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Influence of the Novelty-Seeking Endophenotype on the Rewarding Effects of Psychostimulant Drugs in Animal Models

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Abstract: Novelty seeking (NS), defined as a tendency to pursue novel and intense emotional sensations and experiences, is one of the most relevant individual factors predicting drug use among humans. High novelty seeking (HNS) individuals present an increased risk of drug use compared to low novelty seekers. The NS endophenotype may explain some of the differences observed among individuals exposed to drugs of abuse in adolescence. However, there is little research about the particular response of adolescents to drugs of abuse in function of this endophenotype, and the data that do exist are inconclusive. The present work reviews the literature regarding the influence of NS on psychostimulant reward, with particular focus on adolescent subjects. First, the different animal models of NS and the importance of this endophenotype in adolescence are discussed. Later, studies that have used the most common animal models of reward (self-administration, conditioned place preference paradigms) to evaluate how the NS trait influences the rewarding effects of psychostimulants are reviewed. Finally, possible explanations for the enhanced risk of developing substance dependence among HNS individuals are discussed. In conclusion, the studies referred to in this review show that the HNS trait is associated with: (1) increased initial sensitivity to the rewarding effects of psychostimulants, (2) a higher level of drug craving when the subject is exposed to the environmental cues associated with the drug, and (3) enhanced long-term vulnerability to relapse to drug consumption after prolonged abstinence.

Keywords: Animal models, conditioned place preference, novelty seeking, psychostimulants, rewarding effects, self-administration.

INTRODUCTION

Predisposition to drug addiction is caused by the interaction of many different factors, among which the most documented are a vulnerable phenotype or personality, the drug itself and environment [1]. Individual differences in vulnerability to addiction are thought to exist before the first experience of a drug, and may relate, at least in part, to individual differences in sensitivity to drug reward [2]. Therefore, the study of endophenotypes is a way of clarifying the underlying factors that contribute to making an individual vulnerable to drug addiction [3]. Endophenotypes have been defined as quantitative traits related with a disorder and are heritably determined, mainly state-independent (*i.e*., manifested in periods of health or illness), co-segregate with a disorder within the family, and are more prevalent among non-affected family members than in the general population [4]. In this way, endophenotypes are considered to be traits that are half-way between genotype and phenotype, since both are characterized by predisposing genes and clinical symptoms of a complex disorder [3]. Hence, many authors have used endophenotype to identify markers of susceptibility to drug dependence as the scientific basis of new preventive strategies for individuals at risk and to create successful therapies that mitigate neuropsychiatric diseases [3, 5-8].

Novelty seeking (NS), or sensation seeking, is a personality trait defined as a tendency to pursue novel and intense emotional sensations and experiences [9]. It is employed to refer to individuals who like taking risks with the purpose of achieving stimulation and seeking new environments and situations that make their experiences more intense [10]. The first author who defined the term of novelty or sensation seeking was Zuckerman, who developed a sensation seeking scale together with Link [11], and the most widely used scale for measuring this parameter, known as Zuckerman's Sensation Seeking Scale [10]. Other authors have extended the work of Zuckerman, such as Cloninger, whose Cloninger's Tridimensional Personality Questionnaire (TPQ) is employed to measure the NS trait in humans [12]. Since then, further research has improved understanding of this phenotype [2, 8, 10, 13-17]. NS is a multifaceted behavioural construct that includes thrill-seeking, novelty-preference, risk-taking and harm avoidance, and these personality characteristics are present in individuals at risk of developing a drug use disorder [8].

The endophenotype of NS is one of the most relevant individual factors that predict drug use among humans [2].

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There is considerable evidence that high novelty seekers present an increased risk of drug use compared to low novelty seekers [3, 8, 18-22]. Numerous scientists have highlighted the important contribution of this personality trait to the aetiology and ontogenesis of addiction, which has justified considering the novelty/sensation-seeking trait as a significant neurobiological marker of individuals predisposed to addiction [1, 16, 17]. Additionally, it is known that the NS trait is mediated by the mesolimbic dopaminergic system in a similar way to drug seeking behaviour [23].

Adolescence is the stage of life in whichit is most likely that drug consumption is initiated [17, 24, 25], since high-risk behaviours and increased exploration are typical in this period [26]. Risk-taking behaviour seems to be manifested in adolescence due to enhanced sensation seeking related to changes in functions of dopaminergic activity between childhood and adolescence [27]. Neurobehavioral disinhibition in the frontal cortex circuits observed in human imaging studies suggests that adolescents are more sensitive to reward and evaluate good experiences more positively than they do adverse ones negatively [28, 29]. The adolescent brain operates in a promotivational state due to a limited inhibitory capacity, poor regulatory control, and dopaminergic hyperactivity in the nucleus accumbens (NAcc) when processing appetitive stimuli and amygdala hyperactivity [30]. Therefore, the harm-avoidance system is not effective for avoiding drug consumption when adolescents are exposed to drugs. In consequence, NS behaviour is exhibited before drug consumption [2], and the risk of drug use in high novelty seeking (HNS) adolescentsis increased [31-34]. This early drug-taking has been associated with increased use and dependence in adulthood [35-37]. However, not all users progress to dependence, and this transitionis thought to depend on certain characteristics, of which NS is likely to be one.

A greater sensitivity of HNS young adults to a drug's effects has also been reported [34, 38-40]. Some human studies have demonstrated that high novelty seekers display greater sensitivity to the physiological and psychological effects of psychostimulants in comparison with low novelty seekers [34, 41-43]. Some authors have suggested that high novelty seekers have a tendency to develop addictive behaviour [16], usually at initiation of consumption [33, 44-46], as a consequence of differential reward sensitivities between individuals [17]. However, there is lack of a consensus, as other studies challenge this relationship [47, 48] and the connection between sensation/novelty seeking and addiction risk [22, 49]. Longitudinal studies point to a direct path leading from NS to initiationof drug use [2, 50], but this traithas been shown to be absent in non-abuser siblings of individuals addicted to psychostimulants and to be present in regular consumers who control their consumption of the drug [22]. Individuals with high levels of NS are more likely to experiment with drugs; nevertheless, despite continuous use, they have a relatively low risk of developing dependence when there is no family history of addiction [49]. Moreover, it is important to note that drug use itself enhancesthe NS trait [22].

Therefore, it is currently under debate whether NS truly represents an endophenotype of addiction risk. Studies in humans have not established whether the NS trait is causally related to drug abuse or a consequence of this behaviour. It is important to continue exploring this issue in studies with animal models that allow a better assessment of the causal relationship between NS and vulnerability to the development of addiction [8, 17]. The animal model of novelty exploration or response in rodents has been used to study sensation seeker behaviour vulnerability. Studies show that animal models evaluate similar behavioural patterns to the human novelty/sensation seeking trait [51], in addition to physiological consequences and gene expression patterns [17]. Moreover, they allow the ethical problems surrounding research with humans to be avoided. In this sense, these modelsarea good way to evaluate the vulnerability of human sensation seekers to developing drug addiction.

In the present work, we review the literature on the influence of NS endophenotype on psychostimulant reward, with particular focus on adolescent subjects. First, we discussanimal models of NS (*e.g.*, the inescapable vs. free-choice novelty models) and address differences in the way they measure this endophenotype, which can influence the results obtained regarding the relationship between drugs of abuse and NS in experimental animals. Afterwards, we emphasize the importance of this endophenotype in adolescence, a developmental period with enhanced vulnerability to the effects of drugs of abuse. We then review the studies that have used the most common animal models of reward [intravenous self-administration paradigms and conditioned place preference (CPP)] to evaluate how the NS trait influences the rewarding effects of psychostimulants. Finally, we discuss possible explanations for the enhanced risk of HNS individuals to developing substance dependence, and we draw conclusions about whether NS truly represents an endophenotype of addiction risk.

ANIMAL MODELS OF NOVELTY SEEKING

Novelty-seeking in rodents can be defined as the enhanced specific exploration of novel situations, unknown objects or stimuli. It is a complex behaviour that involves the detection of changes in the environment (cognition), and is related to stress responsiveness [52]. Rodents show an innate preference for novelty [53], and their behaviour in novel environments is conditioned by the interaction of several factors, including activity, motivation to explore and fear/anxiety [54, 55].

Different procedures have been used to screen rats and mice in order to assign them to subgroups according to high or low expression of a given measure. Nowadays, two different approaches are employed to model the NS trait: (1) novelty-induced locomotor reactivity to a new inescapable environment; and (2) preference for novel objects or environments; *i.e.*, a propensity to explore a new object/environment in a free-choice procedure [17, 56-59]. The first approach, and most assessed paradigm, is known as Novelty Responding, which classifies animals as high or low responders according to their locomotor activity in a new inescapable environment. Although commonly considered animal models of the NS trait, some researchers affirm that this is inaccurate, as it is not clear whether the novelty-induced locomotor activity displayed by rodents in an

inescapable environment is an escape behaviour or an exploratory one. Thus, the animal models of preference for novel objects/environments in a free-choice procedure are considered a better measure of NS, since rodents can choose to either approach or avoid novelty in the test [2].

Procedures of Response to Inescapable Novelty

The novel open-field environment was the first test described by Piazza and collaborators [56] to assess the locomotor response of rodents to a novel environment. The median [60], quartile split [61] of distance or activity, and number of rears [62] recorded over 10 min [63], 30 min [64], 1h [63, 65] or 2h [56] are used to categorize the animals as high or low responders [17]. The test consists of placing the animal in a new environment from which it cannot escape, and is therefore considered an inescapable procedure [2]. The novelty response can also be measured by rearing behaviour in an open field, which distinguishes between high and low rearing-activity or vertical-activation (HRA or LRA). This is a stable trait that reflects both emotionality and exploratory activity [66, 67]. Stronger rearing has been observed in HRA in a novel object test, which shows reactivity to novelty and exploratory activity in response to novel stimuli [68].

Activity in a novel environment has also been measured using an exploration box test [66, 69]. This test consists of placing three unknown objects and one familiar food (*i.e.* food pellet) in the same location on five consecutive days. The behavioural measures recorded during this task are locomotor movement and rearing activity for the exploration of the three unfamiliar objects. These measures are used to classify animals in terms of high or low exploratory activity (HE or LE), and indicate exploration behaviour as a whole and with respect to a particular stimulus. Thus, this task has been considered an indicator of inquisitive and inspective exploration [66, 69].

In addition to a novel open-field environment, the wheel-running procedure has been used to classify animals as high or low responders according to their activity in the running wheel. Larson and Carroll [70] assessed both the motor response to novelty (day 1) and locomotor activity on the second day. High responding (HR) rats presented more avidity for wheel-running than low responding (LR) rats, but both showed a similar locomotor activity on day 2. In this way, the procedure aims to distinguish between the response to novel stimuli and the animal's inherent motor activity.

Novelty Seeking Free-Choice Procedures

The novel environment test is the most popular method used to classify animals according to their high or low exploratory behaviour. Animals are first counterbalanced by placing them in one of the two compartments of a CPP or black/white box in order to habituate them to the environment [71-74] during one [62, 75] or more sessions [74]. The door is then opened so that the animals can explore both compartments freely; typically for a 20 min period (test session) [62, 74, 75]. The following behaviours are generally scored: number of crossings between compartments; latency of first time the animal enters the novel compartment, and percentage of time spent in the novel compartment. Animals are then categorized as high or low novelty seekers depending on their novelty-preference score (percentage) in the novel and familiar environment.

Another method similar to the novel environment test is the spontaneous alternation task, in which a Y-maze [62] or T-maze [76] is used. Animals are placed in the stem of the apparatus and are allowed to enter any arm. In a second trial, the animals are free to make the same or an alternative choice. Two paradigms have been used to test spontaneous alternation: the forced trial procedure and free trial procedure. In both cases, animals are confined for 30 sec to either the chosen or forced compartment and then allowed to explore both arms freely in a test phase. Rodents show a higher preference for the noveltycompartment when the election is forced rather than chosen freely by the animal, because the last procedure depends on the bias of the rodent for one side of the apparatus or the other [76-78].

The Hole-board test is considered a useful tool to evaluate novelty preference in rodents [79, 80]. The apparatus consists of a square box, in the floor of which there are equidistant holes and sensors inside the holes that detect the number of head dips performed by the animals. This measure, and the latency time to the first head dip, are used to classify animals as high or low novelty seekers [62, 81, 82]. The emotional response of animals when facing an unfamiliar environment can be estimated and used sometimes to assess anxiety state too [79, 82-85]. This procedure shares certain features with the novelty responder test, such as inescapable condition, though some authors have verified that it is a good measure of NS because it is independent of locomotor activity [2, 85, 86].

The first description of the novel object preference test as a new procedure for evaluating directed exploration was provided by Nicholls and collaborators [87]. In a similar way to the novel environment test, rodents are free to choose between a novel and familiar object. In a playground maze, animals are exposed on consecutive days to several familiar objects during periods of 3 [87], 5 [88] or 10 minutes [74, 75, 89]. The quantity of familiar objects can vary: one novel and eight familiar objects [88], one novel and two familiar objects [75, 89], or one novel and one familiar object [90]. In the last trial, one familiar object is replaced by a new object and the animal's approach to the novel or familiar object is assessed. The measures typically obtained in this test are the latency to explore and time spent exploring the novel object, total number of approaches to the novel object, and the percentage of time spent exploring novel and familiar objects. Rodents are classified as high or low novelty seekers depending on a median [88] or mean [75] split of the duration or percentage of duration spent engaged with the novel object. In the playground maze the animal's locomotion is measured by recording the distance covered by the animals as they cross the maze.

In the novel-object place conditioning paradigm, first described by Bevins and Bardo [91], animals are conditioned to one side of the apparatus paired with a new object that is placed there daily (paired side), while no objects are placed on the other side (unpaired side). Each animal is exposed to

distinct environments for 10 [91] or 15 minutes [92] and is conditioned for 8 [91] or 5 consecutive days [92]. On the test day, rodents are allowed to explore the compartments freely without any object inside the chambers for 10 min. The measure obtained in this test is the time spent in each compartment, with more time being spent in the novelty-paired compartment by high novelty seekers.

Another paradigm similar to the object preference test is object preference on the hole-board, described by Kliethermes and Crabbe [62]. The preference for a novel object or exploration is defined by the sum of the time engaged in head dipping in the holes connecting compartments that contain objects divided by the total time engaged in head dipping. The procedure is identical to the Hole-board test [79], with the exception that two objects are placed in two separate holes.

In summary, novelty-seeking free-choice procedures allow animals to choose to approach or reject novelty: *i.e.*, rodents can freely choose the novel object or environment. However, procedures of response to inescapable novelty do not allow animals to choose freely the novel object or environment because they are confined to a determinate place. In these procedures, the measure used to categorize subjects as high or low novelty-seekers is their response to an inescapable novel environment such as locomotion activity or pressing a lever during a specified period of time. Therefore, novelty-seeking free-choice procedures are currently considered more suitable for categorizing the novelty-seeking trait.

ADOLESCENCE AND NOVELTY SEEKING

Adolescence is a time of major biological and psychological changes and a critical period of development for the central nervous system (CNS) and, more specifically, for the dopaminergic system [93]. In rodents, the term adolescence refers to postnatal day (PND) 21 to PND 60 [94]. Three different stages of adolescence have been distinguished: early adolescence (prepubescent or juvenile, PND 21 to 34), middle adolescence (periadolescent, PND 34 to 46), and late adolescence (young adult, PND 46 to 59) [95-97].

Although adolescence is related mainly with hormonal changes, this developmental period is also marked by critical neural plasticity [98]. Alterations of the dopaminergic system, especially the projections from mesolimbic areas to the prefrontal cortex (PFC), appear to play a critical role in the increased reward-seeking behaviour of adolescent individuals. The adolescent stage is characterized by an increase, a reduction and a redistribution of dopamine (DA) receptor concentration [99]. Despite lower DA release in basal conditions, dopaminergic neurons are capable of delivering much greater amounts of DA if they are stimulated with pharmacological or environmental stimuli [100]. This is probably due to the fact that extracellular DA levels are greater in adolescents [100-103] and the rate of DA increase may be faster at this age [102, 104]. These changes provoke hypersensitivity of the striatal system, which, together with immature inhibitory substrates in the PFC (the "cognitive control" system), leads to an increase in adolescent risk-taking [99, 105, 106]. Therefore, it can be hypothesized that some adaptive behaviours characteristic of adolescence, such as play behaviour or exploration of novel environments or objects, result in enhanced DA release when compared to adulthood [94]. To sum up, the adolescent brain operates in a promotivational state with limited inhibitory and regulatory control, dopaminergic hyperactivity in the NAcc when processing appetitive stimuli, and, finally, hyperactivity in the amygdala, which explains affective intensity and lability, and a weaker harm-avoidance system [107]. Consequently, the relatively early development of the NAcc and amygdala, together with an immature PFC, tilts behaviour toward risk-seeking and sensation-seeking preference [30].

Studies with animal models have confirmed these characteristics in adolescent rodents, which are prone to high risk taking behaviour and increased exploration [26, 25, 108-110], in a similar way to adolescent humans [27]. Therefore, adolescent rodents are more sensitive than their adult counterparts to the rewarding properties of stimuli such as food [111-113], social peers and novelty [92]. Accordingly, adolescents find drugs more rewarding, and for that reason self-administer higher doses of psychostimulants such as cocaine, methamphetamine and amphetamine [102, 114-120]. Moreover, they experience less aversive effects of addictive drugs and reduced withdrawal symptoms [see review 111]. Altogether, these factors favour adolescents' initiation of drug consumption and make them more vulnerable to developing substance abuse disorders.

The NS trait is considered to be more pronounced in adolescent than in adult rodents, as occurs in humans [94], although its influence on drug consumption has generally been studied in adult rodents [16]. Juvenile rodents present greater hyperactivity and exploration in novel environments, an increased social peer interaction, and consummatory behaviours [reviewed in 26, 121]. In addition, adolescent mice have been shown to perform a higher number of explorations than adults in the novel object recognition task and novel environment test of free-choice, in which they spend more time exploring the novel object/environment [75]. In an inescapable, novel environment, adolescent rodents displayed higher novelty-induced locomotor activity than adults when measured during the initial minutes in the open field [58, 122], but not when measured over a longer interval [63, 122], probably because adolescents habituate to novelty more rapidly [58].

NOVELTY SEEKING ENDOPHENOTYPE AND THE REWARDING EFFECTS OF PSYCHOSTIMULANT DRUGS

There is considerable evidence that HNS represent an increased risk of drug use when compared to LNS. However, differences in NS do not always predict drug reward [see reviews 2, 8], probably due to variations in the procedure for evaluating NS or in the drug's effects. With this in mind, this section reviews the studies that have assessed the influence of NS on the rewarding effects of psychostimulant drugs in the most common animal models of reward: the intravenous drug self-administration and CPP paradigms. We have

distinguished between the two main types of animal models of NS, since the results of tests for inescapable and free-choice novelty environment do not always correlate [59, 64, 74, 123], probably due to the fact that they measure different aspects of NS.

Self-Administration Paradigm

Intravenous drug self-administration is a widely used animal model of human drug abuse and dependence, since it is a procedure that allows the reinforcing effects of abuse substances to be measured [124]. Tables **1** and **2** summarises the results of the main studies to have used the self-administration paradigm to evaluate the reinforcing effects of psychostimulants in animals according to their NS phenotype.

Procedures of Response to Novelty

The animal model of response to novelty characterized initially by Piazza and collaborators [56] has been widely used to predict the reinforcing effect of psychostimulants [see reviews 2, 8, 17, 125]. It has been reported that HR rats in a novel environment self-administer more amphetamine than LR rats [56, 57, 125, 126], whether males or females [57]. Moreover, HR rats were shown to acquire amphetamine self-administration with lower doses than LR rats, while their drug intake and motivation for the drug (breaking point) were similar after 11 days of training [125].

Similarly, HR rats acquire cocaine self-administration at lower doses [127-129] and more rapidly [130-132] than their LR counterparts. HR rats also self-administer greater amounts of cocaine and display more regular self-administration at lower doses [60, 129, 133]. Importantly, HR females have been shown to self-administer significantly more cocaine than HR male and LR male and female rats [130, 131].

Although these results suggest that the response to novelty predicts vulnerability to acquire psychostimulant self-administration, other studies have reported a lack of such a relationship for amphetamine [74, 123], methylphenidate [134],

Table 1. Results of the main studies to have used the self-administration paradigm to evaluate the reinforcing effects of psychostimulants in animals classified as high or low novelty seekers according to an inescapable NS paradigm.

Novelty-Seeking Animal Model	Animals	Age	Drug	Main Results in Self-Administration	References
Locomotor response to novelty	Male Sprague-Dawley rats	Adult 280 to 300 g	10 µg/inf amphetamine FR1 i.v.	Only acquired HR	Piazza *et al*., 1989
	Male and female Sprague–Dawley rats	Adult male: 200–225 g or 250-300 g Adult female: 150–175 g	0.01-0.16-0.03 mg/kg/inf amphetamine FR1 to FR5 i.v.	HR>LR	Pierre and Vezina, 1997; Klebaur *et al*., 2001
	Male and female Sprague–Dawley rats	Adult 90-100 PND 250–320 g	0.2-0.219-0.25-0.5-1 mg/kg/inf cocaine FR1 i.v. 0.1 mg/kg/ inf cocaine FR1to FR6 i.v.	HR>LR HR females>HR males	Grimm and See, 1997; Piazza *et al*., 2000; Kabbaj *et al*., 2001; Mantsch *et al*., 2001; Davis *et al*., 2008; Cummings *et al*., 2011
	Male Sprague–Dawley rats	Adult 280–320 g	0.175 mg/kg/inf cocaine FR1 i.v.	Only acquired HR	Marinelli and White, 2000
	Male diversity Outbred (DO) mice	Housing at 4 weeks old Adult	1.0 mg/kg/inf cocaine FR1 i.v.	HR>LR	Dickson *et al*., 2015
	Male Sprague–Dawley rats	Adult 175–200 g	0.1 mg/kg/inf amphetamine FR1 i.v.	HR=LR	Cain *et al*., 2005; Meyer *et al*., 2010
	Male Sprague–Dawley rats	Adult 10 weeks old	0.1 ml of 0.25 mg methylphenidate per infusion FR1 i.v.	HR=LR	de la Peña *et al*., 2014
	Male prague–Dawley rats	Adult 250–320 g	1 mg/kg/inf cocaine FR1 to FR6 i.v. 0.25 mg/kg/inf cocaine FR5 i.v. 0.3-0.8-1 mg/kg/inf cocaine FR1 i.v.	HR=LR	Piazza *et al*., 2000; Mitchell *et al*., 2005; Beckmann *et al*., 2011; Belin *et al*. 2011
	Male Sprague–Dawley rats	Adult 200 g	1 mg/kg/inf MDMA FR1 i.v.	HR=LR	Bird and Schenk, 2013
Wheel running	Female Wistar rats	Adult 250–340 g	0.4 mg/kg/inf cocaine FR1 i.v.	HR=LR	Larson and Carroll, 2005

Table 2. Results of the main studies to have used the self-administration paradigm to evaluate the reinforcing effects of psychostimulants in animals classified as high or low novelty seekers according to a free-choice NS paradigm.

Novelty-Seeking Animal Model	Animals	Age	Drug	Main Results in Self-Administration	References
Novelty place preference	Male Sprague–Dawley rats	Adult 175–200 g 70-75 PND	0.1 mg/kg/inf amphetamine FR1 and FR5 i.v.	HNS>LNS	Cain *et al*., 2005; Meyer *et al*. 2010
	Male Sprague–Dawley rats	Adult 250–300g	0.3-0.8-1 mg/kg/inf cocaine FR1 i.v.	HNS>LNS	Beckmann *et al*., 2011; Belin *et al*., 2011
	Male and female Sprague–Dawley rats	Adult male: 200–225 g Adult female: 150–175 g	0.03-0.16 mg/kg/inf amphetamine FR1 to FR5 i.v.	HR=LR	Klebaur *et al*., 2001
Novel object test	Male Sprague–Dawley rats	Adult 10 weeks old	0.1 ml of 0.25 mg methylphenidate per infusion FR1 i.v.	HNS >LNS	de la Peña *et al*., 2014
	Male Sprague–Dawley rats	Adult 175–200 g	0.01 - 0.1 mg/kg/inf amphetamine FR1 to FR5 i.v.	HR=LR	Cain *et al*., 2005
Hole-board	Male diversity Outbred (DO) mice	Housing at 4 weeks old Adult	1 mg/kg/infcocaine FR1 i.v.	HNS>LNS	Dickson *et al*., 2015

cocaine [59, 60, 64, 129, 135] and 3,4-methylenedioxymethamphetamine (MDMA) [136]. Differences in the operant response measured and the fixed ratio (FR) schedule used, as well as the time to access the drug [74, 125] and the doses administered [59, 60, 64, 129, 135], may have reduced inherent individual differences in subsequent operant responses to the drug in the aforementioned studies. In fact, differences between HR and LR animals in the self-administration of psychostimulants with respect to acquisition of the operant response seem to exist only at low doses.

Novelty Seeking Free-Choice Procedures

Preference for a new environment/object in a free-choice test may also predict amphetamine self-administration. HNS rats have been shown to self-administer more amphetamine [74] or methylphenidate [134] than LNS rats. Moreover, Meyer and collaborators [123], in a study performed across twelve inbred rat strains, reported a relationship between novelty preference ratio and amphetamine infusions, since HNS strains self-administered more amphetamine than LNS ones.

Likewise, free-choice categorized HNS animals show higher vulnerability and severity to cocaine addiction [59]. Rats displaying higher exploration are more predisposed to cocaine consumptionthan low novelty preference rats. HNS animals have higher addiction scores, such as persistent responding when the drug is signalled as unavailable, resistance of the self-administration response to punishment, and a higher breaking point in a progressive ratio (PR) schedule. All these differences have been observed during the acquisition of self-administration with low doses of cocaine [59, 64], but no differences were observed with higher doses [64]. In line with this, female HR rats showed a greater number of responses on the active lever than LR after a priming injection of cocaine, though no significant differences were detected between high and low responders with respect to the maintenance or extinction of cocaine self-administration [70]. However, the number of exploratory nose pokes in the hole-board test of diverse outbred mice strains of both sexes positively correlated with the acquisition of self-administration, the number of cocaine infusions during the FR1 schedule, and the breaking point in the progressive ratio [132].

Nevertheless, the novelty place preference test does not always predict amphetamine self-administration of individuals. Male and female rats, classified as high or low novelty seekers according to the novelty preference test, do not show differences in self-administration of amphetamine [57]. These apparently contradictory results, in addition to the results of the few studies to have used free-choice preference tests, suggest that these NS measures are not as predictive of drug self-administration as individual differences in inescapable novelty (high/low responders) test [2]. A possible explanation is that the inescapable and free-choice novelty tests measure different facets of NS [59, 74, 123]. Several studies have observed a lack of correlation among different tasks that evaluate NS trait [59, 63, 64, 74, 75, 123], suggesting that each NS paradigm assesses different aspects of this trait.

Conditioned Place Preference

CPP is a paradigm that evaluates the conditioned rewarding effects of addictive drugs [137-139]. It is a procedure that assesses positive and pleasant properties of stimuli in a rapid and simple way [140]. In this paradigm, contextual or environmental stimuli acquire secondary appetitive properties (conditioned rewarding effects) when paired with a primary reinforcer [138, 141]. Conditioned reward implies that animals attribute positive incentive value to the cues associated with the primary reinforcer, and thus perform free or voluntary responses to obtain access to said cues [142]. Under appropriate conditions, CPP can be sensitive to a wide range of substances, including psychostimulants [140]. Tables **3** and **4** summarize the results of the main

Table 3. Results of the main studies to have used the CPP paradigm to evaluate the rewarding effects of psychostimulants in animals classified as high or low novelty seekers according to an inescapable NS paradigm.

Novelty-Seeking Animal Model	Animals	Age	Drug	Rewarding Effects of Psychostimulants in CPP	References
Locomotor response to novelty	Male Long Evans rats	PND 46 Adolescent PND 70 Adult	Amphetamine (0.5 or 1.0 mg/kg) i.p.	HR less sensitive to amphetamine CPP (%time)	Mathew *et al*., 2010
	Male Sprague-Dawley rats	290-330g Adult 200-225g Adult	Cocaine (5,10,12,15,20 mg/kg) i.p Amphetamine (0.4mg/kg) s.c	HR=LR acquired CPP	Gong *et al*., 1996 Kosten and Miserendino, 1998 Dietz *et al*., 2007 Capriles *et al*., 2012 Robinet *et al*., 1998
	C57BL/6J male mice	7-8 weeks Adult	Cocaine (4, 8, 12 mg/kg) i.p.	LR>HR in CPP at low doses	Brabant *et al*., 2005 Shimosato and Watanabe, 2003
	Male Slc:ddY mice	5 weeks Adolescent	Cocaine (5, 10, 20mg/kg) i.p.		
	Male and female OF1 mice	PND 35 Adolescent PND 56 Young adult	Cocaine (1mg/kg) i.p.	10 min: young adult HNR>LNS 1h: HR young adult male=LR young adult female acquired CPP	Arenas *et al*., 2014

studies to have used the CPP paradigm to evaluate the rewarding effects of psychostimulants in animals classified as high or low novelty seekers.

Procedures of Response to Novelty

Few studies have evaluated the influence of novelty response in the CPP induced by amphetamine, probably because the first results to be reported were negative. HR and LR rats did not differ in amphetamine CPP at low [143] or high doses [144], and both adolescent and adult HR rats were less sensitive than their LR counterparts to amphetamine in the CPP [122]. Only Pelloux and collaborators [145] reported that response to forced novelty predicted the strength of amphetamine-induced CPP, although only at a low dose.

Similarly, no notable differences were observed between HR and LR rats in the CPP induced by a wide range of doses of cocaine [146-149]. However, significantly higher place preference in HR rats 30 days after post-conditioning test has been reported [148]. In adolescent and adult male mice, the locomotor response to novelty correlated negatively with the magnitude of the CPP induced by low cocaine doses, but not by that induced by higher doses [150, 151]. Recently, another study has reported that male and female HR young adult mice (according to their locomotor response to novelty) develop CPP after conditioning with a subthreshold dose of cocaine, differently to LR mice [63].

The CPP paradigm is generally characterized by a lack of dose-response effects; thus, the use of effective doses for inducing CPP may mask differences between HR and LR animals [137, 152]. Dose-response effects in the CPP paradigm can only be demonstrated by changes in the extinction of conditioned preference or in sensitivity to the reinstatement of drug-CPP [139]. The use of sub-threshold doses of cocaine may be useful to identify animals that are more sensitive to the conditioned rewarding effects of the drug. Another variable to take into consideration is the duration of the test used to classify animals as HR or LR, which may partly explain the lack of an association between the novelty response trait and drug effects in the CPP [58, 63, 122].

Novelty Seeking Free-Choice Procedures

The evaluation of novelty preference in a free-choice procedure seems to detect more differences between high and low novelty seekers. For example, the CPP induced by amphetamine [88, 143] and cocaine [63-75] has been shown to be greater in HNS than in LNS rodents, although other studies have failed to find a relationship between novelty environment preference and amphetamine-induced CPP [145].

Recently, studies in our laboratory have demonstrated that the evaluation of the novelty preference endophenotype depends on the age and/or sex of the mice and the type of test used to measure the NS trait [63, 75]. HNS mice tested in a novel environment in adulthood acquired CPP with subthreshold doses of cocaine, but no differences in CPP were observed between HNS and LNS when they were tested during adolescence [75]. Conversely, according to the hole-board test, HNS adolescent mice were more likely than LNS to develop CPP with subthreshold doses of cocaine. However, adult LNS females showed higher conditioning scores than HNS [63]. These results demonstrate that the behavioural profiles of adolescent and adult animals vary among NS paradigms, suggesting that the different NS tests evaluate different behavioural components of this endophenotype. Thus, the novel environment test can be considered to have a greater predictive capacity to identify "vulnerable-drug" individuals among adult mice, while the hole-board test is more effective for predicting drug vulnerability in adolescents [63, 75].

Table 4. Results of the main studies to have used the CPP paradigm to evaluate the rewarding effects of psychostimulants in animals classified as high or low novelty seekers according to a free-choice NS paradigm.

Novelty-Seeking Animal Model	Animals	Age	Drug	Rewarding Effects of Psychostimulants in CPP	Reference
Novel environment	Male Sprague-Dawley rats	200-225g Adult	Amphetamine (0.4 mg/kg) s.c.	HR>LR higher magnitude of CPP	Robinet *et al*. 1998
Novelty test chambers	Male Wistar rats	180-200g Adult	Amphetamine (0.2 – 3.2mg/kg) s.c.	HR=LR acquired CPP at high doses HR>LR stronger CPP at the lowest dose	Pelloux *et al*. 2004
Novelty test chambers	Sprague-Dawley rats	Adult	Amphetamine (0.75-10mg/kg) i.p.	HNS=LNS acquired CPP	Erb and Parker, 1994
Playground maze	Male Sprague-Dawley rats	200-225g Adult	Amphetamine (1–3 mg/kg) s.c.	HNS>LNS amphetamine CPP (1 mg/kg).	Klebaur and Bardo, 1999
Novel object recognition task Novel environment test	Male and female OF1 mice	PND 35 Adolescent PND 56 Young adult	Cocaine (1mg/kg) i.p.	HNS (Young adult)>LNS acquired CPP	Vidal-Infer *et al*., 2012
Hole-board	Male and female OF1 mice	PND 35 Adolescent PND 56 Young adult	Cocaine (1mg/kg) i.p.	HNS (adolescent) = LNS (young adult female) acquired CPP	Arenas *et al*., 2014
	Male OF1 mice	PND 31 Adolescent (binge) PND 67 Adult(CPP)	Alcohol Binge (2.5g/kg) i.p. + Cocaine (CPP) (1 or 6mg/kg) i.p. MDMA (CPP) (1.25 or 2.5mg/kg) i.p.	HNS=LNS acquisition CPP HNS reinstates cocaine CPP	Montagud-Romero *et al*., 2014
		PND 28/33 Adolescent (binge) PND 60/67 Adult (CPP)	MDMA or Cocaine binge i.p. + Cocaine (CPP) (1mg/kg) i.p. MDMA (CPP) (1.25mg/kg) i.p.	HNS>LNS acquired CPP with both drugs.	Rodríguez-Arias *et al*., 2015 Mateos-García *et al*., 2015

Finally, the influence of the NS trait in the long-term effects of adolescent exposure to drugs have been evaluated in a series of studies [82, 153, 154]. Mice were classified during adolescence as high or low novelty seekers according to the hole-board test and were subsequently exposed to chronic administration of cocaine, MDMA or alcohol. Cocaine- or MDMA-induced CPP was then evaluated in adulthood. Repeated administration of cocaine or MDMA during adolescence was shown to increase the conditioned rewarding effects of these drugs in HNS animals only [82, 154]. Ethanol binge drinking during adolescence increased sensitivity to the rewarding effects of low doses of cocaine and MDMA during adulthood in both HNS and LNS subjects. However, only high novelty seekers showed a reinstatement of cocaine CPP after a priming dose of this drug [153].

NEUROBIOLOGICAL SUBSTRATES OF NOVELTY SEEKING

The endophenotype of NS refers to individual differences in motivation for novelty [9], and the role of mesolimbic DA in motivational processes is well documented [155]. On the other hand, the involvement of the mesolimbic dopaminergic system in the rewarding effects of drugs of abuse has been widely studied [156]. Thus, differences in dopaminergic neurobiological substrates may explain, at least partially, the distinction between high and low novelty seekers and their variable sensitivity to drugs of abuse [17, 157].

There is a great deal of evidence that DA modulates NS behaviour. A free-choice approach to novelty directly activates the reward-relevant mesocorticolimbic dopamine circuitry [2]. Novel stimuli excite DA neurons, especially in the ventral striatum, and activate the brain regions that receive dopaminergic input [17]. Moreover, blockade of the DA transporter (DAT) increases NS behaviour in monkeys without affecting their capacity to select cues that are predictive of reward [158], and disruption of the DAT Dat1 gene diminishes novelty-related behaviour in mice [159]. Similarly, all animal models of NS are sensitive to manipulation of brain DA function [157]. Novelty place preference is blocked by DA antagonists [73, 160] and by depleting DA levels in NAcc with the neurotoxin 6-hydroxydopamine [161]. These findings demonstrate that increased extracellular dopamine levels underlie the positive evaluation of novel stimuli with respect to promoting exploratory behaviour, and suggest that alterations in DA reuptake contribute to excessive NS [158].

Additionally, several brain differences have been identified in HR vs. LR rats, such as higher extracellular DA in the NAcc and striatum, increased velocity of DA uptake in the NAcc, and higher mRNA levels of tyrosine hydroxylase and the DA D1 receptor. Furthermore, HR rats exhibit a

reduced density of accumbal DA D2 receptors, suggesting a decreased number of release-regulating autoreceptors or a compensatory downregulation of postsynaptic receptors in response to increased presynaptic DA release [see review 2]. These differences between HR and LR rats would explain the more intense basal firing of midbrain DA neurons observed in high novelty seekers, which is likely to be due to subsensitivity to impulse-regulating D2 somatodendritic autoreceptors [128]. D4 receptors have also been implicated in the response to novelty, since D4 knockout mice behave in the same way as low responders [17], and administration of an agonist of the D4 receptors has been shown to increase exploration of a novel object in mice [162].

Differential DA signalling between sensation/novelty-seeking personalities in humans has also been reported [163, 164]. Specifically, HNS individuals exhibit higher endogenous DA levels, lower activity of isoforms of monoamine oxidase (MAO), higher activity of dihydroxyphenylalanine (DOPA) decarboxylase, and stronger dopaminergic responses to cues predictive of reward in striatal regions with respect to LNS subjects [see review 157]. Finally, a strong relationship between polymorphism at DA D4 receptor loci and individual differences in NS personality has also been reported [157, 165]. Therefore, differences in the dopaminergic system have been highlighted as a possible explanation of the relation between this trait and drug addiction [16, 17, 166].

On the other hand, the role played bythe serotoninergic (5HT) system in the NS trait has also been assessed. Specifically, serotoninergic receptors (5-HT2C) seem to modulate mesocorticolimbic DA release, thus affecting motivation and behaviour. The 5-HT2C antagonist SB242084 has been shown to increase acquisition of the cocaine-conditioned response only in LR rats (enhancing the hedonic value of cocaine), suggesting that 5-HT2C receptors influence individual differences in cocaine reinforce-related learning/ memory processes [148]. More research is required to throw light on the role of the serotonin system in the influence of the NS endophenotype on the rewarding effects of drugs of abuse.

In summary, the HNS trait seems to be associated with differences in striatal DA function; specifically, higher novelty seekers may have higher endogenous striatal DA levels, stronger dopaminergic responses to reward cues, and lower availability of D2-type (D2/D3/D4) DA receptors in the striatum. Thus, a combination of high dopaminergic tone and a lower density of D2-type receptors in the striatum are potential contributors to the higher NS endophenotype, as reflected by an increased tendency to exhibit approach reactions towards novel stimuli which, on the contrary, elicit aversive reactions in others [157].

CONCLUSION

It is currently under debate whether NS truly represents an endophenotype for addiction risk. There is considerable evidence that high novelty seekers present an increased risk of drug abuse in comparison to low novelty seekers. However, whether this increased vulnerability is due to a greater sensitivity to the rewarding effects of psychostimulants or to early exposure to drugs has been the subject of little study [22, 134]. Nevertheless, the studies referred to in this revision have shown that the HNS trait is associated with increased initial sensitivity to the rewarding effects of psychostimulants, especially at low doses [63, 74, 75, 82, 123, 145, 153, 154]. In addition, HNS represents a higher risk of relapse into cocaine-seeking behaviour when the subject is re-exposed to the environmental cues associated with the drug [148, 153].

Despite the fact that subjects are more likely to become drug users during adolescence, very little research has been carried out regarding the relation between the NS trait and drugs of abuse in adolescent individuals. The NS trait could explain some of the differences observed among individuals exposed to drugs of abuse in adolescence, since we have demonstrated the influence of this endophenotype on the long-term effects of exposure during adolescence to drugs such as cocaine or MDMA [82, 153, 154].

Another important point with which to conclude this review is the fact that the different animal models of NS measure different parameters, as several studies have demonstrated [57, 63, 75, 143, 145, 167]. These different measures of the NS endophenotype may represent distinct behavioural components that are not equivalent, thus highlighting the complexity of the processes involved in the response to novelty. Furthermore, different NS tests involve varying capacities for identify vulnerable-drug individuals in adolescents vs adults. Future research will need to identify which dimensions of human sensation- and/or novelty-seeking are modelled in rodent paradigms and represent vulnerability markers for progression to and maintenance of drug addiction [157, 168].

In conclusion, a major challenge for current research into addiction is to identify the personality traits that predispose individuals to develop a drug use disorder during adolescence. HNS individuals present a greater risk of initiating drug use and developing substance dependence, as they exhibit higher sensitivity to the rewarding effects of psychostimulants and more marked changes after their consumption. Therefore, it is crucial to continue to employ animal models in order to understand better this causal relationship.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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LIST OF ABREVIATIONS

5HT	=	Serotoninergic
5-HT2C	=	Serotoninergic receptors
CNS	=	Central nervous system
CPP	=	Conditioned place preference
DA	=	Dopamine
DAT	=	Dopamine transporter
DOPA	=	Dihydroxyphenylalanine
FR	=	Fixed ratio
HE	=	High exploratory activity
HNS	=	High novelty seeking
HR	=	High responding
HRA	=	High rearing-activity or vertical-activation
i.v.	=	intravenous administration
LE	=	Low exploratory activity
LNS	=	Low novelty seeking
LR	=	Low responding
LRA	=	Low rearing-activity or vertical-activation
MAO	=	Monoamine oxidase
MDMA	=	3,4-methylenedioxymethamphetamine
NAcc	=	Nucleus accumbens
NS	=	Novelty seeking
PFC	=	Prefrontal cortex
PND	=	Postnatal day
PR	=	Progressive ratio
TPQ	=	Tridimensional Personality Questionnaire

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