Review

The runway model of drug self-administration

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ABSTRACT

Behavioral scientists have employed operant runways as a means of investigating the motivational impact of incentive stimuli for the better part of the past 100 years. In this task, the speed with which a trained animal traverses a long straight alley for positive incentive stimuli, like food or water, provides a reliable index of the subject's motivation to seek those stimuli. The runway is therefore a particularly appropriate tool for investigating the drug-seeking behavior of animals working for drugs of abuse. The current review describes our laboratory's work over the past twenty years developing and implementing an operant runway model of drug self-administration. Procedures are described that methodologically dissociate the antecedent motivational processes that induce an animal to seek a drug, from the positive reinforcing consequences of actually earning the drug. Additional work is reviewed on the use of the runway method as a means of modeling the factors that often result in a "relapse" of drug self-administration after a period of abstinence (i.e., a response reinstatement test), as are runway studies that revealed the presence of opposing positive and negative consequences of self-administered cocaine. This body of work suggests that the runway method has served as a powerful behavioral tool for the study of the behavioral and neurobiological basis of drug self-administration.

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There is a long and rich history of preclinical animal research that has led to important insights into the nature of the neurobiological systems underlying drug abuse. The theoretical framework upon which much of this work is based, is the hypothesis that drugs of abuse exert their behavioral effects by artificially acting upon the endogenous neural systems normally engaged when animals interact with natural incentives, like food, water or sex. This suggests that one can think of drugs of abuse as a special class of positive reinforcers, and can therefore apply the same operant/behavioral methods to study drug reinforcement as have been successfully employed to

study the factors that influence the initiation and maintenance of naturally-reinforced behaviors. Over the years, a significant body of evidence has accumulated implicating central dopamine (DA) systems (in particular the mesocorticolimbic neurons originating from cell bodies in the VTA and terminating in such regions as the nucleus accumbens, amygdala and prefrontal cortex) in the goal-seeking behavior of animals working for both natural and drug reinforcers (e.g., see reviews by; Carelli, 2002; Di Chiara et al., 2004; Ikemoto and Panksepp, 1999; Kelley and Berridge, 2002; Robinson and Berridge, 1993; Salamone et al., 2007; Schultz, 1998; Wise, 2004, 2005). However, while investigators might agree that DA systems are important for goal-seeking behavior, there remains considerable debate and disagreement over the precise nature of the role(s) that such systems play. Some see DA pathways as being critical for the rewarding, pleasurable or affective response to drugs (e.g., Esch and

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Stefano, 2004; Peterson, 2005; Volkow et al., 2002), while others see these systems as being predominantly involved in the incentive properties of the drugs ("wanting") and not their rewarding consequences (i.e., "liking") (Berridge, 2007; Robinson and Berridge, 1993). Some have postulated a role for DA mechanisms in the associative processes involved in the acquisition and maintenance of drug self-administration (e.g., Everitt et al., 1999; Hyman et al., 2006) or other higher cognitive functions that are responsible for ensuring that animals appropriately attend to novel, important or salient stimuli in their environment, including those associated with drug availability or delivery (Franken et al., 2005; Ikemoto and Panksepp, 1999; Schultz, 1998). Still other researchers see DA systems as critical for the behavioral activation or arousing properties of incentive stimuli (Kelley et al., 2005; Robbins and Everitt, 2007) and/or the animals' decision to exert effort to seek such stimuli (e.g., Salamone et al., 2007). Despite their number and complexity, theories about the role of DA in goal-seeking behavior tend to distribute themselves into two broad categories — theories that emphasize conditions *antecedent* to the behavioral response (broadly speaking, motivational processes), and those that focus on the *consequences* of operant behavior (that is, reinforcement processes). Of course, while neuroscientists tend to restrict themselves to one side or the other of this debate it's entirely possible that DA systems or subsystems are involved in *both* types of processes. This poses a significant challenge for researchers in this field since the consequences of earning a drug reinforcer necessarily increase the individual's motivation to seek that reinforcer again in the future. As a result, while the two processes – motivation and reinforcement – may be dissociable, they are intricately linked and inherently interactive in the control of goal-seeking behavior. It was in this context that our laboratory set out, two decades ago, to develop a means of studying drug self-administration that permitted for the experimental dissociation of motivational and reinforcement processes in the control of drug-seeking behavior.

1. The runway drug self-administration model

Animal learning researchers have been using operant runways as a tool for the study of goal-seeking motivated behavior for the better part of a century (e.g., see early classic studies by Crespi, 1942; Hull, 1934; Miller, 1944). In such studies, the time required for the subject to traverse the alley (i.e., Run Time) has proven to be a reliable index of the animal's motivation to seek the incentive that is made available upon goal box entry. Put simply, changes in the subject's motivation to seek an incentive produce predictable and reliable shifts in the run times required to get to the goal box. However, despite the wide variety of positive reinforcers and animal species that have been examined using a runway methodology, a review of the literature conducted in the late 1980s revealed no published reports on the use of this method for the study of the motivational impact of drug reinforcers. There were studies of the effects of psychoactive drugs on runway performance of animals working for natural reinforcers (e.g., Miller and Miles, 1935) but none in which the reinforcer itself was a psychoactive drug. One finding, however, suggested that the runway methodology was worthy of additional exploration. White et al. (1977) trained hungry rats to run a straight alley for food reinforcement delivered upon goal-box entry. In addition to the food, each animal received a single IP injection of morphine and was then replaced back into the goal box for 50 min to facilitate the formation of goal box-drug associations. The rats were tested once each day for five days during which the amount of food consumed in the goal box decreased even while the animals ran to the goal box faster each day. The authors attributed the reduction in food consumption to a conditioned taste aversion produced by the food-morphine pairings, and the "para-doxical" increase in running speeds to the reinforcing properties of the morphine. This latter result suggested that the runway had some

potential as a means of measuring the motivation of animals to seek drugs of abuse.

While the task provided some significant technical challenges (the details of which are outside the scope of this review), we were ultimately able to design and build a set of automated operant runways in which animals fitted with intravenous catheters and connected to an elaborate drug-delivery system, would run down an alley and enter a goal box whereupon they received an IV injection of drug. Infrared photo-emitter/detector pairs lining the entire runway fed signals to a desktop computer that controlled the hardware of the apparatus (opening/closing the start and goal doors, activating the syringe infusion pump), as well recorded the positions of the animal in real time so that Start Latency (time to leave the start box) and Run Time (time to enter goal box once the rat had left the start box) could be determined, along with the precise path that the rat took from start box to goal box, on every trial. The details of the apparatus were first published in the form of a technical report that appeared in this journal in 1990 (Geist and Ettenberg, 1990).

In the standard procedure, rats surgically implanted with chronic indwelling jugular catheters traverse a six-foot straight alley once a day in order to enter a goal box where IV drug reinforcement is automatically applied. This method therefore incorporated critical aspects of both of the primary methodologies for modeling drug abuse in the animal laboratory — the traditional lever-press *drug self-administration procedure* and the *conditioned place preference (CPP) test*. Like the lever-press method, in the runway test the delivery of the drug reinforcer is made contingent upon the subject's emission of the appropriate operant response (in this case running down the alley), and like the CPP test, the animal actively seeks a distinct environment (the goal box) that had been previously paired with drug delivery. Note however, that in the traditional operant lever-press box the resulting data set reflects the propensity of a drugged animal to remain drugged. In contrast, and somewhat more akin to the CPP test, the runway procedure assesses the *motivation* of the *undrugged* animal to seek the drug each day. Thus, the behavior of interest (assessed by Run Time) occurs *before* the presentation of the drug reinforcer and hence is unaffected by any confounding or performance-altering consequences of the drug itself. The runway data are therefore somewhat more akin to the data obtained in lever-press experiments employing second order schedules of reinforcement (e.g., Alderson et al., 2000; Di Ciano, 2008) where the responding is maintained by drug-paired cues (conditioned reinforcers) in the absence of the drug reinforcer. One notable difference between these two procedures is that the runway requires less effort on the part of the animal and hence may be less vulnerable to pretreatments that potentially alter the motoric capacity of the subjects. Nevertheless, in both situations the testing protocol is devised to assess the motivational strength of the drug reinforcer before the reinforcer is itself applied. Since relapse of drug abuse behaviors is inherently a motivational problem (the undrugged individual is seeking to re-engage in drug administration) the relevance for this approach is considerable.

To date, runway self-administration has been established in rats working for a variety of drug reinforcers including IV cocaine (e.g., Ben-Shahar et al., 2008; Deroche et al., 1999; Ettenberg and Bernardi, 2006; Ettenberg and Geist, 1991, 1993; Heinrichs et al., 1998; Wakonigg et al., 2003a,b), IV cocaethylene (Raven et al., 2000), IV opiate receptor agonists such as heroin, morphine, remifentanil and alfentanil (Crespo et al., 2006; Ettenberg et al., 1996; McFarland and Ettenberg, 1995; Wakonigg et al., 2003a), IV nicotine (Cohen and Ettenberg, 2007), IV methylenedioxymethamphetamine (MDMA) (Wakonigg et al., 2003b), IV "speedball" (heroin+cocaine) (Guzman and Ettenberg, 2004), as well as SC amphetamine (Ettenberg, 1990), SC morphine (Zernig et al., 2002), oral ethanol (Czachowski,1999), and both intracerebroventricular and intracranial infusions of cocaine (Guzman and Ettenberg, 2007; Guzman et al., submitted for publication).

Conceptually and procedurally, we based our approach on the classic runway work of Crespi (1942) who demonstrated that well-

trained rats running an alley once each day for food, exhibited Run Times that reflected the magnitude of the incentive (amount of food) delivered upon goal-box entry. Additionally, and perhaps more importantly, Crespi (1942) observed that an "unexpected" sudden change in the magnitude of the incentive delivered in the goal box produced an immediate and exaggerated shift in running on the very next trial/day (a phenomenon that has come to be known as the "Crespi effect"). This suggested a means of experimentally dissociating the impact of manipulations on motivational versus reinforcement processes. Conceptually, if an experimental manipulation prior to a given trial (e.g., pretreatment with a DA antagonist drug) altered the motivational capacity of the animal, one ought to see an immediate change in Run Time on that trial; alternatively, a treatment that *selectively* produced an "unexpected" change in the positive reinforcing consequences of the drug should have no impact on test day run times (since the animal would not be aware of the change in reinforcer magnitude until after it had entered the goal box), but would be expected to produce a subsequent shift in motivation *on the very next day/trial*. In this conception, Run Times on any given trial provide an index of the animal's *motivation to seek the reinforcer* on that trial, while changes in Run Times from one trial to the next represent the impact of reinforcement on subsequent motivation. Therefore the runway method provides a means of potentially dissociating the animal's motivation to seek a drug from the reinforcing consequences of actually earning the drug. This review highlights several dissociations that the runway model has identified which may have gone undetected with traditional lever-press self-administration procedures, thereby serving as a powerful addition to the tools available to study drug-motivated behavior.

2. Dissociating the motivational and reinforcing actions of drugs of abuse

Much of our work on the neurobiology of drug-seeking motivation and/or reinforcement has involved investigations of the impact of the D_2-family dopamine receptor antagonist, haloperidol, on the runway behavior of rats working for iv diacetylmorphine (heroin) (e.g., Ettenberg and McFarland, 2003; McFarland and Ettenberg, 1995, 1998a). Each of these studies employed external cues associated with drug delivery to experimentally "activate" or arouse the subjects' motivation to seek heroin. It has long been thought that environmental stimuli associated with drug presentation play an important role in the control of drug-seeking behavior (e.g., O'Brien, 1976). Early attempts to study the role of such stimuli in animal models typically employed extinction procedures in which subjects having experienced cue-drug pairings were tested for their propensity to continue operant behavior for the cue alone in tests of conditioned reinforcement (e.g., Davis and Smith, 1976). In such tests, the animal first emits the operant response and then earns the drug-paired cue. In the human condition, drug relapse is not related to an addict's attempt to work for a stimulus previously paired with a drug of abuse (i.e., as in a conditioned reinforcer model), rather the addict is motivated to seek the drug reinforcer upon exposure to a conditioned environmental stimulus predictive of its availability. We therefore employed a discriminative stimulus procedure where an external cue is presented to the subject prior to the operant response and thereby informs the animal about the availability (an S+ cue) or non-availability (an S− cue) of the drug reinforcer on that trial.

On two distinct trials, each of two olfactory stimuli (orange and almond scents) was presented in a counterbalanced manner as S+ or S− cues that respectively predicted whether or not heroin would be available in the goal-box of the runway (McFarland and Ettenberg, 1995). The use of olfactory cues was intended to take advantage of the fact that rats have a particularly strong sense of smell and indeed the subjects – although tested on only two trials per day – learned within a matter of days to discriminate between the scents and to run reliably

faster when presented with the S+ versus the S− scent. Once the discriminative runway performance was established, animals were pretreated with varying doses of the DA receptor antagonist, haloperidol, prior to their daily testing. Even relatively high doses (0.15 or 0.3 mg/kg IP) of haloperidol did not affect the time required for animals to traverse the runway during either S+ or S− trials. However, on the day following the haloperidol treatment, when the antagonist was no longer present, the rats exhibited slower running in response to the S+, *but only if they had experienced the heroin in the presence of haloperidol on the previous trial*. Animals that on the previous day experienced haloperidol during an S− trial (and hence earned no heroin in the goal box), responded normally to the S+ 24 h later. Thus the slow running of the S+/haloperidol group cannot be accounted for by some kind of nonspecific residual motoric or sedative side-effect the treatment. The significance of these results are twofold: first, the data suggest that the motivation to seek heroin upon S+ presentation is unaffected by pharmacological disruption of dopamine D_2 receptor function; and second, that the impact of receiving heroin during DA receptor antagonism is altered such that the following day the animals are less motivated (run more slowly) in response to the S+. The opiate receptor antagonist, naloxone produced a comparable effect to haloperidol, altering the animals' response to actually earning heroin (i.e., it slowed responding 24 h after a heroin+naloxone runway trial), but had no effect on the activation observed in animals presented an S+ predictive of heroin availability (McFarland and Ettenberg, 1998a). Thus the effect that Crespi (1942) first described over 65 years ago – that an unexpected change in the incentive value of the goal box experience produces a dramatic and immediate change in runway performance on the very next trial/day – appears to require an intact DA system, while the motivational arousal in anticipation of the positive incentive does not.

These conclusions were supported in a subsequent study in which the physiological arousal of the subjects was assessed by radio-telemetrically-obtained heart rate (HR) data (Ettenberg and McFarland, 2003). Here, the S+ produced a large and reliable increase in the HR of animals placed in the start box and presented with a cue predictive heroin availability (the S+). The S+ also induced faster running in the alley in anticipation of heroin delivery upon goal-box entry. In contrast, no such physiological or behavioral increases were observed upon S− cue presentation, which produced slower HR and slower alley running. When challenged with haloperidol, the elevation in HR produced by the heroin-predictive S+ scent remained intact as did the animals' runway performance (the latter result confirming the results from our previous study). However, on the next trial/day when the haloperidol was no longer in the subjects' systems, presentation of an S+ now produced slower HR and run times relative to their normal responses, *but only in those subjects that had experienced the heroin in the presence of the S+ on the previous trial*. Animals that experienced haloperidol prior to a non-reinforced S− trial, responded normally to the S+ 24 h later. It was concluded that haloperidol altered the positive reinforcing consequences of heroin while leaving the motivational capacity of the animal intact.

These results and conclusions are in contradiction to the views of those researchers who have argued that the behavioral impairment produced by DA receptor antagonism is primarily motivational in nature (e.g., Berridge, 2007; Palmiter, 2008; Robinson and Berridge, 1993; Salamone et al., 2007). Nevertheless, these findings are very much consistent with other well-established observations regarding the behavioral effects of DA antagonists. For example, intermittent DA antagonist treatment prior to a subset of reinforced runway trials subsequently produces an increase in resistance to extinction (a "partial reinforcement extinction effect") comparable to that observed in animals periodically experiencing non-reinforced trials (Ettenberg and Camp, 1986). These results seem most parsimoniously accounted for by the notion that non-reinforcement and DA-receptor antagonism can, at least in this procedure, produce highly comparable

behavioral effects. In other studies, DA antagonist challenge did not impair the arousing or activational response of animals to the presentation of food-predictive cues (Horvitz and Ettenberg, 1991; McFarland and Ettenberg, 1999) or cues associated with the delivery of reinforcing brain stimulation (Franklin and McCoy, 1979), nor did it blunt the expression of previously-formed conditioned preferences for drug-paired environments (Beninger and Hahn, 1983). Using a runway procedure, Wasserman et al. (1982) and Franklin (1978) independently examined the effects of DA antagonist treatment on the motivating and reinforcing properties of intracranial electrical stimulation. Rats placed in a start box of a straight alley were motivated to initiate responding by the administration of brief non-contingent "priming" stimulation. The animals then traversed the alley and entered a goal box where they were permitted to lever-press for reinforcing intracranial stimulation. In both these studies, DA antagonist pretreatments reliably elevated the reinforcement thresholds for the intracranial stimulation but did not alter the capacity of "priming" stimulation to motivate animals to initiate alley running. Hence the DA receptor antagonists altered the reinforcing consequences of the brain stimulation but not its capacity to motivate responding.

Perhaps the most well-established and oft-cited behavioral consequence of DA antagonism in reinforcement studies is their tendency to produce extinction-like within-session decrements in operant responding (Wise, 1982, 2004). While there continues to be debate about the significance and interpretation of such findings (e.g., Salamone et al., 1997) there is no disagreement that in such situations treated animals exhibit the capacity to begin responding at normal or near normal levels, thereby demonstrating that motivational processes are left relatively intact during DA antagonist challenge. Response decrements only become prominent as the trial progresses. One might, therefore, argue that it is only after subjects experience the reinforcer under DA antagonist challenge that one typically sees a weakening in behavioral output (Wise, 1982, 2004). This would suggest a motivational change that is secondary to a deficit in reinforcement function — a conclusion supported by the heroin runway studies described above.

These findings are of considerable significance since they suggest that there are two dissociable processes influencing the operant behavior of the animals in the runway. One such process is related to motivation (running speed on any given day) and the other to reinforcement (changes in running speed/motivation from one trial to the next). Of course it is possible that different results will be obtained with the investigation of different drug reinforcers — although haloperidol elicits comparable effects in animals running for food reinforcement (McFarland and Ettenberg, 1998b). It's also possible that motivational effects of DA antagonism could be unmasked if the response requirements of the test were increased. Many years ago, Ettenberg et al. (1981) demonstrated that the same doses of a DA receptor antagonist that greatly impaired lever-press responding, had relatively little impact on operant behavior when the same animals were tested using a nose-poke operant — presumably a less-effortful response. Others have similarly shown that the impact of DA disruption by drugs or lesions on operant behavior was greatest when the response-requirements of the schedule required more effort to be exerted on the part of the animals (e.g., Caul and Brindle, 2001; Ishiwari et al., 2004). It has therefore been suggested that the DA system is part of a circuit that makes effort-related decisions that ensure that the organism overcomes those response constraints that separate it from important, reinforcing or high incentive stimuli (Salamone et al., 2007). From this perspective, attenuation in DA function might render it more difficult for the animal to respond to the work-related challenges imposed by operant tasks and schedules of reinforcement — and hence a decrement in responding ensues. If the animal is provided a less effortful path to the goal (easier response or less strenuous schedule of reinforcement) it demonstrates that its

motivational state remains intact. In the current context, if the runway task with spaced limited trials per day represents a relatively low effortful load, then DA antagonism may have only minimal impact on the animals' runway performance. The problem, however, is that while this hypothesis accounts for the lack of an effect of DA treatment on the runway performance of rats on treatment day, it does not adequately address the observation that the operant behavior is attenuated 24 h later when the animal is retested drug-free. At the very least, DA systems would appear to also be involved in some other process that would normally strengthen the behavior that precedes the delivery of drug and natural reinforcers.

3. Runway response reinstatement test

Another means of studying the motivational impact of drug reinforcers is to assess their ability, or the ability of environmental cues associated with the drugs, to reinstate responding in animals whose operant behavior has been weakened by reinforcer removal (i.e., extinction trials). There have been numerous animal studies employing response-reinstatement tests as a means of modeling the "relapse" back to drug-taking behavior that human addicts often exhibit after a period of abstinence (see reviews by Epstein et al., 2006; Shaham et al., 2003). In the runway version of this test, rats are trained to run an alley once each day for drug reinforcement. After an initial training period, the drug reinforcer is removed and the operant running is permitted to weaken over subsequent extinction trials. A single unexpected reinforced trial reliably reinstates operant responding (running) on the very next trial (24 h later) (Ettenberg, 1990; Ettenberg et al., 1996). Note that in the runway test, the re-exposure to the drug reinforcer occurs following the emission of the operant runway response, as opposed to a non-contingent experimenter-administered injection of the drug that is typically employed in the lever-press procedure (Shaham et al., 2003). The runway version of the reinstatement test is, therefore, particularly comparable to the human condition where relapse probability is extremely high, even after an extended period of abstinence, if the individual is re-exposed to the reinforcing drug (Jaffe, 1980; Ludwig et al., 1974; Meyer and Mirin, 1979). A unique property of the runway task is that reinstatement does not occur until the first post-treatment trial when the animal is tested in an undrugged state — hence the data are protected from contamination by nonspecific performance-altering actions of the drug reinforcer itself, as well as from those of any pretreatments administered in an attempt to alter the response-reinstating properties of that reinforcer. This is particularly relevant to many of the experiments that have involved investigations of the effects on response-reinstatement of selective DA antagonist drugs, which are known to produce alterations in motoric capacity.

In work completed to date, our laboratory has demonstrated runway response-reinstatement in food-, water-, amphetamine- and heroin-reinforced subjects and in each case the behavioral impact of reinforcer delivery was dose-dependently prevented by pretreatment with the DA antagonist, haloperidol (e.g., Ettenberg, 1990; Ettenberg and Horvitz, 1990; Ettenberg et al., 1996; Horvitz and Ettenberg, 1988; McFarland and Ettenberg, 1997). Such work clearly suggests an important role for central DA pathways in the response-reinstating consequences of natural and drug reinforcers. Furthermore, the fact that the response-reinstating effects of heroin are reversed by DA antagonism while heroin self-administration is relatively unimpaired (Ettenberg et al., 1982; Smith and Davis, 1973), may suggest an important distinction between a drug reinforcer's ability to maintain drug-taking behavior (self-administration) and to reinstate such behavior after a period of abstinence. Note again that in each of these studies the consequences of actual reinforcer presentation is what appears to be altered by DA antagonist treatments and not the subject's initial motivation to seek the reinforcer. Thus on treatment day, the animals' Run Times remain normal; only after experiencing

the reinforcer during DA receptor challenge does the operant (motivated) behavior change, i.e., on the next trial 24 h later. Similarly, when reinstatement is initiated in response to the presentation of an olfactory cue that predicts reinforcer availability in the goal box (an S+), DA antagonism does not impair the animals' capacity to reinstate operant running (McFarland and Ettenberg, 1997). Thus the runway results again suggest that haloperidol-induced DA receptor antagonism selectively attenuates the consequences of reinforcer delivery while leaving intact the antecedent motivational state that entices animals to seek that reinforcer.

4. The opponent-process properties of self-administered cocaine

An early and unexpected finding of our research program was the unique behavioral profile of animals running the alley for IV cocaine. In previous studies using natural and drug reinforcers, the subjects run the alley faster as trials progressed. In contrast, while cocaine-reinforced animals exhibited "normal" start latencies, they took progressively longer to actually reach the goal box over trials/days. Data from the infrared emitter–detector pairs lining the base of the runway, revealed that rats were not running more slowly, but rather exhibiting an increased occurrence of a unique stop-and-retreat behavior as the experiment progressed — animals would approach the goal box, stop, and then retreat back to the start box (Ettenberg and Geist, 1991, 1993; see also Heinrichs et al., 1998). These behaviors closely resembled the classic "approach-avoidance" conflict described by Neal Miller (1944) over 60 years ago in animals approaching a goal box that had known mixed positive + negative attributes. Indeed, it was later confirmed that cocaine-induced retreat behaviors were virtually identical to those observed in rats running the alley for a combination of food + mild footshock (Geist and Ettenberg, 1997). Additionally, the location in the alley where retreats occur (at the threshold to the goal box) is consistent with conflict theory (Miller, 1944) as is the fact that, like other forms of conflict behavior, retreat behavior was found to be dose-dependently reversed by pretreatment with anxiolytic agents like diazepam (Ettenberg and Geist, 1991), and more recently buspirone (Ettenberg and Bernardi, 2006). It would seem then that cocaine has both positive and negative properties that together result in the development of ambivalence on the part of the animal about entering the goal box. To be clear, retreat behaviors are not an assay for cocaine's negative or aversive actions but rather reflect the presence of *both* positive *and* negative associations with the goal box. Thus, the animals continue to return to the goal area and eventually do enter and obtain their cocaine. Indeed, when the goal box contains only negative events (e.g., shock, or aversive drugs), the animals remain in the start box and choose not to approach the goal box at all (Geist, unpublished data). Consistent with this view is the fact that the very animals demonstrating retreats in the alley, when put in a two-compartment place preference apparatus consisting of the goal and start boxes, actually spend more time in the goal box thereby indicating that the cocaine has retained its rewarding properties (Ettenberg and Geist, 1991). It is also important to note that the approach-avoidance retreat behaviors described above cannot be attributed to some unknown aversive properties of the goal box itself since when the identical apparatus was used to assess the goal-seeking behavior of animals running for IV heroin, no retreats were observed (e.g., Ettenberg et al., 1996; Ettenberg and Geist, 1993).

Of course, Opponent-Process Theory (Solomon and Corbit, 1974) predicts that *all* self-administered drugs should have dual and opposing properties — so this raises the question of *why* heroin-reinforced animals did not also develop retreat behaviors? The most parsimonious explanation for this may lie in the different pharmacokinetic profiles of heroin and cocaine. While both drugs have a relatively fast onset of action, the peak duration of the reinforcing effects – as evidenced by the inter-response intervals obtained in rats freely lever-pressing for each drug – is considerably briefer in rats working for cocaine than it is for the same or different animals working for heroin. During a standard 3-h test session, with IV doses comparable to those employed in the runway, rats lever-pressing for cocaine responded about twice as frequently (averaging 10–12 self-injections) per hour than did animals working for heroin (averaging about 4–5 inj/h) (Ettenberg et al., 1982; Pettit et al., 1984). This is likely due to the fact that while cocaine's rewarding effects peak and ebb relatively quickly (within minutes) after IV injection (Verebey and Gold, 1988), heroin is first converted to 6-monacteylmorphine and then more slowly to morphine, whose actions greatly extend the duration of opiate effects (Inturrisi et al., 1984; Jenkins et al., 1994). Clearly a longer delay in the onset of any negative properties of heroin would weaken their association with the goal box, and thereby make the development of retreat behaviors less likely. Such an explanation suggests that negative reinforcement processes (to alleviate the aversive consequences of drugs of abuse) may play a more significant role in the acquisition and maintenance of cocaine self-administration than they do for heroin self-administration in the non-addicted animal — a hypothesis certainly worthy of additional empirical investigation.

The occurrence of approach-avoidance retreat behaviors in cocaine-reinforced rats is consistent with clinical reports from human cocaine users who describe an initial euphoric experience that is often followed by an unpleasant state characterized by feelings of anxiety, agitation, depression, anhedonia, and cravings (e.g., Kampman et al., 1998; Mulvaney et al., 1999). Such observations are consistent with Solomon and Corbit's (1974) classic Opponent-Process Theory in which drugs of abuse are hypothesized to produce both positive and negative affective states. As the initial positive affect wanes, a concurrent underlying negative affect is unmasked and becomes prominent. From the drug users' subjective perspective, a drug such as cocaine would produce an initial euphoric experience followed some time later by a negative "crash". In a direct test of this notion, the differential properties of cocaine present either immediately or some time after IV administration were examined using a CPP test. We confirmed that rats developed preferences for an environment paired with the immediate rewarding effects of cocaine but avoided an environment associated with the state present 15-min post-injection (Ettenberg and Bernardi, 2007; Ettenberg et al., 1999; Knackstedt et al., 2002). Thus, the approach-avoidance retreat behaviors observed in the runway can be accounted for by cocaine's biphasic actions: an initial positive "euphoric" effect that is followed by a negative "dysphoric" effect. This might explain Spealman's (1979) classic finding that monkeys lever-pressing for cocaine on one lever, would press a second lever in order to terminate drug availability. More recently, cocaine has now been observed to have anxiogenic properties in a wide variety of animal behavioral tests (e.g., see Ettenberg, 2004). The relationship between cocaine and anxiety is also consistent with reports of cocaine-induced changes in brain benzodiazepine receptors (Goeders, 1991) and increases in the secretion of adrenocorticotropin (ACTH) and corticotropin-releasing factor (CRF) (Moldow and Fischman, 1987; Sarnyai, 1998). Heinrichs et al. (1998) have recently reported that manipulations of CRF in fact modulate the strength observed "goal box avoidance" in animal running a straight alley for IV cocaine. Together, these studies provide clinical, behavioral and neurochemical evidence suggesting that cocaine administration in animals can produce anxiogenic consequences in addition to its more familiar euphoric effects.

5. Summary and conclusions

The runway self-administration test represents a hybrid model of drug-motivated behavior that incorporates the key procedural aspects of both the conditioned place preference and lever-press

self-administration tests. As with the CPP method, animals are tested undrugged for their approach to a distinct location associated with prior drug administration (in this case the goal box); and like the traditional self-administration test, the animals must emit an operant response (in this case running to and entering a goal box) in order to earn their drug delivery. The independent measure in these studies, run time, provides a reliable index of the subjects' motivation to seek the drug that is dissociable from the consequences of actually earning the drug reinforcer. Thus, while run times on any given day reflect the strength of the subjects' motivation to seek the drug on that trial, the reinforcing impact of actually earning the drug are reflected by the changes in run times from one trial to the next. This permits the experimental dissociation of motivational and reinforcing processes in drug-seeking behavior. In the case of cocaine, the runway model has also proven to be sensitive to *both* the positive (approach) and negative (avoidance) properties of the drug in the same animal at the same time. It therefore represents a valuable means for studying the neurobiological basis of cocaine's two opposing drug actions that together undoubtedly determine the nature of cocaine use and abuse.

Of course the runway self-administration test is merely one of several behavioral tools available to the neuroscientist interested in modeling drug abuse in the laboratory. How successful a "tool" it will be, will ultimately depend upon how useful investigators find it for addressing the questions of interest in their own laboratories. For example, Koob and his associates (Ahmed and Koob, 2005; Ahmed et al., 2002; Koob and Le Moal, 2001, 2008) have developed a model of drug addiction based upon the observation that animals provided extensive daily access to self-administered cocaine undergo progressive behavioral and neural changes that are not observed in animals provided more limited access to cocaine — changes that are thought to reflect a transition from "recreational" to compulsive" drug use. Two runway studies have directly examined and provide support for this hypothesis by demonstrating that animals with more extensive self-administration experience exhibit faster run times and reduced retreats for IV cocaine (Ben-Shahar et al., 2008), and were more responsive in tests of cocaine-induced reinstatement (Deroche et al., 1999) compared to animals with more restricted daily self-administration experience. In our laboratory we have recently extended our investigation to animals running for intracranial administration of cocaine into discrete brain regions as a means of determining whether the opposing positive and negative properties of the drug can be spatially, and hence neurobiologically, dissociated (e.g., Guzman et al., submitted for publication). In other recent work with opiate drugs, Crespo and colleagues (2006, 2008) have used runway measures of drug-seeking to implicate muscarinic and nicotinic acetylcholine receptors in the nucleus accumbens as essential for the acquisition of opiate-reinforced behavior. While in an earlier study, Zernig et al. (2002) modified the runway procedure to permit the investigation of the subcutaneously delivered morphine. The authors concluded that the runway served as a relatively simple and effective assay for the reinforcing properties of SC-administered morphine. These examples are all intended to simply illustrate some of the different ways in which the runway methodology has been and continues to be employed as a means of studying the drug-seeking behavior of laboratory animals. In some instances the application of this methodology has yielded data consistent with those obtained using others methods, and in some instances it has provided data that suggest an alternative process or explanation may be at play. Clearly the development and use of alternative methods for modeling substance abuse in animal subjects can only strengthen the ultimate goal of all researchers in this field, that being, of course, to more fully understand the behavioral and neurobiological factors that underlie and are responsible for drug abuse in our society.

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