Published in final edited form as:

Pharmacol Biochem Behav. 2015 November ; 138: 133–141. doi:10.1016/j.pbb.2015.09.020.

Cocaine choice procedures in animals, humans, and treatment-seekers: Can we bridge the divide?

Scott J. Moeller^{1,2,*} and William W. Stoops^{3,4,5,*}

¹Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY

²Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY

³Department of Behavioral Science and Center on Drug and Alcohol Research, University of Kentucky College of Medicine, Lexington, KY

⁴Department of Psychiatry, University of Kentucky College of Medicine, Lexington, KY

⁵Department of Psychology, University of Kentucky College of Arts and Sciences, Lexington, KY

Abstract

Individuals with cocaine use disorder chronically self-administer cocaine to the detriment of other rewarding activities, a phenomenon best modeled in laboratory drug-choice procedures. These procedures can evaluate the reinforcing effects of drugs versus comparably valuable alternatives under multiple behavioral arrangements and schedules of reinforcement. However, assessing drug-choice in treatment-seeking or abstaining humans poses unique challenges: for ethical reasons, these populations typically cannot receive active drugs during research studies. Researchers have thus needed to rely on alternative approaches that approximate drug-choice behavior or assess more general forms of decision-making, but whether these alternatives have relevance to real-world drug-taking that can inform clinical trials is not well-understood. In this mini-review, we (A) summarize several important modulatory variables that influence cocaine choice in nonhuman animals and non-treatment seeking humans; (B) discuss some of the ethical considerations that could arise if treatment-seekers are enrolled in drug-choice studies; (C) consider the efficacy of alternative procedures, including non-drug-related decision-making and ‘simulated’ drug-choice (a choice is made, but no drug is administered) to approximate drug choice; and (D) suggest opportunities for new translational work to bridge the current divide between preclinical and clinical research.

*Correspondence may be addressed to: Scott J. Moeller, 1470 Madison Ave (Room 9-115), New York, NY 10029; Tel: 212-824-8973; Fax: 212-803-6743; scott.moeller@mssm.edu. Correspondence may also be addressed to: William W. Stoops, 465 E. High Street, 204B, Lexington, KY 40507; Tel: 859-257-5383; Fax: 859-257-7684; william.stoops@uky.edu.

Disclosure/Conflict of Interest

None declared.

The authors presented parts of this article during a symposium, chaired by Matthew L. Banks and Michael A. Nader, at the American Society for Pharmacology and Experimental Therapeutics (ASPET) conference in 2014.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

cocaine addiction; choice behavior; laboratory models; self-administration; decision-making; cue reactivity; delay discounting

Introduction

Cocaine use disorder is characterized by a compromised ability to stop or curtail problematic drug use. Diagnostic criteria, for example as specified in the DSM-5, are largely defined by behaviors relevant to drug-seeking and drug-taking (American Psychiatric Association, 2013). Due to this emphasis on behavior, research with non-human animals and humans has sought to model problematic drug-taking behaviors using laboratory self-administration methodologies. One prominent self-administration model, used successfully in research for over three decades (Aigner and Balster, 1978; Banks et al., 2015a), is the drug-choice procedure. The general arrangement for drug-choice procedures is to first have an organism sample a drug reinforcer and an alternative non-drug reinforcer (e.g., a dose of cocaine and a food pellet), and then allow that organism to choose between the options via concurrent schedules of reinforcement (e.g., discrete trials, fixed or progressive ratio). The primary outcomes are typically number of drug choices and/or percent of drug choices.

The drug-choice model has face validity in that it evaluates drug-taking behavior in the presence of some concurrently available (usually palatable), but mutually exclusive, alternative option. For example, choosing drug over the non-drug alternative in this procedure mirrors the diagnostic criterion of using cocaine to the exclusion of other activities (American Psychiatric Association, 2013). Choice procedures also avoid some problems of data interpretation posed by earlier self-administration models in non-human animals, for example addressing the confound that a self-administered drug could reduce response rates due to sedative effects yet still function as a reinforcer (Banks and Negus, 2012). Finally, choice procedures can suggest especially promising treatments. The most effective treatments should not only reduce the reinforcing effects of drugs, but also increase allocation of behavior to non-drug alternatives; drug self-administration methodologies without choice alternatives can assess the former but not the latter. In this vein, choice procedures in which the non-drug alternative is a commodity like food, money, or goods are consistent with, although do not perfectly model (LeSage, 2009), contingency management treatment approaches. In contingency management, which is also a generalized extension of classical token economies, “choices” to abstain from drugs in the natural environment, often verified as negative urine screens, are reinforced with money, vouchers, or tokens that can be exchanged for goods or services (Higgins et al., 2004).

Purpose of the Present Review and Selection Criteria

This mini-review summarizes laboratory cocaine-choice research spanning nonhuman animals and human current users, and potential alternatives for human treatment-seekers. We first review studies that examined the choice between drug reinforcers and non-drug reinforcers in non-human animals and current human users. This work, beyond being elegant and informative in its own right, provides a backdrop for highlighting the problems

of translation to human treatment-seeking populations: for ethical reasons (see below), treatment-seekers are usually prohibited from self-administering actual drugs in laboratory studies. Thus, we next review alternative choice and decision-making procedures that examine choice behavior without direct self-administration, but with the important caveat that these procedures are, at best, approximations of drug-taking behavior. For this reason, we conclude by suggesting some approaches that can help overcome problems of translation between active drug users and treatment-seekers. We do not intend for this mini-review to be exhaustive, nor do we necessarily describe each constituent study in complete depth (e.g., neuroimaging findings, which are included in some studies, are outside the scope of this article). Rather, we describe exemplary, representative studies and overall patterns of results to provide a commentary on current practices and to move the field forward. Throughout this article, we focus on choice outcomes in studies that included alternative reinforcers, including applicable examples from preclinical research, clinical trials, and/or treatment prediction studies.

Preclinical and Human Laboratory Choice Study Outcomes

In this section, we describe four parametrically evaluated variables that influence cocaine choice in non-human animals and non-treatment seeking humans: (1) alternative reinforcer magnitude, (2) alternative reinforcer type, (3) effort necessary to obtain cocaine or the alternative reinforcer, and (4) pharmacological treatment. These results demonstrate the robustness and clarity of the drug-choice approach.

Influence of Alternative Reinforcer Magnitude

In perhaps the earliest study of its kind, four rhesus monkeys chose between doses of cocaine (0.03–0.56 mg/kg/injection) and food (1–16 pellets) in a discrete trials procedure. Increasing the amount of food available, relative to a constant cocaine dose, decreased cocaine choice (Nader and Woolverton, 1991). More recent studies in rhesus monkeys have shown similar results (Huskinson et al., 2015), and also support the converse relationship: that decreasing the amount of the alternative reinforcer (i.e. from three to one food pellets) increased cocaine choice in rhesus monkeys (Woolverton and English, 1997). Studies in rats have similarly shown that increasing saccharin concentration (Cantin et al., 2010) or increasing Ensure® concentration (Thomsen et al., 2013) in concurrently available water resulted in orderly decreases in cocaine choice. A conflicting study in rhesus monkeys, however, showed that increasing the amount of alternative reinforcer (candy-coated chocolates) disrupted choice of lower but not higher cocaine doses (Foltin et al., 2015).

Human laboratory studies have also produced mixed results. In perhaps the earliest human study, four participants made ten choices between 10 mg intranasal cocaine and money (\$0.00–\$2.00); cocaine choice decreased as an orderly function of increasing monetary values (Higgins et al., 1994). More recent research has reached similar conclusions (Higgins et al., 1996; Donny et al., 2004; Vosburg et al., 2010; Greenwald et al., 2014). A number of other human laboratory studies, however, have failed to show that value of an alternative reinforcer changes cocaine choice (Donny et al., 2003; Stoops et al., 2010; Foltin et al., 2015). Most recently, cocaine choice was only decreased when the increased value of an alternative reinforcer was paired with increasing the effort to obtain cocaine (see below for

more detail) (Foltin et al., 2015). Some clinical trial research has shown that increasing the value of the available alternative reinforcer increases likelihood of abstinence from cocaine (Higgins et al., 2007; Garcia-Rodriguez et al., 2009), but other research has not (Petry et al., 2007; Petry et al., 2015). The reasons for these discrepancies across studies are unclear, but could involve the schedule of reinforcement and/or participant characteristics. As an example of the former, a descending schedule of alternative reinforcement (Donny et al., 2004), but not an increasing schedule of alternative reinforcement (Donny et al., 2003), modulated cocaine choice. As an example of the latter, one notable difference in the cited clinical trials research is that studies failing to find positive effects of contingency management included participants maintained on methadone (Petry et al., 2007; Petry et al., 2015). Overall, the reviewed studies indicate that cocaine use can be difficult to disrupt, even in the presence of valuable alternative reinforcers.

Influence of Alternative Reinforcer Type

Type of alternative reinforcer has received comparably less attention. In one study of hungry rats, the availability of sucrose (which satisfies caloric needs) versus saccharin (which does not satisfy caloric needs) was associated with a decreased choice for cocaine (Cantin et al., 2010). Human laboratory studies have similarly revealed an important role for this variable in cocaine choice (Hart et al., 2000; Stoops et al., 2010). In the earlier study (Hart et al., 2000), six participants first sampled an available dose of smoked cocaine (0, 12, 25 or 50 mg) and then made five choices between that sampled dose and either \$5 in cash or a \$5 merchandise voucher. Cocaine choice increased as a function of dose, but cash more effectively decreased cocaine choice than the merchandise voucher. Similarly, the later study showed that money more effectively suppressed cocaine choice than food (Stoops et al., 2010). These human laboratory results are consistent with those of a clinical trial that compared cash and vouchers worth \$0, 25, 50 and 100 for promoting abstinence from cocaine in methadone-maintained patients (Vandrey et al., 2007). Although a more recent clinical trial found no differences between cash and voucher rewards for duration of abstinence (Festinger et al., 2014), higher amounts of cash generally increased biologically verified cocaine abstinence more effectively than vouchers worth the same amount.

Influence of Effort Necessary to Obtain Cocaine or the Alternative Reinforcer

The cost of alternative reinforcers also influences cocaine choice in non-human animals (rhesus monkeys, cynomolgus monkeys, and baboons) (Nader and Woolverton, 1992; Foltin, 1999; Czoty et al., 2005; Banks et al., 2013b) (see Figure 1 for representative results). In the earliest study, increasing the response requirement to obtain food from an FR30 to FR240 or FR480 resulted in nearly maximal cocaine choice in rhesus monkeys (Nader and Woolverton, 1992); in turn, decreasing the response cost for food decreased cocaine choice in rhesus monkeys (Banks et al., 2013b). A more recent study in rhesus monkeys indicated that manipulating response cost for candy did not substantially alter cocaine taking, though detailed data are unavailable for comparison to other studies (Foltin et al., 2015). A study in human cocaine users manipulated response cost for money (i.e., 1, 10, 100 or 1000 responses) while holding the response cost for cocaine doses constant at 100 responses. As with the non-human primates, increasing response cost for the alternative reinforcer increased cocaine self-administration (Stoops et al., 2012a).

Other studies have evaluated how manipulating response cost for cocaine changes choices between cocaine and alternative reinforcers (Czoty et al., 2005; Banks et al., 2013b; Foltin et al., 2015). In the two earlier studies (in rhesus monkeys and cynomolgus monkeys, respectively), increased response cost for cocaine decreased cocaine choice and increased food choice (Czoty et al., 2005; Banks et al., 2013b); in turn, decreasing the response cost for cocaine increased cocaine choice (Banks et al., 2013b). The third study, conducted in humans, instead reported that increased response cost for cocaine needed to be paired with increased alternative reinforcer value to reduce cocaine choice (Foltin et al., 2015).

These laboratory findings have important implications for treatment development. It is unlikely that treatment providers can alter response cost to earn cocaine without confining patients to a treatment facility, jail, or prison, so it is fortunate that the variable they can control (i.e., ease of earning alternative reinforcers) effectively reduces drug taking behavior. Indeed, these outcomes are consistent with clinical trials showing that reducing the effort necessary to receive alternative reinforcers (e.g., starting with easier requirements to earn vouchers or providing reinforcement for reductions in cocaine metabolite levels in urine samples as opposed to for fully negative cocaine urines) can improve treatment outcomes relative to when earning alternative reinforcers is more difficult (Kirby et al., 1998; Preston et al., 2001).

Influence of Pharmacological Treatment

A number of medications have been tested for their ability to alter cocaine self-administration in non-human animal and human laboratory studies (Rush and Stoops, 2012; Howell and Negus, 2014; Verrico et al., 2014). Non-human animal studies, conducted primarily in rhesus monkeys but also in rats, have tested the following medications while specifically using drug-choice procedures: aripiprazole (Thomsen et al., 2008), buspirone (John et al., 2015), d-amphetamine (Negus, 2003; Thomsen et al., 2013; Banks et al., 2015b), fenfluramine (Banks et al., 2011), fluoroamphetamine (Banks et al., 2011), flupenthixol (Negus, 2003), lisdexamfetamine (Banks et al., 2015b), methadone (Negus and Mello, 2004), methamphetamine (Banks et al., 2011), naphthylisopropylamine (Banks et al., 2011), phendimetrazine (Banks et al., 2013c; Banks et al., 2013a), phenmetrazine (Banks et al., 2011, 2013b), quetiapine (Brutcher and Nader, 2015), and xanomeline (Thomsen et al., 2014). In general, drugs that could be considered “agonist replacement” medications like d-amphetamine, lisdexamfetamine, phendimetrazine, and phenmetrazine reduced cocaine choice (Negus, 2003; Banks et al., 2013c; Banks et al., 2013b, a; Thomsen et al., 2013; Banks et al., 2015b). Antagonist-type pharmacotherapies, conversely, either failed to decrease cocaine choice [e.g., buspirone, flupenthixol or methadone (Negus, 2003; Negus and Mello, 2004; John et al., 2015)] or produced only transient decreases in cocaine choice [e.g., quetiapine or aripiprazole (Thomsen et al., 2008; Brutcher and Nader, 2015)]. Xanomeline, a muscarinic M1/M4 receptor agonist, decreased cocaine choice and was not associated with tolerance in rats (Thomsen et al., 2014).

Several of these drugs have also been tested in the human laboratory, including aripiprazole (Haney et al., 2011) (Lofwall et al., 2014), d-amphetamine (Greenwald et al., 2010), and methadone (Foltin and Fischman, 1996). These human laboratory studies are remarkably

consistent with the non-human animal studies. Amphetamine reduced cocaine choice (Greenwald et al., 2010), whereas the other medications failed to change cocaine taking (Lofwall et al., 2014) or actually increased cocaine choice (Haney et al., 2011). A number of other drugs have been evaluated using choice procedures in the human laboratory, including baclofen (Haney et al., 2006), buprenorphine (Foltin and Fischman, 1996), bupropion (Stoops et al., 2012b), butorphanol (Walsh et al., 2001), desipramine (Fischman et al., 1990), ecopipam (Haney et al., 2001), enadoline (Walsh et al., 2001), escitalopram (Verrico et al., 2014), gabapentin (Hart et al., 2004; Hart et al., 2007a; Hart et al., 2007b), memantine (Collins et al., 2007), methylphenidate (Collins et al., 2006), modafinil (Hart et al., 2008; Verrico et al., 2014), and pergolide (Haney et al., 1998). These studies produced largely negative outcomes, likely reflecting the difficulty of completely eliminating cocaine taking in pharmacotherapy clinical trials and contributing to the lack of an FDA approved medication for cocaine use disorder. However, d-amphetamine maintenance consistently reduced cocaine choice relative to alternative reinforcers (Negus, 2003; Greenwald et al., 2010) and promoted abstinence in clinical trials (Grabowski et al., 2001). Bupropion combined with contingency management promoted cocaine abstinence (Poling et al., 2006), reminiscent of human laboratory results indicating bupropion decreases cocaine choice and increases money choice (Stoops et al., 2012b).

Summary

Cocaine choice can be manipulated in multiple ways, particularly by changing the type of alternative reinforcer available or changing the response cost to earn an alternative reinforcer. Other manipulations, like changing alternative reinforcer magnitude or adding a pharmacological pretreatment, may also change cocaine choice. Overall, the results of these studies indicate that cocaine choice procedures assess underlying behavioral and pharmacological mechanisms that contribute to cocaine use disorder, making these models the gold standard for predicting treatment efficacy in clinical trials.

Ethical Issues of the Drug-Choice for Abstainers and Treatment-Seekers

For ethical reasons, these laboratory drug-choice studies do not enroll treatment-seekers (Fischman and Johanson, 1998), who as a population are typically prohibited from receiving actual drugs. Is such exclusion justified on ethical grounds? From an evaluation of the Belmont Principles of respect for persons, beneficence, and justice in research (see Box 1 for expanded discussion), we suggest that recruiting and studying treatment-seeking individuals probably *does not violate* the first Belmont principle (e.g., in terms of undue coercion that might undermine informed consent) but *may violate* the second Belmont principle depending on the individual's unique circumstances (e.g., in terms of personal, social, and societal costs); furthermore, on the basis of the third Belmont principle, it is important and proper to *recruit from the largest possible population* of treatment-seekers allowable.

Box 1**Ethical Considerations in Recruiting and Enrolling Treatment-Seekers in Drug-Choice Research**

The Belmont Report requires consideration of three basic ethical principles regarding participation in research: respect for persons, beneficence, and justice. The first principle emphasizes people's autonomy but also requires that people with diminished autonomy be protected from harm. It remains a matter of debate whether addicted individuals have autonomy over their drug-taking, invoking the competing ideas of addiction as a disease versus addiction as a lack of self-control or a moral failing (Leshner, 1997). Although this debate lies outside the scope of the current review, the ethical issues it raises are important to consider. The main issue with respect to the first principle seems to be whether researchers should conceive of treatment-seeking addicted individuals as having diminished capacity to consent, perhaps being unduly coerced by the potential for drug administration. If these individuals cannot fully consent, should researchers and Institutional Review Boards (IRBs) require a witness to be present during the consenting process? More stringently, should treatment-seeking addicted individuals simply be excluded from participating in all drug choice research for their own protection?

The second principle emphasizes the importance of securing people's well-being by maximizing benefits and minimizing harms. In recruiting and studying treatment seekers, the possibility for harm is high and enduring – for the individual, for his/her family and social network, and for society (Volkow et al., 2011). Thus, it must be resolved whether the scientific gains associated with studying treatment-seekers (e.g., potentially, though not necessarily, better ability to predict the efficacy of new therapeutic agents in clinical trials, scientific coherence with other studies across populations and species) justifies the potential costs that could ensue if a person who is otherwise succeeding in treatment is reintroduced to drugs and subsequently relapses. For the individual, potential costs are legal (e.g., violations of parole or court-mandated treatment, the possibility of future legal or personal safety concerns related to buying/selling of illegal drugs and/or other crimes related to these transactions), social (e.g., potential alienation of family/friends, possible subversion of a therapeutic community), and financial (e.g., cash expenditures related to buying drugs, possible loss of occupation). For the addicted individual's social network, costs could include profound emotional distress, tangible loss of resources (e.g., related to the addicted individual's incarceration or legal fees), and the potential for increased drug use/relapse for a dependent friend or family member (e.g., if that person is simultaneously attempting to quit or reduce drug use). For society, costs could include increased financial burden on tax payers (e.g., for future incarceration) and increased crime that can threaten public safety.

The third principle emphasizes the need to distribute benefits and risks fairly. If the conclusion were that it is appropriate to recruit treatment-seekers as a population, the next question is whom researchers ought to recruit. It would most likely constitute an ethical violation to recruit individuals mandated to treatment by the legal system; barring fundamental judicial changes, consumption of drugs would likely violate conditions of sentencing. Beyond that consideration, however, the conclusions are less clear. For

example, in service of justice and equal access to research participation, should all voluntary treatment-seekers be permitted to participate in drug choice research? Or, in high deference to the second principle, should further restriction be applied depending on the severity of addiction (e.g., as ascertained by a baseline questionnaire, behavioral test, or neuroimaging procedure), with “highly addicted” people being excluded from participation? Also, note that recruitment restriction is in opposition to scientific integrity: the higher the bar for admittance into a choice study, the lower the generalizability to the larger population of treatment-seeking individuals. The exclusion of treatment seekers raises questions about how well findings from these nonhuman animal and human laboratory experiments translate to treatment-seeking cocaine users; indeed, active users and treatment-seekers may differ on crucial variables including treatment motivation (Levesque et al., 2007), recent drug use that may prime further use (Donny et al., 2004), the expectation of receiving an imminent drug reward (Wilson et al., 2012; Wilson et al., 2013), and/or functional changes attributable to abstinence (Nestor et al., 2011; Moeller et al., 2012b). At the extreme, profoundly non-generalizable results raise the question of whether the resulting knowledge justifies inclusion of treatment seekers in the first place.

Several resolutions appear reasonable; none is perfect, as these three ethical principles come into conflict and need to be balanced against one another. For this reason, each researcher needs to carefully consider the ethical issues associated with a given approach for each specific study. One potential avenue for retaining the active drug-choice model is to study all fully consenting treatment-seekers expressing a desire for voluntary treatment, but immediately prior to their actual intake date (i.e., before they actually begin treatment). In one example of this approach, alcohol-dependent treatment-seekers were referred to formal treatment immediately following a study that provided them access to alcohol (Hammarberg et al., 2009). However, in this approach, researchers would need to consider how a deferral of treatment, however brief, might affect participants’ commitment to the therapeutic process. A second potential avenue for retaining the active drug-choice model is to recruit individuals with a strong desire, but not complete readiness, for treatment (Perkins et al., 2015). However, an interest in quitting and an actual attempt to quit reflect distinct stages of behavior change (Prochaska et al., 1992). A third potential avenue, reflecting the bulk of research conducted in treatment-seekers and abstainers (and reviewed below), is to use choice and decision-making tasks that do not involve the administration of active drugs.

Choice Procedures Suitable for Treatment-Seekers

Given the above constraints, active drug-choice procedures are probably inappropriate for treatment-seekers, warranting the use of alternative procedures. Two such procedures include: (1) basic decision-making tasks that incorporate the option for risk-taking and/or can assess maladaptive or impulsive choice (i.e., on the basis that drug choices in addicted individuals are risky, maladaptive, and/or impulsive), with choices in the aggregate often resulting in the net gain or loss of money or points; and (2) choice/decision-making tasks that involve choice for drug-related stimuli or reinforcers, but that do not administer actual

drugs upon the choice being made (Figure 2 presents representative results from these types of studies).

Non-Drug-Related Choice/Decision Tasks

A large body of literature has examined general (i.e., non-drug-related) decision-making deficits in cocaine addiction, using the Iowa Gambling Task (IGT), delay discounting tasks, Cambridge/Rogers Risk Task, and Balloon Analogue Risk Task (BART) [see also review by (Gowin et al., 2013)]. During the IGT (Bechara et al., 1994), participants repeatedly choose from any of four flipped-over decks of cards, which differentially add or subtract points to the participant's total. Two decks are considered high-risk (i.e., high gains but even higher losses), while the other two decks are low-risk (i.e., small gains but even smaller longer-term losses). Accordingly, maximizing profit (total score) requires that participants learn to select from the low-risk decks consistently. Delay discounting tasks assess behavioral allocation between two different reinforcer amounts or types as a consequence of delay interval. That is, such tasks measure the extent to which participants will forgo an immediate but lesser reward in favor of a more temporally distant but greater reward, with steeper discounting of rewards interpreted as a desire for immediate gratification or a failure to consider the value of future outcomes. During the Cambridge/Rogers Risk Task (Rogers et al., 1999), a token is hidden in one of ten boxes [some blue, some red, with varying ratios (e.g., 9:1, 7:3)]; participants predict whether the token is located in a red or a blue box. After responding, participants wager on the confidence of their choice. The amount the participants wager is either added (following a win) or subtracted (following a loss) to ongoing totals. During the BART, which is a computer-simulated balloon pumping procedure, participants decide how many pumps to administer before cashing out (Lejuez et al., 2002). Pumping a balloon to a larger size increases earnings, but if the balloon pops, participants lose all earnings for the trial.

These decision-making procedures are important to examine in the context of drug-choice procedures because, even though they do not involve choice for non-drug-related stimuli or reinforcers, they nonetheless assess one's capacity for adaptive decision-making. Importantly, these non-drug-related decision procedures are also translatable to preclinical and human laboratory studies, using primary reinforcers such as food pellets or juice to replace money, a secondary reinforcer that only acquires value through experience. For example, rats chronically exposed to cocaine show steeper delay discounting rates than control animals [reviewed in (Bari and Robbins, 2013)]. In addition, prospective work in rats shows that steeper discounting (i.e., more impulsive responding) of food rewards predicts the escalation and reinstatement of subsequent cocaine self-administration (Perry et al., 2005; Perry et al., 2008; Anker et al., 2009). Rats have also been trained on analogues of the IGT (Zeeb et al., 2009; Paine et al., 2013; Di Ciano et al., 2015) and BART (Jentsch et al., 2010).

Iowa Gambling Task (IGT)—Although with exceptions (Vassileva et al., 2007; Woicik et al., 2009; Cunha et al., 2011; Verdejo-Garcia et al., 2013), multiple studies have shown that cocaine abusers select more disadvantageous decks on the IGT than healthy controls and/or recreational users (Verdejo-Garcia et al., 2007a; Verdejo-Garcia et al., 2007b; Kjome

et al., 2010; Balconi et al., 2014; Hulka et al., 2014; Balconi and Finocchiaro, 2015), an effect perhaps accentuated in women (van der Plas et al., 2009; Vassileva et al., 2013). Group differences have also been observed in individuals with polysubstance abuse that included abusers of cocaine (Grant et al., 2000; Bechara et al., 2001; Verdejo-Garcia et al., 2006). Interestingly, and of relevance to choice procedures that examine the choice for real reinforcers, this disadvantageous responding may be normalized with the availability of real (versus hypothetical) monetary rewards (Vadhan et al., 2009).

Research using the IGT to predict or track clinical outcome has yielded mixed results. Some studies have found that baseline IGT performance differentiates relapsers/treatment completers from abstainers/treatment drop-outs (Schmitz et al., 2009; Stevens et al., 2013; Verdejo-Garcia et al., 2014), whereas others have not (Verdejo-Garcia et al., 2012; McHugh et al., 2014). In a study of individuals with cocaine (or methamphetamine) addiction and comorbid bipolar disorder, IGT scores predicted the total number of positive drug urine screens during treatment (Nejtek et al., 2013). Thus, there is some evidence that, similarly to laboratory drug-choice procedures, performance on the IGT may predict clinical outcome.

Delay Discounting Tasks—Cocaine abusers discounted delayed monetary rewards more steeply than controls (Coffey et al., 2003; Kirby and Petry, 2004; Heil et al., 2006; Camchong et al., 2011; Crunelle et al., 2013; Hulka et al., 2014; Wesley et al., 2014; Johnson et al., 2015). Furthermore, dependent users have typically exhibited steeper discounting rates than recreational users (Hulka et al., 2014), though not past dependent users (Heil et al., 2006), providing some evidence that performance on this task differentiates addiction from more casual drug use. Interestingly, cocaine use disorder may be associated with more delay discounting than use disorders of non-psychostimulant drugs such as heroin (Bornovalova et al., 2005), alcohol (Kirby and Petry, 2004), or nicotine (Garcia-Rodriguez et al., 2013). However, cocaine abusers tend not to discount as steeply as pathological gamblers (Albein-Urios et al., 2012; Albein-Urios et al., 2014).

In clinical outcome prediction studies, a financial planning intervention (e.g., making monthly budgets) reduced delay discounting in individuals with histories of problematic cocaine and/or alcohol use, and this reduction in delayed discounting predicted abstinence from cocaine (Black and Rosen, 2011). Another study reported that delay discounting predicted abstinence from cocaine across conditions of an experimental manipulation (a contingency management monetary voucher system for negative urines) (Washio et al., 2011). However, changes in cocaine use over a year did not necessarily correspond with differences in delay discounting (Hulka et al., 2015). Thus, delay discounting may be sufficient, though not necessary, to predict future cocaine use in clinical settings.

Other Tasks—A study of the BART did not find differences in task behavior between cocaine abusers and controls (Gorini et al., 2014). The Cambridge/Rogers Risk Task, along with the IGT (see above), distinguished addicted individuals who dropped out of treatment early versus those who remained in treatment (Stevens et al., 2013). Thus, additional research is required to evaluate the efficacy of these tasks in cocaine addiction.

‘Simulated’ or Hypothetical Drug-Choice Tasks

Compared with these aforementioned non-drug-related decision-making tasks, tasks asking addicted individuals to make a drug-relevant decision are ostensibly closer analogues to laboratory drug-choice tasks. The goal of these tasks is to model choice behavior that occurs when individuals are confronted with the option to use drugs, even if they do not receive an active drug reward following their choice. The consideration of making a drug-relevant decision is critical because drug-related cues may exacerbate deficits in decision-making and delay discounting in addicted individuals (Coffey et al., 2003; Bickel et al., 2011; Wang et al., 2012).

Drug-Picture Choice—These tasks compare the choice for viewing drug-related pictures versus viewing standardized (Lang et al., 2008) pleasant (e.g., smiling babies), unpleasant (e.g., disfigurement), and neutral (e.g., household objects) pictures. First, on a task variant with explicit contingencies, participants choose via continued button pressing between two fully-visible side-by-side images from different picture categories. Although the task does not include a reinforcement schedule (i.e., a certain number of presses is not required to yield the picture “reward”), it does include a “working” (button pressing) component that is required to keep the chosen image on the screen for a longer duration (Moeller et al., 2009). This feature is relevant to the modulating variable of effort needed to receive the drug reward, although the task does not vary the effort needed to obtain one reinforcer versus the other. Second, on a task variant with probabilistic contingencies, participants must learn (and re-learn, once deck identities changes) through task experience where their preferred deck(s) are located. On these tasks, cocaine abusers chose more cocaine-related images than healthy controls (Moeller et al., 2009; Moeller et al., 2010; Moeller et al., 2013b). Importantly, the specific contrast of cocaine versus pleasant picture choice, which mirrors the drug-choice procedures described in the first section of this article, was concurrently and/or prospectively associated with more severe addiction symptoms and/or worse drug-related outcomes (Moeller et al., 2009; Moeller et al., 2010; Moeller et al., 2012a; Moeller et al., 2013a).

Delay Discounting of Drug-Related Rewards—Very little cross-sectional research, and to our knowledge no longitudinal research, has examined discounting of hypothetical drug rewards. The available evidence suggests that cocaine abusers discounted hypothetical cocaine rewards more steeply than money (Coffey et al., 2003; Bickel et al., 2011; Wesley et al., 2014). Future work in this area is warranted, particularly because of the potential translation across species.

Summary

Procedures assessing neutral decision-making and simulated drug-choice, which are safe for use in treatment-seekers, are nonetheless approximations of laboratory drug-choice studies. These procedures can typically differentiate individuals with cocaine use disorder from healthy controls, with some evidence that they can further differentiate active users from non-dependent (e.g., recreational) or recently abstaining users. Evidence that these tasks can predict prospective treatment outcomes, however, is either mixed (non-drug-related decision-making tasks) or as yet inconclusive (i.e., not enough studies have examined

simulated drug-choice or delay discounting of drug rewards for firm conclusions to be drawn). Another concern is that the “rewards” in these procedures in the “simulated” drug-choice tasks are abstract, relying on higher-order cognitive reasoning; for this reason, their translation to preclinical animals is doubtful. In contrast, cognitive decision-making studies, which have been translated in animals, lack the crucial drug-related context (i.e., the choice specifically for drugs). Finally, these studies have not yet shown modulation by some of the variables employed in the animal- and non-treatment-seeker studies (e.g., modulation of drug-choice by alternative reinforcer magnitude or relevant medications). These collective limitations underscore the need for new tasks that capture drug-related decision-making and can be translated across species, but that do not administer actual drugs, which are contraindicated for human treatment-seekers for the ethical reasons outlined above and in Box 1.

Future Considerations

Future research should aim to bridge the divide between preclinical work and clinical work. This kind of integration requires overcoming at least two hurdles. First, thoughtful tasks need to be designed and implemented that can be directly translated from non-human animals all the way to human treatment-seekers, and preferably that are amenable to the same modulatory variables that influence cocaine choice in non-human animals and non-treatment seeking humans. Second, preclinical and clinical studies should aim for better consistency in their measured dependent variables.

One task option for integration across species would be to examine the choice for drug cues that previously predicted drug reward versus choice for cues that previously predicted food reward. In animals, this could take the form of choosing to respond to a lever that previously resulted in the receipt of a drug reward versus a lever that previously resulted in the receipt of a food reward. In humans (both treatment-seekers and non-treatment seekers alike), this could take the form of the choice to hold and/or smell a recently used crack pipe versus a palatable dessert. Although such a design could result in extinction in some individuals – indeed, responding to drug-associated stimuli is difficult to maintain in the absence of subsequent drug delivery (Banks et al., 2011, 2013b) – this kind of procedure nonetheless could be informative for a single critical testing session. Such an approach also could potentially be useful in identifying individual differences in the vigor of responding to drug cues. For example, an exciting line of animal research is revealing that, compared with “goal trackers,” “sign trackers” attribute high incentive salience not just to the drug itself, but to the cues predicting drug reward (Flagel et al., 2011; Robinson et al., 2014). If the “sign tracker” versus “goal tracker” distinction is corroborated in humans (which, to our knowledge, remains an open question), one might expect that “sign trackers” will maintain drug-cue responding without drug delivery for longer time intervals, with possible implications for an enhanced propensity to cue-induced relapse outside the laboratory.

Researchers also need to address the issue of inconsistency in measured dependent variables. In particular, whereas self-administration studies focus almost exclusively on drug-maintained behavior, clinical trials focus on both drug-maintained behavior and the role of conditioned/discriminative stimuli including the elicitation of subjective craving. Although

craving is an introspective and subjective state that has no direct parallel in nonhuman animal studies, neuroimaging procedures have the potential to assess bottom-up measures of cue-reactivity across species. For example, one could assess dopamine release in the striatum to conditioned drug cues, using microdialysis in animals (Ito et al., 2000) and positron emission tomography in humans (Volkow et al., 2006). Indeed, for the latter, the magnitude of changes in dopamine neurotransmission during cocaine-cue exposure correlated with self-reported cocaine craving (Volkow et al., 2006). Incorporating stimuli studies, especially into preclinical work, may enhance translation of results to human clinical trials, which often include basal or cue-induced craving as a dependent variable of interest. One could even combine these two procedures, examining an individual's responsiveness to drug cues that no longer predict reward while simultaneously incorporating tools of neuroimaging to assess objective measures of drug "craving."

Conclusion

In this mini-review, we summarized procedures of cocaine choice in cocaine addiction, in combination with some of the established variables that modulate such choice, both in humans and non-human animals. Although these procedures, which offer addicted individuals the opportunity to self-administer actual drugs versus receiving other valuable reinforcers, have high face and predictive validity, for ethical reasons these models cannot be readily deployed in individuals seeking treatment or attempting to abstain. The currently available options for use in treatment-seekers, including neutral decision-making and/or simulated drug-choice procedures, are highly informative for understanding neuropsychological deficits in drug addiction, yet they remain suboptimal for the measurement of actual drug-relevant decision-making. This translational gap presents an exciting opportunity to develop novel drug-choice tasks for use in multiple dependent populations that can objectively, yet noninvasively model and predict real-world drug seeking and clinical outcomes. More effective translation of results from preclinical work to clinical work can facilitate the development of novel medications and/or behavioral interventions that, once they reach clinical trials, may have a better chance of success.

Acknowledgments

This study was supported by grants from the National Institute on Drug Abuse (to SJM: K01DA037452 and R21DA040046; to WWS: R01DA036553, R21DA034095, and R21DA035376). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

- Aigner TG, Balster RL. Choice behavior in rhesus monkeys: Cocaine versus food. *Science*. 1978; 201:534–535. [PubMed: 96531]
- Albein-Urios N, Martinez-Gonzalez JM, Lozano O, Verdejo-Garcia A. Monetary delay discounting in gambling and cocaine dependence with personality comorbidities. *Addict Behav*. 2014; 39:1658–1662. [PubMed: 25047890]
- Albein-Urios N, Martinez-Gonzalez JM, Lozano O, Clark L, Verdejo-Garcia A. Comparison of impulsivity and working memory in cocaine addiction and pathological gambling: Implications for cocaine-induced neurotoxicity. *Drug Alcohol Depend*. 2012; 126:1–6. [PubMed: 22475814]

- Anker JJ, Perry JL, Gliddon LA, Carroll ME. Impulsivity predicts the escalation of cocaine self-administration in rats. *Pharmacol Biochem Behav.* 2009; 93:343–348. [PubMed: 19490925]
- Association AP. Diagnostic and statistical manual of mental disorders. 5. Washington, DC: Author; 2013.
- Balconi M, Finocchiaro R. Decisional impairments in cocaine addiction, reward bias, and cortical oscillation “unbalance”. *Neuropsychiatr Dis Treat.* 2015; 11:777–786. [PubMed: 25848274]
- Balconi M, Finocchiaro R, Campanella S. Reward sensitivity, decisional bias, and metacognitive deficits in cocaine drug addiction. *J Addict Med.* 2014; 8:399–406. [PubMed: 25303980]
- Banks ML, Negus SS. Preclinical Determinants of Drug Choice under Concurrent Schedules of Drug Self-Administration. *Adv Pharmacol Sci.* 2012; 2012:281768. [PubMed: 23243420]
- Banks ML, Blough BE, Negus SS. Effects of monoamine releasers with varying selectivity for releasing dopamine/norepinephrine versus serotonin on choice between cocaine and food in rhesus monkeys. *Behav Pharmacol.* 2011; 22:824–836. [PubMed: 22015808]
- Banks ML, Blough BE, Negus SS. Effects of 14-day treatment with the schedule III anorectic phendimetrazine on choice between cocaine and food in rhesus monkeys. *Drug Alcohol Depend.* 2013a; 131:204–213. [PubMed: 23726979]
- Banks ML, Blough BE, Negus SS. Interaction between behavioral and pharmacological treatment strategies to decrease cocaine choice in rhesus monkeys. *Neuropsychopharmacology.* 2013b; 38:395–404. [PubMed: 22968813]
- Banks ML, Hutsell BA, Schwientek KL, Negus SS. Use of Preclinical Drug vs. Food Choice Procedures to Evaluate Candidate Medications for Cocaine Addiction. *Curr Treat Options Psychiatry.* 2015a; 2:136–150. [PubMed: 26009706]
- Banks ML, Blough BE, Fennell TR, Snyder RW, Negus SS. Effects of phendimetrazine treatment on cocaine vs food choice and extended-access cocaine consumption in rhesus monkeys. *Neuropsychopharmacology.* 2013c; 38:2698–2707. [PubMed: 23893022]
- Banks ML, Hutsell BA, Blough BE, Poklis JL, Negus SS. Preclinical Assessment of Lisdexamfetamine as an Agonist Medication Candidate for Cocaine Addiction: Effects in Rhesus Monkeys Trained to Discriminate Cocaine or to Self-Administer Cocaine in a Cocaine Versus Food Choice Procedure. *Int J Neuropsychopharmacol.* 2015b; 18.10.1093/ijnp/pyv009
- Bari A, Robbins TW. Inhibition and impulsivity: behavioral and neural basis of response control. *Prog Neurobiol.* 2013; 108:44–79. [PubMed: 23856628]
- Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition.* 1994; 50:7–15. [PubMed: 8039375]
- Bechara A, Dolan S, Denburg N, Hinds A, Anderson SW, Nathan PE. Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. *Neuropsychologia.* 2001; 39:376–389. [PubMed: 11164876]
- Bickel WK, Landes RD, Christensen DR, Jackson L, Jones BA, Kurth-Nelson Z, Redish AD. Single- and cross-commodity discounting among cocaine addicts: the commodity and its temporal location determine discounting rate. *Psychopharmacology (Berl).* 2011; 217:177–187. [PubMed: 21487658]
- Black AC, Rosen MI. A money management-based substance use treatment increases valuation of future rewards. *Addict Behav.* 2011; 36:125–128. [PubMed: 20826055]
- Bornoalova MA, Daughters SB, Hernandez GD, Richards JB, Lejuez CW. Differences in impulsivity and risk-taking propensity between primary users of crack cocaine and primary users of heroin in a residential substance-use program. *Exp Clin Psychopharmacol.* 2005; 13:311–318. [PubMed: 16366761]
- Brutcher RE, Nader MA. Effects of quetiapine treatment on cocaine self-administration and behavioral indices of sleep in adult rhesus monkeys. *Psychopharmacology (Berl).* 2015; 232:411–420. [PubMed: 25030802]
- Camchong J, MacDonald AW 3rd, Nelson B, Bell C, Mueller BA, Specker S, Lim KO. Frontal hyperconnectivity related to discounting and reversal learning in cocaine subjects. *Biol Psychiatry.* 2011; 69:1117–1123. [PubMed: 21371689]

- Cantin L, Lenoir M, Augier E, Vanhille N, Dubreucq S, Serre F, Vouillac C, Ahmed SH. Cocaine is low on the value ladder of rats: possible evidence for resilience to addiction. *PLoS One*. 2010; 5:e11592. [PubMed: 20676364]
- Coffey SF, Gudleski GD, Saladin ME, Brady KT. Impulsivity and rapid discounting of delayed hypothetical rewards in cocaine-dependent individuals. *Exp Clin Psychopharmacol*. 2003; 11:18–25. [PubMed: 12622340]
- Collins ED, Vosberg SK, Ward AS, Haney M, Foltin RW. The effects of acute pretreatment with high-dose memantine on the cardiovascular and behavioral effects of cocaine in humans. *Exp Clin Psychopharmacol*. 2007; 15:228–237. [PubMed: 17563209]
- Collins SL, Levin FR, Foltin RW, Kleber HD, Evans SM. Response to cocaine, alone and in combination with methylphenidate, in cocaine abusers with ADHD. *Drug Alcohol Depend*. 2006; 82:158–167. [PubMed: 16213109]
- Crunelle CL, Veltman DJ, van Emmerik-van Oortmerssen K, Booij J, van den Brink W. Impulsivity in adult ADHD patients with and without cocaine dependence. *Drug Alcohol Depend*. 2013; 129:18–24. [PubMed: 23026814]
- Cunha PJ, Bechara A, de Andrade AG, Nicastrì S. Decision-making deficits linked to real-life social dysfunction in crack cocaine-dependent individuals. *Am J Addict*. 2011; 20:78–86. [PubMed: 21175924]
- Czoty PW, McCabe C, Nader MA. Assessment of the relative reinforcing strength of cocaine in socially housed monkeys using a choice procedure. *J Pharmacol Exp Ther*. 2005; 312:96–102. [PubMed: 15340005]
- Di Ciano P, Pushparaj A, Kim A, Hatch J, Masood T, Ramzi A, Khaled MA, Boileau I, Winstanley CA, Le Foll B. The Impact of Selective Dopamine D2, D3 and D4 Ligands on the Rat Gambling Task. *PLoS One*. 2015; 10:e0136267. [PubMed: 26352802]
- Donny EC, Bigelow GE, Walsh SL. Choosing to take cocaine in the human laboratory: Effects of cocaine dose, inter-choice interval, and magnitude of alternative reinforcement. *Drug Alcohol Depend*. 2003; 69:289–301. [PubMed: 12633915]
- Donny EC, Bigelow GE, Walsh SL. Assessing the initiation of cocaine self-administration in humans during abstinence: effects of dose, alternative reinforcement, and priming. *Psychopharmacology (Berl)*. 2004; 172:316–323. [PubMed: 14647955]
- Festinger DS, Dugosh KL, Kirby KC, Seymour BL. Contingency management for cocaine treatment: cash vs. vouchers. *J Subst Abuse Treat*. 2014; 47:168–174. [PubMed: 24746956]
- Fischman MW, Johanson CE. Ethical and practical issues involved in behavioral pharmacology research that administers drugs of abuse to human volunteers. *Behav Pharmacol*. 1998; 9:479–498. [PubMed: 9862072]
- Fischman MW, Foltin RW, Nestadt G, Pearlson GD. Effects of desipramine maintenance on cocaine self-administration by humans. *J Pharmacol Exp Ther*. 1990; 253:760–770. [PubMed: 2338656]
- Flagel SB, Clark JJ, Robinson TE, Mayo L, Czuj A, Willuhn I, Akers CA, Clinton SM, Phillips PE, Akil H. A selective role for dopamine in stimulus-reward learning. *Nature*. 2011; 469:53–57. [PubMed: 21150898]
- Foltin RW. Food and cocaine self-administration by baboons: effects of alternatives. *J Exp Anal Behav*. 1999; 72:215–234. [PubMed: 10503299]
- Foltin RW, Fischman MW. Effects of methadone or buprenorphine maintenance on the subjective and reinforcing effects of intravenous cocaine in humans. *J Pharmacol Exp Ther*. 1996; 278:1153–1164. [PubMed: 8819498]
- Foltin RW, Haney M, Rubin E, Reed SC, Vadhan N, Balter R, Evans SM. Development of translational preclinical models in substance abuse: Effects of cocaine administration on cocaine choice in humans and non-human primates. *Pharmacol Biochem Behav*. 2015; 134:12–21. [PubMed: 25933796]
- Garcia-Rodriguez O, Secades-Villa R, Weidberg S, Yoon JH. A systematic assessment of delay discounting in relation to cocaine and nicotine dependence. *Behav Processes*. 2013; 99:100–105. [PubMed: 23872502]
- Garcia-Rodriguez O, Secades-Villa R, Higgins ST, Fernandez-Hermida JR, Carballo JL, Errasti Perez JM, Al-halabi Diaz S. Effects of voucher-based intervention on abstinence and retention in an

- outpatient treatment for cocaine addiction: a randomized controlled trial. *Exp Clin Psychopharmacol.* 2009; 17:131–138. [PubMed: 19586227]
- Gorini A, Lucchiari C, Russell-Edu W, Pravettoni G. Modulation of risky choices in recently abstinent dependent cocaine users: a transcranial direct-current stimulation study. *Front Hum Neurosci.* 2014; 8:661. [PubMed: 25221496]
- Gowin JL, Mackey S, Paulus MP. Altered risk-related processing in substance users: imbalance of pain and gain. *Drug Alcohol Depend.* 2013; 132:13–21. [PubMed: 23623507]
- Grabowski J, Rhoades H, Schmitz J, Stotts A, Daruzska LA, Creson D, Moeller FG. Dextroamphetamine for cocaine-dependence treatment: a double-blind randomized clinical trial. *J Clin Psychopharmacol.* 2001; 21:522–526. [PubMed: 11593078]
- Grant S, Contoreggi C, London ED. Drug abusers show impaired performance in a laboratory test of decision making. *Neuropsychologia.* 2000; 38:1180–1187. [PubMed: 10838152]
- Greenwald MK, Lundahl LH, Steinmiller CL. Sustained release d-amphetamine reduces cocaine but not 'speedball'-seeking in buprenorphine-maintained volunteers: a test of dual-agonist pharmacotherapy for cocaine/heroin polydrug abusers. *Neuropsychopharmacology.* 2010; 35:2624–2637. [PubMed: 20881947]
- Greenwald MK, Ledgerwood DM, Lundahl LH, Steinmiller CL. Effect of experimental analogs of contingency management treatment on cocaine seeking behavior. *Drug Alcohol Depend.* 2014; 139:164–168. [PubMed: 24685561]
- Hammarberg A, Jayaram-Lindstrom N, Beck O, Franck J, Reid MS. The effects of acamprosate on alcohol-cue reactivity and alcohol priming in dependent patients: a randomized controlled trial. *Psychopharmacology (Berl).* 2009; 205:53–62. [PubMed: 19319508]
- Haney M, Foltin RW, Fischman MW. Effects of pergolide on intravenous cocaine self-administration in men and women. *Psychopharmacology (Berl).* 1998; 137:15–24. [PubMed: 9631952]
- Haney M, Hart CL, Foltin RW. Effects of baclofen on cocaine self-administration: opioid- and nonopioid-dependent volunteers. *Neuropsychopharmacology.* 2006; 31:1814–1821. [PubMed: 16407903]
- Haney M, Rubin E, Foltin RW. Aripiprazole maintenance increases smoked cocaine self-administration in humans. *Psychopharmacology (Berl).* 2011; 216:379–387. [PubMed: 21373790]
- Haney M, Ward AS, Foltin RW, Fischman MW. Effects of ecopipam, a selective dopamine D1 antagonist, on smoked cocaine self-administration by humans. *Psychopharmacology (Berl).* 2001; 155:330–337. [PubMed: 11441422]
- Hart CL, Haney M, Foltin RW, Fischman MW. Alternative reinforcers differentially modify cocaine self-administration by humans. *Behav Pharmacol.* 2000; 11:87–91. [PubMed: 10821213]
- Hart CL, Ward AS, Collins ED, Haney M, Foltin RW. Gabapentin maintenance decreases smoked cocaine-related subjective effects, but not self-administration by humans. *Drug Alcohol Depend.* 2004; 73:279–287. [PubMed: 15036550]
- Hart CL, Haney M, Collins ED, Rubin E, Foltin RW. Smoked cocaine self-administration by humans is not reduced by large gabapentin maintenance doses. *Drug Alcohol Depend.* 2007a; 86:274–277. [PubMed: 16879931]
- Hart CL, Haney M, Vosburg SK, Rubin E, Foltin RW. Gabapentin does not reduce smoked cocaine self-administration: employment of a novel self-administration procedure. *Behav Pharmacol.* 2007b; 18:71–75. [PubMed: 17218799]
- Hart CL, Haney M, Vosburg SK, Rubin E, Foltin RW. Smoked cocaine self-administration is decreased by modafinil. *Neuropsychopharmacology.* 2008; 33:761–768. [PubMed: 17568397]
- Heil SH, Johnson MW, Higgins ST, Bickel WK. Delay discounting in currently using and currently abstinent cocaine-dependent outpatients and non-drug-using matched controls. *Addict Behav.* 2006; 31:1290–1294. [PubMed: 16236455]
- Higgins ST, Bickel WK, Hughes JR. Influence of an alternative reinforcer on human cocaine self-administration. *Life Sci.* 1994; 55:179–187. [PubMed: 8007760]
- Higgins ST, Roll JM, Bickel WK. Alcohol pretreatment increases preference for cocaine over monetary reinforcement. *Psychopharmacology.* 1996; 123:1–8. [PubMed: 8741948]
- Higgins ST, Heil SH, Lussier JP. Clinical implications of reinforcement as a determinant of substance use disorders. *Annu Rev Psychol.* 2004; 55:431–461. [PubMed: 14744222]

- Higgins ST, Heil SH, Dantona R, Donham R, Matthews M, Badger GJ. Effects of varying the monetary value of voucher-based incentives on abstinence achieved during and following treatment among cocaine-dependent outpatients. *Addiction*. 2007; 102:271–281. [PubMed: 17222282]
- Howell LL, Negus SS. Monoamine transporter inhibitors and substrates as treatments for stimulant abuse. *Adv Pharmacol*. 2014; 69:129–176. [PubMed: 24484977]
- Hulka LM, Vonmoos M, Preller KH, Baumgartner MR, Seifritz E, Gamma A, Quednow BB. Changes in cocaine consumption are associated with fluctuations in self-reported impulsivity and gambling decision-making. *Psychol Med*. 2015:1–14.
- Hulka LM, Eisenegger C, Preller KH, Vonmoos M, Jenni D, Bendrick K, Baumgartner MR, Seifritz E, Quednow BB. Altered social and non-social decision-making in recreational and dependent cocaine users. *Psychol Med*. 2014; 44:1015–1028. [PubMed: 23870112]
- Huskinson SL, Woolverton WL, Green L, Myerson J, Freeman KB. Delay discounting of food by rhesus monkeys: Cocaine and food choice in isomorphic and allomorphic situations. *Exp Clin Psychopharmacol*. 2015; 23:184–193. [PubMed: 25938515]
- Ito R, Dalley JW, Howes SR, Robbins TW, Everitt BJ. Dissociation in conditioned dopamine release in the nucleus accumbens core and shell in response to cocaine cues and during cocaine-seeking behavior in rats. *J Neurosci*. 2000; 20:7489–7495. [PubMed: 11007908]
- Jentsch JD, Woods JA, Groman SM, Seu E. Behavioral characteristics and neural mechanisms mediating performance in a rodent version of the Balloon Analog Risk Task. *Neuropsychopharmacology*. 2010; 35:1797–1806. [PubMed: 20375994]
- John WS, Banala AK, Newman AH, Nader MA. Effects of buspirone and the dopamine D3 receptor compound PG619 on cocaine and methamphetamine self-administration in rhesus monkeys using a food-drug choice paradigm. *Psychopharmacology (Berl)*. 2015; 232:1279–1289. [PubMed: 25327444]
- Johnson MW, Johnson PS, Herrmann ES, Sweeney MM. Delay and probability discounting of sexual and monetary outcomes in individuals with cocaine use disorders and matched controls. *PLoS One*. 2015; 10:e0128641. [PubMed: 26017273]
- Kirby KC, Marlowe DB, Festinger DS, Lamb RJ, Platt JJ. Schedule of voucher delivery influences initiation of cocaine abstinence. *J Consult Clin Psychol*. 1998; 66:761–767. [PubMed: 9803694]
- Kirby KN, Petry NM. Heroin and cocaine abusers have higher discount rates for delayed rewards than alcoholics or non-drug-using controls. *Addiction*. 2004; 99:461–471. [PubMed: 15049746]
- Kjome KL, Lane SD, Schmitz JM, Green C, Ma L, Prasla I, Swann AC, Moeller FG. Relationship between impulsivity and decision making in cocaine dependence. *Psychiatry Res*. 2010; 178:299–304. [PubMed: 20478631]
- Lang, PJ.; Bradley, MM.; Cuthbert, BN. Technical Report A-8. Gainesville, FL: University of Florida; 2008. International Affective Picture System (IAPS): Affective ratings of pictures and instruction manual.
- Lejuez CW, Read JP, Kahler CW, Richards JB, Ramsey SE, Stuart GL, Strong DR, Brown RA. Evaluation of a behavioral measure of risk taking: the Balloon Analogue Risk Task (BART). *J Exp Psychol Appl*. 2002; 8:75–84. [PubMed: 12075692]
- LeSage MG. Toward a nonhuman model of contingency management: effects of reinforcing abstinence from nicotine self-administration in rats with an alternative nondrug reinforcer. *Psychopharmacology (Berl)*. 2009; 203:13–22. [PubMed: 18946663]
- Leshner AI. Addiction is a brain disease, and it matters. *Science*. 1997; 278:45–47. [PubMed: 9311924]
- Levesque CS, Williams GC, Elliot D, Pickering MA, Bodenhamer B, Finley PJ. Validating the theoretical structure of the treatment self-regulation questionnaire (TSRQ) across three different health behaviors. *Health Educ Res*. 2007; 22:691–702. [PubMed: 17138613]
- Lofwall MR, Nuzzo PA, Campbell C, Walsh SL. Aripiprazole effects on self-administration and pharmacodynamics of intravenous cocaine and cigarette smoking in humans. *Exp Clin Psychopharmacol*. 2014; 22:238–247. [PubMed: 24467369]

- McHugh MJ, Demers CH, Salmeron BJ, Devous MD Sr, Stein EA, Adinoff B. Cortico-amygdala coupling as a marker of early relapse risk in cocaine-addicted individuals. *Front Psychiatry*. 2014; 5:16. [PubMed: 24578695]
- Moeller SJ, Hajcak G, Parvaz MA, Dunning JP, Volkow ND, Goldstein RZ. Psychophysiological prediction of choice: relevance to insight and drug addiction. *Brain*. 2012a; 135:3481–3494. [PubMed: 23148349]
- Moeller SJ, Beebe-Wang N, Woicik PA, Konova AB, Maloney T, Goldstein RZ. Choice to view cocaine images predicts concurrent and prospective drug use in cocaine addiction. *Drug Alcohol Depend*. 2013a; 130:178–185. [PubMed: 23218913]
- Moeller SJ, Parvaz MA, Shumay E, Beebe-Wang N, Konova AB, Alia-Klein N, Volkow ND, Goldstein RZ. Gene x Abstinence Effects on Drug Cue Reactivity in Addiction: Multimodal Evidence. *J Neurosci*. 2013b; 33:10027–10036. [PubMed: 23761898]
- Moeller SJ, Maloney T, Parvaz MA, Alia-Klein N, Woicik PA, Telang F, Wang GJ, Volkow ND, Goldstein RZ. Impaired insight in cocaine addiction: laboratory evidence and effects on cocaine-seeking behaviour. *Brain*. 2010; 133:1484–1493. [PubMed: 20395264]
- Moeller SJ, Maloney T, Parvaz MA, Dunning JP, Alia-Klein N, Woicik PA, Hajcak G, Telang F, Wang GJ, Volkow ND, Goldstein RZ. Enhanced choice for viewing cocaine pictures in cocaine addiction. *Biol Psychiatry*. 2009; 66:169–176. [PubMed: 19358975]
- Moeller SJ, Tomasi D, Woicik PA, Maloney T, Alia-Klein N, Honorio J, Telang F, Wang GJ, Wang R, Sinha R, Carise D, Astone-Twerell J, Bolger J, Volkow ND, Goldstein RZ. Enhanced midbrain response at 6-month follow-up in cocaine addiction, association with reduced drug-related choice. *Addict Biol*. 2012b; 17:1013–1025. [PubMed: 22458423]
- Nader MA, Woolverton WL. Effects of increasing the magnitude of an alternative reinforcer on drug choice in a discrete-trials choice procedure. *Psychopharmacology (Berl)*. 1991; 105:169–174. [PubMed: 1796123]
- Nader MA, Woolverton WL. Effects of increasing response requirement on choice between cocaine and food in rhesus monkeys. *Psychopharmacology (Berl)*. 1992; 108:295–300. [PubMed: 1523280]
- Negus SS. Rapid assessment of choice between cocaine and food in rhesus monkeys: effects of environmental manipulations and treatment with d-amphetamine and flupenthixol. *Neuropsychopharmacology*. 2003; 28:919–931. [PubMed: 12637948]
- Negus SS, Mello NK. Effects of chronic methadone treatment on cocaine- and food-maintained responding under second-order, progressive-ratio and concurrent-choice schedules in rhesus monkeys. *Drug Alcohol Depend*. 2004; 74:297–309. [PubMed: 15194208]
- Nejtek VA, Kaiser KA, Zhang B, Djokovic M. Iowa Gambling Task scores predict future drug use in bipolar disorder outpatients with stimulant dependence. *Psychiatry Res*. 2013; 210:871–879. [PubMed: 24012163]
- Nestor L, McCabe E, Jones J, Clancy L, Garavan H. Differences in “bottom-up” and “top-down” neural activity in current and former cigarette smokers: Evidence for neural substrates which may promote nicotine abstinence through increased cognitive control. *Neuroimage*. 2011; 56:2258–2275. [PubMed: 21440645]
- Paine TA, Asinof SK, Diehl GW, Frackman A, Leffler J. Medial prefrontal cortex lesions impair decision-making on a rodent gambling task: reversal by D1 receptor antagonist administration. *Behav Brain Res*. 2013; 243:247–254. [PubMed: 23354057]
- Perkins KA, Karelitz JL, Michael VC, Fromuth M, Conklin CA, Chengappa KN, Hope C, Lerman C. Initial Evaluation of Fenofibrate for Efficacy in Aiding Smoking Abstinence. *Nicotine Tob Res*. 2015 pii: ntv085.
- Perry JL, Nelson SE, Carroll ME. Impulsive choice as a predictor of acquisition of IV cocaine self-administration and reinstatement of cocaine-seeking behavior in male and female rats. *Exp Clin Psychopharmacol*. 2008; 16:165–177. [PubMed: 18489020]
- Perry JL, Larson EB, German JP, Madden GJ, Carroll ME. Impulsivity (delay discounting) as a predictor of acquisition of IV cocaine self-administration in female rats. *Psychopharmacology (Berl)*. 2005; 178:193–201. [PubMed: 15338104]

- Petry NM, Alessi SM, Hanson T, Sierra S. Randomized trial of contingent prizes versus vouchers in cocaine-using methadone patients. *J Consult Clin Psychol.* 2007; 75:983–991. [PubMed: 18085914]
- Petry NM, Alessi SM, Barry D, Carroll KM. Standard magnitude prize reinforcers can be as efficacious as larger magnitude reinforcers in cocaine-dependent methadone patients. *J Consult Clin Psychol.* 2015; 83:464–472. [PubMed: 25198284]
- Poling J, Oliveto A, Petry N, Sofuoglu M, Gonsai K, Gonzalez G, Martell B, Kosten TR. Six-month trial of bupropion with contingency management for cocaine dependence in a methadone-maintained population. *Arch Gen Psychiatry.* 2006; 63:219–228. [PubMed: 16461866]
- Preston KL, Umbricht A, Wong CJ, Epstein DH. Shaping cocaine abstinence by successive approximation. *J Consult Clin Psychol.* 2001; 69:643–654. [PubMed: 11550730]
- Prochaska JO, DiClemente CC, Norcross JC. In search of how people change. Applications to addictive behaviors. *Am Psychol.* 1992; 47:1102–1114. [PubMed: 1329589]
- Robinson TE, Yager LM, Cogan ES, Saunders BT. On the motivational properties of reward cues: Individual differences. *Neuropharmacology.* 2014; 76(Pt B):450–459. [PubMed: 23748094]
- Rogers RD, Owen AM, Middleton HC, Williams EJ, Pickard JD, Sahakian BJ, Robbins TW. Choosing between small, likely rewards and large, unlikely rewards activates inferior and orbital prefrontal cortex. *J Neurosci.* 1999; 19:9029–9038. [PubMed: 10516320]
- Rush CR, Stoops WW. Agonist replacement therapy for cocaine dependence: a translational review. *Future Med Chem.* 2012; 4:245–265. [PubMed: 22300101]
- Schmitz JM, Mooney ME, Green CE, Lane SD, Steinberg JL, Swann AC, Moeller FG. Baseline neurocognitive profiles differentiate abstainers and non-abstainers in a cocaine clinical trial. *J Addict Dis.* 2009; 28:250–257. [PubMed: 20155594]
- Stevens L, Betanzos-Espinosa P, Crunelle CL, Vergara-Moragues E, Roeyers H, Lozano O, Dom G, Gonzalez-Saiz F, Vanderplassen W, Verdejo-Garcia A, Perez-Garcia M. Disadvantageous Decision-Making as a Predictor of Drop-Out among Cocaine-Dependent Individuals in Long-Term Residential Treatment. *Front Psychiatry.* 2013; 4:149. [PubMed: 24298260]
- Stoops WW, Lile JA, Rush CR. Monetary alternative reinforcers more effectively decrease intranasal cocaine choice than food alternative reinforcers. *Pharmacol Biochem Beh.* 2010; 95:187–191.
- Stoops WW, Lile JA, Glaser PE, Hays LR, Rush CR. Alternative reinforcer response cost impacts cocaine choice in humans. *Prog Neuropsychopharmacol Biol Psychiatry.* 2012a; 36:189–193. [PubMed: 22015480]
- Stoops WW, Lile JA, Glaser PE, Hays LR, Rush CR. Influence of acute bupropion pre-treatment on the effects of intranasal cocaine. *Addiction.* 2012b; 107:1140–1147. [PubMed: 22168398]
- Thomsen M, Fulton BS, Caine SB. Acute and chronic effects of the M1/M4-preferring muscarinic agonist xanomeline on cocaine vs. food choice in rats. *Psychopharmacology (Berl).* 2014; 231:469–479. [PubMed: 23995301]
- Thomsen M, Barrett AC, Negus SS, Caine SB. Cocaine versus food choice procedure in rats: environmental manipulations and effects of amphetamine. *J Exp Anal Behav.* 2013; 99:211–233. [PubMed: 23319458]
- Thomsen M, Fink-Jensen A, Woldbye DP, Wortwein G, Sager TN, Holm R, Pepe LM, Caine SB. Effects of acute and chronic aripiprazole treatment on choice between cocaine self-administration and food under a concurrent schedule of reinforcement in rats. *Psychopharmacology (Berl).* 2008; 201:43–53. [PubMed: 18612628]
- Vadhan NP, Hart CL, Haney M, van Gorp WG, Foltin RW. Decision-making in long-term cocaine users: Effects of a cash monetary contingency on Gambling task performance. *Drug Alcohol Depend.* 2009; 102:95–101. [PubMed: 19346083]
- van der Plas EA, Crone EA, van den Wildenberg WP, Tranel D, Bechara A. Executive control deficits in substance-dependent individuals: a comparison of alcohol, cocaine, and methamphetamine and of men and women. *J Clin Exp Neuropsychol.* 2009; 31:706–719. [PubMed: 19037812]
- Vandrey R, Bigelow GE, Stitzer ML. Contingency management in cocaine abusers: a dose-effect comparison of goods-based versus cash-based incentives. *Exp Clin Psychopharmacol.* 2007; 15:338–343. [PubMed: 17696680]

- Vassileva J, Gonzalez R, Bechara A, Martin EM. Are all drug addicts impulsive? Effects of antisociality and extent of multidrug use on cognitive and motor impulsivity. *Addict Behav.* 2007; 32:3071–3076. [PubMed: 17507173]
- Vassileva J, Ahn WY, Weber KM, Busemeyer JR, Stout JC, Gonzalez R, Cohen MH. Computational modeling reveals distinct effects of HIV and history of drug use on decision-making processes in women. *PLoS One.* 2013; 8:e68962. [PubMed: 23950880]
- Verdejo-Garcia A, Vilar-Lopez R, Perez-Garcia M, Podell K, Goldberg E. Altered adaptive but not veridical decision-making in substance dependent individuals. *J Int Neuropsychol Soc.* 2006; 12:90–99. [PubMed: 16433948]
- Verdejo-Garcia A, Benbrook A, Funderburk F, David P, Cadet JL, Bolla KI. The differential relationship between cocaine use and marijuana use on decision-making performance over repeat testing with the Iowa Gambling Task. *Drug Alcohol Depend.* 2007a; 90:2–11. [PubMed: 17367959]
- Verdejo-Garcia A, Albein-Urios N, Molina E, Ching-Lopez A, Martinez-Gonzalez JM, Gutierrez B. A MAOA gene*cocaine severity interaction on impulsivity and neuropsychological measures of orbitofrontal dysfunction: preliminary results. *Drug Alcohol Depend.* 2013; 133:287–290. [PubMed: 23755928]
- Verdejo-Garcia A, Albein-Urios N, Martinez-Gonzalez JM, Civit E, de la Torre R, Lozano O. Decision-making impairment predicts 3-month hair-indexed cocaine relapse. *Psychopharmacology (Berl).* 2014; 231:4179–4187. [PubMed: 24728653]
- Verdejo-Garcia A, Betanzos-Espinosa P, Lozano OM, Vergara-Moragues E, Gonzalez-Saiz F, Fernandez-Calderon F, Bilbao-Acedos I, Perez-Garcia M. Self-regulation and treatment retention in cocaine dependent individuals: a longitudinal study. *Drug Alcohol Depend.* 2012; 122:142–148. [PubMed: 22018602]
- Verdejo-Garcia AJ, Perales JC, Perez-Garcia M. Cognitive impulsivity in cocaine and heroin polysubstance abusers. *Addict Behav.* 2007b; 32:950–966. [PubMed: 16876962]
- Verrico CD, Haile CN, Mahoney JJ 3rd, Thompson-Lake DG, Newton TF, De La Garza R 2nd. Treatment with modafinil and escitalopram, alone and in combination, on cocaine-induced effects: a randomized, double blind, placebo-controlled human laboratory study. *Drug Alcohol Depend.* 2014; 141:72–78. [PubMed: 24928479]
- Volkow ND, Baler RD, Goldstein RZ. Addiction: pulling at the neural threads of social behaviors. *Neuron.* 2011; 69:599–602. [PubMed: 21338873]
- Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Childress AR, Jayne M, Ma Y, Wong C. Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. *J Neurosci.* 2006; 26:6583–6588. [PubMed: 16775146]
- Vosburg SK, Haney M, Rubin E, Foltin RW. Using a novel alternative to drug choice in a human laboratory model of a cocaine binge: a game of chance. *Drug Alcohol Depend.* 2010; 110:144–150. [PubMed: 20346597]
- Walsh SL, Geter-Douglas B, Strain EC, Bigelow GE. Enadoline and butorphanol: evaluation of kappa-agonists on cocaine pharmacodynamics and cocaine self-administration in humans. *J Pharmacol Exp Ther.* 2001; 299:147–158. [PubMed: 11561074]
- Wang GB, Zhang XL, Zhao LY, Sun LL, Wu P, Lu L, Shi J. Drug-related cues exacerbate decision making and increase craving in heroin addicts at different abstinence times. *Psychopharmacology (Berl).* 2012; 221:701–708. [PubMed: 22207241]
- Washio Y, Higgins ST, Heil SH, McKerchar TL, Badger GJ, Skelly JM, Dantona RL. Delay discounting is associated with treatment response among cocaine-dependent outpatients. *Exp Clin Psychopharmacol.* 2011; 19:243–248. [PubMed: 21517195]
- Wesley MJ, Lohrenz T, Koffarnus MN, McClure SM, De La Garza R 2nd, Salas R, Thompson-Lake DG, Newton TF, Bickel WK, Montague PR. Choosing Money over Drugs: The Neural Underpinnings of Difficult Choice in Chronic Cocaine Users. *J Addict.* 2014; 2014:189853. [PubMed: 25197609]
- Wilson SJ, Sayette MA, Fiez JA. Quitting-unmotivated and quitting-motivated cigarette smokers exhibit different patterns of cue-elicited brain activation when anticipating an opportunity to smoke. *J Abnorm Psychol.* 2012; 121:198–211. [PubMed: 21859165]

- Wilson SJ, Creswell KG, Sayette MA, Fiez JA. Ambivalence about smoking and cue-elicited neural activity in quitting-motivated smokers faced with an opportunity to smoke. *Addict Behav.* 2013; 38:1541–1549. [PubMed: 22483100]
- Woicik PA, Moeller SJ, Alia-Klein N, Maloney T, Lukasik TM, Yeliosof O, Wang GJ, Volkow ND, Goldstein RZ. The neuropsychology of cocaine addiction: Recent cocaine use masks impairment. *Neuropsychopharmacology.* 2009; 34:1112–1122. [PubMed: 18496524]
- Woolverton WL, English JA. Further analysis of choice between cocaine and food using the unit price model of behavioral economics. *Drug Alcohol Depend.* 1997; 49:71–78. [PubMed: 9476702]
- Zeeb FD, Robbins TW, Winstanley CA. Serotonergic and dopaminergic modulation of gambling behavior as assessed using a novel rat gambling task. *Neuropsychopharmacology.* 2009; 34:2329–2343. [PubMed: 19536111]

Highlights

- Here, we review research on cocaine-choice behavior (versus other reinforcers).
- Modulatory variables that influence cocaine choice are examined and evaluated.
- However, ethics preclude use of these procedures in treatment-seekers.
- Alternative procedures suitable for treatment-seekers are thus considered.
- We conclude by suggesting opportunities for new translational work.

Figure 1.

Example drug choice results, indicating parallel effects in human users (non-treatment-seeking) and non-human animals. Specifically, increasing the cost (effort expenditure) to receive an alternative reinforcer increases cocaine choice in (A) rhesus monkeys and (B) humans. Panel (A) is adapted from (Banks et al., 2013b), with permission from Nature Publishing Group. Panel (B) is adapted from (Stoops et al., 2012a), with permission from Elsevier.

Figure 2.

Alternative procedures safe for use in treatment-seekers, showing group differences between cocaine abusers and healthy controls. Compared with healthy controls, cocaine abusers have (A–B) steeper delay discounting functions, measured with a delay discounting procedure; and (C–D) greater cocaine-picture choice, measured with a ‘simulated’ cocaine choice procedure (no drug is administered). Panels (A–B) are adapted from (Wesley et al., 2014), under the Creative Commons Attribution License. Panels (C–D) are adapted from (Moeller et al., 2009), with permission from Elsevier.