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ORIGINAL PAPER

The Two Faces of Social Interaction Reward in Animal Models of Drug Dependence

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Abstract Drug dependence is a serious health and social problem. Social factors can modify vulnerability to developing drug dependence, acting as risk factors or protective factors. Whereas stress and peer environment that encourage substance use may increase drug taking, strong attachments between family members and peer environment that do not experience drug use may protect against drug taking and, ultimately, drug dependence. The rewarding effects of drug abuse and social interaction can be evaluated using animal models. In this review we focus on evaluating social interaction reward in the conditioned place preference paradigm. We give an overview of how social interaction, if made available within the drug context, may facilitate, promote and interact with the drug's effects. However, social interaction, if offered alternatively outside the drug context, may have pronounced protective effects against drug abuse and relapse. We also address the importance of the weight difference parameter between the social partners in determining the positive or "agonistic" versus the hostile or "antagonistic" social interaction. We conclude that understanding social interaction reward and its subsequent effects on drug reward is sorely needed for therapeutic interventions against drug dependence.

Keywords Drug dependence · Reward · Social interaction · Animal model · Conditioned place preference · Drug context

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Introduction

Drug Addiction

Of the many people that have experience with drugs, only a small percentage becomes dependent. Drug dependence is a multifactorial disorder resulting from an interaction between genetic, social, and environmental factors [1, 2]. There is compelling evidence that environmental and social factors (family and peers) act as risk factors or protective factors that modify vulnerability to developing drug dependence [3, 4]. For example, stress [5] and peer pressure [6] play an important role in increasing drug use and relapse. However, secure attachment or stronger attachment between parents and children acts as a protective factor against drug use [7]. Social interactions may, therefore, be important determinants of drug dependence and relapse. This review focuses on the context in which social interaction occurs and its subsequent impact on drug abuse. We propose that social interaction within the drug context increases the drug's effects. In contrast, social interaction with a conspecific of the same weight and gender, offered outside the drug context or as an alternative to drugs, protects against the drug's effects.

Social Interaction Reward

Animal models can be used to investigate reward-related mechanisms [8]. Social interaction reward can be assessed for drug abuse by applying the conditioned place

preference paradigm (CPP) [9, 10] which is a type of Pavlovian conditioning. Conditioning is conducted in an experimental apparatus consisting of at least two compartments that have distinct visual and tactile cues. If one of the two compartments is associated with the administration of a drug or natural reward during conditioning, the neutral environmental stimuli acquire secondary motivational properties such that they can act as conditioned stimuli which can elicit an approach when the animal is subsequently exposed to these stimuli [11]. Later during the test, the animal can "choose" or "prefer" to spend more time in the compartment associated with the drug/natural reward or the compartment not associated with the drug/natural reward. If the drug or natural reward has rewarding properties, the animal will "prefer" to spend more time in the compartment previously associated with the drug/natural reward. In general, social reward-CPP is assessed by placing the rats during half of the conditioning sessions into a compartment of the CPP with their assigned social partner, and during the other half of the sessions alone in the other compartment of the CPP [12–14]. We, and others [15], have performed social interaction reward-CPP by pairing one compartment with a weight-matched male conspecific, preceded by an i.p. injection of saline, for 15 min and the other compartment with saline only. Animals that spent more time in the social interaction paired compartment than in the saline paired compartment during the CPP test express a preference for social interaction. It has been shown that social interaction CPP was similar using either one or two conditioning sessions/day and either 10 or 30 min conditioning sessions [13] (but see Trezza et al. [14] and Yates et al. [15]). However, social interaction CPP increased as the number of social pairings increased [13]. Interestingly, it has been found that, comparable to drug induced CPP, social interaction CPP can be extinguished and reinstated by a single re-exposure to the social partner in the social-paired compartment [14].

CPP for social play behavior was first reported by Calcagnetti and Schechter [16]. They have shown that dominant juvenile rats conditioned twice daily over 4 days in the CPP apparatus by pairing the preferred compartment with a scopolamine-treated partner (that rendered the partner unable to respond to play solicitations) and the less preferred compartment with a submissive play partner, significantly increased the time spent on the originally less-preferred side after play conditioning [16]. Social play and adult social behavior have both been shown to induce CPP when the originally less-preferred box was paired with a free moving stimulus rat (social) and the preferred box paired with a confined stimulus rat (non-social) [17]. Douglas et al. [12] have assessed social CPP in adolescent (PND 33) and adult (PND 65) male and female Sprague–Dawley rats housed either socially or in isolation and conditioned with either group-housed or isolate-housed partners. They found that the rewarding properties of social interaction vary with age and housing conditions. Indeed, isolated adolescent males expressed the strongest social CPP among all isolated animals and group-housed adolescents developed a preference for the compartment previously paired with similarly housed partners but not with isolated partners [12]. It appears that the high motivation for social interaction during conditioning, as a result of social isolation, might underlie the strong CPP for social interaction expressed by socially isolated rats [14, 15]. In parallel with the findings of Calcagnetti and Schechter, the conditioning of adolescent male Wister rats with methylphenidate-treated partners (that reduce both play solicitation and responsiveness to play solicitation [18]) abolish the expression of social interaction CPP [14]. Thus, this latter study suggests that social play is likely to be the most rewarding aspect of social interaction in adolescent rats [14].

It becomes crucial, then, to investigate which of the sensory components of social interaction mediates its rewarding effects. We have shown in Sprague–Dawley male rats at early adulthood (PND 42–56) that taction, but neither visual nor olfactory cues, is the major rewarding sensory component of the composite stimulus "social interaction" [19]. Indeed, when touch was fully restricted by a glass screen dividing the conditioning compartments, and the only remaining sensory modalities were visual and olfactory cues, place preference shifted to place aversion [19]. Furthermore, physical contact with a rat (Sprague–Dawley at PND 28–42) has been reported to be more robust to establish social reward CPP than limited contact with a rat through a wire mesh barrier [20] or steel bars spaced at a distance of 2 cm and running across the whole length of a partitioning [19]. However, when both rats were placed on the same side of the partitioning, thus decreasing the available area for social interaction from 750 to 375 cm^2, rats did not develop CPP for social interaction despite the fact that the animals could touch each other more intensely than through the bars of the partitioning [19]. Thus, the area available for social contact is also a determinant factor involved in social interaction reward.

In order to determine the behavioral components of social interaction reward, we have recorded and analyzed the training sessions for time spent in direct physical contact and social play, as well as attacks and biting (i.e., aggressive behaviors) [21]. From the first conditioning session onward, the weight-matched male Sprague–Dawley rats at PND 42–56 spent more than 79 % of the test time in direct contact with each other. We found that the time spent in direct contact and the total number of episodes for the different elements of social interaction did not change significantly across the conditioning sessions. The rats fully

engaged in friendly ("agonistic") social interaction during all the four training sessions and no episodes of hostile behavior, i.e., boxing or biting, were observed [21]. C57BL/6 N mice (6–8 weeks) only spent 17 % of the test time in direct contact with each other. Throughout all analyzed pairs, mice also showed no signs of aggression, i.e., no attacks/fighting and no biting. Even though rats spent significantly more time in direct contact with the social interaction partner (79 % of session time) than mice did (17 % of session time), social interaction was rewarding for both rats and mice [21]. Indeed, 71 % of the total C57BL/6N mice versus 85 % of total rats developed conditioned place preference to social interaction [21]. Interestingly social interaction reward was shown to be influenced by genetic variation in mice. Panksepp and Lahvis [22] have reported that social conditioning resulted in a CPP for juvenile mice from A/J, DBA/2J, C57BL/6J but not BALB/cJ, with C57BL/6J being the most, and BALB/cJ the least responsive to social conditioning. They found that social interaction reward is independent of strain differences in exploratory behavior, contextual learning, maternal care or social interaction conditioning [22]. This study is of great importance as genetically based differences in social interaction reward effects could play a substantial role in determining whether the social environment influences sensitivity to drugs [23].

Social Experience Within the Drug Context

Most drugs are experienced among adolescents or young adults in a social context through peer pressure and facilitation of social interaction by drugs of abuse [6]. On the animal experimental level, it has been widely addressed that the subjective effects of several drugs of abuse are enhanced in a social context [24]. For example, it has been found that social opportunity increased ethanol drinking in adult male Long Evans rats [25]. The presence of a social partner led to the facilitation of amphetamine self-administration at a high unit dose in rats. This effect is selective for amphetamine as sucrose pellets responding was inhibited in the presence of a social Sprague–Dawley rat partner [26]. Acquisition of nicotine self administration, paired with the delivery of a sweet solution, is facilitated in adolescent (PND 36–38) Sprague–Dawley rats by the presence, through a panel allowing orofacial contacts, of another rat serving as the demonstrator who had free access to the sweet solution but did not receive nicotine [27]. Furthermore, it was shown that socially familiar, rather than novel unfamiliar rats, were more effective demonstrators in facilitating the acquisition of nicotine self-administration [27]. It has also been shown that social stimulation among monkeys in adjoining cages enhanced the reinforcing strength of phencyclidine [28].

Using the CPP paradigm, Thiel and colleagues investigated interactions between drug and social rewards in adolescent rats. They have shown that the drug experience alone—cocaine [13] or nicotine [29]—and a low number of social pairings alone, failed to produce CPP in male Sprague–Dawley rats (Post natal day PND 28–42), but together produced a significant CPP. This enhancement of social interaction CPP is specific to rewarding drugs. The non-rewarding drug, dextromethorphan (30 mg/kg, i.p), failed to enhance social interaction CPP [13]. These results show that drug reward interacts synergistically with social reward in the CPP model. However, this finding was not observed in a recent study by Grotewold et al. [30] using the same cocaine dose, number of social pairings and time in conditioning chamber. They reported an additive, rather than a synergistic effect, of cocaine and social interaction reward in Sprague–Dawley rats at PND 51–55 [30]. It has been suggested that the discrepancy between the study by Thiel et al. [13] and Grotewold et al. [30] may be due to the different period of adolescent rats (early adolescence vs. late adolescence) when the behavioral experiments of CPP began [30]. Therefore, it is possible that early, rather than late, adolescence is a crucial period for the synergistic interaction between drug reward and social interaction reward [30]. Also, in contrast to Thiel et al. [13], it has been found that both social interaction and methylphenidate alone produce CPP but when they are both given during conditioning no CPP was displayed [14]. The reason for the discrepancy between these studies remains unclear. On the other hand, Watanabe [31] showed that methamphetamine-induced CPP was enhanced in mice only when social interaction occurred between mice receiving the same treatment (methamphetamine), suggesting that sharing the same experience is crucial for the social facilitation of the methamphetamine rewarding effect [31].

The drug social rewards do not only involve an enhancement of drug/social effects, they may also implicate an attenuation of the aversive effects of the drug as shown by Gauvin et al. [32]. Indeed, the conditioned place aversion to ethanol has been shown to be attenuated if it is given in the presence of a sober or intoxicated cohort male Sprague–Dawley [32].

In conclusion, these findings suggest that drug reward and social interaction reward interact and facilitate each other's effects. Further studies are needed to investigate the mechanisms underlying the possible interactions between drug reward and social interaction reward.

Social Experience Outside the Drug Context

The presence of a peer environment that supports and encourages substance use (negative social influences) or, on the contrary, that discourages and supports the non-use

(positive social influences) of drugs may have direct consequences for preventing or increasing drug use [33]. Furthermore, maintaining social networks with peers that do not experience drug use may be an alternative to drug taking [33]. In this respect, we will present an overview of the protocols used to investigate social interaction reward as an alternative to drug abuse, the behavioral and the cellular/molecular findings underlying the positive effects of social interaction reward.

Social Interaction Before the Reinstatement of Cocaine CPP

Male Sprague–Dawley rats at PND 42–56 were conditioned to cocaine 15 mg/kg in the CPP model. After cocaine CPP had been established, subjects were divided into two groups. One group received i.p. saline injections immediately before being put into the former cocaine-paired chamber as well as into the previously saline-paired chamber for one extinction session each (saline extinction). The second group received an i.p. saline injection immediately before being placed into the previously cocaine-paired chamber for 15 min on 1 day but, in contrast to the previous group, was also given the opportunity to have social interaction in the previously saline-paired chamber with a conspecific on the other day (saline extinction + social interaction). Pairing a conspecific with the previously saline associated compartment shifted the rat's preference toward social interaction reward [34]. This shift could be enhanced by one injection of BD1047, the sigma1 receptor antagonist [35]. If the two groups of rats were administered a single i.p. cocaine injection in the previously cocaine-paired compartment in order to induce reinstatement of cocaine CPP, social interaction reward in the alternative side was able to inhibit cocaine induced reinstatement of cocaine CPP [34]. These protective effects of social interaction were paralleled by a reduced activation, as assessed by Zif268 expression, in brain areas known to be involved in drug reinforcement and reward. We have shown that social interaction during extinction of cocaine CPP reversed cocaine CPP-reinstatement-associated Zif268 expression in the nucleus accumbens shell, the central and basolateral amygdala, and the ventral tegmental area [34]. In the nucleus accumbens, cocaine CPP-induced Zif268 expression was found to be reversed by social interaction preferentially in Dynorphin- expressing medium spiny neurons than D2 receptor- expressing medium spiny neurons [36]. Furthermore, we can show that social interaction reward during extinction of cocaine CPP also reduced cocaine-CPP-stimulated FosB expression in the nucleus accumbens shell and core, and increased pCREB (cAMP response element binding protein) expression in the nucleus accumbens shell and the cingulate cortex area 1 (Cg1) [37]. Thus, FosB and pCREB may be implicated in the protective effect of social interaction against cocaine-induced reinstatement of CPP. Ribeiro Do Couto et al. [38] have also investigated the influence of different social experiences on the reinstatement of cocaine-induced CPP in adolescent and adult male OF1 mice. In adolescent mice, living in crowded conditions or cohabitating with a female protects against reinstatement after cocaine priming. In adult mice, cohabitation with a female also inhibits cocaine-induced reinstatement of cocaine CPP [38]. In parallel with our findings, Ribeiro Do Couto et al. [38] have found that after expression and then extinction of cocaine CPP, exposure to females or a brief social interaction with a non-aggressive conspecific in OF1 mice prior to testing, undermined cocaine-induced reinstatement of CPP in grouped adult OF1 mice [38]. Further, environmental enrichment, consisting not only of social interaction but also of inanimate stimulation aimed at enhancing cognitive, sensory and motor functions after the expression of cocaine CPP, also prevented cocaine-induced reinstatement of CPP in C57BL6 mice [39]. Together, these findings suggest that social interaction, if offered in a context that is clearly distinct from the previously drug-associated one, may protect against reinstatement to cocaine.

Social Interaction Versus Cocaine CPP: Concurrent Paradigm

On the test day, the typical CPP procedure reflects a choice between a drug or natural reward-paired environment versus a non reward-paired environemment (saline-paired). That is, when the dose of the stimuli has crossed a reward threshold, higher doses do not produce higher preference for the stimuli- paired environment [40, 41]. Therefore, in a modified variant of the standard CPP procedure, referred to as "reference-conditioning" procedure, a rewarding stimulus considered as reference (e.g., cocaine) can be compared to some other value of the same stimulus (other doses of cocaine) or to a different stimulus (e.g., social interaction) [41]. This procedure seems to increase the sensitivity for detecting conditioned reward as compared to standard CPP procedure [41].

Male Sprague–Dawley rats were conditioned for place preference by pairing cocaine 15 mg/kg with one compartment and social interaction with the other concurrently; both stimuli (15 min social interaction vs. 15 mg/kg i.p. cocaine) produced equal CPP [21, 34, 42]. These results suggest that social interaction has the same conditioned reward value as cocaine at the dose of 15 mg/kg. Also we have shown that pre-acquisition lesioning of the nucleus accumbens core or the basolateral amygdala shifted the animals' preference toward social interaction CPP, whereas a bilateral shell lesion shifted the preference toward

cocaine CPP [42] when tested in a concurrent paradigm. These findings suggest a role of the nucleus accumbens shell in mediating natural reward-associated conditioned stimuli (social interaction) and a role of the nucleus accumbens core and the basolateral amygdala, in mediating drug (cocaine) associated conditioned stimuli [42]. When allowed to choose concurrently between compartments paired either with social interaction or amphetamine, Yates et al. [15] have recently shown that housing conditions (individual vs. paired) and the age of rats [adolescence (PND 28) vs. adult rats (PND 67)] highly influence the choice of preference. Interestingly, whereas individually housed adolescents preferred the compartment paired with social interaction, pair-housed adolescents preferred the compartment paired with amphetamine [15]. In adult rats, regardless of the housing condition, social interaction and amphetamine produced equally strong CPP [15]. This latter finding is in accordance with our own as the age of rats used in our studies and in [15] was corresponding. Indeed, the rats that we used in our study arrived at PND 42–56 (early/young adulthood [43]) and underwent behavioral experiments at PND 49–63, comparable to the age of adult rats (PND 67) used in [15].

In C57BL/6N mice, concurrent place preference conditioning to social interaction and 15 mg/kg cocaine led to a preference for the cocaine paired compartment [21]. These results suggest that social interaction in mice did not compete with the conditioning reward value of 15 mg/kg of cocaine. When reducing the conditioning dose of cocaine from 15 to 0.05 mg/kg, we can show that cocaine at the dose of 0.05 mg/kg and social interaction in the opposite compartment produced equal CPP [21]. This suggests that social interaction in mice has the same conditioned reward value as cocaine at the dose of 0.05 mg/kg. This 300-fold difference between rat and mouse in the relative conditioned reward value of cocaine versus social interaction may be explained by the fact that rats show a persistent preference for sweetness despite a history of extensive cocaine self-administration [44]. Therefore, the enhanced reward value of social interaction in rats as compared to mice may be a normal reflection of species preference for natural rewards.

Brain Regions Mediating Acquisition of Social Interaction CPP and Cocaine CPP

Male Sprague–Dawley rats at PND 42–56 were conditioned with either cocaine or social interaction and the preference for each stimulus alone was then evaluated. Rats acquired robust CPP to either cocaine alone or social interaction alone [21, 34, 45]. We investigated the differential activation of brain regions related to the reward circuitry after acquisition/expression of cocaine CPP or social interaction CPP. We have found that cocaine CPP and social interaction CPP activated almost the same brain regions [45]. However, the granular insular cortex and the dorsal part of the agranular insular cortex were more activated after cocaine CPP, whereas the prelimbic cortex and the core subregion of the nucleus accumbens were more activated after social interaction CPP [45]. These results suggest that the insular cortex appears to be potently activated after drug conditioning learning, whilst activation of the prelimbic cortex—nucleus accumbens core projection seems to be preferentially involved in the conditioning to natural reward such as social interaction.

Using multielectrode array recordings of spontaneous firing of the nucleus accumbens (unseparated shell and core) and adjacent brain regions, we found that cocaine conditioning increased the spike firing frequency in the septal nuclei and that social interaction conditioning increased spike firing in the nucleus accumbens compared to saline control C57BL/6N in mice [46]. This latter study further highlights the role of the nucleus accumbens in mediating social interaction (natural reward) reward learning. These findings also suggest that place preference conditioning for both drug and natural rewards may induce persistent changes in neuronal network activity in the nucleus accumbens and the septum that are still preserved in acute slice preparations [46].

Investigating the positive social experience outside the drug context for drugs other than cocaine, as well as using different protocols for evaluating drug reward, is sorely needed. For instance, it has been reported that in socially-restricted adult Wister rats, as little as 60-min of daily social-physical interaction with another rat in a different environment immediately prior to oral access to morphine was sufficient to completely abolish the isolation-induced increases in morphine consumption [47]. These results support a protective effect of social interaction in reducing drug intake and, basically, expand these protective effects to other drugs of abuse.

Weight Difference in Social Interaction

It is well discussed that social stress exposure increases the initiation of psychostimulant consumption and the vulnerability to relapse in animal models of addiction [48]. One relevant social stress experience is the resident-intruder model in which brief agonistic confrontations occur between a non-aggressive rodent (intruder) that is placed into the home cage of an aggressive rodent (resident). The resident then attacks the intruder to further initiate an aggressive and antagonistic social interaction, "social defeat". After that the intruder can be removed from the resident cage or placed into a protective cage within the resident's cage in order to expose it to the resident's threats

[49]. In these experimental approaches investigating social interaction of the antagonistic type, a weight difference was introduced, ranging from 275 to 350/450 g [50, 51] between the intruder (the smaller rat) and the aggressive social interaction partner (the bigger rat), in order to enhance antagonistic social interaction. These intermittent episodes of social defeat in rats were shown to enhance vulnerability to drug abuse (see Neisewander et al. [24] for a review).

In male Syrian hamsters, when social interaction CPP was tested between older single-housed males and younger group-housed males, having 15 to 20 g weight difference, the animals developed CPP to social interaction, but the effects were significantly stronger in bigger hamsters compared to smaller hamsters [52]. As body weight is positively correlated with social dominance [53], social interaction might be more rewarding in dominant hamsters compared to subordinates [52].

We, and others, have shown that agonistic social interaction is rewarding when the test animal and the stimulus animal (social partner) are sex- and weight-matched conspecific [13, 21, 34]. We investigated the effects of weight difference on social interaction reward in rats by pairing test rats with a stimulus rat of up to twice the weight, i.e., 200 g of weight difference. We found that for test rats, but not for the stimulus rat, there was a significant negative correlation between weight difference and time spent in the interaction-paired compartment [19]. This means the larger the social interaction partner, the less rewarding the interaction became for the smaller, but not for the bigger rat. When the difference in weight reaches 150 g (which corresponds to 75 % of the weight of the test rat), the preference for social interaction was abolished [19]. Therefore, dividing the animals into pairs matched by body weight is of particular importance for an agonistic rewarding social interaction.

Conclusion and Outlook

All the above findings show that social interaction reward, whether it occurs within or outside of the drug taking context, can have determinant impacts on vulnerability to developing drug addiction and sensitivity to drugs. Also, social stress clearly plays a major role in drug dependence as a risk factor, not only for the initiation, maintenance and escalation of drug consumption, but also for relapse [48]. We suggest that social interaction, if available as an alternative to drugs, can have protective effects against drug-induced reinstatement [34]. It seems that social interaction outside the drug context is likely to have an influence on responsivity to stress, acting as an alleviator of daily stressors that may contribute to increased motivation for drug seeking [24]. Further research is needed to investigate the proposed anti-stress role of positive social interaction.

More studies should be conducted on the cellular and molecular level to further understand the synergistic [13] versus protective alternative [34] effects of social interaction reward on drug reward. Indeed, there is conflicting data regarding overlap in neural populations that are affected by natural rewards and drugs. On one hand, Carelli and colleagues have shown that different neural populations were engaged during the self-administration of natural rewards (food, water) versus cocaine in rats nucleus accumbens [54]. On the other hand, it has been shown that there was significant coincidence of neurons activated by methamphetamine and sexual reward in the nucleus accumbens [55]. Therefore, it may be of particular interest to investigate neuronal populations activated after natural reward, drug reward, synergistic impact of both natural and drug reward effects, and the concurrent impact of drug versus natural rewards.

To conclude, understanding drug and social interaction reward is necessary for the development of novel therapeutic approaches for substance dependent individuals.

References

1. Kreek MJ, Nielsen DA, Butelman ER, LaForge KS (2005) Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. Nat Neurosci 8:1450–1457
2. Enoch M-A (2006) Genetic and environmental influences on the development of alcoholism: resilience vs. risk. Ann N Y Acad Sci 1094:193–201
3. Swadi H (1999) Individual risk factors for adolescent substance use. Drug Alcohol Depend 55:209–224
4. Fergusson DM, Boden JM, Horwood LJ (2008) The developmental antecedents of illicit drug use: evidence from a 25-year longitudinal study. Drug Alcohol Depend 96:165–177
5. Sinha R (2001) How does stress increase risk of drug abuse and relapse? Psychopharmacology 158:343–359
6. Haug S, Núñez CL, Becker J, Gmel G, Schaub MP (2014) Predictors of onset of cannabis and other drug use in male young adults: results from a longitudinal study. BMC Public Health 14:1202
7. Iglesias EB, Fernández del Río E, Calafat A, Fernández-Hermida JR (2014) Attachment and substance use in adolescence: a review of conceptual and methodological aspects. Adicciones 26:77–86
8. Zernig G, Ahmed SH, Cardinal RN, Morgan D, Acquas E, Foltin RW, Vezina P, Negus SS, Crespo JA, Stöckl P, Grubinger P, Madlung E, Haring C, Kurz M, Saria A (2007) Explaining the escalation of drug use in substance dependence: models and appropriate animal laboratory tests. Pharmacology 80:65–119
9. Bardo MT, Bevins RA (2000) Conditioned place preference: what does it add to our preclinical understanding of drug reward? Psychopharmacology 153:31–43
10. Tzschentke TM (2007) Measuring reward with the conditioned place preference (CPP) paradigm: update of the last decade. Addict Biol 12:227–462

11. Tzschentke TM (1998) Measuring reward with the conditioned place preference paradigm: a comprehensive review of drug effects, recent progress and new issues. Prog Neurobiol 56: 613–672
12. Douglas LA, Varlinskaya EI, Spear LP (2004) Rewarding properties of social interactions in adolescent and adult male and female rats: impact of social versus isolate housing of subjects and partners. Dev Psychobiol 45:153–162
13. Thiel KJ, Okun AC, Neisewander JL (2008) Social reward-conditioned place preference: a model revealing an interaction between cocaine and social context rewards in rats. Drug Alcohol Depend 96:202–212
14. Trezza V, Damsteegt R, Vanderschuren LJMJ (2009) Conditioned place preference induced by social play behavior: parametrics, extinction, reinstatement and disruption by methylphenidate. Eur Neuropsychopharmacol 19:659–669
15. Yates JR, Beckmann JS, Meyer AC, Bardo MT (2013) Concurrent choice for social interaction and amphetamine using conditioned place preference in rats: effects of age and housing condition. Drug Alcohol Depend 129:240–246
16. Calcagnetti DJ, Schechter MD (1992) Place conditioning reveals the rewarding aspect of social interaction in juvenile rats. Physiol Behav 51:667–672
17. Van den Berg CL, Pijlman FT, Koning HA, Diergaarde L, Van Ree JM, Spruijt BM (1999) Isolation changes the incentive value of sucrose and social behaviour in juvenile and adult rats. Behav Brain Res 106:133–142
18. Vanderschuren LJMJ, Trezza V, Griffioen-Roose S, Schiepers OJG, Van Leeuwen N, De Vries TJ, Schoffelmeer ANM (2008) Methylphenidate disrupts social play behavior in adolescent rats. Neuropsychopharmacology 33:2946–2956
19. Kummer K, Klement S, Eggart V, Mayr MJ, Saria A, Zernig G (2011) Conditioned place preference for social interaction in rats: contribution of sensory components. Front Behav Neurosci 5:80
20. Peartree NA, Hood LE, Thiel KJ, Sanabria F, Pentkowski NS, Chandler KN, Neisewander JL (2012) Limited physical contact through a mesh barrier is sufficient for social reward-conditioned place preference in adolescent male rats. Physiol Behav 105:749–756
21. Kummer KK, Hofhansel L, Barwitz CM, Schardl A, Prast JM, Salti A, El Rawas R, Zernig G (2014) Differences in social interaction-vs. cocaine reward in mouse vs. rat. Front. Behav Neurosci 8:363
22. Panksepp JB, Lahvis GP (2007) Social reward among juvenile mice. Genes Brain Behav 6:661–671
23. Kennedy BC, Panksepp JB, Runckel PA, Lahvis GP (2012) Social influences on morphine-conditioned place preference in adolescent BALB/cJ and C57BL/6J mice. Psychopharmacology 219:923–932
24. Neisewander JL, Peartree NA, Pentkowski NS (2012) Emotional valence and context of social influences on drug abuse-related behavior in animal models of social stress and prosocial interaction. Psychopharmacology 224:33–56
25. Tomie A, Uveges JM, Burger KM, Patterson-Buckendahl P, Pohorecky LA (2004) Effects of ethanol sipper and social opportunity on ethanol drinking in rats. Alcohol Alcohol 39:197–202
26. Gipson CD, Yates JR, Beckmann JS, Marusich JA, Zentall TR, Bardo MT (2011) Social facilitation of d-amphetamine self-administration in rats. Exp Clin Psychopharmacol 19:409–419
27. Chen H, Sharp BM, Matta SG, Wu Q (2011) Social interaction promotes nicotine self-administration with olfactogustatory cues in adolescent rats. Neuropsychopharmacology 36:2629–2638
28. Newman JL, Perry JL, Carroll ME (2007) Social stimuli enhance phencyclidine (PCP) self-administration in rhesus monkeys. Pharmacol Biochem Behav 87:280–288
29. Thiel KJ, Sanabria F, Neisewander JL (2009) Synergistic interaction between nicotine and social rewards in adolescent male rats. Psychopharmacology 204:391–402
30. Grotewold SK, Wall VL, Goodell DJ, Hayter C, Bland ST (2014) Effects of cocaine combined with a social cue on conditioned place preference and nucleus accumbens monoamines after isolation rearing in rats. Psychopharmacology 231: 3041–3053
31. Watanabe S (2011) Drug-social interactions in the reinforcing property of methamphetamine in mice. Behav Pharmacol 22:203–206
32. Gauvin DV, Briscoe RJ, Goulden KL, Holloway FA (1994) Aversive attributes of ethanol can be attenuated by dyadic social interaction in the rat. Alcohol 11:247–251
33. Valente TW, Ritt-Olson A, Stacy A, Unger JB, Okamoto J, Sussman S (2007) Peer acceleration: effects of a social network tailored substance abuse prevention program among high-risk adolescents. Addiction 102:1804–1815
34. Fritz M, El Rawas R, Salti A, Klement S, Bardo MT, Kemmler G, Dechant G, Saria A, Zernig G (2011) Reversal of cocaine-conditioned place preference and mesocorticolimbic Zif268 expression by social interaction in rats. Addict Biol 16:273–284
35. Fritz M, Klement S, El Rawas R, Saria A, Zernig G (2011) Sigma1 receptor antagonist BD1047 enhances reversal of conditioned place preference from cocaine to social interaction. Pharmacology 87:45–48
36. Prast JM, Schardl A, Schwarzer C, Dechant G, Saria A, Zernig G (2014) Reacquisition of cocaine conditioned place preference and its inhibition by previous social interaction preferentially affect D1-medium spiny neurons in the accumbens corridor. Front Behav Neurosci 8:317
37. El Rawas R, Klement S, Salti A, Fritz M, Dechant G, Saria A, Zernig G (2012) Preventive role of social interaction for cocaine conditioned place preference: correlation with FosB/DeltaFosB and pCREB expression in rat mesocorticolimbic areas. Front Behav Neurosci 6:8
38. Ribeiro Do Couto B, Aguilar MA, Lluch J, Rodríguez-Arias M, Miñarro J (2009) Social experiences affect reinstatement of cocaine-induced place preference in mice. Psychopharmacology 207:485–498
39. Solinas M, Chauvet C, Thiriet N, El Rawas R, Jaber M (2008) Reversal of cocaine addiction by environmental enrichment. Proc Natl Acad Sci USA 105:17145–17150
40. Bardo MT, Rowlett JK, Harris MJ (1995) Conditioned place preference using opiate and stimulant drugs: a meta-analysis. Neurosci Biobehav Rev 19:39–51
41. Reichel CM, Wilkinson JL, Bevins RA (2010) Reference place conditioning procedure with cocaine: increased sensitivity for measuring associatively motivated choice behavior in rats. Behav Pharmacol 21:323–331
42. Fritz M, El Rawas R, Klement S, Kummer K, Mayr MJ, Eggart V, Salti A, Bardo MT, Saria A, Zernig G (2011) Differential effects of accumbens core vs. shell lesions in a rat concurrent conditioned place preference paradigm for cocaine vs. social interaction. PLoS One 6:e26761
43. Spear LP (2000) The adolescent brain and age-related behavioral manifestations. Neurosci Biobehav Rev 24:417–463
44. Lenoir M, Serre F, Cantin L, Ahmed SH (2007) Intense sweetness surpasses cocaine reward. PLoS One 2:e698
45. El Rawas R, Klement S, Kummer KK, Fritz M, Dechant G, Saria A, Zernig G (2012) Brain regions associated with the acquisition of conditioned place preference for cocaine vs. social interaction. Front Behav Neurosci 6:63
46. Kummer KK, El Rawas R, Kress M, Saria A, Zernig G (2015) Social interaction and cocaine conditioning in mice increase spontaneous spike frequency in the nucleus accumbens or septal

nuclei as revealed by multielectrode array recordings. Pharmacology 95:42–49
47. Raz S, Berger BD (2010) Social isolation increases morphine intake: behavioral and psychopharmacological aspects. Behav Pharmacol 21:39–46
48. Aguilar MA, García-Pardo MP, Montagud-Romero S, Miñarro J, Do Couto BR (2013) Impact of social stress in addiction to psychostimulants: what we know from animal models. Curr Pharm Des 19:7009–7025
49. Tornatzky W, Miczek KA (1993) Long-term impairment of autonomic circadian rhythms after brief intermittent social stress. Physiol Behav 53:983–993
50. Covington HE, Kikusui T, Goodhue J, Nikulina EM, Hammer RP, Miczek KA (2005) Brief social defeat stress: long lasting effects on cocaine taking during a binge and zif268 mRNA expression in the amygdala and prefrontal cortex. Neuropsychopharmacology 30:310–321
51. Covington HE, Tropea TF, Rajadhyaksha AM, Kosofsky BE, Miczek KA (2008) NMDA receptors in the rat VTA: a critical site for social stress to intensify cocaine taking. Psychopharmacology 197:203–216
52. Gil M, Nguyen N-T, McDonald M, Albers HE (2013) Social reward: interactions with social status, social communication, aggression, and associated neural activation in the ventral tegmental area. Eur J Neurosci 38:2308–2318
53. Drickamer LC, Vandenbergh JG, Colby DR (1973) Predictors of dominance in the male golden hamster (Mesocricetus auratus). Anim Behav 21:557–563
54. Carelli RM, Ijames SG, Crumling AJ (2000) Evidence that separate neural circuits in the nucleus accumbens encode cocaine versus "natural" (water and food) reward. J Neurosci 20:4255–4266
55. Frohmader KS, Wiskerke J, Wise RA, Lehman MN, Coolen LM (2010) Methamphetamine acts on subpopulations of neurons regulating sexual behavior in male rats. Neuroscience 166:771–784