Published in final edited form as:

Pharmacol Biochem Behav. 2009 May ; 92(3): 377–382. doi:10.1016/j.pbb.2009.01.016.

Neurobehavioral Effects of Environmental Enrichment and Drug Abuse Vulnerability

Dustin J. Stairs¹ and Michael T. Bardo²

¹Creighton University Department of Psychology

²University of Kentucky Department of Psychology

Abstract

Environmental enrichment during development produces a host of neurobehavioral effects in preclinical models. Early work demonstrated that enrichment enhances learning of a variety of behavioral tasks in rats and these changes are associated with neural changes in various cortical regions. In addition to promoting superior learning, more recent evidence suggests that environmental enrichment also has a protective effect in reducing drug abuse vulnerability. The current review describes some of the most important environment-dependent neural changes in reward-relevant brain structures and summarizes some of the key findings from the extensive literature showing how enrichment decreases the impact of drugs of abuse. Some critical neural mechanisms that may mediate the behavioral changes are postulated, along with some notes of caution about the limitations of the work cited.

Keywords

Environmental enrichment; isolation; novelty; drug abuse; mesocorticolimbic reward system; drug self-administration; conditioned place preference; locomotor activity; dopamine; corticosterone; stress

While the majority of individuals experiment with drugs, most do not become addicted (Adams et al., 1999). One of the important aspects of drug abuse research is to determine the various factors that underlie individual differences in drug abuse vulnerability. Genetic factors are known to play an important role in individual differences in susceptibility to substance abuse disorders. In a review of twin and adoption studies looking at drug abuse in adolescents, Hopfer and colleagues (2003) found a common genetic influence on substance use across different drugs. However, the review by Hopfer et al. (2003) also indicated that non-genetic factors can influence an individual's susceptibility to drug abuse. For instance, both age and environmental factors have shared influences on the likelihood for substance use among adolescents. In addition, factors such as parental control, after-school activities, social activities and enriching stimuli in the environment can serve as protective factors that can decrease drug use among genetically vulnerable adolescents and adults (Hopfer et al., 2003).

Corresponding Author: Michael T. Bardo, PhD, Professor of Psychology and Director, Center for Drug Abuse Research Translation (CDART), University of Kentucky, 741 S. Limestone, BBSRB, Room 447, University of Kentucky, Lexington, KY 40536-0509, Fax #: 857-257-5750, Phone #: 857-257-6456, Email: E-mail: mbardo@uky.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.

To understand the role of environmental enrichment on vulnerability to drug abuse, controlled experiments using laboratory animals have been conducted. In a typical experiment, rats are housed for several weeks post weaning (beginning ~21 days of age) in either an enriched condition (EC) with novel objects and social cohorts or an isolated condition (IC) without objects or cohorts; a third group can be raised in a social condition (SC) with social cohorts but no novel objects. These three conditions are used to determine the influence of social interaction and environmental novelty on various drug effects during young adulthood. The current review summarizes some key findings of our current state of knowledge in this area and critically evaluates some limitations.

Enrichment-Induced Changes in Neuroanatomy and Neurochemistry

It has been known for about 50 years that environmental enrichment promotes superior learning and alters brain structure (Renner & Rosenzweig, 1987). Early studies found that EC rats have increased cortical thickness, especially in the occipital cortex (Diamond, Krech, & Rosenzweig, 1964). Environmental enrichment also results in neuronal changes in auditory cortex (Engineer et al., 2004), as well as other cortical regions (Renner & Rosenzweig, 1987). At the level of the individual neurons, enrichment increases the size of neuronal cell bodies and nuclei, the number and size of dendrites, as well as increasing dendritic branching and the number of dendritic spines (Diamond, 2001; Rosenzweig & Bennett, 1996). EC rats not only have changes in neuron structure compared to IC rats, they also show alterations in glial cells in brain. Rats raised in enriched conditions have increased astrocytic branching in the brain compared to IC rats (Hawrylak & Greenough, 1995; Sirevaag & Greenough, 1991). Immunohistochemical staining revealed that the density of microglia (typically present after brain injury) decreases following environmental stimulation during infancy (Kolb, Forgie, Gibb, Gorny, & Rowntree, 1998). Environmental enrichment also increases the number of blood capillaries in the brain, as well as increasing metabolic activity as indicated by an increase in the number of mitochondria (Kolb & Whishaw, 1998).

Neuronal changes following enrichment have been found in various mesocorticolimbic structures known to be important in the psychomotor stimulant and rewarding effects of drugs of abuse (Bardo, 1998). For instance, there is a 60% increase in number of dendritic spines found on Type I spiny neurons in striatum of EC rats compared to IC rats (Comery, Stamoudis, Irwin, & Greenough, 1996). There are also increases in dendritic arborization on spiny neurons in nucleus accumbens (NAcc) in EC rats compared to SC rats (Kolb, Gorny, Soderpalm, & Robinson, 2003).

Environmental enrichment not only increases dendritic arborization in striatum and NAcc, but also appears to alter neuronal function in medial prefrontal cortex (mPFC). The mPFC has been implicated in the reinforcing efficacy of abused drugs and in spatial working memory (Aultman & Moghaddam, 2001; Tzschentke & Schmidt, 2000), as well as in control of the stress axis (Crane, Ebner, & Day, 2003; Figueiredo, Bruestle, Bodie, Dolgas, & Herman, 2003; Radley, Arias, & Sawchenko, 2006). The mPFC has excitatory inputs into NAcc (Sesack, Deutch, Roth, & Bunney, 1989), as well as indirect inputs into other structures within the mesocorticolimbic dopamine (DA) pathway (Tzschentke & Schmidt, 2000). EC rats have a decrease in functioning of the DA transporter (DAT) in mPFC, evident by a decrease in the maximum velocity of [³H]DA uptake compared to IC rats (Zhu, Green, Bardo, & Dwoskin, 2004). Using cell surface biotinylation, Zhu et al. (2005) found that EC rats have less DAT protein at the cell surface compared to IC rats, while having similar amounts of internalized DAT protein. The enrichment-induced reduction in functional DAT at the cell surface in mPFC may reflect a compensatory decrease in trafficking due to repeated stimulation of this system with novelty.

Environmental manipulations also appear to affect glutamatergic systems involved in drug reward. For example, EC rats have increased glutamatergic tone mediated via mGluR2 receptors in dorsal PFC compared to IC rats (Melendez, Gregory, Bardo, & Kalivas, 2004). Environment-dependent alterations in frontal cortical glutamatergic activity may not only be important in drug reward, but also with behavioral inhibitory processes as described later.

In addition to environmental enrichment, social rearing alone (no novel objects) alters baseline monoamine neurotransmitter levels in mesocorticolimbic structures. Compared to IC rats, Jones et al. (1991) found that SC rats have increased levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in NAcc. This study also found that SC rats have greater levels of the acetylcholine synthetic enzyme choline acetyltransferase compared to IC rats. Another study found that SC rats have increased basal DA metabolism in mPFC (Jones, Hernandez, Kendall, Marsden, & Robbins, 1992). Thus, social rearing alone contributes to environment-dependent changes in reward-relevant mesocorticolimbic structures.

While many studies indicate that environmental enrichment alters functional monoamine neurotransmission, basal levels of monoamines and receptors do not appear to differ reliably among EC, SC and IC rats. Jones et al., (1992) found no differences in basal levels of DA in NAcc or caudate putamen between SC and IC rats. Basal tissue levels of DA in mPFC also do not differ between SC and IC rats (Heidbreder et al., 2001). Other reports have not observed differences between EC and IC rats in DA tissue concentrations or DA receptor levels in NAcc or striatum using *in vitro* techniques (Bardo, Bowling et al., 1995; Bardo & Hammer, 1991; Bowling, Rowlett, & Bardo, 1993). Thus, environmental enrichment alters the functional activity and turnover of monoamines and other neurotransmitters, rather than steady state levels.

Enrichment-Induced Neurochemical Differences in Drug Effects

Many studies have shown that environmental enrichment alters the neurochemical effects of various drugs of abuse. However, the type of methodology used to detect enrichment-induced differences in the neurochemical response to drugs appears to be important. For example, using an *ex vivo* technique, Bowling et al. (1993) found that enrichment increased dihydroxyphenylalanine (DOPA; a DA precursor) tissue levels in striatum following a DOPA decarboxylase inhibitor, and decreased dihydroxyphenylacetic acid (DOPAC; a DA metabolite) tissue levels in NAcc following amphetamine. However, enrichment had no effect on DOPAC when amphetamine-evoked DA release was assessed using an *in vitro* tissue slice preparation (Bardo, Bowling et al., 1995). Using *in vivo* microdialysis, Jones et al. (1992) found that SC rats had an attenuated response to the amphetamine-induced increase in extracellular DA levels in NAcc and striatum compared to IC rats; the reduced accumbal DA release in SC rats coincides with the decrease in DOPAC levels in SC relative to IC rats (Hall et al., 1998; Jones et al., 1992). In contrast, a subsequent microdialysis study found that EC rats had greater extracellular DA levels in NAcc following intravenous amphetamine compared to IC rats (Bardo, Valone, Robinet, Shaw, & Dwoskin, 1999). The discrepancy between the two microdialysis studies could be due to the differences between the SC and EC rats used in the two different studies. In the Bardo et al (1999) study, EC rats were exposed to daily novelty and thus it can be hypothesized that repeated novelty exposure may sensitize limbic structures, resulting in a greater DA release in NAcc relative to IC rats. This contrasts with the Hall et al, (1998) study in which no novel objects were used with SC rats. In any case, enrichment-induced differences in the neurochemical effects of amphetamine do not likely reflect pharmacokinetic changes, as brain levels of 3[H]-amphetamine are similar in EC and IC rats following systemic injection (Bardo, 1999).

In addition to DA, enrichment alters drug-induced glutamate release as measured by microdialysis. In a study by Rahman and Bardo (2008), glutamate levels in NAcc were elevated by amphetamine to a greater extent in EC rats than in IC rats. Pretreatment with MK-801, a non-competitive N-methyl-D-aspartate receptor antagonist, prevented the acute amphetamine-induced increase in extracellular glutamate levels in NAcc, thus implicating an accumbal glutamatergic mechanism in the environment-dependent effects of amphetamine.

The neurochemical effect of cocaine also is altered following differential housing. SC rats have an attenuated increase in extracellular accumbal DA levels following cocaine infusions compared to IC rats, while this effect is not seen for 5-HT levels (Howes, Dalley, Morrison, Robbins, & Everitt, 2000). This same study showed that SC rats also have a reduced expression of c-fos (an immediate-early gene) in NAcc, dorsal striatum, and central nucleus of the amygdala, following a cocaine injection compared to IC rats. This study illustrates that enrichment-induced differences in DA levels are not specific to amphetamine, but appear to generalize to other psychostimulants.

Enrichment-Induced Behavioral Differences in Drug Effects

Given the enrichment-induced changes in the neurochemical effects of drugs of abuse, it is not surprising that a host of studies have shown enrichment-induced changes in the behavioral effects produced by exposure to either novel stimuli or drugs of abuse. EC rats show an attenuated locomotor response in a novel environment compared to IC rats (Bowling & Bardo, 1994; Bowling et al., 1993; Del Arco, Zhu, Terasmaa, Mohammed, & Fuxe, 2004; Green, Cain, Thompson, & Bardo, 2003; Smith, Neill, & Costall, 1997), and this difference has been attributed to a DA mechanism (Bowling et al., 1993; Jones, Marsden, & Robbins, 1990). In an open field, EC rats have a lower baseline level of locomotor behavior relative to their IC counterparts (Bardo, Bowling et al., 1995; Bowling & Bardo, 1994; Bowling et al., 1993); however, when amphetamine is administered, EC rats have a greater increase in locomotor behavior relative to IC rats (Bardo, Bowling et al., 1995; Bowling & Bardo, 1994; Bowling et al., 1993). While EC rats are more sensitive to acute amphetamine-induced locomotor activity, EC rats show less sensitization following repeated injections of amphetamine or cocaine (Bardo, Bowling et al., 1995; Smith et al., 1997). In the case of nicotine, EC rats are less sensitive than IC rats to both the acute and repeated stimulant effects nicotine (Green et al., 2003). Thus, while enrichment differentially alters the hyperactivity produced by acute administration of different stimulant drugs, the locomotor sensitization produced by repeated administration of stimulant drugs is generally blunted.

Enrichment-induced differences in drug effects are also seen with non-stimulant drugs such as opiates. Using a tail-withdrawal procedure, EC rats are more sensitive to the antinociceptive effects of the kappa opioid receptor agonist spiradoline, as well as to the diuretic effects of spiradoline, compared to IC rats (Smith, Bryant, & McClean, 2003). Environmental enrichment also appears to alter the sensitivity of mu opioid receptors. Relative to IC rats, EC rats are more sensitive to the antinociceptive effects of mu opioid agonists butorphanol and nalbuphine (Smith et al., 2005). This greater sensitivity following enrichment may be due to an increase in opioid receptor density, since SC rats have a higher B_{max} for specific $^3[H]$ -naloxone binding compared to IC rats (Schenk, Britt, Atalay, & Charleson, 1982).

Environmental enrichment has also been found to alter the subjective effects of stimulants using the drug discrimination procedure. Using a two-lever operant procedure to discriminate cocaine from saline, Fowler et. al (1993) found that EC rats were less sensitive to the discriminative stimulus effects of cocaine and amphetamine compared to IC rats. Similarly, EC rats are less sensitive to the discriminative effects of nicotine compared to IC rats (Stairs, Fosdick, Mittelstet, & Schwarzkopf, 2008). The difference between EC and IC rats in

sensitivity to the nicotine cue may result from changes in nicotinic acetylcholine receptors, as EC rats show increased sensitivity to the noncompetitive nicotinic receptor antagonist mecamylamine in blocking the discriminative stimulus effects of nicotine (Stairs, Fosdick et al., 2008).

A number of studies have demonstrated that the abuse liability of drugs is altered by environmental enrichment. Using the place conditioning procedure, following repeated conditioning trials with amphetamine, EC rats show greater conditioned place preference (CPP) relative to both IC and SC rats (Bardo, Bowling et al., 1995; Bowling & Bardo, 1994). Similarly, EC rats show CPP to mu opioid agonists buprenorphine, butorphanol and nalbuphine, whereas IC rats do not (Smith et al., 2005), indicating the EC rats are also more sensitive to the rewarding properties of opiates.

While these studies indicate that rats raised in enriched environments have enhanced sensitivity to the rewarding properties of drugs, a recent study found that housing mice in an enriched environment *following* exposure to repeated cocaine eliminated later cocaine-induced sensitization and CPP (Solinas, Chauvet, Thiriet, El Rawas, & Jaber, 2008). This study also found that enrichment prevented reinstatement of cocaine CPP in mice, suggesting that enrichment may decrease sensitivity to stimulant drugs in individuals with a previous drug history, thus making it potentially useful for preventing relapse.

Although activation of mu opioid receptors produces CPP in rats, activation of kappa opioid receptors results in conditioned place aversion (del Rosario Capriles & Cancela, 2002; Shippenberg & Herz, 1987). When EC and IC rats were tested for place conditioning induced by the kappa opioid agonist spiradoline, EC rats had a greater place aversion than IC rats (Smith et al., 2003). Thus, both the rewarding and aversive effects of opioids are enhanced by environmental enrichment.

Although place conditioning is a reliable procedure to study the rewarding and aversive properties of drugs, it has some limitations (Bardo and Bevins, 2000). In particular, since the procedure can be influenced by changes in the relative novelty of the apparatus compartments, it is possible that drug-induced alterations in the habituation process may complicate interpretation of the results. Also, while it is thought to be a good model for contextual conditioning of drug effects important in relapse and craving, the place conditioning procedure lacks a true discrete operant response. These limitations can be mitigated by using the rodent intravenous self-administration procedure.

When evaluating the effects of environmental enrichment on the reinforcing effects of amphetamine using the self-administration procedure, EC rats self-administer less amphetamine than IC rats at low unit doses (Bardo et al., 2001; Green et al., 2002). In the study by Bardo et al. (2001), EC, SC and IC rats were tested for their propensity to self-administer both a high unit dose of amphetamine (0.1 mg/kg/infusion) and a low unit dose of amphetamine (0.03 mg/kg/infusion). At the high unit dose, there were no group differences, while the low unit dose of amphetamine maintained lower levels of self-administration in both the EC and SC rats compared to the IC rats. Bardo et al. (2001) also assessed both male and female rats, but found no interaction between sex and environment. However, there was a significant three way interaction involving sex, environmental condition, and schedule conditions when behavior was maintained through sucrose reinforcement. Assessment of this interaction revealed that EC females obtained more sucrose pellets than IC and SC females using an intermediate fixed ratio (FR) schedule requirement, while EC male rats did not earn significantly more sucrose pellets. This latter result suggests that environmental enrichment may differentially affect the incentive value of sucrose in female rats compared to male rats.

In the study by Green et al. (2002), the dose effect curve (ranging from 0.001- 0.2 mg/kg per infusion) for amphetamine was determined in both EC and IC rats under FR and progressive ratio (PR) schedules of reinforcement. This study replicated the previous finding that EC rats self-administer significantly less amphetamine at low unit doses on a FR schedule of reinforcement compared to IC counterparts. More important, at low unit doses, EC rats maintained lower breakpoints than IC rats under a PR schedule of amphetamine self-administration (Green et al., 2002). This latter finding suggests that EC rats are less sensitive than IC rats to the reinforcing effect of low doses of amphetamine. Similar results have been found with cocaine self-administration, as SC rats display a rightward shift in the cocaine dose response curve compared to IC rats (Howes et al., 2000). The rightward shift in the cocaine and amphetamine dose effect curves indicates that environmental enrichment decreases the reinforcing potency of stimulants; however, since there is also a downward shift in the maximum response rate for self-administration for both amphetamine (Green et al, 2001) and cocaine (Green and Bardo, unpublished data), enrichment also appears to decrease the reinforcing effect of stimulants.

The ability of environmental enrichment to alter the reinforcing properties of drugs is not limited to stimulants. A study by Deehan, Cain and Kiefer (2007) investigated whether enrichment could alter the reinforcing effect of ethanol. Deehan et al. (2007) found that operant responding for oral doses of alcohol was significantly lower in EC rats compared to IC rats. This study also found when given a choice between the contingent delivery of water or 10% ethanol, IC rats exhibited a preference for the ethanol lever over the water lever, whereas EC and SC rats did not (Deehan et al., 2007). This study indicates that environmental enrichment decreases the reinforcing effect of ethanol, as well as decreasing the preference for oral ethanol.

Potential Mechanisms for Enrichment-Induced Differences in Drug Reward

One puzzling aspect of the results to date lies in the discrepant conclusions drawn from CPP and self-administration studies. As described above, EC rats have been reported to be *more* sensitive to amphetamine reward measured by CPP, but *less* sensitive to the reinforcing properties of amphetamine measured by self-administration. One possible clue for explaining this apparent discrepancy comes from the work showing that EC rats are also more sensitive to the locomotor stimulant effect of amphetamine following acute injection, but are less sensitive to the locomotor sensitization following repeated injections. It may be that EC rats show greater sensitivity to drug reward following initial exposure, but that they show rapid tolerance to this effect with repeated exposures. Since CPP is established with few drug exposures, it may be more sensitive to the initial enrichment-induced increase in drug reward. In contrast, since self-administration requires more prolonged drug exposure, it may be more sensitive to the enrichment-induced diminution in drug reward across repeated administrations.

A second potential explanation for greater levels of amphetamine CPP in EC rats could relate to differences in learning. For example, EC rats may exhibit greater levels of amphetamine CPP because they more readily learn the relationship between internal drug cues and an environmental context. However, this explanation seems unlikely given that EC and IC rats do not differ in the number of sessions needed to acquire drug discrimination using either amphetamine (Fowler 1993) or nicotine (Stairs et al 2008) as the discriminative stimulus. In any case, since drug self-administration is thought to be a more direct measure of drug reward than CPP, the results obtained to date suggest that environmental enrichment protects against drug abuse vulnerability.

While environmental enrichment appears to decrease drug self-administration across various drugs of abuse, little is known about the underlying mechanisms responsible for this effect. It is possible that the difference between EC and IC rats in amphetamine self-administration using

low unit doses may reflect a difference in the rate of extinction or a difference in the reinstatement threshold. The rationale behind this possibility is that, at the beginning of each drug self-administration session, rats begin responding in a drug-free state. If a unit dose is too low, responding may simply extinguish similar to what occurs when saline is substituted for drug. However, if several low dose infusions are earned in rapid succession, total drug intake may accumulate beyond some minimum threshold, thus engendering reliable responding within the session. Based on this notion, the decrease in amphetamine self-administration at a low unit dose in EC rats could represent either an accelerated rate of extinction within the session or an increase in the reinstatement threshold. To assess these possibilities, Stairs et al. (2006) used the reinstatement procedure and found that EC rats extinguished responding faster than IC rats when amphetamine was replaced with saline. When responding was reinstated following a drug prime, IC rats reinstated drug-seeking responses following a pretreatment with a low dose of amphetamine, while EC rats only reinstated responding following pretreatment with a high dose of amphetamine. The higher reinstatement threshold in EC rats, taken together with a more rapid rate of extinction, could eventuate in a loss of responding within the session, thus leading to less drug intake.

A second potential explanation for the enrichment-induced decrease in drug self-administration is that exposure to novelty in EC rats during development may lead to a blunting of the hypothalamo-pituitary-adrenal (HPA) stress axis, resulting in a decreased release of the glucocorticoid corticosterone during the self-administration session. An enrichment-induced blunting of the stress axis would be expected to decrease drug self-administration because acute stressors and other manipulations that elevate corticosterone levels result in an increase in self-administration of low unit doses of stimulant drugs (Deroche, Marinelli, Le Moal, & Piazza, 1997; Deroche-Gamonet et al., 2003; Goeders & Guerin, 1994, 1996). Consistent with this interpretation, a recent study found differences in basal corticosterone levels during a 24-hr period between EC and IC rats, as well as differential amphetamine-induced changes in corticosterone (Stairs, Prendergast, & Bardo, 2008). Specifically, EC rats had significantly lower corticosterone levels at two time points during the light phase of the 24-hr period compared to IC rats. EC rats also had significantly lower levels of corticosterone following amphetamine pretreatments compared to IC rats. The results from these studies indicate that EC rats may have a blunted stress axis that reduces the reinforcing effect of amphetamine compared to IC rats.

A third potential explanation for the enrichment-induced differences in drug self-administration is that EC and IC may differ in impulsive choice, a behavior that has been shown previously to predict drug abuse vulnerability (Perry & Carroll, 2008; Perry, Morgan, Anker, Dess, & Carroll, 2006). In particular, EC rats are less impulsive during the acquisition of a conditioned reinforcement task compared to IC rats (Wood, Siegel, & Rebec, 2006). EC rats are also less impulsive compared to IC rats using a mean adjusting delay procedure (Perry, Stairs, & Bardo, 2008). While Perry et al. (2008) found that EC rats were less impulsive than IC rats, that study also found that pretreatment with amphetamine or methylphenidate dose-dependently decreased impulsive choice in IC rats, but not in EC rats. The enrichment-induced difference in impulsivity could result from the decrease in DAT function in mPFC found in EC rats compared to IC rats (Zhu et al., 2005), especially since DA in mPFC has been implicated in impulsivity (Sokolowski & Salamone, 1994). Taken together, these results suggest that EC rats may show a lower level of drug self-administration than IC rats because they have greater inhibitory control.

Final Comments about Limitations with the Environmental Enrichment Model

While the rodent environmental enrichment model is useful for investigating the role of novelty exposure during development on subsequent drug abuse vulnerability, there are some

limitations in the model that must be considered. For example, the implementation of intravenous self-administration studies may be limited in duration due to concerns with the longevity of catheter patency. Original studies investigating intravenous drug self-administration (Bardo et al., 2001) were limited due to the presence of social cohorts and novel objects in the EC condition that posed problems in maintaining the free end of the catheter attached to the animal. While improvements have been made in the design of EC catheters (Green et al., 2002), careful attention to catheter patency is critical for conducting long-term studies with this model.

In addition to the technical issues in testing EC rats in intravenous drug self-administration, there may be potential differences in the baseline or control rates of behavior between EC and IC rats that can complicate interpretations of the results obtained. For example, since EC rats are relatively insensitive to low unit doses of stimulant drugs and show increased sensitivity to extinction (Stairs et al., 2006), acquisition of responding usually requires that EC rats be trained initially on a high unit dose of drug. Since high unit doses of drug typically engender low response rates, the failure to observe reliable differences in responding between EC and IC rats using a high unit dose of drug may simply reflect a “floor” effect.

Another limitation in interpreting both the locomotor and self-administration results rests with how to express environment-dependent differences in drug effects when the saline-treated control groups differ. Specifically, EC rats have lower baseline levels of ambulatory activity (Bardo, Bowling et al., 1995; Bowling et al., 1993), as well as lower levels of control (saline substitution) progressive ratio responding in the self-administration preparation (Green et al., 2002). In order to control for these baseline differences, the drug effect may be expressed as a percent change from baseline locomotor activity, rather than as absolute values. However, this difference in data presentation could complicate the interpretation of drug effects within each of the two behavioral procedures. This issue has been tested recently in a study conducted by Dr. Mark Smith and his colleagues (personal communication). Smith and colleagues analyzed both cocaine hyperactivity and self-administration data from EC and IC rats, with the data being expressed as either a percent change from baseline control or as absolute values. When locomotor activity or cocaine self-administration data were expressed as absolute values, EC rats showed reduced sensitivity to both cocaine-induced hyperactivity and progressive ratio breakpoints for cocaine, conclusions that corroborate the majority of studies cited above. However, when locomotor activity or cocaine self-administration data were expressed as percent changes from control, EC rats actually showed enhanced sensitivity to both cocaine-induced hyperactivity and progressive ratio breakpoints for cocaine. Since baseline differences in behavior represent intrinsic differences between EC and IC rats, these results highlight the importance of considering the multiple assessments of the data when attempting to depict potential environment-dependent differences in various drug effects.

Also, while both environmental enrichment and drug self-administration methods have aided our understanding of environmental influences on drug taking behavior, there are limitations about the face validity of each of these methods. For instance, although it is often referred to as an enrichment model, one could make a strong argument that it should be referred to as an isolation model. In particular, it does not seem appropriate to consider IC rats as a “control” group because the extreme isolation endured by IC rats is not comparable to any human experience, except perhaps for some tragic clinical cases involving extreme sensory deprivation during childhood. However, regardless whether one considers it an enrichment or isolation model, the results obtained demonstrate that environmental influences control drug abuse vulnerability. As for the face validity of the rodent drug self-administration procedure, there are also concerns about the contrived nature of an operant conditioning environment that lacks social peer influences and availability of alternative reinforcers, variables known to play an important role in human drug abuse vulnerability.

In conclusion, despite some limitations, the use of the rodent environmental enrichment model has led to a better understanding of how exposure to different environments during development alters vulnerability to drugs of abuse. In addition to improving learning (Renner and Rosenzweig, 1987), environmental enrichment also has a beneficial effect on protecting against drug abuse vulnerability. While this model has allowed researchers to begin understanding the underlying neural mechanisms for enrichment-induced changes in sensitivity to abused drugs, most of the research to date has relied on correlation approaches. The next phase of work should attempt to determine experimentally the precise neural mechanisms that subserve the enrichment-induced changes in behavior. Such information could lead to the development of more effective prevention programs tailored to at-risk adolescents, as well as better programs for those seeking treatment.

Acknowledgments

The authors were supported by NIH grants P50 DA05312 and R01 DA12964.

References

- Adams, J.; Bowman, K.; Burke, B.; Casson, L.; Caviness, L.; Coffey, LE., et al. National Household Survey on Drug Abuse Data Collection. Final Report. 1999.
- Aultman JM, Moghaddam B. Distinct contributions of glutamate and dopamine receptors to temporal aspects of rodent working memory using a clinically relevant task. *Psychopharmacology (Berl)* 2001;153(3):353–364. [PubMed: 11271408]
- Bardo MT. Neuropharmacological mechanisms of drug reward: Beyond dopamine in the nucleus accumbens. *Critical Reviews in Neurobiology* 1998;12(12):37–67. [PubMed: 9444481]
- Bardo MT, Bevins RA. Conditioned place preference: what does it add to our preclinical understanding of drug reward? *Psychopharmacology (Berl)* 2000;153(1):31–43. [PubMed: 11255927]
- Bardo MT, Bowling SL, Rowlett JK, Manderscheid P, Buxton ST, Dwoskin LP. Environmental enrichment attenuates locomotor sensitization, but not in vitro dopamine release, induced by amphetamine. *Pharmacol Biochem Behav* 1995;51(23):397–405. [PubMed: 7667360]
- Bardo MT, Hammer RP Jr. Autoradiographic localization of dopamine D1 and D2 receptors in rat nucleus accumbens: resistance to differential rearing conditions. *Neuroscience* 1991;45(2):281–290. [PubMed: 1762680]
- Bardo MT, Klebaur JE, Valone JM, Deaton C. Environmental enrichment decreases intravenous self-administration of amphetamine in female and male rats. *Psychopharmacology (Berl)* 2001;155(3):278–284. [PubMed: 11432690]
- Bardo MT, Valone JM, Robinet PM, Shaw WB, Dwoskin LP. Environmental enrichment enhances the stimulant effect of intravenous amphetamine: Search for a cellular mechanism in the nucleus accumbens. *Psychobiology* 1999;27(2):292–299.
- Bowling SL, Bardo MT. Locomotor and rewarding effects of amphetamine in enriched, social, and isolate reared rats. *Pharmacol Biochem Behav* 1994;48(2):459–464. [PubMed: 8090815]
- Bowling SL, Rowlett JK, Bardo MT. The effect of environmental enrichment on amphetamine-stimulated locomotor activity, dopamine synthesis and dopamine release. *Neuropharmacology* 1993;32(9):885–893. [PubMed: 8232791]
- Comery TA, Stamoudis CX, Irwin SA, Greenough WT. Increased density of multiple-head dendritic spines on medium-sized spiny neurons of the striatum in rats reared in a complex environment. *Neurobiol Learn Mem* 1996;66(2):93–96. [PubMed: 8946401]
- Crane JW, Ebner K, Day TA. Medial prefrontal cortex suppression of the hypothalamic-pituitary-adrenal axis response to a physical stressor, systemic delivery of interleukin-1beta. *Eur J Neurosci* 2003;17(7):1473–1481. [PubMed: 12713650]
- Deehan GA Jr, Cain ME, Kiefer SW. Differential rearing conditions alter operant responding for ethanol in outbred rats. *Alcohol Clin Exp Res* 2007;31(10):1692–1698. [PubMed: 17651466]

- Del Arco A, Zhu S, Terasmaa A, Mohammed AH, Fuxe K. Hyperactivity to novelty induced by social isolation is not correlated with changes in D2 receptor function and binding in striatum. *Psychopharmacology (Berl)* 2004;171(2):148–155. [PubMed: 13680076]
- del Rosario Capriles N, Cancela LM. Motivational effects mu- and kappa-opioid agonists following acute and chronic restraint stress: involvement of dopamine D(1) and D(2) receptors. *Behav Brain Res* 2002;132(2):159–169. [PubMed: 11997146]
- Deroche V, Marinelli M, Le Moal M, Piazza PV. Glucocorticoids and behavioral effects of psychostimulants. II: cocaine intravenous self-administration and reinstatement depend on glucocorticoid levels. *J Pharmacol Exp Ther* 1997;281(3):1401–1407. [PubMed: 9190876]
- Deroche-Gamonet V, Sillaber I, Aouizerate B, Izawa R, Jaber M, Ghazizadeh S, et al. The glucocorticoid receptor as a potential target to reduce cocaine abuse. *J Neurosci* 2003;23(11):4785–4790. [PubMed: 12805318]
- Diamond MC. Response of the brain to enrichment. *Ann Acad Bras Cienc* 2001;73(2):211–220. [PubMed: 11404783]
- Diamond MC, Krech D, Rosenzweig MR. The Effects of an Enriched Environment on the Histology of the Rat Cerebral Cortex. *J Comp Neurol* 1964;123:111–120. [PubMed: 14199261]
- Engineer ND, Percaccio CR, Pandya PK, Moucha R, Rathbun DL, Kilgard MP. Environmental enrichment improves response strength, threshold, selectivity, and latency of auditory cortex neurons. *J Neurophysiol* 2004;92(1):73–82. [PubMed: 15014105]
- Figueiredo HF, Bruestle A, Bodie B, Dolgas CM, Herman JP. The medial prefrontal cortex differentially regulates stress-induced c-fos expression in the forebrain depending on type of stressor. *Eur J Neurosci* 2003;18(8):2357–2364. [PubMed: 14622198]
- Fowler SC, Johnson JS, Kallman MJ, Liou JR, Wilson MC, Hikil AH. In a drug discrimination procedure isolation-reared rats generalize to lower doses of cocaine and amphetamine than rats reared in an enriched environment. *Psychopharmacology (Berl)* 1993;110(12):115–118. [PubMed: 7870869]
- Goeders NE, Guerin GF. Non-contingent electric footshock facilitates the acquisition of intravenous cocaine self-administration in rats. *Psychopharmacology (Berl)* 1994;114(1):63–70. [PubMed: 7846208]
- Goeders NE, Guerin GF. Role of corticosterone in intravenous cocaine self-administration in rats. *Neuroendocrinology* 1996;64(5):337–348. [PubMed: 8930934]
- Green TA, Cain ME, Thompson M, Bardo MT. Environmental enrichment decreases nicotine-induced hyperactivity in rats. *Psychopharmacology (Berl)* 2003;170(3):235–241. [PubMed: 12845407]
- Green TA, Gehrke BJ, Bardo MT. Environmental enrichment decreases intravenous amphetamine self-administration in rats: dose-response functions for fixed- and progressive-ratio schedules. *Psychopharmacology (Berl)* 2002;162(4):373–378. [PubMed: 12172690]
- Hall FS, Wilkinson LS, Humby T, Inglis W, Kendall DA, Marsden CA, et al. Isolation rearing in rats: pre- and postsynaptic changes in striatal dopaminergic systems. *Pharmacol Biochem Behav* 1998;59(4):859–872. [PubMed: 9586842]
- Hawrylak N, Greenough WT. Monocular deprivation alters the morphology of glial fibrillary acidic protein-immunoreactive astrocytes in the rat visual cortex. *Brain Res* 1995;683(2):187–199. [PubMed: 7552354]
- Heidbreder CA, Foxton R, Cilia J, Hughes ZA, Shah AJ, Atkins A, et al. Increased responsiveness of dopamine to atypical, but not typical antipsychotics in the medial prefrontal cortex of rats reared in isolation. *Psychopharmacology (Berl)* 2001;156:338–351. [PubMed: 11549234]
- Hopfer CJ, Crowley TJ, Hewitt JK. Review of Twin and Adoption Studies of Adolescent Substance Use. *Journal of the American Academy of Child and Adolescent Psychiatry* 2003;42(6):710–719. [PubMed: 12921479]
- Howes SR, Dalley JW, Morrison CH, Robbins TW, Everitt BJ. Leftward shift in the acquisition of cocaine self-administration in isolation-reared rats: relationship to extracellular levels of dopamine, serotonin and glutamate in the nucleus accumbens and amygdala-striatal FOS expression. *Psychopharmacology (Berl)* 2000;151(1):55–63. [PubMed: 10958117]
- Jones GH, Hernandez TD, Kendall DA, Marsden CA, Robbins TW. Dopaminergic and serotonergic function following isolation rearing in rats: study of behavioral responses and postmortem and in vivo neurochemistry. *Pharmacol Biochem Behav* 1992;43:17–35. [PubMed: 1384071]

- Jones GH, Marsden CA, Robbins TW. Increased sensitivity to amphetamine and reward-related stimuli following social isolation in rats: possible disruption of dopamine-dependent mechanisms of the nucleus accumbens. *Psychopharmacology (Berl)* 1990;102:364–372. [PubMed: 2251333]
- Jones GH, Marsden CA, Robbins TW. Behavioural rigidity and rule-learning deficits following isolation-rearing in the rat: neurochemical correlates. *Behav Brain Res* 1991;43(1):35–50. [PubMed: 1677579]
- Kolb B, Forgie M, Gibb R, Gorny G, Rowntree S. Age, experience and the changing brain. *Neurosci Biobehav Rev* 1998;22(2):143–159. [PubMed: 9579307]
- Kolb B, Gorny G, Soderpalm AH, Robinson TE. Environmental complexity has different effects on the structure of neurons in the prefrontal cortex versus the parietal cortex or nucleus accumbens. *Synapse* 2003;48(3):149–153. [PubMed: 12645040]
- Kolb B, Whishaw IQ. Brain plasticity and behavior. *Annu Rev Psychol* 1998;49:43–64. [PubMed: 9496621]
- Melendez RI, Gregory ML, Bardo MT, Kalivas PW. Impoverished rearing environment alters metabotropic glutamate receptor expression and function in the prefrontal cortex. *Neuropsychopharmacology* 2004;29(11):1980–1987. [PubMed: 15187985]
- Perry JL, Carroll ME. The role of impulsive behavior in drug abuse. *Psychopharmacology (Berl)* 2008;200(1):1–26. [PubMed: 18600315]
- Perry JL, Morgan AD, Anker JJ, Dess NK, Carroll ME. Escalation of i.v. cocaine self-administration and reinstatement of cocaine-seeking behavior in rats bred for high and low saccharin intake. *Psychopharmacology (Berl)* 2006;186(2):235–245. [PubMed: 16596398]
- Perry JL, Stairs DJ, Bardo MT. Impulsive choice and environmental enrichment: Effects of d-amphetamine and methylphenidate. *Behav Brain Res* 2008;193(1):48–54. [PubMed: 18534693]
- Radley JJ, Arias CM, Sawchenko PE. Regional differentiation of the medial prefrontal cortex in regulating adaptive responses to acute emotional stress. *J Neurosci* 2006;26(50):12967–12976. [PubMed: 17167086]
- Rahman S, Bardo MT. Environmental enrichment increases amphetamine-induced glutamate neurotransmission in the nucleus accumbens: a neurochemical study. *Brain Res* 2008;1197:40–46. [PubMed: 18242591]
- Renner, MJ.; Rosenzweig, MR. Enriched and impoverished environments : effects on brain and behavior. New York: Springer-Verlag; 1987.
- Rosenzweig MR, Bennett EL. Psychobiology of plasticity: effects of training and experience on brain and behavior. *Behav Brain Res* 1996;78(1):57–65. [PubMed: 8793038]
- Schenk S, Britt MD, Atalay J, Charleson S. Isolation rearing decreases opiate receptor binding in rat brain. *Pharmacol Biochem Behav* 1982;16(5):841–842. [PubMed: 6283569]
- Sesack SR, Deutch AY, Roth RH, Bunney BS. Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: an anterograde tract-tracing study with Phaseolus vulgaris leucoagglutinin. *J Comp Neurol* 1989;290(2):213–242. [PubMed: 2592611]
- Shippenberg TS, Herz A. Place preference conditioning reveals the involvement of D1-dopamine receptors in the motivational properties of mu- and kappa-opioid agonists. *Brain Res* 1987;436(1):169–172. [PubMed: 2961413]
- Sirevaag AM, Greenough WT. Plasticity of GFAP-immunoreactive astrocyte size and number in visual cortex of rats reared in complex environments. *Brain Res* 1991;540(12):273–278. [PubMed: 2054618]
- Smith JK, Neill JC, Costall B. Post-weaning housing conditions influence the behavioural effects of cocaine and d-amphetamine. *Psychopharmacology (Berl)* 1997;131(1):23–33. [PubMed: 9181632]
- Smith MA, Bryant PA, McClean JM. Social and environmental enrichment enhances sensitivity to the effects of kappa opioids: studies on antinociception, diuresis and conditioned place preference. *Pharmacol Biochem Behav* 2003;76(1):93–101. [PubMed: 13679221]
- Smith MA, Chisholm KA, Bryant PA, Greene JL, McClean JM, Stoops WW, et al. Social and environmental influences on opioid sensitivity in rats: importance of an opioid's relative efficacy at the mu-receptor. *Psychopharmacology (Berl)* 2005;181:27–37. [PubMed: 15778888]
- Sokolowski JD, Salamone JD. Effects of dopamine depletions in the medial prefrontal cortex on DRL performance and motor activity in the rat. *Brain Res* 1994;642(12):20–28. [PubMed: 8032881]

- Solinas M, Chauvet C, Thiriet N, El Rawas R, Jaber M. Reversal of cocaine addiction by environmental enrichment. *Proc Natl Acad Sci U S A* 2008;105(44):17145–17150. [PubMed: 18955698]
- Stairs, DJ.; Fosdick, J.; Mittelstet, B.; Schwarzkopf, L. Enrichment-induced differences in nicotine drug discrimination. 2008. In preparation
- Stairs DJ, Klein ED, Bardo MT. Effects of environmental enrichment on extinction and reinstatement of amphetamine self-administration and sucrose-maintained responding. *Behav Pharmacol* 2006;17(7): 597–604. [PubMed: 17021392]
- Stairs DJ, Prendergast MA, Bardo MT. Enrichment-induced differences in corticosterone: differential response to amphetamine and glucocorticoid receptor blockade in low dose amphetamine self-administration. In preparation. 2008
- Tzschentke TM, Schmidt WJ. Functional relationship among medial prefrontal cortex, nucleus accumbens, and ventral tegmental area in locomotion and reward. *Crit Rev Neurobiol* 2000;14(2): 131–142. [PubMed: 11513242]
- Wood DA, Siegel AK, Rebec GV. Environmental enrichment reduces impulsivity during appetitive conditioning. *Physiol Behav* 2006;88(12):132–137. [PubMed: 16678224]
- Zhu J, Apparsundaram S, Bardo MT, Dwoskin LP. Environmental enrichment decreases cell surface expression of the dopamine transporter in rat medial prefrontal cortex. *J Neurochem* 2005;93(6): 1434–1443. [PubMed: 15935059]
- Zhu J, Green T, Bardo MT, Dwoskin LP. Environmental enrichment enhances sensitization to GBR 12935-induced activity and decreases dopamine transporter function in the medial prefrontal cortex. *Behav Brain Res* 2004;148(12):107–117. [PubMed: 14684252]