

The Many Facets of the Locomotor Response to a Novel Environment Test: Theoretical Comment on Mitchell, Cunningham, and Mark (2005)

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Several animal studies have shown that there is a positive correlation between locomotor activity in response to a novel environment and acquisition of drug self-administration behavior. This finding led to the assumption that animals with heightened reactivity to novel environments are more sensitive to the rewarding effects of drugs compared with animals with reduced reactivity. But are these individuals really more responsive to drugs, or could they have enhanced sensitivity to rewards in general or even simply be better learners? In the previous issue of this journal, J. M. Mitchell, C. L. Cunningham, and G. P. Mark (2005), investigated these important matters. They reported that the locomotor response to a novel environment does not predict responding for cocaine but reflects overall differences in the ability to learn operant tasks.

Keywords: addiction, locomotor response, learning, operant responding, cocaine

Large interindividual differences are found in drug responding, both in humans and in animals (de Wit, Uhlhuth, & Johanson, 1986; Piazza, Deroche, Rouge-Pont, & Le Moal, 1998). Some subjects more easily acquire drug self-administration and develop drug addiction, whereas others are more resistant. The presence of such interindividual differences suggests that certain individuals could be especially susceptible to the reinforcing effects of cocaine; these individuals could develop self-administration behavior more readily than subjects who are less sensitive to the drug (Piazza et al., 1998; Piazza, Deroche-Gamonet, Rouge-Pont, & Le Moal, 2000). Elucidating the neurobiological correlates of enhanced susceptibility to develop addiction is important, because it may provide important information for understanding determinants of drug addiction.

In 1989, Piazza, Deminiere, Le Moal, and Simon reported that the locomotor response to a novel environment is positively correlated with the ability to acquire amphetamine self-administration behavior. Rats with a high locomotor reactivity to a novel environment (so-called “high responders” or HRs) show enhanced acquisition of amphetamine self-administration behavior compared with animals with a low reactivity to the same environment (“low responders” or LRs). This was a critical finding, because it allowed researchers to “predict,” for the first time, self-

administration behavior in the absence of any drug exposure in an outbred population of animals. By simply screening rats for their response to a novel environment, one could identify “drug-vulnerable” or “drug-resistant” individuals.

This model of enhanced vulnerability to acquire self-administration behavior led to many studies on the neurobiological bases of such vulnerability. To give just some examples, drug-vulnerable animals (HRs) were found to exhibit higher basal and stimulated dopamine levels in the nucleus accumbens and striatum compared with drug-resistant animals (LRs) (Bradberry, Gruen, Berridge, & Roth., 1991; Hooks, Jones, Smith, Neill, & Justice 1991b; Piazza et al., 1991; Rouge-Pont, Piazza, Kharouby, Le Moal, & Simon, 1993). HRs also show heightened firing activity of dopamine neurons compared with LRs and decreased ability to auto-regulate the impulse activity of these neurons (Marinelli & White, 2000). This suggests that enhanced vulnerability to drugs could be the result of a hyperactive dopaminergic system (Marinelli & Piazza, 2005; Piazza et al., 1998).

Clearly, the validity of these results and their relevance to drug vulnerability depend greatly on the nature of the relation between the locomotor response to a novel environment and subsequent drug self-administration behavior. Thus, the validity of the relation, together with the interesting findings reported by Mitchell, Cunningham, and Mark. (2005) will be discussed below. Several features will be examined, such as the specificity of the model with respect to different addictive drugs, the importance of the experimental conditions during testing, and the potential nature of the differences in drug responding. In addition, a description of the different methods of determining the locomotor response to a novel environment will be provided.

Methods to Test Differences in the Locomotor Response to a Novel Environment

Locomotor Activity to a Novel Environment Is a Relative Dimension

When placed in a novel environment such as an activity chamber or a new home cage, not all animals respond with the same

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level of activation; some animals exhibit high locomotor activity, whereas others show lower counts. Two approaches are usually used: The first involves correlation studies. In this case, individual activity scores are plotted against individual responses for the defined behavior (e.g., self-administration), which allows one to determine whether a direct linear relation exists between locomotor activity and the response of interest. The second approach consists in dividing animals into HRs and LRs to this environment. This separation is based either on a median split or on upper or lower percentages of the population. Separating animals into HRs and LRs is arbitrary (because locomotor scores are normally distributed); however, it allows one to make better group comparisons, especially after treatments. For example, one can determine whether a certain treatment affects vulnerable rats (HRs) more than it affects the resistant ones (LRs).

I should note that there is no absolute value that can define high versus low activity counts. Because of this, comparisons of locomotor activity across individuals can only be made *within* a group of rats that are screened at the same time, under exactly the same conditions (generally, >10 rats per screening are required to have a statistically meaningful sample of the population; initial studies by Piazza et al. (1989) screened 16 rats at a time). Pooling locomotor counts across groups that are tested at different times is inappropriate (both for correlation analyses and for group comparisons), because it confounds differences between individuals with those between experimental conditions (day of testing, time of day, and so on). Therefore, if results are to be combined across experiments, individual activity scores should not be expressed as absolute values; they should be normalized according to the activity levels of each screened batch (e.g., see W. Lu, Marinelli, Xu, Worley, & Wolf, 2002). Unfortunately, this is not done in many studies, which reduces the ability to interpret the results.

Activity Scores Differ According to the Type of Environment Used and the Duration of the Test

The types of novel environments that have been used in this model vary across laboratories. Different factors, such as shape,

size, lighting, and so forth, can determine the amount and duration of the novel environment–induced locomotor activation; the smaller the environment, the quicker that the novelty-induced locomotion will subside (Eilam, 2003). The initial apparatus used by Piazza et al. (1989) was a circular corridor created between two concentric cylinders (Figure 1a). Animals move within this corridor, which is identical throughout the apparatus. This physical arrangement is an important consideration because the absence of corners or a center eliminates potential disparities that may be due to a different locomotion used in open versus cornered spaces. When placed in a large open field instead (Figure 1b), animals with high anxiety levels tend to avoid the central portion of the apparatus and locomote more in the periphery, sometimes showing thigmotaxis. This reaction could potentially result in a greater distance traveled, despite lower exploration of the entire arena (Eilam, 2003). Often researchers measure response to novel environments by simply placing an animal in a new cage (Figure 1c) that is physically similar to the home cage. Regardless of the apparatus, an animal's response to the novel environment is usually characterized by initial strong exploratory behavior (locomotion, sniffing, and rearing) that gradually diminishes and eventually ceases once the novelty of the environment has subsided.

The level of activity in response to a novel environment is usually measured over periods of 1–2 hr of exposure to the environment. Such long periods are required to detect differences in the way the animals *react* to the environment as well as differences in the way animals *habituate* to the environment. In fact, many studies have shown that HRs take longer to habituate to the novel environment (i.e., to reach trough activity scores) compared with LRs. Figure 2 shows locomotor activity between HRs and LRs obtained by three different laboratories that have successfully used this approach to determine markers of drug vulnerability across subjects. HR–LR differences are observed after 10 min of exposure to the environment and continue until the animals have become habituated to the environment. Mitchell and colleagues reported that animals in their study were screened for 15 min, which probably allowed detection only of differences in reactivity rather than in habituation to the environment.

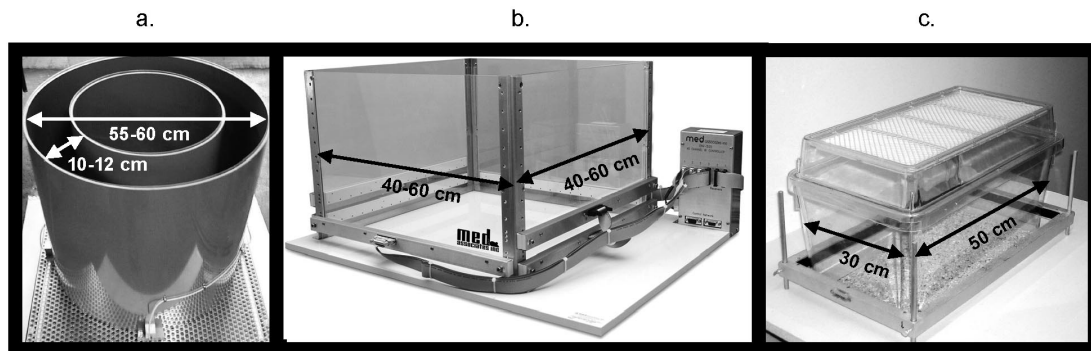


Figure 1. Different test chambers used to test rats' locomotor response to a novel environment: (a) circular corridor, (b) open field, and (c) novel cage that is physically similar to the home cage. The sizes of these apparatuses vary across laboratories; approximate measurements used in the literature appear on the images. Image (a) was obtained by courtesy of Imétron (www.imetronic.com); image (b), model ENV-515, was obtained by courtesy of Med Associates (www.med-associates.com).

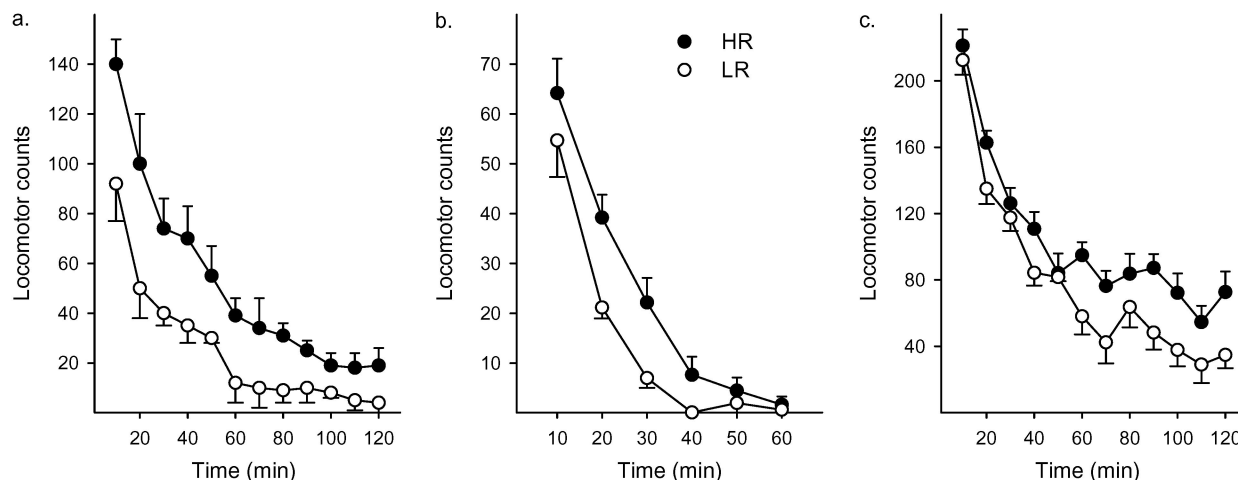


Figure 2. Profiles of the rats' locomotor response to a novel environment. Animals identified as high responders (HRs) and low responders (LRs) show differential reactivity and adaptation to the novel environment. HRs take longer to habituate to the test environment compared with LRs. These profiles are examples of data obtained in different laboratories: (a) P.V. Piazza, $n = 8$ per group, division based on median split, animals screened toward the end of the light phase (approximately 2–4 hr before lights out); (b) M. Marinelli, $n = 6$ per group, division based on median split, animals screened toward the end of the light phase; (c) P. Vezina, $n = 9–10$ per group, division based on upper and lower quartiles, animals screened during the dark phase; modified from data appearing in Suto, Austin, & Vezina, 2001. Vertical lines above and below the points are error bars. Figures are obtained by courtesy of these authors.

The Locomotor Response to a Novel Environment Predicts Subsequent Self-Administration Behavior

Generalization to Different Species and Drugs of Abuse

The initial findings by Piazza et al. (1989) showing that rats with higher locomotor scores exhibit greater acquisition of a low dose of amphetamine were replicated by several other researchers. These studies confirmed that locomotor response to novelty predicts the ability to acquire and maintain self-administration of amphetamine (Cain, Smith, & Bardo, 2004; Klebaur, Bevins, Segar, & Bardo, 2001) but also extended the findings to other abused drugs such as cocaine (Grimm & See, 1997; Mantsch, Ho, Schlussman, & Kreek, 2001; Marinelli & White, 2000; Piazza et al., 2000), nicotine (Suto, Austin, & Vezina, 2001), morphine (Ambrosio, Goldberg, & Elmer, 1995), and ethanol (Nadal, Armario, & Janak, 2002). In addition, this trait was observed both in rats and in mice, suggesting that the finding can be generalized to different species (Marinelli & Piazza, 2005).

Importance of the Experimental Conditions in Acquisition Studies

Self-administration studies are sometimes performed with food-restricted animals or previously food-restricted animals that have been trained to respond for food. Although this practice facilitates subsequent drug intake (K. D. Carr, 2002; L. Lu, Shepard, Scott Hall, & Shaham, 2003), it also introduces the potential confound of stress. Studies on HR–LR differences in drug intake reviewed below, as well as the study described by Mitchell et al., were performed with ad libitum-fed animals and are thus free of this potential confound.

HR–LR differences in the *acquisition* of self-administration behavior are only observed for low drug doses. It has been proposed that these doses are too low to be reinforcing in LRs but not in HRs (Piazza et al., 1998). In other words, HRs could be more sensitive than LRs to low, typically nonreinforcing doses of psychostimulant drugs. In fact, when high drug doses are used, both HRs and LRs learn to self-administer psychostimulant drugs equally well (Piazza et al., 2000). Although HR–LR differences in acquisition of self-administration behavior are only detectable at low drug doses, these doses should be high enough to maintain self-administration behavior across sessions. If doses are very low, HR–LR differences can wane over time because both groups of animals decrease responding across sessions (Pierre & Vezina, 1997).

In the study by Mitchell et al. (2005), acquisition of cocaine self-administration was performed at a moderate dose (250 $\mu\text{g}/\text{kg}$ per infusion), which should produce reliable acquisition behavior in most animals. However, animals were trained to acquire cocaine self-administration on a fixed ratio 5:1 schedule of reinforcement (i.e., they were required to lever-press five times to obtain each cocaine infusion). Acquisition in these conditions produces low rates of self-administration behavior (see figure 3a in Mitchell et al., 2005), which could explain, at least in part, why HR–LR differences were present on Days 2–4 of testing but were not maintained over time. Another reason why HR–LR differences could be reduced over time is not because self-administration decreases in all animals (Pierre & Vezina, 1997) but because LRs increase responding across sessions. They “catch up” and eventually do not differ from HRs. This increased response could be due to improved learning across sessions, which is what Mitchell and colleagues proposed happened with their LR rats. A similar idea

was proposed in a study on ethanol self-administration (Nadal et al., 2002) that illustrated that responding in LRs can increase across sessions.

Although some studies show that HR–LR differences in self-administration behavior can decrease over time, numerous other studies have shown the opposite. Using cocaine or amphetamine as the reinforcer, researchers have shown that HRs do not differ from LRs on the first few days of testing (Days 1–5, according to the study); differences in drug intake develop only over subsequent days of drug exposure (Marinelli & White, 2000; Piazza et al., 1989; Piazza et al., 1990), even when animals are exposed to extended (10 hr/day) daily cocaine access (Mantsch, Ho, Schlussman, & Kreek, 2001). Figure 3 shows an example of how HR–LR differences in self-administration behavior develop after 5 days and are maintained for the remainder (the following 5 days) of the study. In this experiment, animals start off with similar responding abilities; however, after having experienced the drug, HRs perceive the drug as being more reinforcing than LRs.

However, in the studies cited above, drug responding was measured for only 5–10 days, so it was questionable whether HR–LR differences would persist over protracted periods. In experiments carried out over longer periods of time (approximately 1 month), HR rats were found to respond more for psychostimulant drugs across days, doses, and ratios than did LR rats (Klebaur et al., 2001; Piazza et al., 2000; Suto et al., 2001). Similarly, subordinate monkeys, which show higher locomotor activity levels, exhibit greater cocaine intake as measured over at least 1 month (Morgan et al., 2000, 2002). These studies indicate the stability of the HR–LR trait over time, at least in conditions of sustained self-administration behavior across days (Pierre & Vezina, 1997).

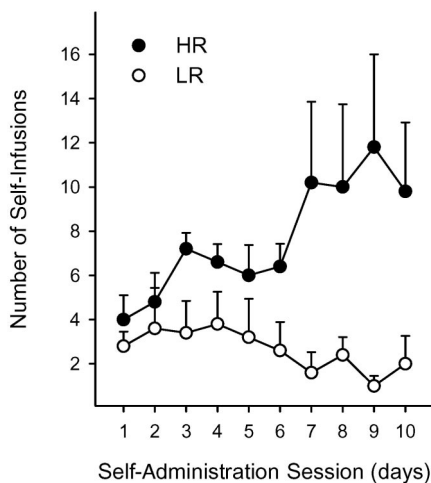


Figure 3. Self-administration of 165 $\mu\text{g}/\text{kg}$ of cocaine tested in high responder rats (HRs represented by dark circles) and low responder rats (LRs, represented by white circles, $n = 5$ per group). Responder status was based on the median split over 120 min of locomotor activity testing). HRs and LRs do not differ for cocaine intake over the first five self-administration sessions; differences in drug intake develop from Day 6 and remain until the end of the experiment. In this experiment, nose pokes in the active hole resulted in an infusion of cocaine; a time-out of 5 s was used after each infusion. Vertical lines above the points are error bars. Unlike previous studies (Marinelli & White, 2000), in this experiment, no discrete cues (light) were associated with responding in the active hole (Marinelli, 1998).

Importance of the Duration of the Locomotor Response to Novelty Test

Most studies showing strong relationships between locomotor response to a novel environment and self-administration behavior used long (> 60 min) as opposed to short (10–15 min) locomotor screening periods. As mentioned above, it is possible that screening animals for long periods of time could “capture” a behavioral trait that predicts different behavioral aspects than those revealed by short screening times. Figure 4 examines the relationship between cocaine self-administration and the locomotor response to a novel environment test, measured over 10, 30, or 120 min. Correlations are strongest when the duration of the locomotor activity test is the longest (120 min). Almost identical results were reported by Suto et al. (2001) for nicotine self-administration. Thus, the correlation coefficients obtained between locomotor counts observed at different times during the response to novelty screen and nicotine self-administration were strong when long durations of the locomotor test were taken into account but were absent when short (<60 min) periods were considered. Thus, screening animals for short periods produces correlations that are weak (see Figure 4), transiently present (Mitchell et al., 2005), or significant when responding is cumulated across days (Grimm & See, 1997). In the latter study, correlations were best observed when taking into account 10 min rather than 5 min of screening time. Together, these data indicate that testing animals for their locomotor response to a novel environment for very short periods does not produce a robust model that can be used to predict cocaine self-administration behavior; longer periods of screening are preferable to obtain the strongest correlations. This finding suggests that the animal’s *adaptation* to the environment is an important factor that needs to be considered when evaluating the locomotor activity in response to novelty. However, although this factor applies to psychostimulants, it might not apply to different drugs such as ethanol; for ethanol self-administration, correlations are obtained when animals are screened for short (10 min) but not long (80 min) periods (Nadal et al., 2002).

Beyond Acquisition of Drug Self-Administration

Further studies have been performed to determine whether HR–LR differences in drug responding are restricted to acquisition of low drug doses. Using dose–response paradigms, researchers have shown that HRs exhibit a vertical upward shift of the dose–response curve for cocaine (Klebaur et al., 2001; Piazza et al., 2000), suggesting that the reinforcing efficacy of the drug is greater in these animals. Furthermore, HRs show greater responding for psychostimulants in progressive ratio schedules of reinforcement (Grimm & See, 1997; Suto et al., 2001), suggesting that HRs work harder to obtain drug rewards. Although the locomotor response to a novel environment predicts acquisition and maintenance of self-administration behavior, it does not appear to predict drug-seeking behavior or the loss of control that is usually typical of addicted humans. Thus, HRs and LRs show similar responding during extinction paradigms, and they reinstate to a similar extent when presented with drug cues (Deroche-Gamonet, Belin, & Piazza, 2004; Sutton, Karanian, & Self, 2000). After protracted self-administration (>2 months) HRs and LRs also seem to show similar drug intake in the presence of adverse consequences and in other paradigms that are indicative of compulsive drug seeking

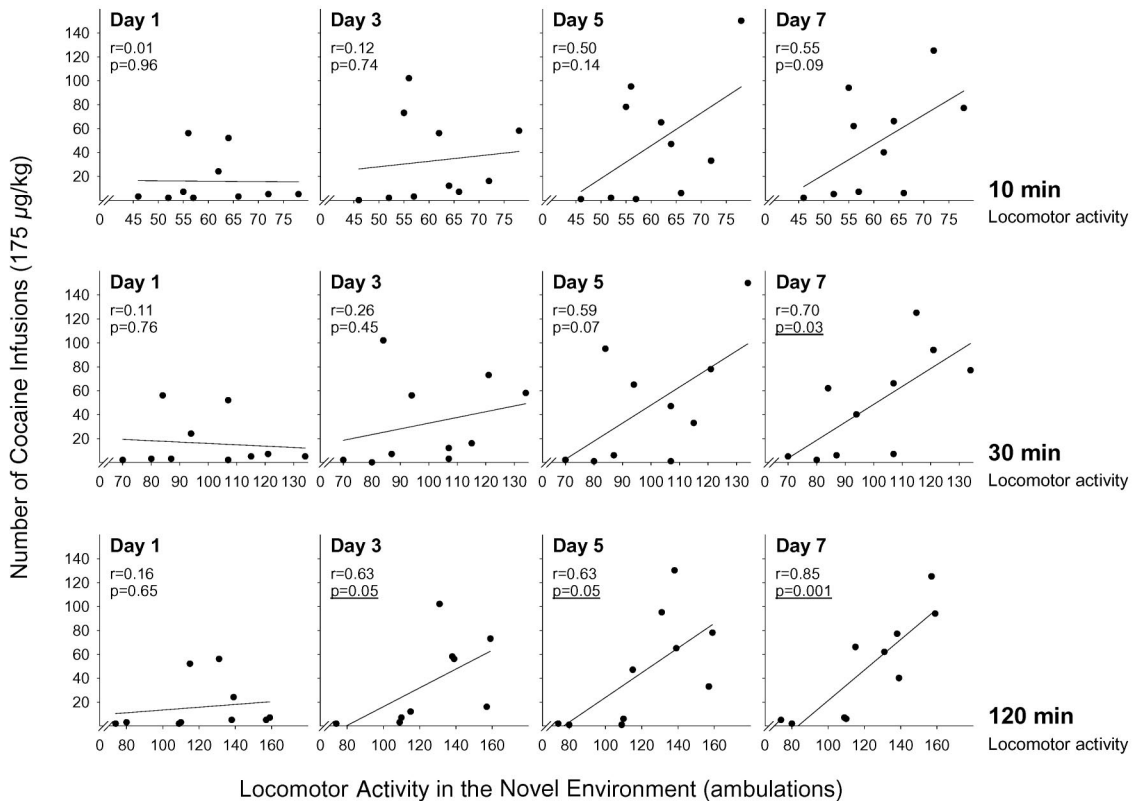


Figure 4. Relation between the locomotor response to a novel environment tested over 10, 30, or 120 min and subsequent cocaine self-administration behavior (reported on Days 1, 3, 5 and 7 of testing). The strongest and more consistent correlations are obtained by considering longer screening times. For all conditions, correlations are absent on the first day of testing for cocaine self-administration behavior. When the locomotor response to a novel environment is tested over 120 min, correlations develop on Day 3 of self-administration testing and are maintained until the end of the experiment (Day 7). In addition, the strength of the correlation increases over time. These correlations are obtained by analyzing data that were reported partially in a previous publication (Marinelli & White, 2000). The r values represent the correlation coefficient obtained with Pearson's correlation test, p values reported in the figures indicate the level of significance; values are underlined when $p < .05$.

(Deroche-Gamonet et al., 2004). These findings indicate that locomotor response to a novel environment can be used to detect differences in sensitivity to psychostimulant drugs and possibly also in the motivation to obtain drugs, but they do not predict drug seeking or loss of control.

What Else Could the Locomotor Response to a Novel Environment Be Used to Predict?

The above data indicate that locomotor response to a novel environment can be used to predict subsequent behavior in some kinds of self-administration tests (acquisition and maintenance), at least if the animals are screened for the locomotor response to novelty test for long periods of time and if the training conditions are appropriate to produce sustained self-administration behavior across days. The question could arise as to whether these findings reflect differences in cocaine sensitivity or simply reflect behavioral characteristics that could be unrelated to drugs.

Differences in Sampling Rates?

Animals that locomote more in a novel environment could also show nonspecific increases in responding (lever-pressing or nose-

poking behavior) that could be erroneously interpreted as greater self-administration behavior. To test potential differences in sampling rates, investigators have tested HR and LR animals for responding in the inactive device or for responding in the absence of the drug. Results indicate that HRs and LRs do not show generalized differences in nonreinforced responding and that there is no relationship between the locomotor response to a novel environment and nose-poking behavior (Cain et al., 2004; Marinelli & White, 2000; Piazza et al., 1990). Thus, it is unlikely that variations in sampling rates can account for individual differences in drug responding and intake.

Differences in Responding for Rewards in General?

If locomotor response to a novel environment is predictive of responding for different drugs of abuse, it is possible that it is predictive of responding for rewards in general. This theory can be tested by examining operant responding for nondrug rewards. In two studies, HRs and LRs responded equally for light cues (Marinelli & White, 2000; Piazza et al., 1990); however, it should be noted that although responding was maintained over 7 days, levels of responding were very low. As mentioned above, when

responding is low, HR–LR differences are rarely robust. In fact, responding for stimuli with greater reinforcing properties yields different results. Relative to LRs, HRs show faster acquisition of sucrose self-administration (Klebaur et al., 2001). On a similar line, animals that show greater amphetamine-induced locomotion and dopamine release also show greater preference for a sucrose solution (Sills & Crawley, 1996; Sills & Vaccarino, 1994), suggesting a positive relation between the ability to respond to natural and drug rewards. Additionally, when tested for operant responding for food, HRs display higher sensitivity to the reinforcing properties of food (Dellu, Piazza, Mayo, Le Moal, & Simon, 1996). These data were confirmed in the study by Mitchell et al. (2005), who reported greater responding for food in animals with greater locomotor response to a novel environment (Figure 4b in Mitchell et al.). Greater responding was most evident on Days 3–8 (see Results section in Mitchell et al., 2005) and decreased on Days 9–12. This indicates that high locomotor response to a novel environment is coupled to high reactivity to rewards in general and not just to drug rewards.

Differences in Learning?

If animals showing greater locomotor response to a novel environment over 15 min show greater responding for many rewards, they could simply be better learners. To test this possibility, Mitchell and colleagues (2005) studied responding for cocaine after having submitted animals to extensive food training on the operant task. After having learned operant responding (with food as the reinforcer), HRs and LRs no longer differed for cocaine self-administration, suggesting that previously observed differences in drug responding were simply the consequence of differences in learning capacities. Unfortunately, cocaine responding was only measured over 3 days, so it is difficult to determine whether differences in drug intake would have developed during subsequent days of testing (as shown in Figure 3, correlations between locomotor response to a novel environment and self-administration often develop *after* 3 days of testing). However, it is interesting that HRs and LRs did not differ in responding for cocaine over 3 days if they had previously been trained to respond for food. In addition, the absence of a correlation between locomotor response to a novel environment and self-administration apparently was maintained over subsequent days as well (J. M. Mitchell, personal communication, March 2005). Finally, Mitchell et al. found that results were similar when two rats that appeared to be outliers (see Figure 1a) were removed (J. M. Mitchell, personal communication, March 2005). Possibly, in these conditions, differences in cocaine responding were indeed a consequence of differences in the ability to learn an operant task.

The idea that response to a novel environment is associated with better instrumental learning is corroborated by the positive correlation between locomotor response to novelty and the day on which the learning of the food self-administration task was achieved (Figure 4a in Mitchell et al., 2005). The “learning threshold” for self-administration behavior is determined with a novel and thoughtful method that uses the trough of the bimodal distribution of lever-pressing over self-administration sessions. This method allows objective measurements of learning, without confounds of arbitrary definitions of learning.

Mitchell et al. (2005) proposed further evidence for learning differences between their HRs and LRs. In animals that received no

previous training on the operant task, a positive correlation was found between locomotor response to a novel environment and cocaine self-administration on Days 2–4 of training but not on subsequent days (Days 5–7). Similarly, for food self-administration, correlations were present during Days 3–8 of testing but not on Days 9–12. As mentioned previously, the authors suggested that once the animals had time to “practice” and learn self-administration behavior, differences between HRs and LRs disappeared. This result implies that HRs, at least those in the study by Mitchell et al., are better learners but not necessarily greater “addicts” or greater responders for rewards in general. Given that animals start off with a moderately difficult schedule of reinforcement (they have to perform five lever presses to obtain each cocaine infusion), it is indeed possible that differences in learning could account for differences in drug intake under this demanding protocol.

Although differences in learning probably did contribute to differences in drug intake in the model by Mitchell et al. (2005), differences in learning are unlikely to explain HR–LR differences in drug responding that have been observed over protracted periods of time in other studies. For example, in dose–response studies, animals are first trained to respond for a high cocaine dose (1000 $\mu\text{g}/\text{kg}$ per infusion) over 10 days on a fixed ration 1:1 of reinforcement (1 response: 1 infusion); once all animals have learned the task equally well, the drug dose is decreased progressively across days. In these conditions, HRs still show greater responding for cocaine relative to LRs, as evidenced by a vertical upward shift of the dose–response curve for cocaine (Piazza et al., 2000). Similar results have been reported in monkeys (Morgan et al., 2000, 2002). This indicates that, once the behavior has been learned, HR–LR differences in drug responding are still maintained and suggests that differences in learning cannot always account for differences in drug responding.

Assuming that animals that show greater drug intake are better learners, it could be interesting to determine whether they are better learners in general or whether this is only restricted to responding for rewards on operant tasks. Such studies are limited; one study reported no difference in HR–LR performance in a recognition memory task for cognitive abilities tested during adulthood; memory impairments in HRs, however, did develop during aging (Dellu, Mayo, Vallee, Le Moal, & Simon, 1994). Another study showed the absence of a relationship between locomotor response to a novel environment and performance on an eight-arm radial maze (Dellu-Hagedorn, 2005). In addition, in that study, animals with poor learning capacities showed the greatest amphetamine-induced locomotion, and a negative correlation was found between learning and drug reactivity. These results indicate that animals with greater reactivity to drugs do not differ from HRs and LRs in learning capacities in general. If they do, it is only for the learning of operant responding.

What About Other Drug-Related Responses?

A different approach to assessing whether locomotor response to a novel environment is potentially related to drug sensitivity is to examine its relation with other behavioral responses to drugs that do not involve operant responding. Conditioned place preference has often been considered an index of the rewarding effects of drugs of abuse (G. D. Carr, Fibiger, & Phillips, 1989; Hoffman, 1989; Tzschenke, 1998). In mice, there appears to be a positive relationship between locomotor response to a novel environment

and the amount of time spent in the drug-paired environment of the conditioned place preference test (Orsini, Buchini, Piazza, Puglisi-Allegra, & Cabib, 2004). In rats, however, data consistently show that locomotor response to novelty does not predict place preference behavior (Erb & Parker, 1994; Gong, Neill, & Justice, 1996; Klebaur & Bardo, 1999; Kosten & Miserendino, 1998). Although a useful test, place conditioning measures changes in the threshold dose of psychostimulant required to produce conditioning; however, once the response is induced, the intensity of its effects does not change as a function of drug dose (Costello, Carlson, Glick, & Bryda, 1989). This test, therefore, is well adapted to measure horizontal shifts in dose–response functions, but it is not well suited to assess changes in the intensity of the rewarding effects of drugs (Bardo & Bevins, 2000), such as those seen between HRs and LRs (Piazza et al., 2000).

Other behavioral responses are therefore useful to examine. HRs show stronger contextual conditioning to drugs (Jodogne, Marinelli, Le Moal, & Piazza, 1994), which is in line with Mitchell et al.'s (2005) idea that these animals could show increased learning capacities. However, HRs also show greater locomotor reactivity to an acute injection of a psychostimulant drug, which is clearly independent of learning. These HR–LR differences are present over a wide range of drug doses. In addition, they are not confounded by differences in locomotor response to the environment per se because they are present after the animal has habituated to the test chamber (Exner & Clark, 1993; Hooks et al., 1991b; Hooks, Jones, Neill, & Justice, 1992; Piazza et al., 1989; 1990; 1998). Finally, HRs develop behavioral sensitization more readily than do LRs (Hooks, Jones, Liem, & Justice, 1992; Hooks, Jones, Neill, & Justice, 1992; Hooks, Jones, Smith, Neill, & Justice 1991a; Pierre & Vezina, 1997). Behavioral sensitization is important in that it reflects drug-induced neuroadaptations that could have an important role in the development of addiction (Robinson & Berridge, 1993; 2001). Overall, these findings show that locomotor response to a novel environment is predictive of several drug-associated behaviors. Some of these, but not all, can be explained by potential differences in learning across animals.

Summary

In summary, the locomotor response to a novel environment test has proven useful for predicting differences in drug sensitivity. However, several considerations should be taken into account. These include screening animals for long enough periods of time to capture individual differences in habituation to the environment and recording relative locomotor scores rather than absolute counts. In addition, acquisition of drug self-administration should be tested over several days to allow differences in responding to emerge; drug doses should also be low enough to allow detection of differences in drug sensitivity, but high enough to maintain self-administration behavior across sessions; and finally, the schedule of reinforcement should be easy enough to reduce potential differences in learning across animals. Even though the study by Mitchell et al. (2005) does not meet all these criteria, it is still extremely valuable because it showed that the ability to learn instrumental responding and drug self-administration behavior are clearly related. In the Mitchell et al. study, animals that showed enhanced locomotor reactivity to a novel environment exhibited higher cocaine self-administration behavior during their first days of exposure to the drug; however, these animals showed higher drug responding simply because they were better instrumental learners. In

fact, once the behavior was learned, differences in drug responding were no longer present.

Regardless of whether individual differences in drug taking can be predicted by the locomotor response to a novel environment or not, this article clearly shows that initial differences in cocaine intake (under moderately demanding schedules of reinforcement) can be explained by differences in the animal's ability to learn operant responding. Thus, when trying to determine the neurobiological bases of differences in drug responding, it is essential to perform appropriate control studies to determine the nature of these differences. Without such controls, one risks studying the neurobiological mechanisms underlying differences in learning abilities, rather than those underlying differences in the reinforcing properties of drugs.

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