Psychopharmacology (2022) 239:1097–1113
https://doi.org/10.1007/s00213-021-06033-0

ORIGINAL INVESTIGATION

Peer presence and familiarity as key factors to reduce cocaine intake in both rats and humans: an effect mediated by the subthalamic nucleus

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Received: 19 July 2021 / Accepted: 16 November 2021 / Published online: 11 January 2022

Abstract

Rationale Stimulant use, including cocaine, often occurs in a social context whose influence is important to understand to decrease intake and reduce associated harms. Although the importance of social influence in the context of drug addiction is known, there is a need for studies assessing its neurobiological substrate and for translational research.

Objectives Here, we explored the influence of peer presence and familiarity on cocaine intake and its neurobiological basis. Given the regulatory role of the subthalamic nucleus (STN) on cocaine intake and emotions, we investigated its role on such influence of social context on cocaine intake.

Methods We first compared cocaine consumption in various conditions (with no peer present or with peers with different characteristics: abstinent peer or drug-taking peer, familiar or not, cocaine-naive or not, dominant or subordinate) in rats ($n=90$). Then, with a translational approach, we assessed the influence of the social context (alone, in the group, in a dyad with familiar or non-familiar peers) on drug intake in human drug users ($n=77$).

Results The drug consumption was reduced when a peer was present, abstinent, or drug-taking as well, and further diminished when the peer was non-familiar. The presence of a non-familiar and drug-naive peer represents key conditions to diminish cocaine intake. The STN lesion by itself reduced cocaine intake to the level reached in presence of a non-familiar naive peer and affected social cognition, positioning the STN as one neurobiological substrate of social influence on drug intake. Then, the human study confirmed the beneficial effect of social presence, especially of non-familiar peers.

Conclusion Our results indirectly support the use of social interventions and harm reduction strategies and position the STN as a key cerebral structure to mediate these effects.

Keywords Addiction · Behaviors · Animal models · Basal ganglia · Epidemiology · Social sciences

Introduction

Recreational drug intake often takes place in a social environment. The social context is known to influence initiation(Neaigus et al. 2006; Sherman and Latkin 2001), persistence(Brewer et al. 1998; Schroeder et al. 2001), increase(Wu et al. 2008), and cessation(Buchanan and Latkin 2008; Latkin et al. 1999) of drug consumption(Kandel 1973, 1985). It is also a major determinant of risky practices, such as sharing injecting equipment(Latkin et al. 1996). A social environment encompasses two types of social factors: distal social factors (i.e., the consumer's broader social environment, which is not present immediately during drug consumption) and proximal social factors (i.e., the immediate social environment of the consumer, during the drug-taking).

Like humans, rats live in a complex social environment(Barnett 1967), showing a large panel of social abilities and behaviors(Schweinfurth 2020) and offering suitable models to elucidate neural processing of drug intake. Interestingly, the influence of distal social factors has been widely studied and, in rats, they mirror the effects highlighted in humans. Likewise, in these

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This article belongs to a Special Issue on Nature vs. Nurture in Addiction Research

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two species, stress, isolation, and rejection are associated with higher rates of drug use(Aloise-Young and Kaeppner 2005; Rusby et al. 2005; Burke and Miczek 2014; Nader et al. 2012; Stairs and Bardo 2009; Miczek et al. 2008). In contrast, strong familial ties in humans(Barnes et al. 2000; Dorius et al. 2004; Pandina et al. 1990; Scheier et al. 1999), and enriched environment in rats, are associated with lower rates of the drug(Burke and Miczek 2014; Nader et al. 2012; Stairs and Bardo 2009; Solinas et al. 2009).

Less is known about the proximal social influence on drug use, and studies on rodents may have contradicting results. Indeed, social interactions may act as an alternative reinforcement over drug use, diverting animals from consumption(Fritz et al. 2011a, b; Venniro et al. 2018), but they can also have a facilitating effect on drug consumption(Smith 2012; Gipson et al. 2011; Tomie et al. 2004; Weiss et al. 2018). Such discrepancy between results may originate from differences in experimental conditions. Notably, the presence of a peer during alcohol consumption has been shown to differently modulate rats' consumption, depending on the familiarity status of the present peer(Maldonado et al. 2008). Similarly, the broader drug experience of this peer present during self-administration could differently affect the consumption(Strickland and Smith 2014). However, in these animal studies, many characteristics of the peers, such as familiarity, dominance status, the former experience of the drug, were not all investigated systematically, nor the neurobiological mechanisms and brain structures involved in the influence of proximal social factors on addiction.

Recent studies on the neuroanatomical basis of the social modulation of drug use have focused on the reward system. Among them, the Nucleus Accumbens (NAc), the amygdala, and the insular cortex are involved in both drug and social interaction reinforcing effects (for review see Pelloux et al 2019). The Subthalamic Nucleus (STN), a deep cerebral structure belonging to the basal ganglia(Albin et al. 1989), has opposite effects on food and drug motivation(Baunez et al. 2005) and is implicated in social-emotional processing(Péron et al. 2010). Thus, it could play a key role in the influence of proximal social factors on drug consumption. Moreover, in former studies, it has been shown that STN lesion impairs the expression of both positive and negative emotional state(Pelloux et al. 2014) and abolishes the influence of positive and negative ultrasonic vocalizations on cocaine intake (Montanari et al. 2020), bringing some clues regarding STN contribution to emotional processing. Since we assumed that the social context and the effect of the presence of a peer on drug intake imply brain structures involved in emotional processes, we have thus focused on the role of STN. We hypothesized that STN activity should modify the influence of social context on drug consumption. Moreover, we hypothesized that manipulating the STN should lead to a change in the social interaction perception of the animals.

Epidemiologic studies have also shown an impact of a peer presence on alcohol consumption (Mohr et al. 2015) and an increased risk for a teenager of becoming a drug user if their friends also consume drugs (Kandel 1980). But, to our knowledge, no study to date has specifically focused on the influence of peer characteristics and drug-using status and their effect on cocaine consumption in humans. Since we hypothesized that STN will change the way you handle social interactions, we can thus hypothesize that peer characteristics would have different effects depending on STN activity. Furthermore, being in presence of a familiar peer or a non-familiar one should not have the same consequence on behaviors. The few existing studies in this area only examined the influence of peer presence and close relationships on outcomes such as alcohol use and craving during stressful events (Preston et al. 2017). To validate this model, there is a need for a translational approach confirming if the same processes are involved, in both humans and rats, regarding the proximal social influence on drug consumption.

In this study, we aimed thus to characterize how the dyad characteristics (familiarity, shared history of drug exposure) could influence cocaine intake and how it could be modulated by STN lesions in self-administering rats. We also investigated the role of STN on social preference to understand how social interaction could be rewarding for adult rats and therefore influence drug consumption. Finally, with a translational research approach, we ran an epidemiologic study in human drug users, allowing us to control that the experimental condition used for rats with a self-administering peer mirrored the processes observed in humans.

Materials and methods

Rat study

Animals and surgery

A total of 90 male Lister Hooded rats (Charles River Laboratories, Saint-Germain-sur-l'Arbresle, and France) were used in the present study. To avoid intervariability of the hormonal cycle, only male rats were used here. They were subjected to STN lesion procedure and then 64 of them were subjected to an intravenous silicon catheter implantation for the self-administration study (see Supplementary Materials for more detailed procedure).

Apparatus

All the drug self-administration experiments were conducted in four custom-built self-administration chambers (60 × 30 × 35 cm) divided into two compartments, separated by a grid. (See Supplementary Materials for more details). A

picture and a schematic diagram of the self-administration chambers are shown in Fig. 1.

As for the social experiments, they were conducted in a rectangular plastic arena (70 × 30 × 40 cm, social preference test) and opaque Perspex boxes (90 × 35 × 33 cm, conditioned place preference). (see Supplementary Materials for more details).

Experimental design

Influence of the presence of peer and its characteristics on cocaine self-administration in sham and STN lesioned rats A total of 2 sets of animals were used in this first experiment. One set of animals (sham $n = 14$, STN lesioned $n = 17$, experiment "abstinent peer") were subjected to the self-administration procedure while a peer was present, allowed to freely move in its compartment, while other animals (sham, $n = 14$, experiment "drug-taking peer") were allowed to take cocaine in presence of another peer also self-administering cocaine.

Both sham and STN lesioned rats were individually trained to pull a chain to self-administer cocaine (80 µg per 90 µl infusion in 5 s, 0.2 mg/kg) under a continuous schedule of reinforcement (fixed ratio 1 (FR1), 1 chain pulling resulted in 1 cocaine injection) for daily 1-h sessions. Since chain pulling is not as easy as pressing a lever, the baseline level of cocaine consumption was too low with the classic dose of 250 µg per 90 µl. We, thus, chose to decrease the dose of cocaine to 80 µg to increase the number of injections taken per session. For half of each group, cocaine was randomly assigned to one of the two chains (the active chain), and the other half of the group had the opposite rule. 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 (i.e., 5 consecutive days with the same number of cocaine injections ± 2), the last 5 days of acquisition were used as a baseline for cocaine consumption when the rats were alone in the apparatus (condition "no peer"). For each 1-h behavioral session, the number of cocaine injections was recorded.

Cocaine self-administration with an abstinent peer The rats were exposed to 4 different conditions, for 5 consecutive days each, each session lasted 1 h:

1) No peer (baseline consumption): The rats were alone in the self-administration chamber during the acquisition of the self-administration behavior. Once they have learned it, the last 5 sessions were kept for analysis.
2) Peer presence: The self-administering rats were in presence of another rat (hereafter "abstinent peer"), having no access to cocaine. This peer could be for some rats "familiar" (i.e., a cage-mate also trained for self-administration; (sham $n = 8$ STN lesioned $n = 6$) or "non-familiar" (i.e., a rat trained for cocaine self-administration but living in a different home-cage; sham $n = 6$ STN lesioned $n = 11$). Observing peers were introduced into the cage after they had a minimum of 4 h of abstinence from cocaine. For the "familiar peer" condition, the dominant status ("dominant" observed by "subordinate" vs. "subordinate" observed by "dominant" peer) was also taken into account, as it could be determined after

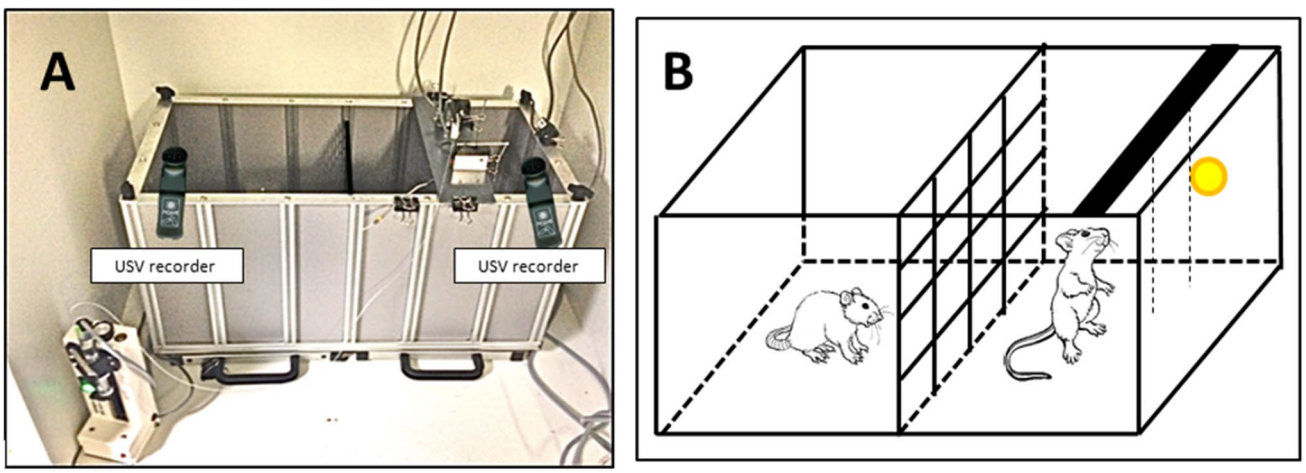

Fig. 1 Picture and schematic representation of the self-administration experimental apparatus. **A** Picture of one experimental box from above. **B** Schematic diagram of the same experimental box from the side. The observing rat is in the left compartment separated by a grid (2.5 × 2.5 cm, allowing visual, auditive, olfactory, and limited tactile interactions between the 2 rats), while the self-administering rat is in the right compartment and has access to two chains (small dotted lines), one of which is the active chain and leads to cocaine delivery

the behavioral assessment described in Supplementary Materials.

3) Post-peer presence: Rats were back alone after exposure to peers (sham $n=14$, STN lesioned $n=17$) in order to assess whether peer presence could have a long-lasting influence on cocaine intake even in absence of this peer.
4) Non-familiar and cocaine-naive peer presence: rats were tested in presence of a rat from another group that had never been exposed to cocaine (sham $n=11$ STN lesioned $n=15$).

The same peer was used for each given rat for the 5 behavioral sessions of a condition.

Cocaine self-administration with a drug-taking peer During this part of the experiment, in the peer presence condition, both rats could have access to cocaine during the 1-h behavioral sessions. Acquisition of the self-administration behavior was done in the "no peer" condition. Then, rats were subjected to 2 conditions:

1) No peer (baseline consumption): when the rats were alone in the self-administration chamber.
2) Peer presence: In the presence of another rat (hereafter "drug-taking peer") also having access to the drug, so the rats could both have access to cocaine during the 1-h session. This peer could be either "familiar" (i.e., a cage-mate also trained for self-administration; $n=6$) or "non-familiar" (i.e., a rat trained for cocaine self-administration but living in a different home-cage; $n=8$).

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

Reinforcing properties of social presence Social preference To examine if the STN is involved in social preference and could modulate a rat's social preference for a social stimulus (a peer) versus an object, we subjected rats to a social preference test (Jacobs and Tsien 2017; Moy et al. 2004). In this procedure, the subject rat is simultaneously exposed to 2 identical cages, one containing an object and the other a social stimulus (either a non-familiar rat or the cage-mate). Subject rat is allowed to freely explore for 5 min both stimuli. Investigation time has been defined, as previously described in Engelmann et al. (1995), as the time spent by the subject actively exploring (sniffing with the tip of the nose within approximately 1 cm of the cage containing the stimulus rat or the object. To reduce the number of animals, the same cohort was used for both familiar and non-familiar stimuli (sham-control rats $n=7$ and STN-lesioned rats $n=9$). The order of testing "familiar" or "non-familiar" stimuli was counterbalanced to prevent a possible effect of repetition of the testing. The objects were changed for each session. The investigatory behavior has been scored by a trained observer. For every test, if the total investigation time was less than 30 s, the results were removed from the analysis.

Conditioned place preference In order to assess whether or not cage-mate presence can be rewarding for a rat, conditioned place preference (CPP) to an environment associated with the presence of the cage-mate was performed. As previously described (Rouaud et al. 2009), the CPP procedure lasted 10 days. Each session was video recorded for further analysis (see Supplementary Materials for more details). On the pre-conditioning day (day 1), 66 sham rats and 14 STN lesioned rats were placed in the CPP apparatus and allowed to explore the two compartments for 15 min. 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, each individual was placed in the middle of the CPP apparatus for 15 min 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.

Outcome

The outcome of the study was the frequency of cocaine intake, defined by the number of cocaine injections during the 1-h cocaine self-administration sessions.

Statistical analysis

To analyze the self-administration experiments, the frequency of cocaine intake was compared according to the state of the STN (intact i.e., sham rats or lesioned), the nature of the social relationship with peer rats (familiar or non-familiar), the history of cocaine exposure of peer rats (naive or non-naive) and whether the peer rat was dominant or subordinate.

Poisson mixed effects models were used to take into account the correlation over time between repeated measures of the outcome. Poisson-mixed models provided, for each explanatory variable associated with the frequency of cocaine intake, an estimate of the incidence rate ratio (IRR) and its 95% confidence interval (CI). IRRs are a measure of the association between the explanatory variable and the frequency of cocaine intake. Confidence intervals not containing 1 indicate a significant association (p-value <0.05).

The following four models were analyzed for sham rats and then for STN lesioned rats, each including a random effect on time (in days), and the following experimental factor:

A) Peer presence: no peer or with an abstinent peer, irrespective of the relationship (i.e., familiar/non-familiar);
B) Familiarity: no peer, with a familiar peer, with a non-familiar peer (only abstinent peers);
C) History of cocaine exposure: no peer, with a naive peer, with an abstinent peer, back alone;
D) Social status: dominant or subordinate (only abstinent familiar peers).

Then the following analyses were performed to take into account the difference between sham and STN lesioned rats, each including a random effect on time (days) and the following experimental factor:

E) Baseline consumption: sham or STN lesioned when alone;
F) Peer presence: sham or STN lesioned (non-naïve and naive peers).

For the social preference test, all variables are expressed as mean number ± SEM and the *p*-value threshold has been set at $\alpha = 0.05$.

Time spent exploring the different stimuli were compared between sham-control and STN-lesioned rats using the Wilcoxon matched-pairs signed-rank test.

Concerning the conditioned place preference, we analyzed the preference score of the rats for the compartment associated with the stimulus. This score was calculated as the time spent in the environment previously paired with the social interaction (test day), minus the time spent in the same compartment before it was associated with the reward (preconditioning day). 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.

Analyses and graphs were carried out using Prism (GraphPad).

Human study

Design

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

Participants

Seventy-seven French-speaking regular stimulant users–defined as using cocaine or methylphenidate ≥ 5 times a month–were recruited in both specialized services for substance use disorders or harm reduction services in Paris and Marseilles between October 2015 and June 2016. We used both entry points to be able to recruit active cocaine users whether in care or not. The services involved accepted that the interviewers of the study could enroll and interview the eligible users attending their services. 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.

Data collection

Data were anonymously collected through a face-to-face standardized questionnaire administered by trained interviewers.

To minimize recall bias, participants retrospectively described episodes during the previous month where they used stimulants. The social environment at the moment of stimulant use was described as follows: alone, with one peer, 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 methylphenidate), drug effect perception (from 1 to 5), concomitant use of other psychoactive substances including alcohol, the location where the episode took place (public versus private), state of mind (positive vs. neutral versus negative), 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 vs. unstable), hazardous alcohol use (AUDIT-C score) (Bush et al. 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 study outcome was the frequency of drug intake, defined as the number of times drugs were consumed in 1 h during each episode.

The frequency of use during one episode (standardized by the duration of the episode) is an interesting measure, especially among cocaine users where the half-life of the drug may require repeated intake. From a public health viewpoint, this frequency is associated with several health risks (e.g. overdoses and other fatal events, as well as unsafe sexual behaviors(Berry and Johnson 2018; Martins et al. 2015; Sordo et al. 2014)).

Statistical analysis

When exploring the relationship between frequency of stimulant use and presence of/type of relationship with the peer, we used all the episodes of stimulant use reported by participants. To take into account within-subject correlation due to repeated measures (i.e., repeated episodes reported by the same individual), we used the Poisson Generalized Estimated Equations (GEE) approach for count data(Liang and Zeger 1986) (see Supplementary Materials for more details).

GEE provided, for each explanatory variable, an IRR estimate and its 95% CI, as a measure of the association between the explanatory variable and the frequency of stimulant use. STATA/SE version 12.1 software for Windows was used for the analyses.

Results

Experiment 1: influence of the presence of peer and its characteristics on cocaine self-administration in sham and STN lesioned rats

Influence of peer presence

Abstinent peer Sham control rats in the "no peer" condition took an average of 13.51 (± standard error of the mean (SEM: 0.82) cocaine injections during the 1-h self-administration sessions. When an abstinent peer was present (familiar or not), the average value decreased to 10.51 (± 0.72) (Fig. 2A). This translates to a 22% decrease in the relative risk of cocaine intake when rats were in the presence of an abstinent peer, compared with when they were alone (IRR [95% CI] = 0.78 [0.71–0.86], $p < 10^{-3}$) (see Supplementary Table S2A). When the STN lesioned rats were alone in the self-administration chamber, they took an average of 12.07 (± 0.59) injections. As previously shown when rats are alone and work under an FR1 schedule of reinforcement not requesting any effort, and during short access sessions (Baunez et al. 2005), there was no significant difference between the sham and the STN lesioned groups in the "no peer" condition ($p = 0.527$, group effect, mixed-effects Poisson regression). When an abstinent peer was placed in the chamber separated by a grid, the STN lesioned rats took less cocaine injections than when with no peer (means 6.63 (± 0.53)) (Fig. 2C). This translates to a 45% decrease in the relative risk of cocaine intake when rats were in the presence of an abstinent peer compared with when they were alone (IRR [95% CI] = 0.55 [0.50–0.61], $p < 10^{-3}$) (see Supplementary Table S2A).

The reduced cocaine intake induced by the presence of a peer was stronger in STN lesioned rats (6.63 (± 0.53)) than in sham rats (10.51 (± 0.72)) ($p = 0.016$, group effect, mixed-effects Poisson regression) (Fig. 2C).

Drug-taking peer When the peer also had access to cocaine (drug-taking peer), we observed a comparable effect to the first part of the experiment where the present peer was abstinent, with no access to the drug (Fig. 2B). First, rats were alone to acquire the self-administration behavior and reached a stable number of cocaine injections (20.04 (± 1.21)). When rats were in a presence of a drug-taking peer, they took an average of 14.84 injections (± 1.27) (Fig. 2B). This represents a 26% decreased risk of consuming cocaine when they were placed in presence of a peer also taking cocaine (IRR [95% CI] = 0.74 [0.68–0.80], $p < 10^{-3}$) (see Supplementary Table S2B) compared with when they were with no peer (see Fig. 5A for levels of consumption).

Chronologically, in this study, after exposure to a non-naive (abstinent cocaine) peer, rats were tested again with no peer to self-administer ("back alone" condition) to be then tested in presence of a non-familiar naive cocaine rat. In sham rats, when the animals were tested in the "back alone" condition after the test of social presence, cocaine consumption returned to a level close to the baseline ("alone") level (11.87 (± 0.48) vs. 13.51 (± 0.82), respectively) (Fig. 2D). In STN lesioned rats, when tested in the "back alone" condition after the test of social presence, the return to baseline level was less obvious (mean 9.08 (± 0.90) vs. 12.07 (± 0.59)) (Fig. 2D).

Influence of peer familiarity

Abstinent peer In sham controls animals, the average number of cocaine injections self-administered during the 1-h sessions was lower when the peer was "non-familiar" (7.60 (± 0.89)) than when "familiar" (12.7 (± 0.94)) (Fig. 3A, left). The Poisson regression analysis showed a 15% decreased relative risk between alone and presence of a familiar peer (IRR [95% CI] = 0.85 [0.76–0.96], $p = 0.009$) (see Supplementary Table S2A). This decrease was further

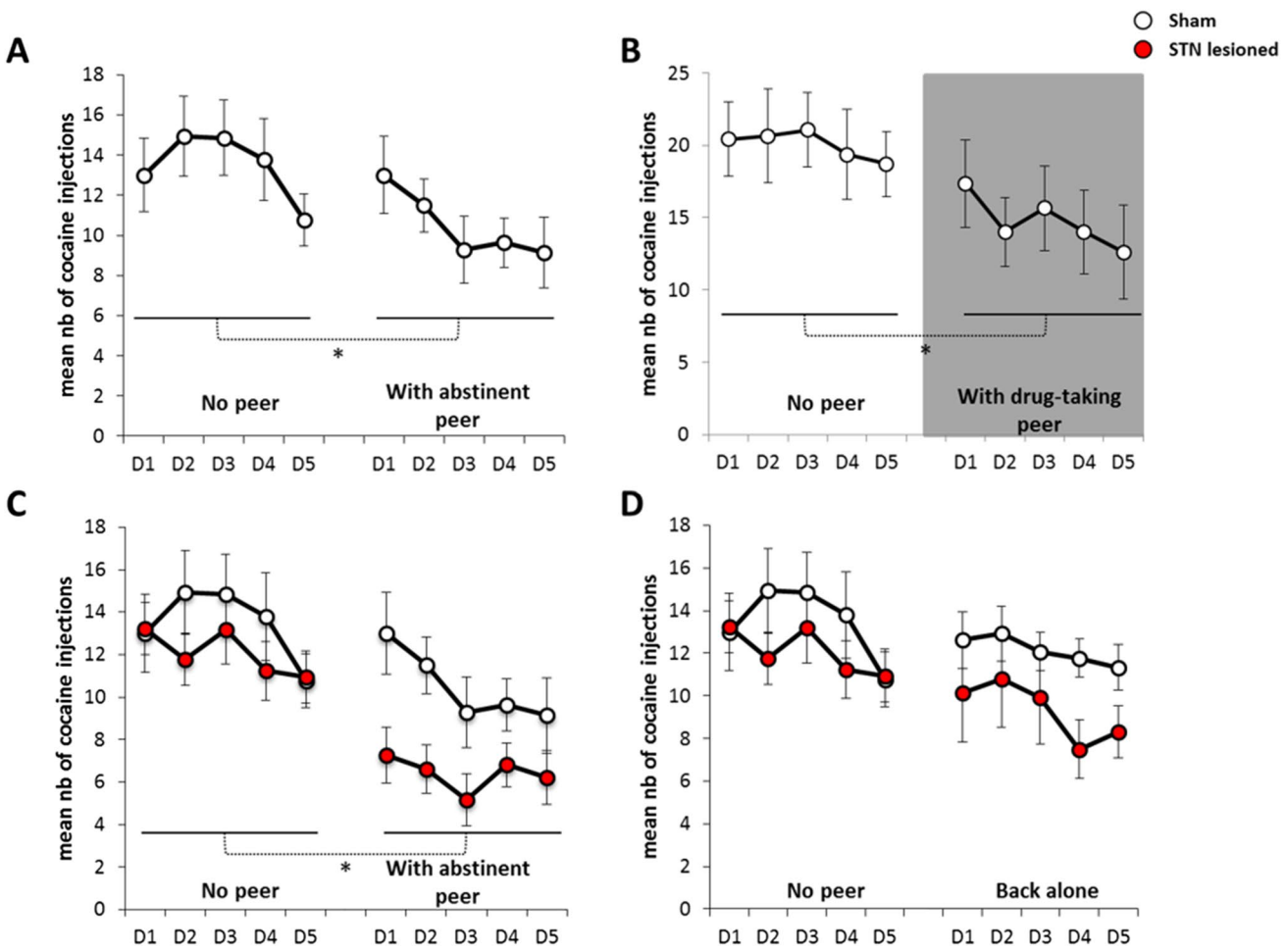

Fig. 2 Influence of the presence of an abstinent or drug-taking peer on cocaine consumption in sham and STN lesioned rats. **A** Influence of the presence of an abstinent peer on cocaine self-administration in rats. The results are illustrated as the mean (±SEM) number of cocaine injections (80 µg/90 µl/injection) per 1 h-session during 5 consecutive sessions of baseline ("no peer," D1 to D5) and during 5 consecutive sessions in presence of a peer ("with an abstinent peer," D1 to D5), for sham control rats (white dots, $n=14$) (*$p<0.05$ group effect, Poisson mixed model). **B** Influence of the presence of a drug-taking peer on cocaine self-administration. The results are illustrated as the mean (±SEM) number of cocaine injections (80 µg/90 µl/injection) per 1-h session during 5 consecutive sessions of baseline ("no peer," D1 to D5) and during 5 consecutive sessions in co-administration ("with a drug-taking peer," D1 to D5, $n=14$) (*$p<0.05$ group effect, Poisson mixed model). **C** Effect of the STN lesion on the influence of the presence of an abstinent peer on cocaine self-administration in rats. The results are illustrated as the mean (±SEM) number of cocaine injections (80 µg/90 µl/injection) per 1-h session during 5 consecutive sessions of baseline ("no peer," D1 to D5) and during 5 consecutive sessions in presence of a peer ("with an abstinent peer," D1 to D5), for sham control rats (white dots, $n=14$) and for the STN lesioned rats (red dots, $n=17$), (*$p<0.05$ group effect, Poisson mixed model)

significant (35%) in presence of a non-familiar peer (IRR [95% CI] = 0.65 [0.55–0.77], $p<10^{-3}$) and also when compared to the condition of presence of a familiar peer (non-familiar vs. familiar peer: IRR = 0.55 [0.35–0.87], $p<0.011$) (see Supplementary Table S2A).

In the STN lesioned rats, no matter the characteristics of the peer, the cocaine intake decreased in the same manner to a low level (observed by familiar: mean 6.87 (±0.73), observed by a non-familiar: mean 6.51 (±0.73)) (Fig. 3A right). The Poisson regression analysis showed a 33% decreased relative risk between no peer and presence of a familiar peer (IRR [95% CI] = 0.57 [0.48–0.68], $p<10^{-3}$) (see Supplementary Table S2A). The reduction of risk to take cocaine was equivalent (36%) when the peer was non-familiar (IRR [95% CI] = 0.54 [0.47–0.61], $p<10^{-3}$), and no significant difference was found for the comparison between presence of an abstinent non familiar versus familiar peer (IRR = 0.81 [0.44–1.51] $p=0.517$) (see Supplementary Table S2A).

Drug-taking peer When rats self-administered cocaine in the presence of a peer who could also take cocaine (Fig. 3C), in

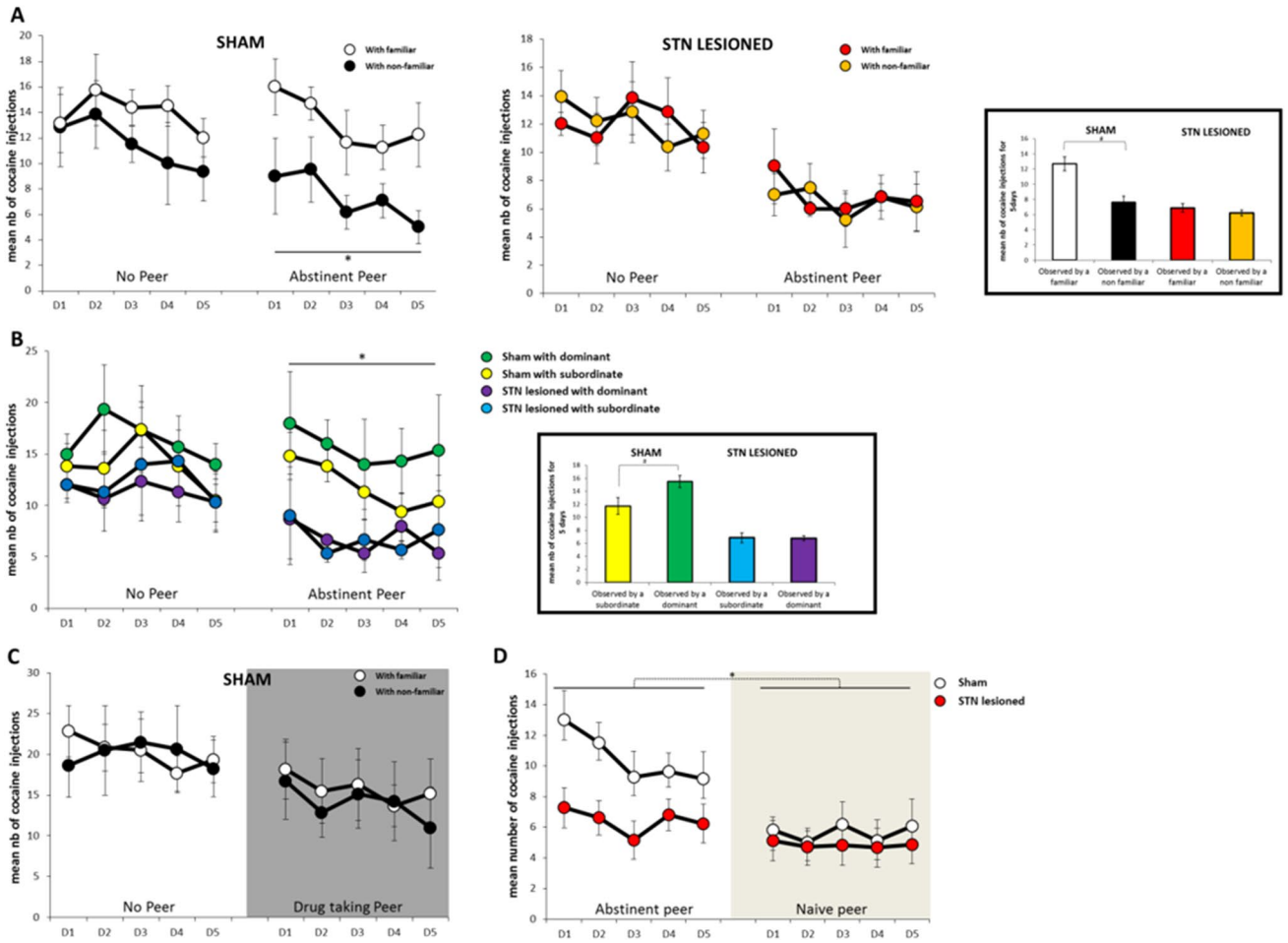

Fig. 3 Influence of the familiarity, dominance status, and history of drug exposure of a peer on cocaine consumption in sham and STN lesioned rats. **A** left panel—influence of familiarity of the abstinent peer on cocaine self-administration in rats. The results are illustrated as the mean (±SEM) number of cocaine injections (80 µg/90 µl/injection) per 1-h session during 5 consecutive sessions of baseline ("no peer," D1 to D5) and during 5 consecutive sessions either in presence of a familiar peer (white dots, sham $n=8$, D1 to D5) or a non-familiar peer (black dots, sham $n=6$, D1 to D5) for sham control rats (*$p<0.05$ group effect, Poisson regression). Right panel—effect of STN lesion on the influence of the familiarity of the present peer on cocaine self-administration in rats. The results are illustrated as the mean (±SEM) number of cocaine injections (80 µg/90 µl/injection) per 1-h session during 5 consecutive sessions of baseline ("no peer," D1 to D5) and during 5 consecutive sessions either in presence of a familiar peer (red dots, STN lesioned $n=6$) or a non-familiar peer (orange dots, STN lesioned $n=11$). Bar plot—the results are illustrated as the mean (±SEM) number of cocaine injections (80 µg/90 µl/injection) per session and averaged for 5 consecutive days of social interaction with either a familiar peer (white bars, sham $n=8$, red bars STN lesioned $n=6$) or a non-familiar peer (black bars, sham $n=6$, orange bars STN lesioned $n=11$), (#$p<0.05$ conditions effects, Poisson regression). **B** Influence of dominance status within familiar peers on cocaine self-administration in both sham and STN lesioned rats. The results are illustrated as the mean (±SEM) number of cocaine injections (80 µg/90 µl/injection) per 1-h session during 5 consecutive sessions of baseline ("no peer," D1 to D5) and during 5 consecutive sessions either in presence of a familiar subordinate peer (yellow dots, sham $n=4$, blue dots STN lesioned $n=3$) or a familiar dominant peer (green dots, sham $n=4$, purple dots STN lesioned $n=3$), (#$p<0.05$ conditions effects, Poisson regression). Bar plot- the results are illustrated as the mean (±SEM) number of cocaine injections (80 µg/90 µl/injection) per session and averaged for 5 consecutive days of social interaction with either its familiar subordinated peer (yellow bars, sham $n=4$, blue bars STN lesioned $n=3$) or its familiar dominant peer (green bars, sham $n=4$, purple bars, STN lesioned $n=3$), (#$p<0.05$ conditions effects, Poisson regression). **C** Influence of familiarity of the drug-taking peer on cocaine self-administration in rats. The results are illustrated as the mean (±SEM) number of cocaine injections (80 µg/90 µl/injection) per 1-h session during 5 consecutive sessions of baseline ("no peer," D1 to D5) and during 5 consecutive sessions either in presence of a familiar drug-taking peer (white dots, $n=6$) or a non-familiar drug-taking peer (black dots, $n=8$). **D** Influence of the peer history of drug exposure on cocaine consumption in sham and STN lesioned rats. The results are illustrated as the mean (±SEM) number of cocaine injections (80 µg/90 µl/injection) per 1-h session for 5 consecutive sessions under the observation of a non-familiar peer with a history of cocaine self-administration (left, an "abstinent peer," D1 to D5, white dots sham $n=14$; red dots STN lesioned $n=17$) and under the observation of a non-familiar peer naive to cocaine (right, "naive peer", D1 to D5: day 1 to 5, white dots sham $n=11$; red dots STN lesioned $n=15$); (*$p<0.05$ conditions effects, Poisson regression)

sham-control animals, the average number of cocaine injections self-administered during the 1-h sessions was equivalent when the peer was "non-familiar" (14.15 (±1.87)) and when it was "familiar" (15.79 (±1.60)) (Fig. 3C). In the mixed Poisson model analysis, we found that compared with being alone, a decreasing relative risk of consumption was observed from being with a familiar peer (22% reduction) (IRR [95% CI] = 0.78 [0.69–0.88], $p < 10^{-3}$) to being with a non-familiar peer (29% reduction)(IRR [95% CI] = 0.71 [0.64–0.79], $p < 10^{-3}$) (see Supplementary Table S2B). However, these decreases were smaller than those observed in the former experiment with abstinent peers.

Influence of the dominance/subordination relationship Further analysis assessing the dominance status revealed that, in sham control animals, the average number of cocaine injections self-administered during the 1-h sessions was lower when the abstinent peer was the familiar-subordinate (11.74 (±1.15)) than when it was the dominant one (15.51 (±0.69)) ($p = 0.036$, group effect, mixed-effects Poisson regression) (Fig. 3B). In STN lesioned rats, no significant difference was found when comparing the frequency of cocaine consumption in rats in the presence of the subordinate (6.86 (+ − 0.67)) and in the presence of the dominant (6.8 (+ − 0.69) familiar peer (Fig. 3B).

Influence of peer history of drug exposure In the presence of a cocaine-naive peer, sham rats significantly reduced their drug intake to an average of 5.64 (±0.56) cocaine injections, in comparison with an average of 10.51 (±0.72) injections in the presence of a non-naive of cocaine peer (familiar to the subject and non-familiar together) (Fig. 3D).

The Poisson model showed a progressive decrease in the risk of cocaine consumption from no peer to the presence of a abstinent peer (22% reduction; IRR [95% CI] = 0.78 [0.71–0.86], $p < 10^{-3}$) and from back alone to the presence of a naive peer (53% reduction; IRR [95% CI] = 0.47 [0.41–0.54], $p < 10^{-3}$) (see Supplementary Table S2A).

STN lesioned rats also significantly decreased their cocaine intake in presence of a cocaine naive peer (4.96 (±0.55)) when compared to the presence of an abstinent peer (6.63 (±0.53)) ($p < 0.05$, conditions effects, Poisson regression) (Fig. 3D). The Poisson model showed a similar decrease in the risk of cocaine consumption from "no peer" to the "presence of an abstinent peer" (45% reduction; IRR [95% CI] = 0.55 [0.50–0.61], $p < 10^{-3}$) and from "back alone" to the "presence of a naive peer" (46% reduction; IRR [95% CI] = 0.54 [0.48–0.61], $p < 10^{-3}$) (see Supplementary Table S2A).

Experiment 2: Reinforcing properties of social presence

Social preference

To evaluate the potential reinforcing properties of social presence, we first tested if the presence of a peer was preferred over an object and whether the STN lesion could affect this discrimination. We thus subjected sham-control and STN-lesioned rats to a social preference test, using a social stimulus (a non-familiar rat or the cage-mate) and an object. As illustrated in Fig. 4A, when the social stimulus was a non-familiar rat, both sham-control and STN-lesioned rats spent more time exploring the cage containing the rat than the one containing an object (sham $n = 7$, W = 28, $p = 0.0156$; lesioned $n = 9$, $W = 45$, $p = 0.0039$ (Wilcoxon matched-pairs signed-rank test)). However, when the cage-mate was used as the social stimulus, only STN-lesioned rats showed a preferential exploration of the cage containing the social stimulus ($W = 45$, $p = 0.0039$ (Wilcoxon matched-pairs signed-rank test) (Fig. 4B); sham-control group: $W = 20$, $p = 0.1094$ (Wilcoxon matched-pairs signed-rank test)). Together, those results highlight the fact that a non-familiar rat is preferred over an object and that STN lesions seem to impair the dissociation between familiar and non-familiar peers.

Conditioned place preference

To check whether or not, the presence of a peer is a positive social context with reinforcing properties, the conditioned place-preference paradigm was used with the presence of the cage-mate. In this paradigm, the rewarding 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).

First, we found no significant differences between the sham control group and STN lesioned group on the preference score (group effect: $p = 0.082$ (Mann–Whitney test), Fig. 4C). Nevertheless, we found a conditioning effect for both groups. Indeed, the preference score for these two groups was different from zero (conditioning effect: $p < 0.001$, (signed-rank test), Fig. 4C). This suggests that adult sham control and STN lesioned rats significantly prefer the compartment associated with the presence of a conspecific.

Further analysis assessing the dominance status revealed that, in the sham control group, the preference score was only significant for the dominant rats (conditioning effect: $p < 0.0001$ (signed-rank test); dominance effect: $p < 0.001$ (Mann–Whitney test), Fig. 4D). Subordinate control rats did not develop any preference or aversion for the compartment associated with the presence of their dominant peer (conditioning effect: $p = 0.68$, (signed-rank test)).

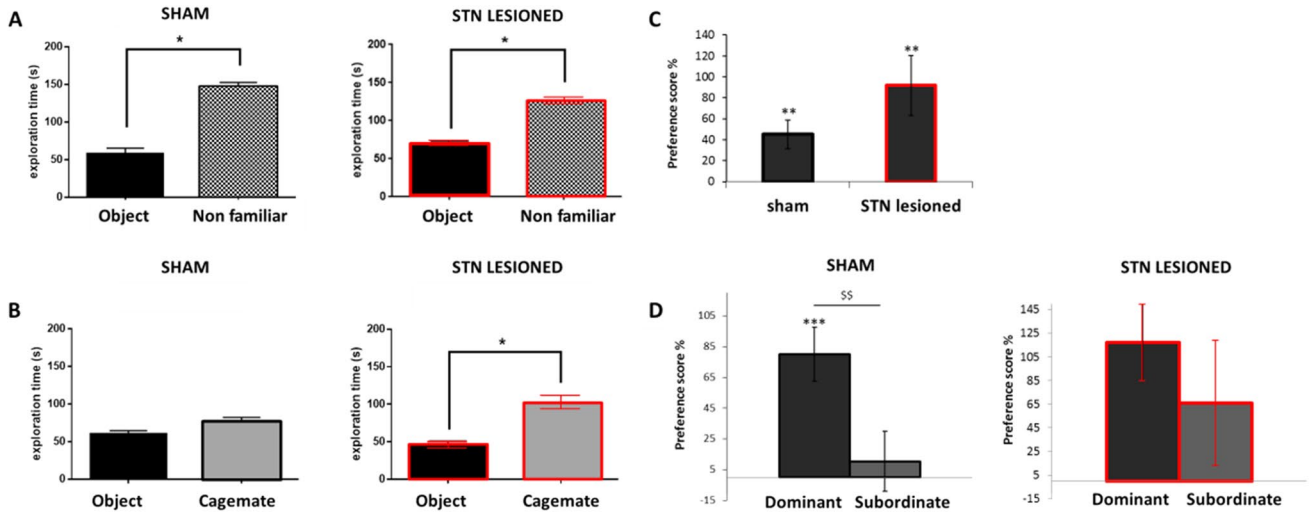

Fig. 4 Effect of the STN lesion on the rewarding properties of social interactions. **A** Effect of the STN lesion on the social preference over an object: preference between a non-familiar peer over an object. The mean exploration time (sec. (±SEM) i.e., the time spent exploring the social stimulus (green bar) and the object (black bar), is represented for sham rats (dark lines, $n=7$) and STN lesioned rats (red lines, $n=9$), ($^{*}p<0.05$ compared to a non-familiar stimulus (Wilcoxon test). **B** Effect of the STN lesion on the social preference over an object: preference between a familiar peer over an object. The mean exploration time (sec., (±SEM) i.e., the time spent exploring the social stimulus (grey bar) and the object (black bar), is represented for sham rats (dark lines, $n=7$) and STN lesioned rats (red lines, $n=9$), ($^{*}p<0.05$ compared to a non-familiar stimulus (Wilcoxon test). **C** Conditioned place preference test for peer presence: effect of the STN lesion on the preference score for the presence of a peer. The mean preference score (±SEM), i.e., the time spent in the compartment paired with the reinforcer on the testing day minus the time spent in this same compartment at day 1 before conditioning is represented for the sham control group (white bar, $n=66$) and for the STN lesioned group (red bar, $n=14$). $^{**}p<0.001$ compared to a theoretical zero (sign test) ($p=0.082$ group comparison sham vs. STN lesioned, Mann–Whitney test). **D** Conditioned place preference test for peer presence: effect of the dominance status on the preference score for the presence of a peer for the control and STN lesion group. The mean preference score (±SEM), i.e., the time spent in the compartment paired with the reinforcer on the testing day minus the time spent in this same compartment at day 1 before conditioning is represented for the dominant rats (black bars, dark line: sham $n=33$; red line: STN lesioned $n=7$,) and for the subordinate (dark grey bars, dark line: sham $n=33$; red line: STN lesioned $n=7$). $^{***}p<0.001$, $^{**}p<0.01$ compared to a theoretical zero (sign test); \$\$ $p<0.01$ significant group comparison (dominant vs. subordinate, Mann–Whitney test)

Possibly due to inter-individual variability, in the STN lesioned group, dominant and subordinate rats did not show any significant differences in their preference score (dominance effect: $p=0.186$, (Mann–Whitney test), Fig. 4D). Nevertheless, only dominant STN rats showed a preference score significantly different from 0 (conditioning effect: $p<0.05$, (signed-rank test), Fig. 4D).

Experiment 3: translational towards human drug users

In humans, among episodes involving one other peer, we note that the latter was always a drug user (for episodes with a group, peers were not characterized). Whether the drug user was actually consuming or not during the same episode was not directly documented, but this is why it was important to perform a rat study in which the peer could also have access to the drug during the same episode.

In the human study, results showed a 37% decreased relative risk of cocaine intake during an episode when one peer was present with respect to alone (IRR [95% CI] = 0.63 [0.42–0.94], $p=0.023$), after adjusting for unstable housing and other drug intakes (stimulant, other including alcohol) (Table 1 and Fig. 5A). These results are in line with those from the rat study, where a decrease in relative risk of cocaine intake was observed in a presence of an abstinent peer (Fig. 5A).

However, there was no significant difference in cocaine intake when a group of peers was present compared with being alone ($p=0.523$) (Table 1).

As for the rat experiment, we also observed a decrease in relative risk of cocaine use during an episode from familiar peer presence (IRR [95% CI] = 0.77 [0.50–1.18], $p=0.233$) to non-familiar peer presence (IRR [95% CI] = 0.48 [0.29–0.77], $p=0.003$), versus being alone (reference category) (Fig. 5B and Table 2).

Other correlates associated with greater frequency of cocaine use in the multivariable analysis were unstable housing (IRR [95% CI] = 2.38 [1.67–3.40], $p<10^{-3}$), daily stimulant use (IRR [95% CI] = 1.60 [1.19–2.15], $p=0.002$) and other substances (alcohol included) concomitantly used during the episode (IRR [95% CI] = 1.16 [0.99–1.35], $p=0.062$).

Table 1 Human study—association between peer presence and cocaine use frequency among humans ($n = 77$ participants, $n = 246$ episodes of cocaine use), GEE Poisson regression, and multivariable analysis

	Coefficient estimate [95% CI]*	IRR [95% CI]*	*P*-value
Social proximal context			
Alone (ref.)	0	1	
With one peer	−0.469 [−0.873; −0.065]	0.63 [0.42; 0.94]	0.023
Group	0.119 [−0.246; 0.485]	1.13 [0.78; 1.62]	0.523
Unstable housing			
No (ref.)	0	1	
Yes	0.822 [0.466; 1.178]	2.28 [1.59; 3.25]	$< 10^{-3}$
Daily stimulant intake			
No (ref.)	0	1	
Yes	0.429 [0.129; 0.730]	1.54 [1.14; 2.07]	0.005
Other drug intake (alcohol included)			
No (ref.)	0	1	
Yes	0.150 [−0.002; 0.302]	1.16 [1.00; 1.35]	0.053

IRR, incidence rate ratio; *CI*, confidence interval

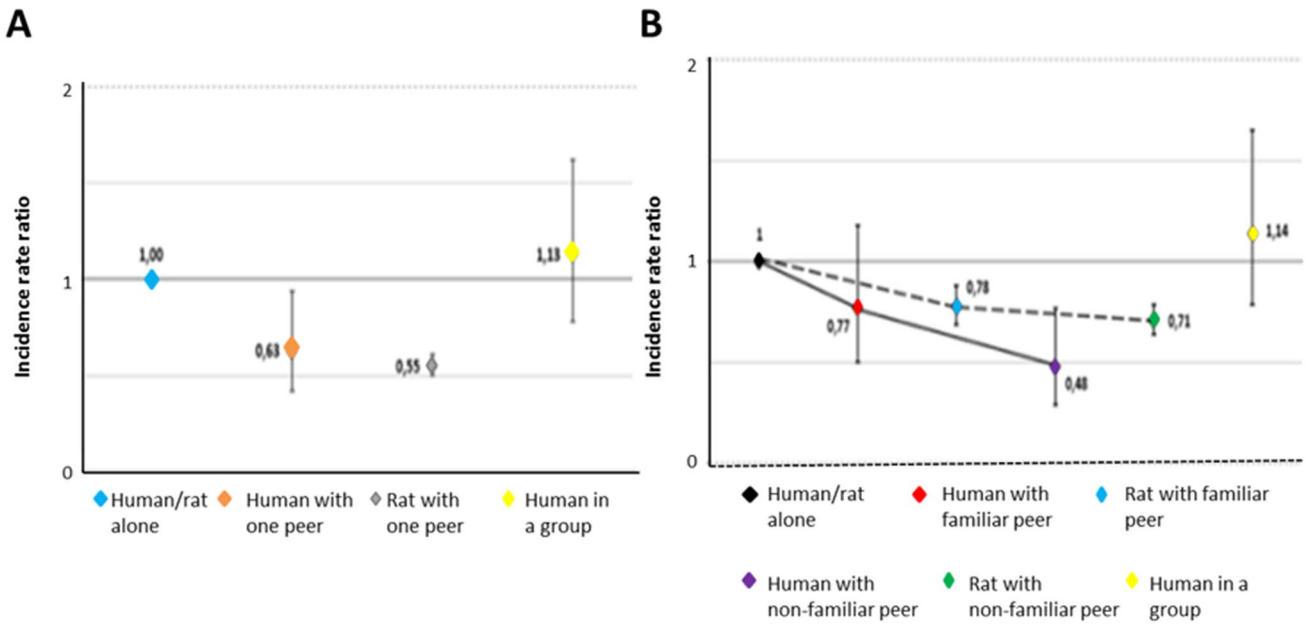

Fig. 5 Translation towards human drug users **A** Adjusted incidence rate ratios of frequency of drug consumption depending on the peer presence in humans and in rats using the condition "alone" (i.e. with no peer) as reference. Blue, orange and yellow diamonds represent the adjusted incidence rate ratio from the multivariable analysis using GEE Poisson model in humans of the variable peer presence (reference = alone): human alone (blue diamond) and human with one peer (orange diamond) and group (yellow diamond). The lower and upper dashes represent, respectively, the lower and upper bounds of the 95% confidence interval. Blue and grey diamond represent the adjusted incidence rate ratio from the multivariable analysis using mixed Poisson model in rats of the variable peer presence (reference = alone): rat with one peer (grey diamond). The lower and upper dashes represent, respectively, the lower and upper bounds of the 95% confidence interval. **B** Adjusted incidence rate ratios for drug consumption depending on peer familiarity in humans and rats using the condition "alone" (i.e. no peer) as reference. Blue, orange and yellow diamonds represent the adjusted incidence rate ratio from the multivariable analysis using GEE Poisson model in humans of the variable familiarity (reference = alone; black diamond: human alone, red diamond: human with familiar peer, purple diamond: human with non-familiar peer). The lower and upper dashes represent, respectively, the lower and upper bounds of the confidence interval. Black, blue and green diamonds represent the adjusted incidence rate ratio from the multivariable analysis using mixed Poisson model in rats of the variable familiarity (reference = alone; blue diamond: rat with familiar peer, green diamond: rat with non-familiar peer). The lower and upper dashes represent, respectively, the lower and upper bounds of the confidence interval

Table 2 Human study—association between familiarity/peer presence and cocaine use frequency among humans ($n = 77$ participants, $n = 246$ episodes of cocaine use), GEE Poisson regression, and multivariable analysis

	Coefficient estimate [95% CI]*	IRR [95% CI]*	*P*-value
Social proximal context and familiarity			
Alone (ref.)	0	1	
Familiar peer	−0.264 [−0.697; 0.170]	0.77 [0.50; 1.18]	0.233
Non-familiar peer	−0.744 [−1.23; −0.256]	0.48 [0.29; 0.77]	0.003
Group	0.130 [−0.239; 0.500]	1.14 [0.79; 1.65]	0.490
Unstable housing			
No (ref.)	0	1	
Yes	0.868 [0.513; 1.222]	2.38 [1.67; 3.40]	$< 10^{-3}$
Daily stimulant intake			
No (ref.)	0	1	
Yes	0.468 [0.171; 0.766]	1.60 [1.19; 2.15]	0.002
Other drug intake (alcohol included)			
No (ref.)	0	1	
Yes	0.145 [−0.007; 0.297]	1.16 [0.99; 1.35]	0.062

**IRR*, incidence rate ratio; *CI*, confidence interval

Discussion

Our study showed that the presence of a peer at the time of stimulant intake has a beneficial reducing effect on stimulant consumption. Furthermore, these effects are modulated by both the familiarity and the former drug-using status of this present peer. Indeed, the lowest level of consumption was observed in presence of a non-familiar peer naïve of cocaine. All these results were similar when rats were in the presence of a peer also allowed to take cocaine, which allowed a more accurate translational comparison with humans. Validating our model, these beneficial effects of the peer presence were also observed in humans, as well as the modulating effect of the peer's familiarity status.

We also addressed in this paper the issue of the neurobiological basis of social influence on drug consumption and showed a particular role for STN. Indeed, reducing STN activity could be even more efficient to potentiate the beneficial effect of the presence of a peer during drug consumption. In fact, in contrast with the sham-control, STN-lesioned rats decreased their consumption in presence of a peer, whatever the familiarity and the former drug-using status of the peer, revealing that STN is involved in social processes, as confirmed in the social preference experiments. This neurobiological approach has not been tested in humans yet, since STN-DBS is only suggested to treat addiction and only DBS of the nucleus accumbens has been published to date. It will certainly be debated soon and taken into account for future therapeutical strategy in Humans.

Finally, we developed and tested in this article a novel approach in terms of design and statistical analysis to conduct translational research on the influence of proximal social factors on a standardized outcome. This could have important repercussions in research on human behaviors and may encourage other behavioral researchers to adopt a similar approach, especially when the research question can be translated into public health actions.

General influence of social presence

The first result of this study is that, in line with former results(Smith 2012), the presence of a peer during cocaine self-administration has beneficial effects on stimulant consumption, supporting the hypothesis that the rewarding properties of social contact may outbalance the reinforcing properties of drug consumption(Fritz et al. 2011a, b) and modulate the affective valence of drug use(Thiel et al. 2009). This explanation is concordant with the results of the conditioned place preference test we performed were rats (housed in pairs) preferred an environment where they were in contact with their home-cage partner over an environment where they remained alone. Interestingly, and more closely to the common drug use situations reported in human subjects, when the present peer could also take the drug, we also observed a decreased consumption. This is opposite to what has been reported in rats acquiring the drug self-administration simultaneously(Smith et al. 2014). In the present study, the animals had acquired the behavior separately and were only tested simultaneously when they had reached a stable intake. This major difference may possibly account for the opposite influence observed here and suggests that social context can be detrimental during the acquisition of behavior but can help reduce it when well established.

Influence of peer familiarity and dominance status

We have shown that sham-control rats decreased more their consumption in presence of a non-familiar peer than in presence of a familiar one when this peer was abstinent. Following the hypothesis above, this result suggests that the

presence of a non-familiar peer would be more rewarding than that of a familiar peer. According to the existing literature, even non-social novel stimuli are more attractive than familiar ones (Hughes 1968). We could thus question the specificity of social stimuli on our effects. However, the social preference experiment revealed that the non-familiar peer was preferred over a non-familiar object, as expected (Thor and Holloway 1982). It is thus likely that the observed self-administration results are due to the social specificity of the stimuli. Furthermore, in the CPP experiment, the presence of the cage-mate appeared to be rewarding only for the dominant animal but not for the subordinate. As a result, it was thus coherent to observe that the presence of the cage-mate only decreased the cocaine consumption for the dominant rats, but not for the subordinates being observed by their dominant peer.

Altogether, our results show that, on one hand, the presence of a non-familiar peer is highly rewarding for rats and leads to decreased cocaine intake. On the other hand, the presence of a familiar peer (i.e., the cage-mate) is also rewarding and leads to decreased stimulant consumption, but only for the dominant rat.

An alternative explanation for the difference between the familiar and non-familiar peer and their influence on self-administration behavior could be that the presence of the latter represents a powerful distractor (Baron 1986). 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. 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). One might hypothesize that a non-using peer may serve as a greater distractor to decrease cocaine intake than a using peer because of a difference in proximity to the separation grid. However, this was not the case since the decrease in cocaine intake was equivalent with an abstaining peer and with a drug-using peer suggesting that the current results do not likely reflect a general distracting effect. Moreover, in line with this hypothesis, it has also been shown by Huguet and colleagues (Huguet et al. 2014) in baboons that social presence, especially if potentially threatening (dominant or non-familiar), could divert attention from the focal task and also consume cognitive control resources. The level of stress induced by the dominance status might play a critical role in this effect as well. It would be interesting to measure the level of cortisol in our animals; although the monkey study has shown that the presence of peers did not modulate cortisol levels (Monfardini et al. 2016).

Interestingly, when the peer could also self-administer cocaine, its familiarity status did no longer influence the consumption of the subject. Those results suggest that the effects of peer drug-using status may outweigh those of its familiarity status, highlighting the importance of considering the different characteristics of proximal social factors to better understand their mechanisms.

Influence of peer drug-using status

Sham-control rats decreased their cocaine consumption more in presence of a peer who did not consume immediately than when in presence of a consuming peer. Furthermore, this decrease was higher when the peer was naïve to the cocaine, highlighting the modulatory effect of the drug-using status of a peer present during cocaine self-administration(Thiel et al. 2009). In line with our results, an econometric analysis has shown that the reinforcing properties of cocaine diminished when the peer present was abstaining(Peitz et al. 2013). This effect could rely on social-learning theories of substance use, suggesting that people in a group of drug users tend to imitate each other(Peitz et al. 2013). Illustrating this theory, Smith et al. have shown that the presence of a rat also self-administering cocaine increases drug consumption during simultaneous acquisition(Smith et al. 2014), as discussed above.

The same influence of social proximal factors in rats and humans?

Although former epidemiological studies have shown the importance of relationships between peers immediately during drug consumption and on the sharing of injecting equipment, drug-seeking(Shadur et al. 2015), and craving(Gyarmathy et al. 2010; Furnari et al. 2015; Linas et al. 2015; Shadur et al. 2015), our experiment is the first studying the nature of the relationship within a dyad of drug-users and to correlate it with cocaine consumption. Results on humans mirrored the effect of the familiarity status found in our rat model with self-administering peers, since like in rats, the presence of a peer decreased cocaine intake, and this decrease was higher if the peer was non-familiar. On the other hand, we were not able to estimate the effect of the peer drug-using status in humans, since, in all drug consumption episodes reported here; the present peer was also a consumer.

Regarding rat and human results, we have to note some limitations in our study. First, while the rats' study design was experimental, the human study collected retrospective information on episodes of stimulant consumption. In the latter, outcomes may be subject to recall and social desirability biases and too confounding. Nevertheless, we questioned participants about their most recent episodes of drug intake to minimize recall biases. Furthermore, as cocaine use may vary across the different episodes, measuring use only from the most recent episode allowed us to simultaneously record the frequency of cocaine consumption and the relationship with a present peer.

Despite these limitations, we found very similar estimates for the association between consumption frequency and the

presence of a drug-using/self-administering peer, with a modulatory role of the familiarity of this peer in both rat and human models.

The STN as a substrate of the influence of social proximal factors on drug intake

Our results show that STN modulates the influence of the presence of a peer on cocaine intake. STN is a part of the basal ganglia and is known to be involved in motivation and addiction-related behaviors (Baunez et al. 2002, 2005; Pelloux et al. 2018; Pelloux and Baunez 2017). Interestingly, our results show that the baseline consumption of STN-lesioned and sham-control rats is similar. This is in line with former studies showing that STN lesion modulates cocaine intake in certain conditions (increased motivation in progressive ratio (Baunez et al. 2005; Rouaud et al. 2009), escalation under FR1 or FR1 after abstinence(Pelloux et al. 2018)). On the contrary, in STN-lesioned rats, the presence of a peer induced a strong decrease in cocaine intake (equivalent to that induced by a non-familiar peer presence in sham control rats). Interestingly, this decrease was not modulated by familiarity, the dominance status, or the drug-using status of the peer.

Furthermore, results of social preference tests showed that STN-lesioned rats had the same preferential exploration for a non-familiar or the cage-mate rat, over an object. Likewise, both dominant and subordinate STN-lesioned rats showed a preference for their cage-mate in the CPP experiment. Altogether, these results suggest that in STN-lesioned rats, familiarity and dominance status no longer modulate the rewarding value of a peer presence. As a result, in STN-lesioned rats, the presence of a peer decreases cocaine intake, independently of its familiarity or dominance status. This suggests that they could no longer make the difference between familiar and non-familiar peers.

Interestingly, in humans, in line with our results, STN-DBS in parkinsonian patients has been shown to blunt facial and vocal emotion recognition (Péron et al. 2010; Buot et al. 2013; Péron et al. 2015; Kalampokini et al. 2020). Deficits in emotional processing have also been observed in STN-lesioned rats (Pelloux et al. 2014), notably in emotional communication (Montanari et al. 2018). Then, the involvement of the STN in social-emotional processes could explain the blunted differential rewarding value of the presence of a peer depending on their characteristics observed in STN-lesioned rats. However, the involvement of the STN in social cognition remains to be further investigated.

To conclude, this study provides three major contributions. First, we have shown that the peer presence, familiarity, and drug-using status of this peer have major effects on drug consumption. Those characteristics must be taken into account to ameliorate existing models in the study of the influence of proximal social factors on drugs consumption. Second, we have shown parallel influences of proximal social factors on cocaine use in rats and humans, notably regarding the effect of the familiarity status of the peer present. This parallel highlights translational potential from rats to humans. The need for translational studies (Caprioli et al. 2009; Kandel and Kandel 2014) is essential for a better understanding of the proximal social factors influence on addiction (Heilig et al. 2016), notably their neurobiological substrates. Finally, we have shown that STN appears to play a critical role in the influence of those factors. Modulating its activity may thus result in an alteration of social context influence on drug use toward decreased cocaine consumption. Since STN deep brain stimulation is proposed as a therapeutic strategy to treat addiction[66], this apparent emotional side-effect could serve to reduce further the drug intake, as seen here in STN lesioned rats.

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.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00213-021-06033-0.

Acknowledgements Our thanks to Dany Palleressompoulle and Joel Baurberg for their technical support, as well as to the animal facilities' personnel. Our thanks also to Silvia Rosellini and Chiara Calzolaio for help with statistical analyses and to Jude Sweeney and Maya Williams for the English revisions and editing of the manuscript.

Author contribution E.G and C.V conducted most of the rats' experiments, with the help of L.G and C.M; S.N and PR conducted the human experiments; C.B, C.V, E.G, P.C, and S.N wrote the paper; A.V, C.P, C.V, E.G, S.N, and P.R conducted the statistical analysis; C.M, C.V, and E.G conducted the histological analysis; C.B, C.V, E.G, K.D, P.H, and Y.P designed the rat experiment; CB, PR, PC, and SN designed the human questionnaire; CB, PC, and PH obtained the funding from A*MIDEX.

Funding This research was funded by CNRS, Aix-Marseille Université (AMU), the "Agence Nationale pour la Recherche" (ANR_2010-NEUR-005–01 in the framework of the ERA-Net NEURON to C.B. and supporting Y.P.), the "Fondation pour la Recherche Médicale" (FRM DPA20140629789 to C.B.), and the support of the A*MIDEX project (ANR-11-IDEX-0001–02) funded by the "Investissements d'Avenir" French Government program, managed by the French National Research Agency (ANR).

Declarations

Conflict of interest The authors declare no competing interests.

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