Neuropsychopharmacology (2011) 36, 569–579

www.neuropsychopharmacology.org

High-Novelty-Preference Rats are Predisposed to Compulsive Cocaine Self-administration

David Belin*[,1,2,3], Nadège Berson[1,2], Eric Balado[1,2], Pier Vincenzo Piazza[1,2] and Véronique Deroche-Gamonet[1,2]

[1]University of Bordeaux, Bordeaux Cedex, France; [2]INSERM U862, Pathophysiology of Addiction, NeuroCentre Magendie, Bordeaux Cedex, France; [3]INSERM AVENIR Team Psychobiology of Compulsive Disorders, Pôle Biologie Santé, CNRS UMR 6187, University of Poitiers, Poitiers cedex, France

Sensation/novelty-seeking is amongst the best markers of cocaine addiction in humans. However, its implication in the vulnerability to cocaine addiction is still a matter of debate, as it is unclear whether this trait precedes or follows the development of addiction. Sensation/novelty-seeking trait has been identified in rats on the basis of either novelty-induced locomotor activity (high-responder (HR) trait) or novelty-induced place preference (high-novelty-preference trait (HNP)). HR and HNP traits have been associated with differential sensitivity to psychostimulants. However, it has recently been demonstrated that HR rats do not develop compulsive cocaine self-administration (SA) after protracted exposure to the drug, thereby suggesting that at least one dimension of sensation/novelty seeking in the rat is dissociable from the vulnerability to switch from controlled to compulsive cocaine SA. We therefore investigated whether HNP, as measured as the propensity to choose a new environment in a free choice procedure, as opposed to novelty-induced locomotor activity, predicts the vulnerability to, and the severity of, addiction-like behavior for cocaine. For this, we identified HR/LR rats and HNP/LNP rats before any exposure to cocaine. After 60 days of cocaine SA, each rat was given an addiction score based on three addiction-like behaviors (persistence of responding when the drug is signaled as not available, high breakpoint under progressive ratio schedule and resistance to punishment) that resemble the clinical features of drug addiction, namely inability to refrain from drug seeking, high motivation for the drug and compulsive drug use despite adverse consequences. We show that, as opposed to HR rats, HNP rats represent a sub-population predisposed to compulsive cocaine intake, displaying higher addiction scores than LNP rats. This study thereby provides new insights into the factors predisposing to cocaine addiction, supporting the hypothesis that addiction is sustained by two vulnerable phenotypes: a 'drug use prone' phenotype such as HR which brings an individual to develop drug use and an 'addiction prone' phenotype, such as HNP, which facilitates the shift from sustained to compulsive drug intake and addiction.
Neuropsychopharmacology (2011) **36,** 569–579; doi:10.1038/npp.2010.188; published online 27 October 2010

Keywords: addiction; cocaine; compulsivity; distributions; novelty; locomotor reactivity

INTRODUCTION

A major challenge for addiction research is to identify the mechanisms involved in the vulnerability to switch from controlled to compulsive cocaine use, thereby allowing efficient preventive and therapeutical strategies targeting those at risk of developing addiction. Thus, even though only 15–20% of the individuals exposed to addictive drugs (Anthony *et al*, 1994) develop an addiction (DSM-IV, APA, 2000), the direct and indirect social and economical costs of this behavioral disorder reach 500 $ billions (Uhl and Grow, 2004; for review see Koob and Le Moal, 2005).

*Correspondence: Dr D Belin, INSERM AVENIR Team Psychobiology of Compulsive Disorders, Pôle Biologie Santé, CNRS UMR 6187, University of Poitiers, Poitiers cedex, France, Tel: +3 354 945 8353, Fax: +3 354 945 4014, E-mail: david.belin@inserm.fr
Received 1 June 2010; revised 8 September 2010; accepted 9 September 2010

Epidemiological studies have revealed a striking association between the sensation/novelty-seeking trait and cocaine abuse or addiction (Franques *et al*, 2000; Franques, 2003; Kreek *et al*, 2005). Thus, sensation/novelty seekers are more prone to experience addictive drugs, akin to various risky activities (Zuckerman *et al*, 1990; Horvath and Zuckerman, 1993; Kalichman *et al*, 1994; Wills *et al*, 1994; Jonah, 1997; Sher *et al*, 2000; Zuckerman and Kuhlman, 2000; Buckman *et al*, 2009; Woicik *et al*, 2009). However, whether the sensation/novelty-seeking trait actually predisposes to develop compulsive cocaine use or is part of the behavioral adaptations induced by protracted drug use remains a matter of debate. Indeed, the demonstration of a relationship between high sensation/novelty-seeking trait, measured before any exposure to addictive drugs and the vulnerability to switch from controlled to compulsive cocaine intake in an experimentally well-controlled condition remains to be established.

It has been proposed that the sensation/novelty-seeking trait can be studied in rodents both by high locomotor

reactivity to a new inescapable environment (high-responder (HR) phenotype; Dellu *et al*, 1996a; Blanchard *et al*, 2009), and high propensity to visit a new environment in a free-choice procedure, ie, novelty-induced conditioned place preference (CPP); high-novelty-preferring (HNP) phenotype; Bardo *et al*, 1996; Cain *et al*, 2005). Although both traits are dependent on the dopaminergic system (Bardo *et al*, 1996), they do not seem to be correlated (Bardo *et al*, 1996; Cain *et al*, 2005, but see Dellu *et al*, 1996b) and predict different dimensions of drug reward (Bardo *et al*, 1996). Thus, HR rats are more vulnerable than low-responder (LR) littermates in their propensity to acquire drug self-administration (SA; Piazza *et al*, 1989, 1990, 2000). In contrast, HNP rats differ from their low-novelty-preferring (LNP) littermates in their vulnerability to express CPP for amphetamine (Bardo *et al*, 1996) but not in their propensity to acquire drug SA (Klebaur *et al*, 2001). Hence, HR and HNP traits may differently contribute to the vulnerability to cocaine addiction.

Using a preclinical model that provides a measure of inter-individual vulnerability to switch from controlled drug use to addiction (Deroche-Gamonet *et al*, 2004), it has been shown that HR rats do not switch more than LRs to compulsive cocaine intake (Belin *et al*, 2008), thereby providing evidence for a dissociation between the propensity to acquire cocaine SA and the vulnerability to develop compulsive cocaine use. This study also suggests that at least one dimension of sensation/novelty seeking in the rat, namely high locomotor response to novelty, does not predict the vulnerability to switch from sustained drug use to addiction. We therefore investigated whether the alternative sensation/novelty-seeking trait in the rat, namely HNP, contributed to the vulnerability to cocaine addiction.

Because of the broad range of methodological procedures addressing locomotor response to novelty and novelty preference (Deminiere *et al*, 1992; Dellu *et al*, 1993; Klebaur and Bardo, 1999; Kabbaj *et al*, 2000; Cain *et al*, 2005; Abreuvillaca *et al*, 2006; Ballaz *et al*, 2007, 2008; Turner *et al*, 2008) that may account for the discrepancies observed in the literature (for review see Bardo *et al*, 1996; Dellu *et al*, 1996b), we tested within a single experiment the involvement of both novelty-induced locomotor activity and novelty preference in the vulnerability to show an addiction-like behavior for cocaine. For this, HR/LR rats and HNP/LNP rats were selected in the upper (HR, HNP) and lower (LR, LNP) quartiles of a population of 40 outbred drug naive animals ranked according to their locomotor response to inescapable novelty and preference for a new environment, respectively. We then subjected the population to extended cocaine SA and measured three addiction-like criteria that are an operationalized version of the hallmarks of drug addiction in the DSM-IV (APA, 2000), namely, (1) inability to refrain from drug seeking, (2) high motivation for the drug, and (3) compulsive drug use despite negative consequences. For this, we measured, respectively, (1) responding for the drug during periods when the drug is not available and signaled as so, (2) increased breakpoints (BPs) under progressive ratio schedule of reinforcement, and (3) resistance to contingent punishment by electric footshocks (Deroche-Gamonet *et al*, 2004; Belin *et al*, 2008, 2009). We analyzed the dimensional relationships between addiction-like behaviors, locomotor reactivity to novelty and novelty preference as well as the phenotype differences, ie, HR *vs* LR, HNP *vs* LNP, in the addiction-like behaviors and in the burst-like pattern of cocaine intake, a behavioral characteristic of addiction (Belin *et al*, 2009).

MATERIALS AND METHODS

Subjects

Adult male Sprague–Dawley rats ($n = 40$) weighing 280–300 g at the beginning of the experiments were individually housed under a reversed 12 h light/dark cycle (lights on at 2000 hours). Temperature ($22 \pm 1^{\circ}C$) and humidity ($60 \pm 5\%$) were controlled. Food and water were available *ad libitum* throughout the experiment, at the exception of the behavioral and SA sessions. Experiments were performed between 0800 hours and 2000 hours, 7 days per week.

Drugs

Cocaine hydrochloride (Cooper, Bordeaux, France) was dissolved in sterile 0.9% saline. The dose of cocaine was calculated as the salt.

Surgery

Intrajugular surgeries were performed according to a procedure previously described (Deroche-Gamonet *et al*, 2004) after locomotor reactivity and novelty preference tests. Briefly, a silastic catheter (internal diameter = 0.28 mm; external diameter = 0.61 mm; dead volume = 12 μl) was implanted in the jugular vein under ketamine (100 mg/kg)/xylacine (1 mg/kg) anesthesia. The proximal end was placed in the right atrium, whereas the distal end was passed under the skin and fixed in the mid scapular region. Rats were allowed to recover for 5–7 days after surgery. During the first 4 days following surgery, rats received an antibiotic treatment (gentamicine, 1 mg/kg i.p.). After surgery, catheters were flushed daily with a saline solution containing unfractionated heparin (100 IU/ml).

Apparatus

Cocaine SA. The SA setup was constituted of 16 chambers made of plexiglass and metal. Each chamber (40 cm long × 30 cm width × 52 cm high) was located within a larger exterior opaque box equipped with exhaust fans that assured air renewal and masked background noise. Briefly, animals were placed daily in a SA chamber, in which their chronically implanted intracardiac catheter was connected to a pump-driven syringe (infusion speed: 20 μl/s). Two holes located in the opposite sides of the SA chamber at 5 cm from the grid floor were used as devices to record responding. A white house light at the top of the chamber allowed its complete illumination. A white cue light (1.8 cm in diameter) was located 9.5 cm above the active hole. A green cue light (1.8 cm in diameter) was located 10 cm right to the white cue light. A blue cue light (1.8 cm in diameter) was located on the opposite wall at 33 cm of the floor on the left side. Experimental contingencies were controlled and data collected with a PC windows-compatible software.

Novelty-induced locomotor activity. The setup was constituted of 16 circular corridors (10 cm wide and 70 cm in diameter). Four photoelectric cells placed at the perpendicular axes of this apparatus automatically recorded locomotion. The locomotor response was recorded over 10 min intervals for a period of 2 h. The score of each animal (number of photocell beam breaks cumulated over this period) was used as an index of individual reactivity to the novel environment.

Novelty preference. The setup has already been described elsewhere (Darnaudery *et al*, 2002). It consisted of six boxes constituted of two equal compartments ($30 \times 30 \times 45$ cm) connected by an alley (30×10 cm large, 45 cm high) with two opposite openings (8 cm), one per compartment, that could be closed by sliding doors. Boxes were covered with opaque plates (30×70 cm large) that isolated apparatus from visual cues in the testing room and maintained light intensity into the boxes at about 0.25 lux. Square parallelepipeds (12×2 cm large, 45 cm high) made of gray Plexiglas were used to create two distinct spatial configurations between the two compartments. The apparatus was equipped with photoelectric beams to record locomotor activity, number of visits and time spent in each compartment.

General Procedures

Novelty-induced locomotor activity. After 15 days of habituation to the facility, all the rats were exposed to circular corridors for 2 h, starting at 6 h after the beginning of the light period.

Novelty preference. A week after the exposure to the circular corridors, the subjects were tested for their preference for novelty in a free-choice procedure. The rats were placed 5 min in the central alley, and then exposed 25 min to one compartment ('familiar'). At the end of this habituation phase, the rats were immediately placed in the central alley for 5 s after which the two doors were simultaneously opened to let the animal explore the whole box (central alley, familiar, and new compartments) for 15 min. The index of novelty preference used was calculated as followed: time spent in the new compartment/(time spent in the new compartment + time spent in the familiar compartment) $\times$ 100.

Self-administration. All the SA experiments were performed during the dark phase of the light/dark cycle as previously described (Deroche-Gamonet *et al*, 2004). Cocaine SA and the three addiction-like behaviors were conducted in exactly the same conditions as previously described (Deroche-Gamonet *et al*, 2004).

Basal training protocol: The daily SA session was composed of three drug components (40 min each) separated by 15 min drug free periods. 'Drug' periods were signaled by the blue cue light, whereas the 'no-drug' periods were signaled by illumination of the entire SA box and extinction of the blue cue light. During the 'no-drug' periods, nose pokes were without scheduled consequences. During the 'drug' periods, introduction of the animal's nose into one hole (active device) turned on the white cue light located above it and then, 1 s later, switched on the infusion pump. The cue light remained on for a total of 4 s. Nose pokes in the other hole (inactive device) had no scheduled consequences. The self-infusion volume was 40 µl (2 s/infusion) and contained 0.8 mg/kg of cocaine. Each infusion was followed by a 40 s time-out period. During the first 5 days, an FR1 schedule of reinforcement (ie, one nose poke resulted in an infusion of 0.8 mg/kg of cocaine) was applied. Then, the FR was first increased to 3 (one to two sessions) and finally to 5 for the rest of the experiment. Criterion for acquisition of cocaine SA was defined by a stable number of self-infusions over at least three consecutive SA sessions ($\pm$ 10%).

Persistence in drug seeking: It was evaluated daily in the basal training protocol by measuring the responding in the active hole during the 'no-drug' periods; drug being unavailable and signaled as such.

Motivation for the drug: It was measured in a progressive-ratio schedule. During the progressive-ratio schedule of reinforcement, drug availability was signaled by the blue cue light. The ratio of responses per infusion was increased after each infusion according to the following progression (10, 20, 30, 45, 65, 85, 115, 145, 185, 225, 275, 325, 385, 445, 515, 585, 665, 745, 835, 925, 1025, 1125, 1235, 1345, 1465, 1585). The maximal number of responses that a rat performed to obtain one infusion (the last ratio completed) is referred to as the BP. The session ceased after either 5 h or when a period of 1 h elapsed since the previously earned infusion.

Resistance to punishment: It was measured when cocaine infusions were associated with an electric shock. During this session, rats were placed for 40 min in the SA chamber. The blue cue light signaling drug availability was on. The schedule was the following. FR1 led to the illumination of the green cue light signaling the presence of the shock. When an FR4 was completed, rats received an electric shock (0.8 mA, 2 s). When FR5 was reached, rats received both an electric shock (0.8 mA, 2 s) and a cocaine infusion (0.8 mg/kg) associated with the corresponding conditioned stimulus (white cue light). Then the green cue light was turned off. The schedule could reinitiate at the end of the time-out period, ie, 40 s after the infusion. If, within a minute, animals did not complete an FR4 or an FR5 leading to shock and shock plus infusion, respectively, the green cue light turned off and the sequence was reinitiated, ie, the following FR1 turned on the green cue light.

Progressive ratio and punishment sessions were performed on day 60 and 72, respectively. Persistence in drug seeking measured over basal training sessions 53–59 was considered for analysis.

Data Analysis

For locomotor reactivity to novelty and novelty preference, the upper and lower quartiles of the population were selected as HR and LRs or HNP and LNP rats, respectively.

For the addiction-like criteria, as previously described (Deroche-Gamonet *et al*, 2004), a subject is positive for one

criterion if he belongs to the 35% highest part of the population. Thus, when a rat belongs to the 35% highest part of the population for none of the criteria, it is identified as 0crit rat and is considered resilient to addiction, however, when one rat belongs to the 35% highest part of the population for each of the three addiction-like criteria, it is identified as 3crit rat and is considered addicted.

The addiction score was calculated for each animal as the sum of the normalized scores for each of the three addiction-like criteria. To calculate a normalized score, the mean of the population is subtracted to each individual value and the result is divided by the standard deviation of the population (see Belin *et al*, 2008, 2009).

The burst-like pattern of cocaine SA was determined by the quantification of events of >5 infusions earned in <5 min occurring during the drug periods of the basal training protocol. Briefly, infusion events were analyzed from a 1-min bin Excel (Microsoft Corporation, Redmond, WA, USA) file. For an infusion n, a 5-min window was drawn that scanned up to the 5 min preceding or the 5 min following the infusion. Then if the sum of the infusions counted within this window was >5, the program initiated the same sequence from the first following infusion that was not included in the window. However, if the sum of the selected events did not reach 5, the same sequence was initiated from the infusion '$n+1$' and so on. The data presented for sessions 10, 30, and 60 are averages of sessions 9–11, 31–33, and 58–60, respectively.

Statistical Analysis

All the data are presented as mean ± SEM. Analyses of variance were used to determine the behavioral differences between the experimental groups. For each analysis, 0, 1, 2, and 3 criteria, LR/HR, or LNP/HNP were used as between-subject factor and time as within-subject factor. On confirmation of significant main effects, differences among individual means were analysed using the Newman–Keuls's *post-hoc* test.

The distributions of the populations were assessed by Kolmogorov–Smirnov (K–S) and χ^2 goodness of fit tests. The relationship between locomotor reactivity to novelty and novelty preference was assessed by a Pearson's correlation. The relationships between the addiction-like criteria (BP, active lever presses during 'no-drug periods', and maintenance of cocaine self-infusions when associated with electric foot shocks), addiction score, burst-like pattern of intake (number of events of >5 infusions in 5 min), and locomotor reactivity to novelty (total photocell beam breaks over 2 h) and/or novelty preference (percentage of time spent in the novel compartment) were assessed by the non-parametric Spearman's correlation analysis.

A principal components analysis was performed to investigate the potential dimensional inter-relationships between addiction, novelty preference and locomotor reactivity (Shaw, 2003). The variables used were: (1) the addiction score, (2) the percentage of time spent in the new environment of the novelty preference test, and (3) the total number of photocell beam breaks in the novelty-induced locomotor activity test. Although three factors were extracted from the analysis, we only represented the two with the highest explanatory value, ie, those which eigenvalue was >0.9.

RESULTS

Locomotor Reactivity to Novelty and Novelty Preference are Two Independent Behavioral Traits

HR rats ($n=10$) showed greater locomotor reactivity to novelty than LR rats ($n=10$; Figure 1a) but did not differ in their novelty preference in a free choice situation (Figure 1b). HNP rats ($n=10$) obviously showed higher preference toward the new compartment than low novelty preference rats (LNP, $n=10$; Figure 1c), but showed similar locomotor reactivities to an inescapable novel environment (effect of group: $F1,18=1.72$, $p=0.2$; Figure 1d) The dissociation between novelty preference and locomotor reactivity to novelty traits was further supported by the absence of correlation between the two phenotypes ($R=-0.11$, $p>0.49$).

A Sub-Population of Rats Develops Addiction-like Behavior after Chronic Exposure to Cocaine SA

After 60 days of cocaine SA, the 40 rats were challenged for their addiction-like behaviors (Deroche-Gamonet *et al*, 2004; Belin *et al*, 2008, 2009). A systematic analysis of the distributions of each of the three addiction-like behaviors revealed that the motivation for the drug and the persistence of drug seeking (Figure 2a and b, Table 1; $n=40$) were best fitted by a log-normal regression (χ^2 and K–S: $p>0.05$), as revealed by the high R^2 value of both log-normal fitting curves (Table 1). In contrast, the distribution of resistance to punishment was bimodal, composed of a first log-normal distribution ($n=27$ or 67.5% of the total population, K–S: $d=0.22451$, $p>0.1$), and a second normal subdistribution ($n=13$ or 32.5% of the total population, K–S: $d=0.15604$ $p>0.1$; Figure 2c) which general regression fit can be described as a three order polynomial equation (Table 1). 3crit addicted rats thus belong to a divergent subpopulation comprising 13 subjects, or 32.5% of the population, highly vulnerable to the development of compulsive cocaine SA. Thus, 3crit addicted rats belong to the extreme percentiles of a continuous population for the motivation for cocaine or the persistence in drug seeking, whereas they belong to an independent, clustered, subpopulation for resistance to punishment.

By combining the individual scores of the three addiction-like behaviors, rats were given an addiction score that was highly proportional to the number of addiction-like criteria they met (significant effect of group: $F_{3,36}=80.03$, $p<0.001$; Figure 2d). As previously described, 3crit, addicted, rats were the only group whose score was above the standard deviation (2.49) and 0crit addiction resilient, rats were the only group with negative scores (Belin *et al*, 2008, 2009). When compared with 0crit rats, 3crit rats thus displayed higher motivation to self-administer the drug, as revealed by a higher BP during a progressive ratio schedule of reinforcement ($F_{1,20}=51.01$, $p<0.001$; Supplementary Figure S1A), higher persistence of drug seeking when the drug was no longer available ($F_{1,20}=112.28$, $p<0.001$; Supplementary Figure S1B) and maintained cocaine SA

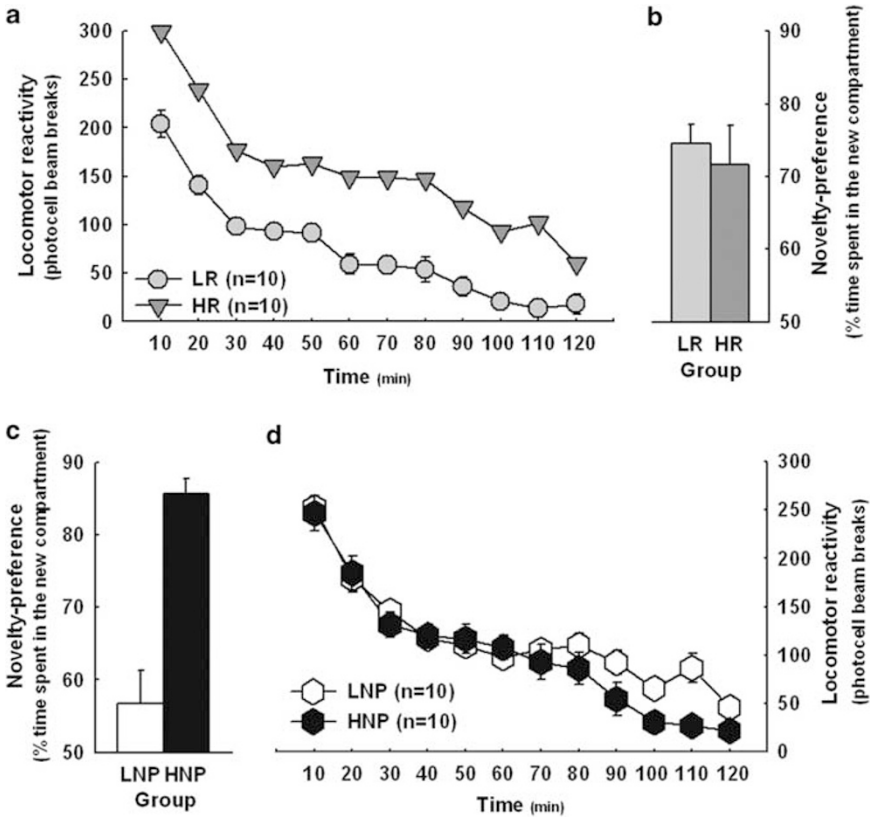

Figure 1 Novelty-induced locomotor activity and novelty preference are unrelated behavioral traits. (a) High-responder rats (HR, $n=10$) displayed greater locomotor activity than low-responder rats (LR, $n=10$) throughout a 2 h exposure to a novel inescapable environment. (b) However, LR and HR rats did not differ in their novelty seeking when given the opportunity to choose between a familiar and a novel compartment, as they spend the same percentage of time in the new compartment. (c) High-novelty-preference rats (HNP, $n=10$) spent more time in the new compartment than low-novelty-preference rats (LNP, $n=10$). (d) However, HNP and LNP rats did not differ in their locomotor response to a novel inescapable environment.

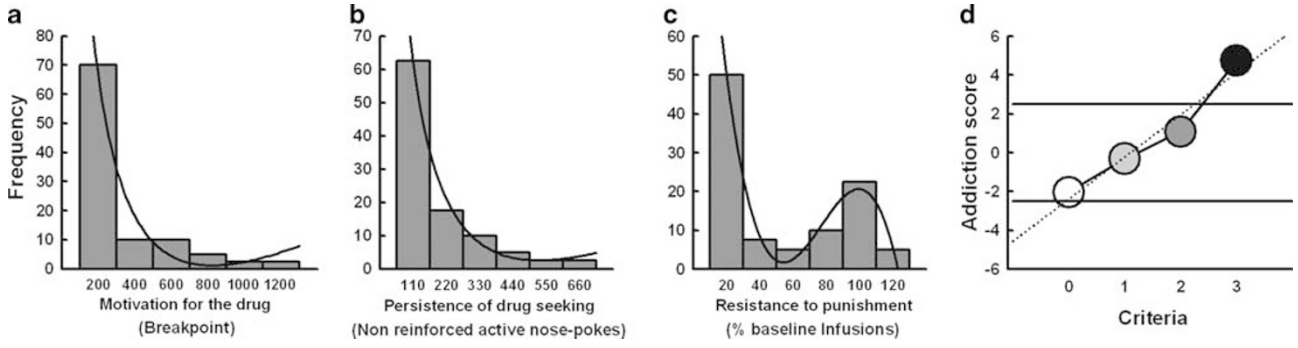

Figure 2 A sub-population of rats develops addiction-like behavior after chronic exposure to cocaine self-administration. a–c Representation of the distribution of each addiction-like criterion. Data are represented as frequencies of observations for each range of score. The whole population ($n=40$) was log-normal distributed for both motivation for cocaine (measured by the breakpoint during a progressive ratio session; a) and inability to refrain from cocaine seeking when it was not available and signaled as so (non-reinforced active nose-pokes; b). However, resistance to punishment (maintenance of drug use and drug seeking despite contingent electric foot-shocks as measured by self-infusions as a percentage of baseline) was best characterized by a bimodal distribution, with a specific normal subpopulation, on the right side of the general distribution, prone to compulsive cocaine intake (c; see Table 1 for more details). (d) Addiction scores of 0crit (addiction resistant rats), 1crit, 2crit and 3crit (addicted) rats. After 60 days of cocaine SA, 0, 1, 2 and 3 addiction-like criteria rats were identified and their addiction score was computed from their respective scores in each of the addiction-like criteria. 3crit rats ($n=6$) were the only group whose score was above the standard deviation (2.49) and 0crit, addiction resilient, rats ($n=16$) were the only group with negative scores.

despite its adverse consequences as revealed by the higher resistance to punishment of drug taking by an electric foot shock ($F_{1,20}=94.53$, $p<0.001$; Supplementary Figure S1C). As compared with 0crit rats, 3crit addicted rats also developed a characteristic burst-like pattern of cocaine intake throughout the SA history (Belin *et al*, 2009), as revealed by a progressive increase in episodes of infusions bursts from day 30 to day 60 (group effect: $F_{1,20}=5.03$, $p<0.05$, time: $F_{2,40}=4.5$, $p<0.05$, group × time interaction: $F_{2,40}=3.82$, $p<0.05$; Supplementary Figure S1D) that were related to the addiction score ($R=0.46$, $p<0.05$).

Table 1 Equation of the Regression Function, Scores and *p*-values of the Goodness of Fit Tests for Each Addiction-like Criterion

	Persistence of drug seeking (non-reinforced active nose pokes)		Motivation (breakpoint)		Resistance to punishment (% basal self-infusions)	
Fitting curve	$y = 109819 - 109816e^{(-0.5(\ln(x/4.78)/47.74)^2)}$		$y = 87777 - 87776e^{(-0.5(\ln(x/4.12)/36.79)^2)}$		$y = -3.2407x3 + 37.331x^2 - 130.86x + 146.67$	
R^2	0.99		0.96		0.98	
	Test value	*p*	Test value	*p*	Test value	*p*
Kolmogorov–Smirnov test	0.11895	0.1276	0.13218	0.1352	—	—
χ^2-test	1.46715	0.2258	1.38597	0.23909	—	—

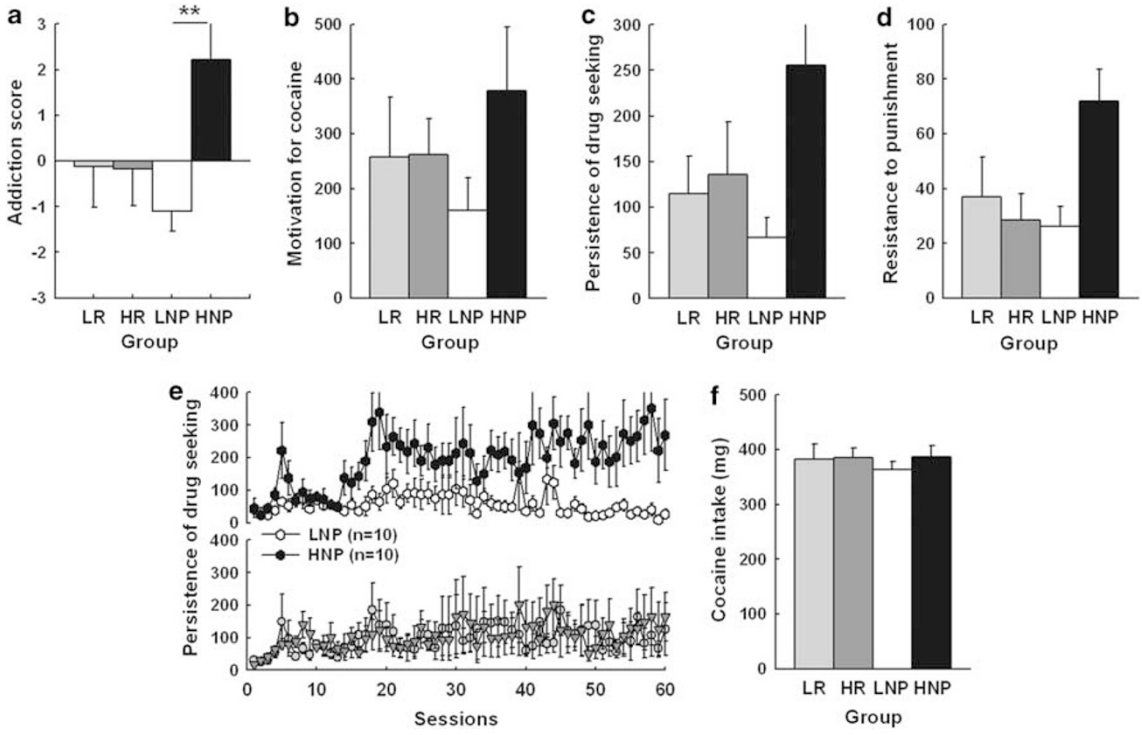

Figure 3 Novelty preference, but not locomotor reactivity to novelty, predicts the development of cocaine addiction-like behavior. Not only did high-novelty-preference (HNP) rats show higher addiction score than low-novelty-preference (LNP) rats (a) but they scored higher on each of the three addiction-like criteria, namely motivation for cocaine (measured by the breakpoint during a progressive ratio session; b) and inability to stop seeking cocaine when it was not available and signaled as so (non-reinforced active nose-pokes; c) and resistance to punishment (maintenance of drug use and drug seeking despite contingent electric foot-shocks; d), compared with LNP rats, HNP rats even showed a progressive development of this inability to refrain from drug seeking over time that has been previously described for 3crit addicted rats (e). These behavioral differences between HNP and LNP rats could not be attributable to differential cocaine intake, as the two groups have been exposed to the same amount of cocaine throughout the experiment (f). When compared with low-responder (LR) rats, high-responder (HR) rats showed no difference in the addiction-like behavioral measures, thereby illustrating that locomotor reactivity to novelty, as opposed to novelty preference, does not predict addiction-like behavior for cocaine.

Novelty Preference, but Not Locomotor Reactivity to Novelty, Predicts the Development of Addiction-like Behavior

Although HR and LR rats showed no difference in either their addiction score ($F < 1$; Figure 3a) or each of the three addiction-like criteria ($F < 1$; Figure 3b–d), HNP rats showed a higher score than LNP animals in their addiction score ($F_{1,18} = 10.59$, $p < 0.01$; Figure 3a) or each of the addiction-like criteria (group effect, $F_{1,18} = 5.95$, $p < 0.05$, group-behavior interaction: $F_{1,18} = 1.74$, $p = 0.19$; Figure 3b–d). These behavioral differences were not attributed to a differential propensity, either between HNP and LNP, or HR and LR rats, to acquire cocaine SA at the dose of 0.8 mg/kg used in this study (Supplementary Figure S2A).

Akin to 3crit addicted rats (Deroche-Gamonet *et al*, 2004, present study, data not shown), HNP rats progressively became unable to refrain from drug seeking during 'no-drug' periods as compared with LNP rats (group effect: $F_{1,18} = 9.23$, $p < 0.01$, group × time interaction:

$F_{59,1062} = 1.73$, $p < 0.001$; Figure 3e), a difference that was not observed between HR and LR rats (Figure 3e). However, HNP rats did not resemble 3crit addicted rats in their development of burst-like pattern of cocaine SA, as HNP rats did not differ from LNP rats, as neither did HR from LR rats in this behavioral feature (Supplementary Figure S2B).

Importantly, the behavioral differences observed between HNP and LNP rats cannot be attributed to a differential cocaine exposure, as the two groups did not differ for their total cocaine intake during the 60 days preceding the assessment of the addiction-like criteria ($F_{1,18} < 1$; Figure 3f).

A dimensional analysis further confirmed that novelty preference, but not locomotor reactivity to novelty, predicts addiction-like behavior (Table 2). Thus not only was novelty preference correlated with the addiction score ($R = 0.389$, $p < 0.02$), but novelty preference was also related to resistance to punishment ($R = 0.31$, $p < 0.05$) and persistence of cocaine seeking ($R = 0.339$, $p < 0.05$; Table 2). As opposed to novelty preference, locomotor response to novelty was related neither to the addiction-like criteria nor to the addiction score (Table 2).

A principal component analysis was then carried out in order to further model the relationships between addiction-like behavior, locomotor reactivity to novelty and novelty preference in the rat (Figure 4). The principal component analysis, with the addiction score, the percentage of time spent in the new compartment of a novelty-induced place preference procedure and the total photocell beam breaks in a 2 h novelty-induced locomotor activity session as variables, revealed that two main factors explain >75% of the total variance of the model.

The first factor, which accounts for 46% of the general variance, is the most representative of the model. Both addiction score and novelty preference, loading >70%, were highly correlated to this factor 1. However, factor 2, which is orthogonal to factor 1 and accounts for 30% of the variance is correlated only to the locomotor reactivity variable (loading 85% on factor 2) and therefore may only represent this behavioral dimension.

Table 2 Dimensional Relationships Between Novelty Preference, Locomotor Reactivity, Addiction Score, and the Three Addiction-like Criteria

	Novelty preference	Locomotor reactivity to novelty
Addiction score	0.39*	−0.058
Resistance to punishment	0.31*	−0.015
Motivation	0.25	0.11
Persistence in drug seeking	0.34*	−0.07

Spearman correlations revealed significant associations between novelty preference and addiction-like behaviour in that the novelty preference trait was correlated to the addiction score, as well as resistance to punishment and persistence of cocaine seeking. However, locomotor response to novelty was correlated to none of the addiction measures. *$p < 0.05$.

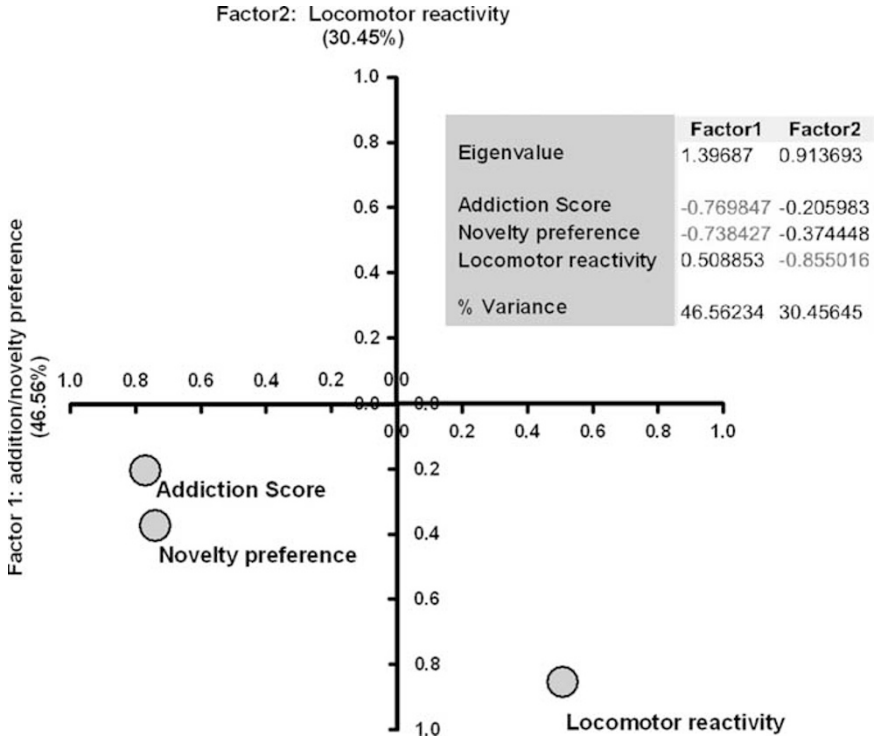

Figure 4 Dimensional analysis of the theoretical relationships between addiction-like behavior, novelty preference and locomotor reactivity to novelty in the rat. A principal component analysis, with the addiction score, the percentage of time spent in the new compartment of a novelty-induced place preference procedure and the total photocell beam breaks in a 2 h novelty-induced locomotor activity session as variables, revealed two factors explaining 77% of the total variance of the model. The first factor, which accounts for 46% of the model, represents the novelty preference/addiction dimension, as the variables used for these two constructs load heavily (>70%) on this factor. However, factor 2, which is orthogonal to the first one, represents the dimension relative to reactivity to novelty, as its representative variable, ie, novelty-induced locomotor activity loads (85%) almost alone on this factor.

DISCUSSION

The dimensional and between-subject analyses of this study reveal that HNP trait predicts the severity of addiction-like behavior for cocaine. Novelty preference was related to addiction both in simple correlation and multidimensional analyses, ie, principal component analysis. In addition, HNP rats identified before drug exposure showed a much higher addiction score than LNP littermates after protracted cocaine SA without differing in their total cocaine intake. This difference was attributable to higher performance in the three addiction-like behaviors. Thus, novelty preference trait predicted several facets of the multisymptomatic model of addiction-like behavior for cocaine used in this study (Deroche-Gamonet *et al*, 2004; Belin *et al*, 2008, 2009).

However, HNP trait in the rat was not correlated to the three addiction-like criteria, but specifically to resistance to punishment and inability to refrain from drug seeking. This result suggests that HNP trait may capture a particular form of vulnerability to compulsive-like behavior and further reinforces the fact that the present addiction model, through the three addiction-like behaviors, captures complementary, but distinct, aspects of a complex psychopathology. The somehow segregated association of novelty preference with specific addiction-like criteria extends a previous relationship described between a behavioral trait, namely, high impulsivity trait, as measured as a high number of premature responses during long inter-trial interval sessions in the five-choice serial reaction time task, and addiction-like behavior in rats, which was attributable exclusively to a tight relationship between impulsivity and resistance to shock-induced punishment of cocaine taking (Belin *et al*, 2008).

Interestingly, although this study replicates our previous demonstration that cocaine addiction in 3crit rats is preceded and accompanied by the development of a characteristic pattern of SA expressed by the emergence of bursts episodes of >5 infusions obtained in <5 min, HNP rats were shown not to develop such burst-like pattern of cocaine SA. This observation suggests that the etiological contribution of novelty preference to cocaine addiction is dissociable from the one of the drug-induced behavioral adaptations to drug taking, ie, burst-like pattern of SA (Belin *et al*, 2009). This is of marked interest in the light of a recent study by Beckmann *et al*, (2010) that revealed a correlation between novelty preference and sign tracking. Sign tracking has been suggested to reflect increased attribution of incentive salience (Tomie *et al*, 2008) and vulnerability to drug addiction (Tomie *et al*, 2008; Beckmann *et al*, 2010). Thereby, novelty preference may be contributing to increased vulnerability to addiction-like behavior through strengthened propensity to acquire Pavlovian incentive salience processes.

These data suggest that more insights into the behavioral factors contributing to increased vulnerability to compulsive cocaine intake may be better achieved from a dimensional approach combining different behavioral traits, each predicting preferentially one dimension of the addiction process. This is also supported by the distributions analysis performed in this study. Because of the large number of animals used in this study, we were able to carry out an analysis of the distributions for each of the addiction-like behavior. Motivation and inability to refrain from drug seeking were distributed according to a log-normal regression, suggesting that the population was spread along a continuum with some outliers (Limpert *et al*, 2001). Resistance to shock-induced punishment, however, was characterized by a bimodal distribution, composed of a log-normal sub-population for the low scores besides which a normal sub-population was identified for the highest scores. A bimodal distribution for compulsive cocaine SA has already been suggested in previous studies (Pelloux *et al*, 2007; Belin *et al*, 2009), in which it was not possible to carry out any mathematical modeling because of the small number of animals they used. Bimodal distributions are very common in life science literature, especially during speciation process (Dieckmann and Doebeli, 1999), whereby one whole population is somehow segregated to two independent populations (Hasegawa *et al*, 2006). Rare in behavioral neuroscience, bimodal distributions have, however, been observed for drug-induced behaviors (Ellenbroek and Cools, 2002), suggesting that the neurobiological substrates of behavioral inter-individual differences need in some cases to be challenged in order to reveal bimodal distribution. Our results suggest that a specific subpopulation in the rat has diverged so that it has become specifically more vulnerable to maintain drug use despite adverse consequences, as measured as resistance to punishment, when chronically exposed to the drug. This hypothesis, although speculative, when transferred to the human situation may resonate well with the Nesse and Berridge's (1997) suggestion that the vulnerability to drug addiction is a matter of evolution.

While providing the first evidence for a positive relationship between novelty preference and addiction-like behaviors, this study confirms our previous observation that locomotor reactivity to novelty does not predict the vulnerability to shift from sustained drug use to cocaine addiction (Belin *et al*, 2008), but does rather predict the propensity to self-administer drugs (Piazza *et al*, 1989, 2000; Belin *et al*, 2008). Thus HR rats readily self-administer cocaine or amphetamine, as well as other addictive drugs, at doses that are not reinforcing in LR rats (Piazza *et al*, 1989; Belin *et al*, 2008; Blanchard *et al*, 2009). However, HR rats do not develop cocaine addiction-like behavior more than LR after extended exposure to the drug (Belin *et al*, 2008) and, as compared with 0crit rats, 3crit, addicted, rats do not show a higher locomotor response to novelty (Deroche-Gamonet *et al*, 2004). Additionally, confirming previous observations (Belin *et al*, 2008), no dimensional relationship was revealed in this study, both from correlation and principal component analyses, between locomotor reactivity and addiction-like behavior. Indeed, the latent variable model resulting from the principal component analysis reveals that only factor 1 represents a latent variable, ie, a theoretical construct that accounts for both novelty preference and addiction severity. Thus factor 1 may represent the dimension whereby the etiological factor 'novelty preference' contributing to increased risk of addiction is related to the severity of addiction-like behavior in rats. However, factor 2 does not provide any new, integrative, construct about the dimensions of the model in that it represents only the locomotor response to novelty dimension.

The dissociation between novelty preference and novelty-induced locomotor activity reported in this study is consistent with previous studies, which repeatedly failed to identify a relationship between these two behavioral traits measured with various approaches including open field, locomotor activity chamber, novel object recognition, place preference tests (Bevins *et al*, 1997; Klebaur *et al*, 2001; Cain *et al*, 2004; Pelloux *et al*, 2004). Both pharmacological (Bardo *et al*, 1990) or molecular (Adriani *et al*, 2009) manipulations of novelty preference have been shown not to impact onto novelty-induced locomotor activation. Thus, although novelty preference and locomotor reactivity to novelty are both blocked by microinfusions of dopaminergic antagonists directly into the nucleus accumbens of rats (Bardo *et al*, 1989; Hooks and Kalivas, 1995; for review see Bardo *et al*, 1996), these two behavioral traits are underlined by dissociable neurobiological mechanisms. These include a prominent role of D1 dopamine receptors in the expression of novelty preference (Bardo *et al*, 1993), as opposed to an implication of the HPA axis specifically in novelty-induced locomotor activity. Indeed, although the HR phenotype is associated with specific alterations of the HPA axis (Piazza *et al*, 1991), novelty preference is not associated with changes in corticosterone secretion (Misslin *et al*, 1982). Thus, while stress-related mechanisms involved in the high sensitivity to addictive drugs found in HR rats (Deroche *et al*, 1993; Rouge-Pont *et al*, 1998; Kabbaj *et al*, 2000) may subserve vulnerability to drug use (for review Piazza and Le Moal, 1998), they may not be implicated in the vulnerability to switch to compulsive cocaine SA (Deroche-Gamonet and Piazza, 2010).

Such a conclusion needs nevertheless further research to fully address the implication of the stress system in the novelty preference test used in this study, especially when one considers the demonstration by Dellu *et al* (1993) in our laboratory that HR rats do seem to prefer a new unexplored arm on a Y maze test. This apparent discrepancy actually illustrates the importance of a standardization of novelty preference procedures. Indeed, depending on the study, novelty preference has been measured in a Y maze (Dellu *et al*, 1993) or a CPP box (present study, Klebaur *et al*, 2001; Cain *et al*, 2004), considering two to five (Dellu *et al*, 1993) or 15 min of novelty exploration (present study, Klebaur *et al*, 2001; Cain *et al*, 2004) tested immediately (present study), 30 min (Dellu *et al*, 1993) or 24 h after the familiar environment exploration (Klebaur *et al*, 2001; Cain *et al*, 2004). Clearly, our procedure and behavioral measures differ in several aspects from the one by Dellu *et al* (1993), such as, among others, duration of the measure of novelty preference, familiar/new compartment size ratio (1 : 1 in this study, 2 : 1 in Dellu *et al* (1993), latency between habituation and novelty preference test. These methodological differences might be responsible for a distinct involvement of stress-related factors in the novelty-preference tests in this study and the one by Dellu *et al* (1993).

Nevertheless, this data suggest that the HR phenotype and its underlying neurobiological mechanisms may be involved in facilitating the initiation of cocaine use, but not in the transition to switch from controlled to compulsive cocaine use (Deroche-Gamonet and Piazza, 2010), that is instead predicted by novelty-preference (present study) and high impulsivity trait (Belin *et al*, 2008). Further research is necessary to determine whether impulsivity and novelty preference contribute additively or interactively to the etiology of cocaine addiction. Also, provided that high impulsive (Economidou *et al*, 2009) and addicted rats (Deroche-Gamonet *et al*, 2004, Belin *et al* 2009) are highly vulnerable to cue- and cocaine-induced reinstatement of cocaine seeking, respectively, an important follow-up study should focus on the relationships between novelty-preference trait and vulnerability to reinstatement, a procedure with great heuristic value for the study of long-term maintenance of drug addiction (Shaham *et al*, 2003; Bossert *et al*, 2005).

These data are consistent with the two-step hypothesis of addiction recently developed by Deroche-Gamonet and Piazza (2010) according to which the development of addiction would be mediated by two different vulnerable phenotypes. The first, a 'drug use prone' phenotype, which is positively correlated with reactivity to novelty, facilitates the development of drug intake and subsequently sustained drug use, setting the conditions for addiction to develop. Indeed addiction appears only after a prolonged period of sustained drug use (Deroche-Gamonet *et al*, 2004). However to shift from sustained drug use to addiction, a second vulnerable phenotype would be necessary, ie, a 'drug addiction prone' phenotype that is predicted so far by novelty seeking (present data) or impulsivity (Belin *et al*, 2008), and that predisposes to compulsive drug intake. This hypothesis fits well with recently published epidemiological data (Swendsen *et al*, 2010) indicating distinct mental disorders as risk factors for substance use and addiction. In conclusion, in conditions, similar to the ones of the real world in which drugs have to be actively seeked at all stages of the addiction process, an individual will need both phenotypes to develop addiction.

Therefore this preclinical data suggest that the correlates of the increased propensity shown by human sensation seekers to use addictive drugs (Zuckerman, 1986) should be dissociated from those associated with the transition from sustained to compulsive drug use. Indeed, not only is sensation seeking a heterogeneous, multifaceted, construct (Zuckerman *et al*, 1978) but it is quantified according to different, not necessarily overlapping (Cloninger, 1988), personality scales including the Zuckerman, Eysenck, Arnett, and Cloninger's scales. A factorial analysis of the different items of the sensation seeking scale developed by Zuckerman and Neeb (1979) revealed four dimensions (Arnett, 1994) namely thrill and adventure seeking, experience seeking, disinhibition, and boredom susceptibility, of which the thrill and adventure seeking and disinhibition sub-scales have been suggested to refer to sensation seeking, whereas the experience seeking and boredom susceptibility sub-scales would refer to novelty seeking (Wohlwill, 1984; Arnett, 1994). Further research is needed to investigate which of these sub-scales is the most predictive of the vulnerability to switch to compulsive cocaine use, thereby clearly refining the relationships between sensation seeking trait and vulnerability to cocaine addiction.

In conclusion, in this study, we developed a behavioral procedure that allows identifying a novelty-seeking trait in the rat based on the preference for a new compartment in a free choice procedure. HNP rats in this procedure were

shown to be vulnerable to develop a high compulsive cocaine taking behavior. Thus this study provides new insights into the factors predisposing to cocaine addiction, comforting the hypothesis that different behavioral phenotypes predispose to different stages of the addiction process, some, such as the HR phenotype, predisposing to drug use, and others, including the high impulsive and HNP phenotypes facilitating the shift to compulsive cocaine intake and addiction.

ACKNOWLEDGEMENTS

This work was supported by the ANR (2005), INSERM, Région Aquitaine, MILDT/INSERM/Inca 2008 grants to PVP and VDG. DB is supported by an INSERM AVENIR grant. The authors thank Dr Ruth McNamara for careful review of the manuscript.

DISCLOSURE

The authors declare no conflict of interests.

REFERENCES

Abreuvillaca Y, Queirozgomes F, Dalmonte A, Filgueiras C, Manhaes A (2006). Individual differences in novelty-seeking behavior but not in anxiety response to a new environment can predict nicotine consumption in adolescent C57BL/6 mice. *Behav Brain Res* **167**: 175–182.

Adriani W, Boyer F, Gioiosa L, Macri S, Dreyer JL, Laviola G (2009). Increased impulsive behavior and risk proneness following lentivirus-mediated dopamine transporter overexpression in rats' nucleus accumbens. *Neuroscience* **159**: 47–58.

Anthony JC, Warner LA, Kessler RC (1994). Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the national comorbidity survey. *Exp Clin Psychopharmacol* **2**: 244–268.

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. American Psychiatric Press: Washington DC.

Arnett J (1994). Sensation seeking: a new conceptualization and a new scale. *Pers Individ Dif* **16**: 289–296.

Ballaz SJ, Akil H, Watson SJ (2007). The CCK-system mediates adaptation to novelty-induced stress in the rat: a pharmacological evidence. *Neurosci Lett* **428**: 27–32.

Ballaz SJ, Akil H, Watson SJ (2008). The CCK-system underpins novelty-seeking behavior in the rat: gene expression and pharmacological analyses. *Neuropeptides* **42**: 245–253.

Bardo M, Donohew RL, Harrington NG (1996). Psychobiology of novelty seeking and drug seeking behavior. *Behav Brain Res* **77**: 23–43.

Bardo M, Neisewander JL, Pierce R (1989). Novelty-induced place preference behavior in rats: effects of opiate and dopaminergic drugs. *Pharmacol Biochem Behav* **32**: 683–689.

Bardo MT, Bowling SL, Robinet PM, Rowlett JK, Lacy M, Mattingly BA (1993). Role of dopamine D1 and D2 receptors in novelty-maintained place preference. *Exp Clin Psychopharmacol* **1**: 101–109.

Bardo MT, Lacy M, Mattingly BA (1990). Effects of apomorphine on novelty-induced place preference behavior in rats. *Pharmacol Biochem Behav* **37**: 89–93.

Beckmann JS, Marusich JA, Gipson CD, Bardo MT (2010). Novelty seeking, incentive salience and acquisition of cocaine self-administration in the rat. *Behav Brain Res* (e-pub ahead of print).

Belin D, Balado E, Piazza PV, Deroche-Gamonet V (2009). Pattern of intake and drug craving predict the development of cocaine addiction-like behavior in rats. *Biol Psychiatry* **65**: 863–868.

Belin D, Mar A, Dalley J, Robbins T, Everitt B (2008). High impulsivity predicts the switch to compulsive cocaine-taking. *Science* **320**: 1352–1355.

Bevins RA, Klebaur JE, Bardo M (1997). Individual differences in response to novelty, amphetamine-induced activity and drug discrimination in rats. *Behav Pharmacol* **8**: 113–123.

Blanchard MM, Mendelsohn D, Stamp JA (2009). The HR/LR model: further evidence as an animal model of sensation seeking. *Neurosci Biobehav Rev* **33**: 1145–1154.

Bossert JM, Ghitza UE, Lu L, Epstein DH, Shaham Y (2005). Neurobiology of relapse to heroin and cocaine seeking: an update and clinical implications. *Eur J Pharmacol* **526**: 36–50.

Buckman JF, Yusko DA, White HR, Pandina RJ (2009). Risk profile of male college athletes who use performance-enhancing substances. *J Stud Alcohol Drugs* **70**: 919–923.

Cain M, Saucier D, Bardo M (2005). Novelty seeking and drug use: contribution of an animal model. *Exp Clin Psychopharmacol* **13**: 367–375.

Cain ME, Smith C, Bardo M (2004). The effect of novelty on amphetamine self-administration in rats classified as high and low responders. *Psychopharmacology (Berl)* **176**: 129–138.

Cloninger CR (1988). A unified biosocial theory of personality and its role in the development of anxiety states: a reply to commentaries. *Psychiatr Dev* **6**: 83–120.

Darnaudery M, Pallares M, Piazza PV, Le Moal M, Mayo W (2002). The neurosteroid pregnenolone sulfate infused into the medial septum nucleus increases hippocampal acetylcholine and spatial memory in rats. *Brain Res* **951**: 237–242.

Dellu F, Mayo W, Piazza PV, Le Moal M, Simon H (1993). Individual differences in behavioral responses to novelty in rats. Possible relationship with the sensation-seeking trait in man. *Pers Individ Dif* **15**: 411.

Dellu F, Mayo W, Vallee M, Maccari S, Piazza PV, Le Moal M *et al* (1996a). Behavioral reactivity to novelty during youth as a predictive factor of stress-induced corticosterone secretion in the elderly—a life-span study in rats. *Psychoneuroendocrinology* **21**: 441–453.

Dellu F, Piazza PV, Mayo W, Le Moal M, Simon H (1996b). Novelty-seeking in rats—biobehavioral characteristics and possible relationship with the sensation-seeking trait in man. *Neuropsychobiology* **34**: 136–145.

Deminiere JM, Piazza PV, Guegan G, Abrous N, Maccari S, Le Moal M *et al* (1992). Increased locomotor response to novelty and propensity to intravenous amphetamine self-administration in adult offspring of stressed mothers. *Brain Res* **586**: 135–139.

Deroche V, Piazza PV, Le Moal M, Simon H (1993). Individual differences in the psychomotor effects of morphine are predicted by reactivity to novelty and influenced by corticosterone secretion. *Brain Res* **623**: 341–344.

Deroche-Gamonet V, Belin D, Piazza PV (2004). Evidence for addiction-like behavior in the rat. *Science* **305**: 1014–1017.

Deroche-Gamonet V, Piazza PV (2010). Transition to addiction. In: Koob GF, Le Moal M, Thompson EB (eds). *Encyclopedia of Behavioral Neuroscience*, Vol. 3. Academic Press: Oxford. pp 422–428.

Dieckmann U, Doebeli M (1999). On the origin of species by sympatric speciation. *Nature* **400**: 354–357.

Ellenbroek BA, Cools AR (2002). Apomorphine susceptibility and animal models for psychopathology: genes and environment. *Behav Genet* **32**: 349–361.

Economidou D, Pelloux Y, Robbins TW, Dalley JW, Everitt BJ (2009). High impulsivity predicts relapse to cocaine-seeking after punishment-induced abstinence. *Biol Psychiatry* **65**: 851–856.

Franques P (2003). Sensation seeking as a common factor in opioid dependent subjects and high risk sport practicing subjects. A cross sectional study. *Drug Alcohol Depend* **69**: 121–126.

Franques P, Auriacombe M, Tignol J (2000). Addiction and personality. *Encephale* **26**: 68–78.
Hasegawa M, Yahara T, Yasumoto A, Hotta M (2006). Bimodal distribution of flowering time in a natural hybrid population of daylily (Hemerocallis fulva) and nightlily (Hemerocallis citrina). *J Plant Res* **119**: 63–68.
Hooks MS, Kalivas PW (1995). The role of mesoaccumbens—pallidal circuitry in novelty-induced behavioral activation. *Neuroscience* **64**: 587–597.
Horvath P, Zuckerman M (1993). Sensation seeking, risk appraisal, and risky behavior. *Pers Individ Dif* **14**: 41–52.
Jonah BA (1997). Sensation seeking and risky driving: a review and synthesis of the literature. *Accid Anal Prev* **29**: 651–665.
Kabbaj M, Devine DP, Savage VR, Akil H (2000). Neurobiological correlates of individual differences in novelty-seeking behavior in the rat: differential expression of stress-related molecules. *J Neurosci* **20**: 6983–6988.
Kalichman SC, Johnson JR, Adair V, Rompa D, Multhauf K, Kelly JA (1994). Sexual sensation seeking: scale development and predicting AIDS-risk behavior among homosexually active men. *J Pers Assess* **62**: 385–397.
Klebaur JE, Bardo M (1999). Individual differences in novelty seeking on the playground maze predict amphetamine conditioned place preference. *Pharmacol Biochem Behav* **63**: 131–136.
Klebaur JE, Bevins RA, Segar TM, Bardo M (2001). Individual differences in behavioral responses to novelty and amphetamine self-administration in male and female rats. *Behav Pharmacol* **12**: 267–275.
Koob GF, Le Moal M (2005). *Neurobiology of Addiction*. Academic Press: London.
Kreek M, Nielsen D, Butelman E, Laforge K (2005). Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. *Nat Neurosci* **8**: 1450–1457.
Limpert E, Stahel WA, Abbt M (2001). Log-normal distributions across the sciences: keys and clues. *Bioscience* **51**: 341–352.
Misslin R, Herzog F, Koch B, Ropartz P (1982). Effects of isolation, handling and novelty on the pituitary—adrenal response in the mouse. *Psychoneuroendocrinology* **7**: 217–221.
Nesse RM, Berridge K (1997). Psychoactive drug use in evolutionary perspective. *Science* **278**: 63–66.
Pelloux Y, Costentin J, Duterte-Boucher D (2004). Differential effects of novelty exposure on place preference conditioning to amphetamine and its oral consumption. *Psychopharmacology* **171**: 277–285.
Pelloux Y, Everitt B, Dickinson A (2007). Compulsive drug seeking by rats under punishment: effects of drug taking history. *Psychopharmacology (Berl)* **194**: 127–137.
Piazza PV, Deminiere JM, Le Moal M, Simon H (1989). Factors that predict individual vulnerability to amphetamine self-administration. *Science* **245**: 1511–1513.
Piazza PV, Deminiere JM, Maccari S, Mormede P, Le Moal M, Simon H (1990). Individual reactivity to novelty predicts probability of amphetamine self-administration. *Behav Pharmacol* **1**: 339–345.
Piazza PV, Deroche-Gamonet V, Rouge-Pont F, Le Moal M (2000). Vertical shifts in self-administration dose-response functions predict a drug-vulnerable phenotype predisposed to addiction. *J Neurosci* **20**: 4226–4232.
Piazza PV, Le Moal M (1998). The role of stress in drug self-administration. *Trends Pharmacol Sci* **19**: 67–74.
Piazza PV, Maccari S, Deminiere JM, Le Moal M, Mormede P, Simon H (1991). Corticosterone levels determine individual vulnerability to amphetamine self-administration. *Proc Natl Acad Sci USA* **88**: 2088–2092.
Rouge-Pont F, Deroche V, Le Moal M, Piazza PV (1998). Individual differences in stress-induced dopamine release in the nucleus accumbens are influenced by corticosterone. *Eur J Neurosci* **10**: 3903–3907.
Shaham Y, Shalev U, Lu L, De Wit H, Stewart J (2003). The reinstatement model of drug relapse: history, methodology and major findings. *Psychopharmacology* **168**: 3–20.
Shaw PJA (2003). *Multivariate Statistics for the Environmental Sciences*. Hodder Arnold: London.
Sher KJ, Bartholow BD, Wood MD (2000). Personality and substance use disorders: a prospective study. *J Consult Clin Psychol* **68**: 818–829.
Swendsen J, Conway KP, Degenhardt L, Glantz M, Jin R, Merikangas KR *et al* (2010). Mental disorders as risk factors for substance use, abuse and dependence: results from the 10-year follow-up of the National Comorbidity Survey. *Addiction* **105**: 1117–1128.
Tomie A, Grimes KL, Pohorecky LA (2008). Behavioral characteristics and neurobiological substrates shared by Pavlovian sign-tracking and drug abuse. *Brain Res Rev* **58**: 121–135.
Turner CA, Flagel S, Clinton S, Akil H, Watson S (2008). Cocaine interacts with the novelty-seeking trait to modulate FGFR1 gene expression in the rat. *Neurosci Lett* **446**: 105–107.
Uhl G, Grow RW (2004). The burden of complex genetics in brain disorders. *Arch Gen Psychiatry* **61**: 223–229.
Wills TA, Vaccaro D, McNamara G (1994). Novelty seeking, risk taking, and related constructs as predictors of adolescent substance use: an application of Cloninger's theory. *J Subst Abuse* **6**: 1–20.
Wohlwill JF (1984). What are sensation seekers seeking. *Behav Brain Sci* **7**: 453.
Woicik PA, Stewart SH, Pihl RO, Conrod PJ (2009). The substance use risk profile scale: a scale measuring traits linked to reinforcement-specific substance use profiles. *Addict Behav* **34**: 1042–1055.
Zuckerman M (1986). Sensation seeking and the endogenous deficit theory of drug abuse. *NIDA Res Monogr* **74**: 59–70.
Zuckerman M, Ball S, Black J (1990). Influences of sensation seeking, gender, risk appraisal, and situational motivation on smoking. *Addict Behav* **15**: 209–220.
Zuckerman M, Eysenck S, Eysenck HJ (1978). Sensation seeking in England and America: cross-cultural, age, and sex comparisons. *J Consult Clin Psychol* **46**: 139–149.
Zuckerman M, Kuhlman DM (2000). Personality and risk-taking: common biosocial factors. *J Pers* **68**: 999–1029.
Zuckerman M, Neeb M (1979). Sensation seeking and psychopathology. *Psychiatry Res* **1**: 255–264.

Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)