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Exposure to nicotine enhances its subsequent self-administration: Contribution of nicotine-associated contextual stimuli

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Abstract

Contextual stimuli present during nicotine exposure can come to act as conditioned stimuli and have been shown to play an important role in ongoing nicotine self-administration. In the present study, we characterized the effects of contextual stimuli previously paired with non-contingent nicotine exposure injections on subsequent nicotine self-administration. Rats were exposed to five injections of either saline or nicotine (0.4 mg/kg, IP) in either their home cage or a self-administration chamber with the levers retracted. Two weeks later, they were allowed to self-administer nicotine (30 µg/kg/infusion, IV) under fixed ratio (FR) schedules of reinforcement across 12 consecutive sessions. Lastly, responding under a progressive ratio (PR) schedule was assessed. Rats exposed to nicotine in the self-administration chamber subsequently increased their intake of nicotine across the FR test days, obtaining more infusions on average by days 7–12 compared to their saline exposed controls. This increase was not due to nicotine exposure alone as rats exposed to nicotine in the home cage did not show this effect. It was also not due to differences in the final ratio achieved between nicotine and saline exposed rats. Although rats exposed to nicotine in the self-administration chambers displayed reduced discrimination between the active and inactive levers during FR testing, they showed increased motivation to self-administer nicotine under the PR schedule. These results indicate that exposure to nicotine can enhance its subsequent self-administration and highlight the contribution of nicotine-associated contextual stimuli to the work output rats ultimately emit to obtain the drug.

Keywords

nicotine; conditioning; exposure; self-administration; sensitization; contextual stimuli

1. Introduction

Epidemiological studies indicate that exposure to nicotine is associated with a greater subsequent predisposition to pursue and become addicted to the drug [1–3]. In animal studies, intermittent as opposed to continuous exposure to nicotine, a pattern associated with initial exposure to the drug, has been shown to produce long-lasting behavioral and neurochemical adaptations associated with increased risk for drug addiction [4–8]. As with

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other abused stimulants [9], adult rats repeatedly exposed to nicotine become sensitized to the locomotor and nucleus accumbens dopamine activating effects of the drug [10–15]. Sensitization of midbrain dopamine neuron reactivity by amphetamine is associated with increased work output and self-administration of amphetamine and cocaine [16, 17]. Curiously, few studies have assessed the effect of exposure to sensitizing regimens of nicotine injections on the subsequent self-administration of nicotine. In one study [18], mixed strain-specific effects of prior nicotine exposure were reported on acquisition of nicotine self-administration, with modest trends for enhancement in some cases and trends for disruption in others. In another study [19], enhanced self-administration was limited to the first few days of acquisition under a fixed ratio 1 (FR1) schedule of reinforcement and was no longer observed when the response criteria to earn an infusion were subsequently increased.

A number of factors can influence the extent to which prior exposure to nicotine affects subsequent responding to the drug, including intensity of the exposure regimen and the withdrawal period between exposure and testing. Generally, a more intense exposure regimen requires a longer withdrawal period in order to allow for the manifestation of sensitization to be observed [20]. Another equally important role has been described for drug-paired stimuli. It is well established that the expression of stimulant sensitization can come under strong environmental stimulus control, so that the presence of drug-paired or drug-unpaired stimuli during testing can regulate the intensity of the sensitized responses observed and in some cases determine whether sensitization is expressed at all [21–23]. An important contribution of such stimuli has been described for the expression of locomotor and nucleus accumbens dopamine sensitization by nicotine [24, 25], as well as for the ability of intermittent nicotine exposure to enhance the subsequent self-administration of amphetamine [5].

Discrete cues coupled with infusions of nicotine are necessary to maintain a high rate of self-administration of the drug [26] and responding for non-drug reinforcers is increased by nicotine even when it is administered non-contingently [27]. These findings illustrate the ability of nicotine to interact associatively and non-associatively with environmental cues and suggest a critical role for these interactions in the self-administration of the drug [28]. Consistent with these findings, contextual stimuli paired with nicotine self-administration have been reported to slow extinction of responding and reinstate drug seeking to a greater extent compared to neutral stimuli [29]. Surprisingly, the ability of nicotine-paired contextual stimuli to subsequently regulate nicotine self-administration has yet to be assessed. Notably, the modest effects of nicotine exposure on nicotine self-administration reported by Adriani et al. [19] and Shoaib et al. [18] were observed following exposure to nicotine in the home cage, not the self-administration chambers. Collectively, the above findings with nicotine and other stimulants suggest that contextual stimuli paired with non-contingent nicotine exposure injections should subsequently enable enhanced responding for the drug. This possibility was tested in the following experiments.

2. Methods and Materials

2.1 Subjects

Male Long-Evans rats weighing 250–275 g on arrival from Harlan Teklad (Madison, WI) were individually housed with food and water available ad libitum in a 12-h light/12-h dark reverse cycle room. Two separate shipments of rats were used for data collection and were both represented in each of the experimental groups. Upon arrival, rats were given 3–5 habituation days prior to the start of any procedures. All experiments were conducted in accordance with the Declaration of Helsinki and the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health. All

procedures were conducted according to a protocol approved by the University of Chicago Institutional Animal Care and Use Committee.

2.2 Self-administration apparatus

Experimental sessions were conducted in 16 operant chambers (31 × 25 × 30 cm; model H10-11R-TC, Coulbourn Instruments, Whitehall, PA) enclosed in sound-attenuating chambers. Two retractable levers (1 active, 1 inactive, each 6 cm above the rod floor) and a cue light (13 cm above the active lever) were positioned on one wall of the chamber. A counterbalanced arm and liquid swivel system consisting of a steel spring tether, a liquid swivel, and an infusion pump (model PHM-100, Med Associates, St. Albans, VT) allowed the rats to move freely in the chamber while attached to an infusion line. The latter was connected to a 10 ml syringe filled with nicotine solution.

2.3 Nicotine exposure

Rats were administered nicotine (0.4 mg/kg; IP) or saline by the experimenter every other day for a total of 5 injections. To assess the effect of nicotine exposure on subsequent self-administration of the drug, rats were transported in their home cage to a room separate from the colony where they were administered saline or nicotine injections in their home cage and returned to the colony 2 hours later (SAL HOME CAGE, n=12; NIC HOME CAGE, n=11). To assess what effect contextual stimuli paired with nicotine during exposure may have on the subsequent self-administration of the drug, rats in two separate groups were given saline or nicotine in the self-administration chamber with the response levers retracted (SAL SA CHAMBER n=11; NIC SA CHAMBER, n=12). Rats that underwent exposure in the self-administration chamber were returned to their home cage 2 hours following each injection. The cue light was illuminated for the entire 2 hours for the rats in the nicotine exposure condition. After the final exposure injection, rats were left undisturbed in their home cage for 9 days prior to surgical procedures. Testing began 5 days later (2 weeks after the final exposure injection). Nicotine [(–) nicotine tartrate] was obtained from Sigma Inc. (Saint Louis, MO), dissolved in sterile saline, and adjusted to pH=7.0 with NaOH. In all cases, the doses administered refer to the freebase.

2.4 Surgery

Rats were anesthetized with a mix of ketamine (100 mg/kg, i.p.) and xylazine (6 mg/kg, i.p.) and surgically implanted with an i.v. catheter into the right external jugular vein as described previously [30]. Catheters were made from silastic tubing (Dow Corning, Inc., Midland, MI) and connected to L-shaped 20 gauge guide cannulae (Plastics One, Roanoke, VA). The cannulae were threaded subcutaneously to a small incision on the head and secured in place with a dental cement head mount anchored to the skull with screws. Catheters were subsequently flushed daily with a sterile 0.9% SAL solution containing 30 IU/ml heparin and 250 mg/ml ampicillin to help maintain patency.

2.5 Nicotine self-administration

Reinforced lever presses on the active lever resulted in an infusion of nicotine (0.03 mg/kg/infusion) delivered in a volume of 0.09–0.11 ml/infusion at a rate of 1.065 ml/minute. For 15 seconds immediately following a reinforced response on the active lever, the cue light above the lever was illuminated and further responses on the lever were without consequence. Testing consisted of 15 daily, 2-hour nicotine self-administration sessions. In the first 12, each session began with an experimenter-delivered intravenous priming infusion. Rats initially obtained infusions on a FR1 schedule of reinforcement. This schedule was increased from FR1 to FR2, FR3 and FR5 once animals earned 5 or more infusions and at least 80% of lever responses were made on the active lever on each of two consecutive

days [31]; adapted from [18]. All presses on the inactive lever were recorded, but had no programmed consequences. Number of lever presses (active and inactive) and nicotine infusions obtained were also recorded. In the final three sessions (13–15), rats were tested under a progressive ratio (PR) schedule. Under this schedule, the number of responses required to earn each successive nicotine infusion was determined by $\text{ROUND}[5 \times \text{EXP}(0.25 \times \text{infusion number}) - 5]$ to produce the following sequence of required lever presses: 1, 3, 6, 9, 12, 17, 24, 32, 42, 56, 73, 95, 124, 161, 208, etc [32]. Daily PR sessions were terminated after 2 hours or after 1 hour elapsed without a drug infusion. Priming nicotine infusions were not given and the inactive lever was retracted during these sessions. The number of lever presses and infusions obtained in each PR session were recorded. After the last session, patency was tested by infusing 0.1 ml of a 20 mg/ml solution of ketamine into the catheters. Rats that failed to lose muscle tone within 5 seconds were excluded from the data analyses.

2.6 Data analyses

The number of infusions obtained on the 12 FR and 3 PR test days were analyzed separately using 3-way between-within analyses of variance (ANOVAs) with context (two levels: home cage and SA chamber) and exposure (two levels: saline and nicotine) as the between factors and test days (12 and 3) as the within factor. Based on the results of these analyses, 2-way between ANOVAs with context and exposure as the factors were subsequently conducted to assess group differences in the number of infusions obtained in the first (days 1–6) and second half (days 7–12) of FR testing as well as on the last day of PR testing. Lever presses over the 12 FR test days were analyzed for each group using 2-way within ANOVAs with response lever (two levels: active and inactive) and test days (12) as the factors. These data included responses made during time out periods. A 3-way between-within ANOVA with context and exposure as the between factors and test days as the within factor was used to analyze the FR schedule attained over the 12 FR test days. Based on the results of this analysis, a 2-way between ANOVA with context and exposure as the factors was subsequently used to assess group differences on the final ratio achieved on FR test day 12. As the specific pairwise group comparisons of interest were limited in number, LSD methods were used for this purpose. ANOVAs and subsequent group comparisons were conducted according to Kirk [43] and Hsu [44]. For ease of presentation, only effects that achieved statistical significance ($p < 0.05$) or showed a non-significant trend ($p < 0.10$) are reported.

3. Results

3.1 FR test days 1–12

Rats exposed to nicotine in the self-administration chamber subsequently obtained more infusions on the FR test days compared to their saline exposed controls (Fig. 1b). This effect was not observed in rats exposed to nicotine in the home cage (Fig. 1a). Analysis with the omnibus 3-way ANOVA indicated only a significant interaction of exposure $\times$ days ($F(11, 462) = 2.62, p < 0.01$). Based on this result, the data were subsequently analyzed with 2-way between ANOVAs which indicated a significant effect of exposure on days 7–12 ($F(1, 42) = 4.97, p < 0.05$) but not on days 1–6 of FR testing. LSD comparisons showed that rats exposed to nicotine in the self-administration chamber earned significantly more infusions compared to their saline exposed controls ($p < 0.01$), an effect not observed in rats exposed to nicotine in the home cage. No other group comparisons achieved statistical significance. Together, these results indicate that previous exposure to nicotine can enhance the number of infusions rats obtain when subsequently given the opportunity to self-administer the drug, but only when they do so in the environment in which they had been

previously exposed to the drug. Thus, nicotine exposure context appeared to contribute importantly to this effect.

To further characterize responding during the 12 FR test days, total active and inactive lever presses were determined across days for each experimental group (Fig. 2a–d). No significant group differences in time out responding were observed at any time. Patterns of lever responding differed between the groups, suggesting that lever discrimination over the 12 FR test days may have been affected by both nicotine exposure and nicotine-associated contextual stimuli. Analyses indicated a significant effect of lever in rats exposed to saline either in the home cage ($F(1,11)=19.73$, $p<0.001$; Fig. 2a) or in the self-administration chamber ($F(1,10)=43.08$, $p<0.001$; Fig. 2b). Rats exposed to saline in the home cage pressed the active lever significantly more than the inactive lever on days 1–6 ($p<0.01$) and 7–12 ($p<0.001$). Similarly, rats exposed to saline in the self-administration chamber also pressed the active lever significantly more than the inactive lever on days 1–6 ($p<0.001$) and 7–12 ($p<0.001$), demonstrating active versus inactive lever discrimination across days in both groups. Different patterns of responding were observed in the nicotine exposed groups. In rats exposed to nicotine in the home cage (Fig. 2c), significant effects of lever ($F(1,10)=24.86$, $p<0.001$) and days ($F(11,110)=2.96$, $p<0.01$) and a significant lever $\times$ days interaction ($F(11,110)=3.14$, $p<0.01$) were observed. Rats exposed to nicotine in the self-administration chamber (Fig. 2d) showed significant effects of lever ($F(1,11)=4.64$, $p=0.054$) and days ($F(11,121)=2.19$, $p<0.05$). Rats exposed to nicotine in the home cage showed significant active versus inactive lever discrimination on days 1–6 ($p<0.01$) and 7–12 ($p<0.001$) and also demonstrated a significant increase in active lever responding from days 1–6 to 7–12 ($p<0.001$). While rats exposed to nicotine in the self-administration chamber also demonstrated significant active versus inactive lever discrimination on days 1–6 ($p<0.01$) and days 7–12 ($p<0.01$), overall, these animals did not show a significant increase in active lever pressing from days 1–6 to 7–12 and the magnitude of the difference between the number of active and inactive lever presses actually diminished and became more variable towards the end of FR testing. The number of active and inactive lever presses emitted no longer differed significantly in this group on days 8, 10, and 12.

Consistent with the analyses of active versus inactive lever discrimination, rats in all groups showed an increase in FR schedule attained as FR testing progressed but, in rats previously exposed to nicotine, this effect was enhanced only in those exposed to nicotine in the home cage (Fig. 2e–f). The omnibus 3-way ANOVA conducted on FR schedule attained over the 12 FR test days indicated a significant effect of days ($F(11,462) = 29.03$, $p<0.001$) and significant context $\times$ days ($F(11,462) = 2.06$, $p<0.05$) and context $\times$ exposure $\times$ days interactions ($F(11,462) = 2.02$, $p<0.05$). The subsequent 2-way ANOVA conducted on the final FR schedule achieved on test day 12 indicated a significant effect of context ($F(1,42)=4.07$, $p<0.05$) and a trend towards a context $\times$ exposure interaction ($F(1,42)=3.33$, $p<0.08$). Rats exposed to nicotine in the home cage showed a trend for an increase in FR schedule achieved relative to their home cage saline exposed controls ($p<0.08$) and a significant increase ($p<0.01$) relative to the rats exposed to nicotine in the self-administration chamber. If anything, the FR schedule achieved by these latter rats was lower towards the end of FR testing relative to their own saline exposure controls.

3.2 PR test days

Consistent with the analyses of infusions obtained on the 12 FR test days, previous exposure to nicotine enhanced work output and as a result the number of infusions obtained on the PR test days, but only in rats tested in the environment in which they had been previously exposed to the drug: the self-administration chamber (Fig. 3). The omnibus 3-way ANOVA indicated a significant effect of exposure ($F(1,42)=5.86$, $p<0.05$) and significant exposure $\times$

context $\times$ days interaction ($F(2,84)=5.71, p<0.01$). The subsequent 2-way ANOVA conducted on the number infusions earned on the last PR test day (day 3) indicated a significant context $\times$ exposure interaction ($F(1,42)=6.63, p<0.05$). On this test day, rats exposed to nicotine in the self-administration chamber, but not those exposed to nicotine in the home cage, obtained significantly more infusions compared to their own saline exposed controls ($p<0.01$). Rats exposed to nicotine in the self-administration chamber also obtained significantly more infusions than rats exposed to nicotine in the home cage ($p<0.05$) and a trend for more infusions than the home cage saline exposed controls ($p<0.07$). Thus, the ability of prior nicotine exposure to enhance its own self-administration was again found to be influenced by the nicotine exposure context.

4. Discussion

In the present experiments, previous intermittent exposure to nicotine, a pattern often associated with initial exposure to tobacco, increased the number of nicotine infusions rats obtained when subsequently given the opportunity to self-administer the drug under both FR and PR schedules of reinforcement. The additional finding that this was observed only when rats were tested in the environment in which they had previously been exposed to similar nicotine injection regimens highlights the influence nicotine-associated contextual stimuli can exert on the behavior rats will emit to obtain the drug.

The present results are consistent with and extend previous findings showing that exposure to nicotine produces sensitization of its locomotor and nucleus accumbens dopamine activating effects [4, 10–15]. They are also consistent with other reports supporting a relation between sensitized midbrain dopamine neuron reactivity and enhanced stimulant self-administration [5, 9, 16, 17, 33]. Together with these findings, the present results support an incentive motivational view of enhanced nicotine intake [8, 9, 34, 35] and the suggestion by some that it is the changes in mesoaccumbens dopamine function induced by previous exposure to nicotine [1] that predisposes individuals to pursue this drug [2, 3].

Nicotine is well known to interact associatively and non-associatively with environmental cues to influence its own self-administration as well as that of non-drug reinforcers [28]. Contextual stimuli previously paired with nicotine have been shown to regulate the expression of locomotor and nucleus accumbens dopamine sensitization by nicotine [24, 25], to slow extinction of responding and promote reinstatement in nicotine self-administering rats [29], to enable enhanced amphetamine self-administration [5], and to increase craving for smoking in humans [36]. The present results extend these findings to show that nicotine associated contextual stimuli can also promote the expression of enhanced nicotine intake in rats and do so two weeks after the last non-contingent nicotine exposure injection and nicotine-context pairing. On the PR test days, rats that worked more obtained more nicotine infusions, reflecting the requirement of the exponential function used for the emission of progressively more lever presses to obtain successive nicotine infusions. Increases in break point observed with this schedule of reinforcement indicate more work output by the animal and are widely interpreted to reflect increased motivation to engage in the self-administration behavior in the face of increasing cost [9, 37]. Interestingly, characterization of responding on the 12 FR test days revealed a more complex relationship between lever pressing and nicotine infusions obtained. On these test days, the FR schedule was increased when rats met two criteria: 5 or more infusions obtained and 80% of lever responses made on the active lever on each of two consecutive days. This approach permitted assessment of the effect of previous nicotine exposure and the presence or absence of nicotine associated contextual stimuli during testing on acquisition of the lever press response as measured by increasing discrimination between the active and inactive levers [18]. Previous exposure to nicotine in the home cage led to an increase in active lever

pressing and an enhancement in lever discrimination over days as well as a trend for a greater increase in FR schedule achieved relative to home cage saline exposed controls. These findings may reflect non-associative effects of nicotine exposure on discrimination learning as have been described for locomotor sensitization [14], enhanced lever pressing for a conditioned reinforcer [38], and resistance to extinction [5].

Interestingly, rats previously exposed to nicotine in the self-administration chamber showed decreasing active versus inactive lever discrimination as FR testing progressed and, if anything, lower FR schedule achieved relative to their saline exposed controls by the end of FR testing. Typically, lack of active versus inactive lever discrimination is taken as an indication of disrupted learning during acquisition. However, these rats clearly learned to discriminate between the active and inactive levers during the first half of FR testing. Considering that these rats showed enhanced work output and more infusions obtained on the PR test days, these results may reflect a progressively perturbed ability to discriminate between the active and inactive levers resulting from the enhanced motivational state engendered in these animals by the nicotine associated contextual stimuli. The reasons for this perturbation remain unknown, but an interesting possibility is that it may be related to enhanced impulsivity. For example, various measures of impulsive behavior have been linked to drug-taking [39] and these are known to be exacerbated following repeated exposure to stimulants including nicotine [40] as well as presentation of drug-paired contextual stimuli [41]. It is unlikely that this perturbation of lever discrimination was a consequence of increased locomotor activity in rats exposed to nicotine in the self-administration chamber. Rats exposed to nicotine in the home cage exhibited significantly more total (active + inactive) lever presses than these animals ($t(21)=1.91$, $p<0.05$) with no perturbation in lever discrimination. It is equally unlikely that prior exposure to the self-administration chamber disrupted learning of the lever discrimination via a pre-exposure effect. Again, rats exposed to nicotine in the self-administration chamber learned to discriminate between levers in the first half of FR testing and no difference in the number of infusions obtained or in active versus inactive lever discrimination was observed throughout FR testing between the saline exposure groups.

Thus, it appears that different effects of nicotine exposure are subject to regulation by nicotine associated contextual stimuli. In the present experiments, these stimuli promoted the expression of enhanced nicotine intake but not enhanced lever discrimination. Consistent with these findings, the incentive motivational and response selecting effects of reward-paired cues were recently found to be dissociable with the former, but not the latter, dependent on brain dopamine transmission [42].

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References

- [1]. Kandel DB, Wu P, Davies M. Maternal smoking during pregnancy and smoking by adolescent daughters. *American Journal of Public Health*. 1994; 84:1407–13. [PubMed: 8092363]
- [2]. Kandel DB, Yamaguchi K, Chen K. Stages of progression in drug involvement from adolescence to adulthood: Further evidence for the gateway theory. *Journal of Studies on Alcohol*. 1992; 53:447–57. [PubMed: 1405637]
- [3]. Osler M, Clausen J, Ibsen KK, Jensen G. Maternal smoking during childhood and increased risk of smoking in young adulthood. *International Journal of Epidemiology*. 1995; 24:710–4. [PubMed: 8550267]

- [4]. Baker LK, Mao D, Chi H, Govind AP, Vallejo YF, Iacoviello M, et al. Intermittent nicotine exposure upregulates nAChRs in VTA dopamine neurons and sensitises locomotor responding to the drug. *European Journal of Neuroscience*. 2013; 37:1004–11. [PubMed: 23331514]
- [5]. Cortright JJ, Sampedro GR, Neugebauer NM, Vezina P. Previous exposure to nicotine enhances the incentive motivational effects of amphetamine via nicotine-associated contextual stimuli. *Neuropsychopharmacology*. 2012; 37:2277–84. [PubMed: 22617358]
- [6]. Govind AP, Vezina P, Green WN. Nicotine-induced upregulation of nicotinic receptors: Underlying mechanisms and relevance to nicotine addiction. *Biochemical Pharmacology*. 2009; 78:756–65. [PubMed: 19540212]
- [7]. Mao D, McGehee DS. Nicotine and behavioral sensitization. *Journal of Molecular Neuroscience*. 2010; 40:154–63. [PubMed: 19669944]
- [8]. Vezina P, McGehee DS, Green WN. Exposure to nicotine and sensitization of nicotine-induced behaviors. *Progress in Neuropsychopharmacology and Biological Psychiatry*. 2007; 31:1625–38.
- [9]. Vezina P. Sensitization of midbrain dopamine neuron reactivity and the self-administration of psychomotor stimulant drugs. *Neuroscience and Biobehavioral Reviews*. 2004; 27:827–39. [PubMed: 15019432]
- [10]. Benwell ME, Balfour DJ. The effects of acute and repeated nicotine treatment on nucleus accumbens dopamine and locomotor activity. *British Journal of Pharmacology*. 1992; 105:849–56. [PubMed: 1504716]
- [11]. Clarke PB, Kumar R. Characterization of the locomotor stimulant action of nicotine in tolerant rats. *British Journal of Pharmacology*. 1983; 80:587–94. [PubMed: 6640208]
- [12]. Iyaniwura TT, Wright AE, Balfour DJ. Evidence that mesoaccumbens dopamine and locomotor responses to nicotine in the rat are influenced by pretreatment dose and strain. *Psychopharmacology*. 2001; 158:73–9. [PubMed: 11685386]
- [13]. Ksir C, Hakan R, Hall DP Jr, Kellar KJ. Exposure to nicotine enhances the behavioral stimulant effect of nicotine and increases binding of [3H]acetylcholine to nicotinic receptors. *Neuropharmacology*. 1985; 24:527–31.
- [14]. Schoffelmeier AN, De Vries TJ, Wardeh G, van de Ven HW, Vanderschuren LJ. Psychostimulant-induced behavioral sensitization depends on nicotinic receptor activation. *Journal of Neuroscience*. 2002; 22:3269–76. [PubMed: 11943828]
- [15]. Shim I, Javadi JI, Wirtshafter D, Jang SY, Shin KH, Lee HJ, et al. Nicotine-induced behavioral sensitization is associated with extracellular dopamine release and expression of c-Fos in the striatum and nucleus accumbens of the rat. *Behavioural Brain Research*. 2001; 121:137–47. [PubMed: 11275291]
- [16]. Suto N, Tanabe LM, Austin JD, Creekmore E, Pham CT, Vezina P. Previous exposure to psychostimulants enhances the reinstatement of cocaine seeking by nucleus accumbens AMPA. *Neuropsychopharmacology*. 2004; 29:2149–59. [PubMed: 15266353]
- [17]. Vezina P, Lorrain DS, Arnold GM, Austin JD, Suto N. Sensitization of midbrain dopamine neuron reactivity promotes the pursuit of amphetamine. *Journal of Neuroscience*. 2002; 22:4654–62. [PubMed: 12040071]
- [18]. Shoaib M, Schindler CW, Goldberg SR. Nicotine self-administration in rats: strain and nicotine pre-exposure effects on acquisition. *Psychopharmacology*. 1997; 129:35–43. [PubMed: 9122361]
- [19]. Adriani W, Spijker S, Deroche-Gamonet V, Laviola G, Le Moal M, Smit AB, et al. Evidence for enhanced neurobehavioral vulnerability to nicotine during periadolescence in rats. *Journal of Neuroscience*. 2003; 23:4712–6. [PubMed: 12805310]
- [20]. Vezina P. Sensitization, drug addiction and psychopathology in animals and humans. *Progress in Neuropsychopharmacology and Biological Psychiatry*. 2007; 31:1553–5.
- [21]. Anagnostaras SG, Robinson TE. Sensitization to the psychomotor stimulant effects of amphetamine: modulation by associative learning. *Behavioral Neuroscience*. 1996; 110:1397–414. [PubMed: 8986341]
- [22]. Stewart J, Vezina P. A comparison of the effects of intra-accumbens injections of amphetamine and morphine on reinstatement of heroin intravenous self-administration behavior. *Brain Research*. 1988; 457:287–94. [PubMed: 3219557]

- [23]. Vezina P, Leyton M. Conditioned cues and the expression of stimulant sensitization in animals and humans. *Neuropharmacology*. 2009; 56(Suppl 1):160–8. [PubMed: 18657553]
- [24]. Reid MS, Ho LB, Berger SP. Effects of environmental conditioning on the development of nicotine sensitization: behavioral and neurochemical analysis. *Psychopharmacology*. 1996; 126:301–10. [PubMed: 8878346]
- [25]. Reid MS, Ho LB, Berger SP. Behavioral and neurochemical components of nicotine sensitization following 15-day pretreatment: studies on contextual conditioning. *Behavioral Pharmacology*. 1998; 9:137–48.
- [26]. Caggiula AR, Donny EC, White AR, Chaudhri N, Booth S, Gharib MA, et al. Cue dependency of nicotine self-administration and smoking. *Pharmacology Biochemistry and Behavior*. 2001; 70:515–30.
- [27]. Donny EC, Chaudhri N, Caggiula AR, Evans-Martin FF, Booth S, Gharib MA, et al. Operant responding for a visual reinforcer in rats is enhanced by noncontingent nicotine: Implications for nicotine self-administration and reinforcement. *Psychopharmacology*. 2003; 169:68–76. [PubMed: 12774186]
- [28]. Caggiula AR, Donny EC, Palmatier MI, Liu X, Chaudhri N, Sved AF. The role of nicotine in smoking: a dual-reinforcement model. *Nebraska Symposium on Motivation*. 2009; 55:91–109. [PubMed: 19013940]
- [29]. Wing VC, Shoaib M. Contextual stimuli modulate extinction and reinstatement in rodents self-administering intravenous nicotine. *Psychopharmacology*. 2008; 200:357–65. [PubMed: 18587561]
- [30]. Pierre PJ, Vezina P. Predisposition to self-administer amphetamine: the contribution of response to novelty and prior exposure to the drug. *Psychopharmacology*. 1997; 129:277–84. [PubMed: 9084067]
- [31]. Suto N, Austin JD, Vezina P. Locomotor response to novelty predicts a rat's propensity to self-administer nicotine. *Psychopharmacology*. 2001; 158:175–80.
- [32]. Richardson NR, Roberts DC. Progressive ratio schedules in drug self-administration studies in rats: a method to evaluate reinforcing efficacy. *Journal of Neuroscience Methods*. 1996; 66:1–11. [PubMed: 8794935]
- [33]. Cortright JJ, Lorrain DS, Beeler JA, Tang WJ, Vezina P. Previous exposure to delta9-tetrahydrocannabinol enhances locomotor responding to but not self-administration of amphetamine. *Journal Pharmacology and Experimental Therapeutics*. 2011; 337:724–33.
- [34]. Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Research Reviews*. 1993; 18:247–91.
- [35]. Stewart J, de Wit H, Eikelboom R. Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. *Psychological Review*. 1984; 91:251–68. [PubMed: 6571424]
- [36]. Conklin CA. Environments as cues to smoke: Implications for human extinction-based research and treatment. *Experimental and Clinical Psychopharmacology*. 2006; 14:12–9. [PubMed: 16503701]
- [37]. Markou A, Weiss F, Gold LH, Caine SB, Schulteis G, Koob GF. Animal models of drug craving. *Psychopharmacology*. 1993; 112:163–82. [PubMed: 7871016]
- [38]. Olsson P, Jentsch JD, Taylor JR. Repeated nicotine exposure enhances responding with conditioned reinforcement. *Psychopharmacology*. 2004; 173:98–104. [PubMed: 14727001]
- [39]. Dalley JW, Everitt BJ, Robbins TW. Impulsivity, compulsivity, and top-down cognitive control. *Neuron*. 2011; 69:680–94.
- [40]. de Wit, H.; Mitchell, SH.; Madden, GJ.; Bickel, WK. Impulsivity: The behavioral and neurological science of discounting. American Psychological Association; Washington, D.C.: 2010. Drug effects on delay discounting; p. 213-41.
- [41]. Xie X, Arguello AA, Reittinger AM, Wells AM, Fuchs RA. Role of nicotinic acetylcholine receptors in the effects of cocaine-paired contextual stimuli on impulsive decision making in rats. *Psychopharmacology*. 2012; 223:271–9. [PubMed: 22526542]
- [42]. Ostlund SB, Maidment NT. Dopamine receptor blockade attenuates the general incentive motivational effects of noncontingently delivered rewards and reward-paired cues without

affecting their ability to bias action selection. *Neuropsychopharmacology*. 2012; 37:508–19. [PubMed: 21918507]

[43]. Kirk, RE. *Experimental Design: Procedures for the Behavioral Sciences*. Brooks/Cole; Pacific Grove, CA: 1968.

[44]. Hsu, JC. *Multiple Comparisons: Theory and Methods*. Chapman and Hall; London, UK: 1996.

Highlights

- Contextual stimuli can regulate the expression of sensitization to nicotine.
- Rats were given nicotine or saline paired with the home cage or test chamber.
- Two weeks later, all rats self-administered nicotine in the test chamber.
- Rats exposed to nicotine in the test chamber later self-administered more nicotine.
- Nicotine-associated stimuli can enhance the incentive motivational effects of nicotine.

Fig. 1.

Previous exposure to nicotine enhances its self-administration but only in rats exposed to the drug in the self-administration chamber: 12 FR test days. Two weeks prior to FR self-administration testing, rats were exposed to nicotine or saline either in the home cage (**a**) or in the self-administration chamber (**b**). Data are shown as mean ($\pm$ SEM) infusions obtained on each of the 12 FR test days (2 hour sessions). **Insets** show mean ($\pm$ SEM) number of infusions obtained on days 7–12 of testing. Numbers at the base of each bar indicate n/group. **, $p < 0.01$, nicotine versus saline exposed.

Fig. 2.

Characterization of lever pressing during FR self-administration testing in rats previously exposed to saline or nicotine in the home cage (**left**) or the self-administration chamber (**right**). Data are shown as mean ($\pm$ SEM) number of active and inactive lever presses over the 12 FR test days (2 hour sessions) in rats previously exposed to saline (**a–b**) or nicotine (**c–d**). **e–f**. Mean ($\pm$ SEM) FR schedule achieved for saline and nicotine exposed rats. Compared to the other groups, rats previously exposed to nicotine in the self-administration chamber showed poor active versus inactive lever discrimination and no effect of nicotine exposure on FR schedule achieved. n/group = 11–12. **, $p < 0.01$, ***, $p < 0.001$, mean active versus inactive lever presses on days 1–6 or 7–12, †††, $p < 0.001$, mean active lever presses on days 7–12 versus 1–6.

Fig. 3.

Previous exposure to nicotine enhances its self-administration but only in rats exposed to the drug in the self-administration chamber: PR test days. Two weeks prior to self-administration testing, rats were exposed to nicotine or saline either in the home cage (**a**) or in the self-administration chamber (**b**). Data are shown as mean ($\pm$ SEM) infusions obtained on each of the 3 PR test days (1–2 hour sessions). **Insets** show mean ($\pm$ SEM) number of infusions obtained on the last PR test day. Numbers at the base of each bar indicate n/group. **, $p < 0.01$, nicotine versus saline exposed.