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Neuropharmacology

Social modulation of drug use and drug addiction

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Abstract:

This review aims to demonstrate how social science and behavioral neurosciences have highlighted the influence of social interactions on drug use in animal models. In neurosciences, the effect of global social context that are distal from drug use has been widely studied. For human and other social animals such as monkeys and rodents, positive social interactions are rewarding, can overcome drug reward and, in all, protect from drug use. In contrast, as other types of stress, negative social experiences facilitate the development and maintenance of drug abuse. However, interest recently emerged in the effect of so-called "proximal" social factors, that is, social interactions during drug-taking. These recent studies have characterized the role of the drug considered, the sharing of drug experience and the familiarity of the peer which interaction are made with. We also examine the few studies regarding the sensorial mediator of social behaviors and critically review the neural mediation of social factors on drug use. However, despite considerable characterization of the factors modulating distal influences, the mechanisms for proximal influences on drug use remain largely unknown.

Introduction

Drug addiction is a psychiatric condition that is not the mere use of drugs but instead is defined by the loss of control over its consumption and by the compulsive and obsessive use of the substance. Not everybody shifts from recreational consumption to abusive and addictive use. Thus, finding the factors promoting or preventing drug use and drug addiction such as social factors is therefore of primary interest. While clinical studies have demonstrated the effect of the social factors on drug use, it is only recently that neuroscience have been diligently looking at the effect of social factors on drug use and addiction in animal models (for review see Heilig et al., 2016). This review aims to demonstrate how behavioral neurosciences have highlighted the influence of social interactions on drug use in animal models. The influence of social factors can be distal from drug use, which means it is occurring at a different time from when the drug is experienced. These factors comprise social housing (grouped or isolated), previous social experiences (prosocial or agonistic) or hierarchical status. Recently, interest have grown for the effect of social factors that are proximal from drug use, those that are present at the same time as drug is experienced. The distinction is important because prosocial and agonistic social interactions do not have the same effect whether they are experienced in the drug context or not (for review see Neisewander et al., 2012). Epidemiological data (Walden et al., 2004; Bahr et al., 2005; Simons-Morton and Chen, 2006) suggest that proximal social factors may be as important, and possibly more important, than distal social factors (for review see Strickland and Smith, 2014).

We will present how distal and proximal social factors prompt or prevent subjects to initiate, maintain or resume drug use. We will also review the sensory modalities and neural substrate that mediate such processes. Human and other non-human animals such as rodents live socially. It has been known for several decades that, rats and mice are social animals (for reviews see Barnett, 1967; Lore and Flannelly, 1977; Blanchard and Blanchard, 1980), making them a good model for studying neuroscience on these issues and this review will focus on animal studies.

Distal social factors

As for the species, social life has many advantages in terms of reproduction, defense, foraging and even survival. For the individual of a social species, the everyday social context has prolonged effects on affective and cognitive processes. These effects can extend distally over other contexts such as the drug context and thus participate in the decision to take the drug.

The lack of social interactions or negative social interactions in the home-cage are aversive and predispose to drug use

As the individual switches from recreational to addictive use, “important social activities are given up or reduced due to substance use” (Association, 2013). Drug addictive individuals often suffers from social isolation and exclusion which can participate to the maintenance of drug use. Isolation and rejection are among the social factors associated with higher rates of male drug use (Aloise-Young and Kaepfner, 2005; Rusby et al., 2005). On the other hand, cessation of drug use has better chance of success when the individuals have the social support from family and friends. A healthy family environment, which can be considered an enriched

environment for animals, is associated with lower rates of drug use in humans (Barnes and Farrell, 1992).

Social isolation and loneliness are aversive and, when experienced chronically, have detrimental effects on mental and physical health (House et al., 1988). In rodents, the solitary housing over extended period (2 to 13 weeks) is a potent stressor accompanied by the deterioration of health (Hatch et al., 1965; Spani et al., 2003; Carnevali et al., 2012) and behavioral alteration resembling anxiety or depressive disorders (Weiss et al., 2004; Stairs et al., 2011), referred as the “isolation syndrome” (for review see Valzelli, 1973).

In addition to the affective and cognitive disturbance of social isolation, it also alters social behavior and this effect depend on sex and stage of development. For instance, group-housed male and female adult rats do not develop CPP for social interaction. Group-housed male and female adolescent rats only develop a preference for social interaction with a grouped-housed, but not with an isolated congener. However, isolation period increases the rewarding effect of social interaction, at various development stages, with adolescent males showing the strongest preference (Douglas et al., 2004). Applied during adolescence, social isolation impedes social play and the social competence acquired from it. For instance, social isolation during adolescence, disrupt rats’ ability, once adults, to assume a submissive posture during an encounter with a dominant, territorial rat (Van den Berg et al., 1999; Von Frijtag et al., 2002). In addition, in the absence of an aggressor, the isolates show less putative de-arousal behaviors, such as grooming and play (Von Frijtag et al., 2002).

In the seminal “Rat Park’ study of Alexander et al. (1978), the authors showed that isolated rats have an exacerbated consumption of a solution of morphine on contrary to socially housed animals, which show little appetite for it. The results have since been replicated and found to be abolished by short- or long-term reversal of housing conditions (Raz and Berger, 2010). Most studies have also reported decreased social drinking of alcohol compared to isolated drinking (for review see Ryabinin and Walcott, 2018). The literature has also provided extended evidence for the predisposing effect of social isolation on drug use in adolescent and adult rats, and monkey (for reviews see Miczek et al., 2008; Stairs and Bardo, 2009; Trezza et al., 2011; Nader et al., 2012; Neisewander et al., 2012; Bardo et al., 2013). Here, we quickly review some key studies characterizing the effect of social isolation on responses to drug of abuse. Isolated rats show a decreased acute locomotor response to the stimulant drugs amphetamine and nicotine (Bowling et al., 1993; Green et al., 2003). Using the conditioned place preference procedure (CPP) where animals associate non-contingent drug injections with a specific context, isolated rats show a reduced preference for the compartment associated with amphetamine, nicotine or opiates relative to rats housed in enriched conditions (EC) (Bowling and Bardo, 1994; Smith et al., 2005; Ewin et al., 2015), but increased cocaine induced CPP at high dose (potentially aversive) when compared to rats housed in standard conditions (Zakharova et al., 2009). These results suggest a reduced sensitivity of isolated animals to the positive and aversive subjective properties of drugs. Over repeated experience with drugs, isolated animals show a greater sensitization to the stimulant effect of amphetamine or cocaine, relative to EC (Bardo et al., 1995; Smith et al., 1997), and compared with animals housed in standard condition. They also readily acquire an operant response to receive infusions of cocaine when grouped

rats fail to reliably self-administer this drug at this dose (Schenk et al., 1987). They maintain a greater self-administration of low unit doses of amphetamine (Bardo et al., 2001; Green et al., 2002) or heroin, although for the latter, difference between isolated and grouped animals dissipate after one week (Bozarth et al., 1989). The transitory effect of social housing on heroin self-administration parallels studies on another sedative drug of abuse, showing greater consumption of alcohol of isolated animals at early but not later stages (Wolffgramm and Heyne, 1991). Finally, isolated animals seem more prone to relapse showing a greater heroin induced CPP after extinction (Turner et al., 2014).

Most experiments have been conducted on adult males but increasing studies are comparing the influence of sex or development stages. Social isolation initially reduces self-administration of nicotine in males, but enhances nicotine intake during later sessions especially in females (Peartree et al., 2017). Adolescent Sprague-Dawley rats female rats consumed more sweetener-supplemented alcohol in isolation than when group-housed while in the same studies adolescent and adult male consume more alcohol in triads versus when isolate-housed (Varlinskaya et al., 2015). This suggest that female might be more vulnerable to the predisposition effect of isolation on drug use. This agrees early studies demonstrating isolation seems more stressful for females than for males (for review see Palanza, 2001). Douglas et al. (2004) found that isolation enhances social conditioned place preference more in males than females. This could suggest either that males are more affected by isolation stress on contrary to what suggested previously. Otherwise, this could suggest that the incentive for social interaction and stress induced by social isolation are dissociable processes that are differentially affected by the sex. The fact that social isolation during adolescence increase the vulnerability to take drugs is not surprising considering the importance of social interaction on the affective and cognitive development (for reviews see Butler et al., 2016; Burke et al., 2017).

All these results suggest that social interactions in rodents protect from developing and maintaining drug use. As a word of caution, previously isolated rats transferred to social housing conditions increases ethanol consumption (Weisinger et al., 1989), suggesting a shift in housing conditions could be even more stressful than social isolation and therefore promote drug use. Moreover, it is still unclear whether the stressful effect of social isolation results from the lack of social interaction per se or from general environmental impoverishment. Analysis of behavioral and neuroanatomical changes caused by an enriched or an impoverished environment suggests that the effects of social and non-social environment are due to different mechanisms (Rosenzweig et al., 1978; Renner and Rosenzweig, 1986). Also, enrichment only partially reverses the social isolation syndrome (Hellems et al., 2004; Grippo et al., 2014). The question remains important as compelling evidences have demonstrated the clear protective effect of enrichment on the development and maintenance of drug use (Solinas et al., 2008) and the protective effect of social interactions may originate from global stimulation of living in groups rather than from social bonding or reward.

Avoiding the adverse consequence of social isolation and seeking the reward of social interaction may ground the cohesion of the group (Panksepp and Lahvis, 2007). However, in social living groups, members are likely to compete for access to limited resources, territories and mating opportunities. Chronic social stress from continuous conflicts can make relationships unstable and stressful (Nyuyki et al., 2012) and can have deleterious effect on health (for review see Lazarus, 1986). Rodents have a greater response to social defeat than other physical stressors (for

reviews see Koolhaas et al., 1997; Blanchard et al., 1998; Sgoifo et al., 2014), and do not appear to develop adaptation against it (Tornatzky and Miczek, 1993; Sgoifo et al., 2002; Covington and Miczek, 2005). Hence, social defeat produces longer-term impacts on physical and mental health (for reviews see Martinez et al., 1998; Sgoifo et al., 1999).

In line with the extensive literature on the precipitating role of stress on drug use and drug addiction, episodic social defeat of adult rats has been shown to promote the acquisition (Haney et al., 1995; Kabbaj et al., 2001) and the maintenance of cocaine self-administration (Covington and Miczek, 2005; Covington et al., 2008), increasing the motivation for the drug (Covington et al., 2008; Quadros and Miczek, 2009) and prompting binge use (Miczek et al., 2011). In addition, social defeat or its reminder increase the reinstatement of extinguished alcohol or morphine seeking behavior (Funk et al., 2005; Do Couto et al., 2006).

Social rank in the home-cage has a complex effect on stress and the predisposition to drug use

While continuous conflicts make relationships unstable and stressful, social hierarchy stabilizes and appeases the group (Durkheim, 1893; Marx and Bottomore, 1964). It is therefore not surprising that group-housed rats form social hierarchy. It is possible to measure the dominance ratio of two animals by several means that we will quickly review here.

-Social interactions between male adult rats during dyadic encounter in the home cage of one of the individuals such as in the resident/intruder test evoke strong aggressive behavior from the resident to affirm dominance over its territory and strong submissive behaviors from the intruder (Martinez et al., 1998). However social status here is mainly driven by the experimenter and does not reflect the complex social and non-social behavior occurring in more ecologically relevant situation.

- Because no dominance can be originally claimed, dyadic encounter in neutral places evokes a mix of offensive-defensive and flight behaviors, rarely seen in the home cage confrontation (Olivier and van Dalen, 1982). Within two rats living in the same home cage, quantification of dominance behaviors is based on the individual identified as making the largest number of 'pins' (when the dominant rat pushes the other rat over and holding it down with its front paws) and dominance grooming or pouncing aimed at the hindquarters where a rat attempts to leap onto its congener (Blanchard et al., 1993). However, in dyadic encounter, attention of an individual is mainly directed or even restricted to the encountered partner (Grant, 1963).

- In tetradic encounter, direct agonistic confrontations are attenuated by the presence of other individuals and the rat is no longer forced to direct its attention to one counter-partner (Wolffgramm, 1990b).

There is little fighting within a colony (Barnett, 1958) and dominance is often maintained through more discrete behaviors.

- Because rodents heavily rely on their sense of smell to explore their environment and because body odors provide essential information about the social status of conspecifics (for review see Brown, 1979), sniffing behavior also serves to transmit the social hierarchy. Indeed, it has been shown that sniffing is a signal of appeasement during social interactions and that rats showing more agonistic behaviors explore their submissive congeners much more than the other way around

(Wesson, 2013) suggesting that quantification of sniffing behavior can inform the social hierarchy of the group.

- The competitive task for a resource (Syme et al., 1974; Malatyńska and Kostowski, 1984) consists in conditioning the rat to have access to a reward (i.e. a bottle of sugar water) when alone. Once the habituation phase is over, all the animals of the same social group are placed together in the experimental arena and the time spent by each animal to drink from the sugar water bottle is measured. The rats having spent the most time drinking are considered dominant, the others, subordinate.

- The cylinder test is also classically used (Lindzey et al., 1961; Messeri et al., 1975). The test consists of a cylinder with a diameter matching the size of the animal, so that, once entered the tube, the animal cannot turn around. An animal is positioned at each end and the dominant is determined as the one having passed through the whole tube, forcing his congener to move back.

Social hierarchy emerges from the interplay between the costs and benefits of agonistic behaviors and social dominance may result from a higher valuation of the benefits or lower valuation of the cost. In fact, rats selectively bred for low saccharin intake are subordinate to high-saccharin-consuming rats when they compete in weight-matched dyads for food (Eaton et al., 2012). Even engaging in offensive aggressive behaviors and winning a fight is highly reinforcing (Grant, 1963; Golden et al., 2017) and therefore support additional incentive for the maintenance of social dominance. On the other hand, social hierarchy has been linked to a more general coping strategy to stress (for review see Koolhaas et al., 2007) with dominant individuals being more resilient to stress, and prone to proactive behaviors such as aggressive and impulsive/risk taking behavior (for reviews see Koolhaas, 2008; Cooper et al., 2015).

The translational value of these experiments should be apprehended with caution as the relationship between stress and the social status is greatly dependent on the group context. Indeed, most studies are conducted in laboratory captive colonies of rodents, where subordinate individuals cannot leave the group and exhibit a higher level of glucocorticoids (GCs), an index of stress (for review see Creel, 2001). In group-housed monkeys, social subordination is stressful (Kaplan et al., 1986; Shively, 1998), consistent with findings in humans suggesting a relationship between socioeconomic status, social conditions, and susceptibility to disease (for review see Adler and Matthews, 1994; Krantz and McCeney, 2002). However, in the wild, dominant individuals, that have to constantly ascertain their status, have higher levels of GCs than subordinates (for review see Creel, 2001).

The influence of social status on drug use has only been conducted in captive colony for obvious technical reasons. In accordance with the effect of social defeat on drug use, subordinate rats drink more alcohol or opiates than dominant rats (Blanchard et al., 1987; Wolffgramm, 1990a; Wolffgramm and Heyne, 1991; Heyne, 1996). These studies concur with studies on monkeys in captive colonies showing increased alcohol self-administration of subordinates (Helms et al., 2012). However, when rats have exacerbated intake and show signs of "behavioral dependence", social factors are no longer relevant (Wolffgramm and Heyne, 1991; Heyne, 1996). The role of the social status on drug use is not even clear during the early stage. In contrast to the predisposition of subordinates to alcohol use, dominant rats identified according to their behaviors during the competitive access to milk shake reward,

maintain higher rates of cocaine self-administration but show no differences in the acquisition, extinction and reinstatement of this behavior (Jupp et al., 2016). Such inconsistency could result from the mean of selecting dominant and subordinate animals or from the fact that the effect of the social status on drug use depend on the subjective effect of the drug (sedative alcohol or opiates vs stimulant cocaine). In addition to the drug considered, environmental context is another factor to consider. In standard condition, selectively bred socially-dominant mice (Dom) show cocaine-induced place preference, while selectively bred submissive mice display a cocaine conditioned place aversion to the drug. However, following a 4-week regimen of Chronic Mild Stress, submissive mice display a marked increase in cocaine CPP, but this regimen has little effect on the cocaine CPP of dominant mice (Yanovich et al., 2018). As for today, the role of the social status on drug use thus remains difficult to define.

Contact with drug experienced peer in the home-cage predispose to drug use.

The distal influence of the social context does not always protect from drug use. In fact, animal housed with experienced animals favor the development of drug use. Social transmission of alcohol use has been demonstrated in rodents (for review see Strickland and Smith, 2014). Even animals housed with peer that passively experienced alcohol are predisposed to consume alcohol (Fernández-Vidal and Molina, 2004). Similar results have been observed with animals housed with cocaine experienced peers. Rats housed with cocaine experienced peers demonstrate a greater escalation of cocaine intake than rats paired with a drug naïve partner (Robinson et al., 2016). The social transmission of food preference is mediated by olfactory cues passing from demonstrator to observer, providing observers with information concerning demonstrators' diets and that these olfactory cues are sufficient to bias diet selection by observers (Galef and Wigmore, 1983). It is tempting to suggest the same process likely occurs during the social transmission of alcohol intake. However, the intravenous route of cocaine self-administration renders socially transmitted cocaine through olfactory cues unlikely.

Proximal social factors and drug use

Social interactions are rewarding and can overcome drug reward

As mentioned above, social life has many advantages in terms of reproduction, defense, foraging and even survival. However, individuals of the group do not likely draw the advantages of social living. Instead groups are formed because social interaction are inherently rewarding. Positive social interactions, like other types of reward, generate a positive feeling, facilitate learning and approach behaviors towards associated stimuli (for review see Trezza et al., 2011). In rodents, social interactions between adults and specialized social behavior between adults and young, such as maternal behavior or between young such as social play are strong incentive in rodents. Adults rats develop a preference for a compartment associated with non-aggressive social interactions (Douglas et al., 2004) and cross an elevated T maze to gain access to a partner (Werner and Anderson, 1976).

Recent studies of pro-social behavior in rats have also demonstrated that rats are able to release a trapped rat from a restraint tube (Ben-Ami Bartal et al., 2011; Hachiga et al., 2018). Similarly, mothers develop a preference for a compartment previously associated with pups (Fleming et al., 1994; Panksepp and Lahvis, 2007) and lever press to gain access to pups (Hauser and Gandelman, 1985) (Lee et al., 2000). Finally, adolescent rats develop a preference for social interaction (Douglas et al., 2004) and lever press to gain the opportunity to interact with same-age congeners (Ikemoto and Panksepp, 1992). In fact, adolescent rats prefer a compartment where they previously experience social play at the expense of another compartment where they previously experienced interaction with a partner rendered unresponsive to play solicitations (Calcagnetti and Schechter, 1992). In the adults, we have shown that only the dominant rats exhibit a place preference for a compartment associated with the social presence of the home-cage partner (Giorla et al., 2018).

Social reward in rodents can overcome drug reward. Rats prefer a compartment previously paired with social interaction between gender- and weight matched male conspecific at the expense of a compartment previously paired with cocaine (Kummer et al., 2014) or amphetamine (Yates et al., 2013). In addition, pairing the compartment with social interaction in rats prevents the reinstatement of the preference for a compartment associated with cocaine (Fritz et al., 2011a). The option for social interaction suppresses the choice for methamphetamine even in rats that meet criteria for addiction (Venniro et al., 2018). Similarly, the incentive salience of pups for mothers can exceed that of cocaine during the early postpartum period (Mattson et al., 2001; Mattson et al., 2003; Seip and Morrell, 2007; Pereira and Morrell, 2010). This parallels clinical studies showing that drug addicted women decrease their cocaine use during late pregnancy and lactation (for reviews see Chapman and Wu, 2013), and are more likely to ask for help to stop using drugs.

However, few studies have demonstrated the inability of social interaction to distract from drug use. Kummer et al. (2014) show that mice have a clear preference for the compartment associated with a moderate dose of cocaine over the compartment paired with social interaction. Also, in the 'rescue' paradigm, a rescuer rat press a lever to release a rat trapped in a plastic restrainer even at the expense of sucrose self-administration. However, rats with a history of heroin self-administration do not release their cage mate and continue to self-administer heroin (Tomek et al., 2018). It thus appears in these conditions that a familiar peer in distress does not divert from seeking heroin. Such models are arguably of high translational significance for the situation of the human addict.

In these procedures, the protective role of social interaction as an alternative reinforcement on drug use, at least at early stages, may likely relate to the ability of social interaction to distract from drug use. However, the effect of social interaction on drug abuse greatly depends on the nature and quality of an individual's social group. For example, a good predictor of teen drug use is determined by the drug use of the group of friends (for review see Kandel, 1980). Of course, adolescents who use drugs tend to choose friends who use drugs, but longitudinal data indicate that the effect of drug user peers and the choice for drug user peers on the use of drug are about equal in strength (Kandel, 1980). Nevertheless, the peer pressure to take drugs seems to be true when the actors are adolescent and especially when they all have access to the drugs. In this situation, the promoting effect of proximal social interaction on drug use happened when peers are present during the first drug experiences. In this situation, peers can be an incentive to use drug, potentiate (or

repress) the rewarding effect of drugs, act as a demonstrator sustaining imitation learning of drug use or act as discriminatory stimulus for drug use. More detailed analyses of what modulates drug intake in case of peer presence is important to address the few studies that have investigated these issues to date.

Presence of an abstaining peer

The direct influence of peer presence on drug self-administration has shown different results that may be due to differences in the experimental conditions. Rats drink more from an ethanol sipper when the sipper predict social contact with a same sex peer (Tomie et al., 2004) suggesting that social interaction can act as an incentive for drug use. In adolescent rats, cocaine or nicotine CPP is increased by the presence of a peer, suggesting that a peer increases the affective valence of drug use (Thiel et al., 2008; Thiel et al., 2009). On operant behavior, the presence of a peer separated by a Plexiglas panel facilitates amphetamine self-administration at a high dose, but not at a low dose in single-housed adult rats (Gipson et al., 2011). In similar condition using a Plexiglas divider, the same effect has been observed for nicotine (Chen et al., 2011). Notably, in this latter study, the peer clearly serves as a demonstrator. By transmitting through the holes of the plexiglass divider the olfactory-gustatory cues associated with the operant response (licking), the demonstrator prompts the observer to imitate the operant behavior. In contrast in Gipson et al. (2011)'s study, the partner is not given the opportunity for operant behavior, more likely representing a discriminative stimulus for drug availability for the self-administering rat. In fact, a recent study shows that a peer previously present during acquisition of cocaine self-administration can be used as a discriminative cue to induce reinstatement after extinction (Weiss et al., 2018).

In contrast to the facilitating effect of peer presence on drug use, rats reduce cocaine self-administration in the presence, through a grid, of an abstaining rat, naïve to cocaine (Smith, 2012). The ability of the peer to distract from self-administering the drug seems to depend on the animal's receptivity to the partner. Indeed, as female rats are more receptive to males during proestrus, the presence of a male greatly distracts from cocaine and heroin self-administration during this period while males are minimally influenced by the hormonal status of a female partner (Lacy et al., 2016).

We also observed the similar reducing effect of the presence of an observing peer separated by a grid on cocaine intake in male adult rats. Interestingly, our rat study paralleled our human study based on questionnaires regarding the last episodes of drug consumption and the presence of peers in groups or dyads and found similar beneficial effect of social presence at reducing drug intake in both rats and humans (Giorla et al., 2018). Interestingly, in our procedure, the level of intake decreased the most when the peer was naïve to the drug (Giorla et al., 2018), suggesting that the behavior towards the drug of the congener is also an important factor to evaluate.

Presence of a peer also consuming

The transmission of drug related states amongst peers seems important in the valuation of the drug. The CPP induced by methamphetamine is greater when two mice share the same drug-experience relative to when a mouse is conditioned together with a "sober congener" (Watanabe, 2011, 2015). Also, previous morphine

experiences with morphine experiencing peers increases the ability to acquire CPP induced by high dose of morphine (20mg/Kg subcutaneously) when they are conditioned alone. This suggest that peer co-experiencing drug promote the rewarding effect of drug use. However, the presence of peers that share the same experience of morphine has been shown to prevent the acquisition of CPP induced by a low dose of morphine (1mg/Kg, intraperitoneally) in adults mice (Watanabe, 2013, 2015). The co-experience of low to moderate doses of morphine (0.25 to 5 mg/Kg subcutaneously) also prevents the acquisition of the morphine CPP in adolescent mice from the social bl/C57 but not from relatively less social BALB/C strains (Kennedy et al., 2012).The contrasting effect of social proximal effect on drugs of different classes parallels clinical and preclinical studies showing the predominant use of stimulant in outdoor social environment while the use of opiates is predominantly solitary and indoor (for review see Badiani and Spagnolo, 2013).

Experiments using drug self-administration have also shown various effects. As discussed before, social group are less prone to use drug than isolated animals. However, Logue et al. (2014) observed that male adolescent, but not female or adult, C57BL/6J mice consume more alcohol when housed in group than when isolated. Siblings of prairie voles, a highly sociable rodents, exhibit greater preference for ethanol over water when housed together, than housed separately (Anacker et al., 2011).

In non-human primates, it has been shown that rhesus macaques consume more phencyclidine in the presence of a congener that has also access to the drug (Newman et al., 2007). Similarly, rats allowed to interact through a grid during acquisition of cocaine self-administration take more cocaine if both have access to cocaine than if only one rat has access to it (Smith, 2012; Peitz et al., 2013). In the same procedure, rats tested with a drug-experienced partner acquire cocaine self-administration faster and emit more active lever presses than rats tested with a cocaine-naïve partner (Smith et al., 2014). Prairie vole drink more alcohol when it is facing the congener on the other side of a mesh-divider than when placed on the other side of the cage (Anacker et al., 2012). These findings suggest that the behavior of a peer, as opposed to merely the presence of a peer, is the critical factor determining how social presence will affect drug consumption.

In our experiment, rats acquired the self-administration alone and were tested with a peer afterwards. In these conditions, we observed a decreased consumption in presence of the peer. (Giorla et al., 2018).

Altogether, these results suggest the presence of a peer may either predispose drug use through imitation or distract from drug use depending at which stage of drug use the presence of a peer occurs and how receptive the user is to peers. Such complex interactions could explain the different directions that have been observed depending on the matching of drug experience, the sex and the social housing conditions (Tomie et al., 2014; Tomie et al., 2016). Characterizing the factors that influences these opposing processes are important to understand the effects of peer on drug use. Studies have shown that when the distracting effects of direct physical interaction are removed through plexiglass divider, the stimulating effects of social interaction on ethanol drinking are evident (Tomie et al., 2014; Tomie et al., 2015). Another relevant factor is the familiarity of the congener.

Presence of a stranger or familiar peer and dominance status influence

The social response greatly differs whether the congener is familiar or is a stranger. For instance, pain sensitivity is increased in the presence to a familiar congener similarly in pain but not a stranger congener also experiencing pain (Langford et al., 2006). Also, the expression of pro-social behavior depends on strain familiarity. When giving the ability to release congener from a restrainer, rats do when the congener is a cage-mate or a same strain stranger (that “looks” like their cage mate) but not when the rats are from a strain they have not been previously paired with (Ben-Ami Bartal et al., 2014).

The familiarity with the peer also plays a critical role in social modulation of drug use. The greatest facilitation of alcohol drinking is observed when rats interacted with a familiar alcohol-intoxicated and in a lesser extend to a familiar sober rat. In contrast, interaction with an unfamiliar and sober rat reduced drinking. Notably, females do not seem to be sensitive to familiarity (Maldonado et al., 2008). We have also shown that the presence of an abstaining unfamiliar peer reduces cocaine intake to a larger extent than that of a familiar peer (the cage mate) Interestingly, in our human parallel study, drug users report a lower consumption when in presence of strangers than familiar peers (Giorla et al., 2018).

Also when we tested the influence of a familiar cage mate peer, we found that the dominance status plays a role in the rewarding effect of social interaction. We have shown that the presence of the cage mate is only rewarding in the CPP for the dominant rat (Giorla et al., 2018), in line with a former study in hamsters (Gil et al., 2013). However, when analyzing the influence of dominance on cocaine self administration in presence of a familiar peer, no significant effect was found (Giorla et al., 2018).

Which sensory modalities are critical for the effect of social modulation of drug use?

Visual stimulation

Observing someone can be considered a social reward (Anderson, 1998; Deaner et al., 2005). The simple observation of an image of a congener also has reinforcing effects in macaques (Fujita and Watanabe, 1995; Fujita et al., 1997) and rhesus monkeys spend more time looking at faces than more neutral pictures (Wilson and Goldman-Rakic, 1994). In addition, after training monkeys to use a joystick to view videos of congeners, it has been shown that, in a choice experiment, monkeys prefer to watch videos involving other monkeys rather than having food reward (Andrews and Rosenblum, 1993).

It is commonly admitted that primates heavily rely on visual stimulus on contrary to rodents. For instance, social play which is highly rewarding in juvenile (for review see Trezza et al., 2011) is not affected by blindness {Siviy, 1987 #276}. However, recent data suggest the role of visual stimulation in rodent social behavior. Watanabe et al. (2016) showed that mice were able to discriminate different behaviors from videos and develop a preference videos showing fight or copulation over sniffing behavior, suggesting a role of visual stimulation in social interaction. It is highly likely that visual stimulation sustains imitation behavior. Visual stimulus seems also to play a key role in “emotional contagion” in mice. Indeed, the hyperalgesia induced by the presence to a familiar but not a stranger congener is mediated through visual rather than olfactory or auditory cues (Langford et al., 2006). Visual stimulation may also convey the reinforcing effect of social interaction with a familiar peer. Rats learn a novel lever-pressing response that produces access to a familiar

partner even if they are only provided visual feedback and physical contact is prevented (Angermeier, 1960).

Physical contact

The role of other sensory modalities in social interaction seems also important. Other forms of “emotional contagion” that transfer to both stranger and familiar congener is not mediated by visual but olfactory stimulation (Smith et al., 2016). Angermeier (1960) also showed that rats lever press to access an unfamiliar congener but only if they have contact, even limited, with the new partner.

Consequently, the rewarding effect of or receptivity to familiar vs unfamiliar congener seems to depend on different modalities, with processes directed toward a familiar congener requiring at least visual stimulation while those directed toward an unfamiliar congener requiring physical contact or/and olfactory stimulation.

The critical role of physical contact in social interaction have also been suggested when Wolffgramm (1990b) observed that the effect of isolation resembles those of group housed in cages that limit physical contact, suggesting (Wolffgramm, 1990b). In fact, the most rewarding sensory component of social interaction is physical contact. Even a simple limited contact between rats, through a grid, can induce a CPP (Kummer et al., 2011; Peartree et al., 2012), while visual and auditory stimulation through a plexiglass partition cannot (Kummer et al., 2011). In juvenile, somatosensory feedback play a key role in the highly rewarding social play as xylocaine anesthesia of the back of the juvenile pairs greatly depresses social play (Siviy and Panksepp, 1987).

Unfortunately, apart from this latter study, most of the studies do not dissociate the somatosensory, olfactory or auditory stimulation from physical contact.

Smell

In rodent species, body odors provide essential information about the sex, social and reproductive status of conspecifics (Brown, 1979). Mice explore more a petri dish containing the bedding of their own home cage or that of other mice over empty petri dish or petri dish containing fresh bedding (Seillier and Giuffrida, 2016). Home cage odors support the development of CPP. Notably, only subordinate mice showed CPP to home cage odors (Fitchett et al., 2006). Olfactory cues also mediate some form of “emotional contagion” (Smith et al., 2016; Laviola et al., 2017) suggesting a role in social communications. In fact, olfactory cues play a key role in social transmission of food preference (for review see Wrenn, 2004).

The physiological effects of odors are mediated through the vomeronasal organ and the main olfactory epithelium. Lesions of the main olfactory epithelium by irrigation of the nasal cavity with a solution of zinc sulfate into the nares in males results in a decrease of aggressive behaviors normally directed against unfamiliar males (Flannelly and Thor, 1976) but have limited effect on social play in adolescent (Thor and Holloway, 1982) and does not disrupt social sniffing behavior (Wesson, 2013).

Auditory stimulation

Audition play a key role in social play as evidence through ablative procedures. Indeed, deafness greatly suppresses social play in juvenile rats (Siviy and Panksepp, 1987). Results from devocalized rats have shown that vocalizations promote and maintain playful interactions with familiar (Kisko et al., 2015b) but not unfamiliar peers (Kisko et al., 2015a). The role of audition in social behavior of adult

rats seems more ambiguous. Adult males are more likely to escalate playful encounters into serious fights when one partner was devocalized (Kisko et al., 2015a) but preventing residents from hearing intruder has no detectable effect on any aggressive behavior. (Takahashi et al., 1983). As mentioned above, the hyperalgesia induced by the presence to a familiar but not a stranger congener is not mediated through auditory cues (Langford et al., 2006). The limited studies using ablative studies is difficult to clearly defined the role of audition in social behaviors despite considerable studies on the auditory communication in rodents. Like all social animals, rats are capable of communication with each other, but also with other species.

Audible vocalizations

First, rats can provide audible squeal sounds of 2 to 4 KHz (for review see Nitschke, 1982). These sounds are cries of alarm, which often express pain or discomfort. They can be emitted to dissuade a predator from approaching (for review see Litvin et al., 2007) or to the attention of humans, in anticipation, or during unpleasant treatment or manipulation.

Ultrasonic vocalization (USV)

The natural way of communicating in rats is through the emission of ultrasonic vocalizations (USVs) (Burgdorf et al., 2008). But, although researchers had identified the vocalizations of rats in the ultrasound spectrum by the 1960s, their real study only started several years later (for review see Brudzynski, 2009). In an experimental setting, USVs are an effective means of inferring the emotional state of animals (for review see Brudzynski, 2007).

The vocalizations of adult rats can be classified into two broad categories, according to their frequency of emission. First, vocalizations called "22KHz" reflect a negative emotional state. Rats emit these vocalizations in case of danger or in anticipation of a potentially threatening situation (for review see Brudzynski, 2009). These vocalizations are also useful in case of unpleasant stimulus. There are also other situations in which rats will emit 22KHz vocalizations. These include fighting situations (Lore et al., 1976), but also during certain sexual contacts (Barfield and Geyer, 1972). Although emitted in negative emotional situations, it should be noted that 22KHz vocalizations do not directly express the pain of animals. Indeed, a rat subjected to an acute pain stimulus ceases to vocalize in these frequencies. These vocalizations are associated with the anxiety created by these painful stimuli but not with the pain itself (Jourdan et al., 2002).

The second major class of USVs, called "50KHz", reflects a positive emotional state for the rat. Positive vocalizations are much more heterogeneous than negatives and are divided into several categories, based on the profile of their frequency and duration (for review see Brudzynski, 2015). Firstly, they can be separated into "flat" vocalizations (flat, FL), ie the frequency of the vocalization emitted remains constant throughout the duration of the emission, or else at " frequency modulated " (FM, ie the frequency is modulated during the duration of the transmission of the vocalization). The two types, FL and FM, however, have the same peak frequency, between 45 and 55KHz. Regarding the duration of vocalization, the 50KHz FL have a duration of about 10-100ms and their frequency range can range from 35 to 50KHz. The 50KHz FM have a longer duration, since they can last from 20 to 150ms and their frequency range is between 40 and 80KHz (Wohr et al., 2008; Takahashi et al.,

2010). These vocalizations are also called "social vocalizations" and are expressed in positive or neutral contexts (ie non-aggressive, non-aversive or "friendly") such as sexual contact or the expectation of interaction with a congener (Bialy et al., 2000). The emission of positive USVs is also related to the anticipation and / or the search for social interactions. Rats exploring environments frequently occupied by other rats, even in their absence emit positive vocalizations (Brudzynski and Pniak, 2002). The authors have further shown that the amount of vocalization emitted is proportional to the number of individuals having occupied this space.

Rats also emit vocalizations of pleasure in anticipation of a certain number of rewards. Indeed, it has been shown that rats emit more 50KHz vocalization in anticipation of electrical stimulation of the ventral tegmental area (Burgdorf et al., 2000).

Although flat and frequency modulated 50KHz vocalizations are issued in positive situations, there is a difference of context in which they are transmitted. Indeed, the 50KHz FM are emitted in very rewarding situations (Burgdorf et al., 2011) whereas the 50KHz FL are identified as having a role of social coordination and serve as vocalizations of contact (Wohr et al., 2008). Finally, some data have shown a dissociation of vocalizations within 50KHz FM. Some vocalizations show rapid frequency oscillations ("trill") while others do not exhibit this characteristic (for review see Brudzynski, 2013).

There is wide variability in the level of emission of USV. For example, the emission level of USVs varies according to the dominance status. In fact, most of the time, the USVs are emitted by the dominant rat, while the dominated rat emits much fewer vocalizations (Thomas et al., 1983). There are also important individual difference in the propensity to emit positive or negative ultrasonic vocalizations. Tickling rats make them emit positive USVs in some rats. Rats that emit the most positive USVs make more risky decision in ambiguous situation (Rygula et al., 2012).

Ultrasonic vocalization and drug addiction.

Rats emits 50KHz USVs to the administration or the anticipation of drug that increased over repeated administration (for review see Barker et al., 2015). Notably, the type of emission over the course of self-administration change across time starting with trills with flat after more extended self-administration history. This suggest change in valuation of drug over the course of drug history (Maier et al., 2012). This parallel tolerance of the hedonic effect of the drug over the course of drug taking history.

On the other hand, withdrawal from drug use evoke 22kHz negative ultrasonic vocalizations (for review see Barker et al., 2015).

Communications of such affective appraisal among a group remains elusive but the function of USV has been demonstrated in USV replay studies (Brudzynski and Chiu, 1995). Positive 55 kHz ultrasonic vocalizations are rewarding. Rats approach playback of 55 kHz ultrasonic vocalizations (Wohr and Schwarting, 2007) and lever press for them (Burgdorf et al., 2008). In contrast, rats hearing negative 22 kHz show fight/flight/freeze stress responses (Sales, 1991; Brudzynski and Chiu, 1995; Beckett et al., 1996; Commissaris et al., 2000).

In a recent study, we have shown that the playback of positive USV of a non-familiar rat can reduce cocaine intake (Montanari et al., 2018). This mirror our previous study showing that presentation of an unfamiliar peer after acquiring self-administration alone induce positive ultrasonic vocalization and reduce self-

administration (Giorla et al., 2018). In contrast, play back of negative USV transiently increase self-administration (Montanari et al., 2018). These results highlight the critical role of vocal communication in the influence of proximal social factors on drug consumption.

Neurobiological substrate of social influence on drug use

Distal social factors

The neurobiology of social influence has been extensively assessed for distal social factors such as play behavior (for review see Vanderschuren et al., 1997). Here we will critically review their main conclusions and discussed the role of some less studied substrata of social behaviors. Generally, studies on neural basis of social behaviors have highlighted the role of dopamine and opioid systems in this rewarding behavior, but also the cholinergic system for its involvement in the attentional processes required for social interactions. Distal social influences such as social rearing context (maternal separation, isolation) act as stressors and have been shown to affect the serotonergic, dopaminergic and opioid systems, as well as the hypothalamic-pituitary-adrenal axis (for review see Bardo et al., 2013). The roles of these neurotransmitters and neuromodulators are not restricted to social stimuli, more likely sustaining or repressing the hedonic/rewarding functions of the nucleus accumbens, arousing functions of the hypothalamus and/or prefrontal executive functions in response to social stimuli or the lack of them.

In contrast, while the neuropeptide oxytocin reduces more generally anxiety, potentially affecting social performance, it seems to act more specifically on social behaviors mainly enhancing affiliative prosocial behaviors or regulates cooperation and conflict among humans in the context of intergroup relations (for review see Shamay-Tsoory and Abu-Akel, 2016). Similarly, oxytocin has a prosocial effect in rodents (for review see Insel, 2010). Yet, accumulating evidence reveals that the effects of OT is context dependant and have on some occasion anti-social effect suggesting, the role in social salience rather than valence (for review see Shamay-Tsoory and Abu-Akel, 2016). Preclinical and clinical studies have demonstrated the ability of oxytocin to reduce intoxication, tolerance to and withdrawal from drugs (Bowen and Neumann, 2017; Pedersen, 2017). The critical role of oxytocin in the nucleus accumbens, the prefrontal cortex, the central nucleus of the amygdala on various drug-related behaviors using metamphetammine, cocaine, heroin and alcohol has been recently reviewed (Leong et al., 2018).

Recent studies on the neuroanatomical basis of the social modulation drug use have push interest further from the “classical” reward system. Amongst them, some have demonstrated that the insular cortex is both implicated in the subjective effect of the drug and involved in prosocial behaviors (for review see Heilig et al., 2016).

We and others have also studied the effect of the subthalamic nucleus, the only glutamatergic structure of the basal ganglia that receive direct projection from the prefrontal cortex. Alteration of this structure have opposite effect on food and drug rewards (Baunez et al., 2005). It is also particularly sensitive to the reducing effect oxytocin on methamphetamine induced activation (Carson et al., 2010) giving it an interesting role in the social modulation of drug use.

Extended methamphetamine reduced oxytocin receptor density in the nucleus accumbens and the subthalamic nucleus (Baracz et al., 2016b), suggesting a modulatory effect of drug on oxytocin. In addition, injection of oxytocin in the nucleus

accumbens core or in the subthalamic nucleus (STN) reduces reinstatement of metamphetamine seeking behavior (Baracz et al., 2015; Baracz et al., 2016a) and reduces ethanol intake when injected intracerebroventricularly (Peters et al., 2017), suggesting a role of oxytocin on drug use. The mechanisms by which oxytocin could affect the drug-related behaviors is hypothesized to be a facilitating effect of oxytocin on the rewarding effects of prosocial behaviour at the expense of drug-related rewards (Leong et al., 2018).

Nevertheless, the studies carried out in this context do not make it possible to know what are the neurobiological mechanisms and the cerebral structures involved in the influence of the distal social factors on the phenomena of addiction.

Proximal social factors

There is to date no published study assessing directly the neurobiology of proximal social factors during drug consumption. Studies offering the choice between social reward and drug reward have assessed neurobiological substrate. One study has shown that rats choosing between the social reward and cocaine reward in a CPP paradigm have a level of oxytocin expression in the paraventricular nucleus of hypothalamus intermediate between animals experiencing only one of the two rewards (Liu et al., 2016). With the same procedure, inactivation of the core of the nucleus accumbens or the BLA shift the CPP away from cocaine toward social interaction while lesioning the AcbSh produced the opposite effect (Fritz et al., 2011b). In the study assessing the choice between volitional social reward and methamphetamine or heroin, an increased inhibitory activity in the central amygdala and inhibition of the anterior ventral insular cortex have been shown to be critical for the influence of social reward access at diminishing incubation (Venniro et al., 2018). In the rescue paradigm where social interaction does not detract from drug use, the neurobiological substrate has not yet been investigated (for review see Tomek and Olive, 2018).

Since both reward and emotion processes are involved when a peer is present during drug consumption, we could hypothesize that the prefrontal cortex and the amygdala should be involved. Given what has been reported on the role of oxytocin on prosocial behaviours and the influence of oxytocin when injected in the STN (see above), we have however investigated the effects of lesions of the STN in the influence of presence of a peer on cocaine intake. The STN is part of the basal ganglia and has been shown to regulate motivation. Indeed, lesions or high frequency deep brain stimulation of the STN decrease motivation for cocaine, while increasing that for sweet food (Baunez et al., 2005; Rouaud et al., 2010) and prevent escalation or reescalation of cocaine, heroin or alcohol intake (Pelloux and Baunez, 2017; Wade et al., 2017; Pelloux et al., 2018). In another hand, STN lesions have also been shown to blunt affective responses to sweet or bitter solutions and to alcohol (Pelloux et al., 2014; Pelloux and Baunez, 2017). We have tested the effects of STN excitotoxic lesions in rats self-administering cocaine in presence of an abstaining familiar or unfamiliar peer. STN lesions reduced the drug intake, but abolished the difference between familiar and unfamiliar peer (Giorla et al, data unpublished). In the experiment testing the effects of USV playback on cocaine intake, STN lesions blocked the influence of USV and cocaine intake remained stable (Montanari et al., 2018).

These recent experiments highlight a critical role of STN at mediating the influence of proximal social factors on drug intake. Further studies will be necessary to identify the entire network involved in these effects.

Conclusion

Understanding the modulation of social factors to drug use and drug addiction is important to improve prevention strategy for the initiation and maintenance of drug use and particularly in teenager who are particularly both vulnerable to drugs and sensitive to their peer. It is also important for adult drug addicted individuals for whom social context can either promote or prevent relapse. The social context (familiarity, experience with drugs of the congeners), substance seem to be important factors that may be critical to take into account. Many other factors remain to be investigated. A better understanding of the neurobiological substrate of these influences is necessary and only few studies have investigated this issue. The potential translation to human drug users is highly valuable and could lead to better reduction harm policies and possible future treatment strategies.

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