermore, environmental enrichment and other experimental paradigms can be used to search for molecular targets to facilitate development of novel therapeutic molecules that can be called 'enviromimetics' (Hannan, 2004). In this section, we will focus on two major neurodegenerative brain diseases implicating the nigro-striatal dopamine system, i.e., Huntington's, and Parkinson's diseases, to illustrate the capacity for gene–environment interactions and experience-dependent plasticity to delay onset and slow progression of brain disorders.

### *Huntington's disease*

Huntington's disease (HD) is an autosomal dominant brain disease involving cognitive deficits (culminating in dementia), psychiatric disorders (e.g. depression) and motor symptoms (e.g. chorea), due to progressive neurodegeneration, particularly in the cerebral cortex and striatum. The disease is caused by a trinucleotide (CAG) repeat mutation, encoding an expanded polyglutamine tract in the huntingtin protein. The polyglutamine tract appears to confer a 'toxic gain of function' in the N-terminus of the mutant huntingtin protein, leading to a range of molecular and cellular changes, including altered protein-protein interactions, gene expression, molecular trafficking, inter- and intra-neuronal signaling, synaptic plasticity and adult neurogenesis (reviewed by Spires and Hannan, 2007). Of particular relevance to the present review is the evidence for disrupted cellular plasticity, including adult neurogenesis and synaptic plasticity, in transgenic mouse models of HD (Murphy et al., 2000; Lazic et al., 2004; Grote et al., 2005; Gil et al., 2005; Mazarakis et al., 2005; Grote and Hannan, 2007).

In transgenic mouse models of HD it has been demonstrated that home-cage environmental enrichment delays the onset and progression of motor symptoms (van Dellen et al., 2000; Hockly et al., 2002; Spires et al., 2004) as well as cognitive deficits (Nithianantharajah et al., 2008). Investigations into the mechanisms mediating these experience-dependent effects have identified spatiotemporally regulated molecular and cellular changes in response to both environmental enrichment (Spires et al., 2004; Spires et al., 2005; Glass et al., 2004) and voluntary physical exercise on running wheels (Pang et al., 2006). This has involved examination of gene expression, neuronal morphology, synaptic plasticity, neurogenesis and other measures of experience-dependent changes in specific brain regions of wild-type and transgenic mice. For instance, symptomatic mouse model of HD housed in an enriched environment showed increased proliferation and neuronal maturation, as well as neuronal morphological changes that could underlie some of the beneficial effects of enrichment (Lazic et al., 2006).

These findings indicate that the modulatory effects of environmental enrichment are mediated by experience-dependent changes in transcription of specific genes, synaptogenesis and adult neurogenesis, some of which may be mimicked by a newly proposed class of therapeutics, enviromimetics (Hannan, 2004; reviewed by Nithianantharajah and Hannan, 2006).

### *Parkinson's disease*

Parkinson's disease (PD) is a neurodegenerative disorder, primarily involving progressive motor symptoms such as tremor, and caused by degeneration of dopaminergic neurons in the substantia nigra. The genetics of PD is complex and gene mutations for various familial forms of PD continue to be identified, making it difficult until recently to establish animal models with appropriate construct validity. Nevertheless, established rodent models involving the use of toxins, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), to induce targeted degeneration show some face validity and have proved highly informative. These toxins induce specific degeneration of dopamine neurons as they enter these neurons through the dopamine transporter (DAT) that has long been known to be a neuronal gate to neurotoxins. Indeed, the DAT transports specific neurotoxins from the extracellular space into the cytosol of dopamine neurons. Neurotoxins are then concentrated into synaptic vesicles by the vesicular monoamines transporter, protecting the neurons by lowering free cytoplasmic concentrations of these substrates (reviewed by Uhl, 1998).

The DAT protein appears implicated in MPTP toxicity, a role largely determined by *in vitro* studies. Using $DAT^{-/-}$ mice, the direct evidence of the DAT requirement for *in vivo* MPTP-induced nigral degeneration

was demonstrated at the cell body level (Bezard et al., 1999). Indeed, the number of DA neurons of the substantia nigra compacta of the $DAT^{-/-}$ mice was not affected by the treatment with MPTP. In addition, the decrease in number of DAT sites in $DAT^{+/-}$ mice to half of normal levels provides decreased accessibility of $MPP^+$ into the neuron and thus MPTP was found to be less toxic in $DAT^{+/-}$ mice compared to wild-type. These findings suggest that, if an unknown endogenous neurotoxin is responsible of this human disease, individual vulnerability may be related to levels of DAT expressed. If true, a simple assessment of these levels may prove beneficial in preventive medicine or early diagnosis of the disease.

While genetic studies have identified mutations as rare causes for familial parkinsonism (Polymeropoulos et al., 1996), the effects of life experience on the incidence of Parkinson's disease is suggested only from epidemiological studies (Olanow and Tatton, 1999). However, much more is known as to the beneficial effects of exercises and behavioral stimulation following brain injury. For instance, PD patients have shown significant improvement in motor function as well as increased life span following physical therapy (see Kleim et al. for a review, 2003). In addition, physical exercise early in life can by itself be protective against the development of PD (Sasco et al., 1992). In parallel, it has been hypothesized that people tend to reduce motor activities that depend on nigro-striatal function in pre-clinical phases of PD, which may hasten the decline of motor function (Kleim et al., 2003). It should be noted however, that not all exercise and motor enrichment regimens are beneficial as some reports show for instance that extreme forced exercise in humans can be lethal to neurons, probably through the potential rise in plasma-reactive oxygen species, and have been linked to several neurological disorders (Chevion et al., 2003).

In intact animals, skilled movement training and forced complex acrobatic exercises enhances neuroplasticity and synaptogenesis. In rodent models of PD, exercise or complex living environments have been applied before or after insult and were shown to provide behavioral and neurochemical beneficial effects. For instance, enhancing the frequency and intensity of physical activity before or shortly after exposure to a dopaminergic neurotoxin can improve behavioral outcome and prevent dopamine terminal degeneration (Kleim et al., 2003; Tillerson et al., 2003), whereas, forced restriction of forelimb use after exposure to the neurotoxin may exaggerate degeneration (Tillerson et al., 2002). Environmental enrichment was also shown to be beneficial in an animal model of PD as mice raised in an enriched environment were shown to be 200% more resistant to MPTP compared to mice raised in a standard environment (Bezard et al., 2003). Indeed, while mice raised in a standard environment showed a 75% loss of DA neurons, mice raised in an enriched environment showed only 40% of such loss. This is achieved by down regulating the expression of DAT (Bezard et al., 2003). These data provide a direct demonstration that positive early-life experiences, involving increased mental and physical activities, may have beneficial consequences, reducing the probability of developing late-onset neurological disorders such as PD.

Animal studies have indicated several mechanisms through which exercise could improve function. For instance, paw-placing elicits phasic activity, as shown by multiunit recording studies, that may be critical to synaptic and circuit reconstruction (Jones et al., 1999). Sensorimotor stimulation may influence other factors and help spare the remaining neurons in the injured system from permanent damage, or participate in a more effective post-injury compensation (Robinson et al., 1994). These factors include increased blood flow and angiogenesis, increased neurogenesis, synaptogenesis and dendritic arborization, (van Praag et al., 2000), alterations in neurotransmission systems, such as DA terminal sprouting in the case of animal models of PD, induction of immediate early genes (Liste et al., 1997) and expression of endogenous neurotrophic and growth factors (Carro et al., 2001; Bezard et al., 2003).

*Alzheimer's disease*

Alzheimer's disease (AD) is the most common form of dementia and its age dependence means that the incidence of AD is increasing with extensions in life expectancies. Neurodegeneration in AD predominantly affects the cerebral cortex, and a number of genes have been implicated in familial forms of AD, in particular amyloid precursor protein (APP) and the presenelins, which support the hypothesis that amyloid-mediated mechanisms are pivotal in pathogenesis (reviewed by Masters et al., 2006). However, other neuropathological and genetic studies have also implicated proteins such as tau and apolipoprotein E (ApoE) in AD pathogenesis, and identified various molecular and cellular mechanisms using transgenic mouse models.

Environmental enrichment has been found to alter behavioral, cellular and molecular aspects of pathogenesis in a range of transgenic AD mouse models (Levi et al., 2003; Jankowsky et al., 2003, 2005; Arendash et al., 2004; Lazarov et al., 2005), and enhanced voluntary physical exercise alone also induces beneficial effects (Adlard et al., 2005). For instance, and despite stable beta-amyloid plaque load, amyloid precursor protein (APP)-23 transgenic mice raised in an enriched environment showed improved water maze performance, an up-regulation of hippocampal neurotrophin 3 and brain-derived neurotrophic factor and increased hippocampal neurogenesis (Wolf et al., 2006). Environmentally enriched transgenic mice expressing both human mutant presenilin-1 and the amyloid precursor protein outperformed mice in standard housing, and were behaviorally indistinguishable from non-transgenic mice across multiple cognitive domains (Costa et al., 2007). Mutant APP transgenic AD mice were also housed in a "complete enrichment" environment with social, physical and cognitive stimulation that not only involved various crawl-tubes and platforms, running wheels and toys changed weekly but also novel and complex environments for at least 1 h three times a week. These mice showed protection against cognitive impairment (working memory, reference learning, and recognition/identification), decreased brain β-amyloid deposition, and increased hippocampal synaptic immunoreactivity (Cracchiolo et al., 2007).

While the behavioral data has generally been consistent with epidemiological data (reviewed by Valenzuela and Sachdev, 2006), suggesting that increased mental and physical activity can delay onset of AD, the effects of environmental enrichment on amyloid-related disease correlates have been variable. This may reflect both the variety of experimental paradigms, but also the fact that the relationship between molecular and cognitive aspects of AD is highly complex (reviewed by Spires and Hannan, 2007).

A growing number of studies describe the beneficial effects of enriched environment and training in animal models of epilepsy (for a recent review see Dhanushkodi and Shetty, in press). Enriched environment was shown to prevent seizures and hippocampal neurodegeneration (Young et al., 1999). However, mice that already have induced seizures showed improved learning and memory abilities after being raised in an enriched environment but no concurrent evidence of reduced epilepsy was ever shown.

## Beneficial effects of environmental stimulation on drug addiction

Of the many people that experience the effects of psychoactive drugs only a small percentage develops the compulsive use typical of drug addiction (O'Brien et al., 1986). Genetic background (genotype) could account for these differences but historical and environmental factors together with personal characteristics (phenotype) may also play a major role in the development of drug addiction. The ability to make genetic changes in a predetermined way has provided an invaluable new tool to study individual molecular players involved in neurotransmission and their implication in the response to drugs of abuse. A striking example of the relevance of such studies has been

obtained from DAT knockout mice (Jaber et al., 1997). Results obtained with this line of mice established not only the central importance of the DAT as the key element controlling extracellular DA levels but its role as an obligatory target for the behavioral and biochemical action of drugs of abuse such as amphetamine and cocaine (for a review see Jaber, 2006).

Another genetic factor influencing individual vulnerability to develop cocaine abuse seems to be glucocorticoid hormones. These hormones activate two related transcription factors, the glucocorticoid receptor (GR) and the mineralocorticoid receptor. Selective inactivation of the GR gene in the brains of mice profoundly flattened the dose-response function for cocaine intravenous self-administration and suppressed sensitization, two experimental procedures considered relevant models of addiction (Deroche-Gamonet et al., 2003). Importantly, the absence of GR did not modify the basal behavioral and molecular effects of cocaine but selectively modified the excessive response to the drug spontaneously present in certain vulnerable individuals or induced by repeated drug exposure in others.

This line of work using transgenic mice has strengthened the molecular point of view of drug addiction where psychoactive drugs produce their effects on behavior, feelings and perception by acting on specific sites in central nervous system thus modifying neuronal targets (Nestler, 2001). However, this pharmacological explanation does not account for several observations showing that drugs have different effects in relation with the circumstance related to their intake (Kelleher and Morse, 1968). Inspired by pavlovian conditioned reflexes (1927), Wikler (1948) was among the first to propose a role of associative factors in drug addiction. More recently, it has been shown that being subjected to repeated aggression may represent a factor that predisposes or precipitates drug self-administration thus creating situations that overwhelm the capacity of self-adjustment (Piazza and Le Moal, 1998). Swadi (1999) proposed that the wide array of risk factors involved in drug addiction in adolescent humans can be condensed into three main domains: constitutional predisposition, environmental factors (family and peers) and life events. Home environment alone seems to constitute the major risk or protective factor. Indeed, drug addiction seems to be more frequent in people living in degraded areas or in people that undergo difficult experiences during their childhood (UN ECS, 1999). On one hand, negative early-life experiences, such as childhood maltreatment, are associated with an enhanced risk of adolescent and adult alcohol and substance use disorders (De Bellis, 1999). On the other hand, positive family relationships, involvement and attachment appear to discourage drug use and prevent drug addiction (Jessor and Jessor, 1980). Thus, a positive environment, especially during critical periods of development, could have certain protective effects against drugs of abuse.

Indeed, pre-clinical studies in rodents and primates show that severe stress experienced early in life induces a cascade of physiological, neurobiological and hormonal events, which result in dysregulation of biological reward pathways in the brain and in stress response systems (McEwen, 2000; Sanchez et al., 2001). As observed in humans, individual response to drugs may differ greatly in experimental animals. For example, in rodents some subjects, remarkably active upon the first exposure to an open field (High Responders, HR), present an increased vulnerability to drugs whereas rats that have a somewhat reduced reactivity to novel environments (Low Responders, LR) are relatively resistant (Piazza et al., 1989, 2000). This vulnerability is characterized by an augmented sensitivity to the conditioned (Jodogne et al., 1994) and unconditioned (Piazza et al., 1989) effects of drugs and by an increase in self-administration of drugs (Piazza et al., 2000). In addition, recent work in rodents shows that a behavior that presents striking similarities to the behavioral profile of addicts develops after a long period of cocaine self-administration. For this, researchers have used intravenous self-administration, the best procedure for the study of voluntary drug intake in laboratory animals, over a time frame of about 3 months. Behaviors resembling those currently considered the hallmarks of substance dependence were evaluated: drug-seeking behavior even when the drug is unavailable, unusually high desire for the drug, continued drug use even in the face of adverse consequences. In addition, the propensity to relapse to drug seeking was also investigated. It was then reported that only a small subset of animals become "addicts" and that it is the interaction between a long exposure to drug and a vulnerable phenotype that seems to determine the development of addiction (Deroche-Gamonet et al., 2004).

While hundreds of studies have investigated the negative influences of stress on the effects of drugs and have provided important information on the mechanisms underlying such changes, little attention has been dedicated to environmental manipulations that provide protection against drugs' effects and, thus, may mimic positive life experiences. An efficient way to provide such a positive environment in laboratory settings is by raising animals in enriched environments, as described above. Little attention has been dedicated to the study of the potential influences of positive life experiences in general, and enriched environments in particular, on development of drug dependence. In addition, the neurochemical, cellular and molecular modifications induced by environments in areas known to play a pivotal role in drug addiction such the mesolimbic dopaminergic system are also to be determined.

In rats, environmental enrichments was shown to decrease the activating effects of drugs such as amphetamine (Bowling et al., 1993) or nicotine (Green et al., 2003) and to reduce amphetamine self-administration (Bardo et al., 2001). However, the effects of enriched environments in these studies were compared to isolated environments and not to standard environments, which could have maximized the effects of enrichment. In line with these results, but using standard environments as a control, it has been shown recently that mice raised in enriched environments show less locomotor activity in response to an injection of cocaine than mice raised in a standard environment (Bezard et al., 2003). In addition, using a conditioned place preference paradigm, it was found that the rewarding effects of cocaine are blunted in mice raised in an enriched environment compared to mice raised in standard environments. Enriched mice also show less activation in response to repeated administration of cocaine injections and reduced responses to cocaine challenges (Solinas et al., in press). On the other hand, at the cellular and molecular levels, enriched mice show lower levels of DAT, the main molecular target of cocaine, and higher striatal levels of neurotrophins such as BDNF than mice raised in a standard environment. In addition, cocaine-induced expression of immediate early genes such as *c-fos* was different between standard and enriched mice suggesting that plasticity processes may also be altered in relation to the environment. Indeed, striatal cDNA arrays showed that mice reared during adolescence in an enriched environment have several alterations in the levels of mRNA coding for proteins involved in cell proliferation, cell differentiation, signal transduction, transcription and translation, cell structure and metabolism (Thiriet et al., 2005). Altogether, these findings suggest that environmental enrichment may be crucial in determining resistance to drugs of abuse such as cocaine. Investigating the protective role of environmental enrichment on the drug addiction phenomenon should greatly extend our knowledge of the mechanisms of vulnerability to drugs and the environmental determinants of such vulnerability. In addition, identifying environmental determinants and the cellular and molecular basis of individual vulnerability to drug abuse might reduce the costs related to long rehabilitation pathways. Research success in the field of drug abuse that leads to improved treatment of drug addiction, in the widest possible sense, will have significant strategic impact.

The beneficial effect of environmental enrichment in animal models of psychiatric disorders is not restricted to addiction as recent evidence has shown that environmental manipulations may have relevance in understanding gene–environment interactions in schizophrenia and, as we will see below, depression. For example, analysis of cellular and behavioral changes in phospholipase C-beta1 (PLC-beta1)

knockout mice suggests that this signalling pathway is crucial for activity-dependent cortical development and associated cognitive and sensorimotor functions which are known to be disrupted in schizophrenia (Hannan et al., 2001; Spires et al., 2005; McOmish et al., 2007). Specific behavioral deficits in these mice can be rescued by environmental enrichment, providing evidence for gene–environment interactions of relevance to the pathogenesis of schizophrenia (McOmish et al., 2007).

Comprehending the influence of environmental factors on psychiatric disorders necessitates a multidisciplinary approach to the acquisition of knowledge and the study of neural mechanisms at different levels. In this process, new neurobiological factors may be discovered that will become the targets for new medication in psychiatry.

## Do animal models of depression require standard housing? Environmental enrichment as a challenge

Depression, a debilitating illness characterized, among other symptoms, by depressed mood, anhedonia, hypothalamic-pituitary-adrenal axis dysfunctions and vegetative disturbances, affects 2–5% of the Western countries population in its most severe form and approximately 20% of the population in its milder forms (Nestler et al., 2002; Sullivan et al., 2002; Weissman et al., 1996). As shown by Caspi et al. (2003), the pathophysiology of this disease seems to depend on an interaction between a vulnerable genotype (including the presence of one or two copies of the short promoter allele encoding the serotonin transporter) and the occurrence of three or more major adverse life events. However, just as an adverse environment is apparently able to precipitate the onset of depression, a positive upbringing may also exert protective or beneficial effects on the emergence of mental disorders. Thus, at the same time that neuroscientists were getting closer to the biological basis of depression, psychiatrists were becoming aware of the fact that behavioral/cognitive therapies proved effective in alleviating its symptoms (Hollon et al., 2002). Given the economical and psychological burden associated with depression, it is not surprising that countless animal models have been designed to understand its etiology and develop novel potential therapeutic strategies (see Nestler et al., 2002 and Kalueff et al., 2007 for comprehensive reviews). In this section we will describe the rationale underlying animal models of depression and how environmental enrichment may inform, on one hand as to potential therapeutic strategies, and on the other hand, raise fundamental questions as to the validity of the aforementioned models.

Animal models of depression revolve around two major objectives: (1) the induction of a depressive-like phenotype through genetic, pharmacological and/or environmental manipulations (the independent variable); (2) the analysis of the individual behavioral, neurological and endocrine alterations analogous to human depression (dependent variables). Several authors have already highlighted the strengths and limitations of both the independent and the dependent variables adopted to first induce and then characterize a 'depressed' phenotype in rodents (Nestler et al., 2002; Kalueff et al., 2007). Given the scopes of this review, rather than duplicating informative and extensive reviews to which the reader is referred, here we aim to (i) describe the rationale and methodology underlying early-life-based animal models of depression; (ii) discuss environmental enrichment as a tool to investigate the compensatory potentials of individual adaptive capacities; (iii) discuss why the effects of environmental enrichment may bring into question the validity of the aforementioned models.

### *Early-life-based animal models of depression: rationale, methodology and principal findings*

The notion that stressors in infancy might predispose to mood disorders in adulthood is not a recent idea. For example, in 1918 Sigmund Freud proposed that 'every neurosis in an adult is built upon a neurosis which has occurred in his childhood' Freud (1918). However, it has not been until the pivotal studies of Harry Harlow in monkeys (Harlow et al., 1964) and Otto Weininger (1954) and Seymour Levine (1957) in rats that this hypothesis started undergoing the challenge of scientific testing. Thus, Weininger (1954), Levine (1957) and Harlow et al. (1964) demonstrated that a simple manipulation of the neonatal environment such as maternal separation is sufficient to persistently modify the development of those behavioral and neuroendocrine systems involved in the pathophysiology of depression. Hundreds of studies thereon have addressed the effects of neonatal mother–offspring separation of various lengths on the development of the stress response system in mammals (reviewed in Meaney, 2001; Pryce and Feldon, 2003; Macrì and Wurbel, 2006).

The paradigm of maternal separation in rodents generally takes the form of repeated 3–6 h daily separations between postnatal day 1 and the second or third week of life (Pryce and Feldon, 2003 for a review). These protocols induce a primary disturbance of the mother–offspring interaction and in turn mimic a form of disrupted attachment (Bowlby, 1988) and infantile stress. Independent studies reported that maternal separation increases plasma levels of adreno-cortico-tropic-hormone (ACTH) and corticosterone in basal conditions and after a stressor, corticotropin-releasing-factor (CRF) in the cerebro-spinal-fluid, and reduces glucocorticoid receptor levels in the hippocampus (Macrì and Wurbel, 2006). Additionally, early maternal separation is associated with reduced serotonin reuptake transporter in the raphe nucleus and increased behavioral immobility in the forced swim test (Lee et al., 2007) and the open field (Plotsky and Meaney, 1993; Liu et al., 1997; Macri et al., 2004). Finally, repeated mother–offspring separations have been shown to reduce motivation to self-administer palatable food in rats which could be considered a form of anhedonia (Ruedi-Bettschen et al., 2005, Matthews and Robbins, 2003). Thus, consolidated experimental evidence supports the view that the behavioral and neuroendocrine abnormalities induced by maternal separation in rodents closely resemble those observed in depressed patients.

A different paradigm aimed at investigating how individual developmental trajectories are shaped by early adverse conditions is prenatal stress. Clinical observations related stress during pregnancy to the appearance of emotional disturbances, hyperactivity and depression in the adult progeny (Huttunen and Niskanen, 1978; Watson et al., 1999). In order to mimic these alterations, pregnant rats are subjected to various types of stressors: such as tail suspension, crowding, repeated electric shocks, noise or saline injections (Maccari et al., 2003). Alternatively, Morley-Fletcher et al. (2003) and Laviola et al. (2004) exposed pregnant dams to 3 daily 45-min restraint sessions between gestational days 11–12 and delivery. Similar to maternal separation, prenatal stress is known to induce a variety of phenotypes in the offspring closely resembling those observed in depressed patients. Adult rat offspring born to dams exposed to stress during pregnancy show an upregulated hypothalamic-pituitary-adrenocortical (HPA) axis reactivity (in terms of both ACTH and corticosterone responses to stress), altered circadian rhythms of hormonal release and sleep-wake cycles, increased immobility in the forced swim test and reduced social propensity (Laviola et al., 2003; Maccari et al., 2003; Weinstock, 1997, 2001). Additionally, just as maternal separations effects mapped back onto core mediators of depression, so also prenatal stress modifies not only HPA-mediated responses and behavioral indicators of depressed mood, but also serotonergic transmission. For example, Van den Hove et al. (2006) observed that adult rats born to dams exposed to restraint stress during pregnancy, showed reduced 5-HT1A receptor binding in the ventral hippocampus.

The success of early-life stress paradigms as models of depression stems from a series of theoretical, empirical and methodological considerations. First, these models mimic several aspects of depression whereby their effects impinge on the HPA axis and on the serotonergic system, which is generally dysfunctional in depressed

patients. Second, the isomorphism between the model and the human situation is also evident in some of the behavioral, endocrine and neurological responses associated with early stress in adult offspring (see above). Additionally, the fact that the stressors are applied early in ontogeny mimics the premature dependency of human depression. Finally, since the phenotypic alterations can be observed several months after the treatment, the model itself seems to possess a substantial degree of stability. This aspect is further supported by the fact that, notwithstanding few negative findings, independent scientists have observed similar effects (Plotsky and Meaney 1993; Macri et al., 2004; Pryce et al., 2001; Laviola et al., 2004; Morley-Fletcher et al., 2003; Maccari et al., 2003; Weinstock, 1997, 2001).

*Early-life stress and 'reciprocal' treatments*

We have previously mentioned the importance that behavioral/cognitive therapies may have in alleviating the symptoms of human depression. It has been in this realm that 'reciprocal' treatments (Nestler et al., 2002) began to be sought with the goal of reversing the negative effects of infantile stress. The primary goal was to design a treatment able to increase the stimulation received by developing offspring. The intermediate goal was to demonstrate that such stimulation might benefit the developing individual and counteract the effects of an adverse perinatal environment. This would finally lead to the development of novel potential therapeutic strategies.

Two ontogenetic treatments (i.e. applied during plastic stages of development, neonatal life and adolescence) that *per se* have often been reported to reduce emotionality and HPA-mediated responses in the adult offspring received substantial consideration: early handling and environmental enrichment. Thus, both early handling in infancy (3–15 min daily mother–offspring separation during the first 2 weeks of life) (Macri et al., 2004) and environmental enrichment (increased complexity in the physical conditions of a laboratory animal during adolescence) (Laviola et al., 2004) have effects that appear to be opposite to those exerted by prenatal and early postnatal stress. As reviewed by Fox et al. (2006), both early handling and environmental enrichment in rats reduce emotionality in the open field and elevated plus-maze, reduce ACTH and corticosterone response to various stressors (electric shock and 20-min restraint), and increase glucocorticoid receptor expression, 5-HT and 5-HIAA levels in the hippocampus (Fernandez-Teruel et al., 2002).

Based on the 'protective' effects (Fox et al., 2006) exerted by early handling and environmental enrichment, a number of authors addressed the possibility that stimulating environments might compensate for the negative effects of early-life stress (Francis et al., 2002; Morley-Fletcher et al., 2003; Laviola et al., 2004; Escorihuela et al., 1994). These studies demonstrated that stimulating environments during development were able to mitigate the consequences of negative early-life events. For example, Francis et al. (2002) demonstrated that access to an enriched environment was able to reverse the anxiogenic effects of maternal separation both in terms of open field exploration and novelty-induced suppression of feeding and in terms of corticosterone release following a stressor. Similarly, Laviola et al. (2004) and Morley-Fletcher et al. (2003) showed that environmental enrichment during adolescence eliminates the outcomes of prenatal stress on corticosterone response to restraint and reactivity to an immune-suppressive agent. The same compensatory effects of environmental enrichment were observed on playful behavior (Morley-Fletcher et al., 2003). Finally, environmental enrichment has been shown to exert effects on serotonergic transmission that are opposite to those exerted by prenatal stress and maternal separation. For example, Rasmuson et al. (1998) showed that rats reared in an enriched environment for 30 days had significantly higher 5-HT1A receptor mRNA expression in the dorsal hippocampus. Thus, these animal studies demonstrated that reciprocal treatments aimed at mimicking the 'positive' clinical effects of behavioral/cognitive therapies (Hollon et al., 2002) were effective in reversing the consequences of early-life stress. However, just as the aforementioned studies met the proposed goal to demonstrate the compensatory capabilities of a stimulating environment in animal models of emotional disorders, they also posed a fundamental question related to the stability of the models themselves. As a matter of fact, it still remains unanswered to what extent environmental enrichment and early handling are of relevance to a treatment as complex as psychotherapy. Alternatively, they might just be considered milder variations in housing conditions and, at best, reflect the adoption of a healthier life style. Resolving this dichotomy might help clarify whether the outcomes of a stimulating condition (environmental enrichment and early handling) inform potential therapeutic strategies or whether they highlight the limitations of current animal models. In particular, given the rather unspecific nature of early handling and environmental enrichment, one provocative proposal is that current models of depression might suffer from limited robustness if they are susceptible to environmental perturbations.

Human depression is a pervasive disease that, despite cross-cultural variability (Demyttenaere et al., 2004), can be observed in extremely different contexts. It seems thus surprising that the observations, upon which present and past research has been built, have been conducted under a single 'standard' condition. Under these circumstances, rather than limiting our view to the 'ameliorative' effects of enrichment, it is possible to ask what is so special about standard housing conditions and why subjects exposed to early stress consistently exhibit a depressed phenotype only under those very conditions.

Relevant information for this debate could be obtained from the drug addiction research field. As a matter of fact whereas, as we have discussed previously, important individual differences exist in the vulnerability to drug addiction in humans, most models of drug addictions are easily obtained in most animals under many conditions. Such evidence has led some authors to question the validity of these models and to propose that the lack of non-drug reward alternatives represents an important bias in current models of addiction (Ahmed, 2005). However, a recent study by Piazza et al. (2000) that took into account the distribution of excessive drug-taking and drug-seeking behaviours among a population of rats housed in standard conditions before the beginning of self-administration and in isolated conditions afterwards, found that only 17% of the rats self-administering cocaine developed a addiction-like condition characterized by the contemporary presence of 3 criteria of addiction whereas the others show no or less severe forms of addiction (Deroche-Gamonet et al., 2004). Importantly, in humans, the percentage of cocaine users that become addicted is estimated at 15% (Anthony, 1992). Thus, this study indicates that standard housing conditions could in some instances be adapted for the study of human brain disorders. Moreover, studies such as this one, highlight the fact that whereas a behavioral phenotype can constitute a model of disease, taking into account how this phenotype is differentially expressed by different individuals may help provide further validity to animal models.

## What to do with environmental enrichment and how relevant this is to animal models of brain disorders?

*Environmental stimulation: Beneficial or puzzling?*

The effects of environmental stimulation described are generally considered ameliorative, beneficial, protective or any other synonym denoting a positive connotation. However, each coin has its flip side. From a parsimonious perspective, the simplest forms of environmental stimulation in rodents consist of the provision of social partners and shelters. Rather than representing enrichment or even some form of 'treatment', the presence of social partners and shelters should reflect the norm to a rodent in its natural environment. Additionally, environmental enrichment of various forms is already standard in many facilities across Europe. Finally, the compulsory provision of some sort of enrichment to laboratory rodents has already been integrated in

the European legislation (2007/526/CE). From this perspective, rather than representing a threat to standardization (Tsai et al., 2003), environmental enrichment might be regarded as an additional variation in housing conditions that has already become an integral part of neuroscience studies. Attention, we believe, should be drawn to the fact that this variation largely affects the results of traditional and 'validated' animal models of human pathologies. Therefore, just as environmental enrichment is a valid tool to address the potential of individual adaptive capacities, so also it provides a source of experimental variation that challenges the validity of current animal models of neurologic, psychiatric and behavioral disorders.

*Are we unintentionally addressing gene–environment interaction in standard laboratory cages?*

As already introduced, Caspi et al. (2003) elegantly demonstrated that the pathogenesis of human depression depends on the interaction between natural predispositions and adverse environmental conditions (Fig. 2). In order to test this hypothesis, we need to design experiments in which natural predispositions (mimicked through genetic and/or environmental manipulations) and adverse life events are systematically combined. The fact that environmental enrichment by definition '… refers to housing conditions, either home cages or exploratory chambers, that facilitate enhanced sensory, cognitive and motor stimulation relative to standard housing conditions …' (Nithianantharajah and Hannan, 2006) indirectly suggests that standard housing might represent an impoverished situation to experimental subjects. Additionally, as discussed elsewhere, experimental subjects reared in standard cages often display symptoms reminiscent of poor welfare and 'aberrant or maladaptive brain functions' (Wuerbel, 2001). Along this line, we may consider standard cages as

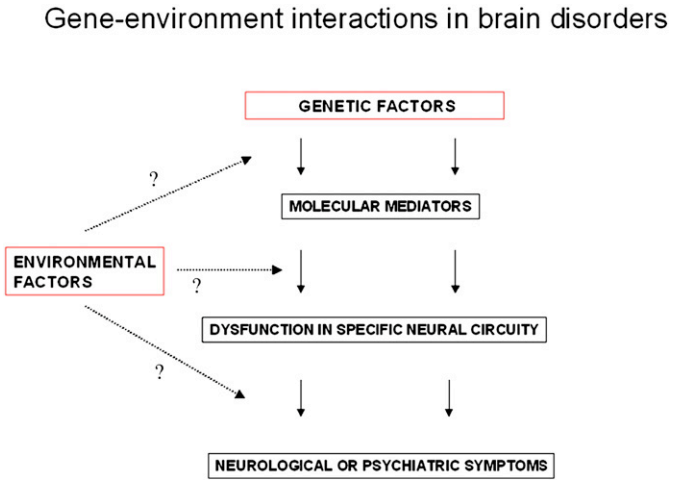


**Fig. 2.** Gene–environment interactions in brain disorders. Neurological and psychiatric disorders result from a genetic predisposition, unique for each disorder, and a variety of environmental factors, which can act during prenatal, postnatal or adult life. This simple schema illustrates how the pathogenesis of each brain disorder can be studied at molecular, cellular and behavioural levels. However, understanding cellular and molecular mediators is insufficient, as we ultimately must also be able to elucidate environmental modulators, and associated gene–environment interactions, if we are to have a sophisticated comprehension of pathogenesis, thus facilitating development of new therapeutic approaches.

**Fig. 1.** Mice housed in a standard environment (back) or enriched environment (front). Housing conditions can vary significantly within laboratories. In M Jaber's laboratory for instance, mice are randomly divided after weaning (3 weeks of age), in two different housing environmental conditions in groups of 4 for at least 2 months: standard environments that consists of common cage housing (30×15×15 cm) and enriched environment which consists of larger (75×45×25 cm) cages containing a running wheel, a small house and 4–5 toys. The running wheel and the small house are always present in the cage whereas the toys are changed once a week with new toys of different shape and color. (Photo credit P. Dumas, EURELIOS, France).

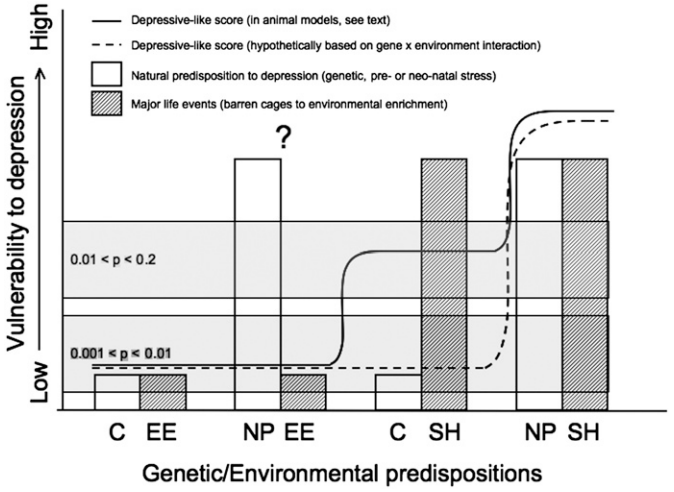


**Fig. 3.** Illustration of four potential different scenarios aimed at studying the natural/predisposition — environment interaction in the pathogenesis of depression. The value on the *Y*-axis represents hypothetical vulnerability to develop a depressive-like phenotype in animal models (from low to high). Clear histograms represent the natural-predisposition component of depression: this can be mimicked through genetic manipulations and/or early stress. Dashed histograms represent the environmental component associated with the development of a depressive-like phenotype (major life events in humans): in this case enriched environments in animal models are related to low vulnerability while standard housing conditions relate to higher vulnerability. The dashed line represents the expected depression score based on a gene–environment interaction. If the gene–environment interaction were complete, depression would not be observed unless both factors combined to induce the depressed phenotype. The question mark indicates the fact that present experimental evidence does not allow concluding that environmental enrichment is 'always' related to the absence of a depressed-like phenotype. The full line represents the 'depressive' phenotype extracted by animal literature whereby NP/SH subjects show depressive symptoms compared to C/SH subjects, which, in turn show a depressed phenotype compared to C/EE. The two shaded areas indicate the hypothetical probability to detect significant effects when NP/SH condition is tested against the other three conditions. Although hypothetical, this model might explain why sometimes significant effects are observed and sometimes these effects are not significant. The model also suggests that some of the studies claiming to investigate the contribution of a single factor are indeed unintentionally addressing gene–environment interaction. C = Control; EE = Environmental enrichment; NP = Natural predisposition; SH = Standard housing.

detrimental to animal well being thereby representing a second factor (chronic exposure to poor living conditions) in animal models of depression.

Looking again at depression, it is possible to prefigure four different scenarios and their expected effects on the development of a 'depressed' phenotype: no predisposition (e.g. wild-type control, C)/ no environmental adversity (e.g. environmental enrichment, EE); natural predisposition (NP; e.g. prenatal stress, genetic preparation)/ no environmental adversity (EE); no predisposition (C)/environmental adversity (standard housing, SH); natural predisposition (NP)/environmental adversity (SH). Although necessarily simplified, this model makes some general predictions. Given the interactive nature of individual and environmental factors in the pathogenesis of depression we should detect significant effects when the NP/SH combination is tested against all the other combinations (dashed line in Fig. 3). However, as discussed in the previous sections, some of these treatments may induce an individual depressive phenotype independently of a second factor. Therefore, should the interaction between the two factors be of limited efficacy or should the effect of a single factor prevail over the other, the power of our experimental protocols might be devalued. This seems to be particularly likely in the light of the fact that the C/SH combination constitutes the typical control group. The model depicted in Fig. 3 may thus help in clarifying why some effects are not consistently observed in independent studies, and why elucidating the contribution of multiple factors is hindered by a limited consideration of appropriate control groups.

## Concluding remarks

Research on the effects of environmental enrichment in rodents has been important in the discovery of developmental plasticity of brain and behavior, including its therapeutic effects on neurodegenerative diseases and recovery from stroke and other forms of brain damage. While the examples provided above have focused on some major neurodegenerative, psychiatric, and behavioral disorders, it is clear that environmental factors can modulate pathogenesis and progression in all brain disorders, even those such as HD that were once considered the epitome of genetic determinism.

While gene–environment interactions and experience-dependent plasticity demonstrated in animal models of brain disorders have proved highly informative, we are a long way from explaining the detailed mechanisms involved. Increased levels of mental and physical activity can induce a wide range of molecular, cellular and behavioral changes, in both disease models and healthy controls. However the current challenge is to provide mechanistic insights and a theoretical framework to understand these processes, particularly in key areas such as epigenetics.

In the previous section we detailed why we believe that environmental enrichment may challenge the validity of current animal models of brain diseases and we used depression as an example. Additionally, given present legislation, methodological considerations and empirical findings, it does not seem to be wise to disregard environmental enrichment as a potential source of confound in experimental protocols (Tsai et al., 2003). It is therefore timely to integrate environmental enrichment into experimental designs in order to increase the validity of our findings. This integration might follow two complementary paths: (i) Assuming standard housing as potentially detrimental to animal well being, environmental enrichment should become the standard control group. Given the difficulty in standardizing enriched conditions, rather than proposing a golden standard we would suggest the provision of basic forms of enrichment (e.g. nesting material and shelters) and a detailed description of the adopted strategy in the method section. This possibility is as yet not very likely given the scarcity of studies unequivocally demonstrating that standard housing is *per se* affecting animal well being. This aspect awaits further experimental testing. (ii) Environmental enrichment should become a control group in order to address whether allegedly robust animal models of neurodegenerative and psychiatric disorders resist the challenge of differential rearing conditions. In other words, when claiming a model as 'valid', be it genetic, environmental or both, we must test whether it reflects a stable phenomenon or whether it reflects a laboratory-(or housing condition-) specific outcome.

Independently on the specific approach to be taken, we believe that the two aforementioned possibilities may largely benefit laboratory animal welfare. The growing need to take into account their well being (Wuerbel, 2007) urges the scientific community to design novel strategies aimed at refining subjects' living conditions and reducing their number. The first approach might improve laboratory animals' living conditions by providing environments in which species-specific behavioral elements can be expressed to a larger extent compared to current standard housing conditions. Complementarily, should the second approach increase the reliability of present animal models of human pathologies, the net result would be a long-term reduction in laboratory animals' use. Specifically, preclinical investigations aimed at developing novel medications dissipate large amounts of resources due to animal models not resisting the transition to clinical trials (i.e. limited external validity). We propose that, although the adoption of different control conditions may in the short-term involve a redefinition of current baselines, this approach can largely benefit external validity and ultimately lead to a reduction in laboratory animals' use.

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