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Reward Comparison: The Achilles' heel and hope for addiction

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Abstract

In the words of the late Charles Flaherty, reward comparison is commonplace. Rats and man, it appears, compare all rewards and this capacity likely contributes to our ability to select the most appropriate reward/behavior (food, water, salt, sex), at the most ideal level (e.g., a certain sweetness), at any given time. A second advantage of our predisposition for reward comparison is that the availability of rich alternative rewards can protect against our becoming addicted to any single reward/behavior. Thus, the potential protective effects of natural rewards/enrichment are addressed. Despite this, behavior can become inflexible when, through the development of addiction, stress, drug, or cues elicit craving, withdrawal, and ultimately, drug-seeking. Drug-seeking corresponds with a 'window of inopportunity', when even potent natural rewards have little or no impact on behavior. During this time, there is a unitary solution to the need state, and that solution is drug. The present animal model explores this 'window of inopportunity' when natural rewards are devalued and drug-seeking is engaged and considers a mode of possible intervention.

Addiction: The magnitude and nature of the problem

According to figures provided by the National Institute on Drug Abuse <http://www.nida.nih.gov/Infofacts/index.html>, in 2004, 34.2 million Americans used cocaine at least once, 7.8 million Americans used crack at least once, 2.4 million Americans used heroin (87% under the age of 26), and there were 450,000 current users of ecstasy. There were 14.6 million users of marijuana in 2004 and 70.3 million Americans smoking cigarettes. These large numbers are even more problematic because many individuals become addicted and addiction, more often than not, is not resolved following even extended periods of abstinence. In fact, addiction is a disease of chronic relapse [1], which costs society an estimated \$484 billion dollars/year as the addict repeatedly cycles from addiction to abstinence, withdrawal, drug-seeking, and relapse. Clearly, recovery of even part of these dollars through the successful treatment of the disease would constitute quite an economic stimulus package.

Along with society, the addict and his or her family also are adversely affected because addiction is associated with an apparent devaluation of, and inattention to, natural rewards. According to DSM-IV, substance abuse and dependence involve a failure to fulfill major obligations at work, school, or home, the giving up of important social, occupational, or recreational activities, and continued drug use despite recurrent physical, legal, social, or psychological problems. This categorization is substantiated by published data showing that the human addict weighs less, is more often absent from work, fails to respond appropriately to monetary rewards, and more often has his or her children removed from the home due to neglect [2–5].

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Natural rewards: Potential for hope

Although it is the case that drug-induced devaluation of natural rewards is an Achilles' heel for the addict and devastating for his or her family, it also is true that natural rewards may be the addict's best natural defense against substance abuse, addiction, and relapse. For example, Higgins et al. [6] have shown that abstinence is greatly improved when human drug addicts are given the opportunity to 'work' for (i.e., to stay abstinent for) tokens to purchase canoes, bicycles, or college credits, for example. The key, then, is to understand the conditions under which drugs devalue natural rewards and, alternatively, the conditions under which natural rewards might serve to protect against substance abuse and addiction. To this end, we continue to hone the first animal model for the systematic study of drug-induced devaluation of natural rewards [7,8]. We will describe this model and discuss what has been learned about devaluation, drug-taking, and the potential protective effects of natural rewards on substance abuse, addiction, and relapse.

The Model: Experimenter delivered drug

Since the mid 1950s it has been known that rats avoid intake of a gustatory conditioned stimulus (CS), such as saccharin, after it has been paired with an aversive, illness-inducing agent such as lithium chloride (LiCl) or x-radiation [9-11]. This phenomenon, referred to as a conditioned taste aversion (CTA), was found to occur following a single taste-illness pairing and even when using relatively long intervals between access to the CS and exposure to the aversive unconditioned stimulus (US). As such, the phenomenon generated a great deal of controversy because it challenged then basic principles of animal learning theory.

It was amid this controversy scientists discovered that not only putatively aversive agents, but also drugs of abuse, suppress intake of a gustatory CS following repeated taste-drug pairings [12]. Effective drugs include morphine [13-15], cocaine [16], amphetamine [17], ethanol, flurazepam, chlordiazepoxide [14,18,19], nicotine [20], amobarbital and phenobarbital [19] and heroin [21]. Rats, then, avoid intake of a taste cue following pairings with not only LiCl, but also with all drugs of abuse tested, across a range of doses [22], when administered intraperitoneally (ip), subcutaneously (sc), intravenously (iv), and even, in some cases, when administered directly into the nucleus accumbens [17,23-26].

Given the climate, this phenomenon also was interpreted, almost immediately, as a CTA [18]. Even so, it was viewed as highly paradoxical that such drugs, drugs that were readily self-administered by rats and man [27], also evidenced aversive properties in the CTA paradigm. Indeed, in three key experiments, avoidance of the taste cue was found to be accompanied, in the exact same study, by faster running for the drug [28], more time spent in the drug-paired compartment in a conditioned place preference task [29], and avid self-administration of the drug [24]. Since this time, additional evidence has been generated to show that addictive agents have aversive properties [25,30,31] and the aversive response to the taste cue following taste-drug pairings has been attributed to a range of factors including stimulus novelty, drug shyness (i.e., fear of novel drug or drug-induced state), fear [32], and positive conditioned suppression (i.e., where responding is suppressed by stimuli that precede the response-independent presentation of shock or food, for example) [33-36].

While it is the case that rats clearly avoid intake of a taste cue when paired with a putatively aversive US, such as LiCl, for example, in 1982 Flaherty and Checke [37] reported that rats also avoid intake of a saccharin CS when paired, in once daily sessions, with a highly preferred 32% sucrose solution. This phenomenon was referred to as an *anticipatory* contrast effect because reduced intake of the saccharin cue was thought to be due to anticipation of the availability of the preferred sucrose reward in the very near future. Indeed, in a subsequent within subjects study, it was shown that the reduction in intake of the taste cue depended upon

the value of the 32% sucrose reward anticipated in the near future, not upon the memory of the 32% sucrose solution received 24 h earlier [38]. Anticipatory contrast effects, then, depend upon the development of a Pavlovian associative relationship between the saccharin CS and the sucrose US [39] and the lesser reward CS is avoided in anticipation of the imminent availability of the preferred reward US [39,40].

Given this information, we hypothesized that rats avoid intake of a drug-associated taste cue because the value of the taste cue pales in comparison to the powerful drug reward anticipated in the very near future [7]. By way of indirect support, a great deal of data suggest that drugs of abuse are rewarding and that drug-induced suppression of CS intake is not like that induced by LiCl. Specifically, drugs of abuse are readily self-administered [for review, see 27] and they support the development of conditioned place preferences [41-44]. Unlike drugs of abuse that support a reduction in CS intake, but an increase in instrumental responding (as described above), LiCl suppresses both consummatory and instrumental responding [24,28,29]. Rats do not work for LiCl. Finally, as discussed previously [45], Parker [22,46-49] used the Taste Reactivity test [50] and showed that intraoral delivery of a LiCl-paired CS led to both a decrease in ingestive responses (e.g., tongue protrusions, paw licking, and mouth movements) and an increase in active rejection responses (e.g., gapes, chin rubs, and paw treading). The intraoral delivery of a drug-associated CS, on the other hand, led to a decrease in ingestive responses, with no clear increase in active rejection responses [46-48,51].

Dissociations of this nature argued against a CTA account, but did little to address the potential merits of the reward comparison hypothesis. To this end, we reasoned that if the reward comparison hypothesis was correct, then drug-induced suppression of CS intake should be sensitive to factors that affect anticipatory contrast effects. LiCl-induced CTAs, on the other hand, should be relatively impervious to these factors/manipulations. In accordance with this prediction, the suppressive effects of drugs of abuse and sucrose, but not those of LiCl, are greatly attenuated by food and water deprivation [52-55]. The suppressive effects of cocaine and sucrose, but not LiCl, are greater in drug sensitive Lewis, than less sensitive Fischer, rats [16,56]. The suppressive effects of cocaine and sucrose, but not LiCl, are augmented in rats with a history of chronic morphine treatment [57]. Finally, bilateral lesions of the gustatory thalamus or gustatory cortex disrupt the suppressive effects of morphine, cocaine, and sucrose, but have no impact on the development of a LiCl-induced CTA [58-65]. Taken together, the data confirm that drug-induced suppression of CS intake is not mediated by a conditioned taste aversion like that induced by the aversive agent. To the contrary, avoidance of the gustatory CS appears to be due, at least in part, to drug-induced devaluation of the natural reward cue, much like that which occurs when a similar taste cue predicts the impending availability of a palatable sweet (see [45] for a full discussion of these data).

Of course, despite a number of parallels, drugs of abuse are not sweets. Moreover, while there is a great deal of evidence for overlap in the underlying neural substrates [66,67], there also is evidence for separate circuits [68]. Drug-induced devaluation of CS intake (i.e., an anticipatory contrast-like mechanism), then, may contribute to avoidance of the drug-associated taste cue, but avoidance of the drug-associated taste cue also may be mediated by something else. Specifically, evidence suggests that onset of cue-induced craving and/or withdrawal may contribute to avoidance of the drug-associated taste cue. With experimenter-delivered drug, we have found that avoidance of a saccharin cue following a single saccharin-morphine pairing is accompanied by a full blunting of the accumbens dopamine response to the saccharin reward cue [69]. While negative contrast (reward devaluation) may contribute to this finding with dopamine [70], this blunting also could be explained by the onset of cue-induced craving and/or withdrawal because accumbens dopamine levels also are blunted following the onset of naltrexone-induced withdrawal [71]. Second, using experimenter-delivered drug, we have found large individual differences whereby some rats are more likely to avoid intake of the

drug-associated taste cue than are others and greater avoidance of the taste cue is associated with greater cue-induced elevation of circulating corticosterone [72]. As with the dopamine data, the conditioned elevation in circulating corticosterone also could be interpreted as evidence of cue-induced craving and/or withdrawal because circulating corticosterone levels are known to be elevated during naloxone-precipitated withdrawal [73].

The Model: Drug self-administration

Although we have learned a great deal about drug-induced suppression of CS intake using the passive model of drug delivery, use of the drug self-administration paradigm has obvious advantages. At base, we predicted that greater avoidance of CS intake would be associated with greater drug self-administration if, as proposed by the reward comparison hypothesis, avoidance of the taste cue was due to anticipation of the rewarding properties of the drug. To test this hypothesis, rats were catheterized so they could 'consume' not only the saccharin cue, but also the cocaine US. Specifically, after 5 min access to 0.15% saccharin, the saccharin spout was withdrawn and an empty spout was advanced. The rats then could respond on a fixed ratio schedule of reinforcement where completion of 10 licks on the empty spout led to an iv infusion of cocaine (0.33 mg/infusion/1 h). As shown previously with slightly different procedures [24], rats suppressed intake of the saccharin CS following repeated daily pairings with self-administered cocaine. Moreover, as with the passive administration of drug [72], individual differences were evident whereby some rats (referred to as large suppressors) were more likely than others (referred to as the small suppressors) to avoid intake of the saccharin cue following daily saccharin-cocaine pairings. These individual differences in intake of the CS also were accompanied by individual differences in 'intake' of the drug. Specifically, greater avoidance of the taste cue, was correlated with greater cocaine self-administration and greater cocaine-seeking following a period of one to six months of abstinence [data not shown, see 8].

These drug self-administration data show that avoidance of the taste cue and the propensity to self-administer drug go hand-in-hand. This finding is in keeping with the hypothesis that the reduction in intake of the gustatory CS is due to the rewarding properties of the drug. Of course, it also is in keeping with the idea that, through classical conditioning, the taste cue comes to elicit cue-induced craving and/or withdrawal. The onset of cue-induced withdrawal following taste-naloxone pairings, however, is not only accompanied by avoidance of the taste cue, but also by frank aversive taste reactivity behavior following its intraoral delivery [74]. As stated, rats do not emit clear aversive orofacial responses following brief intraoral delivery of a taste cue paired with experimenter-delivered drug [22,⁴⁹,⁷⁵]. Whether self-administered drugs, on the other hand, would support the development of such conditioned aversive taste reactivity behavior, however, was not known. In an effort to address this question, we used a within subjects design where the intraoral delivery (200 ul every min over a 30 min period) of one flavored saccharin solution (the CS+) predicted the opportunity to self-administer cocaine for 2 h, while the intraoral delivery of another flavored saccharin solution (the CS-), on a different day, predicted the opportunity to self-administer saline for 2 h [76]. Following conditioning, taste reactivity behavior was measured after the intraoral infusion of the CS- and then the CS + using an EMG electrode placed into the anterior digastric muscle (a requisite jaw opener) and videotape. Single unit activity also was recorded in real time using a fine microwire array in the nucleus accumbens. The results revealed aversive taste reactivity behavior (i.e., gapes) when the CS+ was infused intraorally at test and greater aversive taste reactivity behavior was associated with greater avoidance of the cocaine-associated taste cue when examined in a separate 2-bottle intake test. Moreover, greater aversive taste reactivity also predicted a shorter latency to take drug, greater within session load up behavior, and faster acquisition of steady state responding for cocaine. Finally, this shift in the affective response to the saccharin cue from reward to aversion was tracked by a similar shift in the coded response of single cells in

the NAc from primarily inhibition (as seen with the intraoral delivery of putatively rewarding gustatory stimuli) to primarily excitation (as seen with the intraoral delivery of putatively aversive gustatory stimuli) [77].

Together, the data show that rats associate a taste cue with the availability of a drug of abuse following taste-drug pairings. Avoidance of the taste cue appears, at least in part, to be due to anticipation of the potent rewarding properties of the drug. Thus, the suppressive effects of sweets and drugs, but not LiCl, are similarly affected by the deprivation state of the rat, selectively bred strains (but see [45] for a discussion), a history of chronic morphine treatment, and lesions of the gustatory thalamocortical pathway. Avoidance of a taste cue that predicts the availability of a highly preferred sucrose solution, however, is likely not one-in-the-same with avoidance of a taste cue that predicts the availability of a drug of abuse. Drugs of abuse have potent CNS properties and preparation for such a perturbation undoubtedly elicits the onset of a conditioned compensatory response [78]. In the absence of drug, the conditioned compensatory response can be experienced as withdrawal in rats and humans and can, in fact, be lethal [79-81]. Thus, we hypothesize that cue-induced craving and/or withdrawal contribute to avoidance of the taste cue following taste-drug pairings. As discussed, such an interpretation can account for avoidance of the taste cue (withdrawal is associated with anhedonia [82]), blunting of the accumbens dopamine response to the taste cue, elevated circulating corticosterone, and the onset of aversive taste reactivity following the intraoral delivery of the drug-associated cue. Were the animal in a state of cue-induced craving and/or withdrawal, the best correction for the onset of this aversive state would be drug. In accordance, and as discussed, greater avoidance of the taste cue and greater aversive taste reactivity was associated with a shorter latency to take drug, greater load-up, greater drug-taking, more rapid acquisition of drug self-administration and greater drug-seeking [8,76]. Future studies will need to track the development of this conditioned compensatory response to determine how various factors might affect the individual propensity for drug-induced devaluation, cue-induced craving/withdrawal, drug-taking and drug-seeking over time.

Natural Rewards: The best natural defense against substance abuse, addiction, and relapse

As mentioned, while it is the case that drug addicted individuals pay too little attention to natural rewards including food, employment, money, and even caring for one's offspring, it also is the case that natural rewards can provide great protection against drug taking, drug-seeking, and relapse. The goal here is to determine which natural rewards can be protective, when in development (e.g., adolescence and/or adulthood) they need to be presented to be protective, and whether they are effective in preventing disease in acquisition or in treating disease during maintenance and/or relapse. In general, it appears that all natural rewards can be protective. Drug self-administration is reduced by the availability of a sweet such as saccharin or a glucose + saccharin mixture [83-85]. Drug self-administration is reduced by the availability of a running wheel, particularly in females [86]. Finally, drug self-administration is reduced when rats simply are housed in an enriched environment offering conspecifics and novel objects [87-89].

Exposure to these natural rewards is protective when provided during adolescence and adulthood or when provided during adulthood alone. For example, environmental enrichment provided during adolescence and into adulthood reduces acquisition of drug self-administration behavior in rats [87-89]. Environmental enrichment also is protective in rats when provided during adulthood alone [90]. Sweets and even chow are protective when presented in adulthood concurrent with the opportunity to self-administer drug [83-85]. Finally, the sweets need not be concurrently available to be protective in adult rats. A history of brief daily access (5 min)

to a highly palatable 1.0 M sucrose solution (but not 0.1 M sucrose) was sufficient to greatly reduce subsequent acquisition of drug-taking behavior in adult rats [91].

The availability of an alternative natural reward can reduce acquisition, maintenance, and reinstatement of drug-taking behavior. The concurrent availability of a highly palatable glucose + saccharin solution reduced both acquisition and maintenance of cocaine self-administration behavior [85]. Just prior availability of the glucose + saccharin solution reduced drug-induced reinstatement of cocaine-seeking behavior in adult rats [92]. Housing in an enriched environment has been shown to slow acquisition, facilitate extinction, and reduce subsequent drug-induced reinstatement of amphetamine self-administration in rats [87-90]. Finally, as mentioned, the opportunity to earn tokens for non-drug rewards greatly reduced relapse in a cocaine-addicted adult population of humans [6].

The ‘window of inopportunity’: When natural rewards are without effect

So, why if natural rewards are so remarkably protective do we have such a problem with substance abuse and addiction in American society? This circumstance has to do with the paucity of natural rewards/enrichment in some segments of our society, the failure to systematically use alternative natural rewards in the treatment of the disease, and perhaps most importantly, identification of a ‘window of inopportunity’ where alternative natural rewards, regardless of their inherent value, have little or no access to behavior. I will discuss this window, but before doing so must clearly state that, when presented outside of this relatively narrow window, natural rewards are very effective in protecting against acquisition, maintenance, and reinstatement (i.e., relapse) of drug-taking behavior.

So, what is this ‘window of inopportunity’? Basically, when stress, drug, or cues elicit seeking, all bets are off. This is the window of inopportunity. This is the time when natural rewards, no matter how powerful, fail to deter drug-seeking behavior. In our model, we know that 20 min access to a saccharin cue is sufficient to fully blunt the dopamine response to a first injection of morphine [69]. The sweet solution, then, can initially confer some protection against the potent rewarding properties of the drug. Over repeated trials, however, we also know that rats come to avoid the natural reward cue. This occurs because the natural reward, in this case, is a perfect predictor of drug availability. As such, the cue is avoided (it actually becomes aversive under certain conditions [76,⁹³]) and drug-seeking is initiated. As described, this shift in the affective response to the natural reward cue in the rat is accompanied by a shift in the neural code in single cells in the nucleus accumbens [76]. Likewise, nicotine-addicted humans also exhibit an aversive affective response when cues predict the future opportunity to smoke [94] and, at that time (i.e., when waiting to smoke), the caudate nucleus registers a smaller response to monetary gains and losses [95]. Natural rewards, then, have little impact when one is in anticipation of, or in pursuit of, drug. Indeed, when the drug-addicted animal or human is in a cue-induced state of craving and withdrawal the drug is the best, if not the only, means of correction.

Competing motivations: Closing the ‘window of inopportunity’

Drug-seeking animals and humans, then, behave as though they need the drug. They seek to satisfy this need state much as they seek food when hungry, water when thirsty, and salt when sodium deficient [65]. When these biological drive states are activated, there is a single goal and there can be no substitute. This is the state of the addict when actively engaged in drug-seeking. One means by which to derail this unitary goal-seeking behavior may be to elicit a competing biological need state. Along with satiety (e.g., a reduction in hunger by food intake), onset of a competing motivation (e.g., thirst or salt hunger) serves as an independent means by which to interrupt one ongoing motivated behavior to allow for another [96]. Relevant to this consideration, we have found that acute sleep deprivation completely prevents drug-induced

reinstatement during extinction in low drug-taking rats [97]. The need for sleep may not be the drive of choice, but the data suggest that onset of a competing biological need state, such as thirst or salt need, for example, where attention to the new drive is paramount, may disengage drug-seeking behavior and, thereby, close this window of inopportunity. Further study is necessary to test the merits of this hypothesis.

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References

1. Leshner AI, Koob GF. Drugs of abuse and the brain. *Proc Assoc Am Physicians* 1999;111(2):99–108. [PubMed: 10220804]
2. Goldstein RZ, et al. Subjective sensitivity to monetary gradients is associated with frontolimbic activation to reward in cocaine abusers. *Drug Alcohol Depend* 2007;87(23):233–40. [PubMed: 16997508]
3. Jones S, Casswell S, Zhang JF. The economic costs of alcohol-related absenteeism and reduced productivity among the working population of New Zealand. *Addiction* 1995;90(11):1455–61. [PubMed: 8528030]
4. Nair P, et al. Risk factors for disruption in primary caregiving among infants of substance abusing women. *Child Abuse Negl* 1997;21(11):1039–51. [PubMed: 9422825]
5. Santolaria-Fernandez FJ, et al. Nutritional assessment of drug addicts. *Drug Alcohol Depend* 1995;38(1):11–8. [PubMed: 7648992]
6. Higgins ST, et al. Achieving cocaine abstinence with a behavioral approach. *Am J Psychiatry* 1993;150(5):763–9. [PubMed: 8480823]
7. Grigson PS. Conditioned taste aversions and drugs of abuse: a reinterpretation. *Behav Neurosci* 1997;111(1):129–36. [PubMed: 9109631]
8. Grigson PS, Twining RC. Cocaine-induced suppression of saccharin intake: a model of drug-induced devaluation of natural rewards. *Behav Neurosci* 2002;116(2):321–33. [PubMed: 11996317]
9. Nachman M, Ashe JH. Learned taste aversions in rats as a function of dosage, concentration, and route of administration of LiCl. *Physiol Behav* 1973;10(1):73–8. [PubMed: 4697023]
10. Garcia J, Kimmeldorf KJ, Koelling RA. Conditioned aversions to saccharin resulting from exposure to gamma radiation. *Science* 1955;122:157–158. [PubMed: 14396377]
11. Smith JC, Morris DD, Hendricks J. Conditioned Aversion to Saccharin Solution with High Dose Rates of X-Rays as the Unconditioned Stimulus. *Radiat Res* 1964;22:507–10. [PubMed: 14155862]
12. Le Magnen J. Peripheral and systemic actions of food in the caloric regulation of intake. *Ann N Y Acad Sci* 1969;157(2):1126–57. [PubMed: 5255624]
13. Sherman JE, et al. Rewarding and aversive effects of morphine: temporal and pharmacological properties. *Pharmacol Biochem Behav* 1980;13(4):501–5. [PubMed: 7433482]
14. Cappel H, LeBlanc AE, Endrenyi L. Aversive conditioning by psychoactive drugs: effects of morphine, alcohol and chlordiazepoxide. *Psychopharmacologia* 1973;29(3):239–46. [PubMed: 4702275]
15. Miller JS, et al. Conditioning of morphine-induced taste aversion and analgesia. *Psychopharmacology (Berl)* 1990;101(4):472–80. [PubMed: 2167492]
16. Glowa JR, Shaw AE, Riley AL. Cocaine-induced conditioned taste aversions: comparisons between effects in LEW/N and F344/N rat strains. *Psychopharmacology (Berl)* 1994;114(2):229–32. [PubMed: 7838912]
17. Cappel H, LeBlanc AE. Conditioned aversion to saccharin by single administrations of mescaline and d-amphetamine. *Psychopharmacologia* 1971;22(4):352–6. [PubMed: 5133436]
18. Lester D, Nachman M, Le Magnen J. Aversive conditioning by ethanol in the rat. *Q J Stud Alcohol* 1970;31(3):578–86. [PubMed: 5466397]

19. Vogel JR, Nathan BA. Learned taste aversions induced by hypnotic drugs. *Pharmacol Biochem Behav* 1975;3(2):189–94. [PubMed: 1144479]
20. Castane A, et al. Attenuation of nicotine-induced rewarding effects in A2A knockout mice. *Neuropharmacology* 2006;51(3):631–40. [PubMed: 16793068]
21. Grigson PS, Twining RC, Carelli RM. Heroin-induced suppression of saccharin intake in water-deprived and water-replete rats. *Pharmacol Biochem Behav* 2000;66(3):603–8. [PubMed: 10899377]
22. Parker LA. Taste reactivity responses elicited by reinforcing drugs: a dose-response analysis. *Behav Neurosci* 1991;105(6):955–64. [PubMed: 1777108]
23. Shoaib M, Stolerman IP. Conditioned taste aversions in rats after intracerebral administration of nicotine. *Behav Pharmacol* 1995;6(4):375–385. [PubMed: 11224346]
24. Wise RA, Yokel RA, DeWit H. Both positive reinforcement and conditioned aversion from amphetamine and from apomorphine in rats. *Science* 1976;191(4233):1273–5. [PubMed: 1257748]
25. Bechara A, van der Kooy D. Opposite motivational effects of endogenous opioids in brain and periphery. *Nature* 1985;314(6011):533–4. [PubMed: 2986002]
26. Mucha RF, Herz A. Preference conditioning produced by opioid active and inactive isomers of levorphanol and morphine in rat. *Life Sci* 1986;38(3):241–9. [PubMed: 3941594]
27. van Ree JM. Reinforcing stimulus properties of drugs. *Neuropharmacology* 1979;18(12):963–9. [PubMed: 530378]
28. White N, Sklar L, Amit Z. The reinforcing action of morphine and its paradoxical side effect. *Psychopharmacology (Berl)* 1977;52(1):63–6. [PubMed: 403559]
29. Reicher MA, Holman EW. Location preference and flavor aversion reinforced by amphetamine in rats. *Animal Learning & Behavior* 1977;5:343–346.
30. Blanchard DC, Blanchard RJ. Cocaine potentiates defensive behaviors related to fear and anxiety. *Neurosci Biobehav Rev* 1999;23(7):981–91. [PubMed: 10580312]
31. Ettenberg A, Geist TD. Animal model for investigating the anxiogenic effects of self-administered cocaine. *Psychopharmacology (Berl)* 1991;103(4):455–61. [PubMed: 2062985]
32. Conditioned disgust, but not conditioned taste avoidance, may reflect conditioned nausea in rats. In: Parker, LA.; Limebeer, CL.; Rana, SA., editors; T, S.; Reilly, S., editors. *Conditioned Taste Aversion Behavioral and Neural Processes*. Oxford University Press; New York: 2008. p. 92–113.
33. Goudie AJ. Aversive stimulus properties of drugs. *Neuropharmacology* 1979;18:971–979. [PubMed: 394018]
34. Hunt T, Amit Z. Conditioned taste aversion induced by self-administered drugs: paradox revisited. *Neurosci Biobehav Rev* 1987;11(1):107–30. [PubMed: 3554039]
35. Parker LA. Taste avoidance and taste aversion: evidence for two different processes. *Learn Behav* 2003;31(2):165–72. [PubMed: 12882375]
36. Stolerman, IP.; D'Mello, GD. Oral self-administration and the relevance of conditioned taste aversions. In: Thompson, T.; Dews, P.; McKim, WA., editors. *Advances in behavioral pharmacology*. Academic Press; New York: 1981. p. 169–214.
37. Flaherty CF, Checke S. Anticipation of incentive gain. *Animal Learning and Behavior* 1982;10:177–182.
38. Flaherty CF, Rowan GA. Anticipatory Contrast: Within-subjects analysis. *Animal Learning & Behavior* 1985;13:2–5.
39. Flaherty CF, Grigson PS. From contrast to reinforcement: role of response contingency in anticipatory contrast. *J Exp Psychol Anim Behav Process* 1988;14(2):165–76. [PubMed: 3367102]
40. Flaherty, CF. Incentive Relativity. In: Gray, J., editor. *Problems in the Behavioural Sciences*. New York: Cambridge University Press; 1996.
41. Bardo MT, Miller JS, Neisewander JL. Conditioned place preference with morphine: the effect of extinction training on the reinforcing CR. *Pharmacol Biochem Behav* 1984;21(4):545–9. [PubMed: 6504952]
42. Reilly S, Grigson PS, Norgren R. Parabrachial nucleus lesions and conditioned taste aversion: evidence supporting an associative deficit. *Behav Neurosci* 1993;107(6):1005–17. [PubMed: 8136054]

43. Blander A, et al. Conditioned place preference: an evaluation of morphine's positive reinforcing properties. *Psychopharmacology (Berl)* 1984;84(1):124–7. [PubMed: 6436880]
44. Katz RJ, Gormezano G. A rapid and inexpensive technique for assessing the reinforcing effects of opiate drugs. *Pharmacol Biochem Behav* 1979;11(2):231–3. [PubMed: 504302]
45. Grigson, PS.; Twining, RC.; Freet, CS.; Wheeler, RA.; Geddes, RI. Drug-induced suppression of conditioned stimulus intake: Reward, Aversion, and Addiction. In: T, S.; Reilly, S., editors. *Conditioned Taste Aversion: Behavioral and Neural Processes*. Oxford University Press; NY: 2008. p. 74-91.
46. Parker LA. Taste reactivity responses elicited by cocaine-, phencyclidine-, and methamphetamine-paired sucrose solutions. *Behav Neurosci* 1993;107(1):118–29. [PubMed: 8447949]
47. Parker LA. Defensive burying of flavors paired with lithium but not amphetamine. *Psychopharmacology (Berl)* 1988;96(2):250–2. [PubMed: 3148152]
48. Parker LA. Behavioral conditioned responses across multiple conditioning/testing trials elicited by lithium- and amphetamine-paired flavors. *Behav Neural Biol* 1984;41(2):190–9. [PubMed: 6487218]
49. Parker LA. Rewarding drugs produce taste avoidance, but not taste aversion. *Neurosci Biobehav Rev* 1995;19(1):143–57. [PubMed: 7770194]
50. Grill HJ, Norgren R. The taste reactivity test I. Mimetic responses to gustatory stimuli in neurologically normal rats. *Brain Res* 1978;143(2):263–79. [PubMed: 630409]
51. Parker LA, Carvell T. Orofacial and somatic responses elicited by lithium-, nicotine- and amphetamine-paired sucrose solution. *Pharmacol Biochem Behav* 1986;24(4):883–7. [PubMed: 3714782]
52. Grigson PS, Cornelius K, Wheeler DS. The suppressive effects of intraperitoneal cocaine are augmented when evaluated in nondeprived rats. *Pharmacol Biochem Behav* 2001;69(12):117–23. [PubMed: 11420076]
53. Bell SM, et al. Effects of food deprivation on conditioned taste aversions in rats. *Pharmacol Biochem Behav* 1998;60(2):459–66. [PubMed: 9632229]
54. Gomez F, Grigson PS. The suppressive effects of LiCl, sucrose, and drugs of abuse are modulated by sucrose concentration in food-deprived rats. *Physiol Behav* 1999;67(3):351–7. [PubMed: 10497952]
55. Grigson PS, et al. Water-deprivation prevents morphine-, but not LiCl-induced, suppression of sucrose intake. *Physiol Behav* 1999;67(2):277–86. [PubMed: 10477060]
56. Grigson PS, Freet CS. The suppressive effects of sucrose and cocaine, but not lithium chloride, are greater in Lewis than in Fischer rats: evidence for the reward comparison hypothesis. *Behav Neurosci* 2000;114(2):353–63. [PubMed: 10832796]
57. Grigson PS, et al. Chronic morphine treatment exaggerates the suppressive effects of sucrose and cocaine, but not lithium chloride, on saccharin intake in Sprague-Dawley rats. *Behav Neurosci* 2001;115(2):403–16. [PubMed: 11345965]
58. Geddes RI, Han L, Baldwin AE, Norgren R, Grigson PS. Gustatory insular cortex lesions disrupt drug-induced, but not Lithium chloride-induced suppression of conditioned stimulus intake. *Behavioral Neuroscience* 2008;122(5):1038–1050. [PubMed: 18823161]
59. Flynn FW, et al. Central gustatory lesions: II. Effects on sodium appetite, taste aversion learning, and feeding behaviors. *Behav Neurosci* 1991;105(6):944–54. [PubMed: 1777107]
60. Grigson PS, Lyuboslavsky P, Tanase D. Bilateral lesions of the gustatory thalamus disrupt morphine- but not LiCl-induced intake suppression in rats: evidence against the conditioned taste aversion hypothesis. *Brain Res* 2000;858(2):327–37. [PubMed: 10708684]
61. Mackey WB, Keller J, van der Kooy D. Visceral cortex lesions block conditioned taste aversions induced by morphine. *Pharmacol Biochem Behav* 1986;24(1):71–8. [PubMed: 3945668]
62. Reilly S, Pritchard TC. Gustatory thalamus lesions in the rat: II. Aversive and appetitive taste conditioning. *Behav Neurosci* 1996;110(4):746–59. [PubMed: 8864266]
63. Reilly S, Bornovalova M, Trifunovic R. Excitotoxic lesions of the gustatory thalamus spare simultaneous contrast effects but eliminate anticipatory negative contrast: evidence against a memory deficit. *Behav Neurosci* 2004;118(2):365–76. [PubMed: 15113262]
64. Schroy PL, et al. Role of gustatory thalamus in anticipation and comparison of rewards over time in rats. *Am J Physiol Regul Integr Comp Physiol* 2005;288(4):R966–80. [PubMed: 15591157]

65. Scalera G, Grigson PS, Norgren R. Gustatory functions, sodium appetite, and conditioned taste aversion survive excitotoxic lesions of the thalamic taste area. *Behav Neurosci* 1997;111(3):633–45. [PubMed: 9189278]
66. Carr KD. Chronic food restriction: enhancing effects on drug reward and striatal cell signaling. *Physiol Behav* 2007;91(5):459–72. [PubMed: 17081571]
67. Kelley AE, Berridge KC. The neuroscience of natural rewards: relevance to addictive drugs. *J Neurosci* 2002;22(9):3306–11. [PubMed: 11978804]
68. Carelli RM, Ijames SG, Crumling AJ. Evidence that separate neural circuits in the nucleus accumbens encode cocaine versus “natural” (water and food) reward. *J Neurosci* 2000;20(11):4255–66. [PubMed: 10818162]
69. Grigson PS, Hajnal A. Once is too much: Conditioned changes in accumbens dopamine following a single saccharin-morphine pairing. *Behavioral Neuroscience* 2007;121:1234–1242. [PubMed: 18085877]
70. Genn RF, Ahn S, Phillips AG. Attenuated dopamine efflux in the rat nucleus accumbens during successive negative contrast. *Behav Neurosci* 2004;118(4):869–73. [PubMed: 15301614]
71. Shaham Y, Stewart J. Stress reinstates heroin-seeking in drug-free animals: an effect mimicking heroin, not withdrawal. *Psychopharmacology (Berl)* 1995;119(3):334–41. [PubMed: 7675970]
72. Gomez F, Leo NA, Grigson PS. Morphine-induced suppression of saccharin intake is correlated with elevated corticosterone levels. *Brain Res* 2000;863(12):52–8. [PubMed: 10773192]
73. Nunez C, et al. Activation of stress-related hypothalamic neuropeptide gene expression during morphine withdrawal. *J Neurochem* 2007;101(4):1060–71. [PubMed: 17286593]
74. McDonald RV, Parker LA, Siegel S. Conditioned sucrose aversions produced by naloxone-precipitated withdrawal from acutely administered morphine. *Pharmacol Biochem Behav* 1997;58(4):1003–8. [PubMed: 9408206]
75. Parker LA, et al. Amphetamine and morphine produce a conditioned taste and place preference in the house musk shrew (*Suncus murinus*). *J Exp Psychol Anim Behav Process* 2002;28(1):75–82. [PubMed: 11868236]
76. Wheeler RA, T RC, Jones JL, Slater JM, Grigson PS, Carelli RM. Cue-induced negative affect: A behavioral and neural mechanism of cocaine seeing. *Neuron* 2008;57(5):774–785. [PubMed: 18341996]
77. Roitman MF, Wheeler RA, Carelli RM. Nucleus accumbens neurons are innately tuned for rewarding and aversive taste stimuli, encode their predictors, and are linked to motor output. *Neuron* 2005;45(4):587–97. [PubMed: 15721244]
78. Siegel S, Ramos BM. Applying laboratory research: drug anticipation and the treatment of drug addiction. *Exp Clin Psychopharmacol* 2002;10(3):162–83. [PubMed: 12233979]
79. Siegel S. Pavlovian conditioning and heroin overdose: Reports by overdose victims. *Bulletin of the Psychonomic Society* 1984;22(5):428–430.
80. Siegel, S. Classical Conditioning, Drug Tolerance, and Drug Dependence. In: B, FB.; Isreal, Y.; Kalant, H.; Popham, RE.; Schmitt, W.; Smart, RG., editors. *Research advances in alcohol and drug problems*. Plenum Press; New York: 1983. p. 207–246.
81. O'Brien CP, et al. Classical conditioning in drug-dependent humans. *Annals of the New York Academy of sciences* 1992;564:400–415.
82. Kenny PJ, et al. Conditioned withdrawal drives heroin consumption and decreases reward sensitivity. *J Neurosci* 2006;26(22):5894–900. [PubMed: 16738231]
83. Lenoir M, Ahmed SH. Supply of a nondrug substitute reduces escalated heroin consumption. *Neuropsychopharmacology* 2008;33(9):2272–82. [PubMed: 17971831]
84. Lenoir M, et al. Intense sweetness surpasses cocaine reward. *PLoS ONE* 2007;2(1):e698. [PubMed: 17668074]
85. Carroll ME, Lac ST, Nygaard SL. A concurrently available nondrug reinforcer prevents the acquisition or decreases the maintenance of cocaine-reinforced behavior. *Psychopharmacology* 1989;97(1):23–9. [PubMed: 2496421]
86. Cosgrove KP, Hunter RG, Carroll ME. Wheel-running attenuates intravenous cocaine self-administration in rats. Sex differences. *Pharmacol Biochem Behav* 2002;73(3):663–71. [PubMed: 12151042]

87. 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]
88. Bardo MT, et al. Environmental enrichment decreases intravenous self-administration of amphetamine in female and male rats. *Psychopharmacology (Berl)* 2001;155(3):278–84. [PubMed: 11432690]
89. 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):373–8. [PubMed: 12172690]
90. Puhl MD, Blum JS, Acosta-Torres S, Grigson PS. An enriched environment protects against cocaine seeking and taking in adult male rats. *Society for Neuroscience Abstracts*. 2008
91. Twining RC, Grigson PS. Reward history, rather than current reward value, affects acquisition of cocaine self-administration. In preparation.
92. Liu C, Grigson PS. Brief access to sweets protect against relapse to cocaine-seeking. *Brain Res* 2005;1049(1):128–31. [PubMed: 15935999]
93. Twining R, Bolan M, Grigson PS. Yoked delivery of cocaine is aversive and protects against the motivation for drug in rats. Submitted.
94. Sayette MA, Wertz JM, Martin CS, Cohn JF, Perrott MA, Hobel J. Effects of smoking opportunity on cue-elicited urge: A facial coding analysis. *Experimental and Clinical Psychopharmacology* 2003;11(3):218–227. [PubMed: 12940501]
95. Wilson SJ, et al. Effect of smoking opportunity on responses to monetary gain and loss in the caudate nucleus. *J Abnorm Psychol* 2008;117(2):428–34. [PubMed: 18489219]
96. Grigson PS. Like drugs for chocolate. Separate rewards modulated by common mechanisms? *Physiol Behav* 2002;76(3):389–95. [PubMed: 12117575]
97. Puhl MD, Fang J, Grigson PS. Acute Sleep Deprivation Increases the Rate and Efficiency of Cocaine Self-Administration, But Not the Perceived Value of Cocaine Reward in Rats. Submitted.