OF RATS AND MEN: PEER PRESENCE AND FAMILIARITY ARE KEY FACTORS WHICH MODULATE DRUG INTAKE

Short title: A stranger presence decreases cocaine intake

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ABSTRACT

Social environment influences drug consumption, its persistence and evolution. Little is known regarding the influence of the presence of a peer during drug consumption and especially how the relationship between peers (familiarity and dominance) can influence drug consumption. We used here a translational and transdisciplinary approach to explore the influence of peer presence and peer familiarity in rats and humans that self-administer stimulants. In rats, cocaine intake was compared when rats were alone with intake when peers with different characteristics (familiar or not, cocaine naive or not, dominant or subordinate) were present. In humans, 77 cocaine and/or methylphenidate users were asked to detail their most recent drug use episodes and their relationship with peers present at consumption. The results show that in both humans and rats, the risk of cocaine/stimulant consumption was significantly reduced by 37% and 32%, respectively, when a peer was present. Moreover, the lowest risk of consumption was consistently observed when the peer was unfamiliar (vs familiar) with a further 38% and 17% risk reduction, respectively. In rats, a decreased risk of consumption was greater when the peer was cocaine naive (vs non-cocaine naive).

The presence of a non-familiar and possibly drug-naive peer is the most efficient condition to diminish stimulant intake. Our results indirectly support the use of harm reduction strategies, in particular supervised consumption rooms for stimulant users.

INTRODUCTION

Drug use often occurs in a social environment that can influence drug consumption patterns and related behaviors. A social environment encompasses two types of factors: distal social factors (i.e. present in an individual's broader social environment, but may not be immediately present when drug use occurs) and proximal social factors (i.e., immediately present at the time of drug use).

The influence of distal social factors on drug use has been widely studied. Stress, isolation and rejection are associated with higher rates of drug use in humans (Aloise-Young & Kaeppner, 2005; Rusby, Forrester, Biglan, & Metzler, 2005) and in animal models (Burke & Miczek, 2014; M. A. Nader, Czoty, Nader, & Morgan, 2012; Stairs & Bardo, 2009). In contrast, strong familial ties are associated with lower rates of drug use in humans (Barnes, Reifman, Farrell, & Dintcheff, 2000; Dorius, Bahr, Hoffmann, & Harmon, 2004; Pandina, Labouvie, Johnson, & White, 1990; Scheier, Botvin, Diaz, & Griffin, 1999), while an enriched environment for animals is associated with lower rates in rodents and monkeys (Burke & Miczek, 2014; J. Nader et al., 2012; Stairs & Bardo, 2009). In humans, epidemiological studies have shown that social network characteristics in people who use drugs are major determinants of drug use initiation (Neaigus et al., 2006; Sherman & Latkin, 2001), persistence (Brewer, Catalano, Haggerty, Gainey, & Fleming, 1998; Schroeder et al., 2001), increase (Wu, Eschbach, & Grady, 2008) and cessation (Buchanan & Latkin, 2008; C. A. Latkin, Knowlton, Hoover, & Mandell, 1999). They are also major determinants of risk practices, such as sharing injecting equipment (C. Latkin, Mandell, Vlahov, Oziemkowska, & Celentano, 1996).

To our knowledge, no study to date has specifically focused on the influence of peer

presence, peer characteristics and peer familiarity and their effect on stimulant consumption in humans. The few existing studies in this area only examined the influence of peer presence and close relationships on outcomes such as alcohol use (Mohr, Arpin, & McCabe, 2015) and craving during stressful events (Preston et al., 2017).

With respect to animals, studies examining proximal social factors and drug use are relatively recent and suggest the following: 1) social contact and drug use are both rewarding, although social contact may outweigh the rewarding effect of drug use (Fritz, El Rawas, et al., 2011; Fritz, Rawas, et al., 2011) 2) the presence of peers influences drug consumption (Smith, 2012), 3) this influence is substance-specific (Gipson et al., 2011) and, 4) whether or not the peer is also self-administering a drug can differently influence the self-administration behavior (Strickland & Smith, 2014). However, in these animal studies, many characteristics of the peers such as familiarity, dominance status, former experience of the drug, were not investigated.

The influence of proximal social factors is of particular interest when exploring the use of stimulants such as cocaine or non-prescribed methylphenidate for several reasons. First, cocaine is one of the most widely used drugs worldwide and constitutes a major health care burden with many health-related consequences. Methylphenidate is a stimulant medication indicated for attention deficit and hyperactivity disorders, which is diverted by people who use drugs (PWUD) (Chen et al., 2016; Frauger et al., 2016). Second, there is currently no standard pharmacologic treatment to treat individuals with stimulant addiction. Therefore, understanding the influence of social factors may help in the design of interventions to reduce stimulant use. Third, cocaine and methylphenidate are characterized by a short half-life, which can lead to very frequent consumption. Finally, a translational study assessing the influence of proximal social factors has shown that cocaine is preferentially taken outside

home in human drug users and outside the home cage in rats (non-resident rats), in contrast with heroin which is preferentially used at home .

To date, research on the influence of proximal social factors in animal and human studies remains sparse. Accordingly, in the present study we used a translational research approach to explore to what extent peer presence, peer relationship (familiarity and dominance/subordination) and peer drug exposure history, can influence drug consumption in rats self-administering cocaine and in people using stimulants.

RESULTS

Human study

Description of Human Study Group's Characteristics

The median[IQR] frequency of stimulant consumption was 1.05[0.05-2.6] when subjects were alone and 1[0.3-2]when with peers.

Table 1 describes participant characteristics (N=77) and details of drug use episodes involving intranasal and intravenous routes of administration (n=77; 246 episodes).

More than 80% of the study sample were males with median age of 41 years. By definition they were all stimulant users and more than one third reported daily use. Median age at first use was 17 years. Most reported polysubstance use, approximately half were classified as hazardous alcohol users and 45% as heavy smokers (more than 20 cigarettes/day). One third reported having a high school certificate and 42% declared stable housing. The majority (66.2%) reported financial problems.

This study group reported 246 episodes (on average 3.2 episodes per person) of stimulant use alone (26.8%), with a peer (48.8%) or in a group (24.4%). The majority of episodes reported by the study group occurred in presence of a familiar peer (29.4%), followed by

alone (26.9%) and within a group (24.5%) while episodes of stimulant use alone accounted for 19.2%. It is worth noting that in 67.1% of the reported episodes, study participants had injected the drug, and that most episodes of stimulant use occurred in a public space. The majority of episodes occurred in the afternoon and the median number of substances used (including alcohol) at any episode was 2. Two thirds of the study sample reported either cocaine use alone or with methylphenidate.

Rat and Human studies

Influence of peer presence

Rats in the "alone" condition took an average of 13 (+/- 1.8) cocaine injections during the one-hour self-administration session. When a peer was present (familiar or not), the average value was 10 (+/- 1.6) (Fig. 1A). We observed a 34% decrease in the risk of consuming cocaine when rats were in presence of a peer, compared with being alone (IRR[95%CI]=0.66[0.61-0.71], $p<0.0002$). This means that when they were alone, rats had a 52% increased risk of consuming cocaine [IRR: 1.52=1/0.66] compared with when they were with peers (Fig. 1B).

In the human study, results showed a 37% decreased risk of drug use during an episode when one peer was present with respect to when alone (IRR[95%CI] =0.63[0.42 ; 0.93], $p=0.023$), i.e. a 59% [IRR: 1.59=1/0.63] greater risk of consuming cocaine when they were alone (Fig. 1B). However, there was no significant reduced risk when a group of peers were present compared to being alone.

Influence of peer familiarity

In the rat study, the average number of cocaine injections self-administered during the one-hour sessions was lower when the peer was “non-familiar” (7.6 (±0.34)) than when “familiar” (12.7 (±0.24)) (Fig. 2A). The Poisson model analysis showed an increasing risk of consumption from the presence of a non-familiar peer (IRR=1, reference group), to that of a familiar peer (IRR[95%CI]: 1.20[1.02-1.42]) to the condition of being “alone” (IRR[95%CI]: 1.73[1.50-1.98]) (Fig. 2B). It is worth noting that confidence intervals of IRR for “familiar peer” and “being alone” did not overlap. This means that there was a significant difference in drug consumption between “familiar peer” and “being alone”.

These results are in line with those from multivariable analyses in humans, where an increased gradient of stimulant use frequency was observed from non-familiar peer presence (reference category, IRR=1) to familiar peer presence (IRR[95%]=1.62[1.07;2.44]; p-value=0.02), to being alone (IRR[95%]=2.10[1.30;3.41]; p-value=0.003) (Fig. 2B) and to being with a group of peers (IRR[95%]=2.40[1.59;3.61]; p-value<0.0001).

In other words, with respect to the presence of a familiar peer, a further decreased risk of using cocaine was observed when in the presence of a non-familiar peer: a 17% significant reduction (1/1.20=0.83) in rats and a 38% (1/1.62=0.62) significant reduction in humans.

Other correlates associated with greater frequency of stimulant use in the multivariable analysis were unstable housing (IRR[95%CI] =2.38[1.67 ; 3.40], p<0.0001), daily stimulant use (IRR[95%CI] =1.60[1.18; 2.15], p=0.002) and number of other substances concomitantly used during the episode (IRR[95%CI] =1.16 [0.99 ; 1.34], p=0.063).

Influence of peer history of drug exposure

Chronologically, in the rat study, after exposure to a non-naive peer, rats were tested again on their own ("alone again"). Cocaine consumption then returned to the baseline level ($t=-1.324$, $p>0.18$, Fig.3A).

In the presence of a cocaine-naive peer, rats took an average of 5.6 (±1.2) cocaine injections, and an average of 10.5 (±1.6) injections in the presence of a non-naive peer (familiar and non-familiar included) (Fig. 3B). The Poisson model showed an increasing gradient in the frequency of cocaine consumption from the presence of a naive peer (IRR=1) to the presence of a non-naive peer (IRR[95%CI]: 1.80 [1.57; 2.06], $p<0.0001$, to the "back alone" (i.e. post-peer) condition (IRR[95%CI]: 2.10[1.84-2.40], $p<0.0001$), to the "alone" condition (2.31[2.03- 2.63], $p<0.0001$).

In humans, among episodes involving one other peer, we noted that the latter was always a drug user (for episodes with a group, peers were not characterized).

Dominance/subordination relationship

No significant difference was found when comparing the frequency of cocaine consumption in rats in the presence of a subordinate and in the presence of a dominant familiar peer. Similarly, no significant subordination or dominance effect was found in the analysis of data on humans (in terms of economic dependence and the leader role in drug use contexts). It thus seems that dominance plays a small role in social factors modulating drug use.

DISCUSSION

The present study reveals that the influence of proximal social factors on stimulant use is similar in rats and humans. Our results show that 1) the presence of a peer at the time of

stimulant intake has a beneficial effect, in that the frequency of stimulant consumption is reduced; 2) the presence of a non-familiar peer is associated with an even greater decrease in drug use in both human and rats. In other words, in decreasing order, the highest risks of consumption are observed when alone, then with a familiar peer and then with a non-familiar peer; 3) the frequency of cocaine consumption was lower in rats whose peers were cocaine naive than in rats with non-naive peers or rats which were alone (this condition could not be tested in humans); 4) no significant effect of peer dominance/subordination was seen in terms of drug consumption.

General influence of social presence

The main result of this study is that in both humans and rats, cocaine (or stimulant) consumption decreased in the presence of a peer. This confirms previous results in rat-based studies where, just as was the case in our experimental conditions, only one of the two rats used cocaine (Smith, 2012). This result therefore supports the hypothesis that the rewarding and reinforcing properties of drugs also depend on whether other individuals are present at the time of drug exposure. Moreover, Thiel and colleagues (2009)(Thiel, Sanabria, & Neisewander, 2009) showed in adolescent male rats, that conditioned place preference for nicotine was modified in the presence of a peer. They concluded that the presence of a peer modulates the affective valence of drug use(Thiel et al., 2009).

The reduced frequency of cocaine consumption observed here when peers are present can be explained according to Fritz and Douglas' hypothesis that the rewarding effect of social contact (Douglas, Varlinskaya, & Spear, 2004) may outweigh the rewarding effects of drug use (Fritz, El Rawas, et al., 2011; Fritz, Rawas, et al., 2011). This explanation is concordant with the results of the conditioned place preference test we performed in our rat-based

experiment (see supplementary material) where rats (housed in pairs) preferred an environment where they were in contact with their home-cage peer over an environment where they remained alone. This rewarding effect depends however on the dominant/subordinate relationship, as the presence of a dominant peer was not found to be rewarding for the subordinate peer. Since there was no peer dominance/subordination relationship effect on the frequency of stimulant intake in the present study, this rewarding component seems to play a limited role. That said, we were not able to measure this relationship in humans since there was no significant association between being in the company of peer(s) and having a particular mental state (positive, neutral or negative) (data not shown).

Furthermore, in line with our results, an econometric analysis has also shown that reinforcing properties of cocaine diminish when a rat is in presence of an abstaining peer (Peitz et al., 2013). This effect is explained by social-learning theories of substance use, which suggest that members of peer groups of PWUD influence each other by imitation (Peitz et al., 2013), which could thus be the case in our rat study, but would not explain the human results, since peers were all PWUD as well.

Another explanation could be related to whether or not the peer is under the effect of cocaine at the time of the interaction. It has been shown that adolescent rats increase their ethanol consumption in the presence of an ethanol-intoxicated sibling, but not with a sibling exposed to water or coffee. This suggests that the intoxication status of the peer is an important factor in the way social interaction will affect behavior (Hunt, Holloway, & Scordalakes, 2001). In the present study, at the time of the interaction, only the tested rat had access to the drug while the peer had a minimum of 4 hours of abstinence from cocaine,

and was therefore regarded as no longer being under the influence of its previous cocaine injections.

Is social presence a stressor?

Given the well-known association between stress and increased drug intake in both rats and humans (Piazza & Le Moal, 1998), one might hypothesize that the presence of a peer would increase frequency of cocaine consumption, assuming that an observer could induce some stress. This hypothesis can be ruled out however, since it has been previously shown that in rats and monkeys, the presence of a peer during behavioral execution of a task does not affect blood cortisol levels (Monfardini et al., 2016; Tzeng, Cherng, Wang, & Yu, 2016). Furthermore, the emission of ultrasonic vocalizations (USV) can also be used as a stress indicator. Indeed, stress has been shown to reduce tickling-induced positive 50kHz USV in rats (Popik, Potasiewicz, Pluta, & Zieniewicz, 2012). In contrast, in the present experiment, the presence of a peer increased levels of 50 kHz USV (data not shown), while decreasing drug consumption. This suggests that the presence of a peer is not stressful, but rather reinforcing. Since it has been shown that cocaine by itself can induce the emission of positive USV (Avvisati et al., 2016), our results confirm that increased USV emissions here are more related to the presence of a peer than to cocaine itself.

Influence of peer familiarity

Our findings show that, in both rats and humans, cocaine consumption was lower when the peer was a non familiar than when he/she was familiar. This shows that familiarity is an additional factor that modulates drug consumption. With respect to other types of behavior, in birds, Guillette et al., 2016 showed that familiarity with a peer present during a task

performance can affect a bird's behavior (Guillette, Scott, & Healy, 2016). More specifically, the study showed that in male zebra finches, nest-building skill is socially transmitted only if the demonstrator is a familiar peer and not a stranger. Put briefly, birds use social information, copying the choice only if made by a familiar peer.

Is a non-familiar peer a stressor?

To return to our study, as discussed above, a stressful situation is usually associated with fewer positive USV in rats. We found this to be true when the peer was not familiar (data not shown). Although non-familiar peers may be considered as creating more stress than familiar peers, the reduced risk of cocaine consumption in our experiment does not argue in favor of a stress effect.

Moreover, in a study examining episodes of stress among humans with substance-use disorders, Preston et al. found that stress events were more likely to occur in situations of social company (interactions with acquaintances, friends, or on the phone) than with family (spouse, child), in places with greater overall activity (bars, outside, walking) and in situations where unexpected experiences occur (interactions with strangers) (Preston et al., 2017).

These results may seem counterintuitive. Indeed, it is known that an emotionally positive context reduces drug consumption (Bardo, Klebaur, Valone, & Deaton, 2001). In our study, rats in the presence of their cage-mate emitted a higher number of positive USV, suggesting an emotionally positive context, although they consumed more cocaine than when in presence of a non-familiar peer.

It is known that the primary effect of cocaine is the inhibition of dopamine reuptake, leading to increased extracellular dopamine levels (Wise, 1984). Furthermore, it has been shown that the presence of a peer increases extracellular dopamine levels (Tzeng et al., 2016). If the

mere presence of a peer induces a dopamine increase, it might well be possible that a ceiling effect could prevent cocaine from increasing the level further, and this could result in decreased drug efficacy and therefore decreased drug use. The fact that the frequency of cocaine consumption in our study was even lower in the presence of a non-familiar peer would then suggest that extracellular levels of DA can be modulated by levels of familiarity. This remains to be investigated.

Finally, another possible explanation for the difference between the familiar versus non-familiar peer's influence on self-administration behavior is that the presence of the latter represents a powerful distractor (Zajonc, 1965). A subject's attention may be focused on the non-familiar peer rather than on the drug, consequently leading to decreased frequency of drug consumption.

In line with this hypothesis, a recent study in monkeys has shown that the presence of a peer increases the activity of attention-related cerebral structures(Monfardini et al., 2016).

Influence of peer history of drug exposure

The other important result of the present study is that a history of cocaine use in an observer rat induced a higher frequency of drug consumption than the presence of a non-familiar cocaine-naive peer. This result was not likely to be observed in humans, since the peer present during stimulant use was always a drug user.

Although epidemiological studies have highlighted the importance of the relationship within the network between peers at the moment of drug use and on the sharing of injecting equipment (Gyarmathy et al., 2010), drug seeking (Furnari et al., 2015; Linas et al., 2015; Mohr et al., 2015; Shadur, Hussong, & Haroon, 2015) and craving, the human study reported here is the first to explore the nature of the relationship within a dyad of peers, and to

correlate it with cocaine consumption. It is also the first to find a direct effect of peer familiarity on drug consumption levels.

Some study limitations need to be acknowledged. The design of the rat study is experimental while the human study is observational and cross-sectional and collected retrospective information on episodes of stimulant consumption. In this last case, the outcome may be subject to recall and social desirability biases and to confounding. However, we did as much as possible to minimize recall bias in the design as explained in the methods section. Although there is a risk of underreporting consumption in humans, this is not likely to affect comparison with the rat model. Furthermore, we analyzed data using Poisson regression models (mixed model for rats, GEE for humans) and to control confounding, adjusted for possible confounders in the human study. Despite these limitations, we found very similar estimates for the association between frequency of consumption and the presence or familiarity of a peer in both models, as the graphs clearly show.

In conclusion, this study's results, by showing parallel influences of proximal social factors on the frequency of drug consumption in rats and humans, highlight translation potential from rats to humans. The need for translational studies (Caprioli et al., 2009; Kandel & Kandel, 2014) is essential for a better understanding of the role played by social factors in addiction (Heilig, Epstein, Nader, & Shaham, 2016) and forces us to search for new models and solutions to translate as many aspects of behavior as we can.

Peer presence, peer familiarity and history of drug use, all have major effects on drug consumption. To better understand social influence mechanisms in drug addiction, research must now examine the neurobiological substrate of these observations.

Understanding how proximal social factors modulate drug consumption will help in the design of novel preventive and therapeutic strategies including social interventions to target

drug-using populations. Furthermore, the presence of a non-familiar and possibly drug-naive peer would appear to be a driver for diminished stimulant intake. Given that there is still space for improvement in the management of cocaine-related disorders, these results may be crucial to develop harm reduction strategies for stimulant users. At the clinical level, this would translate into involving peers in treatment education. At the health policy level, it would mean promoting the use of harm reduction strategies, such as peer education on injection and the deployment of supervised consumption rooms.

METHODS

Human study

Design

The human study (DDYADS) is a cross-sectional survey implemented between October 2015 and June 2016 in 5 cities in France characterized by high prevalence of illicit drug use (Marseille, Paris, Montreuil, Saint Denis, Nice).

Participants

Seventy-seven French-speaking regular stimulant users – defined as using cocaine or methylphenidate ≥5 times a month– were recruited in different sites, including methadone centers, harm reduction centers, low-threshold mobile health units, and through word-of-mouth referrals, between October 2015 and June 2016. Non-prescribed methylphenidate was also considered as cocaine users may switch from cocaine to methylphenidate and vice-versa in the areas where the study was conducted, depending on black market availability and costs. The study received authorization from the national French Data Protection Authority (CNIL) and Aix-Marseille University's institutional review board. All participants

provided written informed consent. More information about enrollment and data collection can be found in Supplement 1.

Data collection - Humans

Data were anonymously collected through a face-to-face standardized questionnaire administered by trained interviewers Interviews were conducted in a dedicated room at centers or in a café and lasted from 30 to 60 minutes. Participants were remunerated with a €15 gift voucher for completing the interview.

To minimize recall bias, participants retrospectively described episodes during the previous month where they used stimulants.

Social environment at the moment of stimulant use was described as follows: alone, with one peer (dyads), with a group (i.e., 2 or more peers). For episodes involving the participant and one peer, information on the peer was collected. Peers were considered "familiar" if they were close friends or relatives, and if the participant could speak about his/her intimate life with them. Otherwise, peers were considered "non-familiar". Participants were considered subordinate if they were economically dependent on the peer or if the peer was the leader in terms of drug use contexts (e.g. paying for the drug). Each *drug use episode* was characterized as follows: principal route of administration (intravenous, intranasal), type of stimulant (cocaine or non-prescribed methylphenidate), drug effect perception (from 1 to 5), concomitant use of other psychoactive substances including alcohol. It also included information about the location where the episode took place (public versus private), the respondent's state of mind (positive versus neutral versus negative), the number of times drugs were consumed (including alcohol) and episode duration. We also collected data on *participant characteristics* including age, gender, employment status, educational level,

housing situation (stable versus unstable), hazardous alcohol use (AUDIT-C score) (Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998), financial problems, including economic dependence on the peer, and the number of days the participant had used stimulants in the previous month.

Outcome

The outcome was the mean number of times drugs were consumed in one hour during an episode (i.e. frequency of drug intake).

Statistical analysis

We considered each drug intake episode reported during the interview as a statistical unit. In order to take into account the within-subject correlation due to repeated measures (i.e., drug use episodes in the previous month) reported by the same individual, we used the Generalized Estimated Equation approach for Poisson count data (Liang & Zeger, 1986).

Two models were built. In the first, we tested the role of peer presence (alone, with one peer, with a group i.e., two or more peers) on the frequency of stimulant use, after taking into account potential correlates/confounders including: 1) context of the stimulant use episode: type of location (private versus public place), route of administration (intravenous, intranasal), state of mind (positive, neutral, negative), number of other substances concomitantly used (including alcohol); 2) participant characteristics: gender, age, educational level (< high school certificate versus ≥ high school certificate), employment status, stable housing (i.e. renter or owner of their personal housing versus other), financial

difficulties, hazardous alcohol use (AUDIT-C ≥4 for men and ≥3 for women), and number of days of stimulant use during the previous month (daily stimulant user versus other).

The second model was built to examine the role of peer familiarity (alone, with one familiar peer, with one non-familiar peer, with a group) on the frequency of drug intake after taking into account the potential correlates/confounders described in the first model.

Variables with a p-value < 0.20 in the univariable analysis were considered eligible for multivariable analyses. A backward selection procedure was used to determine the final multivariable model. We set the p-value threshold at $\alpha = 0.05$ for the latter. All estimates of incidence rate ratio (IRR) were reported with their 95% confidence intervals (95%CI) and tests were two-sided. STATA version 12 for Windows was used for the analyses.

The amount of missing data was negligible in explanatory variables, and zero in the outcome.

Sample size

We calculated that 70 individuals with at least 1 episode of cocaine/methylphenidate consumption with a peer, with 50% of them being exposed to a familiar peer, would be adequate to highlight a significant association (IRR=2.2) between familiarity and cocaine consumption frequency, with an alpha error risk =0.05 and a power of 80%.

Animal Study

Animals & surgery

In the present study, 14 male Lister Hooded rats (Charles River Laboratories, Saint-Germain-sur-l'Arbresle, France) were housed in pairs upon their arrival. Rats were handled 2-3 times a week. They were maintained under 12-h light/dark cycles and had ad libitum access to food and water. All procedures were conducted in accordance with the European Community

Council Directive of November 24, 1986 (86/609/EEC), and the national French Agriculture and Forestry Ministry (decree 87-849). Using standard surgical procedures, silicon catheters were inserted into the right jugular vein of the rats. They exited dorsally between the scapulae. Further information on surgery and the apparatus used are provided in Supplement.

Apparatus

The experiment was conducted in four custom-built self-administration (SA) chambers (60 cmx 30 cmx 35 cm) made of opaque Perspex and divided into two compartments, separated by a grid. One of the two compartments was equipped with 2 chains and a stimulus light located on the right-hand wall. The grid allowed each rat visual, auditory and olfactory communication, limited tactile contact with its peer, and prevented each rat from accessing the tethering system of its peer. Drug infusions were delivered via intrajugular route of administration through tubing protected by a stainless steel spring, connected to 10 ml cocaine syringes positioned on motorized pumps (Razel Scientific Instruments, St. Albans, VT, USA) outside of the chamber.

All the chambers and pumps described above were controlled by a custom-built interface and associated software (built and written by Y. Pelloux).

Experimental Procedure

A group of rats (n=14) were individually trained to pull a chain to self-administer cocaine (80µg per 90µl infusion in 5s) under a continuous schedule of reinforcement (Fixed Ratio 1 (FR1), 1 chain pulling results in 1 cocaine injection) for daily one-hour sessions. Cocaine was randomly assigned to one or the other of the two chains (the active chain). Pulling the active

chain switched on the cue-light, delivered the cocaine to the blood stream and started a 20-s "time-out" during which any further pulling was recorded as perseveration, but had no other consequence. Pulling the other chain (inactive chain) was also recorded, as an error, and had no consequence. Once consumption became stable, the last 5 days of acquisition were used as a baseline for cocaine consumption when the rats were alone in the apparatus (condition "alone", n=14).

The rats were then exposed to 3 different self-administration conditions for 5 consecutive days each:

1) Peer Presence: In the presence of another rat (hereafter "peer") having no access to cocaine. This peer could be either familiar (N=8; i.e. a cage-mate also trained for self-administration) or a stranger (hereafter "non-familiar peer") (N=6; i.e. a rat trained for cocaine self-administration but living in a different home-cage). Peers were introduced into the cage after they had a minimum of 4 hours of abstinence from cocaine.

The same familiar and non-familiar peers were used for the same rat for all behavioral sessions.

2) Post-peer presence: Rats were "back alone" after exposure to peers (N=14) in order to assess whether peer presence could influence cocaine intake in future "alone" sessions.

3) Non-familiar and cocaine-naive peer presence: rats from another group that had never been exposed to cocaine (N=11).

Dominance/subordination relationships are described for familiar peers in Supplement 1.

For each one-hour behavioral session, the number of cocaine injections was recorded.

Statistical analysis

We assessed the association between the number of cocaine injections during the one-hour cocaine self-administration session (outcome; i.e. frequency) and the nature of the social relationship (i.e., familiar, not familiar) with rat peers or the history of cocaine exposure of rat peers (naive vs non-naive). Poisson mixed models were used to take into account - as a random effect factor - repeated measures over time of the outcome.

The following four models were analyzed, each one taking the day as a random effect factor and the following experimental factor:

A) Peer presence: alone or with a non-naive peer, irrespective of the relationship (i.e. familiar/not familiar)

B) Familiarity: alone, with familiar peer, with non-familiar peer (only non-naive peers)

C) History of cocaine exposure: alone, with naive peer, with non-naive peer, back alone

D) Social status: dominant or subordinate (only non-naive familiar peers)

Statistical significance was set at $\alpha=0.05$. STATA version 12 for Windows was used for the analyses.

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Figure legends

Figure 1: Influence of the presence of a peer on cocaine consumption

Fig1A. Influence of the presence of a peer on cocaine self-administration in rats.

The results are illustrated as the mean (± SEM) number of cocaine injections (80µg/90µl/injection) per 1h-session during 5 consecutive sessions of baseline ("alone", D1 to D5) and during 5 consecutive sessions in presence of a peer ("with non-naive observer", D1 to D5, n=14). ***: p<0.0001 GLM analysis

Fig1B. Adjusted incidence rate ratios (risk) of frequency of drug consumption depending on the peer presence in humans and in rats. Reference = "presence of one peer".

Black and red squares represent the adjusted rate ratio from the multivariable analysis using GEE Poisson model in humans of the variable peer presence (reference=human with a peer): human alone (black square) and human with group (red square). The lower and upper dashes represent, respectively, the lower and upper bounds of the confidence interval.

Blue square represents the adjusted rate ratio from the multivariable analysis using GEE Poisson model in rats of the variable peer presence (reference=rat with a peer). The lower and upper dashes represent, respectively, the lower and upper bounds of the confidence interval.

Figure 2: Influence of the familiarity with a peer on cocaine consumption

Fig2A. Influence of familiarity with an abstaining peer on cocaine self-administration in rats.

The results are illustrated as the mean (± SEM) number of cocaine injections (80µg/90µl/injection) for an average of 5 consecutive days of social interaction with either a familiar peer (striped blue bar, n=8) or an **unknown** peer ("non-familiar", dark blue bar, n=6). *: p<0.01 GLM analysis.

Fig2B. Adjusted incidence rate ratios (i.e. risk) for drug consumption depending on peer familiarity in humans and rats. Reference = "non-familiar peer"

Black and red squares represent the adjusted rate ratio from the multivariable analysis using GEE Poisson model in humans of the variable familiarity (reference=human with a non-familiar peer; black square: human alone, red striped square: human with familiar peer, red

square: human in group). The lower and upper dashes represent, respectively, the lower and upper bounds of the confidence interval.

Blue squares represent the adjusted rate ratio from the multivariable analysis using GEE Poisson model in rats of the variable familiarity (reference=rat with a non-familiar peer; blue striped square: rat with familiar peer, blue square: rat alone). The lower and upper dashes represent, respectively, the lower and upper bounds of the confidence interval.

Figure 3: Influence of the drug history of the observing peer on cocaine intake in rats

Fig3A. Return to baseline cocaine consumption when rats are tested alone again.

The results are illustrated as the mean (± SEM) number of cocaine injections (80µg/90µl/injection) per 1h-session for 5 consecutive days at baseline ("Alone", D1 to D5: day 1 to 5) and for 5 consecutive sessions alone after the experience of being in the presence of a non-naive peer ("Back alone", D1 to D5: day 1 to 5).

Fig3B. Influence of drug history of the observing peer on cocaine self-administration in rats. The results are illustrated as the mean (± SEM) number of cocaine injections (80µg/90µl/injection) per 1h-session for 5 consecutive sessions under observation of a non-familiar peer with a history of cocaine self-administration (left, "non -naive peer", D1 to 5: day 1 to 5) and under observation of a non-familiar peer **naive** to cocaine (right, "**naive** peer", D1 to D5: day 1 to 5) ***: $p<0.001$ GLM analysis.

Table 1. HUMANS- Characteristics of the study sample (N=77) and drug use at any episode reported by participant (n=246)

	Study sample N=77
Male gender	83.1
Age – *years*	41 [34; 47]
Daily stimulant use	36.4
Age at first drug use	17 [15 ; 22]
>20 cigarettes per day	44.7
Hazardous alcohol use[2]	48.7
Stable housing	41.6
Financial problems	66.2
High school certificate	32.0

	Study sample N=246*
Peer presence	
Alone	26.8
Presence of one peer	48.8
Presence of a group (2 or more peers)	24.4
Familiarity	
Alone	26.9
Familiar peer	29.4
Non-familiar peer	19.2
Presence of a group (two or more peers)	24.5
Route of drug administration	
Sniffing	32.9
Injection	67.1
Private (vs Public) site when using drugs	39.6
Time of drug use	
Morning	26.6
Afternoon	42.2
Evening/Night	31.1
Type of drug intake	
cocaine and/or cocaine +methylphenidate	73.6
Methylphenidate	26.4

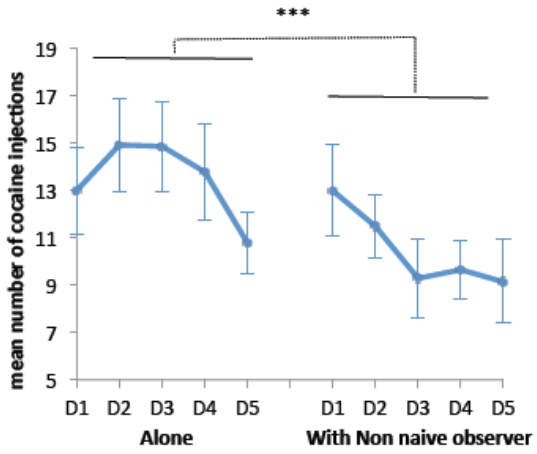
[1]including alcohol

[2] AUDIT-c score ≥3 for women and ≥4 for men

*the denominator may be lower due to missing information for some variables (always below 10%)

Figure 1

A


***
mean number of cocaine injections
19
17
15
13
11
9
7
5
D1 D2 D3 D4 D5
Alone
D1 D2 D3 D4 D5
With Non naive observer

B

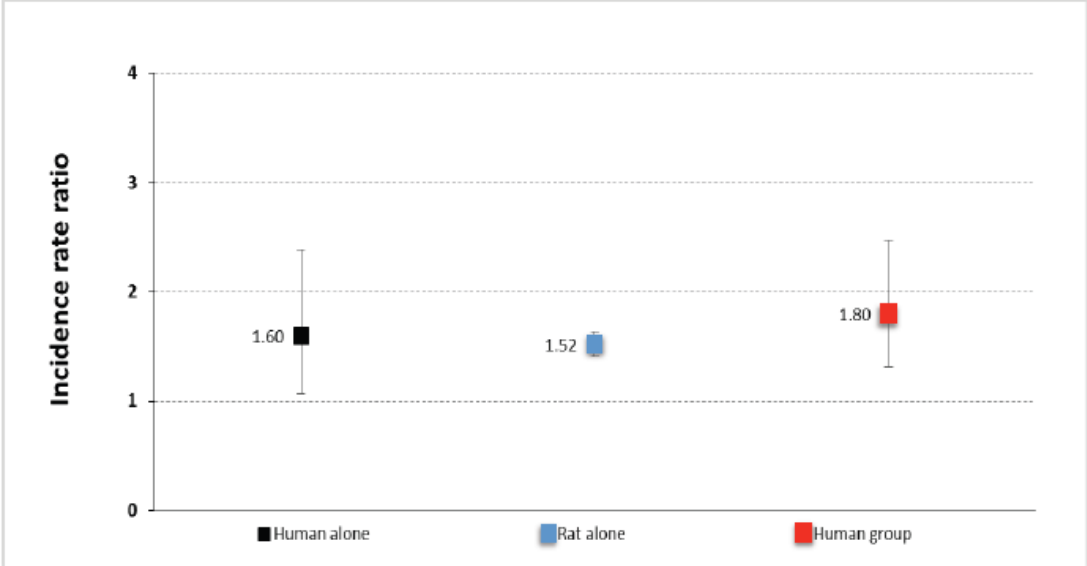
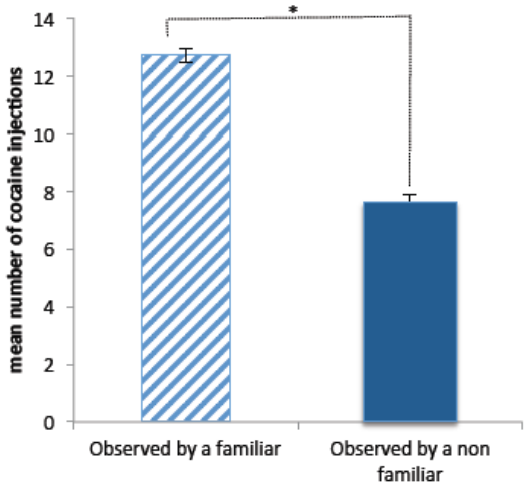

Incidence rate ratio
4
3
2
1
0
1.60
1.52
1.80
Human alone
Rat alone
Human group

Figure 2

A


*
14
12
10
8
6
4
2
0
mean number of cocaine injections
Observed by a familiar
Observed by a non familiar

B

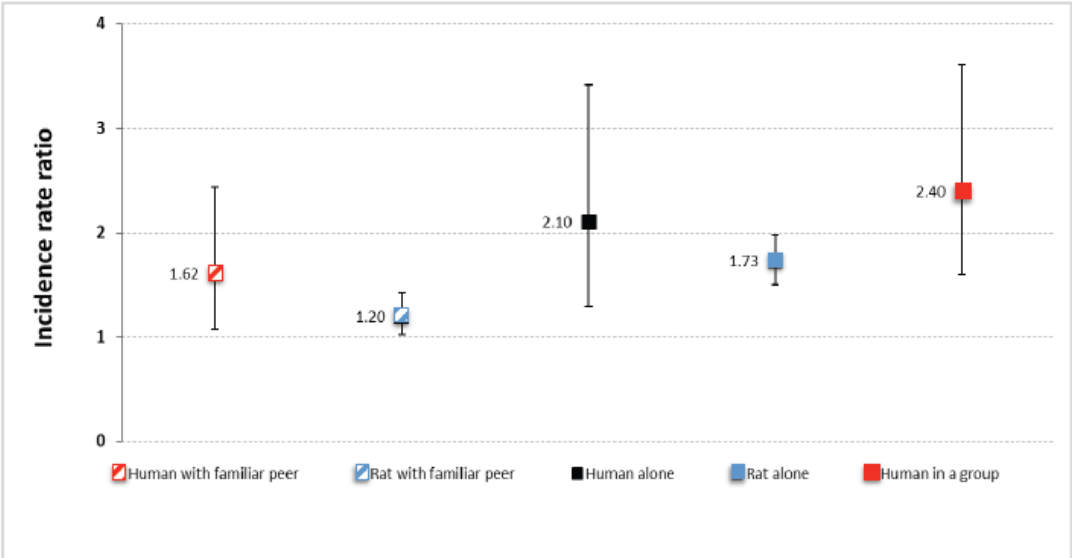
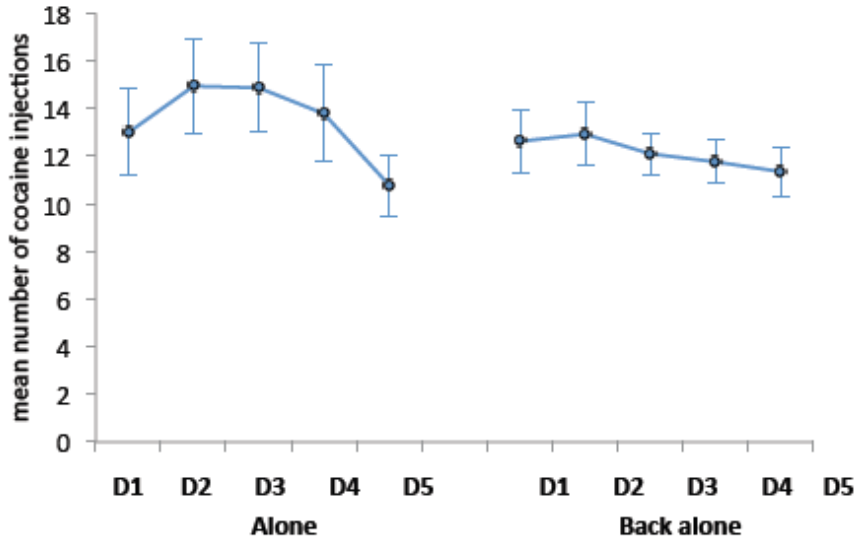
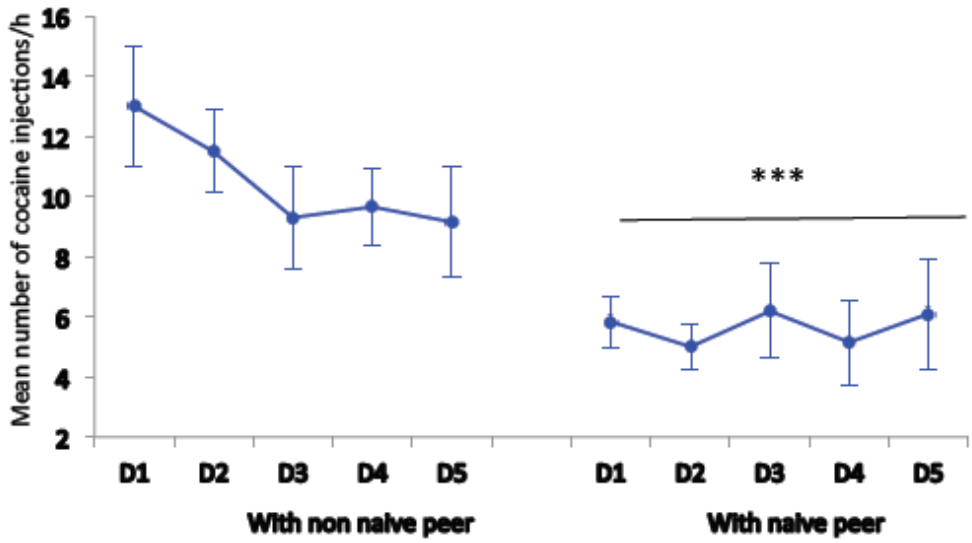

4
3
2
1
0
Incidence rate ratio
1.62
1.20
2.10
1.73
2.40
Human with familiar peer
Rat with familiar peer
Human alone
Rat alone
Human in a group

Figure 3

A


mean number of cocaine injections
18
16
14
12
10
8
6
4
2
0
D1
D2
D3
D4
D5
Alone
D1
D2
D3
D4
D5
Back alone

B


Mean number of cocaine injections/h
16
14
12
10
8
6
4
2
***
D1
D2
D3
D4
D5
With non naive peer
D1
D2
D3
D4
D5
With naive peer

Supplementary Information

Rat experiment

Surgery

Rats were anesthetized with ketamine (100 mg/Kg, s.c., Imalgène 1000, Merial, Lyon, France) and medetomidine (0,85 mg/Kg, s.c., Domitor, Orion Pharma, Espoo, Finland) and then subjected to intravenous implantation of catheters. At the end of surgery, medetomidine was reversed by 0.2 mg (4.28 mg/Kg, s.c.) atipamezole (Antisedan, Orion Pharma, Espoo, Finland). From this point forward, catheters were flushed daily with 0.2 ml of a sterile saline solution containing heparin (Heparin Sodium, Sanofi, Paris, France; 5000 U.I/ml) and enrofloxacin (Baytril 5%, Bayer, Loos, France; 50 mg/ml). Catheters were also regularly tested with propofol (Propovet, Abbott, 10 mg/ml) to confirm their patency.

Apparatus

Conditioned place preference experiment

The experiment was performed in two opaque Perspex boxes (90 cm length x 35 cm width x 33 cm height) divided into two main compartments - A and B (45 x 35 x 33 cm each) - which were used for the conditioned place preference test. Compartments A and B differed in the spatial organization of 2 columns. During conditioning, the compartments were separated by an opaque screen to confine the animals to one or the other. During habituation and testing, the screen was removed, allowing the animals to explore the entire apparatus.

Experimental Procedures

Conditioned place preference experiment

In order to assess whether or not cage-mate presence can be rewarding for a rat, conditioned placed preference to an environment associated with the presence of the cage-mate was performed.

As previously described (Rouaud et al 2010), the CPP procedure lasted 10 days. Each session was video recorded for further analysis. On the pre-conditioning day (Day 1), 66 rats were placed in the CPP apparatus and allowed to explore the two compartments for 15 minutes. The time spent in each compartment was recorded manually in seconds to determine a possible natural preference for each rat. During conditioning, rats were exposed for 30 min either to their cage-mate in their less-preferred compartment on days 2, 4, 6 and 8 or to no other rat in their initially preferred compartment on days 3, 5, 7 and 9. On day 10, all rats were placed in the middle of the CPP apparatus for 15 minutes and both compartments were made accessible for exploration. The time spent in each compartment was recorded manually in seconds and the score of preference for the compartment associated with the presence of the cage-mate was calculated.

Dominance status

For the social interaction and CPP studies, dominance status within each pair of rats was assessed by behavioral observation during the first conditioning session of the CPP experiment. The number of pinning and pouncing for each rat was recorded during a 15-min period of interaction. The “dominant” rat was assumed to be the one doing the most pinning and pouncing. The other rat was qualified as “subordinate”.

Data analysis and statistics

Conditioned place preference experiment

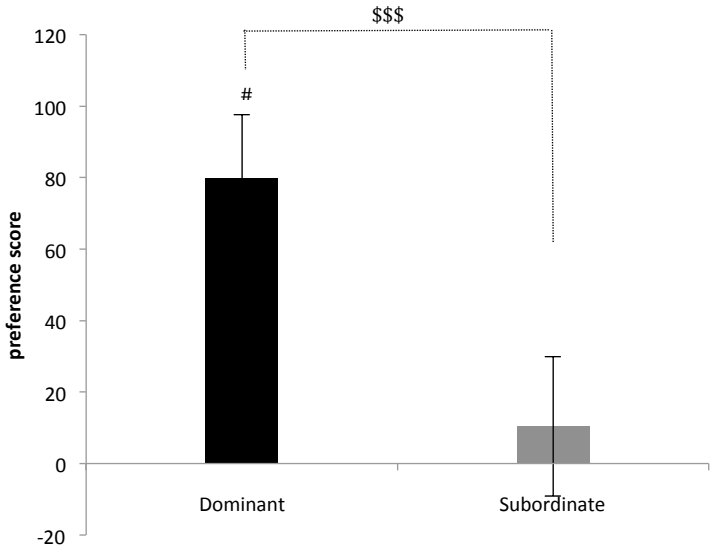
We analyzed the preference score of the rats for the compartment associated with the stimulus. This score was calculated by calculating the time spent in the environment previously paired with the social interaction, minus the time spent in the same compartment

before it was associated with the reward. This gave us an indication of the positive or negative memory that the animal had of its social experience. The non-parametric Mann-Whitney test was used for the conditioned place preference experiment to assess the group effect while the Wilcoxon signed rank test was used for the conditioning effect.

Results

Conditioned place preference according to the presence of a peer

To check whether or not the presence of a peer is a positive social context, the possible reinforcing properties of social interaction with the cage-mate were tested using the place-conditioning paradigm. In this paradigm, the reward effects of a given reinforcer (here, social interaction) are inferred by comparing the time spent in a specific environment previously paired with the reinforcer with the time spent in the same compartment before its association with the supposed reward (i.e. preference score). In this experiment, only the dominant rats showed a preference for the environment associated with social interactions with their subordinate (conditioning effect: $P<0.002$, group effect: $p<0.008$, Suppl. Fig.1). The subordinates did not exhibit any preference for or aversion to the compartment associated with the presence of their dominant peer.



Suppl. Fig. 1: Preference score (± SEM) for the environment associated with the presence of the cage-mate for dominant (black bar) and subordinate (grey bar) rats in the conditioned place preference paradigm.

The preference score (±SEM) is presented as the time spent in the compartment associated with social interaction on the test day (in sec) minus the time spent in this compartment on the preconditioning day (in sec). #:$p<0.05$ Wilcoxon signed rank test for conditioning effect, $$$:$p<0.001$ Mann-Whitney test for group effect.