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Review

Validation crisis in animal models of drug addiction: Beyond non-disordered drug use toward drug addiction

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ABSTRACT

In standard drug self-administration settings, animals have no choice than drug use. As a result, serious doubt exists about the interpretation of drug use in experimental animals. Is it symptomatic of an underlying addiction state or merely an expectable response to lack of choice? This incertitude in turn casts a shadow over many behavioral and neurobiological changes that have been well documented in animals following extended drug self-administration. Do they reflect pathological dysfunctions or normal neurobiological adaptations? Here I address these questions by focusing on intravenous cocaine self-administration in the rat as a paradigm example. Overall, available evidence shows that when a valuable behavioral option, even a biologically or physiologically inessential one, is made available during access to cocaine self-administration, most rats readily abstain from cocaine use in favor of the alternative reward regardless of the amount of past cocaine use. Only a small minority of rats continue to self-administer the drug despite the opportunity of making a different choice. This pattern of results (i.e., abstinence in most rats; cocaine preference in few rats) maps well onto what is currently known about the epidemiology of human cocaine addiction. It is thus possible that the minority of cocaine-preferring rats would be homologous to the minority of human cocaine users with a diagnosis of addiction while the remaining majority of abstinent rats would be resilient to cocaine addiction. Choice could represent an objective method of selection of addicted animals for future research on the neurobiological dysfunctions that are hypothesized to underlie cocaine addiction. Other competing interpretations of the same pattern of results are also discussed at the end of this review.

Contents

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The goal of this review is to provide a novel perspective on experimental modeling of human drug addiction in laboratory animals. The review mainly focuses on intravenous cocaine self-administration in the rat – which is by far the most frequently used animal species in experimental addiction research (see Section 2.1 below) – but its main conclusions should also hopefully be relevant to other drugs of abuse, routes of self-administration and animal species. Overall I propose that offering a choice during access to drug self-administration could uniquely allow one to identify and select drug-addicted rats among those that self-administer drugs merely by default of other options. Though the use of a choice-based approach in future experimental research on drug addiction is strongly advocated here, it must nevertheless be acknowledged that depending on the research question, there is ample room for other types of self-administration approaches.

1. Labeling, defining and modeling cocaine addiction

1.1. Dependence or addiction: words of choice and choice of words

In current official diagnostic nomenclatures (e.g., 4th version of the American Psychiatric Association Diagnostic and Statistical Manual [DSM] of Mental Disorders), the term "dependence" is preferred to the word "addiction" to label the same behavioral disorder (see Section 1.3 below). However, several authors have recently called for a reversal of preference—a call that will be apparently followed in the forthcoming 5th version of the DSM (Miller and Holden, 2010). As put bluntly by O'Brien et al. (2006), the choice of the term "dependence" over the term "addiction was "a serious mistake" which caused "confusion among clinicians" with negative consequences to the patients. Using a more historical approach, Maddux and Desmond (2000) have also cogently argued for the replacement of the term "dependence" by the term "addiction". According to them, the preference for the term "dependence" is no longer justified for three main reasons: (1) "addiction more clearly suggests a behavioral disorder than does dependence"; (2) "addiction is less likely to be confused with physical dependence" and other forms of dependence; and finally, (3) the original reason in favor of the use of dependence is no longer valid, that is, there is today no risk of confusion between habituation (or accommodation) and addiction. In this review, preference is also exclusively given to the word "addiction". However, as will be explained later in the end of this review, one of the disadvantages of this choice is that addiction is widely used across different scientific disciplines with competing, even opposite, meanings (see Section 4.1 below).

1.2. Rates of cocaine use and addiction

Cocaine is currently the second most used illegal drug in the European Union, after cannabis, and its use is increasing (EMCDDA, 2009). About 13 millions adults aged 15–64 have used cocaine at least once in their life. It is further estimated that 4.5 millions used cocaine in the last year. In France, for instance, lifetime prevalence of cocaine use among schooled adolescents has increased over the past 10 years (EMCDDA, 2009). Fortunately, most cocaine users eventually quit cocaine use to engage in other, more socially valued occupations and activities. Only a minority of cocaine users escalate their drug consumption and eventually transition to a state of addiction. In the US, it is estimated that less than 10% of cocaine users develop a DSM-based diagnosis of cocaine addiction within 2 years of use (Reboussin and Anthony, 2006) which roughly correspond to an annual incidence of 0.5 million addicted individuals. The extrapolation of this rate of addiction to Europe predicts that about one additional million Europeans will become addicted to cocaine in the near future. The relatively high rate of cocaine addiction in both the US and in Europe probably explains why it now represents one of the paragons of addiction.

1.3. Cocaine addiction from a rational choice perspective

The most perplexing aspect of cocaine addiction from a rational choice perspective is that addicted individuals apparently behave against their best interests and judgments (Bechara, 2005; Paulus, 2007; Redish et al., 2008; Heyman, 2009). They seek and take more cocaine at the expense of other activities or occupations (i.e., DSM-IV criteria 4, 5 and 6) that are generally, though not necessarily, more rewarding in the long-term and that are otherwise accessible. The latter condition is significant because it allows, at least in principle, the distinction of addicted individuals from other drug users who take cocaine by default of other valuable choices (Alexander, 2008). In cocaine addiction, the progressive neglect of alternative behaviors in favor of drug procurement and consumption eventually results in important opportunity costs (e.g., poor education; job loss; marital dissolution; legal sanction) that should normally motivate abstinence from cocaine use. However, even in the face of such costs, many cocaine addicts continue to seek and to take cocaine. Everything happens as if they had lost the ability to make free, rational and voluntary choice. One of the critical challenges for the neuroscience of cocaine addiction is to identify the underlying neurobiological dysfunctions of this apparent loss of ability to make rational and voluntary choices (Koob and Le Moal, 2006).

1.4. Modeling cocaine addiction in experimental animals: doubts and pitfalls

Human brain imaging studies have consistently found cocaine addiction-related metabolic changes in several cortical brain regions involved in normal choice-making processes, notably in the orbitofrontal cortex—a phylogenetically conserved prefrontal cortical region that is also dysfunctional in other compulsive disorders (Volkow et al., 1991, 2005; Volkow and Fowler, 2000). However, because of limitations in the spatial and temporal resolution of brain imaging technologies and in the correlational design of human studies, the origin, nature and causal effect of these cortical changes remain poorly understood. As a result, there is still little hope to use this neurobiological knowledge to inform the diagnosis, prognosis and/or treatment of drug addiction (Hyman, 2007a). Further scientific advancement in our understanding of the neurobiological basis of cocaine addiction will thus continue to require parallel experimental research on laboratory animals which permit invasive neurobiological investigations not feasible in humans. Paradoxically, however, though cocaine addiction has long been conceptualized in reference to rational choice, little neurobiological research on animals has so far examined drug self-administration in a context of choice (Ahmed, 2005). As will be shown below, in

standard experimental settings, animals have free access to cocaine self-administration with no or little valuable alternative actions or activities (Ahmed, 2005). As a result, serious doubt exists about the interpretation of cocaine use in animals. Is it symptomatic of an underlying addiction state or merely an expectable response to the lack of choice? This incertitude in turn casts a shadow over many behavioral and neurobiological changes that have been documented in animals following cocaine self-administration. Do they reflect pathological dysfunctions or normal neurobiological adaptations to rewarding experiences and behaviors? For instance, over the past 20 years, the neurobiology of drug sensitization – which is by itself a fascinating drug-induced long-lasting neuroplastic process – has been intensely studied from the circuit level down to the molecular intracellular levels (Vanderschuren and Kalivas, 2000; Hyman et al., 2006; Hyman, 2007b; Robinson and Berridge, 2008). However, there is still little certitude about the role of drug sensitization in the pathophysiology of cocaine addiction. Similarly, escalation of drug use and its reinstatement after a period of extinction or incubation are now well-documented behavioral phenomena (Epstein et al., 2006; Ahmed, in press). However, their interpretation as behavioral signs of addiction in animals, though relevant and plausible, remains nevertheless uncertain because these behaviors occur in experimental settings devoid of other behavioral options than drug use. It is predicted that taking full measure of this situation could lead to a validation crisis that in turn will lead to a change in the way animal models of addiction are conceived and validated.

As it turns out, a recent series of experiments from our laboratory found that when offered a choice between cocaine and a nondrug alternative that is otherwise inessential for growth, survival and reproduction (i.e., drinking water sweetened with saccharin), the large majority of rats readily stop taking cocaine (Lenoir et al., 2007; Cantin et al., 2009). This abstinence from cocaine self-administration was observed even following extended drug use and escalation of consumption. In fact, no matter how heavy was past cocaine self-administration, only a small minority of animals (i.e., about 10%, see Section 3.4 below) continued to self-administer cocaine despite the opportunity of making another valuable choice. This pattern of results maps well onto the known epidemiology of human cocaine addiction, as summarized above, and is consistent with a very recent laboratory study in humans showing that when given a choice between money and cocaine, cocaine users with a diagnosis of addiction choose more cocaine than non-addicted long-term users (Walsh et al., 2010). Thus, it is possible that the minority of cocaine-preferring rats would be homologous to the minority of humans with a diagnosis of cocaine addiction while the majority of abstinent rats would be resilient to cocaine addiction (Cantin et al., 2009). Resilience to drug addiction has long been suspected in humans (Harding, 1983; Zinberg, 1984; Shiffman, 1989; Robins, 1993; Shewan and Dalgarno, 2005; Warburton et al., 2005) but could not be firmly established, mostly because it is difficult to control retrospectively for differences in drug self-exposure and/or availability in humans. Comparing the minority of cocaine-preferring rats with the resilient majority could thus bring unprecedented insights into the neurobiological dysfunctions that are hypothesized to underlie cocaine addiction. Other possible interpretations of the same results exist, however, and will be also discussed at the end of this review.

2. Deconstruction of animal models of cocaine addiction

The goal of this section is to present a brief historical overview of scientific research on intravenous drug self-administration in experimental animals. This overview is not intended to be exhaustive or representative. Its goal is 2-fold: to praise the earlier researchers who have founded the field of animal drug self-administration and to reveal that since its birth, this field has regrettably largely neglected the role of choice in studying and analyzing cocaine addiction in experimental animals.

2.1. A brief history of experimental research on animal drug self-administration

About 50 years ago, back into the twentieth century, James Weeks (1962) – an American experimental pharmacologist working at Upjohn Company, Kalamazoo, Michigan – published a 2-page article in *Science* entitled "Experimental morphine addiction" describing, in his words, a "method for automatic intravenous injections in unrestrained rats." Adult female, albino rats were reported to learn a novel, lever-press response to self-administer morphine "through a polyethylene cannula passed down the jugular vein into the right heart" (p. 143). This work established for the first time that "the rate of self-injection varied inversely with dose" of morphine (p. 143), suggesting that rats were regulating opiate intake. At about the same time, Thompson and Schuster (1964) reported similar findings in adult, male rhesus monkeys that were physically restrained. Interestingly, in those two seminal series of experiments, animals were first made physically dependent on morphine before being allowed to self-administer the drug. Presumably, the rationale for doing this was that at the time, animals, unlike humans, were not expected to spontaneously take morphine (Spragg, 1940; Coppock et al., 1956). Or, put more technically, morphine was not expected to act as a positive reinforcer in nonhuman animals.

The subsequent history is well known. Few years later, morphine and other drugs of abuse, including cocaine, were definitively shown to possess genuine positive reinforcing effects in animals [for reviews contemporary to this period, see (Schuster and Thompson, 1969; Thompson and Pickens, 1970; Goldberg, 1976; Johanson, 1978; Pickens et al., 1978; Spealman and Goldberg, 1978; Yanagita, 1978, 1980; Griffiths et al., 1980; Schuster and Johanson, 1981; Woods, 1983)]. In one of the most enduring contribution to the field, Deneau et al. (1969) reported that initially drug-naïve rhesus macaques "self-administered those drugs which man abuses severely" (p. 46). As formulated by the authors, "animals preferred to exist under the influence of the drug's effects" (p. 46). This seminal study also showed the existence of a significant degree of individual variation in the propensity to self-administer certain drugs of abuse that could be reduced by drug pre-exposure. It also established that the day-to-day pattern of drug self-administration can considerably vary as a function of the self-administered drug. For instance, morphine maintained a stable, nycthemeral pattern of drug self-administration while cocaine induced an "erratic increase [in intake] culminating in convulsions and death within 30 days." All these seminal findings have been reproduced many times, with some interesting variation across species, strains, sexes, age groups and individual animals. It is now almost a platitude to state that most drugs abused by humans can act as positive reinforcers in nonhuman animals (Schuster and Thompson, 1969; Thompson and Pickens, 1970; Goldberg, 1976; Johanson, 1978; Pickens et al., 1978; Spealman and Goldberg, 1978; Yanagita, 1978; Griffiths et al., 1980; Yanagita, 1980; Schuster and Johanson, 1981; Woods, 1983; Young and Herling, 1986; Wise, 1987; Yokel, 1987; Katz, 1989, 1990; Roberts and Goeders, 1989; Brady, 1991; Campbell and Carroll, 2000; Lynch and Carroll, 2001).

Of historical note, it is intriguing to mention that 1 year before the seminal publication of James Weeks, Robert Clark, Charles Schuster and Joseph Brady (1961) published a 2-page article, also in *Science*, showing that water-deprived rhesus monkeys readily learn to press a lever "to drink" saline through an intravenous indwelling catheter in the internal jugular vein. Importantly, monkeys readily

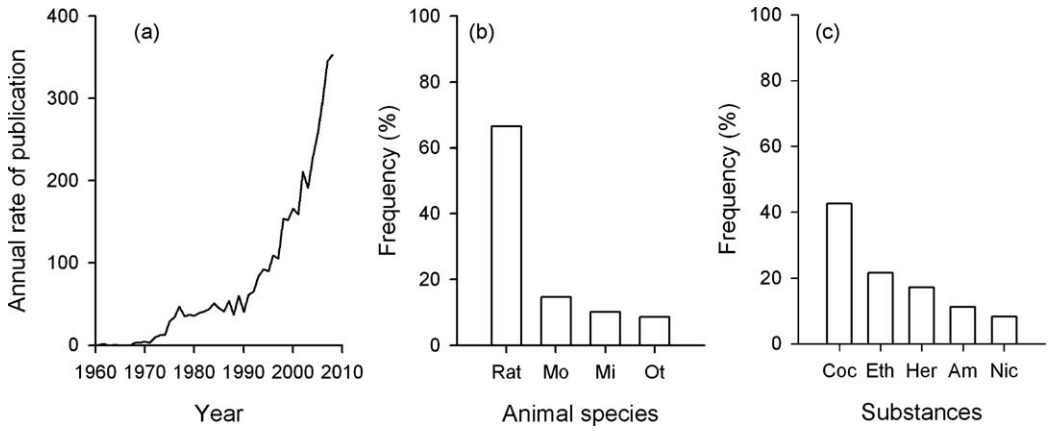

Fig. 1. Scientific research output on animal drug self-administration. (a) Annual rate of publication of journal articles in the PubMed Central (PMC) database that contain in the abstract or the title words that begin with the following root terms: "self-administ" (e.g., self-administration, self-administering, self-administered) OR "self-inject" OR "self-infus". (b) Frequency (in percent of total) of journal articles in the PMC database that used rat/s, monkey/s (Mo), mouse/mice (Mi) or other (Ot) animals as experimental subjects for drug self-administration. (c) Frequency (in percent of total) of journal articles in the PMC database that tested cocaine (Coc), alcohol/ethanol (Eth), heroin/morphine (Her), amphetamine/methamphetamine (Am) or nicotine (Nic) for self-administration. All searches in the PMC database were limited to research on animals published in primary journal articles. Review articles were excluded.

stopped to lever-press for intravenous saline when provided with *ad libitum* oral water. As summarized by the authors, lever-pressing for saline was shown to "be conditioned, extinguished, reconditioned, and brought under stimulus control" (p. 1829). Though this article has fallen into almost complete oblivion soon after its publication (it has been cited only 4 times since 1961), it nevertheless provided an initial, valid demonstration that intravenous self-administration of a substance (i.e., rate of responding above initial operant level) is not, in itself, sufficient evidence for inference of an addiction state.

The discovery that most drugs of abuse can be spontaneously self-administered by laboratory animals marked the birth of modern research on drug addiction. Since then, the annual rate of publication of research on animal drug self-administration has kept increasing exponentially, from 1 publication in 1962 to more than 350 in 2008 (Fig. 1a). By far, most of this research has been conducted in rats, as estimated from primary journal articles in the PubMed Central database (Fig. 1b). Specifically, about 66% of published research on animal drug self-administration used rats as experimental subjects, compared to about 14% and 10% that used monkeys and mice, respectively. Furthermore, the most studied drug is, by a large margin, cocaine which accounts for more than 40% of published research on drug self-administration (Fig. 1c). Thus, overall, most experimental research on animal models of drug addiction was done in rats self-administering cocaine which partly explains the focus on rat cocaine self-administration in the present review.

Over the past 20 years, the different stages of cocaine self-administration, including acquisition, maintenance, escalation and reinstatement after extinction, have been studied extensively both at a behavioral and neurobiological level. Of particular interest, most of these stages were recently shown to be influenced by the length of exposure to cocaine self-administration. This research has been recently reviewed exhaustively elsewhere (Koob et al., 2004; Ahmed, in press). Overall, there is now good evidence showing that following extended access to cocaine self-administration, rats are more likely to escalate drug consumption (Ahmed and Koob, 1998), to work harder (Paterson and Markou, 2003) and to take more risk to seek and/or to obtain cocaine (Vanderschuren and Everitt, 2004). In addition, there is now strong evidence that the ability of cocaine to reinstate cocaine seeking after extinction – a behavioral phenomenon that has been considerably studied over the past 10 years as a model of relapse or craving (Shalev et al., 2002; Epstein et al., 2006; Kalivas, 2009) – is increased following extensive cocaine self-administration (Mantsch et al., 2004; Ahmed and Cador, 2006; Kippin et al., 2006; Knackstedt and Kalivas, 2007). Altogether, these behavioral effects strongly suggest that the reinforcing and/or incentive value of cocaine increases with extended drug use. However, as will be discussed later, without a reference to other rewarding activities, the relative magnitude of this increase in cocaine value remains poorly understood. Specifically, it is unknown whether it would be sufficient to set in motion the downward spiral of cocaine addiction, with increasing drug use over and above other nondrug-related activities.

2.2. Cocaine self-administration in animals: compulsion or expectable response to lack of choice

Animal cocaine self-administration is often presented as one of the best animal model in psychiatry. No doubt this model has good face, predictive and constructive validities for non-addictive drug use in humans. The key issue, however, is whether and to which extent one can extend these validities to cocaine addiction. One potential obstacle to this extension of validity is that since the seminal work by Weeks, rats have been tested for drug self-administration in experimental settings devoid of other opportunities which sharply contrast with the richness of possibilities or opportunities open to human drug users in the real world (Schwartz, 2004; Alexander, 2008). More specifically, in standard operant settings, alternative options to drug use exist but have either little intrinsic value (e.g., pressing an inactive lever, an action with no programmed effect) or are contextually weakly motivated (e.g., sleeping during the active period; grooming or exploration in a confined, bare and familiar environment) (Herrnstein, 1970). In other words, though non-null, the degree of freedom of experimental animals during drug access is nevertheless abnormally restricted. Facing such a low degree of freedom, it is perhaps no wonder why most rats self-administer most drugs that humans self-administer, including cocaine. The major challenge for experimental addiction research, however, is to determine among rats that self-administer cocaine which and how many can be considered addicted to cocaine and which and how many take cocaine merely by default of other valuable options.

3. Having the choice during access to cocaine self-administration

Previous research in rats has shown that concurrent access to a natural rewarding activity during access to cocaine can indeed

influence cocaine self-administration (Campbell and Carroll, 2000; Ahmed, 2005). For instance, in a seminal series of experiments, Marilyn Carroll and colleagues showed that concurrent access to water sweetened with saccharin and glucose reduces the proportion of rats that eventually acquire cocaine self-administration and can also decrease the maintenance of cocaine self-administration after acquisition (Carroll et al., 1989; Carroll and Lac, 1993). Similarly, over the past 30 years, research in nonhuman primates choosing between food and cocaine (or heroin) has provided some of the best evidence for the powerful role of alternative reinforcers in drug self-administration (Griffiths et al., 1975; Wurster et al., 1977; Aigner and Balster, 1978; Woolverton and Balster, 1979; Elsmore et al., 1980; Griffiths et al., 1981; Nader and Woolverton, 1991; Paronis et al., 2002; Negus, 2003; Gasior et al., 2004). Notably, in one particularly significant study, food-restricted monkeys were allowed to choose between different doses of cocaine and different number of food pellets. It was found that most monkeys (i.e., 3 out of a total of 4) preferred the highest amount of food to the maximal dose of cocaine (Nader and Woolverton, 1991). This previous research is clearly consistent with the view advanced here that in standard experimental settings, some animals may take cocaine merely by default of other rewarding activities. By following up on this seminal research, we were recently able to increase its generality and validity across a wide range of factors and conditions (Lenoir and Ahmed, 2007, 2008; Lenoir et al., 2007; Cantin et al., 2009). The next section summarizes this more recent research.

3.1. Introducing choice during access to cocaine: a methodological prolegomenon

We first developed and validated a discrete-trials choice procedure in drug-naïve animals to assess the distribution of initial preferences (Lenoir et al., 2007). This procedure was then tested in rats following extended cocaine self-administration and escalation of consumption (Sections 3.3 and 3.4 below). Briefly, rats were allowed to choose during several consecutive daily sessions between two alternative actions: pressing on one of two levers to obtain one intravenous bolus of cocaine (0.25 mg or about 0.75 mg/kg) or on the other lever to drink water sweetened with saccharin (0.2%). Each daily choice session consisted of several discrete trials, spaced by 10 min, and divided into two successive phases, sampling and choice (Lenoir et al., 2007). During sampling, each lever was presented alternatively, thereby allowing rats to separately perform each action and thus to learn its specific consequence before making their choice. Immediately upon action completion, the lever retracted until the next sampling trial. During choice, the cocaine- and saccharin-associated levers were presented simultaneously and rats were free to respond on either lever to obtain the corresponding reward. Immediately upon action selection, the two levers retracted simultaneously until the next trial. As a result, selecting one reward excluded the alternative reward, thereby allowing rats to express their preference (i.e., choice was mutually exclusive or either/or). Or in terms of opportunity costs, the cost of selecting one reward corresponded to the loss of opportunity of obtaining the other reward.

Several additional features of this procedure need to be explicitly stated at the outset to avoid subsequent confusion and/or misinterpretation. First, the dose of cocaine tested in the series of experiments summarized below is a moderate to high dose that has been extensively used in previous research in rats (Ahmed and Koob, 1998; Ahmed et al., 2002; Ahmed and Cador, 2006). As will be described below, however, similar choice outcomes were also obtained with higher doses of cocaine. Second, saccharin is a rewarding artificial sweetener in both rats and humans that is otherwise inessential for growth, survival and reproduction (Smith and Sclafani, 2002). The rewarding efficacy of sweet taste can be modulated, but does not require, any prior food or fluid restriction (Collier and Novell, 1967; Berridge, 1996; Chandrashekar et al., 2006; de Araujo et al., 2008). Importantly, consistent with previous research (Smith and Sclafani, 2002), we recently found that when given a choice, rats largely prefer sucrose (5–20%) – a natural sugar – over the highest concentration of saccharin tested in the choice procedure (0.2%) (Eric Augier and Serge Ahmed, unpublished results). Thus, saccharin should not be considered necessarily as a particularly high reward, contrary to what we initially hypothesized (Lenoir et al., 2007). Third, during choice, rats were neither food or water-deprived. Thus, hunger or thirst is not a significant explanandum in this specific procedure. Fourth, choice trials were limited to few per day (i.e., 8) to prevent the eventual confounding effect of differential reward satiation on assessment of reward value (Elsmore et al., 1980). Fifth, each type of reward was available in a closed economy, meaning that except during testing, rats had no other opportunity to access either type of reward (Hursh, 1980; Collier and Johnson, 1997). Finally, the minimum inter-trial interval was set at 10 min to reduce the direct anorexigenic effect of cocaine accumulation on ingestive behavior—an effect that would obviously promote cocaine choice, as suggested previously (Aigner and Balster, 1978). Note that trial spacing in itself is not the cause of rats' relative lack of interest in cocaine; when no other choice is available, rats self-administer cocaine with forced inter-dose intervals of 10 min or even longer (Fitch and Roberts, 1993; Lenoir et al., 2007).

3.2. Most animals stop cocaine use when given a choice

Naïve rats were trained under 3 reward conditions. The first two reward conditions were control conditions aimed at separately measuring the effectiveness of each type of reward. In those control conditions, only responding on one lever was rewarded by the corresponding reward (cocaine or saccharin); responding on the other lever remained unrewarded. In the third, experimental condition, responding on one lever was rewarded by cocaine and responding on the alternate lever was rewarded by saccharin (for additional details, see (Lenoir et al., 2007)). As expected, when only one response was rewarded by either cocaine or saccharin, rats developed a significant preference for it and ignored the non-rewarded lever (Fig. 2a). This result demonstrates that when presented alone, each type of reward effectively and selectively reinforced and maintained responding. This result confirms previous research showing that when no other valuable choice is available, rats do self-administer cocaine. Surprisingly, however, the rate of preference acquisition (i.e., number of days to reach a stable preference) was slower when behavior was rewarded with cocaine than with sweetened water (Fig. 2b), suggesting that the former reward is probably less efficacious than the latter. This interpretation is confirmed by the outcome of the experimental condition. When responding on either lever was rewarded, rats developed a rapid and marked preference for sweetened water and almost completely ignored cocaine (Fig. 2a and b), a finding that is consistent with previous research in rats with concurrent access to cocaine and saccharin (Carroll et al., 1989; Carroll and Lac, 1993). Interestingly, this preference was acquired and persisted despite near maximal sampling of the cocaine lever (Lenoir et al., 2007). Finally, after stabilization of preference, the latency to choose cocaine was greater than the latency to choose sweet water (Fig. 2c). Since the latency to respond is generally inversely related to the magnitude of the upcoming reward, this outcome provides additional, independent confirmation that the reward value of cocaine is weaker than that of sweetened water in rats.

When offered a choice between either taking an intravenous bolus of cocaine or drinking water sweetened with saccharin, rats took cocaine almost exclusively during the sampling period

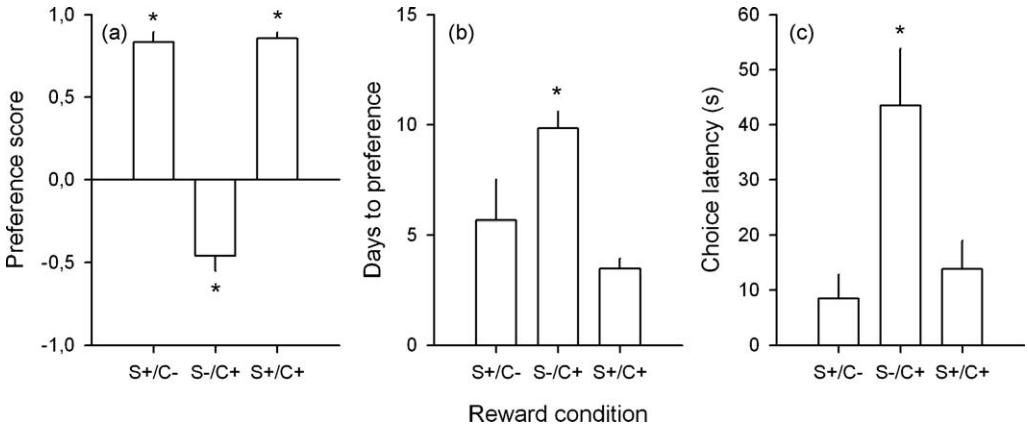

Fig. 2. The effects of choice on cocaine self-administration. (a) Choice (mean ± SEM) between the saccharin-associated lever (S) and the cocaine-associated lever (C) across reward conditions (S+/C−: only responses on lever S are rewarded; S−/C+: only responses on lever C are rewarded; S+/C+: responses on both levers are rewarded). Preference scores were normalized as described previously (Lenoir et al., 2007). The horizontal dotted line at 0 indicates the indifference level. Scores above 0 indicate a preference for sweet water while values below 0 indicate a preference for cocaine. *Different from the indifference level ($P < 0.05$). (b) Number of days (mean ± SEM) before stabilization of preference scores (i.e., at least 3 consecutive sessions of stable preference). *Different from the other two reward conditions. (c) Latency (mean ± SEM) of choice-making in seconds ($P < 0.05$). *Different from the other two reward conditions ($P < 0.05$). Adapted from Lenoir et al. (2007).

(i.e., when no alternative was available). Though very low (i.e., maximum fixed at 2 doses), cocaine sampling was nevertheless sufficient to induce a robust sensitization to the psychomotor effects of cocaine that was indistinguishable from that seen in control rats that only had access to cocaine during choice and that eventually preferred to respond on the cocaine lever (Lenoir et al., 2007). Cocaine sensitization is a well-documented behavioral change associated with persistent alterations in brain glutamate and dopamine synapses (Vanderschuren and Kalivas, 2000; Hyman et al., 2006) and is generally associated with an increase in the incentive or motivational value of the drug, as measured using different reward assessment methods (Robinson and Berridge, 2008). However, though sensitization undeniably occurred in rats that had the choice between cocaine and saccharin, it was apparently not sufficient to override initial saccharin preference and promote cocaine preference (Lenoir et al., 2007).

Several limiting factors could be advanced to explain the unexpected preference for sweet water in cocaine-sensitized rats. First, it could be argued that the dose of cocaine, though behaviorally effective, was nevertheless not sufficiently high to compete with the reward value of the alternative option. To address this important issue, once rats had acquired a stable preference for water sweetened with saccharin, they were tested with increasing doses of cocaine. Cocaine doses were increased from 0.25 up to the sub-convulsive dose of 1.5 mg per infusion. Surprisingly, though increasing doses of cocaine produced a clear dose-dependent increase in forward locomotion (Fig. 3a), rats nevertheless continued to prefer sweetened water over cocaine (Fig. 3b). This outcome suggests that the maximal reward value of cocaine is bounded and is apparently lower than that of water sweetened with 0.2% of saccharin. More quantitative information about the relative value of cocaine is given below.

Second, it could be argued that once acquired, preference for sweet taste would persist because of some sort of behavioral inertia, unrelated to the difference in value between the two rewards. Specifically, since rats rapidly acquired an almost exclusive preference for sweet water, they would subsequently have little experience with cocaine and thus little opportunity to change their preference in its favor. To address this issue, rats were first trained in the choice procedure under the following reward condition: responding on one lever was rewarded by cocaine while responding on the other lever was not rewarded by the alternative reward. Once they developed a stable preference for the cocaine lever, they were then offered the choice between cocaine and sweetened water. Rats rapidly shifted their preference away from cocaine toward sweetened water, suggesting that behavioral inertia is unlikely a significant factor in the persistence of sweet preference (Fig. 4a). To further address this issue, other rats were

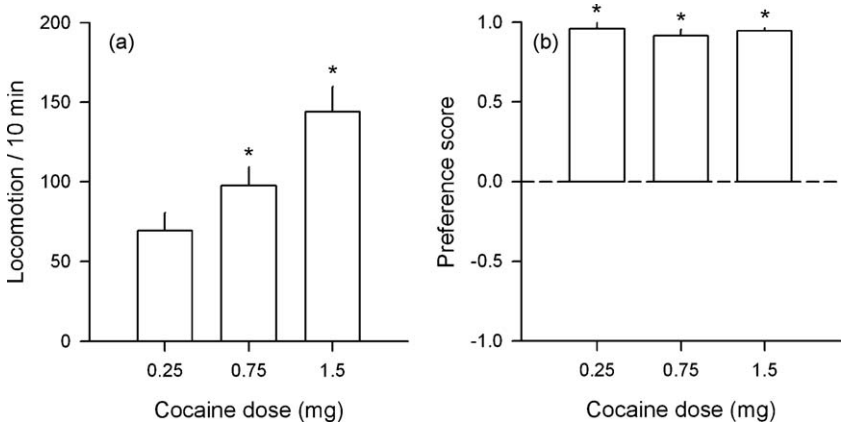

Fig. 3. The effects of cocaine dose on choice. (a) Cocaine-induced locomotion as a function of dose. Locomotion (i.e., mean number of cage crossings ± SEM) was measured during 10 min after the first cocaine self-injection of the first day of each dose substitution. *Different from the lowest dose ($P < 0.05$). (b) Choice between cocaine and sweet water (mean ± SEM) as a function of dose. *Different from the indifference level ($P < 0.05$). Adapted from Lenoir et al. (2007).

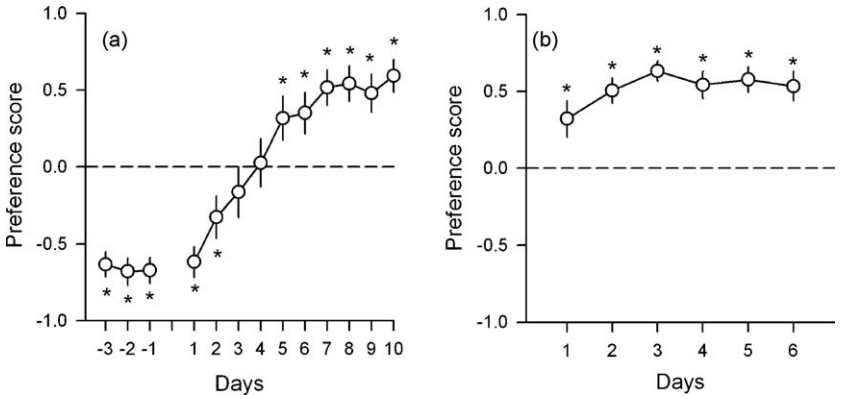

Fig. 4. Sweet preference is not due to behavioral inertia. (a) Reversal of preference in rats which had first acquired a preference for lever C under the S−/C+ condition. The first 3 days (−3 to −1) correspond to baseline choice under the S−/C+ condition. The next 10 days correspond to choice after the shift to the S+/C+ reward condition. Adapted from Lenoir et al. (2007). (b) Immediate expression of sweet preference in rats previously trained to stably self-administer cocaine and sweet water on alternate days under a continuous reinforcement schedule. *Different from the indifference level ($P < 0.05$). Adapted from Cantin et al. (2009).

first trained on alternate days to lever-press to self-administer either cocaine or saccharin under a fixed-ratio 1 (FR1) schedule of reinforcement. The number of rewards was limited to 30 per session to equal the number of pairings of each lever with its corresponding reward. After acquisition and stabilization of cocaine and saccharin self-administration, rats were then trained in the choice procedure. Surprisingly, prior FR1 training accelerated, rather than retarded, the expression of sweet preference (Cantin et al., 2009). In fact, rats presented a significant preference for sweetened water as early as the first day of choice testing; the magnitude of this preference increased thereafter (Fig. 4b). This outcome shows that during FR1 training, rats had independently attributed a lower value to the cocaine lever compared to the saccharin lever, a process that does not support a role for behavioral inertia in sweet preference. Finally, to definitively rule out behavioral inertia, rats were trained in a modified choice procedure. Briefly, the sampling period was replaced by 1 h of continuous access to cocaine under a FR1 schedule. Thus, everyday before choice testing, rats were allowed to self-administer cocaine continuously. If behavioral inertia played a significant role in choice performance, then one should expect that rats will continue – at least transiently – to respond on the cocaine lever during choice. Contrary to this prediction, however, rats self-administered cocaine (on average 15 injections per hour) during the first hour but they almost immediately shifted their response to the saccharin lever during choice (Lenoir et al., 2007). This rapid, within-session reorientation of behavior away from cocaine to sweet water clearly demonstrates that the persistence of sweet preference is not attributable to behavioral inertia. Thus, the same rats self-administer cocaine when no other choice is available but readily abstain from cocaine self-administration when offered a valuable, nondrug alternative.

Overall, the research reviewed above demonstrates that the reward value of intravenous cocaine is weaker than the value of taste sweetness in cocaine-sensitized rats with a limited exposure to cocaine self-administration. But what is exactly the magnitude of this difference in reward value in saccharin-preferring rats? To address this question, the number of responses or cost required to earn sweetened water was gradually increased above that of cocaine until reversal of preference and thus identification of the point of indifference or subjective equality. The latter provides a quantitative estimation of the relative value of cocaine. As one would expect, when the relative cost of sweetened water increased, rats progressively shifted their preference to cocaine (Cantin et al., 2009). At the highest relative cost (i.e., 16 times that for cocaine), virtually all rats shifted their preference to cocaine (Cantin et al., 2009). Importantly, the point of indifference was reached when the cost of sweetened water was about 7 times that for cocaine (Cantin et al., 2009). This large cost ratio suggests that the value of cocaine is much lower than the value of sweetened water. The weak relative value of intravenous cocaine may also explain why a 6-fold increase in cocaine dose (see above) was apparently not sufficient to shift preference to cocaine. Finally, to further quantify the relative value of cocaine, the point of indifference or subjective equality between cocaine and saccharin was measured as a function of the concentration of saccharin (0.0016–0.2%). As expected, the cost-effect curve for saccharin preference was shifted to the right with increasing concentrations of saccharin. As a result, the point of indifference between cocaine and saccharin increased quasi-linearly with the concentration of saccharin, from 1 to about 8. Of special interest, the point of indifference between cocaine and saccharin was near 1 at the lowest saccharin concentration of 0.0016%, suggesting that on average intravenous cocaine was worth the costs of this very low concentration (Nathalie Vanhille and Serge Ahmed, unpublished data). Thus, the value of intravenous cocaine lies closer to the bottom than to the top of the rat's value ladder. These findings are consistent with recent behavioral economic research showing that the reward value of food is largely greater than the reward value of intravenous cocaine in hungry rats from different strains (Christensen et al., 2008a, 2009).

3.3. *Animals abstain from cocaine use no matter how heavy was past drug use*

Preference for sweet water was observed in either initially cocaine-naïve rats or in rats with a limited exposure to cocaine self-administration. As evoked above, however, there is now good behavioral evidence showing that the value of cocaine increases following extended cocaine self-administration and escalation of consumption. Thus, one key question is to determine whether and to which extent this increase in cocaine value can be sufficient to override initial saccharin preference and shift preference toward cocaine use. To answer this question, rats were first allowed to have daily extended access to cocaine self-administration during several weeks before choice testing. As expected, following extended access to cocaine self-administration, most rats escalated their consumption of cocaine (Fig. 5a). Surprisingly, however, when allowed to choose between cocaine and saccharin, most rats rapidly acquired a strong preference for the saccharin lever (Fig. 5b) and this regardless of the cocaine dose available (i.e., 0.25–1.5 mg per injection) (Lenoir et al., 2007). In fact, sweet preference reached statistical significance as soon as the second day of testing, a rate of acquisition that was comparable to that seen in

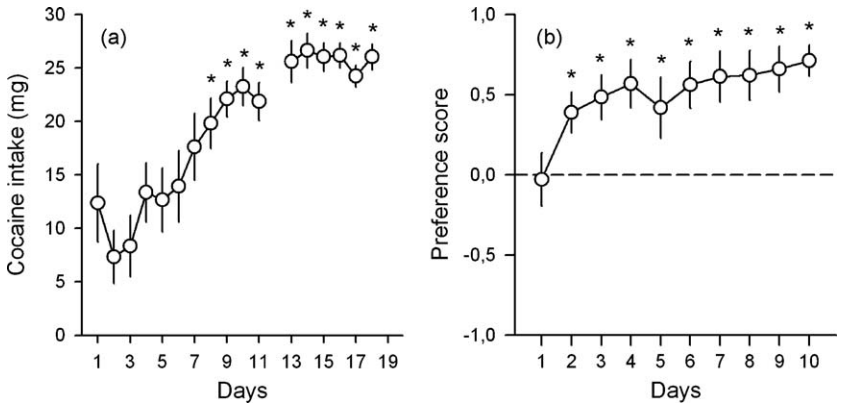

Fig. 5. Sweet preference following extended cocaine self-administration. (a) Escalation of cocaine self-administration during extended access to a high dose of cocaine (0.75 mg per injection). Data corresponding to the 12th day are missing due to a computer failure. *Different from the first day ($P < 0.05$). (b) Choice between cocaine and sweet water (mean ± SEM) after cocaine intake escalation. *Different from the indifference level ($P < 0.05$). Adapted from Lenoir et al. (2007).

initially naïve rats (see Fig. 5b). Thus, extended exposure to cocaine self-administration apparently did not override sweet preference in the majority of individuals. Using a different approach, Christensen et al. (2008b) have recently reached the same conclusion.

3.4. Only a minority of animals continue to take cocaine despite choice

In all the experiments described above, though the large majority of rats stopped cocaine use, a small minority nevertheless continued to take cocaine despite the opportunity of making a different choice. Out of a total of 184 rats tested in the choice procedure over the past 5 years, only 16 individuals (i.e., 8.7%) expressed a preference for intravenous cocaine (i.e., cocaine choices >50% of completed trials). Importantly, preference for cocaine was not attributable to a mere lack of interest in or aversion to sweetened water since during sampling trials, cocaine-preferring rats earned as many accesses to sweetened water and drank as much as the majority of other rats (Cantin et al., 2009). To assess the impact of past cocaine use on the frequency of cocaine-preferring individuals, the total amount of self-administered cocaine before choice testing was calculated for each individual. This amount ranged from 0 to 486 mg and defined 5 levels of severity (Cantin et al., 2009). Surprisingly, the frequency of cocaine-preferring individuals remained stable around about 10%. Thus, no matter how intense was the level of past cocaine use, cocaine preference remains rare and exceptional in rats with alternative possibilities during drug access. It is important to note that the heaviest level of past cocaine use considered here was clearly shown in previous research to affect brain function compared to lower levels of past cocaine use (Ahmed et al., 2002, 2003, 2005; Ferrario et al., 2005; Edwards et al., 2007; Madayag et al., 2007; Briand et al., 2008a,b; George et al., 2008; Ben-Shahar et al., 2009; Orio et al., 2009). However, these neurobiological changes were apparently not sufficient to bias choice-making in favor of cocaine use, at least in the majority of rats.

4. Choice as a sieve for cocaine addiction

Since the seminal work by Weeks, ample research has established that when no valuable options to drug use are available, most rats readily learn to self-administer cocaine and escalate cocaine intake following extended drug use (Ahmed, in press). In contrast, as shown here, when a valuable behavioral option, even a biologically or physiologically inessential one (i.e., for survival or reproduction), is made available during drug access, most rats readily abstain from cocaine use in favor of the alternative behavior regardless of the amount of past cocaine use (Lenoir et al., 2007; Cantin et al., 2009). Only a minority of rats (i.e., about 10%) continue to self-administer cocaine despite the opportunity of making a different choice. At least two alternative interpretations can be envisioned to explain this intriguing pattern of results. Since these interpretations intimately depend on two different scientific conceptions of the nature of cocaine addiction, I will first provide a very brief outline of these conceptions.

4.1. Disease- versus choice-based conceptions of cocaine addiction

Broadly speaking, there are currently at least two overarching scientific conceptions of drug addiction: disease-based versus choice-based conceptions. According to the disease-based conception, drug addiction is a chronic relapsing disorder, not unlike other chronic diseases, such as, for instance, asthma and diabetes (Jellinek, 1952; Lyvers, 2000; McLellan et al., 2000; Hyman, 2005, 2007b). More specifically, drug addiction would be a brain disease that robs the person's ability to make free, voluntary and rational choice. As put recently very explicitly by Steve Hyman, drug addiction would be characterized by a "diminished ability to control drug use, even in the face of factors that should motivate cessation of drug use in a rational agent willing and able to exert control over behavior" (Hyman, 2007b). As expected, this conception of drug addiction fits well with the American Psychiatric Association Diagnostic and Statistical Manual (DSM)'s general conception of mental disorders. Accordingly, a negative psychological condition is considered as a psychiatric disorder if it is symptomatic of "some underlying dysfunction in the individual" and is "not merely an expectable reaction to a particular event" or situation (Martin et al., 2008). In the absence of objective evidence for disorder-associated brain dysfunctions (which is the rule in psychiatry), the latter criterion can serve as an exclusion criterion to improve diagnosis validity by reducing the rate of false positives (Wakefield et al., 2002, 2007; Wakefield, 2007). For instance, the DSM-based diagnosis of major depressive disorder currently incorporates a bereavement exclusion criterion to exclude from diagnosis individuals who meet the required inclusive criteria of this disorder but who are experiencing a severe, though normal, sadness in reaction to the death of a loved one (Wakefield et al., 2007). According to this general conception, forms of drug use that are better explained as "an expectable reaction" to some situation or condition should thus be excluded from a diagnosis of addiction (e.g., drug use as self-medication or by default of other options) (Alexander, 2008).

Alternatively, there are a set of other scientific views that define drug addiction as a voluntary choice (Schelling, 1980; Thaler and Shefrin, 1981; Herrnstein and Prelec, 1991; Heyman, 1996, 2009; Ainslie, 2000), though not in the sense of a rational lifetime decision as in certain theories of rational addiction (Becker and Murphy, 1988; Schaler, 2000; Dalrymple, 2006). The drug user does not choose rationally and in advance to become a drug addict. The transition to drug addiction happens as an unexpected and unwanted consequence of suboptimal, though normal, daily choice-making. For instance, though impulsive choice-making (i.e., choice of the best immediate options without regard to better long-term options) is very prevalent in both young and adult humans, it can under some circumstances lead to addiction (e.g., increased drug availability combined with lack of opportunity) (Heyman, 2009). In this general conception, there would be no pathological loss of control and no brain dysfunction that rob the individual's ability to make voluntary, free choices. Even at the very bottom of the downward spiral of drug addiction, the drug addict would still keep his/her ability to exert control over drug use and would even be able to quit, with or without professional help, under propitious circumstances (Heyman, 2009). The conception of drug addiction as a voluntary though irrational, choice is supported by high rates of spontaneous recovery from addiction and is consistent with the efficacy of psychosocial interventions for cocaine addiction such as, for instance, voucher-based treatment (Heyman, 2009).

It may seem shocking, perhaps even scandalous, that after almost a century of debate and research on addiction, the scientific community as a whole did not reach yet a consensus on the nature of drug addiction and that two general conceptions of addiction still co-exist and compete with each other. However, the scientific arguments on both sides are solid and coherent and, in the absence of established evidence for drug addiction-related neuropathology in humans, there is currently no scientific basis for choosing one conception over the other. In the following, I will show how each conception of addiction can differently interpret why despite extensive cocaine use most rats abstain from cocaine use when given the opportunity to make a different choice while a minority continues to take the drug.

4.2. Resilience and vulnerability to cocaine addiction in animals and humans

According to the brain disease conception of addiction, this pattern of results could be interpreted as evidence for resilience and vulnerability to cocaine addiction. In standard experimental settings, resilient rats would take cocaine merely by default of other options. Their behavior would be "merely an expectable reaction" to an abnormal situation (i.e., lack of choice or opportunity) and would not necessarily reflect an underlying addiction-related dysfunction. As a result, neuroadaptive changes documented in the brain of these rats should not be necessarily interpreted as evidence for addiction-specific pathological changes. These changes could indeed also reflect normal neuroplastic adaptations to novel and unique behavioral experiences. In contrast to the majority of resilient rats, a small minority of rats (i.e., about 10%) continue to take cocaine despite the opportunity of making a different choice (Lenoir et al., 2007; Cantin et al., 2009). Within the brain disease framework of drug addiction, this minority of cocaine-preferring rats could be homologous to the minority of human cocaine users who eventually become addicted to cocaine following extended drug use (Fig. 6). Comparing this minority of rats with the majority of resilient rats could thus bring unprecedented insights into the neurobiological dysfunctions that are hypothesized to underlie cocaine addiction. From a methodological standpoint, the choice procedure described here could serve as a sort of sieve for cocaine addiction: it would weed out resilient rats and only retain rats potentially addicted to cocaine (Cantin et al., 2009). In support of the validity of this choice-based method of selection, a recent laboratory study in humans showed that when given a choice between cocaine and money, cocaine users with a DSM-based diagnosis of addiction choose cocaine more frequently than non-addicted long-term cocaine users, regardless of the amount of money available (Walsh et al., 2010).

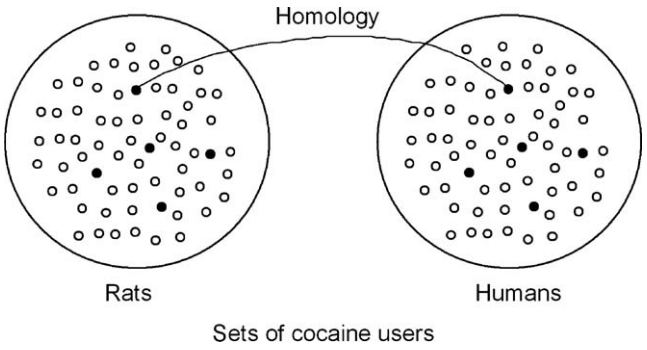

Fig. 6. Venn diagrams illustrating the hypothesis that the minority of cocaine-preferring rats (closed circles in the left set) would be homologous to the minority of cocaine users with a diagnosis of cocaine addiction (closed circles in the right set). The open circles on the left and right set represent the majority of rats that abstain from cocaine self-administration when given a choice or the majority of human cocaine users who do not become addicted to cocaine.

The interpretation of our choice data in terms of resilience and vulnerability to addiction maps well with what we know about the epidemiology of drug addiction in general and of cocaine addiction in particular. As mentioned earlier in the Introduction, only a minority of cocaine users (i.e., less than 10%) eventually become addicted to cocaine following extended drug use (Reboussin and Anthony, 2006), suggesting that about 90% of cocaine users are likely to be resistant to cocaine addiction. One of the most direct evidence for human resilience to drug addiction, however, comes from a now old, though still valid, epidemiological survey by Lee Robins and co-workers (Robins et al., 1974; Robins, 1993). This survey reported that the large majority of Vietnam veterans (about 90%) who had used heroin on a chronic basis in Vietnam, even to the point of becoming physically dependent, readily and durably stopped heroin use upon return from war (Robins, 1993). Only a minority of individuals (i.e., about 10%) continued to use heroin after the war. For soldiers during the Vietnam's war, there was little opportunity and heroin use was a cheap, easily available way to make "life in service bearable", "enjoyable" and also probably to cope with the stress of war (Robins, 1993). As a result, soldiers were probably using heroin by default of other rewarding or outlet activities, and not because they lost power to control drug use. This interpretation explains why despite chronic and heavy heroin use and evidence of physical dependence, so many veterans (i.e., 90%) permanently quitted heroin use upon return to home. Thus, despite chronic, heavy heroin consumption, most soldiers remained resistant to heroin addiction. I am not aware of equivalent evidence for resilience to cocaine addiction after chronic, heavy cocaine use in humans. However, there is evidence for resilience to addiction-like behavior to chronic dopaminergic medication in Parkinson disease (Evans and Lees, 2004; Voon et al., 2009). To compensate for the irreversible loss of midbrain dopamine neurons due to neurodegeneration, Parkinsonian patients receive chronic dopamine replacement therapies, including the dopamine precursor levodopa and direct dopamine agonists. In the course of this chronic treatment, some of these patients eventually develop excessive dopaminergic medication use, despite severe motor and non-motor side effects (Voon et al., 2009). This syndrome is often called the dopamine dysregulation syndrome and is currently

hypothesized to be akin to a state of drug addiction (Evans and Lees, 2004). It is currently estimated that this syndrome appears only in a small minority of patients chronically treated with dopamine replacement therapies (i.e., less than 10%), suggesting thus that the remaining majority is likely to be resilient to this syndrome despite years of dopaminergic medication use.

The hypothesis that in rats, like in humans, only a minority of cocaine users would become addicted to cocaine, even after extensive drug use, was previously reached by other researchers using a different approach (Deroche-Gamonet et al., 2004; Belin et al., 2008). Though innovative and interesting, the validity of this approach should nevertheless be considered with caution. It is based on a circular statistical method that limits a priori and arbitrarily to less than 33% the maximum possible frequency of rats with an addiction-like behavior. Obviously, such a method of selection could only find what it was designed at the outset to find, that is a minority of potentially addicted individuals. This outcome should therefore not be considered as an objective demonstration of resilience or vulnerability to cocaine addiction in rats. In contrast, the choice-based method of selection advocated here does not set arbitrarily and in advance a limit to the maximum possible frequency of cocaine-preferring rats. In principle, this frequency could attain 100%. The fact that the observed maximum frequency was much lower (i.e., about 10%) could objectively demonstrate, rather than presuppose, that cocaine addiction only affects a minority of individuals among a sea of resilient ones.

4.3. Cocaine abstinence in animals and behavioral treatment for cocaine addiction

According to the choice-based conception of addiction, cocaine abstinence in rats offered a nondrug alternative would not necessarily rule out cocaine addiction. It could even be reinterpreted as strong preclinical support for voucher-based treatment for cocaine addiction (Carroll and Lac, 1993; Ahmed, 2005; Lenoir and Ahmed, 2008; Lesage, 2009). In this view cocaine addiction is a normal, though suboptimal, voluntary choice that could be reversed by interventions on environmental contingencies. In voucher-based therapy, a novel reinforcement contingency is established between cocaine abstinence in cocaine users with a diagnosis of addiction and an alternative reinforcer (Higgins et al., 1991, 1994; Carroll and Onken, 2005; Lussier et al., 2006; Stitzer and Petry, 2006). Specifically, cocaine abstinence is encouraged by rewarding it with vouchers that could be exchanged for other desirable goods or activities. To phrase it in a way that emphasizes similarity with the choice studies in rats, during voucher-based treatment, cocaine addicts face a mutually exclusive choice between cocaine use and other rewarding activities. Though the money value of these alternative activities are relatively low (i.e., generally less than 15 dollars a day), voucher-based therapy, together with standard counseling, has proven to be one of the most effective psychosocial interventions for promoting abstinence and preventing relapse in cocaine addiction (Dutra et al., 2008). As expected, however, though most cocaine addicts respond positively to voucher-based treatment, some do not. In light of these clinical findings, one can indeed reinterpret choice-induced abstinence from cocaine self-administration in most rats, not as evidence for resilience to cocaine addiction, but as a preclinical model of the efficacy of contingency management therapy for cocaine addiction. In this reinterpretation, the minority of rats that continue to take cocaine despite the opportunity to make a different choice would correspond to the minority of human cocaine addicts who fail to respond positively to this therapy. Finally, it is important to note that though voucher-based treatment programs are successful, they do not always remain effective over extended periods of time. In addition, individuals who enroll in such programs are not necessarily representative of the majority of cocaine addicts. Thus, more research remains to be done in this area.

4.4. Current indeterminacy in the interpretation of cocaine abstinence in animals

Let's take stock of what we have achieved so far. There exists a significant degree of indeterminacy in the interpretation of choice-induced abstinence from cocaine use in rats. In the disease-based conception of addiction, this behavior would rule out addiction while its absence (i.e., cocaine preference) would point to an addiction state. In contrast, in the choice-based conception of addiction, choice-induced cocaine abstinence would suggest instead that most rats, though not all, can be "treated" by targeted interventions on environmental contingencies. Arguably, the same problem of indeterminacy seems also to affect the interpretation of other forms of abstinence in experimental animals such as, for instance, punishment-induced abstinence from cocaine self-administration (Grove and Schuster, 1974; Smith and Davis, 1974; Johanson, 1977; Bergman and Johanson, 1981). It has been recently shown that when lever-pressing for cocaine is punished by footshock, most rats stop cocaine self-administration while few other rats continue (Deroche-Gamonet et al., 2004; Pelloux et al., 2007). Punishment-induced cocaine abstinence can also receive two different interpretations, depending on one's conception of addiction. Again in the disease-based conception of addiction, this behavior would rule out addiction while its absence (i.e., resistance to punishment) would point to a compulsion or addiction state. In contrast, in the choice-based conception of addiction, punishment-induced cocaine abstinence would suggest instead that most rats, though not all, can be "treated" by punishment-based therapy. At present, it seems that there exists no objective criterion for excluding one interpretation in favor of the other. In addition, it should be mentioned here that punishment contingencies do not represent an effective therapeutic option in humans. Perhaps one way out from this dilemma would be to postulate that there exist out there in the real world not one but several forms of drug addiction, including a disease form that would be rare and resistant to environmental contingencies (i.e., alternative choices; punishment) and other voluntary forms that would be more prevalent and sensitive to these contingencies (Redish et al., 2008).

4.5. Future preclinical research on choice and drug addiction

Another, more obvious way to resolve this indeterminacy is to increase research effort to better understand the role of choice in animal drug self-administration. First, in most previous research, only one type of alternative to drug self-administration was tested, that is, food-related rewarding activities (e.g., drinking sweetened water). It will be important in the future to test other kinds of behavioral alternatives such as, for instance, novelty exploration or social interaction. Second, it will also be interesting to assess the effects of nondrug alternatives on different aspects of drug self-administration or reinforcement, including drug-induced reinstatement of drug seeking after extinction. There is already some good evidence showing that supply of an alternative after extinction can dramatically influence drug reinstatement (Liu et al., 2005; Ping and Kruzich, 2008). This observation has important implications for the current interpretation of drug reinstatement in terms of habitual or compulsive drug seeking but more research is clearly needed to secure the generality of these findings. Third, the effects of choice during drug exposure or access should be systematically extended to other major drugs of abuse. As a matter of fact, similar effects were recently obtained in rats following extensive heroin self-administration and escalation of heroin consumption (Lenoir et al., 2008). In addition, after long-term, heavy alcohol consump-

tion, rats that were selected for high-ethanol intake readily stopped drinking alcohol when offered a sweet solution as an alternative choice (Terenina-Rigaldie et al., 2004). Fourth, the effects of choice on drug self-administration should be generalized across different strain of rats. The series of choice experiments summarized above were all conducted in only one strain of rats: the Wistar strain—a widely used rats strain in the field (i.e., about 500 primary journal articles in the PubMed Central database reported having used Wistar rats as subjects for drug self-administration) that is very sensitive to cocaine self-administration (Freeman et al., 2009). Fifth, it will be also interesting to compare the effects of choice during drug self-administration across several animal species. Of particular interest, in one particularly significant study, food-restricted monkeys were allowed to choose between different doses of cocaine and different number of non-sweetened food pellets. It was found that most monkeys (i.e., 3 out of a total of 4) preferred the highest amount of food (4×1-g pellets) to the maximal dose of cocaine, an outcome that is fully consistent with the main conclusions of the present review (Nader and Woolverton, 1991). Among choice studies in monkeys, this study seems to be an exception, however. In virtually all other studies, the focus was on cocaine preference and, consequently, experimental conditions were designed to favor its expression. For instance, in many studies, monkeys were allowed to choose between increasing doses of cocaine and a fixed, relatively small, amount of food (Aigner and Balster, 1978; Woolverton and Balster, 1979; Nader and Woolverton, 1990, 1991, 1992a,b; Nader et al., 1993; Paronis et al., 2002; Negus, 2003, 2004, 2005a,b; Gasior et al., 2004; Negus and Mello, 2004). As one could expect, in those conditions, almost all monkeys preferred the highest dose of cocaine. In addition, in several recent studies, the cost of cocaine (i.e., FR10) was much lower than the cost of food (i.e., FR100), thereby favoring cocaine preference (Negus, 2003, 2004, 2005a,b; Negus and Mello, 2004). As summarized here, when the cost of saccharin is much higher than the cost of cocaine, rats too prefer cocaine (Cantin et al., 2009). Because of their phylogenetic, genomic and behavioral proximity to humans, it will be interesting in future research to determine whether the pattern of choice data obtained in rats generalizes to nonhuman primates.

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