REVIEW

Emotional valence and context of social influences on drug abuse-related behavior in animal models of social stress and prosocial interaction

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Abstract

Rationale Social factors are important determinants of drug dependence and relapse.

Objectives We reviewed pre-clinical literature examining the role of social experiences from early life through the development of drug dependence and relapse, emphasizing two aspects of these experiences: (1) whether the social interaction is appetitive or aversive and (2) whether the social interaction occurs within or outside of the drug-taking context.

Methods The models reviewed include neonatal care, isolation, social defeat, chronic subordination, and prosocial interactions. We review results from these models in regard to effects on self-administration and conditioned place preference established with alcohol, psychostimulants, and opiates.

Results We suggest that in general, when the interactions occur outside of the drug-taking context, prosocial interactions are protective against drug abuse-related behaviors, whereas social stressors facilitate these behaviors. By contrast, positive or negative social interactions occurring within the drug-taking context may interact with other risk factors to enhance or inhibit these behaviors.

Conclusions Despite differences in the nature and complexity of human social behavior compared to other species, the evolving animal literature provides useful models for understanding social influences on drug abuse-related behavior that
will allow for research on the behavioral and biological mechanisms involved. The models have contributed to understanding social influences on initiation and maintenance of drug use, but more research is needed to understand social influences on drug relapse.

Introduction

There is growing interest among neuroscience researchers in the role of social influences on the development of drug dependence and relapse. The development of drug dependence is thought to occur in stages and ultimately manifests as a chronic relapsing disorder (Kalivas and O'Brien 2008; Le Moal and Koob 2007). Initial drug use typically occurs during adolescence or early adulthood and is heavily influenced by peers (Bohnert et al. 2009; Ferguson and Meehan 2011; Fergusson et al. 2008; Schulden et al. 2009). In fact, human drug users often report that their initial desire to take drugs is to affiliate with other users (Baker et al. 2004; Sussman 2005). It is important to consider how social context, among other environmental factors, contributes to the initial rewarding effects of the drug-taking experience because individual differences in sensitivity to the drug and how rewarding one finds the initial drug experience are predictive of future dependence (Haertzen et al. 1983; Pomerleau 1995). Most people consume drugs without serious consequences, while others gradually lose control over drug taking and eventually meet the diagnostic criteria for substance abuse or dependence. Attempts to remain

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abstinent become increasingly difficult across the spectrum of abuse and dependence, and the risk of relapse is persistent (Gawin 1991; O'Brien et al. 1990). Drug craving and relapse are often precipitated by a lapse (i.e., sampling drug), exposure to drug-associated cues, and stress (O'Brien et al. 1998; Shaham et al. 2003; Wikler 1973), and the latter two factors are often social in nature (Bohnert et al. 2009; Childress et al. 1993; Sinha 2001).

Social interactions are crucial for survival and reproduction, and accordingly, they are powerful determinants of behavior. This review emphasizes two aspects of social interactions that are important for understanding their impact on vulnerability to drug abuse: (1) the emotional valence (i.e., positive versus negative) of the social experience and (2) the context in which the social interaction occurs (i.e., within or outside of the drug-taking context; see Fig. 1). First, we review the influence of early life social experience on drug abuse-related behaviors established later in life. These models include neonatal care and post-weaning rearing conditions, each of which has conditions that are positive (i.e., adequate care, social interactions with peers) or negative (i.e., inadequate care, isolation). These manipulations are far removed from the drug experience, and therefore, distinctions regarding whether they occur within or outside of the drug-taking context are not considered. Next, we review social influences that occur outside of the drug context proximal to the time of drug experience, followed by social influences occurring within the drug context at the time of drug experience. Within both of these parts of the manuscript, we review positive social factors including social housing and acute appetitive social

interactions, and negative social factors including isolation housing, acute isolation, and repeated episodes of social defeat (SD) with or without chronic subordination. Based on this review, we suggest that in general, social interactions occurring outside of the drug-taking context are protective against drug abuse when the interactions are positive but are risk factors when the interactions are negative. In contrast, positive or negative social interactions within the drug-taking context may interact with other situational events or individual differences to facilitate or inhibit vulnerability to initiate and maintain drug-taking and drug-seeking behaviors.

Early life social experiences prior to initiation of drug use

Clinical research has shown that negative childhood stressors such as household dysfunction, parental neglect, and parental emotional/physical abuse can increase risk of psychopathology in adulthood (Chapman et al. 2004; Dube et al. 2001; Wright et al. 2009). Accordingly, early life social stressors are risk factors for the development of drug and alcohol abuse (Anda et al. 2008, 1999; Dube et al. 2003, 2006; Strine et al. 2012; Young et al. 2006).

Neonatal care

Several models have been employed to examine effects of early life social experiences on subsequent vulnerability to substance abuse, including maternal deprivation models in

Fig. 1 Heuristic model summarizing inhibitory versus facilitatory social influences on drug abuse-related behaviors, depending to some degree on whether the experience occurs outside or within (circle) the context (i.e., place) where the drug is experienced. Positive social experiences appear in blue, and negative social experiences appear in red. See text for some exceptions
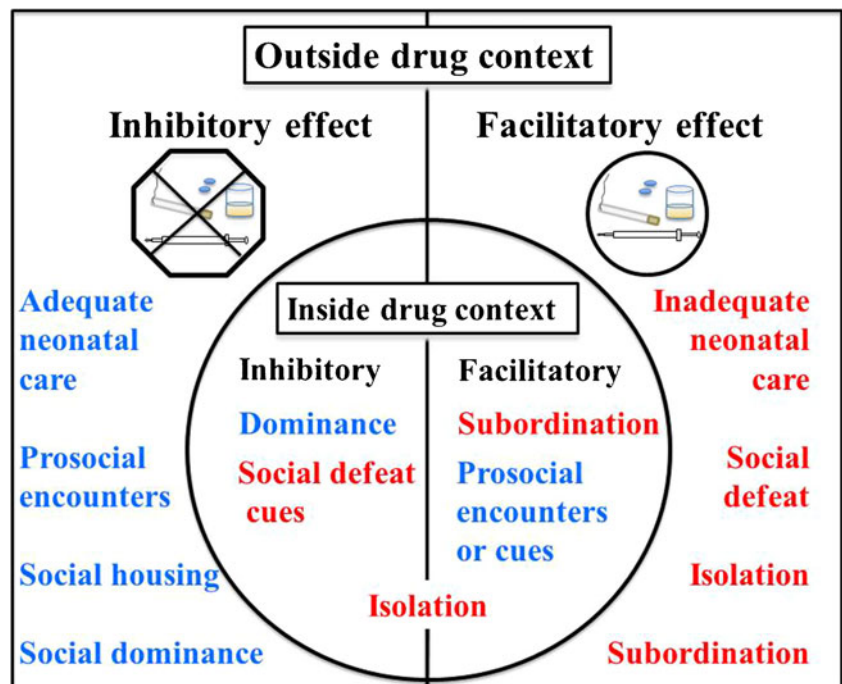
which monkeys or rodents are either peer reared or artificially reared, and models in which neonatal rodents are separated from their mother and placed on a heating pad either as a litter (maternal separation; MS) or individually (neonatal isolation; NI). When discussing the latter two models, we denote the separation time by a number representing minutes (e.g., NI15=neonatal isolation for 15 min; MS360=maternal separation for 6 h). The type(s) of controls used in rodent studies varies but generally consists of at least one of the following: (1) animal facility-reared (AFR) controls that are left undisturbed except for custodial care, (2) non-handled (NH) controls that are left undisturbed except for minimal cage changes by the experimenter, and (3) MS0 controls that are handled and returned to the dam each time experimental animals undergo separation (i.e., controls for handling).

The pioneering work of Harlow and colleagues demonstrated that maternal deprivation for the first 6 months of life in monkeys produced long-lasting behavioral disruption and difficulty coping with stress (Arling and Harlow 1967; Chamove et al. 1973; Harlow et al. 1965). In general, prolonged maternal deprivation or separation results in hyper-responsiveness of the hypothalamic–pituitary–adrenal (HPA) axis in adulthood (Anisman et al. 1998; Levine 2000; Walker et al. 1991). In contrast, the pioneering work of Levine (1957) gave rise to a literature demonstrating that brief separations, sometimes referred to as handling, increase resilience to stress in adulthood in rodents and monkeys (Campbell and Spear 1999; Denenberg et al. 1967; Levine and Mody 2003; Meaney et al. 1991). These findings suggest a quadratic function with respect to resilience across stress intensities, reminiscent of the Yerkes–Dodson law which asserts an inverted U-shaped relationship between performance and stress or arousal intensity (Yerkes and Dodson 1908).

The effects of maternal separation on drug abuse-related behaviors in rodents are generally consistent with an inverted U-shaped resilience function. Brief MS (≤15 min) typically protects animals against alcohol and stimulant self-administration compared to AFR and NH controls (see Table 1), whereas prolonged MS (≥60 min) can reverse the protective effects of brief separation and increase vulnerability to self-administer drugs compared to controls (see Table 2). In contrast to brief MS, NI15 male rats exhibit enhanced ethanol intake compared to NH controls (Lancaster 1998), suggesting that even brief NI enhances vulnerability perhaps because isolation is a more severe stressor than brief MS. Brief MS is actually most similar to natural rearing conditions in which brief parental separations may be necessary for food foraging (Moffett et al. 2006). Furthermore, in rats, maternal behavior toward the pups typically increases once they are returned (Der-Avakian and Markou 2010; Francis and Kuhar 2008;

Marmendal et al. 2004) and is likely that the increase in maternal care offsets the stress of brief MS, rendering the experience overall more positive compared to controls.

Parental neglect is a risk factor for substance abuse in humans (Altman et al. 1996) that is reliably captured across species by animal models of inadequate neonatal care. For instance, offspring of rodent mothers displaying less attentive behavior toward their pups consume more ethanol and cocaine as adults than the offspring of high attentive mothers (Isengulova et al. 2009; van der Veen et al. 2008). Studies in rhesus monkeys have consistently found elevated ethanol consumption in both male and female peer-reared monkeys compared to mother-reared monkeys (Barr et al. 2004, 2009; Fahlke et al. 2000; Higley et al. 1991, 1996; Newman et al. 2009). Although findings with rodent MS/NI models have been less consistent, the bulk of evidence suggests that prolonged MS facilitates alcohol, stimulant, and opiate self-administration later in life as summarized in Table 2. Table 2 also shows that a number of studies have failed to observe effects of MS on alcohol and cocaine self-administration or have found the opposite effect of a decrease in alcohol or cocaine intake (see table for references). The reason for these discrepancies is not clear; however, effects of MS/NI are complicated by several experimental parameters (e.g., litter composition, length and number of separations, age when separations and testing take place) that may contribute to differences across studies. In some cases, MS effects are uncovered after additional manipulations, such as naltrexone pre-treatment or post-weaning isolation rearing (Advani et al. 2007; Daoura and Nylander 2011; Fahlke et al. 1997), suggesting that sensitivity to detecting MS/NI effects may be enhanced by additional stressors.

Sex differences likely contribute to the discrepancies across MS/NI studies. The studies that failed to detect effects of prolonged MS on ethanol consumption were conducted with female rats (Gustafsson et al. 2005; Roman et al. 2004), and some studies comparing the effects of brief NI or prolonged MS on ethanol intake across sexes only found effects in males (Lancaster 1998; Roman and Nylander 2005). These findings suggest that males are more sensitive to early rearing stress effects on propensity to drink ethanol later in life. Additionally, even though both male and female peer-reared monkeys exhibit enhanced drinking relative to mother-reared monkeys, sex differences in the genes involved have been found, with vulnerability linked to the serotonin transporter gene promoter in females (Barr et al. 2004) and to the dopamine D1 receptor in males (Newman et al. 2009). With stimulants, effects of MS/NI are more variable in females than males. Increases in stimulant intake have been detected in female NI60 (Kosten et al. 2006) and female MS180–360 rats (Matthews et al. 1999; Moffett et al. 2006) relative to female NH controls. However, decreases in

Table 1 Effects of brief maternal separation (≤15 min) on drug abuse-related behaviors in rodents

Model[a]	Drug	Dose	Effect[b]	References[c]
CPP	Amphetamine	2–5 mg/kg, i.p.	↓ Amphetamine-CPP	Campbell and Spear 1999
Self-administration	Cocaine	0.5–1.0 mg/kg, i.v.	↓ Cocaine intake	Flagel et al. 2003 (only males and only when handled during the 1st and not 2nd post-natal week); Moffett et al. 2006; Weinberg 1987
		0.5–1.0 mg/kg, i.v.	↑ Cocaine intake	Flagel et al. 2003 (only in females and only when handled during the 2nd and not 1st post-natal week)
	Ethanol	2–10 %, oral	↓ Ethanol preference and/or intake	Hilakivi-Clarke et al. 1991; Jaworski et al. 2005 (NH but not AFR controls); Ploj et al. 2003 (effect in subgroup of high drinkers); Roman et al. 2003, 2005 (only in alcohol-preferring females)
		2–20 %, oral	Ø ethanol preference and/or intake	Daoura and Nylander 2011; Daura et al. 2011; Huot et al. 2001; Gustafsson and Nylander 2006; Gustafsson et al. 2005, 2007; Oreland et al. 2011; Roman et al. 2004
			↑ Ethanol intake	Lancaster et al. 1998 (adolescent onset in males; adult onset in females)

[a] Controls were either AFR, NH, or MS0 unless otherwise specified

[b] Ø represents no effect

[c] Annotations refer to comparisons made within the cited reference

intake have also been reported in female NI60 (Kosten et al. 2004) and in female MS360 rats on the first day of acquisition only (Matthews et al. 1999). The discrepancies across studies using females may be due to confounding effects of fluctuating gonadal steroid hormones that are known to alter cocaine abuse-related behavior in female rats (Fuchs et al. 2005; Jackson et al. 2006; Kippin et al. 2005; Roth et al. 2004). Furthermore, hormonal influences on cocaine effects in females are altered by NI60 (Kosten et al. 2005). Finally, sex may interact with timing of MS as Flagel et al. (2003) found sex differences in cocaine self-administration that were dependent upon the age at which the separations were initiated (see Table 1 for details).

Age at the time of testing for drug consumption is another important factor as MS/NI effects are more robust in adults than younger animals. For instance, MS360 adolescent rats fail to exhibit the enhanced ethanol intake that is observed in adults (Daoura et al. 2011). Although it is possible that the impact of MS is greater in adults, it seems more likely that MS effects are masked by higher alcohol consumption in adolescent rats relative to adult rats.

Effects of MS on stimulant abuse-related behavior may be due to changes in sensitivity to reward systems. For instance, male MS210 rats exhibit lower intracranial self-stimulation (ICSS) thresholds than NH controls in response to amphetamine (Der-Avakian and Markou 2010), consistent with sensitized reward as a result of prolonged MS. However, conditioned place preference (CPP) established with cocaine or methamphetamine is decreased in rodents undergoing NI15 or prolonged MS with or without other stressors (Campbell and Spear 1999; Dimatelis et al. 2012; Hays et al. 2012). These findings may reflect attenuation of stimulant reward or impaired associative processes needed to establish CPP. Nevertheless, other studies have failed to find differences in the rewarding or aversive effects of stimulants after prolonged MS (Faure et al. 2009; Matthews and Robbins 2003; Roma et al. 2008), and Matthews and Robbins (2003) found that MS360 females show greater ICSS elevating effects by the dopamine D2 antagonist raclopride relative to MS2 control females, consistent with enhanced anhedonia. Discrepancies regarding MS effects on stimulant reward enhancement may be due to differences in the MS protocols used (see Der-Avakian and Markou 2010 for discussion).

Effects of MS on opiate reward are also somewhat discrepant. A relatively harsh, prolonged MS procedure results in anhedonic-like increases in ICSS thresholds that are not altered by either morphine or naltrexone (Michaels et al. 2007). In contrast, morphine-CPP is enhanced in animals undergoing MS or NI for ≥180 min relative to NH or AFR controls (Michaels and Holtzman 2008; Vazquez et al. 2005, 2007), suggesting enhanced opiate reward. Consistent with this finding, morphine-CPP is also enhanced in artificially reared male rats compared to mother-reared controls (Lomanowska et al. 2006). Interestingly, conditioned place aversion (CPA) produced by the kappa receptor agonist spiradoline is attenuated in males, but not females, undergoing prolonged MS relative to NH controls (Michaels and

Table 2 Effects of prolonged maternal separation (≥60 min) on drug abuse-related behaviors in rodents

Model[a]	Drug	Dose	Effect[b]	References[c]
CPP	Cocaine	2 mg/kg, i.p.	↓ Cocaine-CPP	Hays et al. 2012
	Methamphetamine	1 mg/kg, i.p.	Ø methamphetamine-CPP	Faure et al. 2009
		1 mg/kg, i.p.	↓ Methamphetamine-CPP	Dimatelis et al. 2012
	Morphine	3–10 mg/kg, s.c.; 2 mg/kg, i.p.	↑ Morphine-CPP	Michaels and Holtzman 2008; Vazquez et al. 2005b, 2007 (evident as resistance to extinction)
Intracranial self-stimulation (ICSS)	Amphetamine	0.5 mg/kg, i.p.	↑ Amphetamine-induced lowering of ICSS threshold	Der-Avakian and Markou 2010
		0.2–1.0 mg/kg, i.p.	Ø amphetamine-induced lowering of ICSS threshold	Matthews and Robbins 2003
	Morphine	0.3–3.0 mg/kg, s.c.	Ø morphine-induced lowering of ICSS threshold	Michaels et al. 2007
	Heroin	0.06–0.6 mg/kg, i.p.	↓ Heroin-induced lowering of ICSS threshold	Matthews and Robbins 2003
Self-administration	Amphetamine	25 mg/l oral	↑ Amphetamine intake	Vazquez et al. 2006
	Cocaine	0.0625–0.5 mg/kg, i.v.	↑ Cocaine intake	Kosten et al. 2000, 2004 (males only), 2006; Matthews et al. 1999 (females only and only at 0.08 mg/kg), Moffett et al. 2006; Zhang et al. 2005
		100 mg/l, oral; 1.5 mg/kg, i.v.	Ø cocaine intake	Lynch et al. 2005; Vazquez et al. 2006
		0.05–0.5 mg/kg, i.v.	↓ Cocaine intake	Kosten et al. 2004 (females only); Matthews et al. 1999
	Morphine	25 mg/l, oral	↑ Morphine intake	Vazquez et al. 2005b, 2006
	Ethanol	6–20 %, oral	↑ Ethanol intake	Cruz et al. 2008; Daora et al. 2011 (adults); Huot et al. 2001; Ploj et al. 2003 (effect in subgroup of high drinkers but not overall); Roman et al. 2005 (only in alcohol-preferring males)
		2–20 %, oral	Ø ethanol preference or intake	Daoura and Nylander 2011; Daoura et al. 2011 (adolescents); Gustafsson et al. 2005; Gustafsson and Nylander 2006; Marmendal et al. 2004, 2006; Oreland et al. 2011; Roman et al. 2004 (only females tested); Vazquez et al. 2006
		8–10 %, oral	↓ Ethanol preference and intake	Gustafsson et al. 2007; Jaworski et al. 2005 (compared to NH but not AFR controls); Roman et al. 2005 (only in alcohol-preferring females)
Extinction	Cocaine history		↑ Cocaine seeking	Lynch et al. 2005
Cocaine reinstatement	Cocaine history	0.5–2.0 mg/kg, i.v. priming dose	Ø reinstatement of cocaine seeking	Zhang et al. 2005
Cue reinstatement	Cocaine history		↑ Cue reinstatement	Lynch et al. 2005

[a] Controls were either AFR, NH, or MS0

[b] Ø represents no effect

[c] Annotations refer to comparisons made within the cited reference

Holtzman 2008). Collectively, these findings suggest that early life stress may not only enhance the rewarding effects of morphine, but may also attenuate the aversive effects produced by kappa opiate receptors agonists.

Although few studies have examined the effects of maternal care on vulnerability to drug relapse, the evidence to date suggests that prolonged MS/NI may enhance vulnerability. Cocaine-seeking behavior during extinction or cue reinstatement, but not cocaine-primed reinstatement, is enhanced in NI60 rats (Lynch et al. 2005; Zhang et al. 2005). Furthermore, global withdrawal measures following cessation of a continuous morphine infusion are higher in MS180 male and female rats, as well as MS15 female rats, relative to respective NH

controls (Kalinichev et al. 2001), factors that may motivate maintenance of drug use.

As shown in Fig. 1, we conclude that models of neonatal care suggest that inadequate care increases vulnerability to drug abuse later in life, whereas attentive care is protective. This relationship is observed across classes of abused drugs.

Rearing conditions post-weaning

Housing conditions post-weaning provide a model for assessing early life social influences on drug abuse-related behaviors during adulthood. Several different housing conditions have been investigated that include varying degrees of enrichment (e.g., novel objects, opportunity to forage or exercise, etc.). Given that the present focus is on social influences, we limited our review to studies comparing isolation to social housing with two or more same-sex conspecifics during the post-weaning period.

The majority of the isolation-rearing literature suggests that this condition increases alcohol, stimulant, and opiate intake later in life compared to social rearing (see Table 3 for references). The increase in alcohol intake observed with isolation rearing manifests across a range of concentrations, as low as 5 % (Advani et al. 2007; Wolffgramm 1990) and as high as 20 % (Wolffgramm and Heyne 1991). Isolation-rearing effects appear to enhance sensitivity to stimulants given that intake is increased relative to controls at low doses during both acquisition (Schenk et al. 1987) and maintenance of self-administration (Bardo et al. 2001; Boyle et al. 1991; Ding et al. 2005; Howes et al. 2000). Isolation-reared rats also acquire cocaine self-administration at a faster rate and escalate intake at a lower dose of cocaine when switched from limited to extended daily access compared to social-housed rats (Gipson et al. 2011a). Similarly, isolation-reared rats self-administer more sufentanil aerosol, an opiate receptor agonist, during long access acquisition sessions compared to social controls, although this effect dissipates with limited-access sessions during the maintenance phase (Weinhold et al. 1993). An increase in oral morphine consumption also occurs in isolate-reared rats compared to social-reared rats (Alexander et al. 1978). Developmental studies of prolonged isolation suggest that animals are more sensitive to isolation effects during rearing than in adulthood (Lopez et al. 2011; Schenk et al. 1990). One caveat is that animals in these studies were tested for alcohol consumption at different ages, and therefore, it is unclear whether age at the time of isolation or testing accounts for these differences.

Other behavioral measures in studies of isolation-rearing effects on drug abuse-related behaviors provide some insight regarding potential mechanisms involved. For instance, Lodge and Lawrence (2003) observed increased anxiety-like behavior as well as preference for alcohol relative to water, suggesting that anxiety likely contributes to the increased vulnerability. Also, in a cocaine self-administration study, Ding et al. (2005) found higher response rates on both the active (i.e., activates reinforcer delivery) and inactive levers in isolated rats, resulting in shorter inter-reinforcement intervals compared to social-housed rats. They suggest that the enhanced self-administration behavior in isolated rats reflects greater impulsivity, thereby rendering these rats more vulnerable to cocaine. More recent studies report that impulsive rats do not show indiscriminate responding (Belin et al. 2008; Dalley et al. 2007). Furthermore, the enhanced drug intake in isolated rats is not likely due to a non-specific propensity to lever press because these rats initially show lower sucrose reinforcement rates than rats reared in an enriched environment, and this effect dissipates during maintenance (Bardo et al. 2001). One possibility is that isolation-reared rats become more aroused during self-administration than social-reared rats and direct this excess energy toward a drug-related behavior (i.e., indiscriminate lever pressing) while titrating drug intake by response rates on the active lever.

There is evidence suggesting that sensitivity to drug and natural rewards may be enhanced as a result of isolation rearing, which may contribute to enhanced drug self-administration. For instance, Hall et al. (1998) found that both alcohol and sucrose consumption are increased in isolation-reared rats, although in contrast, others have found no change or a transient decrease in sucrose consumption (Bardo et al. 2001; McCool and Chappell 2009). Early research examining effects of isolation rearing on drug-CPP suggests that sensitivity to opiate and stimulant reward is either reduced or unchanged relative to that observed in social-reared controls (Bowling and Bardo 1994; Schenk et al. 1983, 1985, 1986; Wongwitdecha and Marsden 1996), in contrast to more recent studies suggesting enhanced sensitivity (Kennedy et al. 2011; Zakharova et al. 2009). The reason for these discrepancies is likely related to the apparatus. The latter studies used an unbiased apparatus to avoid preference shifts due solely to reduction of aversion (Carr 1989), whereas the former studies used either a biased apparatus or an apparatus with clear Plexiglas dividers to confine rats to a drug-paired quadrant of an open field. The ability to see other animals during conditioning introduces a social component (Gipson et al. 2011b) that may have interfered with conditioning in the isolation-reared rats relative to controls. Importantly, the enhanced sensitivity to opiate reward reported by Kennedy et al. (2011) is due to an interaction between isolation rearing and the genetic propensity for social behavior in mice to influence morphine-CPP. In the relatively social mouse strain (C57BL/6 J), the dose–effect function for morphine-CPP was similar in isolate- and social-reared mice, but in a less social strain (BALB/cJ), the

Table 3 Effects of isolation rearing immediately post-weaning on drug abuse-related behaviors in rodents

Model	Drug	Dose	Effect	References
Self-administration	Amphetamine	0.03 mg/kg, i.v.	↑ Amphetamine intake	Bardo et al. 2001
		0.004–0.25 mg/kg, i.v.; 0.025 mg/ml, oral	Ø amphetamine intake	Bardo et al. 2001; Schenk et al. 1988; Zimmerberg and Brett 1992
		0.25 μg/side, intracranial (NAc)	↓ Amphetamine intake	Phillips et al. 1994a[b]
	Cocaine	0.04–0.75 mg/kg, i.v.	↑ Cocaine intake	Boyle et al. 1991; Ding et al. 2005; Gipson et al. 2011a[a]; Howes et al. 2000; Schenk et al. 1987; Phillips et al. 1994b[b]
		0.023–1.5 mg/kg, i.v.	Ø cocaine intake	Boyle et al. 1991; Howes et al. 2000; Phillips et al. 1994a[b],b[b]; Schenk et al. 1987
		0.047–1.5 mg/kg, i.v.; 40 mg%, oral	↓ Cocaine intake	Howes et al. 2000; Morse et al. 1993[b]; Phillips et al. 1994a[b]; Schenk et al. 1987[b]
	Morphine	0.5 mg/ml, oral	↑ Morphine intake	Alexander et al. 1978[b]
	Sufentanil aerosol	50 μg/ml, inhalation	↑ Sufentanil intake	Weinhold et al. 1993[b]
	Ethanol[c]	5–20 %, oral	↑ Ethanol intake	Advani et al. 2007 (males, only in females with a history of MS); Deehan et al, 2007[b]; Hall et al. 1998; Lodge and Lawrence 2003[b]; Lopez et al. 2011; McCool and Chappell 2009[b]; Sanna et al. 2011; Schenk et al. 1990[b]; Wolffgramm 1990[b]; Wolffgramm and Heyne 1991[b]
		2–20 %, oral	Ø ethanol intake	Advani et al. 2007; Doremus et al. 2005; McCool and Chappell 2009[d]; Rockman et al. 1988[b]; Schenk et al. 1990[b]
		2.5–10 %, oral	↓ Ethanol intake	Pisu et al. 2011
		10 %, oral training dose	Ø extinction responding for ethanol	McCool and Chappell 2009
CPP	Amphetamine	0.031–2.0 mg/kg, s.c.	Ø amphetamine-CPP	Bowling and Bardo 1994; Schenk et al. 1986
		1.5, 5 mg/kg, i.p.	↓ Amphetamine-CPP	Wongwitdecha and Marsden 1996
	Cocaine	5, 10 mg/kg, i.p.	↑ Cocaine-CPP	Zakharova et al. 2009
		0.31–2.5 mg/kg, s.c.	↓ Cocaine-CPP	Schenk et al. 1986
	Morphine	5.0 mg/kg, s.c.	↑ Morphine-CPP	Kennedy et al. 2011 (BALB: anti-social strain)
		0.25–5.0 mg/kg, s.c.	Ø morphine-CPP	Kennedy et al. 2011 (B6: social strain)
		0.25 mg/kg, s.c.	↓ Morphine-CPP	Kennedy et al. 2011 (BALB: anti-social strain)
	Heroin	80 μg/kg, s.c.	Ø heroin-CPP	Schenk et al. 1983
		20–40 μg/kg, s.c.	↓ Heroin-CPP	Schenk et al. 1985; Schenk et al. 1983
Extinction CPP	Cocaine	12.5 mg/kg, i.p. training dose	↓ Weeks to extinguish cocaine-CPP	Ribeiro Do Couto et al. 2009
Reinstatement CPP		50 mg/kg, i.p. training dose	Ø reinstatement	Ribeiro Do Couto et al. 2009 (25 mg/kg, s.c. priming dose)
		50 mg/kg, i.p. training dose	↓ Reinstatement	Ribeiro Do Couto et al. 2009 (12 mg/kg, s.c. priming dose)

Isolation immediately post-weaning (i.e., beginning PND 20–25)

[a] Enriched environment control (Note – in all other studies controls were socially reared)

[b] Isolation housing ≥90 days

[c] Choice ethanol consumption

[d] Forced consumption only

isolation-reared mice showed greater morphine-CPP at a high, but not a low, dose relative to social-reared mice. When collapsed across dose, there was a non-significant tendency in both strains for isolate-reared mice to exhibit higher magnitude morphine-CPP relative to social-reared mice.

Collectively, these studies suggest that post-weaning isolate housing affects brain reward and stress systems such that under some genetic and experimental conditions, these effects likely contribute to enhanced vulnerability to stimulants and opiates.

As shown in Table 3, a number of studies failed to find differences in drug self-administration between isolated and socially reared animals, and a few studies found a decrease in drug consumption in isolated animals relative to social-housed controls (see Table 3 for references). Although there are some exceptions, in general, it appears that isolation rearing decreases stimulant self-administration when a relatively longer period of isolation is used (i.e., ≥90 days). Dose of cocaine may also contribute to discrepancies given that a high dose of 1.5 mg/kg i.v. either produced a decrease or no effect (Phillips et al. 1994a, b). Higher doses of cocaine tend to be aversive (Nomikos and Spyraki 1988), and therefore, it is possible that isolated rats are more sensitive to the aversive effects of high cocaine doses than the social-reared controls, resulting in lower intake. These studies also used a different strain of rats, the Lister hooded strain, suggesting that strain differences may contribute to the discrepancies. Consistent with this idea, Morse et al. (1993) reported a strain-dependent decrease in oral cocaine intake in isolated DBA/2 J mice compared to C57BL/6 J mice.

Similar to inadequate neonatal care, studies investigating early life housing conditions reveal that animals reared in isolation display increased drug intake and motivation for drugs of abuse. Collectively, these pre-clinical findings are consistent with the human literature on adverse childhood experiences increasing risk of drug and alcohol abuse later in life.

Social experiences proximal in time to the drug experience but occurring outside of the drug context

Isolation versus social housing outside of drug context

Little is known about the effects of isolation versus social housing on intravenous drug intake because most studies employing intravenous drug self-administration utilize isolation housing for practical reasons, such as the ability to isolate drug intake for individual subjects and to avoid catheter damage. Furthermore, the majority of the literature on housing effects has compared isolation housing to environmental enrichment, but the latter model confounds social influences on drug intake with other components of enrichment. There is a literature examining housing effects on alcohol intake as reviewed previously (Becker et al. 2011). The present review will emphasize those studies that dissociated housing manipulations from other environmental stressors (e.g., novel context isolation, restraint). As summarized in Table 4, studies comparing isolation to social housing suggest that intake of ethanol and heroin is higher in isolated animals than social-housed animals, although some studies have failed to find housing effects on ethanol

intake (see Table 4 for references). The only study to examine social housing effects outside of the cocaine self-administration context in adults found no effect during acquisition or maintenance (Bozarth et al. 1989). Also, no effects on morphine-, heroin-, or cocaine-CPP have been observed across isolated and social-housed adult rodents (Herzig and Schmidt 2005; Ribeiro Do Couto et al. 2009; Schenk et al. 1985).

Protective effects of social housing in adults have been found in the extinction/reinstatement model. Specifically, rats trained to self-administer cocaine while isolation housed and then switched to social housing during a period of forced abstinence exhibit less cocaine-seeking behavior under extinction and less cue reinstatement of extinguished cocaine-seeking behavior relative to rats that remained isolated (Thiel et al. 2009b, 2010). Housing conditions failed to alter cocaine-primed reinstatement in this study. The protective effects of social housing are further enhanced by other environmental enrichments, which has been demonstrated using reinstatement of cocaine-CPP (Solinas et al. 2008, 2009), and stress and cue reinstatement of cocaine-seeking behavior (Chauvet et al. 2009; Thiel et al. 2010). The detrimental effects of isolation housing have also been demonstrated in adult OF1 mice that are moved from group housing to isolation after establishing cocaine-CPP. These mice exhibit an increase in resistance to extinction of the CPP compared to those that remain group housed, as well as an increase in sensitivity to cocaine-primed reinstatement of extinguished cocaine-CPP (Ribeiro Do Couto et al. 2009).

In conclusion, isolation outside of the drug context appears to increase the propensity to self-administer ethanol and opiates and to increase the incentive motivational effects of cocaine-associated cues.

Brief SD in rodents outside of drug context

Bullying or physical attack and the resulting psychological trauma from such social interactions are risk factors for substance abuse (Back et al. 2000; Brown et al. 1999; Niedhammer et al. 2011; Traweger et al. 2004). Although episodes of physical violence/trauma that are associated with increased vulnerability sometimes occur in the drug-taking context, this experience more often occurs outside of the drug-taking context, such as school or the workplace. One ethologically relevant rodent model of such experience is the resident–intruder model in which brief agonistic confrontations occur between a non-aggressive rodent (i.e., intruder) that is placed into the home cage of an aggressive rodent (i.e., resident). The resident then attacks the intruder, and upon reaching a criterion of SD (i.e., usually the intruder lying motionless in a supine position for several seconds), the intruder is either removed from the cage or placed into a

Table 4 Isolation-housing effects outside of drug context on drug abuse-related behaviors in rodents

Model	Drug	Dose	Effect	References
Self-administration	Cocaine	1.0 mg/kg, i.v.	Ø cocaine intake	Bozarth et al. 1989
	Heroin	0.1 mg/kg, i.v.	↑ Heroin intake	Bozarth et al. 1989
	Ethanol[a]	8–25 %, oral	↑ Ethanol intake	Ehlers et al. 2007[b](alcohol-preferring rats only); Juarez and Vazquez-Cortes 2003[c]; Roske et al. 1994
		2–15 %, oral	Ø ethanol intake	Lopez et al. 2011; Thorsell et al. 2005[c]
CPP	Cocaine	3.125–50 mg/kg, i.p.	Ø cocaine-CPP	Ribeiro Do Couto et al. 2009
	Heroin	20 μg/kg, s.c.	Ø heroin-CPP	Schenk et al. 1985
	Morphine	10 mg/kg, i.p.	Ø morphine-CPP	Herzig and Schmidt 2005
Extinction	Cocaine history		↑ Resistance to extinction	Ribeiro Do Couto et al. 2009; Thiel et al. 2009b[d]
Cue reinstatement	Cocaine history		↑ Reinstatement	Thiel et al. 2010
Cocaine reinstatement	Cocaine history	10 mg/kg, i.p. priming dose	Ø reinstatement	Thiel et al. 2009b
		12 mg/kg, i.p. priming dose	↑ Reinstatement	Ribeiro Do Couto et al. 2009

Isolation began in adolescence or adulthood; comparisons social-housed controls unless otherwise specified

[a] Choice ethanol consumption

[b] Isolation housing ≥90 days

[c] Forced consumption only

[d] Enriched environment control

smaller protective, yet semi-open, enclosure within the resident's cage in order for the defeated rat to experience continued threat (Tornatzky and Miczek 1993).

In general, SD increases vulnerability to stimulant self-administration, especially in animals with a history of stimulant self-administration. Miczek and colleagues reported that SD increases cocaine intake during maintenance of limited-access self-administration sessions (Boyson et al. 2011), particularly when low doses of cocaine are available (Miczek and Mutschler 1996). This laboratory also consistently finds increases in cocaine intake as a result of episodic SD in animals given binge access (i.e., 24 h) to cocaine (Boyson et al. 2011; Covington et al. 2005; Covington and Miczek 2001, 2005; Quadros and Miczek 2009). Unlike other stressors, the activating effects of SD/threat stress persist for weeks to months without habituating (Covington et al. 2005; Miczek and Mutschler 1996). Under limited-access maintenance sessions, SD increases response rates during timeouts, suggesting a loss of control over cocaine seeking (Miczek and Mutschler 1996). Under binge conditions, SD shortens the inter-reinforcer interval at high doses of cocaine and increases the persistence of responding before the rat discontinues binging (Covington et al. 2005). Some studies find that SD increases cocaine intake on a progressive ratio (PR) schedule of reinforcement (Covington and Miczek 2005; Covington et al. 2008; Quadros and Miczek 2009), although other studies have failed to find this effect (Boyson et al. 2011; Covington and Miczek 2001; Yap and Miczek 2007). There are several issues regarding interpretation of

changes in PR responding (Katz 1990), but the model provides insight into reinforcer effectiveness (Rowlett 2000) and motivation for drug (Markou et al. 1993). It seems unlikely that changes in motivation alone account for the less reliable effects of SD on PR versus binge responding because SD enhances cocaine-primed reinstatement of extinguished cocaine-CPP in OF1 mice (Ribeiro Do Couto et al. 2009), which is another model thought to assess incentive motivational effects of cocaine. It is possible that the differences between PR versus binge responding may involve cocaine's locomotor activating effects, which may be more pronounced during a binge due to higher drug intake relative to PR testing. In any case, together with findings from the other self-administration models, it seems that both cocaine reinforcement and incentive motivation for cocaine are enhanced as a result of SD.

Brief SD also has facilitative effects on initial acquisition of cocaine self-administration, although these effects are observed under more limited conditions than the effects of SD on maintenance. Male rats exposed to daily brief episodes of SD over 4 consecutive days acquire cocaine self-administration twice as fast as non-defeated controls when the rats are given continuous access (Tidey and Miczek 1997). With daily limited access, however, similar SD parameters fail to reliably produce effects during initial acquisition sessions (Covington and Miczek 2001; Cruz et al. 2011; Quadros and Miczek 2009), although one study found that an increase in cocaine intake emerged during the

third session in stressed rats relative to controls (Haney et al. 1995). Male rats classified as either having a high response (HR) or a low response (LR) to amphetamine–induced locomotion are differentially affected by SD. Specifically, HR rats exhibit delayed acquisition following SD compared to non-defeated HR controls, but during later sessions, intake is similar in defeated and non-defeated HR rats (Kabbaj et al. 2001). By contrast, LR rats exhibit similar intake during early acquisition sessions regardless of SD history, but during later trials, defeated LR rats self-administer more than non-defeated LR controls. Overall, SD seems to have less impact on initial acquisition than it does on intake during maintenance sessions, perhaps due to greater sensitivity to detect SD effects during maintenance in individuals who would otherwise be at lower risk.

The effects of SD outside of the drug-taking context on alcohol intake are complex due to timing issues, variation in number of defeats, and individual differences. Rats tested immediately before or after brief SD or threat of defeat during maintenance of alcohol self-administration exhibit either no change or a decrease in alcohol consumption (Funk et al. 2005; van Erp and Miczek 2001; van Erp et al. 2001). The decrease in alcohol consumption is consistent with the general suppressant effects that stressors have on ongoing behavior (e.g., Meerlo et al. 1996). In contrast, when access to alcohol is delayed 2 h post-defeat, rats exhibit an increase in alcohol intake (Caldwell and Riccio 2010). Croft et al. (2005) also found a delayed increase in alcohol preference in a selected subgroup of low alcohol-preferring C57/BL/10 mice with a history of repeated SD that emerged about 2 weeks after the last defeat episode. This effect is observed with daily SD episodes over 5 consecutive days, but not when the five episodes are experienced once/week nor when only a single episode is experienced. Sillaber et al. (2002) also reported time-dependent increases in alcohol intake in C57/BL/6 J adult male CRH1 knockout mice in which exposure to brief episodes of SD stress for 3 consecutive days increased alcohol intake compared to pre-stress baselines, effects absent in control mice. The time delay in increased alcohol consumption in contrast to the immediate increases in stimulant consumption after brief SD outside of the drug context is likely related to differences in the effects of these drugs on performance. Under stress, it seems advantageous to consume stimulants to achieve increased energy and other performance-enhancing effects, whereas it seems disadvantageous to consume ethanol due to its performance-interfering effects.

The effects of brief intermittent SD stress on drug intake may also involve altered motivation for drug or changes in sensitivity of reward systems. For instance, Funk et al. (2004) found that after a period of protracted alcohol withdrawal when motivation is high, SD produced a transient increase in alcohol intake. In the CPP model, adult male rats

experiencing a brief episode of SD/threat immediately before conditioning with an aversive dose of ethanol (1 g/kg) fail to acquire the CPA that is observed in controls, perhaps due to enhanced rewarding and/or attenuated aversive effects of ethanol (Funk et al. 2004). Alternatively, it is possible that the SD interfered with learning the drug-context association in the latter study. Brief SD enhances sensitivity to stimulant-CPP in both adolescents and adults (Burke et al. 2011; McLaughlin et al. 2006). The enhancement observed in adolescents is specific to SD stress, as no change in amphetamine-CPP is observed in adolescent rats pre-exposed to foot-shock stress (Burke et al. 2011). Collectively, these findings suggest that intermittent episodes of SD in rodents enhance sensitivity to the rewarding effects of drugs of abuse.

Only one study to our knowledge has examined the effects of brief SD on opiate intake, which failed to reveal any effect on heroin intake; however, defeated rats given access to cocaine in combination with heroin (i.e., speedball) continue to self-administer for a longer period of time during a binge than non-defeated controls (Cruz et al. 2011). Although the enhancement of speedball self-administration may be due to SD effects on cocaine, rather than heroin, reinforcement/motivation, it is possible that motivation to seek opiates may also contribute because SD reinstates extinguished morphine-CPP (Ribeiro Do Couto et al. 2006), a measure of incentive motivation for morphine.

In summary, the literature with stimulants suggests that brief SD outside of the drug context increases vulnerability. However, with alcohol, there are important differences in the timing of SD effects with immediate suppressive effects and delayed facilitatory effects. More research is needed to examine effects of SD on opiate self-administration.

Social hierarchy outside of drug context

Social hierarchies develop over time among monkeys and rodents when they are housed in groups. Within these hierarchies, chronic subordination is stressful in both species (Blanchard et al. 2001; Nader et al. 2012a). The physical and social environments vary from semi-natural habitats to standard home cages in which multiple animals are housed. Once established, dominance-subordinate hierarchies are maintained for prolonged periods (Blanchard et al. 1977, 1995). The strength of the agonistic interactions within these colonies varies considerably, with larger natural habitats, access to females, and competition for resources producing higher levels of aggression. In addition, specific colony features such as housing temperature, light/dark cycles, species, strain, colony group size, stability, and age range all impact the quality of colony member interactions (Blanchard and Blanchard 1990; Honess and Marin 2006; Kitchen and Beehner 2007).

Chronic social subordination stress experienced outside of the drug-taking context generally increases vulnerability to drugs of abuse. Both moderately and severely fight-stressed subordinate NIH-Swiss mice increase ethanol intake; however, only severely fight-stressed subordinates prefer alcohol to water (Hilakivi-Clarke and Lister 1992). Importantly, this difference is not seen prior to establishing social hierarchies, indicating that submissive mice escalate their alcohol intake only after severe subordination stress. Furthermore, subordinate male rats consume twice as much ethanol during weekly 24-h isolation sessions compared to dominant rats, and these effects persist for up to a year (Wolffgramm and Heyne 1991). A negative correlation between alcohol intake and dominance rank was observed under the stable social conditions of individual and contact caging (i.e., housing with separators that allow for limited social contact), but not under group housing; however, when housing conditions were rotated, dominant rats increased their consumption. Following an 18-month washout period, ethanol was reoffered and the influence of social dominance on ethanol choice was initially present but disappeared after four weeks; during the following 10 weeks, no significant differences between dominant and non-dominant rats were detected. Interestingly, this study also found that subordinate rats consume twice as much diazepam as dominant rats, suggesting that chronic social subordination stress increases the intake of anxiolytic drugs in general.

In contrast to the facilitatory effects of subordination on alcohol intake, chronic social stress involving daily 5-min SD episodes as well as 5 weeks of continuous threat while living in a protected enclosure within the resident's cage reduces cocaine intake during 24-h binge access (Miczek et al. 2011). Conversely, chronic subordination stress enhances cocaine choice in group-housed male monkeys given concurrent FR and PR access to both food and cocaine (Czoty et al. 2005), and subordinate male monkeys self-administer more total cocaine relative to dominant monkeys (Morgan et al. 2002). Interestingly, after transitioning from individual to group housing, dominant male monkeys exhibit substantially reduced cocaine self-administration acquisition rates across a range of doses. However, after prolonged cocaine self-administration, the differences in drug intake between dominant and subordinate male monkeys disappear (Czoty et al. 2004), but re-emerge following 8 months of extended abstinence (Czoty et al. 2010). Dominant female monkeys appear more sensitive to cocaine reinforcement because they acquire self-administration at lower doses than subordinate monkeys (Nader et al. 2012b). It is unclear why both increases and decreases in cocaine intake are observed with chronic social stress, but differences in species, sex, and predictability of the stress or differences in the intensity of the stressors (i.e., daily physical defeat in rats vs. possible defeat in monkeys) are possibilities. In any case, these studies suggest that subordination stress generally increases vulnerability, not only for initiation of drug use, but also relapse.

The effects of chronic social subordination stress on opiate intake have not been investigated. However, Coventry et al. (1997) found time-dependent effects of chronic SD stress and its interaction with the social hierarchy on morphine-CPP. When rats were tested 3 days after SD, only subordinate rats exhibited morphine-CPP. In contrast, 7 days following defeat, morphine-CPP was evident in the defeated rats that maintained their dominant status but not in those that became subordinate. These data suggest that subordination stress causes dynamic regulatory changes in opiate systems that alter sensitivity to morphine reward.

Prosocial experiences occurring outside of the drug context

The attitude of peers toward drugs can influence initiation of drug use, dependence, and relapse (Bohnert et al. 2009; Buchanan and Latkin 2008; Valente et al. 2007). The key distinction is whether peers encourage or discourage drug-taking. Positive attitudes toward drug use may facilitate initiation and use (Bohnert et al. 2009; Buchanan and Latkin 2008), and we suggest that this risk factor is most salient among peers at the time of drug availability. In fact, in some cases, social reinforcement in the drug-taking context may serve as the primary reinforcer, rather than the drug effect per se (Geckova 2005; Sussman 2005). In contrast, negative attitudes toward drug use among peers may protect against initiation of drug use. Furthermore, maintaining affiliations with such peers may be an alternative reinforcer that serves to discourage drug seeking and drug taking (Valente et al. 2007).

In animal models, positive social experiences outside of the drug context are protective against drug abuse-related behaviors. For instance, 60-min pairings with a conspecific immediately prior to oral access to morphine in a different environment attenuate isolation-induced increases in morphine consumption in isolate-housed rats (Raz and Berger 2010). Also, Fritz, Zernig, and colleagues (2011) found that cocaine and social rewards compete with each other in the CPP model. The CPP model utilizes two distinctly different conditioning compartments of an apparatus to create different contexts during conditioning. When rats receive either a conspecific or cocaine paired with one end compartment of the apparatus (i.e., reward-paired context) and saline paired with the other end compartment (i.e., neutral context), young adult male rats exhibit a preference for the reward-paired context. However, if the conspecific is paired with one context and cocaine is paired with the other during conditioning, rats fail to show CPP likely because each context is associated with a reward that is of equal value

to the other, and therefore, the drug reward context and social reward context are equally preferred. In addition, after establishing a preference for a cocaine-paired context (i.e., cocaine-CPP), pairing a conspecific with the previously saline-paired side shifts the rats' preferences away from the cocaine-paired side in favor of the social reward-paired side. Furthermore, after establishing cocaine-CPP to a given side and then extinguishing the CPP, social reward conditioning in the alternate side inhibits cocaine-primed reinstatement of cocaine-CPP (Fritz et al. 2011). Finally, Ribeiro Do Couto et al. (2009) found that after establishing cocaine-CPP and then extinguishing the CPP, a brief encounter with a non-aggressive conspecific 30 min prior to testing prevents cocaine-primed reinstatement of the CPP in OF1 mice. Although there is little research to date on brief prosocial encounters outside of the drug context, the results thus far consistently support a protective effect in reducing drug intake and drug-primed incentive motivation.

Social experiences occurring within the drug context

Drug intake in the home cage of isolate- versus social-housed animals

The influence of isolation versus social housing conditions on vulnerability to drugs of abuse has been investigated in animals that are housed and tested within the context in which they have access to drug. The findings from these studies are complicated by several factors including strain, age, length of isolation, and whether or not the housing conditions remain the same throughout the experiment or are changed during the course of the experiment. Rodents housed in isolation consume more ethanol (Deatherage 1972; Ehlers et al. 2007; Juarez and Vazquez-Cortes 2003; Parker and Radow 1974; Wolffgramm and Heyne 1991; Yanai and Ginsburg 1976) and morphine (Raz and Berger 2010) compared to social-housed rodents; however, other studies find the opposite with isolated rodents consuming less ethanol (Anacker et al. 2011a; Doremus et al. 2005; Thorsell et al. 2005) and cocaine (Smith 2012) compared to social-housed rodents, and other studies finding no difference in consumption between isolated and social-housed groups (Deatherage 1972; Kulkosky et al. 1980; Schenk et al. 1990).

In some cases, lower drug intake in isolated animals may be due to social facilitation of drug intake in the social condition rather than an inhibitory effect of isolation. Social facilitation was first observed in monkeys that self-administered more phencyclidine when in the presence of another monkey than when in isolation (Newman et al. 2007). Similarly, Smith (2012) housed rats in duplex operant conditioning chambers that were separated by a mesh

barrier, allowing for some social interaction. He found that cocaine intake was increased when both rats in the dyad had access to cocaine compared to dyads in which only one of the two rats had access to cocaine and compared to isolated controls. Also, alcohol consumption increases in rats when they are transitioned from isolated to social housing (Weisinger et al. 1989). Using a highly social strain of voles, Anacker et al. (2011a) found that those living in duplex contact housing consumed more ethanol than those living in isolation housing. A follow up experiment using the same design but giving rats access to a saccharin solution found no differences in consumption across groups, suggesting that the social facilitation observed is specific to ethanol.

In contrast to social facilitation, others have demonstrated social protection against drug intake. For instance, Raz and Berger (2010) have demonstrated that isolation increases oral consumption of morphine relative to social housing. In addition, when rats in this study were switched from social housing to isolation housing, they exhibited an increase in morphine consumption. Furthermore, a brief social interaction outside of the home cage attenuated the effects of isolation housing on morphine consumption. Similarly, Wolffgramm and Heyne (1991) demonstrated that when rats are switched from group housing to contact cages that allowed some social interaction with neighbors, alcohol consumption increased. Furthermore, rats that were housed in the latter condition and then switched to isolation housing also showed increased alcohol consumption. However, rats that were isolation housed and switched to group housing showed a decrease in alcohol consumption. In a recent study, Anacker et al. (2011b) found that isolated prairie voles classified as high drinkers decrease alcohol consumption when transferred to duplex contact housing with a low drinker, although in a few cases, the low drinker increased alcohol consumption to match the high drinker (Anacker et al. 2011b). These findings suggest that voles adjust their drinking level to that of a peer, highlighting the importance of sociality on drug intake.

The conditions under which social housing facilitates versus protects animals against drug intake are presently unclear. Doremus et al. (2005) found a decrease in alcohol preference and intake in isolated adults, but not isolated adolescents, suggesting that age influences drug intake when drug is available in the home cage. Stress intensity may also play a role. There are individual differences in perceived stress that are due to genetic and environmental influences. Similar to the Yerkes–Dodson function, motivation for drug across intensities of stress may be an inverted U-shaped function for which it is reasonable to predict that initial isolation (relatively mild stressor) may produce arousal that motivates alcohol consumption, whereas long-term isolation (severe stressor) may produce depression and anhedonia that may interfere with drug seeking. Along this

line of reasoning, moving rats from social housing to a less social condition or isolation in the Wolffgramm study may have resulted in stress-induced increases in alcohol intake, whereas the highly social prairie voles in the Anacker study may find the isolation stress more severe, resulting in less motivation to consume alcohol. Indeed, the highly social prairie vole exhibits a decrease in alcohol preference when moved from social housing to isolation (Anacker et al. 2011a). Further research is needed to understand the circumstances and mechanisms of social housing conditions in the drug context on drug intake.

Transitioning animals from social housing to isolation results in a complex pattern of changes in ethanol intake that varies across sexes and with the procedures used. For instance, alternating periods of social versus isolated housing in rodents and monkeys increase ethanol intake during the isolation periods, and in monkeys, ethanol intake is elevated above that of controls continuously housed in isolation (Kraemer and Mckinney 1985; Mediratta et al. 2003). McKenzie-Quirk and Miczek (2008) found a similar effect in male monkeys transitioning from social housing to isolation, whereas ethanol intake in female monkeys was not affected by the transition. However, these authors also found that placing a monkey into a smaller clear Plexiglas enclosure within the home cage while also removing other cohabitating monkeys for 20 min suppressed all fluid intake regardless of sex. Thus, it is clear that procedural differences affect the outcome of transitions from social to isolation housing on ethanol intake, perhaps related to length of isolation and social history prior to isolation.

Social defeat-conditioned cues within the drug context

To our knowledge, the effects of brief SD within the drug context have not been examined. However, Funk et al (2005) paired an odor cue with SD outside of the drug-taking context and found that when the cue was presented within the drug context, rats decrease alcohol self-administration. This finding suggests that cues predictive of SD have an inhibitory effect on alcohol intake.

Social hierarchy within the drug context

Social hierarchy effects within the drug context have only been investigated for ethanol intake, and the findings in both monkeys and rodents suggest that subordination increases vulnerability. Subordinate rats initiate ethanol intake faster and consume more than dominant rats regardless of whether there is high competition for resources (Blanchard 1992; Blanchard et al. 1987) or relatively little competition (Ellison 1987; Ellison et al. 1983; Pohorecky 2006, 2008, 2010). Social hierarchy effects on ethanol intake in male mice exposed to daily brief SD while also living in a cage

that allowed for transmission of social threat cues differ across strains as increases in ethanol intake are observed in subordinate, but not dominant, male C57BL/6 J mice (Kudryavtseva et al. 1991, 2006), whereas dominant and subordinate CBA/lac did not differ (Kudryavtseva et al. 1991). These differences may simply reflect strain differences in stress susceptibility or an effect of stressor intensity as the C57BL/6 J subordinates experienced attack three times more than the CBA/lac subordinates. More recently, McKenzie-Quirk and Miczek (2008) found that dominance rank is inversely correlated with alcohol intake in male and female squirrel monkeys given daily 15-min sessions in a Plexiglas chamber located within a colony consisting of four to ten adult monkeys in multi-generational, mixed-sex social groups. The increase in vulnerability to alcohol with subordination is an interesting contrast to the decrease in alcohol self-administration by an SD-associated cue, suggesting that animals in these models may have different coping strategies (e.g., stay with group versus flee) that interact with alcohol differently.

Prosocial-conditioned cues within the drug context

Cues (e.g., odor or drinking spout) associated with positive social experiences outside of the drug context can facilitate alcohol intake when animals are subsequently given access to alcohol. For instance, a drinking spout that is associated with access to a conspecific subsequently facilitates acquisition of ethanol intake and escalates consumption of higher concentrations of ethanol in rats (Tomie et al. 2004). The scent of alcohol on a peer can also be associated with the prosocial interaction with that peer and subsequently facilitate alcohol consumption. For example, pre-exposure to an intoxicated peer, but not a sober peer, facilitates drinking in pre-weanling and adolescent rats later given access to ethanol when alone (Hunt et al. 2001). Male rats appear more sensitive to the familiarity of the social conspecific because they only increase drinking when exposed to a familiar intoxicated peer, whereas females increase drinking regardless of partner familiarity (Hunt et al. 2000; Maldonado et al. 2008). Another example is that pre-exposure to an intoxicated peer later shifts approach behavior away from an initially preferred vanilla-scented hole to an alcohol-scented hole (Fernandez-Vidal and Molina 2004). These findings demonstrate that social conditioning readily occurs and influences drug intake even when an individual is alone with access to drug.

Brief prosocial encounters within the drug context

Most drug use is initiated among peers during adolescence and young adulthood in social contexts (Geckova 2005; Ramirez et al. 2012; Sussman 2005). There has been a

recent surge of research investigating the effects of prosocial encounters within the drug context in animals that, for the most part, has shown social facilitation of drug self-administration and drug-CPP (see Table 5). Maintenance of amphetamine self-administration is facilitated in male rats that have a conspecific in an adjacent compartment sharing a clear Plexiglas wall with the self-administration cage (Gipson et al. 2011b). This effect is selective for amphetamine as rats reinforced with sucrose pellets showed a disruption of intake. Acquisition of nicotine self-administration paired with oral delivery of a sweet-scented solution is also facilitated in male and female adolescent rats by the presence of a conspecific located in an adjacent cage who is drinking the scented solution (Chen et al. 2011); the divider between the cages was perforated to allow the transfer of olfactory cues. Without the conspecific, rats fail to increase licking on an active spout that resulted in the solution + nicotine compared to an inactive spout, and rats pre-trained to lick for the solution without a conspecific present show a decrease in licking when nicotine delivery is also made contingent upon licking the active spout. The social facilitation is stronger in the presence of a familiar rat than a novel rat, suggesting that social, rather than novel, cues drive the facilitation. We have also found that male rats

at the transition from adolescence to adulthood self-administer more nicotine on the first day of acquisition when they are in duplex self-administration chambers that have a wire mesh common wall than in chambers that have a solid common wall (Peartree et al. 2011). In contrast, nicotine self-administration in age-matched female rats was not affected by chamber type initially; however, only females in the solid wall condition showed escalation of nicotine intake across sessions, suggesting social suppression of nicotine intake in females.

Increases in stimulant self-administration in a social context may be due to enhancement of drug reward by the social context (i.e., presence of another rat). Limited social contact through a mesh wall is rewarding in rats as both adolescents and adults exhibit CPP for a compartment in which another rat is present behind a wire mesh divider (Kummer et al. 2011; Peartree et al. 2012). We have shown that both nicotine and cocaine reward interact synergistically with social reward in adolescent rats using the CPP model (Thiel et al. 2008, 2009a). In these studies, neither the drug experience alone nor the social encounter alone was sufficient to produce CPP, but when experienced together, significant CPP was observed. In a follow up experiment, we paired nicotine or saline with both sides of the CPP

Table 5 Prosocial interactions occurring *within* the drug context on drug abuse-related behaviors in rodents

Model	Drug	Dose	Effect	Type of social interaction	References
Self-administration	Amphetamine	0.1 mg/kg, i.v.	↑ Amphetamine intake	Conspecific behind Plexiglas wall	Gipson et al. 2011b
	Nicotine	0.015 mg/kg, i.v.	↑ Nicotine intake (males only)	Conspecific self-administering in chamber with mesh separating wall	Peartree et al. 2011
		0.015 mg/kg, i.v.	↓ Nicotine intake (females only)	Conspecific self-administering in chamber with mesh separating wall	Peartree et al. 2011
		15–30 μg/kg, i.v.	↑ Nicotine intake	Conspecific self-administering olfactory–gustatory drug-CS in chamber with perforated Plexiglas separating wall	Chen et al. 2011
	Ethanol[a]	3–10 %, oral	↑ Ethanol intake	Social-conditioned cue (scent of ethanol on intoxicated conspecific)	Hunt et al. 2000, 2001; Maldonado et al. 2008
CPP	Methamphetamine	2 mg/kg, i.p.	↑ Amphetamine-CPP	Drug + conspecific US during conditioning	Watanabe 2011 (only if conspecific is in similar drug state)
	Cocaine	2 mg/kg, i.p.	↑ Cocaine-CPP	Drug + conspecific US during conditioning	Thiel et al. 2008
	Nicotine	0.1 mg/kg, s.c.	↑ Nicotine-CPP	Drug + conspecific US during conditioning	Thiel et al. 2009a
	Morphine	0.25–5 mg/kg, s.c.	↑ Morphine-CPP	Drug + conspecific US during conditioning	Kennedy et al. 2011 (anti-social strain of mice)
			↓ Morphine-CPP	Drug + conspecific US during conditioning	Kennedy et al. 2011 (social strain of mice)
	Ethanol	4 g/kg 20 %, oral	↓ Ethanol CPA	Drug + conspecific US during conditioning	Gauvin et al. 1994
CPP-like procedure	Ethanol		↑ Approach to ethanol cue	Social-conditioned cue (scent of ethanol on intoxicated conspecific)	Fernandez-Vidal and Molina 2004

[a] Choice ethanol consumption

apparatus during conditioning to remove the potential influence of drug conditioning while establishing social reward-CPP. We found that rats undergoing social reward conditioning in a nicotine state exhibited enhanced social reward-CPP compared to rats that were in a saline state. These findings demonstrate that the nicotine-enhanced social reward-CPP observed previously was not due to additive effects of a weak drug-CPP and a weak social reward-CPP, but rather, these two rewards interacted synergistically to produce a stronger reward than either alone (Thiel et al. 2009a). More recently, Watanabe (2011) showed that methamphetamine-CPP is enhanced in adult mice conditioned with another mouse given methamphetamine but not in adult mice conditioned with another mouse given saline, demonstrating that social facilitation of stimulant reward only occurs when both partners share the drug experience.

In contrast to the above findings, Trezza et al. (2009) found an inhibitory interaction between methyphenidate and social rewards in rats, where both a conspecific and methyphenidate alone produce CPP, but when both are given together during conditioning, no CPP is observed. Similarly, morphine-CPP is attenuated in mice conditioned with a conspecific, and this effect is more robust in singly housed mice than socially housed mice (Kennedy et al. 2011). The reason for the differences in social and drug reward interactions across studies is unclear. Methylphenidate reduces play behavior (Vanderschuren et al. 2008), and therefore, Trezza et al. (2009) suggest that the methylphenidate state reduces the incentive value of the social interaction, thereby inhibiting methylphenidate-CPP. However, nicotine and cocaine also reduce play behavior yet enhance social reward-CPP (Thiel et al. 2008, 2009a), suggesting that a reduction in play is not sufficient to predict an inhibitory interaction. Species and procedural differences may also contribute to the apparent discrepancies across studies.

It is also possible that a reduction of the aversive effects of initial drug exposure by the presence of a conspecific may contribute to the interaction between drug and social rewards. For instance, rats given a dose of ethanol that produces CPA fail to show CPA if ethanol is given in the presence of an intoxicated or sober conspecific (Gauvin et al. 1994). Furthermore, acute nicotine increases corticosterone in adolescent rats only when they experience the nicotine alone and not when they are with another nicotine-treated rat, suggesting that social context reduces the stressful effects of acute nicotine administration (Pentkowski et al. 2011).

In conclusion, these findings suggest that prosocial interactions occurring within the drug context likely facilitate stimulant reward and reinforcement, which may play an important role in the development of drug dependence. Further research is needed to determine whether brief prosocial interactions within the drug context facilitate the rewarding effects of other drugs of abuse and to understand the mechanisms underlying facilitatory drug and social reward interactions.

Potential mechanisms of social influences on drug abuse-related behavior and concluding remarks

We have emphasized that the emotional valence of social circumstances and whether they occur within or outside of the drug-taking context are important determinants of their influence on drug abuse-related behaviors. Social experiences occurring during early development impact an individual's ability to cope with stress, increasing vulnerability to substance abuse later in life (Sinha 2008). In general, animal models of early life stress are consistent with the human literature, and these models are useful for examining underlying genetic influences and neural mechanisms (e.g., Barr et al. 2004; Newman et al. 2009). Capturing the developmental underpinnings of vulnerability to substance abuse is highly complex as reflected by the inconsistencies in the animal literature, and further research in this area is needed to refine the validity of these models.

Social experiences outside of the drug-taking context likely have an influence on responsivity to stress and cognitive processes, such as decision making and impulsivity, that contribute to vulnerability to drug abuse (Lupien et al. 2009; Piazza and Le Moal 1998; Redish et al. 2008; Uhart and Wand 2009), with positive social experiences prior to initiation of drug use having an inhibitory effect and negative social experiences having a facilitatory effect. For instance, the reinforcing effects of positive social experiences outside of the drug-taking context may prevent or decrease the desire to initially seek and/or continue taking drugs, similar to the impact of other alternative reinforcers and environmental enrichment observed previously (Bardo et al. in press; Campbell and Carroll 2000; Carroll 1998; Podlesnik et al. 2006). In addition, positive social experiences outside of the drug-taking context may provide a social buffer that alleviates some of the negative effects of daily life stressors that might otherwise motivate drug seeking. In contrast, negative social experiences occurring outside of the drug-taking context may sensitize drug reward and/or stress pathways, leading to increased risk for initiating drug use (Tidey and Miczek 1997) or to escalation of recreational drug use in an attempt to self-medicate (Boyson et al. 2011; Covington et al. 2005; Covington and Miczek 2001, 2005; Quadros and Miczek 2009). Indeed, human adolescent and adult populations that have been exposed to bullying or physical attack outside of the drug-taking context exhibit increased vulnerability to initiate and continue using drugs of abuse (Back et al. 2000; Brown et al. 1999; Niedhammer et al. 2011; Traweger et al. 2004).

The impact of negative social encounters within the drug-taking context may vary depending on the nature and degree of the stressor. For instance, brief, predictable stressors that engage escape strategies, such as physical attack or cues predictive of threat, may initially suppress drug taking and

seeking because individuals under these circumstances are focused on responding to the stress. This idea is consistent with the findings that a cue associated with SD inhibits alcohol self-administration (Funk et al. 2005) and with the suppressant effects that stressors have on ongoing behavior in general (e.g., Meerlo et al. 1996). However, once the physical threat is no longer present in the environment, animals may seek drug in an attempt to self-medicate. This idea is consistent with increased alcohol intake when access to alcohol is offered 2 h post-defeat (Caldwell and Riccio 2010). By contrast, chronic, unpredictable stressors that are unavoidable may heighten reward sensitivity or produce attempts to self-medicate, resulting in facilitated drug-taking and drug-seeking behaviors. This idea is consistent with the findings that chronic social subordination experienced within the drug-taking context enhances drug intake and/or drug seeking (e.g., Blanchard et al. 1987; Ellison 1987; McKenzie-Quirk and Miczek 2008). Therefore, it is important to fully elucidate the impact that social stressors have on the underlying neural mechanisms regulating drug-taking and drug-seeking behaviors. Understanding these processes not only has implications for understanding initiation and escalation of drug use, but may also help inform the development of behavioral and pharmacological treatment strategies that alleviate or prevent the negative consequences of chronic social stress.

The first drug use almost always occurs in a social context and is sometimes motivated by social reinforcement rather than drug reinforcement (Geckova 2005; Ramirez et al. 2012; Sussman 2005). The impact of positive social encounters within the drug context likely depends, in part, on motivation for such encounters, with higher motivation related to higher vulnerability. This enhanced vulnerability may be related to a sense of safety or trust. For instance, the peptide neurotransmitter oxytocin is released in response to appetitive social stimuli (Baskerville and Douglas 2010; Insel 1992) and causes a decrease in anxiety (Bowen et al. 2011; McGregor et al. 2008; Windle et al. 1997) and an increase in trust in humans (Kosfeld et al. 2005). The increase in trust may then enhance the influence of peers to engage each other in drug use.

Social context may also decrease the salience of aversive drug effects (Gauvin et al. 1994). Such effects may involve differences in HPA axis function in social versus isolated contexts. For instance, rats given nicotine or amphetamine in a social context fail to exhibit the drug-induced elevation of plasma corticosterone that is observed in isolated rats (Pentkowski et al. 2011; Stairs et al. 2011). In addition, most drugs of abuse are known to enhance the effects of other rewarding stimuli (Wise 1996) and, in the case of nicotine, can even render non-pharmacological stimuli reinforcing even though they intrinsically have little if any reinforcing effects (e.g., see Chaudhri et al. 2006 for recent review).

Thus, social context likely provides a key constituent of the reward experience during initial drug use, with drug and social rewards interacting synergistically to produce a stronger, perhaps neurobiologically unique, reward experience than either of these stimuli alone (Thiel et al. 2008, 2009a). Therefore, it is important to understand the neural mechanisms underlying interactions between social and drug reward that are experienced together in the drug context. Such interactions have implications for understanding initiation of drug use.

Another important reason to consider social reward and reinforcement occurring at the time of drug taking is the associative learning that occurs between these stimuli. There is a growing appreciation in neuroscience for the role of learning in the maintenance and relapse of drug abuse and dependence, with much attention given to the ability of environmental stimuli that have become associated with drug effects to elicit craving and/or habitual drug-seeking behavior (Everitt and Wolf 2002). Relatively few studies have investigated the reverse: the ability of drug stimulus effects to acquire conditioned reinforcing effects via pairing with social reinforcers. It is clear that drugs of abuse produce interoceptive stimulus effects that can serve as discriminative stimuli during operant conditioning and as occasion setters in Pavlovian conditioning (Morrison and Stephenson 1969; Palmatier and Bevins 2007; Palmatier et al. 2005; Stolerman et al. 1984). Furthermore, several laboratories have demonstrated that drug effects can become conditioned stimuli via association with other reinforcers (e.g., Carey et al. 1999; Murray and Bevins 2007; Reilly and Revusky 1992). For instance, in humans, preference for placebo over diazepam is reversed by pairing diazepam with earning a higher amount of money on an experimental task relative to that earned after placebo (Alessi et al. 2002). The authors suggest that the most parsimonious explanation for the switch in preference is that diazepam acquired conditioned reinforcing effects via pairing with the higher amount of money earned. We hypothesize that interoceptive effects of drugs that are experienced repeatedly with social reinforcement early during the course of drug use acquire conditioned reinforcing effects via association with social reinforcement. It is possible that the brain attributes high incentive value to the interoceptive effects of drugs as a result of their association with social reward, an effect that may be enhanced by drug-induced facilitation of learning. If this is the case, then in addition to the pharmacological effects of drugs, social reward-conditioned effects of drugs may also contribute to drug addiction. For instance, exposure to drug could increase subsequent drug intake due to social reward-conditioned effects, similar to the way exposure to drug-conditioned cues can motivate drug-seeking behavior in animals and humans when reinforced by the cues (e.g., cue reinstatement in rats, needle freak phenomenon in humans;

O'Brien et al. 1993; Stewart 1983). It is possible that such learning engages neural pathways involved in social reward that may be unique from those engaged by the drug and that their discovery may lead to novel therapies for drug abuse.

In closing, we suggest that it is critical to consider social history and social context in animal models directed toward understanding initiation of drug use, the development of dependence, and relapse. Vulnerability to initiate drug use is influenced by sensitivity to both drug reward and aversive effects, which are determined, in part, by social history and social context. For instance, upon initial drug use, positive social contexts may interact synergistically with drug reward. Such an effect may be greater when social motivation is high due to an impoverished social history, whereas a rich social history may be protective against positive social context interactions with drug. Understanding the contribution of social factors to initial drug experience is important because the degree to which one finds initial drug experience pleasurable is related to the risk of developing dependence (Haertzen et al. 1983). Escalation of drug intake and development of dependence are also influenced by social factors. For instance, negative social experiences may motivate attempts to self-medicate or to escalate recreational drug use, thereby contributing to the development of dependence. In contrast, positive social history or situations where positive social interaction is available as an alternative reinforcer likely are protective against the development of drug addiction. Finally, although little pre-clinical research has examined social influences on drug relapse, early findings suggest that positive social experiences outside of the drug-taking context are protective against cue-elicited motivation for drug (Fritz et al. 2011; Ribeiro Do Couto et al. 2009; Solinas et al. 2008; Thiel et al. 2009b). We suggest that associations between positive social interactions and drug within the drug-taking context are likely powerful motivators of relapse. These ideas need further empirical support, but if upheld, the field may gain new insight to inform the development of behavioral and pharmacological treatment strategies for drug addiction.

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