



Non-pharmacological factors that determine drug use and addiction

Serge H. Ahmed^{#1}, Aldo Badiani^{#2,3}, Klaus A. Miczek^{#4,5}, and Christian P. Müller^{#6}

¹Université de Bordeaux, Institut des Maladies Neurodégénératives, UMR 5293, 146 rue Léo-Saignat, F-33000 Bordeaux, France; CNRS, Institut des Maladies Neurodégénératives, UMR 5293, 146 rue Léo-Saignat, F-33000 Bordeaux, France.

²Department of Physiology and Pharmacology, Sapienza University of Rome, Piazzale Aldo Moro 5, 00185 Rome, Italy.

³Sussex Addiction Research and Intervention Centre (SARIC), School of Psychology, University of Sussex, BN1 9RH, Brighton, UK.

⁴Psychology Department, Tufts University, Bacon Hall, 530 Boston Avenue, Medford, MA, 02155, USA.

⁵Department of Neuroscience, Sackler School of Graduate Biomedical Sciences, Boston, MA, 02111, USA.

⁶Department of Psychiatry and Psychotherapy, University Clinic, Friedrich-Alexander-University Erlangen-Nuremberg, Schwabachanlage 6, 91054 Erlangen, Germany

These authors contributed equally to this work.

Abstract

Based on their pharmacological properties, psychoactive drugs are supposed to take control of the natural reward system to finally drive compulsory drug seeking and consumption. However, psychoactive drugs are not used in an arbitrary way as pure pharmacological reinforcement would suggest, but rather in a highly specific manner depending on non-pharmacological factors. While pharmacological effects of psychoactive drugs are well studied, neurobiological mechanisms of non-pharmacological factors are less well understood. Here we review the emerging neurobiological mechanisms beyond pharmacological reinforcement which determine drug effects and use frequency. Important progress was made on the understanding of how the character of an environment and social stress determine drug self-administration. This is expanded by new evidence on how behavioral alternatives and opportunities for drug instrumentalization generate different patterns of drug choice. Emerging evidence suggests that the neurobiology of non-

Corresponding author: Christian P. Müller, Section of Addiction Medicine, Department of Psychiatry and Psychotherapy, Friedrich-Alexander-University Erlangen-Nuremberg, Schwabachanlage 6, Erlangen 91054, Phone: +49 (0) 9131 85 36896, Christian.mueller@uk-erlangen.de.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

pharmacological factors strongly determines pharmacological and behavioral drug action and may, thus, give rise for an expanded system's approach of psychoactive drug use and addiction.

Keywords

drug abuse; drug addiction; drug instrumentalization; social stress; environment

1. Introduction

Drug addiction is a common psychiatric disorder. It carries a burden for individuals and for society (Nutt et al., 2007; Rehm et al., 2009; Degenhardt et al., 2009). Despite decades of intensive research, there is still no widely effective treatment available which may cure the symptoms of addiction or target its origin in a way to re-establish a controlled drug use or complete abstinence from drugs. To understand how drug addiction develops is still a major challenge for behavioral neuroscience and psychiatry. Early views on addiction development are centered around the understanding of psychoactive drugs as pharmacological reinforcer (Wise, 1994, 2002; Koob, 1992; Koob et al., 1998) and addiction as an aberrant learning mediated by the reinforcement- (Di Chiara 1995) and stress system (Koob and LeMoal, 1997; Koob et al., 2004; Koob, 2009). More recent views have acknowledged a role of various memory systems in the establishment of drug use and addiction (White, 1996; Nestler, 2002; Kelley, 2004; Hyman et al., 2006; Robbins et al., 2008; Müller and Schumann, 2011a, 2011b; Müller, 2013) and of impulse control (Ahmed et al., 2002; Vanderschuren and Everitt, 2004; Belin et al., 2008; Everitt et al., 2008; Hopf and Lesscher, 2014). Although there have been attempts to promote one explanatory model over others (Koob and Volkow, 2016; Volkow et al., 2016), there is currently no generally agreed model that captures the whole phenomenon in humans and its underlying socioeconomic, environmental and neurobiological mechanisms (Hall et al., 2015; Badiani et al., 2018; Müller, 2018).

While the pharmacological action of widely used psychoactive drugs is increasingly understood (e.g. McBride et al., 1999; Spanagel, 2009), it does not allow yet to develop a full systems view of how drugs work. This has to consider organisms with a spectrum of physical and psychological properties. Individuals live in rather complex environments with various niches (Laland et al., 2000; Badiani, 2013), multiple behavioral demands (Müller and Schumann, 2011a, 2011b) and opportunities (Ahmed, 2010) and generally in a social context (Burke and Miczek, 2014). Here we review some of the non-pharmacological determinants of psychoactive drug action, their possible contribution to addiction development and related neurobiological mechanisms. Thereby, we focus on recent developments that particularly contributed to broaden our understanding. They are related by the fact that they modulate drug use and addiction, but emerged from largely independent lines of research.

2.1. The reinforcing effects of addictive drugs: it's all about location

As noted by Kendler and colleagues in a seminal paper (2003) “a central question in the etiology of drug abuse is the extent to which the risk factors for the use or misuse of a

particular class of psychoactive substances are specific to that class or are non-specific in that they predispose the individual to the use or misuse of a wide range of such compounds". Studies conducted in adult male twins showed that genetic factors do not contribute significantly to the substance-specificity of drug abuse. In contrast, environmental influences unique to the person appear to be the sole determinants of the substance-specificity of drug abuse (Kendler et al. 2003). Interestingly, the relative contribution of genetic and environmental influences seems to be very different for cocaine versus heroin abuse. Indeed, Kendler and colleagues (2003) found that genetic factors account for two thirds of variance in the vulnerability to cocaine abuse, versus only one fifth for heroin abuse. These findings not only unveil a fundamental dissociation in the risk factors for cocaine versus heroin addiction, but also run contrary to widespread assumptions about the nature of environmental influences on drug abuse and drug preference. The role of context is usually conceptualized in the light of substantially unitary theories of drug addiction (Badiani et al. 2011). Adverse life experiences, for example, are thought to facilitate drug abuse in general (Moeller 2012; Sinha 2008). The animal models that have been developed to investigate this interaction reflect this assumption (Caprioli et al. 2007a). Similarly, drug related cues are thought to trigger drug seeking in a more or less substance-specific manner, but through largely overlapping mechanisms based on associative learning (Moeller 2012; Jasinska et al. 2014). However, as discussed in the next sections, evidence from animal and human studies is beginning to shed some light on the substance-specificity of at least some type of drug–environment interactions.

2.1.1. Cocaine versus heroin preference as a function of setting in the rat

Intravenous self-administration experiments in the rat have shown that the psychological setting has a powerful influence on the preference for opiates versus psychostimulants. In these experiments some rats were housed in the self-administration chambers (Resident rats). Other rats were transferred to the self-administration chambers only for the testing sessions (Non Resident rats). Thus, although the test environment, i.e., the self-administration chamber, was physically identical, Resident rats were tested 'at home' whereas Non Resident rats were tested 'outside the home'. Resident rats self-administered more heroin than Non Resident rats (Caprioli et al. 2008) whereas Non Resident rats self-administered more cocaine and amphetamine than Resident rats (Caprioli et al. 2007b, 2008). Resident rats were also more motivated to work for heroin than Non Resident rats. This was indicated by progressive ratio experiments in which the number of lever presses required to obtain a single drug infusion was progressively increased either within session (Caprioli et al. 2008) or over subsequent sessions (Caprioli et al. 2009). The opposite was observed for cocaine (Caprioli et al. 2007, 2009). Most important, when the rats were given the opportunity to choose between heroin and cocaine within the same session for several consecutive sessions (Caprioli et al. 2009), the Resident rats tended to prefer heroin, whereas the Non Resident rats tended to prefer cocaine, with a five-fold shift in the heroin/cocaine preference ratio (Fig. 1).

2.1.2. Setting preferences for cocaine versus heroin use as a function of drug in humans with substance use disorder

The findings in rats were translated to humans in experiments in which individuals with heroin and cocaine use disorder were asked to report on the preferred setting of use for the two drugs. They indicated opposite preferences: heroin was mostly used at home whereas cocaine was mostly used outside the home (Caprioli et al., 2009; Badiani and Spagnolo, 2013). Similar results were observed for both solitary and social use and for all routes of drug administration, indicating that these preferences were not a mere consequence of social or practical considerations (Fig. 2). The findings from the rat studies summarized in the previous section (Tab. 1) indicate that the results obtained in humans were not a trivial consequence of the addicts' conscious decision to take a sedative drug in a place where one can relax, and an activating drug where one can move around. Instead, they reflected fundamental and substance-specific influences of setting on the response to drugs.

2.1.3. Why do human and rats prefer using cocaine and heroin in different context?

To account for the ability of the setting to influence in opposite ways the reinforcing effects of heroin and cocaine, it has been proposed that the overall rewarding effects of addictive drugs are the result of a complex interaction between their central and peripheral effects and the setting of drug use (Badiani, 2013). In the presence of a mismatch between exteroceptive information (setting) and interoceptive information generated by central and peripheral drug actions, the affective valence of drug experience would be more negative than in conditions in which there was no such a mismatch. A specific instance of this theory is represented by the arousal state mismatch hypothesis. By activating noradrenergic transmission both centrally and peripherally, via blockade of norepinephrine reuptake; (Billman, 1995; Sofuoglu and Sewell, 2009), cocaine produces a state of arousal which usually occurs when an individual is exposed to exciting, potentially dangerous contexts. Such a state of arousal would be at odds with presumably quiet and safe domestic settings, hence a 'mismatch', but not with exciting non domestic settings. In contrast to the sympathomimetic effects of cocaine, heroin depresses the central nervous system and produces parasympathomimetic-like effects such as bradycardia (Haddad and Lasala, 1987; Thornhill et al., 1989; Nilsson et al., 2016). When heroin is taken at outside the home, there is a mismatch between exteroceptive information requiring alertness and vigilance and interoceptive information signaling reduced arousal and relaxation. In summary, the setting of drug use provides "an ecological backdrop" against which the central and peripheral effects of drugs are appraised. When a mismatch between exteroceptive and interoceptive information is detected, the rewarding effect of the drug is thwarted (Badiani, 2013). The sedative effects of heroin would be at odds with exciting, potentially dangerous non-home settings, resulting in another type of mismatch, but not in a domestic setting.

Preliminary support for this hypothesis comes from experiments with drugs that, like opiates, produce sedation or that, like psychostimulants, produce arousal (Fig. 3). Indeed, we found that rats self-administer more alcohol, which by acting as an allosteric agonist at γ -amino-butyric acid (GABA)_A receptors produces sedation and anxiolysis, at home than outside the home (Testa et al., 2011). This is consistent with findings from an epidemiological study in heavy drinkers (Nyaronga et al., 2009). On the other hand,

ketamine, which shares with psychostimulants the ability to activate adrenergic transmission by acting as an agonist at α - and β -adrenergic receptors (Bevan et al., 1997), is preferentially self-administered outside the home, both by humans and by rats (De Luca et al., 2011, 2012).

Two main predictions originate from the hypothesis highlighted above. The first prediction is that the positive valence of the affective response to cocaine would be greater outside the home than at home, whereas the opposite would occur for heroin. The second prediction is that in response to heroin and cocaine the activity levels of brain areas implicated in processing drug reward, including the prefrontal cortex (PFC) and the striatum (Volkow et al., 1999; Cox et al., 2009) would be influenced in opposite manner by the setting. In the following sections we will examine the findings of two recent studies aimed at investigating these two predictions.

2.1.4. The affective response to cocaine and heroin is influenced in opposite directions by the environmental context both in humans and in rats

We used ultrasonic vocalizations (USVs) in the range of 50 kHz to investigate the affective response to heroin and cocaine in the rat. It has been reported that rats emit 50-kHz USVs when exposed to natural rewarding stimuli (White et al. 1990; Knutson et al. 1998; Panksepp and Burgdorf 2000; Burgdorf et al. 2000) as well as to addictive drugs (Knutson et al. 1999; Maier et al. 2010). Consistent with the arousal state mismatch hypothesis, we found that at home, rats emit more 50-kHz USVs when self-administering heroine than when self-administering cocaine (Fig. 4). Outside the home, the rats emit more 50-kHz USVs in response to cocaine than to heroine (Avvisati et al., 2016).

These findings were extended to humans in a recent translational study by De Pirro and colleagues (2018), who used a novel test of emotional states to investigate the affective response to heroin and cocaine in humans with substance use disorder (SUD) who co-abused the two drugs. The affective state produced by heroin was appraised as more pleasant when the drug was used at home than when it was when used outside the home, whereas the affective state produced by cocaine was rated as more pleasant when the drug was used outside the home then when used at home. More specifically, the results confirmed that the shift in the affective valence of heroin occurred in combination with its sedative effects, whereas the shift in the affective valence of cocaine occurred in association with its arousing effects.

2.1.5. Drug-setting interactions in brain reward regions

A series of studies in which rats received non-contingent drug administrations have shown that drug-induced expression of immediate early genes, used as an index of neuronal activation, in the PFC and in the striatal complex is powerfully modulated by environmental context (Badiani et al., 1998, 1999; Uslaner et al. 2001a, 2001b; Ferguson et al., 2004; Hope et al., 2006; Paolone et al., 2007; Celentano et al., 2009). Most important, these studies show that the pattern of changes as a function of context is very different in the case of opiates, morphine or heroin, versus psychostimulants, such as cocaine and amphetamine.

Very recently we conducted a study to begin exploring the neural basis of drug-setting interactions in humans with SUD, using an emotional imagery task and functional Magnetic Resonance Imaging (fMRI). We hypothesized a double dissociation, as a function of drug and setting, in the activity levels of the PFC and the striatum. Indeed, the results confirmed our prediction. Interestingly, the portion of the striatum involved in the interaction was the dorsal caudate and not the ventral striatum (Volkow et al., 2006; Wong et al., 2006; Boileau et al., 2007; Cox et al., 2017). Furthermore, we found the same double dissociation bilaterally in the cerebellum, which has been recently implicated in drug addiction (for a review see: Miquel et al., 2009; Moulton et al., 2014). Indeed, the traditional view of the cerebellum as a primarily motor structure has undergone a radical revision in the past decade based on evidence indicating its role in the computation of emotional perception, the evaluation of emotional contexts, and the regulation of emotional states in relation to context-dependent tasks (Schmahmann, 1996, 2004; Schmahmann and Sherman, 1998; Scheuerecker et al., 2007; Stoodley, 2012; Buckner, 2013; Adamaszek et al., 2014, 2017; Van Overwalle et al., 2015). In summary, those findings suggest that the fronto-striatal-cerebellar network is implicated in the contextualization of drug-induced affect.

2.1.6. Drug setting interaction and vulnerability to relapse

The propensity to relapse into drug seeking after a period of abstinence is one of the defining characteristics of substance use disorders (American Psychiatric Association 2013). Relapse can be precipitated by a variety of triggers including exposure to small amounts of the drug, such as a snort of cocaine (Jaffe et al. 1989). Using an animal model of drug-induced relapse (Shaham et al., 2003), Leri and Stewart (2001) have shown that drug ‘priming’ can be substance-specific. Rats that had been trained to self-administer both heroin and cocaine relapse in fact into heroin-seeking when primed with the heroin and into cocaine-seeking when primed with cocaine. We have shown that even the priming effects of cocaine versus heroin are influenced by the setting in opposite manner (Montanari et al. 2015). Indeed, rats that had been trained to self-administer both heroin and cocaine, and were then given, after a period of abstinence, priming injections of heroin or cocaine, relapsed into heroin seeking, but not cocaine seeking at home. Outside the home, they relapsed into cocaine seeking, but not heroin seeking (Fig. 5).

2.1.7. It is all about locations

The findings discussed in the previous sections suggest that the effects of opiates and psychostimulants in both rats and humans (Tab. 1) depend on dissociable psychological and neural substrates. They also indicate that therapeutic approaches to addiction should take the peculiarities of different drug classes and the settings of drug use into account. This challenges standard unitary models of drug reward and drug addiction that focus on shared substrates of drug action and on shared neuroadaptations to drug exposure (for a discussion of this issue see also: Badiani et al. 2011, 2018; Badiani 2013, Badiani 2014). Furthermore, by emphasizing the distinctive effects of different classes of drugs and the importance of the context of drug use, these findings have potential clinical implications. For example, it would be important to verify if the setting can influence in a substance-specific manner the initial phases of drug use in humans, as seen in rats (Caprioli et al. 2007b, 2008). Another important aim for future research would be to assess the influence of the setting on the

propensity of polydrug users to relapse into using one drug instead of others, as shown in rats (Montanari et al. 2015). This might have potential therapeutic implications, especially for the prevention of relapse in real world settings, e.g. via Ecological Momentary Interventions (Epstein et al., 2009).

2.2. Escalation of drug self-administration as a result of experiences with social stress

Experience with social stress determines how readily an individual begins to seek and take drugs, escalates drug intake to a compulsive level, and relapses after abstinence periods (Sinha 2001; Sinha 2008). The host of factors determining the initiation, escalation and relapse of drug seeking and taking comprises distal genetic predispositions and proximal environmental and social triggers as well as pharmacological variables that interact with each other. Experience with several types of stress, including novelty stress causes individuals to initiate cocaine and other stimulant use earlier (Piazza and LeMoal 1996). Stressful experiences prompt more rapid transitions to high-dose and binge patterns of cocaine use (Kreek et al. 2005). Self-report studies document stronger cocaine cravings during stress imagery (Sinha et al. 1999). By contrast the link between stress and alcohol consumption is more complex and limited to stress-susceptible individuals. For the last decades preclinical laboratory models of stress have led to many inconsistent findings with regard to subsequent alcohol preference and intake (as reviewed by Pohorecky 1981, 1990; Becker et al. 2011; but see Noori et al. 2014). Here, the focus is on the understudied mechanisms via which social stress promotes alcohol and psychomotor stimulant self-administration in preclinical animal models using ethologically and experimentally validated methods. Both the intensely rewarding effects of cocaine and other drugs of abuse as well as the ostensibly aversive effects of social stress rely on the activation of the mesocorticolimbic dopamine (DA) systems which, in turn, is modulated by neuropeptides. Ever since the discovery of their amino acid sequence (Vale et al. 1981), extra-hypothalamic neuropeptides such as corticotrophic releasing factor (CRF; encoded by the CRH gene) have received considerable attention because - not the least of which - of their significant role in the neural network that mediates drug abuse initiation, escalation and relapse in preclinical models (Bernardi et al. 2017; Sarnyai et al. 2001).

Early on we observed that accumulating experiences with social defeat stress in recombinant inbred mice induces analgesia as a result of activation of endogenous opioid peptides that act on mu- and delta receptors (Miczek et al. 1982). More recently, our focus has been on brief episodes of social defeat stress and the ensuing neuroplastic changes in DA, brain derived neurotrophic factor (BDNF)- and CRF signaling that ultimately led to persistently escalated cocaine self-administration and alcohol consumption in rodent models (Miczek et al. 2008; Miczek and Mutschler 1996; Norman et al. 2015). Initially, we sought to investigate under which conditions brief episodes of mild or moderate social defeat stress escalate intravenous cocaine self-administration in adult or adolescent male and female rats and mice. By targeting the CRF/glucocorticoid system, we explored whether the effects of periodic social defeat stress can be prevented by pharmacological protection of CRF receptor subtypes or, alternatively, can also be reversed after an abstinence phase.

2.2.1. Intermittent vs. continuous social stress and IV cocaine self-administration

The activational effects of mild to moderate stress contrast with the debilitating, impairing effects of uncontrollable more intense stress. This inverted U-shaped relationship applies also to social stress (Miczek et al. 2008; Sapolsky 2015). A key variable is the intermittency of social stress. After Long-Evans rats are exposed to intermittent episodes of social defeat stress in four brief confrontations with an aggressive resident rat, they acquire subsequently cocaine self-administration more quickly, are often more resistant to progressively higher work demands for obtaining cocaine, and self-administer cocaine at higher rates during 24-h unlimited access (Fig. 6; Boyson et al. 2014; Holly et al. 2012; Leonard et al. 2017; Miczek et al. 2011; Miczek and Mutschler 1996; Shimamoto et al. 2015; Tidey and Miczek 1997). Ongoing studies in mice provide further evidence of escalated cocaine self-administration several weeks after experiencing ten intermittent episodes of social defeat stress (Yap et al. 2015; Arena et al. in progress). By contrast, prolonged exposure to social subordination stress in rats induces divergent effects, namely reduced cocaine self-administration (Miczek et al. 2011; Shimamoto et al. 2015). This latter effect is part of a depressive-like profile that is often referred to as anhedonia (Berton et al. 2006; Papp et al. 1991; Rygula et al. 2005). These initial studies emphasize how important timing of social stress episodes is in the production of consistent and robust changes in alcohol and cocaine intake.

2.2.2. Social stress in female vs. male rodents and IV cocaine self-administration

Women are more likely to initiate cocaine use at a younger age (Chen and Kandel 2002), transition from first use to dependence at a faster rate (McCance-Katz et al. 1999), consume more readily cocaine in a “binge”-like pattern (O’Brien and Anthony 2005), self-administer cocaine more often (Chen and Kandel 2002), and are more likely to relapse (Ignjatova and Raleva 2009) than men. It has been challenging to develop a preclinical model of social stress in females, although recently valiant attempts have been proposed to artificially induce a male to attack a female mouse (Harris et al. 2018; Takahashi et al. 2017). With a focus on female-female rivalry, post-partum female rodents will threaten and attack reliably an intruder female (Haney and Miczek 1989). Under these conditions, the socially stressed intruder female has revealed much larger cocaine effects than males that were subjected to the same schedule of four social defeat episodes over the course of 10 days (Fig. 7; Holly et al. 2012). Specifically, female rats displayed larger behavioral sensitization and more persistent dopamine response to a cocaine challenge ten days after the last of four defeat episodes. Importantly, from a translational perspective, females with a history of brief episodes of social defeat stress self-administered significantly more cocaine during a 24-h unlimited access “binge.” These data support the hypothesis that females with a history of brief episodes of social stress show a larger and more persistent behavioral and neural cross-sensitization as well as escalated cocaine self-administration than males. Some correlational evidence points to estrogens as contributors to the mechanistic source for the interaction between the experience with brief episodes of social defeat stress and subsequent cocaine self-administration (Becker and Koob 2016).

2.2.3. Social stress in adolescence and adult cocaine self-administration in a rodent model

Consistent evidence points to experiences with social stress not only in adulthood, but especially in adolescence as significant promoters of increased drug use (Hoffmann et al. 2000; Nelson et al. 1995; Tharp-Taylor et al. 2009). It has proven difficult to capture the essential features of social stress in adolescent rodent models for the purpose of investigating the mediating neural mechanisms that promote drug self-administration later in life. In a recent series of experiments, male resident rats were selected for their propensity to attack reliably adolescent rats during four brief encounters (Burke et al. 2016; Burke and Miczek 2015). Four brief episodes of social defeat stress during adolescence (i.e. P35-44) were sufficient to significantly escalate cocaine self-administration when the drug was available during progressively higher behavioral demands (i.e. progressive ratio schedule of cocaine reinforcement) and during a 24-h continuous access “binge” (i.e. fixed ratio schedule of cocaine reinforcement). These results extend those with adult rats that were subjected to the same intermittent social defeat protocol (Covington and Miczek 2005). Future work needs to delineate a critical period during which brief episodes of social defeat stress must occur in order to induce neuroadaptations that lead to escalated cocaine self-administration 40 days after the last stress episode. Altogether, these data show that brief episodes of social defeat stress early in life are sufficient to induce large increases in cocaine binges later in life.

2.2.4. Species-generalities of social defeat stress: focus on rat and mouse

While most preclinical research focuses on mice, rats and non-human primates, considerable insight into the neural mechanisms of social stress can be gained by studying animal species with divergent social organizations. When individuals disperse, mark and defend their territory such as, for example, tree shrews or certain species of mice and hamsters (Berdoy and Drickamer 2007; Fuchs and Flügge 2002; Greenberg et al. 2015; Huhman 2006; Kollack-Walker et al. 1997), species-specific coping mechanisms can be identified. By contrast, so-called social species such as voles, rats and non-human primates cope with an elaborate repertoire of submissive and defensive displays that enable cohesive social groups (Koolhaas et al. 2011; Von Holst 1998). In laboratory research precise control of the timing, intensity and frequency of social confrontations is implemented in order to define the necessary and sufficient conditions of social stress in mice, rats and non-human primates that result in escalated alcohol and drug self-administration.

Parametric studies have identified robust and persistent effects of brief episodes of social defeat stress in mice and rats. For example, four brief episodes, separated by three days, emerged as sufficient to engender augmented motor activation in rats upon a challenge with a low dose of amphetamine or cocaine (Covington and Miczek 2001). Similar behavioral sensitization was evident in outbred Swiss-derived and inbred C57BL/6J mice after ten brief confrontations with an aggressive resident opponent, each separated from the next by one day (Han et al. 2017; Yap et al. 2015). Ten days after the last social confrontation rats and mice began to self-administer cocaine intravenously. Two to three weeks later, they were subjected to a probe during which they were reinforced for their responding by progressively higher demands (i.e. progressive ratio schedule of cocaine reinforcement). Social stress-experienced rats were subjected to a second probe, during

which they had unlimited access to cocaine for 24 h (“binge”). Both mice and rats with a history of intermittent episodes of social defeat stress self-administered cocaine at higher rates. Specifically, mice and rats acquired cocaine self-administration at higher rates (Leonard et al. 2017; Tidey and Miczek 1996; Arena et al. unpublished data), increased cocaine self-administration at low to intermediate unit doses of cocaine during limited access sessions (Miczek and Mutschler 1996; Yap and Miczek 2007; Arena et al. unpublished) and reinstated cocaine self-administration after several weeks of extinction or abstinence (Han et al. 2017). In addition, social stress-experienced rats achieved higher break points than controls when cocaine reinforcement was scheduled after progressively higher behavioral demands (Burke and Miczek 2015; Covington and Miczek 2005). From a translational perspective, the most important and robust effect of prior experience with repeated episodes of social defeat stress is the subsequent escalation of cocaine self-administration during unlimited access (“binge”) in rats, even weeks after the last stress episode (Boyson et al. 2014; Burke and Miczek 2015; Covington et al. 2005; Covington and Miczek 2001; Holly et al. 2012; Quadros and Miczek 2009; Leonard et al., unpublished data). Mice self-administer cocaine in a “burst-and-pause” pattern, whereas most rats self-administer with metronomelike regularity, and this pattern is maintained even after social defeat stress (but see: Tornatzky and Miczek 2000). Even though variations in the social stress parameters and in the specific species of the stressed individual produce important differences in coping with stress, the escalation of cocaine seeking and taking is consistently seen after experiences with intermittent episodes of social stress.

2.2.5. Reinstatement of cocaine seeking and social stress

A particularly intriguing consequence of brief episodes of social defeat stress is their triggering long-lasting neuroadaptations. The behavioral and pharmacological evidence for these persistent adaptations is revealed several weeks after the experience of the last episode of social defeat stress. At this point in the protocol, mice have acquired and maintained cocaine self-administration, undergone two weeks of abstinence and then are exposed to the contextual cues associated with previous cocaine self-administration. When stress-experienced mice are exposed to the operandum that was previously reinforced with cocaine infusions, they increase their rate of responding. This increase in reinstated cocaine-seeking points to the long-lasting effects of brief social stress experiences (Han et al. unpublished data).

2.2.6. Intensity of social stress and alcohol consumption

The cross-sensitization between social stress episodes and drugs is readily demonstrated with psychomotor stimulants, but emerges under more limited conditions also with alcohol. An important issue in comparing the effects of social stress in males and females is how accurately the stress experiences are matched in both sexes. One strategy is to focus on male-male vs. female-female rivalries in order to engender sex-specific coping behavior (Newman et al., in preparation). Another strategy relies on a consistent stimulus animal that delivers the social stress either to males or females, usually as a result of artificial stimulation (Takahashi et al. 2017). The intensity of social stress and its frequency per unit time are key parameters that determine how subsequent alcohol consumption is affected (Fig. 8; Hwa et al. 2016; Norman et al. 2015). Brief episodes of social defeat stress in graded

intensities result in systematically escalated alcohol consumption. In male mice, ten days after having experienced daily episodes of social defeat stress while exposed to 30 attack bites engendered consumption of maximally 20-25 g/kg ethanol (20% w/v) every day for at least 4-8 weeks. The daily consumption of alcohol escalates even further to ca. 30 g/kg/day ethanol in female outbred or B6 mice (Hwa et al. 2011; Newman et al., in preparation). By contrast, when social stress is inescapable, more intense, longer and more frequent, it impairs many neurobiological functions (Sapolsky 2015), among them also cocaine self-administration and alcohol consumption (Fig. 6; Miczek et al. 2011; Norman et al. 2015; Shimamoto et al. 2015; Van Erp and Miczek 2001). The ascending limb of the inverted U delineates the activational effects of social stress on alcohol and cocaine self-administration, whereas the impairing, deleterious effects of social stress characterize the descending limb of inverted U. The neurobiological mechanisms for the two limbs of the inverted U await adequate identification.

2.2.7. Intermittent vs. continuous access to alcohol

In addition to the escalating effects of intermittent episodes of social defeat stress, a further stressful intervention that potentially escalates alcohol consumption is intermittent access to alcohol (Hwa et al. 2011; Hwa et al. 2013; Hwa et al. 2015; Simms et al. 2008). Intermittent access escalates also intravenous cocaine self-administration in rats (Kawa et al. 2016). Intermittency emerged as a key feature of access conditions to induce a persistently escalated level of alcohol consumption both in mice and rats. Specifically, 24-h access to 20% w/v ethanol in one of two concurrently available bottles every other day led to persistently and preferentially increased consumption of alcohol (Hwa et al. 2011). In a further series of experiments, the interactive effects of two stress manipulations was investigated by initially exposing B6 mice to ten intermittent episodes of social defeat stress and subsequently providing access to alcohol on alternating days in a 2-bottle choice protocol for four weeks (Hwa et al. 2016; Newman et al. 2018). Both a history of intermittent social defeat stress and intermittent access to alcohol resulted in significant escalation of alcohol consumption relative to non-stressed mice with continuous access to 2-bottle choice of water and alcohol. When male mice experienced both stressors, they drank ca. 25 g/kg/24 h alcohol for four weeks whereas non-stressed mice with continuous access consumed less than 15 g ethanol/kg per day. It will be of considerable interest to learn about the phasic and tonic changes in aminergic systems that are the basis for the intermittency effects of both social stress and alcohol access conditions.

2.2.8. Candidate mechanisms for social stress: Corticosterone and CRF interacting with mesocorticolimbic dopamine

While the actions of each stressor are based on specific neural networks (Pacak and Palkovits 2001), most types of social stress are characterized by increased HPA activity in the laboratory and in the field (Covington and Miczek 2005; Fuchs and Flügge 2002; Norman et al. 2015; Sapolsky 1990; Sapolsky 1992; Sgoifo et al. 1998). Engaging in offensive aggressive behavior or defensive-submissive behavior is accompanied by large increases in glucocorticoid activity as is evident in the winners and losers of an agonistic confrontation (Covington and Miczek 2005; Schuurman 1980; Von Holst 1969). A critical difference between the so-called stress hormones in winners and losers is the much faster

recovery to the homeostatic levels in the former relative to the latter. In brief resident-intruder confrontations that are limited to five minutes, it takes several hours for plasma corticosterone levels to return to baseline values in intruder rats (Miczek et al. 1991).

A further important feature of the corticosterone activation during brief episodes of social stress is the lack of habituation during the course of repeated social confrontations with different opponents. Plasma corticosterone values on the first day of social conflict in the intruder rat did not differ from those on the 10th day (Covington and Miczek 2005). Similarly, after 10 days of brief daily agonistic confrontations, intruder mice continued to secrete significantly elevated corticosterone (Norman et al. 2015), pointing to persistent hypothalamic–pituitary–adrenal (HPA) axis activation.

An influential hypothesis links glucocorticoids to the sensitizing influence of repeated exposure to psychomotor stimulants or stressors, supported by data from pharmacological, surgical and genetic manipulations of glucocorticoids (Marinelli et al. 1997; Piazza et al. 1991). However, it is now evident that the neural circuitry for behavioral sensitization as induced by repeated stress or stimulant drugs can be dissociated from the transition to escalated drug self-administration (Miczek et al. 2008). Pharmacological blockade of corticosterone synthesis or glucocorticoid receptors can block cocaine reinstatement (Piazza et al. 1994), diminish motivation to self-administer cocaine (Deroche-Gamonet et al. 2003). This can also reduce stress-escalated alcohol consumption during continuous or intermittent access (Newman et al. 2018).

In addition to the activation of the HPA axis, considerable evidence points to the significance of extra-hypothalamic CRF as modulator of canonical amines. Substantial data implicate the amygdaloid complex, particularly the central and basolateral nuclei, intercalated cells and the projections to the bed nucleus of the stria terminalis as sites of expression and action for CRF and CRFR1 (Jennings et al. 2013; Silberman et al. 2013; Zorrilla et al. 2014). In several experimental protocols for investigating the link between stress and drug taking, CRF was found to increase in the amygdala in alcohol-withdrawing rats (Pich et al. 1995). CRF receptor expression is also upregulated after a history of alcohol consumption (Sommer et al. 2008). CRF signaling in the amygdala has been implicated in the transition to dependence as a result of repeated cycles of access to alcohol followed by abstinence (Breese et al. 2005; Spanagel et al. 2014).

CRF signaling in subregions of the ventral tegmental area (VTA) has received less attention than other brain regions that receive projections from the amygdala such as the bed nucleus of stria terminalis (BNST), lateral hypothalamus and hippocampus (Pitkänen et al. 2000). Yet, the interactions between CRF and DA in the VTA are critical for the motivation of many conditioned and unconditioned behaviors including also escalated drug seeking and taking (Holly and Miczek 2016; Koob and Volkow 2010; Wise 2004). It remains unresolved how ostensibly aversive, stressful events as well as intensely rewarding drug experiences result in increased DA activity in the VTA and escalated alcohol and cocaine seeking and taking. Electrophysiological, in vivo microdialysis and fast scan voltammetry methods provided correlative evidence for increased DA activity in animals that were exposed to social defeat, electric shock pulses or other stressors (Abercrombie et al. 1989; Anstrom et

al. 2009; Brischoux et al. 2009; Imperato et al. 1991; Tidey and Miczek 1996). Intra-VTA microinfusion of a non-selective CRF antagonist such as alpha-helical CRF can block DA release that is evoked by a footshock stressor (Wang et al. 2005). CRF R1 knockdown in the VTA reduces stress-induced cocaine seeking in mice (Chen et al. 2014). In a binge model of alcohol consumption, VTA DA neurons of juvenile mice showed potentiation of NMDAR currents which was blocked by a CRFR1 antagonist (Sparta et al. 2013).

The role of CRF signaling in the VTA is demonstrated in studies of social stress that led to the escalation of intravenous cocaine self-administration and oral alcohol consumption in mice and rats (Burke et al. 2016; Han et al. 2017). Intra-VTA microinfusion of a CRFR1 antagonist significantly decreased alcohol intake in mice and rats that accessed alcohol intermittently or continuously in a two-bottle choice protocol (Hwa et al. 2013). The blockade of intake was even more pronounced when the mice had experienced social defeat stress previously and consequently escalated their alcohol consumption (Hwa et al. 2016; Newman et al. 2018). Importantly, CRFR1 antagonist treatment was also shown to increase DA release in the nucleus accumbens (NAc) (Fig. 9; Hwa et al. 2016). In addition to the prominent role of CRFR1 in stress-escalated alcohol consumption, initial evidence has been collected that the intra-VTA microinjection of antagonists of CRF binding protein (CRFBP) and CRFR2 reduce alcohol intake in a binge model of alcohol consumption (Albrechet-Souza et al. 2015).

Activation of both CRFR1 and CRFR2 in the VTA during social defeat stress is necessary for the induction and later expression of behavioral and neural cross-sensitization to cocaine and escalated cocaine self-administration in a 24-h “binge” (Boyson et al. 2014). Intra-VTA antagonism of CRFR1 in the posterior VTA and CRFR2 in the anterior VTA during each of four intermittent social defeat episodes prevented subsequent escalated cocaine self-administration in a 24-h binge and later, after forced abstinence, cocaine seeking in a reinstatement test (Fig. 10; Holly et al. 2016; Leonard et al. 2017). These findings point to CRF in the VTA as a critical signal during the social stress episode that engenders not only a phasic response, but also induces a persistent elevation in CRF tone (Holly et al. 2016). We hypothesize that the CRF signal is critical for a subpopulation DA VTA cells that ultimately result in escalated motivation for alcohol and drug consumption.

Interpretation of the functional significance of DA release in the mesocorticolimbic projections has been complicated by the observation that both intensely rewarding and aversive stimuli activate these cells. Moreover, the activation of DA by ostensibly aversive experiences such as social defeat stress escalates cocaine self-administration and alcohol consumption as well as dopamine release in the accumbens and prefrontal cortex.

2.3. Drug instrumentalization in drug use and addiction

It is generally agreed that drug addiction constitutes a maladaptive behavior (Nesse and Berridge, 1997). In contrast, controlled drug use was suggested to have under certain circumstances real and/or subjectively perceived beneficial effects on behavioral performance, the achievement of life goals and well-being. This view is supported by a large number of interviewing studies with drug users (Lende and Smith, 2002; Lende et al., 2007;

Hagan et al., 2009; Singh et al. 2014; Morgan et al., 2013; Wolf et al., 2014; Ross et al., 2018). It can explain at a psychological level why psychoactive drug consumption is established and well maintained by the majority of humans around the globe without necessarily leading into a drug addiction. Human beings are not developmentally determined to automatically establish this behavior. Instead, they have to learn it. This learning is based on the capability to learn and teach it (Hopitt and Laland, 2013; Müller et al., 2012; Kline, 2015; Müller, 2015), given the ability to modify food consumption according to non-nutritional needs (Rodriguez and Wrangham, 1993; Lozano, 1998; Huffman, 2003; Müller and Schumann, 2011a). The learning of drug use behaviors may, thus, include a de novo learning by trial-and-error, e.g., for newly emerging substances (Hassan et al., 2017), or a learning by cultural inheritance (Dean et al., 2012; Hassan et al., 2013; Hopitt and Laland, 2013; Kline, 2015; Müller, 2015).

Drug users, who acknowledge subjectively perceived psychological benefits of drug consumption (Baum-Baicker, 1985; Chick, 1999; Peele and Brodsky, 2000), are not consuming in an arbitrary fashion. If drug use would be solely determined by the pharmacological properties of a drug, one would expect the use of a particular drug emerging under all individual predispositions (sets) and all environmental contexts (settings) to a comparable degree. But this is not the case for any of the known psychoactive drugs. It was recently suggested that non-addicted users consume drugs because the subsequent effects on mental states can be used for a better performance of goal directed behaviors (Müller and Schumann, 2011a, 2011b; Müller, 2017). Thereby, psychoactive drugs are '*instrumentalized*'. An instrument can be conceived as "something that helps to achieve a goal, which would not be achievable or require a higher workload without the use of the instrument" (Müller and Schumann, 2011a). Drug instrumentalization refers to a two-step psychological process which consists of two interlinked processes: A.) the psychoactive drug is sought and consumed in order to change the present mental state of a person into a previously learned mental state, and B.) subsequently, the induced mental state allows for a better performance of another, previously established behavior (Müller and Schumann, 2011a, 2011b; Müller, 2017).

Mental states are the subjectively perceived working modes of the brain. They influence how the external and internal environments are perceived, how memory is formed and retrieved, and how autonomic and behavioral responses of an organism are organized. Mental states change frequently, and are essentially determined by the different functional working modes of the modulatory transmitter systems, such as, e.g., the dopaminergic-, serotonergic-, acetylcholinergic-, noradrenergic-, and various neuropeptidergic systems of the brain (Müller and Schumann, 2011a). These rather slowly acting ascending systems control the fast information processing in diencephalic and telencephalic target regions of the brain (Castren, 2005; Müller et al., 2011). Importantly, these modulatory transmitter systems determine the efficacy of an organism in performing previously established instrumental behaviors, i.e., the question of how effective an expected goal can be reached. Whenever an organism pursues a specific goal by performing a behavior, it can be assumed that there is usually one particular mental state which allows for most efficient performance. In real life, however, the challenge is frequently to perform a goal directed behavior when not being in an optimal mental state for it, e.g., driving a car when tired and inattentive. Humans can do

this to a certain extent, but less efficiently. It requires more effort and/or a positive outcome is less certain. Psychoactive drugs can work as instruments in that they can change a present mental state into a desired mental state in a short and predictable time frame (Müller and Schumann, 2011a, 2011b; Müller, 2017).

For psychoactive drugs, distinct ‘instrumentalization goals’ have been reported in humans, often described as drug taking motivations (Brown et al., 1980; Maloff et al., 1981; Brown, 1985; Cooper et al., 1995; Baum-Baicker, 1985; Chick, 1999; Heath, 2000; Peele and Brodsky, 2000; Lende et al., 2007). While classical reinforcement theory would assume that pharmacological drug action in the brain is basically the same under all those circumstances, recent findings suggest that quite distinct pharmacological actions and brain pathways serve different drug instrumentalization goals. Here we discuss current progress in modeling drug instrumentalization in animals in order to investigate underlying neurobiological mechanisms. It should be noted that those models draw essentially from previously established models of drug seeking and self-administration, from context dependent drug choice and behavioral alternatives as described above.

Since drug instrumentalization is more than just drug seeking and self-administration, it requires also a more elaborate experimental design to investigate it. If drug instrumentalization is demonstrated in a healthy organism, a goal directed behavior needs to be established. Then it has to be shown that drug self-administration really improves parameters of the goal directed behavior. In a non-healthy organism, first a disease model has to be established and proven as a valid model for a challenged (e.g. stressed) or pathological mental state (e.g. depression). Then it has to be shown that drug self-administration is more pronounced in this mental state and finally reverses the state towards a normal (control) state (Müller, 2018). Here we discuss in how far that has been shown for distinct instrumentalization goals and which insights into neurobiological mechanisms this has yielded. For those human instrumentalization goals where no direct animal evidence is available, plausible mechanisms derived from pharmacological profiles of the used drugs are discussed.

2.3.1. Improved social interaction

Social interaction can be considered as a group of goal directed behaviors with innate rewarding effects (Matthews et al., 2005; Panksepp and Lahvis, 2007). Several psychoactive drugs can change the mental states in a way which facilitates social interactions with conspecifics. They include alcohol (Glynn et al., 1983; Bradizza et al., 1999; Kuntsche et al., 2005), marijuana (Zvolensky et al., 2007; Bonn-Miller et al., 2007; Hartwell et al., 2012), cocaine (O’Malley et al., 1985; Lende, 2005), and other psychostimulants (White et al., 2006; Davey et al., 2007; Hassan et al., 2013), nicotine and caffeine (Eissenberg and Balster, 2000; Cauli and Morelli, 2005), when used in a low to medium dose range (Segal, 1985; Cato, 1992; Boys et al., 1999, 2001; Simons et al., 2000; Boys and Marsden, 2003; Morgan et al., 2013).

In humans, alcohol reduces social inhibition, the discomfort in social situations, and social anxiety, and increases social approach behavior (Baum-Baicker 1985; Peele and Brodsky 2000; Carrigan et al. 2008; Booth and Hasking 2009). These effects occur after lower doses

of alcohol and are mediated by multiple mechanisms in the brain (McBride et al. 2002; Tupala and Tiihonen 2004; Harris et al. 2008; Spanagel, 2009). An important mediator is the interaction of alcohol with GABA_A-receptor signaling. GABA is the most abundant inhibitory transmitter in the brain that is crucial for conditioned suppression of behavior (Feldmann et al., 1997). Alcohol can enhance GABAergic activity at the GABA_A-receptor, which is directly responsible for a reduction in anxiety and behavioral disinhibition. Alcohol is well known to increase monoaminergic signaling in the mesolimbic system of the brain (Di Chiara and Imperato 1988; Spanagel, 2009; Müller and Homberg, 2015). These neurochemical effects were shown to reduce the reward threshold of the brain (Koob et al. 1998), which may enhance the incentive value of social reward (Ikemoto and Panksepp 1999; Ross and Young 2009). However, alcohol can have disruptive effects on social cognition most likely mediated by its action in higher cortical areas (Burnett et al. 2010; Uekermann and Daum 2008).

Psychostimulant drugs, such as cocaine, amphetamine, methylphenidate, methamphetamine, and methylenedioxymethamphetamine (ecstasy, MDMA), are also self-administered by humans in a social context, such as, e.g., in clubs or at parties (Britt and McCance-Katz 2005; White et al. 2006). Psychostimulants in a low-medium dose range enhance general arousal and increase attention. During periods of prolonged social interaction, they suppress fatigue (Fischman and Schuster 1980) and enhance aggression (Emley and Hutchinson 1983). Rats acutely increase their intake of cocaine following exposure to an aggressive dominant resident animal that they cannot avoid or escape from (Miczek and Mutschler, 1996). This increase in drug intake can be interpreted, at least partly, as an attempt to instrumentalize some of the psychopharmacological effects of cocaine to better cope with some aspects of the negative psychological experience caused by an otherwise uncontrollable social stressor.

All used psychostimulant drugs in this context are known to acutely enhance extracellular activity of DA, serotonin (5-HT), and noradrenaline (NA) in the mesolimbic system (Ritz and Kuhar 1989; Ritz et al. 1990) by their interaction with respective monoamine transporters (Johanson and Fischman 1989; Seiden et al. 1993; Green et al. 2003; Müller et al. 2007a; Pum et al. 2007; Nutt et al., 2015). Thereby, noradrenergic effects may account for the sustained attention (Aston-Jones et al. 1999), 5-HT may mediate the anxiolytic (Schwartz et al. 1998; Ho et al. 2004; Müller et al. 2008) and aggression-enhancing effects of these drugs (Licata et al. 1993; Quadros et al. 2010), while DA may enhance salience of social stimuli (Berridge and Robinson, 2003). Animal models of psychoactive drug self-administration with the goal to improve social interaction are, to the best of our knowledge, not established yet.

Several psychoactive drugs have been reported to be used by non-addicts to facilitate social interactions. Exaggerated drug use for this instrumentalization goal, however, may also facilitate the transition to habitual drug use and addiction (e.g. Wagner and Anthony, 2002; Müller, 2017).

2.3.2. Facilitation of sexual behavior

Mating behavior is a goal directed behavior with very high rewarding properties (Patrick and Maggs, 2008). Sexual behavior in humans may include a behavioral complex that encompasses partner seeking, approach behavior, up to actual sexual intercourse. Numerous drugs which are instrumentalized to improve social interactions also work well for sexual behavior facilitation. Drugs frequently reported to be used for this purpose are alcohol, cannabis, amphetamines, ecstasy, and cocaine (Maier, 1926; Boys et al., 1999, 2001; Boys and Marsden, 2003). There is evidence for an association between alcohol drinking, drunkenness and the likelihood for sexual intercourse in humans, particular in adolescents and young adults (Lavikainen et al 2009; Patrick and Maggs 2008; Wells et al. 2010).

Psychostimulant drugs may serve to improve chances for sexual behavior, but may later interfere with physical performance during sexual intercourse in males (Maier 1926; Waldorf et al. 1991). In particular the acute effects on DA in the mesolimbic system might render an individual more responsive to sexual cues and making a potential partner appear more 'attractive' (Koob et al. 1998; Ikemoto and Panksepp, 1999). Currently, there are no animal models that convincingly demonstrate voluntary self-administration of psychoactive drugs to enhance mating behavior in conditions that resemble the human situation, i.e. with numerous rules installed in the shape of passive avoidance. Thus, the biological mechanisms of drug instrumentalization for this goal warrant investigation.

2.3.3. Improved cognitive performance and counteracting fatigue

Good cognitive abilities improve the outcome of complex goal directed behaviors in animals and humans (Arria and Wish, 2006). During wakefulness and depending on work load, the cognitive capacity usually declines over the activity phase of an organism. Pharmacological means that artificially extend periods of high cognitive capacity may, consequently, appear to be beneficial for the individual. While there is little evidence for drugs to significantly increase cognitive performance in a healthy individual with full mental capacity, there is evidence suggesting that mild impairments due to exhaustion, fatigue or mood swings can be attenuated with psychoactive drugs (Boys and Marsden, 2003; Lende et al., 2007; Morgan et al., 2013; Singh et al., 2014; Padwa et al., 2014; Brand et al., 2016). Performance pressure is often perceived as stressful and psychoactive drugs become a mean of "every day doping" for neuro-enhancement (Wolff and Brand, 2013; Ross et al., 2018).

A widely used psychoactive drug to keep people awake is caffeine, a major psychoactive ingredient of coffee, tea, chocolate, and soft drinks. Caffeine when consumed post-trial was shown to enhance the consolidation of long-term memories in humans (Borota et al., 2014). During waking, the brain adenosine levels, steadily increase and may eventually trigger fatigue and sleep (Huston et al. 1996; Porkka-Heiskanen et al. 1997; Hong et al. 2005). Caffeine is an antagonist of adenosine A1- and A2A receptors, and by that way blocks action of accumulating adenosine (Cauli and Morelli 2005).

Another widely used legal drug is nicotine, the active compound in tobacco (Le Foll and Goldberg 2006). Recent research suggests that rats can learn to increase their intake of nicotine before a cognitively demanding task (Nesil et al., 2015). This behavior could

represent an attempt to instrumentalize the cognitive-enhancing effects of nicotine in anticipation of a cognitive effort. Nicotine is a nicotinic acetylcholine (ACh) receptor agonist (Markou 2008). Nicotinic ACh-receptor stimulation in the brain facilitates attention and subsequently learning and memory (Thiel, 2003; Sarter et al., 2005). Nicotine was shown to enhance attention and cognitive performance in animals (Decker et al. 1995; Hahn and Stolerman 2002) and in non-smoking humans (Rezvani and Levin 2001). In human smokers, however, cognitive abilities usually decline after smoking cessation. This can be reversed by nicotine (Mansvelder et al. 2006). In the brain, nicotine increases not only ACh-, but also NA activity (Mitchell 1993; Wonnacott 1997). Both may interact in their attention improving effects. Nicotinic ACh-receptor stimulation has also a direct effect on mesolimbic DA activity (Pontieri et al., 1996; McBride et al. 1999; Wonnacott et al. 2000; Markou, 2008). By these mechanisms, nicotine may enhance the incentive properties non-drug reinforcer (Harrison et al. 2002; Kenny and Markou 2006).

Psychostimulant drugs have been widely used to increase cognitive performance over long periods of time (Grinspoon and Hedblom 2005; Davey et al. 2007; McCabe et al. 2005; Arria and Wish 2006; White et al. 2006; Sussman et al. 2006; Teter et al. 2006; Lende et al. 2007). At doses that induce no or only a minor 'high' and little withdrawal effects, psychostimulants were shown to increase arousal and attention in humans for long periods of time (Higgins et al. 1990; Stillman et al. 1993) or attenuate sleep-deprivation induced deficits (Fischman and Schuster 1980). In particular the acute effects on noradrenergic activity may mediate this action (Johanson and Fischman 1989; Usher et al. 1999; Seiden et al. 1993; Green et al. 2003). Animal models of psychoactive drug-self administration with the goal to improve cognitive performance are, to the best of our knowledge, not established yet. One possible first step to overcome these difficulties would be to test if and to what extent animals can instrumentalize a psychotropic drug that has no or only weak rewarding effects. For instance, modafinil is a psychostimulant drug that has cognitive-enhancing effects with weak rewarding effects in rodents when available for i.v. self-administration (Deroche-Gamonet et al., 2002). If animals are able to instrumentalize the cognitive-enhancing effects of modafinil, then we should expect that they should adjust their intake as a function and in anticipation of the specific cognitive demands and domains of different tasks. In addition, we should also expect that animals may reduce or even stop their intake of modafinil if provided with alternative means or shortcuts to solve the same cognitive tasks. This research will be pivotal to demonstrate drug instrumentalization in animals, with little confounding by the search of drug reward. Alternatively, we could also design tasks where animals are offered a choice between at least two drugs of abuse while they are pursuing a well-identified nondrug-related goal. This will complement previous research on animals' drug of choice as a function of the context (Badiani, 2013). In this situation, we should expect that animals would opt for the drug that produces psychopharmacological effects that are the most congruent, or the least incongruent, with the pursuit of that goal. If such a model was developed and validated, it could be used to begin to study the neural basis of drug instrumentalization. Of particular interest, it will be important to know how the brain represents drugs as instruments, as opposed to drugs as goals, and how it compares these representations with those of behavioral alternative means.

Taken together, accumulating evidence supports the view that several psychoactive drugs are instrumentalized specifically to enhance cognitive performance. Long term regular use of these drugs can induce tolerance for the cognitive effects and even lead to cognitive deficits (Vonmoos et al., 2013; Wolff et al., 2014; Havranek et al., 2015; Müller, 2017).

2.3.4. Facilitated recovery and coping with psychological stress

Modern societies require humans to perform many behaviors at high cognitive demand for long periods of time (Anders, 1961). Individuals have little time during their activity periods to efficiently recover and possibly cope with activity related psychological stress. Several psychoactive drugs were reported to improve recovery and to enhance stress coping (Segal, 1985; Baum-Baicker, 1985; Peele and Brodsky, 2000; Amendt, 2003; Morgan et al., 2013). Humans instrumentalize alcohol (Cooper et al., 1988, 1992; Kuntsche et al., 2005), cannabis (Bonn-Miller et al., 2007; Zvolensky et al., 2007), cocaine (Waldorf et al., 1991; Lende, 2005), methamphetamine (Lende et al., 2007), barbiturates, benzodiazepines, and other sedative anxiolytic drugs (Boyd et al., 2009) to cope with stress (Segal, 1985; Lader, 1994; Boys et al., 1999, 2000; Bradizza et al., 1999; Perkins, 1999; Boys and Marsden, 2003; De Las Cuevas et al., 2003).

Two of the major pharmacological effects of alcohol are the inhibition of excitatory glutamatergic transmission and enhancement of inhibitory GABAergic activity (Spanagel 2009). Barbiturates and benzodiazepines also modulate the GABA_A-receptor (Ito et al. 1996), though at other binding sites than alcohol, and allosterically enhance responses to the inhibitory transmitter GABA (Allison and Pratt 2003). Enhanced GABA_A-receptor signaling may reduce innate anxiety and conditioned anxiety. By their interaction with neocortical GABA_A-receptors (Feldman et al. 1997), sedative drugs like alcohol may attenuate memory of aversive events (Curran, 1991).

The interplay between stress and alcohol consumption has been extensively investigated in animal studies. Thereby, various types of stress have been modeled. Acute physiological stress was modeled by, e.g., foot shock, restraint, or forced swim stress. Psychological stress was induced by, e.g., overcrowding, social defeat or social isolation. While there is the general view that stress is associated with increased alcohol drinking, findings in animal models are equivocal, in that they show a reduction, no effect or an increase of consumption after stress. In contrast, chronic stress, e.g. by maternal separation or chronic isolation, in particular when exposed at young age, tend to be more reliable inducer of enhanced alcohol consumption (Spanagel, 2009; Vengeliene et al., 2008; Becker et al., 2011). Stress typically refers to a disruption of homeostasis by external or internal events. While the effects of various stressors on homeostasis in the brain and on body function are now well characterized (de Kloet et al., 1998; Koob, 1999; Oliveira et al., 2017), little is known about whether alcohol self-administration would partially re-establish homeostasis. A stressed brain/organism is different from an unstressed one, with partially chronic dysregulations. Those can cause alcohol to have different effects than in a normal organism (Müller et al., 2017). This is something that should actually be tested when doing drinking studies in animals. On the other hand, alcohol can have stress effects by itself, i.e. chronic self-

administration can induce allostasis in various functional systems of the brain and body periphery (Huber et al., 2017; Becker et al., 2011).

Psychoactive drug self-administration to improve coping with stress has been observed in animal models for various drugs. Intravenous self-administration of heroin is increased when rats are exposed to mild stress in the shape of unavoidable food shocks (Shaham and Stewart, 1994). While the stress appears to enhance the reinforcing efficacy of the drug, it remained unclear whether endogenous stress markers and stress-related behavior were directly attenuated by the drug. Physical and emotional social defeat stress can increase morphine consumption in mice. Stress induces an increase of FosB immunoreactivity in mesocorticolimbic brain areas (Nikulina et al., 2008; Cooper et al., 2017), effects that resemble changes during establishment of drug addiction (Perotti et al., 2008). In how far morphine would reduce behavioral signs of stress and re-establish homeostasis or enhances drug-like effects in the brain, remains to be determined.

A wide spread illicit psychoactive drug that is instrumentalized to cope with stress is cannabis (Boys et al., 1999, 2000). The main psychoactive compound of cannabis is 9-tetrahydrocannabinol (THC; Iversen, 2000), an exogenous ligand at cannabinoid (CB) receptors (Mechoulam et al., 1998). It was shown that a direct CB1 receptor activation may effectively enhance the extinction of aversive memories (Marsicano et al., 2002).

Interestingly, social stress was also found to increase the self-administration of non-sedating drugs, such as cocaine, in animals and humans. It was speculated that this might improve an active coping and enhance a “flight or fight” response (Müller and Schumann, 2011a). Stress modifies the function of the mesolimbic DA system (Miczek et al., 2011; Kreibich et al., 2009) and its excitatory (Garcia-Keller et al., 2016) and inhibitory inputs (McLaughlin et al., 2003; Polter et al., 2017), in a way to cross-sensitize the system to subsequent psychostimulant behavioral effects and to their self-administration propensity (Cruz et al., 2011; Miczek et al., 2011). A single episode of social defeat stress can increase the mesocorticolimbic expression of the immediate early gene cFos, which is an indicator of neuronal activation (Miczek et al., 2011; Cooper et al., 2017). Psychostimulant drugs like cocaine increase cFos (Miczek et al., 2011; Schöpf et al., 2015). However, cocaine can counteract the social defeat stress effects on c-fos activation in distinct brain regions (Nikulina et al., 1998; Miczek et al., 2011). This effect may serve as an example of how cocaine exerts a seemingly paradoxical effect in a stressed animal that may work towards a re-establishment of homeostasis. However, the same studies showed that days later an augmented effect emerges, which suggests that potential acute instrumentalization effects of the drug revert after a short time and render the organism in a drug-sensitized state that actually facilitates addiction-development (Miczek et al., 2011). In the brain, μ - and κ -opioid receptor signaling and its activation by endogenous enkephalin and dynorphin, respectively, was enhanced after stress (McLaughlin et al., 2003; Nikulina et al., 2008; Polter et al., 2017). This effect was directly linked to stress-induced immobility and analgesia. In the VTA-NAc projection it may trigger the enhanced sensitivity for cocaine reward and the reinstatement of drug self-administration (McLaughlin et al., 2003; Miczek et al., 2011; Polter et al., 2014). Cocaine self-administration in order to cope with social stress was

predominantly observed in animals with low spontaneous activity (Kabbaj et al. 2001), which suggest a dependency of instrumentalization efficacy on personality traits.

Overall, numerous psychoactive drugs are currently used to facilitate recovery and coping with stress by non-addicts. A chronic and escalating drug use for this instrumentalization goal may result in restlessness and a hyper-anxious state during withdrawal, and may result in compulsive drug use to overcome this state (Müller, 2017).

2.3.5. Self-medication for psychiatric disorders and mental problems

Mental disorders are characterized by the prolonged persistence of a mental state that is subjectively perceived as aversive and/or imposes significant problems and suffering for one's own or others well-being. Underlying mental state changes may constitute a temporary, recurrent, or continuous breakdown in the homeostasis of one or more modulatory transmitter systems of the brain (Khantzian, 1997; Kapur, 2003; Krishnan and Nestler, 2008; Quednow et al., 2010; Schneider et al., 2017). It is now well documented that certain psychiatric disorders are associated with enhanced consumption of particular types of drugs and frequently with an addiction to those drugs (Robbins and Everitt, 1999). Drug action in those patients may be completely different from normal organisms and their benefits beyond simple pharmacological reinforcement. It was reported by patients that psychoactive drugs may provide at least a temporary relief from suffering and/or enhanced 'functioning' in everyday life (e.g. Lende et al., 2007; Padwa et al., 2014). This may also account for mental states that are perceived as aversive, e.g. being in a depressed mood, but not fulfilling the strict diagnostic criteria of a psychiatric disorder (Boys et al., 2001; Boys and Marsden, 2001; Boyd et al., 2006; Morgan et al., 2013).

In humans of western societies, the most frequently used legal drug for this instrumentalization goal is alcohol. Numerous studies suggest that a moderate alcohol consumption is associated with better health, more close friendships, and more family support than total abstinence (Peele and Brodsky, 2000; Rodgers et al., 2000; Taylor et al., 2005; Mondaini et al., 2009; Skogen et al., 2009). Moderate alcohol consumption was also linked to lower rates of stress-induced depression (Lipton, 1994; Tizabi et al., 2018), and reduced the risk of somatic diagnoses as well as anxiety and depression compared to complete abstainers (Peele and Brodsky, 2000; Skogen et al., 2009). Evidence supports the view that alcohol is consumed to provide relief from negative affect (Peele and Brodsky, 2000; Bulley et al., 2016). There is a considerable co-morbidity of the diagnoses 'major depression' and 'alcohol addiction' in clinical populations (Brown et al., 1995; Preuss et al., 2002). However, this encompasses at least two different populations with possibly, distinct pathogenic pathways. A prevalent major depression may cause alcohol abuse and addiction. Alternatively, an initially established alcohol addiction may give rise to depression development (Room, 2000; Schuckit et al., 1997, 2006, 2007, 2013).

Mammalian cell membranes predominantly consist of sphingolipids, cholesterol and (glycero)phospholipids. Sphingolipids are composed of a hydrophilic head group and a ceramide molecule. Ceramide consists of a D-erythro-sphingosine and a fatty acid of variable length with 2-36 carbon atoms in the acyl chain (Sandhoff, 2010). Sphingolipid molecular interactions are coordinated by membrane cholesterol (Brown and London, 1998;

London and London, 2004; Megha et al., 2006). The interactions of sphingolipids with cholesterol result in an ordered membrane structure with stable domains in the liquid-ordered- or gel-like phase (Simons and Ikonen, 1997; Harder and Simons, 1997; Brown and London, 1998; London and London, 2004; Megha et al., 2006). Such domains spontaneously segregate from other glycerophospholipids in the membrane. Due to their membrane floating properties, these domains were named lipid rafts (Simons and Ikonen, 1997; Eggeling et al., 2009). The most abundant sphingolipid, sphingomyelin, can be hydrolyzed to ceramide, which has the tendency to spontaneously self-associate. This process results in the formation of ceramide-enriched membrane microdomains that may fuse to large ceramide-enriched macrodomains (Veiga et al., 1999; Grassmé et al., 2001a, 2001b, 2002a; Fanzo et al., 2003). The generation of a very high concentration of receptor proteins, e.g. for neurotransmitters, within small plasma membrane domains seems to be prerequisite for transmembrane signaling via the clustered receptors (Gulbins and Kolesnick, 2003). Decreasing levels of either cholesterol or sphingomyelin in the brain, which was observed after learning or stress in animals (Huston et al. 2013; Oliveira et al., 2017), also changes the composition of lipid rafts. This can directly affect receptor affinity, their signaling properties, and subsequent internalization (Fantini et al., 2009; Ramstedt and Slotte, 2006; Nothdurfter et al., 2010, 2013).

The generation of ceramide within extracellularly-oriented lipid rafts/membrane domains, i.e. in the outer leaflet of the plasma membrane, is mediated by the enzyme acid sphingomyelinase (ASM; Grassmé et al., 2001a; Henry et al., 2013). Several neutral- and alkaline sphingomyelinases have been identified, defined by the optimal pH for respective enzyme activity (Henry et al., 2013; Kornhuber et al., 2015). A disruption of the sphingolipid rheostat in the brain can be one pathogenic pathway into depression/anxiety. ASM over-expressing mice (tgASM) showed higher ASM activity and ceramide production in the hippocampus (Gulbins et al., 2013). Increased ceramide levels in the hippocampus resulted in reduced levels of neurogenesis, neuronal maturation, and neuronal survival (Gulbins et al., 2013, 2015), which is normally associated with a depression-like phenotype (Santarelli et al., 2003). Consistent with these previous observations, tgASM mice showed a depression/anxiety-like phenotype in several tests including the novelty-suppressed-feeding test, the splash-test, open field, light-dark-box, and forced-swim test (Gulbins et al., 2013; Kornhuber et al., 2014; Müller et al., 2015). However, ceramides do not directly control synaptic structure or function in the hippocampus (Gulbins et al., 2013). Antidepressant drugs, many of which appear to be functional inhibitors of ASM (Albouz et al., 1986; Kornhuber et al., 2010, 2011), reversed the effects of chronic unpredictable stress on behavior in wild type and tgASM animals, but not in ASM KO mice. These findings provide a common stress- as well as genetically triggered pathway into a sphingolipid-mediated depression (Gulbins et al., 2013; Kornhuber et al., 2014; Grassme et al., 2015; Müller et al., 2015).

The clinically observed co-morbidity of depression with alcohol addiction appears to have two causal pathways. In one pathway, alcohol addiction develops first with a depression occurring as induced by the alcohol consumption. This pathway is supported by findings showing that alcohol enhances the activity of ASM and results in increased ceramide levels in cell cultures (Pascual et al., 2003; Saito et al., 2005), in rodent models (Saito et al., 2010;

Liangpunsakul et al., 2012), and in humans (Reichel et al., 2010, 2011). In another pathogenetic pathway, however, the depression manifests first leading to an enhanced alcohol consumption and finally addiction (Room, 2000; Schuckit et al., 1997, 2006, 2007, 2013). In those patients, alcohol was suggested to be used and instrumentalized to ameliorate the suffering from depression/anxiety (Müller and Schumann, 2011a, Müller, 2015). How those seemingly paradoxical effects of the alcohol work in the brain of a depressed organism was recently identified. Mice with a hyperfunction of acid sphingomyelinase are not only depressive, but consume also significantly more alcohol and escalate consumption after withdrawal (Müller et al., 2017). Free-choice alcohol consumption in a two-bottle free-access paradigm, but not forced injections of equivalent amounts of alcohol, partly reversed the ASM hyperactivity in tgASM mice. Importantly, the alcohol self-titration also normalized the depressive symptoms up to the level of WT animals. ASM hyperactivity resulted in an attenuation of the most abundant sphingomyelin species in the NAc and dorsal hippocampus (DH). Alcohol drinking in WT mice had a similar effect on the sphingolipid rheostat. In tgASM mice, however, alcohol drinking had a paradoxical effect in that it partially reversed the genetically induced deficit in the NAc, but not in the DH. These findings not only suggest a highly brain-region selective control of the sphingolipid rheostat, but also locally selective effects of the self-administered alcohol. Depressive tgASM mice also showed a gross attenuation of DA- and 5-HT tissue levels in the brain. Alcohol drinking almost completely reversed this deficit in the tgASM mice, but had an opposite effect in WT mice (Müller et al., 2017). This study showed in particular that it is not only the pharmacological effect of the alcohol that matters, but the possibility for the organism to self-titrate the consumed amount. It also highlights that a psychoactive drugs can have quite distinct effects depending on the mental state of an organism (Müller and Kornhuber, 2017). These findings confirm animal models which showed that voluntary alcohol self-administration may reduce depressive symptoms and by that way sustain high consumption rates (Ciccocioppo et al., 1999; Tizabi et al., 2018).

Posttraumatic stress disorder (PTSD) is associated with an enhanced consumption and addiction to psychoactive drugs (Stewart, 1996; Roberts et al., 2015). Acute severe stress causes an enhanced responsiveness to mild stressors at endocrine and behavioral level. It enhances the reinforcing action of psychostimulant drugs, alcohol and opiates, and their self-administration and resistance to extinction acutely, as well as long after the stress has ended (Piazza et al., 1989; Pizzimenti et al., 2017; Logrip et al., 2012). In most cases, a PTSD emerges first and triggers development of drug abuse and addiction. However, precedent drug abuse may also enhance vulnerability to stressful events. The self-medication hypothesis that is now well supported by human data suggests that patients consume psychoactive drugs to control their PTSD symptoms (Khantzian, 1985, 1997). Alcohol was reported to dampen arousal and reduce physiological reactivity to stressors (Stewart, 1996; Sher et al., 2005). Thereby, a tension reduction may act as a negative reinforcer and further drive alcohol consumption (Conger, 1951). Alcohol may also reduce fear and avoidance behavior and intrusive cognitive symptoms, such as distressing recollections of the aversive event (Stewart, 1996). Depending on the type of stress used to model PTSD, an increase in consumption may not occur immediately, but with some time delay (van Erp and Miczek, 2001, van Erp et al., 2001). It is now understood how acute severe stress sensitizes the

reward system for psychoactive drug effects and by that way makes it more vulnerable to addiction development (Yap and Miczek, 2008; Manjoch et al., 2016). The mechanisms of how the self-administration of psychoactive drugs can revert some of the brain dysfunctions induced by PTSD, however, are currently less well understood.

Patients with schizophrenia show an increased consumption of nicotine and cannabis (Hughes et al., 1986; Mobascher and Winterer, 2008). While those drugs may exacerbate positive symptoms, such as hallucinations (Perry and Perry, 1995), aversive negative symptoms, such as the flattening of affect, and cognitive impairments, might be improved by nicotine (Rezvani and Levin, 2001; Potvin et al., 2003). It is well known that schizophrenic patients consume nicotine and marijuana/cannabis at a level that exceeds that of the normal population, frequently resulting in a comorbid drug addiction. Reports from patients and experimental investigations suggest that those drugs may ease suffering from negative symptoms and, to a certain degree, improve cognitive impairments (Dome et al., 2010; Newhouse et al., 2011).

The improvement of cognitive deficits in schizophrenia has been shown in a rat model. Schizophrenia-like cognitive deficits in latent inhibition and a delayed non-matching to sample test were induced by maternal immune activation (MIA) with lipopolysaccharide (LPS) during gestation. MIA did not enhance nicotine self-administration in the offspring. Nicotine self-administration ameliorated the MIA-induced cognitive deficits, but had no effects in a saline control group (Waterhouse et al., 2018).

In a recent study, nicotine effectively improved cognitive deficits in a mouse model of schizophrenia resembling a human condition. A human genome wide association study in schizophrenia patients yielded the rs16969968 single nucleotide polymorphism (SNP) of the human *CHRNA5* gene as significantly associated. This gene codes for the $\alpha 5$ subunit of the nicotinic ACh receptor (nAChR; Schizophrenia Working Group of the Psychiatric Genomics Consortium; 2014). This SNP was associated with enhanced risk for schizophrenia as well as tobacco smoking. It leads to a substitution of aspartic acid by asparagine at the 398 locus of the human $\alpha 5$ subunit of the nAChR. The functional implications of this SNP were subsequently investigated in a mouse model. Transgenic mice expressing the human $\alpha 5$ SNP showed deficits in social behavior and in sensorimotor gating, both typical symptoms of schizophrenia. Disrupted $\alpha 5$ subunit function was associated with a decrease in GABA interneuron-driven prefrontal cortex layer II/III microcircuit activity. This effect directly translates to the frontal brain hypoactivity observed in schizophrenia patients. Continuous nicotine administration for 2 days via mini pump delivery normalized the firing of neurons selectively in $\alpha 5$ -deficient mice (Koukoulis et al., 2017). These findings suggest that nicotine self-administration is particularly effective in ameliorating cortical dysfunction in a subpopulation of schizophrenics, those with a polymorphism of the $\alpha 5$ nAChR (Koukoulis et al., 2017; Müller and Kornhuber, 2017).

Altogether, several psychoactive drugs were found to be useful by individuals suffering from psychiatric disorders to temporarily ameliorate at least some disease symptoms or subjective suffering from them. Prolonged and escalating drug use for this goal, however, may

eventually potentiate disease symptoms and result in a co-morbid addiction disorder (Robbins and Everitt, 1999; Müller, 2017).

2.3.6. Sensory curiosity – expanded perception horizon

Boredom is a mildly aversive mental state, perceived in the absence of novel sensory input. One may readily assume that the search for novelty and new environments is a driving force to expose an individual to stimuli and environments where new stimulus–reward contingencies exist that can be learned (Kelley et al., 1990; Thiel et al., 1999). Novelty and new sensations can be considered as primary reinforcer in humans and animals (Zuckerman, 1990; Weil, 1998). Novelty seeking has been shown to be an at-risk phenotype for drug abuse with a shared genetic base (Zuckerman, 1990; Mielenz et al., 2018). A psychoactive drug-induced mental state change may well constitute a novelty effect, at least during the first consumption episodes. Unique subjective drug effects are reflected in the discriminative stimulus properties of a drug in humans and animal models (Overton, 1968; Stolerman, 1992). After repeated exposure, the drug effects on mental state are not novel anymore and other than the rewarding novelty effects are required to maintain drug seeking and consumption. If there are no other instrumentalization goals emerging, the consumption of this particular drug may cease (Nichols, 2004).

A particular group of psychoactive drugs used to change sensation and perception of the external world and to increase self-understanding and self-discovery are hallucinogenic drugs, including natural compounds, like mescaline and psilocybin, as well as semi-synthetic drugs, like lysergic acid diethylamide (LSD) (Cato, 1992; Boys et al., 1999, 2000; Tupper, 2002, 2003; Boys and Marsden, 2003; Nichols, 2004; Morgan et al., 2013). A similar instrumentalization might also apply to the enactogenic drug, MDMA (Boys et al., 1999, 2000), which has a hallucinogenic profile and induces a unique feeling of ‘divine oneness’ with the world (Halberstadt and Nichols, 2010). Phencyclidine, ketamine and γ -hydroxybutyrate (GHB) are drugs used in the club and rave scene. At high dose, they can have profound hallucinogenic effects (Weir 2000; Britt and McCance-Katz, 2005; Wolff and Winstock, 2006; Hassan et al., 2017). Also cannabis was reported to be consumed in order to expand self- and environmental perception (Bonn-Miller et al., 2007; Zvolensky et al., 2007).

In a dull and familiar environment, with no or very little valuable stimulation, like that in a standard operant box, animals may also take drugs as a mean to obtain and experience some artificial stimulation. They may also use drugs as a mean to amplify or increase the gain of the brain reward circuits to otherwise neutral environmental stimuli (Ahmed and Koob, 2005; Keramati et al., 2017). Of course, in such impoverished environments, animals have also no access to alternative valuable rewards and thus their drug use could also be partly motivated by the search of novelty reward. Long-term and escalating drug use for this instrumentalization goal may result in dangerous activities and schizophrenia-like psychoses (Müller, 2017).

2.3.7. Euphoria, hedonia, and high

The pursuit of euphoria or happiness is probably the greatest motivation in human life (Tatarkiewicz, 1976; Marcuse, 1984). In humans, this subjective feeling is frequently occurring during/after the receipt of a primary or secondary reward, or with the unexpected change in reward contingencies, i.e. when a formerly meaningless stimulus now predicts reward availability or a formerly useless behavior. While the biological function of the subjective perception of euphoria is still under debate (Berridge, 2000; Alcaro and Panksepp, 2011), it appears that the amount of euphoria we perceive is related to human well-being. It was argued that mood enhancement alone and subsequent facilitation of virtually all kind of goal directed behaviors is a psychological benefit gained from psychoactive drug use (Peele and Brodsky, 2000; Lende and Smith, 2002). Psychoactive drugs like heroin, morphine, cocaine, amphetamine, methamphetamine, methylphenidate, and MDMA in middle to high doses can induce a strong feeling of euphoria and an emotional 'high' (e.g. Resnick et al., 1977; Javaid et al., 1978). They are used for this reason by non-addicts (Boyd et al., 2006; Teter et al., 2006; McCabe et al., 2007; Zacny and Lichtor, 2008). A certain degree of euphoria can also be induced by other drugs of abuse, such as alcohol, cannabis, LSD, benzodiazepines, and nicotine (e.g. Boys et al., 1999, 2000; Boys and Marsden, 2003; Sher et al., 2005). However, the latter are usually not reported to be primarily consumed for this reason.

Psychoactive drugs were claimed to produce their strong euphoria-inducing effects by a massive increase of the extracellular DA activity in the NAc (Di Chiara and Imperato 1989; Di Chiara 1995), which is a key structure of the brain's reward circuitry (Olds and Milner 1954; Wise 1980, 1994). The mechanisms how the pharmacologically distinct drug classes converge on the mesolimbic DA signaling have been elucidated in detail (Koob 1992; Di Chiara and North 1992; Volkow et al. 1997; Ameri 1999; McBride et al. 1999). In humans, drug-induced euphoria is usually more intense than naturally occurring euphoria. And so is the amplitude and slope of the DA increase in the NAc (Müller and Huston, 2007; Samaha and Robinson, 2005). However, several conceptual problems emerged with this hypothesis (Salamone et al. 1996), thus, leading to a conceptual and anatomical distinction of stimulus induced "wanting" and "liking" (Robinson and Berridge, 1993; Berridge and Robinson, 2003). According to this view, DA may not code for the euphoria, but rather for "wanting" and signal a reward-related prediction error (Hollerman and Schultz 1998; Schultz 2000). This may not only apply for pleasant appetitive stimuli, but also for aversive stimuli (Young et al. 1993; Brischoux et al. 2009; Matsumoto and Hikosaka 2009). While DA may still have an outstanding role for reinforcement learning, drug use and addiction (Robbins and Everitt 1996; Ikemoto and Panksepp 1999), it is no longer the principal signal associated with euphoria or 'liking'. Euphoria and the 'liking' of a stimulus may, instead, be mediated by endogenous opioid- and GABAergic mechanisms (Berridge and Robinson 2003; Berridge and Kringelbach, 2015). Besides those two, also other transmitter systems and signaling cascades have been identified as modulators of the euphoria-inducing and reinforcing effects of psychoactive drugs (Nestler and Aghajanian 1997; Koob 1999; Everitt and Wolf 2002; Kalivas and Volkow 2005; Williams and Adinoff 2007; Heilig and Koob 2007; Müller and Homberg, 2015).

However, chronic over-instrumentalization of a drug for this instrumentalization goal frequently results in tolerance to the euphoria effects and a subsequent escalation of intake, which may result in an addiction development (Koob and LeMoal, 1997; Heilig and Koob, 2007).

2.3.8. Other instrumentalization goals

Besides the above discussed instrumentalization goals, there are other behaviors that humans report to benefit from psychoactive drugs in a non-addicted consumption. Other instrumentalization goals include the 'Improvement of physical appearance and attractiveness' (Garattini et al. 1978; Goldstein 1990; Boys et al. 1999, 2000; Boys and Marsden 2003), the 'Facilitation of spiritual and religious activities' (Abel, 1980; Streatfeild, 2001; Jay, 2010), and the 'Improvement of physical performance' (e.g. sport doping) (Müller and Schumann, 2011a, 2011b, Müller, 2017). Since they may apply exclusively to humans, no animal models have been developed so far. An important motive for drug self-administration in animals and humans is also to self-medicate for physical problems and its indicator, pain (Colpaert et al., 2001). However, to the best of our knowledge there are no mechanistic insights available that go beyond pharmacological action of the drugs used for those purposes.

2.4. Drug seeking and taking depends on behavioral alternatives

2.4.1. Drugs as goals and instruments

To take stock, evidence suggests that individuals seek and take drugs not merely or even primarily as pharmacological rewards but also as means or instruments to reach other valued ends or goals (Müller and Schumann, 2011a; Pickard, 2012; Sullivan and Hagen, 2002). Beside their rewarding effects, drugs of abuse also produce specific psychopharmacological effects, some of which can be instrumentalized to facilitate the pursuit and attainment of certain specific goals (Badiani et al., 2011; Khantzian, 1997; Müller and Schumann, 2011a). For instance, at low to moderate doses, alcohol can produce anxiolytic effects that certain individuals intently seek and use to overcome their anxiety in certain social settings to better pursue and attain other pursuits that they value (e.g., approach to and interaction with a future potential mate) (de Wit and Sayette, 2018; Edwards, 2000). In other words, alcohol would not be a goal in and of itself but a mean to reach a different nondrug-related goal. In the real world, these two facets of drug use – which are relatively easy to separate in theory – are often entangled, mainly because people tend to use drugs both as a mean and as an end (Edwards, 2000; Müller and Schumann, 2011a; Zinberg, 1984). This may contribute to explain why the recourse to drugs as instruments has been relatively overlooked until recently. Nevertheless, serious consideration of this recourse seems to uniquely explain some important aspects of drug use that were previously difficult to account for from an exclusive drug reward-centric perspective, such as, for instance, the psychopharmacological specificity of drug use discussed above. Indeed, since different drugs produce different psychopharmacological effects, the recourse to drug instrumentalization is expected to be largely drug-specific, a prediction that is borne out by mounting evidence from research on both humans and animals (Badiani, 2013; Badiani et al., 2011).

2.4.2. Behavioral alternatives modulate the recourse to drug instrumentalization

Importantly, the recourse to drug instrumentalization should not only depend on how the psychopharmacological effects of a specific drug help an individual to pursue and attain certain nondrug-related goals but also on whether other relevant behavioral alternatives to attain those same goals are available. Such recourse is thus predicted to be particularly likely and/or prevalent in situations or settings that offer no or little behavioral alternatives. This may contribute to explain why drug use and substance use disorders tend to be more prevalent or endemic in human populations that live in economically and socially impoverished environments in which, by definition, access to behavioral alternatives is lacking or limited (Alexander, 2008; Hart, 2013; Hartnoll, 1990; Heilig et al., 2016; Orford, 2013). For instance, though smoking occurs in several different socioeconomic contexts, there is nevertheless a pronounced socioeconomic gradient in the prevalence of drug use and substance use disorders (Jarvis and Wardle, 2006; Peretti-Watel et al., 2009). Limited access to behavioral alternatives may also contribute to explain why abstinence is difficult to maintain in the long term as it is frequently interrupted by recurring relapses. It is indeed difficult to give up drug use if one has limited access to relevant behavioral substitutes. A critical aspect of addiction treatment consists in helping addicts to find meaningful and accessible behavioral alternatives to drug use (McKay, 2017; Miller et al., 2011). This aspect is even a core principle of some prominent therapies, such as contingency management therapy (Dutra et al., 2008; Higgins et al., 1991; Stitzer and Petry, 2006). Consistent with this view, when spontaneous recovery occurs, it does when addicts undergo important life changes, generally in their late 30s that open up a wide range of new alternative opportunities, e.g. a new fulfilling job and/or social relationships (Heyman, 2009; Heyman, 2013). However, since in underprivileged environments, nondrug reward alternatives are also limited, one cannot exclude the possibility that people also seek drugs as pharmacological rewards, i.e., drug rewards as goals, and not only or even predominantly as means or instruments to achieve other nondrug-related pursuits. At present, it is difficult to see how one could tease out apart these different, albeit not mutually exclusive, interpretations. As we will see below, the same difficulty also exists in experimental research on animal drug self-administration.

2.4.3. Behavioral alternatives in animal models of drug addiction

The lack of access to behavioral alternatives during access to drugs for self-administration is endemic to mainstream research on laboratory animals since its inception in the early 60s (Ahmed, 2005, 2010, 2018). Animals frequently used in this research, such as rats, descend from wild social species, but in experimental settings they are typically raised and tested in asocial or nonsocial environments that one would consider to be extreme – abnormal and even traumatic if applied to a human individual (Heilig et al., 2016). For instance, laboratory rats used in addiction research are typically raised and tested in a state of relative isolation and/or extreme environmental poverty since weaning. When one considers this state of affairs seriously, it becomes plausible that animals, like humans, could use drugs not only or even predominantly to seek drug reward, but also as a mean to self-medicate a negative psychological condition and/or to adjust to an impoverished environment (Alexander and Hadaway, 1982; Heilig et al., 2016; Wolffgramm, 1991). This has led some researchers to propose that the standard drug self-administration setting may represent a good model of

impoverished environments that favor drug use in humans (Ahmed, 2005; Ahmed and Koob, 2005). This hypothesis seems to be generally consistent with research showing that drug taking can be strongly modulated by the availability of behavioral alternatives during drug access. This evidence has been reviewed extensively elsewhere (Ahmed, 2005, 2010, 2012, 2017) and will only be briefly summarized below. However, it is important to note at the outset that this evidence is currently only suggestive and does not provide yet unequivocal support for drug instrumentalization in laboratory animals. This is mainly because, apart perhaps from some drug self-medication studies, involving the use of non-addictive substances (de Roode et al., 2013; Huffman, 2003; Shurkin, 2014), there is just an emerging formal demonstration that animals could use drugs as pharmacological instruments to pursue and attain other nondrug-related goals. Such a demonstration requires methodological approaches able to distinguish in animals between drug use as a goal and drug use as a mean or instrument. This is not entirely surprising, however, as it is generally difficult to disentangle goals versus means in behavioral research on animals (Allison, 1993; Staddon, 1979; Timberlake and Allison, 1974).

Nevertheless, there is some suggestive evidence, mainly from experimental research on animals that adapt drug use as a function of the current situation and/or internal physiological state. For instance, there is evidence that rats take more cocaine when hungry and in a context where food is absent (Carroll et al., 1979). This increase in drug intake could reflect, at least partly, an attempt by rats to instrumentalize the powerful anorexigenic effects of cocaine to suppress or reduce hunger when no other behavioral alternative is available. However, this interpretation should be tempered by the fact that hungry rats do also take more opiates which are known to have orexigenic effects (Carroll et al., 1981).

The access to behavioral alternatives during drug access could reduce drug use by reducing the need to recourse to drug instrumentalization. By far, the most used behavioral alternative in experimental research on animals is a behavior or response that is reinforced by a palatable food reward, typically sucrose or saccharin (Ahmed, 2005, 2010, 2012, 2017; Ahmed et al., 2013). In a typical experiment, animals have thus the choice between taking a drug and engaging in an alternative course of action aimed at obtaining and consuming a food reward. This food alternative-centric design may reduce the generalizability of this research. However, recent unpublished research in rats indicates that similar findings can also be obtained with other behavioral alternatives, such as positive social interaction (Marco Venniro and Yavin Shaham, personal communication).

The influence of a behavioral alternative on drug use is not absolute, but largely depends on the prevailing choice setting (Ahmed, 2017). For instance, access to a palatable food reward during access to i.v. heroin for self-administration decreases heroin use only when the effort required to obtain the drug is relatively important (Lenoir and Ahmed, 2008) or when the choice between the two rewards is mutually exclusive (Fig. 11) (Ahmed, 2017). For instance, when rats must choose either saccharin or heroin, the large majority opts for the nondrug alternative, even when relatively high doses of heroin are available for choice (Lenoir et al., 2013; Madsen and Ahmed, 2015; Secci et al., 2016; Tunstall et al., 2014; Vandaele et al., 2016). In some experiments, all rats stop to use heroin entirely in favor of the behavioral alternative and this abstinence persists during several weeks (Venniro et al.,

2017b). Similar results have also been found when the drug available for exclusive choice was cocaine (Augier et al., 2012; Cantin et al., 2010; Guillem and Ahmed, 2017; Kearns et al., 2016; Kerstetter et al., 2012; Lenoir et al., 2007; Madsen and Ahmed, 2015; Perry et al., 2013; Tunstall and Kearns, 2013, 2016; Tunstall et al., 2014; Vandaele et al., 2016), methamphetamine (Caprioli et al., 2015a; Caprioli et al., 2017; Caprioli et al., 2015b; Venniro et al., 2017a) or nicotine (Huynh et al., 2017; Panlilio et al., 2015). This spontaneous abstinence behavior can be interpreted as an animal model of contingency management therapy for addiction treatment (Ahmed, 2010; Venniro et al., 2017a). Briefly, in contingency management, addicts also face a mutually exclusive choice between drug use and a nondrug behavioral alternative, typically a voucher that can be used subsequently to purchase nondrug commodities (Higgins et al., 1991). Recent research on animals has shown that relapse after cessation of contingency management involves activation of a glutamatergic pathway that links the anterior insular cortex to the central amygdala pathway (Venniro et al., 2017a).

This research demonstrates that introducing behavioral alternatives during drug access can lead under some circumstances to reduced drug intake and even precipitate long-term abstinence. However, the behavioral interpretation of this observation remains largely uncertain. In particular, we do not know if animals stop using drugs because behavioral alternatives represent alternative means that reduce the need to recourse to drug instrumentalization, or merely because they represent competing reward goals. The crux of the problem is that we lack valid models of drug instrumentalization in animals. When an animal takes a specific drug in a particular context or setting, it is difficult to know if it seeks to exploit some of the resulting drug effects as a mean or instrument to pursue and attain other nondrug-related goals, which are often unspecified or unknown and/or if it pursues the drug rewarding effects as a goal in and of itself. This is further compounded by the fact that in a typical drug self-administration study, we ignore what are the specific nondrug-related goals that animals are hypothesized to pursue, if any.

3. Summary and Outlook

Non-pharmacological factors in psychoactive drug abuse and addiction have been recognized for some time. How they act at neurobiological level is now emerging for some of them. Thereby, they may still appear as independent factors mediated by largely distinct brain mechanisms. However, in human reality of a drug consumer they act together. Related to the reviewed progress, drug taking can be considered as a drug, acting on an individual that is submitted to a social environment, to stress, but having opportunities to choose between drugs and even instrumentalize them to improve efficacy of other behaviors. There are also behavioral alternatives to drug consumption. All these factors, and presumably some more, ultimately shape the behavioral repertoire of an individual in which drug seeking and taking is initially just one among many expressed behaviors. Under specific multifactorial, actively chosen and passively incurred environmental conditions (Müller et al., 2012), the behavioral repertoire may change. In that, drug related behaviors increase, and alternatives drop in their likelihood. In this respect the discussed mechanisms converge and may, each on its own right contribute to such a development. On the other hand they also offer ways of prevention and strategies for addiction treatment.

While the pharmacological effects of psychoactive drugs are increasingly understood and neurochemical alterations during addiction development identified, it remains to be acknowledged that this is still insufficient for a satisfactory understanding of drug abuse and addiction. Current neuropharmacological models fail at several crucial points. First, they frequently do not incorporate essential observations on human drug abuse and addiction (Hall et al., 2015; Badiani et al., 2018; Müller, 2018). They are still too much restricted to one or few systems in their causal accounts. And, the mechanisms of controlled drug use, which is for many drugs an acceptable behavior (Heath, 2000; Müller and Schumann, 2011a, 2011b), are frequently conceived as identical with those of addiction, which is clearly pathologic. As such no overarching system's concept of controlled drug use and addiction is currently available. Second, the predictions that the available neuropharmacological models make for addiction prevention and treatment are relatively poor. Hardly any of the pharmacotherapies derived from those models work to an extent that allows us to claim them as theory based rational treatment (McCreary et al., 2015; Müller, 2018). While the findings reviewed above seriously question the common models that focus mainly on the pharmacological drug action in the brain, they also provide a perspective for future research strategies and envision alternative addiction prevention and treatment approaches.

Thereby, a driving force may be the increasingly emerging insights into the neurobiology of non-pharmacological mechanisms of drug abuse and addiction. This should have implications on how drug use and addiction might be conceptualized in the future. Neither controlled drug use nor addiction can be understood as the consequence of dysregulations in a single brain target or transmission system. Nor can single functional pathways or systems in the brain, like the reward system, fully account for highly individual and complex drug action and long term effects. An expanded system's approach needs to address multiple dimensions. Thereby, the "system" should be no longer a pathway in the brain, the brain, or even the brain with a surrounding organism, but expanded to the environment and the virtually always present interaction with it. It may even be necessary and useful to systematically develop our understanding of the "environment" concept as passively incurred versus actively chosen and shaped (Laland et al., 2000; Müller et al., 2012). In fact, there is no drug effect on the brain alone, no effect on the organism alone, but always on the organism in a particular environment with active as well as passive interactions (Müller et al., 2012). Likewise do all drug-related behaviors, from searching to consumption, take place in an environment that may or may not be shaped and searched out by the drug user (Laland et al., 2000).

Active as well as passive environmental interactions of the drug consuming individual receive now a peripheral physiological as well as neurophysiological base in our understanding, which emerges as a strong determinant of the pharmacological drug effects. An expanded system's understanding of drug abuse and addiction should, therefore, incorporate mental states (sets), passive environmental conditions (settings), active environmental conditions (stress responses and behavioral alternatives) as well as the manifold drug instrumentalization opportunities. Individualized treatment approaches of drug addiction may also benefit from recognizing the disorder as a multi-causal and multi-dimensional development.

Acknowledgements

S.H.A. was supported by the French Research Council (CNRS), the Université de Bordeaux, and the Fondation pour la Recherche Médicale (FRM DPA20140629788). A.B. received Strategic Development Funding from the University of Sussex. K.A.M. received support from US National Institutes of Health grants R01-DA031734 and R01-AA013983. C.P.M. was supported by the Interdisciplinary Center for Clinical Research Erlangen, Projects E13 and E22, and by research grant MU2789/8-1 from the Deutsche Forschungsgemeinschaft.

Abbreviations

Ach	acetylcholine
ASM	acid sphingomyelinase
BDNF	brain derived neurotrophic factor
BNST	bed nucleus of stria terminalis
CB	cannabinoid
CRF	corticotrophic releasing factor
CRFBP	corticotrophic releasing factor binding protein
CRFR	corticotrophic releasing factor receptor
DA	dopamine
DH	dorsal hippocampus
5-HT	5-hydroxytryptamine/ serotonin
fMRI	functional magnetic resonance imaging
GABA	γ -amino-butyric acid
GHB	γ -hydroxybutyrate
HPA	hypothalamic–pituitary–adrenal
LPS	lipopolysaccharide
LSD	lysergic acid diethylamide
MDMA	methylenedioxymethamphetamine/ ecstasy
MIA	maternal immune activation
NAc	nucleus accumbens
NA	noradrenaline
nAChR	nicotinerbic acetylcholine receptor
PFC	prefrontal cortex
USVs	ultrasonic vocalizations

PTSD	posttraumatic stress disorder
SNP	single nucleotide polymorphism
SUD	substance use disorder
tgASM	acid sphingomyelinase over-expressing
THC	9-tetrahydrocannabinol
VTA	ventral tegmental area
WT	wild type

References

- Abel EL, 1980 *Marihuana: The First Twelve Thousand Years*. Plenum Press, New York.
- Abercrombie ED, Keefe KA, DiFrischia DS, Zigmond MJ, 1989 Differential effect of stress on in vivo dopamine release in striatum, nucleus accumbens, and medial frontal cortex. *J. Neurochem* 52, 1655–1658. [PubMed: 2709017]
- Adamaszek M, D'Agata F, Ferrucci R, Habas C, Keulen S, Kirkby KC, Leggio M, Mariën P, Molinari M, Moulton E, Orsi L, Van Overwalle F, Papadelis C, Priori A, Sacchetti B, Schutter DJ, Styliadis C, Verhoeven J, 2017 Consensus Paper: Cerebellum and Emotion. *Cerebellum* 16, 552–576. [PubMed: 27485952]
- Ahmed SH, Kenny PJ, Koob GF, Markou A, 2002 Neurobiological evidence for hedonic allostasis associated with escalating cocaine use. *Nat. Neurosci* 5, 625–626. [PubMed: 12055635]
- Ahmed SH, 2005 Imbalance between drug and non-drug reward availability: a major risk factor for addiction. *Eur. J. Pharmacol* 526(1–3), 9–20. [PubMed: 16263108]
- Ahmed SH, 2010 Validation crisis in animal models of drug addiction: beyond non-disordered drug use toward drug addiction. *Neurosci. Biobehav. Rev* 35, 172–184. [PubMed: 20417231]
- Ahmed SH, 2012 The science of making drug-addicted animals. *Neuroscience* 211, 107–125. [PubMed: 21864653]
- Ahmed SH, 2017 Trying to make sense of rodents' drug choice behavior. *Prog. Neuropsychopharm. Biol. Psychiat*, in press.
- Ahmed SH, 2018 “A walk on the wild side” of addiction: the history and significance of animal models, in: Pickard H, Ahmed SH (Eds.), *The Routledge Handbook of Philosophy and Science of Addiction*. Routledge, New York, pp. 192–204.
- Ahmed SH, Koob GF, 2005 Transition to drug addiction: a negative reinforcement model based on an allostatic decrease in reward function. *Psychopharmacology (Berl)* 180(3), 473–490. [PubMed: 15731896]
- Ahmed SH, Lenoir M, Guillem K, 2013 Neurobiology of addiction versus drug use driven by lack of choice. *Curr. Opin. Neurobiol* 23(4), 581–587. [PubMed: 23428657]
- Albouz S, Le Saux F, Wenger D, Hauw JJ, Baumann N, 1986 Modifications of sphingomyelin and phosphatidylcholine metabolism by tricyclic antidepressants and phenothiazines. *Life Sci.* 38, 357–363. [PubMed: 3945166]
- Albrecht-Souza L, Hwa LS, Han X, Zhang EY, DeBold JF, Miczek KA, 2015 Corticotropin releasing factor binding protein and CRF₂ receptors in the ventral tegmental area: modulation of ethanol binge drinking in C57BL/6J mice. *Alcohol Clin. Exp. Res* 39, 1609–1618. [PubMed: 26247973]
- Alcaro A, Panksepp J, 2011 The SEEKING mind: primal neuro-affective substrates for appetitive incentive states and their pathological dynamics in addictions and depression. *Neurosci. Biobehav. Rev* 35, 1805–1820. [PubMed: 21396397]
- Alexander BK, 2008 *The globalisation of addiction: a study in poverty of the spirit*. Oxford University Press, New York.

- Alexander BK, Hadaway PF, 1982 Opiate addiction: the case for an adaptive orientation. *Psychol. Bull* 92(2), 367–381. [PubMed: 7146233]
- Allison J, 1993 Response deprivation, reinforcement, and economics. *J. Exp. Anal. Behav* 60(1), 129–140. [PubMed: 16812695]
- Allison C, Pratt JA, 2003 Neuroadaptive processes in GABAergic and glutamatergic systems in benzodiazepine dependence. *Pharmacol. Ther* 98, 171–195. [PubMed: 12725868]
- Amendt G, 2009 *No Drugs No Future*. Europa Verlag, Hamburg.
- Ameri A, 1999 The effects of cannabinoids on the brain. *Prog. Neurobiol* 58, 315–348. [PubMed: 10368032]
- American Psychiatric Association, 2013 *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.
- Anders G (1956). *Die Antiquiertheit des Menschen, Band 1: Über die Seele im Zeitalter der zweiten industriellen Revolution* [The obsolescence of human beings, volume 1: The soul in the age of the second industrial revolution]. Munich: Beck.
- Anstrom KK, Miczek KA, Budygin EA, 2009 Increased phasic dopamine signaling in the mesolimbic pathway during social defeat in rats. *Neuroscience* 161, 3–12. [PubMed: 19298844]
- Arria AM, Wish ED, 2006 Nonmedical use of prescription stimulants among students. *Pediatr. Ann.* 35, 565–571. [PubMed: 16986451]
- Aston-Jones G, Rajkowski J, Cohen J, 1999 Role of locus coeruleus in attention and behavioral flexibility. *Biol. Psychiatry* 46, 1309–1320. [PubMed: 10560036]
- Augier E, Vouillac C, Ahmed SH, 2012 Diazepam promotes choice of abstinence in cocaine self-administering rats. *Addict. Biol* 17, 378–391. [PubMed: 21955224]
- Avvisati R, Contu L, Stendardo E, Michetti C, Montanari C, Scattoni ML, Badiani A, 2016 Ultrasonic vocalization in rats self-administering heroin and cocaine in different settings: evidence of substance-specific interactions between drug and setting. *Psychopharmacology (Berl)* 233, 1501–1511. [PubMed: 26960696]
- Badiani A, 2013 Substance-specific environmental influences on drug use and drug preference in animals and humans. *Curr. Opin. Neurobiol* 23, 588–596. [PubMed: 23622777]
- Badiani A, Spagnolo PA, 2013 Role of environmental factors in cocaine addiction. *Curr. Pharm. Des* 19, 6996–7008. [PubMed: 23574438]
- Badiani A, Oates MM, Day HE, Watson SJ, Akil H, Robinson TE, 1998 Amphetamine-induced behavior, dopamine release, and c-fos mRNA expression: modulation by environmental novelty. *J. Neurosci* 18, 10579–10593. [PubMed: 9852594]
- Badiani A, Oates MM, Day HE, Watson SJ, Akil H, Robinson TE, 1999 Environmental modulation of amphetamine-induced c-fos expression in D1 versus D2 striatal neurons. *Behav. Brain Res* 103, 203–209. [PubMed: 10513588]
- Badiani A, Belin D, Epstein D, Calu D, Shaham Y, 2011 Opiate versus psychostimulant addiction: the differences do matter. *Nat. Rev. Neurosci* 12(11), 685–700. [PubMed: 21971065]
- Badiani A, Berridge KC, Heilig M, Nutt DJ, Robinson TE, 2018 Addiction research and theory: a commentary on the Surgeon General's Report on alcohol, drugs, and health. *Addict. Biol* 23, 3–5. [PubMed: 28224686]
- Baum-Baicker C, 1985 The psychological benefits of moderate alcohol consumption: a review of the literature. *Drug Alcohol Depend.* 15, 305–322. [PubMed: 4053968]
- Becker HC, Lopez MF, Doremus-Fitzwater TL, 2011 Effects of stress on alcohol drinking: a review of animal studies. *Psychopharmacology (Berl)* 218, 131–156. [PubMed: 21850445]
- Becker JB, Koob GF, 2016 Sex differences in animal models: focus on addiction. *Pharmacol. Rev* 68, 242–263. [PubMed: 26772794]
- Belin D, Mar AC, Dailey JW, Robbins TW, Everitt BJ, 2008 High impulsivity predicts the switch to compulsive cocaine-taking. *Science* 320, 1352–1355. [PubMed: 18535246]
- Berdoy M, Drickamer LC, 2007 *Comparative social organization and life history of Rattus and Mus*. In: Wolff JO, Sherman PW (eds) *Rodent societies: an ecological and evolutionary perspective*. University of Chicago Press, Chicago and London, pp 380–392.

- Bernardi RE, Broccoli L, Hirth N, Justice NJ, Deussing JM, Hansson AC, Spanagel R, 2017 Dissociable role of corticotropin releasing hormone receptor subtype 1 on dopaminergic and D1 dopaminergic neurons in cocaine seeking behavior. *Front. Behav. Neurosci* 11, 221. [PubMed: 29180955]
- Berridge KC, 2000 Measuring hedonic impact in animals and infants: microstructure of affective taste reactivity patterns. *Neurosci. Biobehav. Rev* 24, 173–198. [PubMed: 10714382]
- Berridge KC, Robinson TE, 2003 Parsing reward. *Trends Neurosci.* 26, 507–513. [PubMed: 12948663]
- Berridge KC, Kringelbach ML, 2015 Pleasure systems in the brain. *Neuron* 86, 646–664. [PubMed: 25950633]
- Berton O, McClung CA, DiLeone RJ, Krishnan V, Renthal W, Russo SJ, Graham D, Tsankova NM, Bolanos CA, Rios M, Monteggia LM, Self DW, Nestler EJ, 2006 Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. *Science* 311, 864–868. [PubMed: 16469931]
- Bevan RK, Rose MA, and Duggan KA, (1997). Evidence for direct interaction of ketamine with alpha 1- and beta 2-adrenoceptors. *Clin. Exp. Pharmacol. Physiol* 24, 923–926. [PubMed: 9406657]
- Billman GE, 1995 Cocaine: a review of its toxic actions on cardiac function. *Crit. Rev. Toxicol* 25, 113–132. [PubMed: 7612173]
- Boileau I, Dagher A, Leyton M, Welfeld K, Booij L, Diksic M, Benkelfat C, 2007 Conditioned dopamine release in humans: a positron emission tomography [¹¹C] raclopride study with amphetamine. *J. Neurosci* 27, 3998–4003. [PubMed: 17428975]
- Bonn-Miller MO, Zvolensky MJ, Bernstein A, 2007 Marijuana use motives: concurrent relations to frequency of past 30-day use and anxiety sensitivity among young adult marijuana smokers. *Addict. Behav* 32, 49–62. [PubMed: 16647822]
- Booth C, Hasking P, 2009 Social anxiety and alcohol consumption: the role of alcohol expectancies and reward sensitivity. *Addict. Behav* 34, 730–736. [PubMed: 19464809]
- Borota D, Murray E, Keceli G, Chang A, Watabe JM, Ly M, Toscano JP, Yassa MA, 2014 Post-study caffeine administration enhances memory consolidation in humans. *Nat. Neurosci* 17, 201–203. [PubMed: 24413697]
- Boyd CJ, McCabe SE, Cranford JA, Young A, 2006 Adolescents' motivations to abuse prescription medications. *Pediatrics* 118, 2472–2480. [PubMed: 17142533]
- Boys A, Marsden J, Griffiths P, Fountain J, Stillwell G, Strang J, 1999 Substance use among young people: the relationship between perceived functions and intentions. *Addiction* 94, 1043–1050. [PubMed: 10707442]
- Boys A, Marsden J, Strang J, 2001 Understanding reasons for drug use amongst young people: a functional perspective. *Health Educ. Res* 16, 457–469. [PubMed: 11525392]
- Boys A, Marsden J, 2003 Perceived functions predict intensity of use and problems in young polysubstance users. *Addiction* 98, 951–963. [PubMed: 12814501]
- Boys A, Marsden J, 2003 Perceived functions predict intensity of use and problems in young polysubstance users. *Addiction* 98, 951–963. [PubMed: 12814501]
- Boyson CO, Holly EN, Shimamoto A, Albrechet-Souza L, Weiner LA, DeBold JF, Miczek KA, 2014 Social stress and CRF-dopamine interactions in the VTA: role in long-term escalation of cocaine self-administration. *J. Neurosci* 34, 6659–6667. [PubMed: 24806691]
- Bradizza CM, Reifman A, Barnes GM, 1999 Social and coping reasons for drinking: predicting alcohol misuse in adolescents. *J. Stud. Alcohol* 60, 491–499. [PubMed: 10463805]
- Brand R, Wolff W, Ziegler M, 2016 Drugs As Instruments: Describing and Testing a Behavioral Approach to the Study of Neuroenhancement. *Front Psychol.* 7, 1226. [PubMed: 27582720]
- Breese GR, Chu K, Dayas CV, Funk D, Knapp DJ, Koob GF, Le DA, O'Dell LE, Overstreet DH, Roberts AJ, Sinha R, Valdez GR, Weiss F, 2005 Stress enhancement of craving during sobriety: A risk for relapse. *Alcohol Clin. Exp. Res* 29, 185–195. [PubMed: 15714042]
- Brischoux F, Chakraborty S, Brierley DI, Ungless MA, 2009 Phasic excitation of dopamine neurons in ventral VTA by noxious stimuli. *Proc. Natl. Acad. Sci. U. S. A* 106, 4894–4899. [PubMed: 19261850]

- Britt GC, Cance-Katz EF, 2005 A brief overview of the clinical pharmacology of 'club drugs'. *Subst. Use Misuse* 40, 1189–1201. [PubMed: 16048813]
- Brown SA, Goldman MS, Inn A, Anderson LR, 1980 Expectations of reinforcement from alcohol: their domain and relation to drinking patterns. *J. Consult Clin. Psychol* 48, 419–426. [PubMed: 7400427]
- Brown DA, London E 1998 Functions of lipid rafts in biological membranes. *Annu. Rev. Cell. Dev. Biol* 14, 111–136. [PubMed: 9891780]
- Brown SA, 1985 Expectancies versus background in the prediction of college drinking patterns. *J. Consult Clin. Psychol* 53, 123–130. [PubMed: 3980817]
- Brown SA, Inaba RK, Gillin JC, Schuckit MA, Stewart MA, Irwin MR, 1995 Alcoholism and affective disorder: clinical course of depressive symptoms. *Am. J. Psychiatry* 152, 45–52. [PubMed: 7802119]
- Buckner RL, 2013 The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging. *Neuron* 80, 807–815. [PubMed: 24183029]
- Bulley A, Miloyan B, Brilot B, Gullo MJ, Suddendorf T, 2016 An evolutionary perspective on the co-occurrence of social anxiety disorder and alcohol use disorder. *J. Affect. Disord* 196, 62–70. [PubMed: 26914963]
- Burgdorf J, Panksepp J, 2001 Tickling induces reward in adolescent rats. *Physiol. Behav* 72, 167–173. [PubMed: 11239994]
- Burke AR, DeBold JF, Miczek KA, 2016 CRF type 1 receptor antagonism in ventral tegmental area of adolescent rats during social defeat: prevention of escalated cocaine self-administration in adulthood and behavioral adaptations during adolescence. *Psychopharmacology* 233, 2727–2736. [PubMed: 27251131]
- Burke AR, Miczek KA, 2014 Stress in adolescence and drugs of abuse in rodent models: role of dopamine, CRF, and HPA axis. *Psychopharmacology (Berl)* 231, 1557–1580. [PubMed: 24370534]
- Burke AR, Miczek KA, 2015 Escalation of cocaine self-administration in adulthood after social defeat of adolescent rats: role of social experience and adaptive coping behavior. *Psychopharmacology* 232, 3067–3079. [PubMed: 25943168]
- Burnett S, Sebastian C, Cohen KK, Blakemore SJ, 2010 The social brain in adolescence: Evidence from functional magnetic resonance imaging and behavioural studies. *Neurosci. Biobehav. Rev* 35(8), 1654–64. [PubMed: 21036192]
- Burock MA, Dale AM, 2000 Estimation and detection of event-related fMRI signals with temporally correlated noise: A statistically efficient and unbiased approach. *Hum. Brain Mapp* 11, 249–260. [PubMed: 11144754]
- Cantin L, Lenoir M, Augier E, Vanhille N, Dubreucq S, Serre F, Vouillac C, Ahmed SH, 2010 Cocaine is low on the value ladder of rats: possible evidence for resilience to addiction. *PLoS One* 5(7), e11592. [PubMed: 20676364]
- Caprioli D, Celentano M, Dubla A, Lucantonio F, Nencini P, Badiani A, 2009 Ambience and drug choice: cocaine- and heroin-taking as a function of environmental context in humans and rats. *Biol. Psychiatry* 65, 893–899. [PubMed: 19217078]
- Caprioli D, Celentano M, Paolone G, Badiani A (2007a) Modeling the role of environment in addiction. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 31, 1639–1653. [PubMed: 17889978]
- Caprioli D, Paolone G, Celentano M, Testa A, Nencini P, Badiani A, 2007b Environmental modulation of cocaine self-administration in the rat. *Psychopharmacology (Berl)* 192, 397–406. [PubMed: 17297633]
- Caprioli D, Celentano M, Paolone G, Lucantonio F, Bari A, Nencini P, Badiani A (2008) Opposite environmental regulation of heroin and amphetamine self-administration in the rat. *Psychopharmacology (Berl)* 198, 395–404. [PubMed: 18463850]
- Caprioli D, Venniro M, Zeric T, Li X, Adhikary S, Madangopal R, Marchant NJ, Lucantonio F, Schoenbaum G, Bossert JM, Shaham Y, 2015 Effect of the Novel Positive Allosteric Modulator of Metabotropic Glutamate Receptor 2 AZD8529 on Incubation of Methamphetamine Craving After Prolonged Voluntary Abstinence in a Rat Model. *Biol. Psychiatry* 78(7):463–73. [PubMed: 25861699]

- Caprioli D, Zeric T, Thorndike EB, Venniro M, 2015 Persistent palatable food preference in rats with a history of limited and extended access to methamphetamine self-administration. *Addict. Biol* 20(5):913–26 [PubMed: 25582886]
- Caprioli D, Venniro M, Zhang M, Bossert JM, Warren BL, Hope BT, Shaham Y, 2017 Role of Dorsomedial Striatum Neuronal Ensembles in Incubation of Methamphetamine Craving after Voluntary Abstinence. *J. Neurosci* 37(4), 1014–1027. [PubMed: 28123032]
- Carrigan MH, Ham LS, Thomas SE, Randall CL, 2008 Alcohol outcome expectancies and drinking to cope with social situations. *Addict. Behav* 33, 1162–1166. [PubMed: 18550293]
- Carroll ME, France CP, Meisch RA, 1979 Food deprivation increases oral and intravenous drug intake in rats. *Science* 205(4403), 319–321. [PubMed: 36665]
- Carroll ME, France CP, Meisch RA, 1981 Intravenous self-administration of etonitazene, cocaine and phencyclidine in rats during food deprivation and satiation. *J. Pharmacol. Exp. Ther* 217(2), 241–247. [PubMed: 6112257]
- Castren E, 2005 Is mood chemistry? *Nat. Rev. Neurosci* 6, 241–246. [PubMed: 15738959]
- Cato BM, 1992 Youth's recreation and drug sensations: is there a relationship? *J. Drug Educ* 22, 293–301. [PubMed: 1484327]
- Cauli O, Morelli M, 2005 Caffeine and the dopaminergic system. *Behav. Pharmacol* 16, 63–77. [PubMed: 15767841]
- Celentano M, Caprioli D, Dipasquale P, Cardillo V, Nencini P, Gaetani S, Badiani A, 2009 Drug context differently regulates cocaine versus heroin self-administration and cocaine-versus heroin-induced Fos mRNA expression in the rat. *Psychopharmacology (Berl)* 204, 349–360. [PubMed: 19169671]
- Chick J, 1999 Can light or moderate drinking benefit mental health? *Eur. Addict. Res* 5, 74–81. [PubMed: 10394037]
- Chen K, Kandel D, 2002 Relationship between extent of cocaine use and dependence among adolescents and adults in the United States. *Drug Alcohol Depend.* 68, 65–85. [PubMed: 12167553]
- Chen NA, Jupp B, Sztainberg Y, Lebow M, Brown RM, Kim JH, Chen A, Lawrence AJ, 2014 Knockdown of CRF1 receptors in the ventral tegmental area attenuates cue- and acute food deprivation stress-induced cocaine seeking in mice. *J. Neurosci* 34, 11560–11570. [PubMed: 25164654]
- Ciccocioppo R, Panocka I, Froidi R, Colombo G, Gessa GL, Massi M, 1999 Antidepressant-like effect of ethanol revealed in the forced swimming test in Sardinian alcohol-preferring rats. *Psychopharmacology (Berl)* 144, 151–157. [PubMed: 10394996]
- Colpaert FC, Tarayre JP, Alliaga M, Bruins Slot LA, Attal N, Koek W, 2001 Opiate self-administration as a measure of chronic nociceptive pain in arthritic rats. *Pain* 91(1–2), 33–45. [PubMed: 11240076]
- Conger JJ, 1951 The effects of alcohol on conflict behavior in the albino rat. *Q. J. Stud. Alcohol* 12(1), 1–29. [PubMed: 14828044]
- Cooper ML, Frone MR, Russell M, Mudar P, 1995 Drinking to regulate positive and negative emotions: a motivational model of alcohol use. *J. Pers. Soc. Psychol* 69, 990–1005. [PubMed: 7473043]
- Cooper SE, Kechner M, Caraballo-Perez D, Kaska S, Robison AJ, Mazei-Robison MS, 2017 Comparison of chronic physical and emotional social defeat stress effects on mesocorticolimbic circuit activation and voluntary consumption of morphine. *Sci. Rep* 7, 8445. [PubMed: 28814751]
- Covington HE, Kikusui T, Goodhue J, Nikulina EM, Hammer RP, Miczek KA, 2005 Brief social defeat stress: long lasting effects on cocaine taking during a binge and *Zif268* mRNA expression in the amygdala and prefrontal cortex. *Neuropsychopharmacology* 30, 310–321. [PubMed: 15496936]
- Covington HE, Miczek KA, 2001 Repeated social-defeat stress, cocaine or morphine. Effects on behavioral sensitization and intravenous cocaine self-administration “binges”. *Psychopharmacology* 158, 388–398. [PubMed: 11797060]

- Covington HE, Miczek KA, 2005 Intense cocaine self-administration after episodic social defeat stress, but not after aggressive behavior: dissociation from corticosterone activation. *Psychopharmacology* 183, 331–340. [PubMed: 16249907]
- Cox SML, Benkelfat C, Dagher A, Delaney JS, Durand F, McKenzie SA, Kolivakis T, Casey KF, Leyton M, 2009 Striatal Dopamine Responses to Intranasal Cocaine Self-Administration in Humans. *Biol. Psychiatry* 65, 846–850. [PubMed: 19249751]
- Cox SML, Yau Y, Larcher K, Durand F, Kolivakis T, Delaney JS, Dagher A, Benkelfat C, Leyton M, 2017 Cocaine Cue-Induced Dopamine Release in Recreational Cocaine Users. *Sci. Rep* 7, 46665. [PubMed: 28443614]
- Cruz FC, Quadras IM, Hogenelst K, Planeta CS, Miczek KA, 2011 Social defeat stress in rats: escalation of cocaine and 'speedball' binge self-administration, but not heroin. *Psychopharmacology (Berl)* 215, 165–175. [PubMed: 21197616]
- Curran HV, 1991 Benzodiazepines, memory and mood: a review. *Psychopharmacology (Berl)* 105, 1–8. [PubMed: 1684055]
- Davey J, Richards N, Freeman J, 2007 Fatigue and beyond: patterns of and motivations for illicit drug use among long-haul truck drivers. *Traffic. Inj. Prev* 8, 253–259. [PubMed: 17710715]
- de Kloet ER, Vreugdenhil E, Oitzl MS, Joels M, 1998 Brain corticosteroid receptor balance in health and disease. *Endocr. Rev* 19, 269–301. [PubMed: 9626555]
- de las Cuevas C, Sanz E, de la Fuente J, 2003 Benzodiazepines: more 'behavioural' addiction than dependence. *Psychopharmacology (Berl)* 167, 297–303. [PubMed: 12669174]
- De Luca MT, Badiani A, 2011 Ketamine self-administration in the rat: evidence for a critical role of setting. *Psychopharmacology (Berl)* 214, 549–556. [PubMed: 21069515]
- De Luca MT, Meringolo M, Spagnolo PA, Badiani A, 2012 The role of setting for ketamine abuse: clinical and preclinical evidence. *Rev. Neurosci* 23(5–6), 769–80. [PubMed: 23159868]
- De Pirro S, Galati G, Pizzamiglio L, Badiani A 2018 The affective and neural correlates of heroin vs. cocaine use in addiction are influenced by environmental setting but in opposite directions. *J Neurosci.* 38, 5182–5195. [PubMed: 29760180]
- de Roode JC, Lefevre T, Hunter MD, 2013 Ecology. Self-medication in animals. *Science* 340(6129), 150–151. [PubMed: 23580516]
- de Wit H, Sayette M, 2018 Considering the context: social factors in responses to drugs in humans. *Psychopharmacology (Berl)* 235(4), 935–945. [PubMed: 29470605]
- Decker MW, Brioni JD, Bannon AW, Arneric SP, 1995 Diversity of neuronal nicotinic acetylcholine receptors: lessons from behavior and implications for CNS therapeutics. *Life Sci.* 56, 545–570. [PubMed: 7869835]
- Degenhardt L, Whiteford H, Hall W, Vos T, 2009 Estimating the burden of disease attributable to illicit drug use and mental disorders: what is 'Global Burden of Disease 2005' and why does it matter? *Addiction* 104, 1466–1471. [PubMed: 19686517]
- Delgado MR, Locke HM, Stenger VA, Fiez JA, 2003 Dorsal striatum responses to reward and punishment: effects of valence and magnitude manipulations. *Cogn. Affect. Behav. Neurosci* 3, 27–38. [PubMed: 12822596]
- Deroche-Gamonet V, Darnaudery M, Bruins-Slot L, Piat F, Le Moal M, Piazza PV, 2002 Study of the addictive potential of modafinil in naive and cocaine-experienced rats. *Psychopharmacology (Berl)* 161(4), 387–395. [PubMed: 12073166]
- Deroche-Gamonet V, Sillaber I, Aouizerate B, Izawa R, Jaber M, Ghozland S, Kellendonk C, Le Moal M, Spanagel R, Schutz G, Tranche FS, Piazza PV, 2003 The glucocorticoid receptor as a potential target to reduce cocaine abuse. *J. Neurosci* 23, 4785. [PubMed: 12805318]
- Di Chiara G, Imperato A, 1988 Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc. Natl. Acad. Sci. U. S. A* 85, 5274–5278. [PubMed: 2899326]
- Di Chiara G, North RA, 1992 Neurobiology of opiate abuse. *Trends Pharmacol. Sci* 13, 185–193. [PubMed: 1604711]
- Di Chiara G, 1995 The role of dopamine in drug abuse viewed from the perspective of its role in motivation. *Drug Alcohol Depend.* 38, 95–137. [PubMed: 7671769]

- Dome P, Lazary J, Kalapos MP, Rihmer Z, 2010 Smoking, nicotine and neuropsychiatric disorders. *Neurosci. Biobehav. Rev* 34(3), 295–342. [PubMed: 19665479]
- Dougherty DD, Shin LM, Alpert NM, Pitman RK, Orr SP, Lasko M, Macklin ML, Fischman AJ, Rauch SL, 1999 Anger in healthy men: a PET study using script-driven imagery. *Biol. Psychiatry* 46, 466–472. [PubMed: 10459395]
- Dutra L, Stathopoulou G, Basden SL, Leyro TM, Powers MB, Otto MW, 2008 A meta-analytic review of psychosocial interventions for substance use disorders. *Am. J. Psychiatry* 165(2), 179–187. [PubMed: 18198270]
- Edwards G, 2000 Alcohol: the world favorite drug. Penguin Books, New York.
- Eissenberg T, Balster RL, 2000 Initial tobacco use episodes in children and adolescents: current knowledge, future directions. *Drug Alcohol Depend.* 59 Suppl 1, S41–S60. [PubMed: 10773437]
- Eggeling C, Ringemann C, Medda R, Schwarzmann G, Sandhoff K, Polyakova S, Belov VN, Hein B, von Middendorff C, Schönle A, Hell SW 2009 Direct observation of the nanoscale dynamics of membrane lipids in a living cell. *Nature* 457, 1159–1162. [PubMed: 19098897]
- Emley GS, Hutchinson RR, 1983 Unique Influences of 10 Drugs Upon Post-Shock Biting Attack and Preshock Manual Responding. *Pharmacol. Biochem. Behav* 19, 5–12. [PubMed: 6684777]
- Everitt BJ, Wolf ME. 2002 Psychomotor stimulant addiction: a neural systems perspective. *J. Neurosci* 22[9], 3312–3320. [PubMed: 11978805]
- Everitt BJ, Belin D, Economidou D, Pelloux Y, Dailey JW, Robbins TW, 2008 Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction. *Philos. Trans. R. Soc. Lond B Biol. Sci* 363, 3125–3135. [PubMed: 18640910]
- Fantini J, Barrantes FJ, 2009 Sphingolipid/cholesterol regulation of neurotransmitter receptor conformation and function. *Biochim. Biophys. Acta* 1788, 2345–2361. [PubMed: 19733149]
- Fanzo JC, Lynch MP, Phee H, Hyer M, Cremesti A, Grassmé H, Norris JS, Coggeshall KM, Rueda BR, Pernis AB, Kolesnick R, Gulbins E 2003 CD95 rapidly clusters in cells of diverse origins. *Cancer Biol. Ther* 2, 392–395. [PubMed: 14508111]
- Feldman RS, Meyer JS, Quenzer LF, 1997 Principles of Neuropsychopharmacology. Sinauer Associates, Sunderland.
- Ferguson SM, Thomas MJ, Robinson TE, 2004 Morphine-induced c-fos mRNA expression in striatofugal circuits: modulation by dose, environmental context, and drug history. *Neuropsychopharmacology* 29, 1664–1674. [PubMed: 15138436]
- Fischman MW, Schuster CR, 1980 Cocaine effects in sleep-deprived humans. *Psychopharmacology (Berl)* 72, 1–8. [PubMed: 6780998]
- Fuchs E, Flügge G, 2002 Social stress in tree shrews: Effects on physiology, brain function, and behavior of subordinate individuals. *Pharmacol. Biochem. Behav* 73, 247–258. [PubMed: 12076743]
- Garcia-Keller C, Kupchik YM, Gipson CD, Brown RM, Spencer S, Bollati F, Esparza MA, Roberts-Wolfe DJ, Heinsbroek JA, Bobadilla AC, Cancela LM, Kalivas PW, 2016 Glutamatergic mechanisms of comorbidity between acute stress and cocaine self-administration. *Mol. Psychiatry* 21, 1063–1069. [PubMed: 26821978]
- Garattini S, Borroni E, Mennini T, Samanin R, 1978 Differences and similarities among anorectic agents In: *Central Mechanisms of Anorectic Drugs*, Eds Garattini S, Samanin R. Raven Press: New York.
- Glynn RJ, Lo Castro JS, Hermos JA, Bosse R, 1983 Social contexts and motives for drinking in men. *J. Stud. Alcohol* 44, 1011–1025. [PubMed: 6664085]
- Goldstein PJ, 1990 Anabolic steroids: an ethnographic approach. *NIDA Res. Monogr* 102, 74–96. [PubMed: 2079978]
- Grassmé H, Jekle A, Riehle A, Schwarz H, Berger J, Sandhoff K, Kolesnick R, Gulbins E 2001 CD95 signaling via ceramide-rich membrane rafts. *J. Biol. Chem* 276, 20589–20596. [PubMed: 11279185]
- Grassmé H, Schwarz H, Gulbins E 2001 Molecular mechanisms of ceramide-mediated CD95 clustering. *Biochem. Biophys. Res. Commun* 284, 1016–1030. [PubMed: 11409897]
- Grassmé H, Jendrosseck V, Bock J, Riehle A, Gulbins E 2002 Ceramide-rich membrane rafts mediate CD40 clustering. *J. Immunol* 168, 298–307. [PubMed: 11751974]

- Grassme H, Jernigan PL, Hoehn RS, Wilker B, Soddemann M, Edwards MJ, Müller CP, Kornhuber J, Gulbins E, 2015 Inhibition of Acid Sphingomyelinase by Antidepressants Counteracts Stress-Induced Activation of P38-Kinase in Major Depression. *Neurosignals* 23, 84–92. [PubMed: 26682751]
- Green AR, Mehan AO, Elliott JM, O'Shea E, Colado MI, 2003 The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'). *Pharmacol. Rev* 55, 463–508. [PubMed: 12869661]
- Greenberg GD, Steinman MQ, Doig IE, Hao R, Trainor BC, 2015 Effects of social defeat on dopamine neurons in the ventral tegmental area in male and female California mice. *Eur. J. Neurosci* 42, 3081–3094. [PubMed: 26469289]
- Grinspoon L, Hedblom P, 2005 A historical overview of amphetamines In: Harris N (Ed.), *Amphetamines*, Thomson Gale, Detroit, pp. 19–30.
- Gulbins E, Kolesnick R, 2003 Raft ceramide in molecular medicine. *Oncogene* 22, 7070–7077. [PubMed: 14557812]
- Gulbins E, Palmada M, Reichel M, Luth A, Bohmer C, Amato D, Müller CP, Tischbirek CH, Groemer TW, Tabatabai G, Becker KA, Tripal P, Staedtler S, Ackermann TF, van Brederode J, Alzheimer C, Weller M, Lang UE, Kleuser B, Grassme H, Kornhuber J, 2013 Acid sphingomyelinase-ceramide system mediates effects of antidepressant drugs. *Nat. Med* 19, 934–938. [PubMed: 23770692]
- Gulbins E, Walter S, Becker KA, Halmer R, Liu Y, Reichel M, Edwards MJ, Müller CP, Fassbender K, Kornhuber J, 2015 A central role for the acid sphingomyelinase/ceramide system in neurogenesis and major depression. *J. Neurochem* 134, 183–192. [PubMed: 25925550]
- Guillem K, Ahmed SH, 2017 Preference for Cocaine is Represented in the Orbitofrontal Cortex by an Increased Proportion of Cocaine Use-Coding Neurons. *Cereb. Cortex* 28(3):819–832.
- Haddad GG, Lasala PA, 1987 Effect of parasympathetic blockade on ventilatory and cardiac depression induced by opioids. *Respir. Physiol* 67, 101–114. [PubMed: 3103183]
- Hagen EH, Sullivan RJ, Schmidt R, Morris G, Kempter R, Hammerstein P, 2009 Ecology and neurobiology of toxin avoidance and the paradox of drug reward. *Neuroscience* 160, 69–84. [PubMed: 19233250]
- Hahn B, Stolerman IP, 2002 Nicotine-induced attentional enhancement in rats: effects of chronic exposure to nicotine. *Neuropsychopharmacology* 27, 712–722. [PubMed: 12431846]
- Halberstadt AL, Nichols DE, 2010 Serotonin and Serotonin Receptors in Hallucinogen Action In: Müller CP and Jacobs BL (Eds.), *Handbook of the Behavioral Neurobiology of Serotonin*, Academic Press, London, pp. 621–636.
- Hall W, Carter A, Forlini C, 2015 The brain disease model of addiction: is it supported by the evidence and has it delivered on its promises? *Lancet Psychiatry* 2, 105–110. [PubMed: 26359616]
- Han X, DeBold JF, Miczek KA, 2017 Prevention and reversal of social stress-escalated cocaine self-administration in mice by intra-VTA CRFR1 antagonism. *Psychopharmacology* 234, 2813–2821. [PubMed: 28698920]
- Haney M, DeBold JF, Miczek KA, 1989 Maternal aggression in mice and rats towards male and female conspecifics. *Aggress. Behav* 15, 443–453.
- Harder T, Simons K 1997 Caveolae, DIGs, and the dynamics of sphingolipid-cholesterol microdomains. *Curr. Opin. Cell Biol* 9, 534–542. [PubMed: 9261060]
- Harris AZ, Atsak P, Bretton ZH, Holt ES, Alam R, Morton MP, Abbas AI, Leonardo ED, Bolkan SS, Hen R, Gordon JA, 2018 A novel method for chronic social defeat stress in female mice. *Neuropsychopharmacology* 43, 1276–1283. [PubMed: 29090682]
- Harris RA, Trudell JR, Mihic SJ, 2008 Ethanol's molecular targets. *Sci. Signal* 1, re7. [PubMed: 18632551]
- Harrison AA, Gasparini F, Markou A, 2002 Nicotine potentiation of brain stimulation reward reversed by DH beta E and SCH 23390, but not by eticlopride, LY 314582 or MPEP in rats. *Psychopharmacology (Berl)* 160, 56–66. [PubMed: 11862374]
- Hart CL, 2013 *High price*. Harper Collins, New York.
- Hartnoll R, 1990 Non-pharmacological factors in drug abuse. *Behav. Pharmacol* 1(4), 375–384. [PubMed: 11175422]

- Hartwell KJ, Back SE, McRae-Clark AL, Shaftman SR, Brady KT, 2012 Motives for using: a comparison of prescription opioid, marijuana and cocaine dependent individuals. *Addict. Behav* 37, 373–378. [PubMed: 22284583]
- Hassan Z, Muzaimi M, Navaratnam V, Yusoff NH, Suhaimi FW, Vadivelu R, Vicknasingam BK, Amato D, von Hörsten S, Ismail NI, Jayabalan N, Hazim AI, Mansor SM, Müller CP, 2013 From Kratom to mitragynine and its derivatives: Physiological and behavioural effects related to use, abuse, and addiction. *Neurosci. Biobehav. Rev* 37, 138–151. [PubMed: 23206666]
- Hassan Z, Bosch OG, Singh D, Narayanan S, Kasinather BV, Seifritz E, Kornhuber J, Quednow BB, Müller CP, 2017 Novel Psychoactive Substances-Recent Progress on Neuropharmacological Mechanisms of Action for Selected Drugs. *Front. Psychiatry* 8, 152. [PubMed: 28868040]
- Havranek MM, Vonmoos M, Müller CP, Büetiger JR, Tasiudi E, Hulka L, Preller KH, Mössner R, Grünblatt E, Seifritz E, Quednow BB, 2015 Serotonin transporter and tryptophan hydroxylase gene variations mediate working memory deficit of cocaine users. *Neuropsychopharmacology* 40, 2929–2937. [PubMed: 26013962]
- Heath DB, 2000 *Drinking Occasions: Comparative Perspectives on Alcohol and Culture*. Brunner/Mazel, Philadelphia.
- Heilig M, Koob GF, 2007 A key role for corticotropin-releasing factor in alcohol dependence. *Trends Neurosci.* 30, 399–406. [PubMed: 17629579]
- Heilig M, Epstein DH, Nader MA, Shaham Y, 2016 Time to connect: bringing social context into addiction neuroscience. *Nat. Rev. Neurosci* 17(9), 592–599. [PubMed: 27277868]
- Henry B, Ziobro R, Becker KA, Kolesnick R, Gulbins E 2013 Acid sphingomyelinase. *Handb Exp. Pharmacol* 215, 77–88.
- Heyman GM, 2009 *Addiction: a disorder of choice*. Harvard University Press, Cambridge.
- Heyman GM, 2013 Quitting drugs: quantitative and qualitative features. *Annu. Rev. Clin. Psychol* 9, 29–59. [PubMed: 23330937]
- Higgins ST, Bickel WK, Hughes JR, Lynn M, Capeless MA, Fenwick JW, 1990 Effects of intranasal cocaine on human learning, performance and physiology. *Psychopharmacology (Berl)* 102, 451–458. [PubMed: 2096405]
- Higgins ST, Delaney DD, Budney AJ, Bickel WK, Hughes JR, Foerg F, Fenwick JW, 1991 A behavioral approach to achieving initial cocaine abstinence. *Am. J. Psychiatry* 148(9), 1218–1224. [PubMed: 1883001]
- Ho YJ, Pawlak CR, Guo LH, Schwarting RKW, 2004 Acute and long-term consequences of single MDMA administration in relation to individual anxiety levels in the rat. *Behav. Brain Res* 149, 135–144. [PubMed: 15129777]
- Hoffmann JP, Cerbone FG, Su SS, 2000 A growth curve analysis of stress and adolescent drug use. *Subst. Use Misuse* 35, 687–716. [PubMed: 10807152]
- Hollerman JR, Schultz W, 1998 Dopamine neurons report an error in the temporal prediction of reward during learning. *Nat. Neurosci* 1, 304–309. [PubMed: 10195164]
- Holly EN, Boyson CO, Montagud-Romero S, Stein DJ, Gobrogge KL, DeBold JF, Miczek KA, 2016 Episodic social stress-escalated cocaine self-administration: role of phasic and tonic corticotropin releasing factor in the anterior and posterior ventral tegmental area. *J. Neurosci* 36, 4093–4105. [PubMed: 27053215]
- Holly EN, Miczek KA, 2016 Ventral tegmental area dopamine revisited: effects of acute and repeated stress. *Psychopharmacology* 233, 163–186. [PubMed: 26676983]
- Holly EN, Shimamoto A, DeBold JF, Miczek KA, 2012 Sex differences in behavioral and neural cross-sensitization and escalated cocaine taking as a result of episodic social defeat stress in rats. *Psychopharmacology* 224, 179–188. [PubMed: 22926005]
- Hong ZY, Huang ZL, Qu WM, Eguchi N, Urade Y, Hayaishi O, 2005 An adenosine A(2A) receptor agonist induces sleep by increasing GABA release in the tuberomammillary nucleus to inhibit histaminergic systems in rats. *J. Neurochem* 92, 1542–1549. [PubMed: 15748171]
- Hopf FW, Lesscher HM, 2014 Rodent models for compulsive alcohol intake. *Alcohol* 48, 253–264. [PubMed: 24731992]
- Hopitt W, Laland KN, 2013 *Social Learning*. Princeton University Press, Princeton.

- Huber SE, Zoicas I, Reichel M, Mühle C, Büttner C, Ekici AB, Eulenburg V, Lenz B, Kornhuber J, Müller CP, 2018 Prenatal androgen receptor activation determines adult alcohol and water drinking in a sex-specific way. *Addict. Biol* 23(3), 904–920. [PubMed: 28776866]
- Huffman MA, 2003 Animal self-medication and ethno-medicine: exploration and exploitation of the medicinal properties of plants. *Proc. Nutr. Soc* 62, 371–381. [PubMed: 14506884]
- Hughes JR, Hatsukami DK, Mitchell JE, Dahlgren LA, 1986 Prevalence of smoking among psychiatric outpatients. *Am. J. Psychiatry* 143, 993–997. [PubMed: 3487983]
- Huhman KL, 2006 Social conflict models: can they inform us about human psychopathology? *Horm. Behav* 50, 640–646. [PubMed: 16870189]
- Huston JP, Haas HL, Boix F, Pfister M, Decking U, Schrader J, Schwarting RK, 1996 Extracellular adenosine levels in neostriatum and hippocampus during rest and activity periods of rats. *Neuroscience* 73, 99–107. [PubMed: 8783234]
- Huston JP, Kornhuber J, Mühle C, Japtok L, Komorowski M, Mattern C, Reichel M, Gulbins E, Kleuser B, Topic B, De Souza Silva MA, Müller CP, 2016 A sphingolipid mechanism for behavioral extinction. *J. Neurochem* 137, 589–603. [PubMed: 26788861]
- Huynh C, Fam J, Ahmed SH, Clemens KJ, 2017 Rats quit nicotine for a sweet reward following an extensive history of nicotine use. *Addict. Biol* 22(1), 142–151. [PubMed: 26374708]
- Hwa LS, Chu A, Levinson SA, Kayyali TM, DeBold JF, Miczek KA, 2011 Persistent escalation of alcohol drinking in C57BL/6J mice with intermittent access to 20% ethanol. *Alcohol Clin. Exp. Res* 35, 1938–1947. [PubMed: 21631540]
- Hwa LS, DeBold JF, Miczek KA, 2013 Alcohol in excess: CRF₁ receptors in the rat and mouse VTA and DRN. *Psychopharmacology* 225, 313–327. [PubMed: 22885872]
- Hwa LS, Holly EN, DeBold JF, Miczek KA, 2016 Social stress-escalated intermittent alcohol drinking: modulation by CRF-R1 in the ventral tegmental area and accumbal dopamine in mice. *Psychopharmacology* 233, 681–690. [PubMed: 26576941]
- Hwa LS, Nathanson AJ, Shimamoto A, Tayeh JK, Wilens AR, Holly EN, Newman EL, DeBold JF, Miczek KA, 2015 Aggression and increased glutamate in the mPFC during withdrawal from intermittent alcohol in outbred mice. *Psychopharmacology* 232, 2889–2902. [PubMed: 25899790]
- Hyman SE, Malenka RC, Nestler EJ, 2006 Neural mechanisms of addiction: the role of reward-related learning and memory. *Annu. Rev. Neurosci* 29, 565–598. [PubMed: 16776597]
- Ignjatova L, Raleva M, 2009 Gender difference in the treatment outcome of patients served in the mixed-gender program. *Bratisl. Lek. Listy* 110, 285–289. [PubMed: 19507662]
- Ikemoto S, Panksepp J, 1999 The role of nucleus accumbens dopamine in motivated behavior: a unifying interpretation with special reference to reward-seeking. *Brain Res. Brain Res. Rev* 31, 6–41. [PubMed: 10611493]
- Imperato A, Puglisi-Allegra S, Casolini P, Angelucci L, 1991 Changes in brain dopamine and acetylcholine release during and following stress are independent of the pituitary-adrenocortical axis. *Brain Res.* 538, 111–117. [PubMed: 2018923]
- Ito T, Suzuki T, Wellman SE, Ho IK, 1996 Pharmacology of barbiturate tolerance/dependence: GABAA receptors and molecular aspects. *Life Sci.* 59, 169–195. [PubMed: 8699929]
- Iversen LL, 2000 *The Science of Marijuana*. Oxford University Press, Oxford.
- Jaffe JH, Cascella NG, Kumor KM, Sherer MA, 1989 Cocaine-induced cocaine craving. *Psychopharmacology (Berlin)* 97, 59–64. [PubMed: 2496428]
- Jarvis MJ, Wardle J, 2006 Social patterning of individual health behaviours: the case of cigarette smoking, in: Marmot M, Wilkinson RG (Eds.), *Social Determinants of Health*. Oxford University Press, Oxford, pp. 224–237.
- Jasinska AJ, Stein EA, Kaiser J, Naumer MJ, Yalachkov Y, 2014 Factors modulating neural reactivity to drug cues in addiction: a survey of human neuroimaging studies. *Neurosci. Biobehav. Rev* 38, 1–16. [PubMed: 24211373]
- Javaid JI, Fischman MW, Schuster CR, Dekirmenjian H, Davis JM, 1978 Cocaine plasma concentration: relation to physiological and subjective effects in humans. *Science* 202, 227–228. [PubMed: 694530]
- Jay M, 2010 *High Society Mind-Altering Drugs in History and Culture*. Thames and Hudson.

- Jennings JH, Sparta DR, Stamatakis AM, Ung RL, Pleil KE, Kash TL, Stuber GD, 2013 Distinct extended amygdala circuits for divergent motivational states. *Nature* 496, 224–228. [PubMed: 23515155]
- Johanson CE, Fischman MW, 1989 The pharmacology of cocaine related to its abuse. *Pharmacol. Rev* 41, 3–52. [PubMed: 2682679]
- Kabbaj M, Norton CS, Kollack-Walker S, Watson SJ, Robinson TE, Akil H, 2001 Social defeat alters the acquisition of cocaine self-administration in rats: role of individual differences in cocaine-taking behavior. *Psychopharmacology (Berl)* 158, 382–387. [PubMed: 11797059]
- Kalivas PW, Volkow ND, 2005 The neural basis of addiction: A pathology of motivation and choice. *Am. J. Psychiatry* 162, 1403–1413. [PubMed: 16055761]
- Kapur S, 2003 Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am. J. Psychiatry* 160, 13–23. [PubMed: 12505794]
- Kawa AB, Bentzley BS, Robinson TE, 2016 Less is more: prolonged intermittent access cocaine self-administration produces incentive-sensitization and addiction-like behavior. *Psychopharmacology (Berl.)* 233, 3587–3602 [PubMed: 27481050]
- Kearns DN, Kim JS, Tunstall BJ, Silberberg A, 2017 Essential values of cocaine and non-drug alternatives predict the choice between them. *Addict. Biol* 22(6):1501–1514 [PubMed: 27623729]
- Kelley AE, Cador M, Stinus L, 1990 Exploration and its measurement. A psychopharmacological perspective In: Boulton AA, Baker GB and Greenshaw AJ (Eds.), *Neuromethods 13 - Psychopharmacology*, Humana Press, pp. 95–143.
- Kelley AE, 2004 Memory and addiction: shared neural circuitry and molecular mechanisms. *Neuron* 44, 161–179. [PubMed: 15450168]
- Kendler KS, Jacobson KC, Prescott CA, Neale MC, 2003 Specificity of genetic and environmental risk factors for use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. *Am. J. Psychiatry* 160, 687–695. [PubMed: 12668357]
- Kenny PJ, Markou A, 2006 Nicotine self-administration acutely activates brain reward systems and induces a long-lasting increase in reward sensitivity. *Neuropsychopharmacology* 31, 1203–1211. [PubMed: 16192981]
- Keramati M, Durand A, Girardeau P, Gutkin B, Ahmed SH, 2017 Cocaine addiction as a homeostatic reinforcement learning disorder. *Psychol. Rev* 124(2), 130–153. [PubMed: 28095003]
- Kerstetter KA, Ballis MA, Duffin-Lutgen S, Carr AE, Behrens AM, Kippin TE, 2012 Sex Differences in Selecting Between Food and Cocaine Reinforcement are Mediated by Estrogen. *Neuropsychopharmacology* 37(12), 2605–2614. [PubMed: 22871910]
- Khantzian EJ, 1985 The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. *Am. J. Psychiatry* 142, 1259–1264. [PubMed: 3904487]
- Khantzian EJ, 1997 The self-medication hypothesis of substance use disorders: a reconsideration and recent applications. *Harv. Rev. Psychiatry* 4, 231–244. [PubMed: 9385000]
- Kline MA, 2015 How to learn about teaching: An evolutionary framework for the study of teaching behavior in humans and other animals. *Behav. Brain Sci* 38, e31. [PubMed: 24856634]
- Knutson B, Burgdorf J, Panksepp J, 1999 High-frequency ultrasonic vocalizations index conditioned pharmacological reward in rats. *Physiol. Behav* 66, 639–643. [PubMed: 10386908]
- Knutson B, Burgdorf J, Panksepp J, 2002 Ultrasonic vocalizations as indices of affective states in rats. *Psychol. Bull* 128, 961–977. [PubMed: 12405139]
- Kollack-Walker S, Watson SJ, Akil H, 1997 Social stress in hamsters: Defeat activates specific neurocircuits within the brain. *J. Neurosci* 17, 8842–8855. [PubMed: 9348352]
- Koob GF, 1992 Drugs of abuse: anatomy, pharmacology and function of reward pathways. *Trends. Pharmacol. Sci* 13, 177–184. [PubMed: 1604710]
- Koob GF, LeMoal M, 1997 Drug abuse: Hedonic homeostatic dysregulation. *Science* 278, 52–58. [PubMed: 9311926]
- Koob GF, Sanna PP, Bloom FE, 1998 Neuroscience of addiction. *Neuron* 21, 467–476. [PubMed: 9768834]

- Koob GF, 1999 Stress, corticotropin-releasing factor, and drug addiction. *Ann. N. Y. Acad. Sci* 897, 27–45. [PubMed: 10676433]
- Koob GF, Ahmed SH, Boutrel B, Chen SA, Kenny PJ, Markou A, O'Dell LE, Parsons LH, Sanna PP, 2004 Neurobiological mechanisms in the transition from drug use to drug dependence. *Neurosci. Biobehav. Rev* 27, 739–749. [PubMed: 15019424]
- Koob GF, 2009 Neurobiological substrates for the dark side of compulsivity in addiction. *Neuropharmacology* 56 Suppl 1, 18–31. [PubMed: 18725236]
- Koob GF, Volkow ND, 2010 Neurocircuitry of addiction. *Neuropsychopharmacology* 35, 217–238. [PubMed: 19710631]
- Koob GF, Volkow ND, 2016 Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry* 3, 760–773. [PubMed: 27475769]
- Koolhaas JM, Bartolomucci A, Buwalda B, de Boer SF, Flügge G, Korte SM, Meerlo P, Murison R, Olivier B, Palanza P, Richter-Levin G, Sgoifo A, Steimer T, Stiedl O, van Dijk G, Wöhr M, Fuchs E, 2011 Stress revisited: A critical evaluation of the stress concept. *Neurosci. Biobehav. Rev* 35, 1291–1301. [PubMed: 21316391]
- Kornhuber J, Tripal P, Reichel M, Mühle C, Rhein C, Muehlbacher M, Groemer TW, Gulbins E, 2010 Functional Inhibitors of Acid Sphingomyelinase (FIASMA)s: a novel pharmacological group of drugs with broad clinical applications. *Cell. Physiol. Biochem* 26, 9–20. [PubMed: 20502000]
- Kornhuber J, Muehlbacher M, Trapp S, Pechmann S, Friedl A, Reichel M, Mühle C, Terfloth L, Groemer TW, Spitzer GM, Liedl KR, Gulbins E, Tripal P, 2011 Identification of novel functional inhibitors of acid sphingomyelinase. *PLoS. ONE* 6, e23852. [PubMed: 21909365]
- Kornhuber J, Müller CP, Becker KA, Reichel M, Gulbins E, 2014 The ceramide system as a novel antidepressant target. *Trends Pharmacol. Sci* 35, 293–304. [PubMed: 24793541]
- Kornhuber J, Rhein C, Müller CP, Mühle C, 2015 Secretory sphingomyelinase in health and disease. *Biol. Chem* 396, 707–736. [PubMed: 25803076]
- Koukoulis F, Rooy M, Tziotis D, Sailor KA, O'Neill HC, Levenga J, Witte M, Nilges M, Changeux JP, Hoeffler CA, Stitzel JA, Gutkin BS, DiGregorio DA, Maskos U, 2017 Nicotine reverses hypofrontality in animal models of addiction and schizophrenia. *Nat. Med* 23(3):347–354. [PubMed: 28112735]
- Kreek MJ, Bart G, Lilly C, LaForge KS, Nielsen DA, 2005 Pharmacogenetics and human molecular genetics of opiate and cocaine addictions and their treatments. *Pharmacol. Rev* 57, 1–26. [PubMed: 15734726]
- Kreibich AS, Briand L, Cleck JN, Ecke L, Rice KC, Blendy JA, 2009 Stress-induced potentiation of cocaine reward: a role for CRF R1 and CREB. *Neuropsychopharmacology* 34, 2609–2617. [PubMed: 19675537]
- Krishnan V, Nestler EJ, 2008 The molecular neurobiology of depression. *Nature* 455, 894–902. [PubMed: 18923511]
- Kuntsche E, Knibbe R, Gmel G, Engels R, 2005 Why do young people drink? A review of drinking motives. *Clin. Psychol. Rev* 25, 841–861. [PubMed: 16095785]
- Lader M, 1994 Anxiolytic drugs: dependence, addiction and abuse. *Eur. Neuropsychopharmacol* 4, 85–91. [PubMed: 7919947]
- Laland KN, Odling-Smee J, Feldman MW, 2000 Niche construction, biological evolution, and cultural change. *Behav. Brain Sci* 23, 131–146. [PubMed: 11303338]
- Lavikainen HM, Lintonen T, Kosunen E, 2009 Sexual behavior and drinking style among teenagers: a population-based study in Finland. *Health Prom. Int* 24(2), 108–119.
- Le Foll B, Goldberg SR, 2006 Nicotine as a typical drug of abuse in experimental animals and humans. *Psychopharmacology (Berl)* 184, 367–381. [PubMed: 16205918]
- Lende DH, Smith EO, 2002 Evolution meets biopsychosociality: an analysis of addictive behavior. *Addiction* 97, 447–458. [PubMed: 11964060]
- Lende DH, 2005 Wanting and drug use: a biocultural approach to the analysis of addiction. *ETHOS* 33[1], 100–124.
- Lende DH, Leonard T, Sterk CE, Elifson K. 2007 Functional methamphetamine use: The insider's perspective. *Addict. Res. Ther* 15[5], 465–477.

- Lenoir M, Ahmed SH, 2008 Supply of a nondrug substitute reduces escalated heroin consumption. *Neuropsychopharmacology* 33(9), 2272–2282. [PubMed: 17971831]
- Lenoir M, Cantin L, Vanhille N, Serre F, Ahmed SH, 2013 Extended heroin access increases heroin choices over a potent nondrug alternative. *Neuropsychopharmacology* 38(7), 1209–1220. [PubMed: 23322185]
- Lenoir M, Serre F, Cantin L, Ahmed SH, 2007 Intense sweetness surpasses cocaine reward. *PLoS One* 2(1), e698. [PubMed: 17668074]
- Leonard MZ, DeBold JF, Miczek KA, 2017 Escalated cocaine “binges” in rats: enduring effects of social defeat stress or intra-VTA CRF. *Psychopharmacology* 234, 2823–2836. [PubMed: 28725939]
- Leri F, Stewart J, 2001 Drug-induced reinstatement to heroin and cocaine seeking: a rodent model of relapse in polydrug use. *Exp. Clin. Psychopharmacol* 9, 297–306 [PubMed: 11534540]
- Liangpunsakul S, Rahmini Y, Ross RA, Zhao Z, Xu Y, Crabb DW, 2012 Imipramine blocks ethanol-induced ASMase activation, ceramide generation, and PP2A activation, and ameliorates hepatic steatosis in ethanol-fed mice. *Am. J. Physiol. Gastrointest. Liver Physiol* 302, G515–G523. [PubMed: 22194417]
- Licata A, Taylor S, Berman M, Cranston J, 1993 Effects of cocaine on human aggression. *Pharmacol. Biochem. Behav* 45, 549–552. [PubMed: 8332615]
- Lipton RI, 1994 The effect of moderate alcohol use on the relationship between stress and depression. *Am. J. Public Health* 84, 1913–1917. [PubMed: 7998629]
- Logrip ML, Zorrilla EP, Koob GF, 2012 Stress modulation of drug self-administration: implications for addiction comorbidity with post-traumatic stress disorder. *Neuropharmacology* 62, 552–564. [PubMed: 21782834]
- London M, London E 2004 Ceramide selectively displaces cholesterol from ordered lipid domains (rafts): implications for lipid raft structure and function. *J. Biol. Chem* 279, 9997–10004. [PubMed: 14699154]
- Lozano GA, 1998 Parasitic stress and self-medication in wild animals. *Adv. Stud. Behav* 27, 291–317.
- Maier HW, 1926 *Der Kokainismus*. Georg Thieme, Leipzig.
- Maier EY, Ma ST, Ahrens A, Schallert TJ, Duvauchelle CL, 2010 Assessment of ultrasonic vocalizations during drug self-administration in rats. *J. Vis. Exp*, 41.
- Madsen HB, Ahmed SH, 2015 Drug versus sweet reward: greater attraction to and preference for sweet versus drug cues. *Addict. Biol* 20(3), 433–444. [PubMed: 24602027]
- Maloff D, Becker HS, Fonaroff A, Rodin J, 1981 Informal social controls and their influence on substance use In: Zinberg NE and Harding W (Eds.), *Control Over Intoxicant Use: Pharmacological, Psychological and Social Considerations*, Human Science Press, U.S., pp. 5–35.
- Manjoch H, Vainer E, Matar M, Ifergane G, Zohar J, Kaplan Z, Cohen H, 2016 Predator-scent stress, ethanol consumption and the opioid system in an animal model of PTSD. *Behav. Brain Res* 306, 91–105. [PubMed: 26965572]
- Mansvelder HD, van Aerde KI, Couey JJ, Brussaard AB, 2006 Nicotinic modulation of neuronal networks: from receptors to cognition. *Psychopharmacology (Berl)* 184, 292–305. [PubMed: 16001117]
- Marcuse L, 1984 *Philosophie des Glücks* 2nd edn. Diogenes, Zürich.
- Marinelli M, Rouge-Pont F, Deroche V, Barrot M, Jesus-Oliveira C, Le Moal M, Piazza PV, 1997 Glucocorticoids and behavioral effects of psychostimulants. I: Locomotor response to cocaine depends on basal levels of glucocorticoids. *J. Pharmacol. Exp. Ther* 281, 1392–1400. [PubMed: 9190875]
- Markou A, 2008 Review. Neurobiology of nicotine dependence. *Philos. Trans. R. Soc. Lond B Biol. Sci* 363, 3159–3168. [PubMed: 18640919]
- Marsicano G, Wotjak CT, Azad SC, Bisogno T, Rammes G, Cascio MG, Hermann H, Tang J, Hofmann C, Zieglansberger W, Di Marzo V, Lutz B, 2002 The endogenous cannabinoid system controls extinction of aversive memories. *Nature* 418, 530–534. [PubMed: 12152079]
- Matsumoto M, Hikosaka O, 2009 Two types of dopamine neuron distinctly convey positive and negative motivational signals. *Nature* 459, 837–841. [PubMed: 19448610]

- Matthews TJ, Abdelbaky P, Pfaff DW, 2005 Social and sexual motivation in the mouse. *Behav. Neurosci* 119, 1628–1639. [PubMed: 16420165]
- McBride WJ, Murphy JM, Ikemoto S, 1999 Localization of brain reinforcement mechanisms: intracranial self-administration and intracranial place-conditioning studies. *Behav. Brain Res* 101, 129–152. [PubMed: 10372570]
- McBride WJ, Le AD, Noronha A, 2002 Central nervous system mechanisms in alcohol relapse. *Alcohol Clin. Exp. Res* 26, 280–286. [PubMed: 11964569]
- McCabe SE, Knight JR, Teter CJ, Wechsler H, 2005 Non-medical use of prescription stimulants among US college students: prevalence and correlates from a national survey. *Addiction* 100, 96–106. [PubMed: 15598197]
- McCabe SE, Cranford JA, Boyd CJ, Teter CJ, 2007 Motives, diversion and routes of administration associated with nonmedical use of prescription opioids. *Addict. Behav* 32, 562–575. [PubMed: 16843611]
- McCance-Katz EF, Carroll KM, Rounsaville BJ, 1999 Gender differences in treatment-seeking cocaine abusers—implications for treatment and prognosis. *Am. J. Addict* 8, 300–311. [PubMed: 10598213]
- McCreary AC, Müller CP, Filip M, 2015 Psychostimulants: Basic and Clinical Pharmacology. *Int. Rev. Neurobiol* 120, 41–88. [PubMed: 26070753]
- McKay JR, 2017 Making the hard work of recovery more attractive for those with substance use disorders. *Addiction* 112(5), 751–757. [PubMed: 27535787]
- McLaughlin JP, Marton-Popovici M, Chavkin C, 2003 Kappa opioid receptor antagonism and prodynorphin gene disruption block stress-induced behavioral responses. *J. Neurosci* 23, 5674–5683. [PubMed: 12843270]
- Mechoulam R, Fride E, Di Marzo V, 1998 Endocannabinoids. *Eur. J. Pharmacol* 359, 1–18. [PubMed: 9831287]
- Megha BO, London E, 2006 Cholesterol precursors stabilize ordinary and ceramide-rich ordered lipid domains (lipid rafts) to different degrees. Implications for the Bloch hypothesis and sterol biosynthesis disorders. *J. Biol. Chem* 281, 21903–21913. [PubMed: 16735517]
- Miczek KA, Mutschler NH, 1996 Activational effects of social stress on IV cocaine self-administration in rats. *Psychopharmacology (Berl)* 128(3), 256–264. [PubMed: 8972545]
- Miczek KA, Nikulina EM, Takahashi A, Covington HE, Yap JJ, Boyson CO, Shimamoto A, de Almeida RM, 2011 Gene expression in aminergic and peptidergic cells during aggression and defeat: relevance to violence, depression and drug abuse. *Behav. Genet* 41, 787–802. [PubMed: 21416141]
- Miczek KA, Nikulina EM, Shimamoto A, Covington HE, 2011 Escalated or suppressed cocaine reward, tegmental BDNF and accumbal dopamine due to episodic vs. continuous social stress in rats. *J. Neurosci* 31, 9848–9857. [PubMed: 21734276]
- Miczek KA, Thompson ML, Shuster L, 1982 Opioid-like analgesia in defeated mice. *Science* 215, 1520–1522. [PubMed: 7199758]
- Miczek KA, Thompson ML, Tornatzky W, 1991 Subordinate animals: Behavioral and physiological adaptations and opioid tolerance In: Brown MR (ed) *Stress: Neurobiology and Neuroendocrinology*. Marcel Dekker, New York, pp 323–357
- Miczek KA, Yap JJ, Covington HE, 2008 Social stress, therapeutics and drug abuse: preclinical models of escalated and depressed intake. *Pharmacol. Ther* 120, 102–128. [PubMed: 18789966]
- Mielenz D, Reichel M, Jia T, Quinlan EB, Stöckl T, Mettang M, Zilske D, Kirmizi-Alsan E, Schönberger P, Praetner M, Huber SE, Amato D, Schwarz M, Purohit P, Brachs S, Spranger J, Hess A, Büttner C, Ekici AB, Perez-Branguli F, Winner B, Rauschenberger V, Banaschewski T, Bokde AL, Büchel C, Conrod PJ, Desrivieres S, Flor H, Frouin V, Gallinat J, Garavan H, Gowland P, Heinz A, Martinot JL, Lemaitre H, Nees F, Paus T, Smolka MN, Schambony A, Bäuerle T, Eulenburg V, Alzheimer C, Lourdasamy A, Schumann G, Müller CP, 2018 EFhd2/Swiprosin-1 is a common genetic determinant for sensation-seeking/low anxiety and alcohol addiction. *Mol. Psychiatry* 23(5), 1303–1319. [PubMed: 28397836]
- Miller WR, Forchimes AA, Zweben A, 2011 *Treating addiction*. The Guilford Press, New York.

- Miquel M, Toledo R, Garcia LI, Coria-Avila GA, Manzo J, 2009 Why Should We Keep the Cerebellum in Mind When Thinking About Addiction? *Curr. Drug Abuse Rev* 2, 26–40. [PubMed: 19630735]
- Mitchell SN, 1993 Role of the Locus-Ceruleus in the Noradrenergic Response to A Systemic Administration of Nicotine. *Neuropharmacology* 32, 937–949. [PubMed: 8295716]
- Mobascher A, Winterer G, 2008 The molecular and cellular neurobiology of nicotine abuse in schizophrenia. *Pharmacopsychiatry* 41 Suppl 1, S51–S59. [PubMed: 18756421]
- Moeller FG, 2012 Sex, stress, and drug cues in addiction. *Am. J. Psychiatry* 169, 351–353. [PubMed: 22476673]
- Montanari C, Stendardo E, De Luca MT, Meringolo M, Contu L, Badiani A, 2015 Differential vulnerability to relapse into heroin versus cocaine-seeking as a function of setting. *Psychopharmacology (Berl)* 232, 2415–2424. [PubMed: 25662790]
- Morgan CJ, Noronha LA, Muetzelfeldt M, Fielding A, Curran HV, 2013 Harms and benefits associated with psychoactive drugs: findings of an international survey of active drug users. *J. Psychopharmacol* 27, 497–506. [PubMed: 23438502]
- Moulton EA, Elman I, Becerra LR, Goldstein RZ, Borsook D, 2014 The cerebellum and addiction: insights gained from neuroimaging research. *Addict. Biol* 19, 317–331. [PubMed: 24851284]
- Müller CP, Huston JP, 2007 Dopamine activity in the occipital and temporal cortices of rats: dissociating effects of sensory but not pharmacological stimulation. *Synapse* 61, 254–258. [PubMed: 17230551]
- Müller CP, Carey RJ, Huston JP, De Souza Silva MA, 2007 Serotonin and psychostimulant addiction: focus on 5-HT1A-receptors. *Prog. Neurobiol* 81, 133–178. [PubMed: 17316955]
- Müller CP, Carey RJ, Wilkisz M, Schwenzner S, Jocham G, Huston JP, De Souza Silva MA, 2008 Acute anxiolytic effects of cocaine: the role of test latency and activity phase. *Pharmacol. Biochem. Behav* 89, 218–226. [PubMed: 18191997]
- Müller CP, Schumann G, 2011a Drugs as instruments: a new framework for non-addictive psychoactive drug use. *Behav. Brain Sci* 34, 293–310. [PubMed: 22074962]
- Müller CP, Schumann G, 2011b, To use or not to use: Expanding the view on non-addictive psychoactive drug consumption and its implications, *Behav. Brain Sci* 34, 328–347. [PubMed: 22379623]
- Müller CP, Pum ME, Amato D, Schüttler J, Huston JP, De Souza Silva MA, 2011 The in vivo neurochemistry of the brain during general anesthesia. *J. Neurochem* 119, 419–446. [PubMed: 21883214]
- Müller CP, Lenz B, Kornhuber J, 2012 Gene-independent heritability of behavioural traits: don't we also need to rethink the "environment"? *Behav. Brain Sci* 35, 374–375. [PubMed: 23095396]
- Müller CP, 2013 Episodic memories and their relevance for psychoactive drug use and addiction. *Front. Behav. Neurosci* 7, 34. [PubMed: 23734106]
- Müller CP, 2015 Eyes on the price: Human culture and its teaching. *Behav. Brain Sci* 38, e51. [PubMed: 26787290]
- Müller CP, Homberg JR, 2015 The role of serotonin in drug use and addiction. *Behav. Brain Res* 277C, 146–192.
- Müller CP, Reichel M, Mühle C, Rhein C, Gulbins E, Kornhuber J, 2015 Brain membrane lipids in major depression and anxiety disorders. *Biochim. Biophys. Acta* 1851, 1052–1065. [PubMed: 25542508]
- Müller CP, 2017 Non addictive drug use: The way forward In: Wolff K, White J and Karch S (Eds.), *The SAGE Handbook of Drugs and Alcohol Studies – Biological Approaches*, SAGE, London, pp. 411–434.
- Müller CP, Kornhuber J, 2017 Biological evidence for paradoxical improvement of psychiatric disorder symptoms by addictive drugs. *Trends Pharmacol. Sci* 38, 501–502. [PubMed: 28389130]
- Müller CP, Kalinichenko LS, Tiesel J, Witt M, Stöckl T, Sprenger E, Fuchser J, Beckmann J, Praetner M, Huber SE, Amato D, Mühle C, Büttner C, Ekici AB, Smaga I, Pomierny-Chamiolo L, Pomierny B, Filip M, Eulenburg V, Gulbins E, Lourdasamy A, Reichel M, Kornhuber J, 2017

- Paradoxical antidepressant effects of alcohol are related to acid sphingomyelinase and its control of sphingolipid homeostasis. *Acta Neuropathol.* 133, 463–483. [PubMed: 28000031]
- Müller CP, 2018 Animal models of psychoactive drug use and addiction - Present problems and future needs for translational approaches. *Behav. Brain Res* doi: 10.1016/j.bbr.2017.06.028.
- Mondaini N, Cai T, Gontero P, Gavazzi A, Lombardi G, Boddi V, Bartoletti R, 2009 Regular moderate intake of red wine is linked to a better women's sexual health. *J. Sex. Med* 6(10), 2772–2777. [PubMed: 19627470]
- Nelson RJ, Demas GE, Huang PL, Fishman MC, Dawson VL, Dawson TM, Snyder SH, 1995 Behavioural abnormalities in male mice lacking neuronal nitric oxide synthase. *Nature* 378, 383–386. [PubMed: 7477374]
- Nesil T, Kanit L, Pogun S, 2015 Nicotine intake and problem solving strategies are modified during a cognitively demanding water maze task in rats. *Pharmacol. Biochem. Behav* 138, 156–163. [PubMed: 26436562]
- Nesse RM, Berridge KC, 1997 Psychoactive drug use in evolutionary perspective. *Science* 278, 63–66. [PubMed: 9311928]
- Nestler EJ, Aghajanian GK, 1997 Molecular and cellular basis of addiction. *Science* 278, 58–63. [PubMed: 9311927]
- Nestler EJ, 2002 Common molecular and cellular substrates of addiction and memory. *Neurobiol. Learn. Mem* 78, 637–647. [PubMed: 12559841]
- Newhouse PA, Potter AS, Dumas JA, Thiel CM, 2011 Functional brain imaging of nicotinic effects on higher cognitive processes. *Biochem. Pharmacol* 82(8), 943–951. [PubMed: 21684262]
- Newman EL, Albrechet-Souza L, Andrew PM, Auld JG, Burk KC, Hwa LS, Zhang EY, DeBold JF, Miczek KA, 2018 Persistent escalation of alcohol consumption by mice exposed to brief episodes of social defeat stress: suppression by CRF-R1 antagonism. *Psychopharmacology*, doi: 10.1007/s00213-018-4905-9.
- Nichols DE, 2004 Hallucinogens. *Pharmacol. Ther.* 101, 131–181. [PubMed: 14761703]
- Nikulina EM, Marchand JE, Kream RM, Miczek KA, 1998 Behavioral sensitization to cocaine after a brief social stress is accompanied by changes in fos expression in the murine brainstem. *Brain Res.* 810(1–2), 200–210. [PubMed: 9813326]
- Nikulina EM, Arrillaga-Romany I, Miczek KA, Hammer RP, 2008 Long-lasting alteration in mesocorticolimbic structures after repeated social defeat stress in rats: time course of mu-opioid receptor mRNA and FosB/DeltaFosB immunoreactivity. *Eur. J. Neurosci* 27, 2272–2284. [PubMed: 18445218]
- Nilsson M, Poulsen JL, Brock C, Sandberg TH, Gram M, Frøkjær JB, Krogh K, Drewes AM, 2016 Opioid-induced bowel dysfunction in healthy volunteers assessed with questionnaires and Mri. *Eur. J. Gastroenterol. Hepatol* 28, 514–524. [PubMed: 26795566]
- Norman KJ, Seiden JA, Klickstein JA, Han X, Hwa LS, DeBold JF, Miczek KA, 2015 Social stress and escalated drug self-administration in mice I. Alcohol and corticosterone. *Psychopharmacology* 232, 991–1001. [PubMed: 25242256]
- Noori HR, Helinski S, Spanagel R, 2014 Cluster and meta-analyses on factors influencing stress-induced alcohol drinking and relapse in rodents. *Addiction Biol.* 19, 225–232.
- Nothdurfter C, Tanasic S, Di Benedetto B, Rammes G, Wagner EM, Kirmeier T, Ganal V, Kessler JS, Rein T, Holsboer F, Rupprecht R, 2010 Impact of lipid raft integrity on 5-HT3 receptor function and its modulation by antidepressants. *Neuropsychopharmacology* 35: 1510–1519. [PubMed: 20200506]
- Nothdurfter C, Tanasic S, Di Benedetto B, Uhr M, Wagner EM, Gilling KE, Parsons CG, Rein T, Holsboer F, Rupprecht R, Rammes G, 2013 Lipid raft integrity affects GABAA receptor, but not NMDA receptor modulation by psychopharmacological compounds. *Int. J. Neuropsychopharmacol* 16: 1361–1371. [PubMed: 23217923]
- Nutt D, King LA, Saulsbury W, Blakemore C, 2007 Development of a rational scale to assess the harm of drugs of potential misuse. *Lancet* 369, 1047–1053. [PubMed: 17382831]
- Nutt DJ, Lingford-Hughes A, Erritzoe D, Stokes PR, 2015 The dopamine theory of addiction: 40 years of highs and lows. *Nat. Rev. Neurosci* 16, 305–312. [PubMed: 25873042]

- Nyaronga D, Greenfield TK, McDaniel PA, 2009 Drinking context and drinking problems among black, white, and hispanic men and women in the 1984, 1995, and 2005 U.S. National Alcohol Surveys. *J. Stud. Alcohol Drug* 70, 16–26
- O'Brien MS, Anthony JC, 2005 Risk of becoming cocaine dependent: epidemiological estimates for the United States, 2000–2001. *Neuropsychopharmacology* 30, 1006–1018. [PubMed: 15785780]
- O'Malley PM, Johnston LD, Bachman JG, 1985 Cocaine use among American adolescents and young adults. *NIDA Res. Monogr* 61, 50–75. [PubMed: 3932881]
- Olds J, Milner P, 1954 Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *J. Comp. Physiol. Psychol* 47, 419–427. [PubMed: 13233369]
- Oliveira TG, Chan RB, Bravo FV, Miranda A, Silva RR, Zhou B, Marques F, Pinto V, Cerqueira JJ, Di Paolo G, Sousa N, 2016 The impact of chronic stress on the rat brain lipidome. *Mol. Psychiatry* 21, 80–88. [PubMed: 25754084]
- Orford J, 2013 *Power, powerlessness, and addiction*. Cambridge University Press, Cambridge.
- Overton DA, 1968 Visual cues and shock sensitivity in the control of T-maze choice by drug conditions. *J. Comp. Physiol. Psychol* 66, 216–219. [PubMed: 5672632]
- Pacak K, Palkovits M, 2001 Stressor specificity of central neuroendocrine responses: Implications for stress-related disorders. *Endocr. Rev* 22, 502–548. [PubMed: 11493581]
- Padwa H, Ni YM, Barth-Rogers Y, Arangua L, Andersen R, Gelberg L, 2014 Barriers to drug use behavior change among primary care patients in urban United States community health centers. *Subst. Use. Misuse* 49, 743–751. [PubMed: 24354547]
- Panksepp JB, Lahvis GP, 2007 Social reward among juvenile mice. *Genes Brain Behav* 6, 661–671. [PubMed: 17212648]
- Panlilio LV, Hogarth L, Shoaib M, 2015 Concurrent access to nicotine and sucrose in rats. *Psychopharmacology (Berl)* 232(8), 1451–1460. [PubMed: 25366874]
- Papp M, Willner P, Muscat R, 1991 An animal-model of anhedonia – attenuation of sucrose consumption and place preference conditioning by chronic unpredictable mild stress. *Psychopharmacology* 104, 255–259. [PubMed: 1876670]
- Pascual M, Valles SL, Renau-Piqueras J, Guerri C, 2003 Ceramide pathways modulate ethanol-induced cell death in astrocytes. *J. Neurochem* 87, 1535–1545. [PubMed: 14713309]
- Patrick ME, Maggs JL, 2008 Short-term changes in plans to drink and importance of positive and negative alcohol consequences. *J. Adolesc* 31, 307–321. [PubMed: 17651796]
- Peele S, Brodsky A, 2000 Exploring psychological benefits associated with moderate alcohol use: a necessary corrective to assessments of drinking outcomes? *Drug Alcohol Depend.* 60, 221–247. [PubMed: 11053757]
- Perkins HW, 1999 Stress-motivated drinking in collegiate and postcollegiate young adulthood: life course and gender patterns. *J. Stud. Alcohol* 60, 219–227. [PubMed: 10091960]
- Peretti-Watel P, Constance J, Seror V, Beck F, 2009 Cigarettes and social differentiation in France: is tobacco use increasingly concentrated among the poor? *Addiction* 104(10): 1718–1728. [PubMed: 19681803]
- Perrotti LI, Weaver RR, Robison B, Renthal W, Maze I, Yazdani S, Elmore RG, Knapp DJ, Selley DE, Martin BR, Sim-Selley L, Bachtell RK, Self DW, Nestler EJ, 2008 Distinct patterns of DeltaFosB induction in brain by drugs of abuse. *Synapse* 62, 358–369. [PubMed: 18293355]
- Perry EK, Perry RH, 1995 Acetylcholine and hallucinations: disease-related compared to drug-induced alterations in human consciousness. *Brain Cogn.* 28, 240–258. [PubMed: 8546852]
- Perry AN, Westenbroek C, Becker JB, 2013 The Development of a Preference for Cocaine over Food Identifies Individual Rats with Addiction-Like Behaviors. *PLoS One* 8(11), e79465. [PubMed: 24260227]
- Piazza PV, Deminiere JM, Le Moal M, Simon H, 1989 Factors that predict individual vulnerability to amphetamine self-administration. *Science* 245, 1511–1513. [PubMed: 2781295]
- Piazza PV, Lemoal M, 1996 Pathophysiological basis of vulnerability to drug abuse: Role of an interaction between stress, glucocorticoids, and dopaminergic neurons. *Ann. Rev. Pharmacol. Toxicol* 36, 359–378. [PubMed: 8725394]

- Piazza PV, Maccari S, Deminiere JM, Le Moal M, Mormede P, Simon H, 1991 Corticosterone levels determine individual vulnerability to amphetamine self-administration. *Proc. Natl. Acad. Sci. U.S. A* 88, 2088–2092. [PubMed: 2006148]
- Piazza PV, Marinelli M, Jodogne C, Deroche V, Rouge-Pont F, Maccari S, LeMoal M, Simon H, 1994 Inhibition of corticosterone synthesis by metyrapone decreases cocaine- induced locomotion and relapse of cocaine self-administration. *Brain Res.* 658, 259–264. [PubMed: 7834350]
- Pich EM, Lorang M, Yeganeh M, de Fonseca FR, Raber J, Koob GF, Weiss F, 1995 Increase of extracellular corticotropin-releasing factor-like immunoreactivity levels in the amygdala of awake rats during restraint stress and ethanol withdrawal as measured by microdialysis. *J. Neurosci* 15, 5439–5447. [PubMed: 7643193]
- Pickard H, 2012 The purpose in chronic addiction. *AJOB Neuroscience* 3, 40–49. [PubMed: 22724074]
- Pitkänen A, Pikkarainen M, Nurminen N, Ylinen A, 2000 Reciprocal connections between the amygdala and the hippocampal formation, perirhinal cortex, and postrhinal cortex in rat. A review. *Ann. N.Y. Acad. Sci* 911, 369–391. [PubMed: 10911886]
- Pizzimenti CL, Navis TM, Lattal KM, 2017 Persistent effects of acute stress on fear and drug-seeking in a novel model of the comorbidity between post-traumatic stress disorder and addiction. *Learn. Mem* 24, 422–431. [PubMed: 28814468]
- Pohorecky LA, 1981 The interaction of alcohol and stress – a review. *Neurosci. Biobehav. Rev* 15, 438–459.
- Pohorecky LA, 1991 The interaction of alcohol and stress – an update of human research. *Alcohol Clin. Exp. Res* 5, 209–229.
- Polter AM, Barcomb K, Chen RW, Dingess PM, Graziane NM, Brown TE, Kauer JA, 2017 Constitutive activation of kappa opioid receptors at ventral tegmental area inhibitory synapses following acute stress. *Elife*, doi: 10.7554/eLife.23785.
- Pontieri FE, Tanda G, Orzi F, Di Chiara G, 1996 Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. *Nature* 382, 255–257. [PubMed: 8717040]
- Porkka-Heiskanen T, Strecker RE, Thakkar M, Bjorkum AA, Greene RW, McCarley RW, 1997 Adenosine: a mediator of the sleep-inducing effects of prolonged wakefulness. *Science* 276, 1265–1268. [PubMed: 9157887]
- Potvin S, Stip E, Roy JY, 2003 Schizophrenia and addiction: An evaluation of the self-medication hypothesis. *Encephale* 29, 193–203. [PubMed: 12876543]
- Preuss UW, Schuckit MA, Smith TL, Danko GR, Dasher AC, Hesselbrock MN, Hesselbrock VM, Nurnberger JI, 2002 A comparison of alcohol-induced and independent depression in alcoholics with histories of suicide attempts. *J. Stud. Alcohol* 63, 498–502. [PubMed: 12162295]
- Pum M, Carey RJ, Huston JP, Müller CP, 2007 Dissociating effects of cocaine and d-amphetamine on dopamine and serotonin in the perirhinal, entorhinal, and prefrontal cortex of freely moving rats. *Psychopharmacology (Berl)* 193, 375–390. [PubMed: 17468969]
- Quadros IM, Miczek KA, 2009 Two modes of intense cocaine bingeing: increased persistence after social defeat stress and increased rate of intake due to extended access conditions in rats. *Psychopharmacology* 206, 109–121. [PubMed: 19513697]
- Quadros IM, Takahashi A, Miczek KA, 2010 Serotonin and Agression In: Müller CP and Jacobs BL (Eds.), *Handbook of the Behavioral Neurobiology of Serotonin*, Academic Press, London, pp. 687–714.
- Quednow BB, Geyer MA, Halberstadt AL, 2010 Serotonin and Schizophrenia In: Müller CP and Jacobs BL (Eds.), *Handbook of the Behavioral Neurobiology of Serotonin*, Academic Press, London, pp. 585–620.
- Ramstedt B, Slotte JP, 2006 Sphingolipids and the formation of sterol-enriched ordered membrane domains. *Biochim. Biophys. Acta* 1758, 1945–1956. [PubMed: 16901461]
- Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J, 2009 Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet* 373, 2223–2233. [PubMed: 19560604]
- Reichel M, Greiner E, Richter-Schmidinger T, Yedibela O, Tripal P, Jacobi A, Bleich S, Gulbins E, Kornhuber J, 2010 Increased acid sphingomyelinase activity in peripheral blood cells of acutely

- intoxicated patients with alcohol dependence. *Alcohol Clin. Exp. Res* 34, 46–50. [PubMed: 19860808]
- Reichel M, Beck J, Mühle C, Rotter A, Bleich S, Gulbins E, Kornhuber J, 2011 Activity of secretory sphingomyelinase is increased in plasma of alcohol-dependent patients. *Alcohol Clin. Exp. Res* 35, 1852–1859. [PubMed: 21595704]
- Resnick RB, Kestenbaum RS, Schwartz LK, 1977 Acute systemic effects of cocaine in man: a controlled study by intranasal and intravenous routes. *Science* 195, 696–698. [PubMed: 841307]
- Rezvani AH, Levin ED, 2001 Cognitive effects of nicotine. *Biol. Psychiatry* 49, 258–267. [PubMed: 11230877]
- Ritz MC, Kuhar MJ, 1989 Relationship Between Self-Administration of Amphetamine and Monoamine Receptors in Brain - Comparison with Cocaine. *J. Pharm. Exp. Therap* 248, 1010–1017.
- Ritz MC, Cone EJ, Kuhar MJ, 1990 Cocaine inhibition of ligand binding at dopamine, norepinephrine and serotonin transporters: a structure-activity study. *Life Sci.* 46, 635–645. [PubMed: 2308472]
- Robbins TW, Everitt BJ, 1996 Neurobehavioural mechanisms of reward and motivation. *Curr. Opin. Neurobiol* 6, 228–236. [PubMed: 8725965]
- Robbins TW, Everitt BJ, 1999 Drug addiction: bad habits add up. *Nature* 398, 567–570. [PubMed: 10217139]
- Robbins TW, Ersche KD, Everitt BJ, 2008 Drug addiction and the memory systems of the brain. *Ann. N. Y. Acad. Sci* 1141, 1–21. [PubMed: 18991949]
- Roberts NP, Roberts PA, Jones N, Bisson JI, 2015 Psychological interventions for post-traumatic stress disorder and comorbid substance use disorder: A systematic review and meta-analysis. *Clin. Psychol. Rev* 38, 25–38. [PubMed: 25792193]
- Robinson TE, Berridge KC, 1993 The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res. Brain Res. Rev* 18, 247–291. [PubMed: 8401595]
- Rodgers B, Kortan AE, Jorm AF, Christensen H, Henderson S, Jacomb PA, 2000 Risk factors for depression and anxiety in abstainers, moderate drinkers and heavy drinkers. *Addiction* 95, 1833–1845. [PubMed: 11177498]
- Rodriguez E, Wrangham R, 1993 Zoopharmacognosy: the use of medicinal plants by animals. *Recent Adv. Phytochem* 27, 89–105.
- Room R, 2000 The more drinking, the more fun; but is there a calculus of fun, and should it drive policy? *Drug Alcohol Depend.* 60, 249–250. [PubMed: 11053758]
- Ross HE, Young LJ, 2009 Oxytocin and the neural mechanisms regulating social cognition and affiliative behavior. *Front. Neuroendocrinol* 30, 534–547. [PubMed: 19481567]
- Ross MM, Arria AM, Brown JP, Mullins CD, Schiffman J, Simoni-Wastila L, dos Reis S, 2018 College students' perceived benefit-to-risk tradeoffs for nonmedical use of prescription stimulants: Implications for intervention designs. *Addict. Behav* 79, 45–51. [PubMed: 29247881]
- Russell JA, Anna W, Mendelsohn GA, 1989 Affect Grid: A single-item scale of pleasure and arousal. *J. Pers. Soc. Psychol* 57, 493–502.
- Rygula R, Abumaria N, Flügge G, Fuchs E, Ruther E, Havemann-Reinecke U, 2005 Anhedonia and motivational deficits in rats: Impact of chronic social stress. *Behav. Brain Res* 162, 127–134. [PubMed: 15922073]
- Saito M, Saito M, Cooper TB, Vadasz C, 2005 Ethanol-induced changes in the content of triglycerides, ceramides, and glucosylceramides in cultured neurons. *Alcohol Clin. Exp. Res* 29, 1374–1383. [PubMed: 16131844]
- Saito M, Chakraborty G, Hegde M, Ohsie J, Paik SM, Vadasz C, Saito M, 2010 Involvement of ceramide in ethanol-induced apoptotic neurodegeneration in the neonatal mouse brain. *J. Neurochem* 115, 168–177. [PubMed: 20663015]
- Salamone JD, 1996 The behavioral neurochemistry of motivation: methodological and conceptual issues in studies of the dynamic activity of nucleus accumbens dopamine. *J. Neurosci. Methods* 64, 137–149. [PubMed: 8699874]
- Samaha AN, Robinson TE, 2005 Why does the rapid delivery of drugs to the brain promote addiction? *Trends Pharmacol. Sci.* 26, 82–87. [PubMed: 15681025]

- Sandhoff R 2010 Very long chain sphingolipids: tissue expression, function and synthesis. *FEBS Lett.* 584, 1907–1913. [PubMed: 20035755]
- Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C, Hen R, 2003 Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* 301, 805–809. [PubMed: 12907793]
- Sapolsky RM, 1990 Stress in the wild. *Sci. Am* 262, 116–123. [PubMed: 2294581]
- Sapolsky RM, 1992 Cortisol concentrations and the social significance of rank instability among wild baboons. *Psychoneuroendocrinology* 17, 701–709. [PubMed: 1287688]
- Sapolsky RM, 2015 Stress and the brain: individual variability and the inverted-U. *Nat. Neurosci* 18, 1344–1346. [PubMed: 26404708]
- Sarnyai Z, Shaham Y, Heinrichs SC, 2001 The role of corticotropin-releasing factor in drug addiction. *Pharmacol. Rev* 53, 209–243. [PubMed: 11356984]
- Sarter M, Hasselmo ME, Bruno JP, Givens B, 2005 Unraveling the attentional functions of cortical cholinergic inputs: interactions between signal-driven and cognitive modulation of signal detection. *Brain Res. Brain Res. Rev* 48, 98–111. [PubMed: 15708630]
- Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014 Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 511, 421–427. [PubMed: 25056061]
- Schmahmann JD, 1996 From movement to thought: anatomic substrates of the cerebellar contribution to cognitive processing. *Hum. Brain Mapp* 4, 174–198. [PubMed: 20408197]
- Schmahmann JD, 2004 Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. *J. Neuropsychiatry Clin. Neurosci* 16, 367–378. [PubMed: 15377747]
- Schneider M, Levant B, Reichel M, Gulbins E, Kornhuber J, Müller CP, 2017 Lipids in psychiatric disorders and preventive medicine. *Neurosci. Biobehav. Rev* 76, 336–362. [PubMed: 27317860]
- Schöpf I, Easton AC, Solati J, Golub Y, Kornhuber J, Giese KP, Müller CP, 2015 alphaCaMKII autophosphorylation mediates neuronal activation in the hippocampal dentate gyrus after alcohol and cocaine in mice. *Neurosci. Lett* 591, 65–68. [PubMed: 25700946]
- Schuckit MA, Tipp JE, Bergman M, Reich W, Hesselbrock VM, Smith TL, 1997 Comparison of induced and independent major depressive disorders in 2,945 alcoholics. *Am. J. Psychiatry* 154, 948–957. [PubMed: 9210745]
- Schuckit MA, Smith TL, Chacko Y, 2006 Evaluation of a depression-related model of alcohol problems in 430 probands from the San Diego prospective study. *Drug Alcohol Depend.* 82, 194–203. [PubMed: 16257139]
- Schuckit MA, Smith TL, Danko GP, Pierson J, Trim R, Nurnberger JI, Kramer J, Kuperman S, Bierut LJ, Hesselbrock V, 2007 A comparison of factors associated with substance-induced versus independent depressions. *J. Stud. Alcohol Drugs*, 68, 805–812. [PubMed: 17960298]
- Schuckit MA, Smith TL, Kalmijn J, 2013 Relationships among independent major depressions, alcohol use, and other substance use and related problems over 30 years in 397 families. *J. Stud. Alcohol Drugs* 74, 271–279. [PubMed: 23384375]
- Schultz W, 2000 Multiple reward signals in the brain. *Nat. Rev. Neurosci* 1, 199–207. [PubMed: 11257908]
- Schuurman T, 1980 Hormonal correlates of agonistic behavior in adult male rats. *Prog. Brain Res* 53, 415–420. [PubMed: 7192876]
- Schwartz RK, Thiel CM, Müller CP, Huston JP, 1998 Relationship between anxiety and serotonin in the ventral striatum. *Neuroreport* 9, 1025–1029. [PubMed: 9601661]
- Segal B, 1985 Confirmatory analyses of reasons for experiencing psychoactive drugs during adolescence. *Int. J. Addict* 20, 1649–1662. [PubMed: 3833802]
- Secchi ME, Factor JA, Schindler CW, Panlilio LV, 2016 Choice between delayed food and immediate oxycodone in rats. *Psychopharmacology (Berl)* 233(23–24), 3977–3989 [PubMed: 27678551]
- Seiden LS, Sabol KE, Ricaurte GA, 1993 Amphetamine - Effects on Catecholamine Systems and Behavior. *Annual Review of Pharmacology and Toxicology* 33, 639–677.
- Sgoifo A, Stilli D, de Boer SF, Koolhaas JM, Musso E, 1998 Acute social stress and cardiac electrical activity in rats. *Aggress. Behav* 24, 287–296.

- Shaham Y, Stewart J, 1994 Exposure to mild stress enhances the reinforcing efficacy of intravenous heroin self-administration in rats. *Psychopharmacology (Berlin)* 114(3), 523–527. [PubMed: 7855213]
- Shaham Y, Shalev U, Lu L, de Wit H, Stewart J, 2003 The reinstatement model of drug relapse: history, methodology and major findings. *Psychopharmacology (Berl)* 168, 3–20. [PubMed: 12402102]
- Sher KJ, Grekin ER, Williams NA, 2005 The development of alcohol use disorders. *Annu. Rev. Clin. Psychol* 1, 493–523. [PubMed: 17716097]
- Shimamoto A, Holly EN, Boyson CO, DeBold JF, Miczek KA, 2015 Individual differences in anhedonic and accumbal dopamine responses to chronic social stress and their link to cocaine self-administration in female rats. *Psychopharmacology* 232, 825–834. [PubMed: 25178816]
- Shurkin J, 2014 News feature: Animals that self-medicate. *Proc. Natl. Acad. Sci. U.S.A* 111(49), 17339–17341. [PubMed: 25492915]
- Silberman Y, Matthews RT, Winder DG, 2013 A corticotropin releasing factor pathway for ethanol regulation of the ventral tegmental area in the bed nucleus of the stria terminalis. *J. Neurosci* 33, 950–960. [PubMed: 23325234]
- Simms JA, Steensland P, Medina B, Abernathy KE, Chandler LJ, Wise R, Bartlett SE, 2008 Intermittent access to 20% ethanol induces high ethanol consumption in Long-Evans and Wistar rats. *Alcohol Clin. Exp. Res* 32, 1816–1823. [PubMed: 18671810]
- Simons K, Ikonen E, 1997 Functional rafts in cell membranes. *Nature* 387, 569–572. [PubMed: 9177342]
- Simons J, Correia CJ, Carey KB, 2000 A comparison of motives for marijuana and alcohol use among experienced users. *Addict. Behav* 25, 153–160. [PubMed: 10708331]
- Singh D, Müller CP, Vicknasingam BK, 2014 Kratom (*Mitragyna speciosa*) dependence, withdrawal symptoms and craving in regular users. *Drug Alcohol Depend.* 139, 132–137. [PubMed: 24698080]
- Sinha R, 2001 How does stress increase risk of drug abuse and relapse? *Psychopharmacology* 158, 343–359. [PubMed: 11797055]
- Sinha R, 2008 Chronic stress, drug use, and vulnerability to addiction. *Ann. N.Y. Acad. Sci* 1141, 105–130. [PubMed: 18991954]
- Sinha R, Catapano D, O'Malley S, 1999 Stress-induced craving and stress response in cocaine dependent individuals. *Psychopharmacology* 142, 343–351. [PubMed: 10229058]
- Skogen JC, Harvey SB, Henderson M, Stordal E, Mykletun A, 2009 Anxiety and depression among abstainers and low-level alcohol consumers. The Nord-Trøndelag Health Study. *Addiction* 104, 1519–1529. [PubMed: 19686521]
- Sofuoglu M, Sewell RA, 2009 Norepinephrine and stimulant addiction. *Addict. Biol* 14, 119–129. [PubMed: 18811678]
- Sommer WH, Rimondini R, Hansson AC, Hipskind PA, Gehlert DR, Barr CS, Heilig MA, 2008 Upregulation of voluntary alcohol intake, behavioral sensitivity to stress, and amygdala *Crhrl* expression following a history of dependence. *Biol. Psychiatry* 63, 139–145. [PubMed: 17585886]
- Spanagel R, 2009 Alcoholism: a systems approach from molecular physiology to addictive behavior. *Physiol Rev.* 89, 649–705. [PubMed: 19342616]
- Spanagel R, Noori HR, Heilig M, 2014 Stress and alcohol interactions: animal studies and clinical significance. *Trends Neurosci.* 37, 219–227. [PubMed: 24636458]
- Sparta DR, Jennings JH, Ung RL, Stuber GD, 2013 Optogenetic strategies to investigate neural circuitry engaged by stress. *Behav Brain Res.* 255, 19–25. [PubMed: 23684554]
- Staddon JER, 1979 Operant behavior as adaptation to constraint. *J. Exp. Psychol. Gen* 108(1), 48–67.
- Stewart SH, 1996 Alcohol abuse in individuals exposed to trauma: a critical review. *Psychol. Bull* 120, 83–112. [PubMed: 8711018]
- Stillman R, Jones RT, Moore D, Walker J, Welm S, 1993 Improved performance 4 hours after cocaine. *Psychopharmacology (Berl)* 110, 415–420. [PubMed: 7870911]

- Stitzer M, Petry N, 2006 Contingency management for treatment of substance abuse. *Annu. Rev. Clin. Psychol* 2, 411–434. [PubMed: 17716077]
- Stolerman I, 1992 Drugs of abuse: behavioural principles, methods and terms. *Trends Pharmacol. Sci* 13, 170–176. [PubMed: 1604709]
- Stoodley CJ, 2012 The cerebellum and cognition: evidence from functional imaging studies. *Cerebellum* 11, 352–365. [PubMed: 21373864]
- Streatfeild D, 2001 Cocaine. *An Unauthorized Biography*. St Martin's Press, New York.
- Sullivan RJ, Hagen EH, 2002 Psychotropic substance-seeking: evolutionary pathology or adaptation? *Addiction* 97(4), 389–400. [PubMed: 11964056]
- Sussman S, Pentz MA, Spruijt-Metz D, Miller T, 2006 Misuse of 'study drugs:' prevalence, consequences, and implications for policy. *Subst. Abuse Treat. Prev. Policy* 1, 15.
- Takahashi A, Chung JR, Zhang S, Zhang H, Grossman Y, Aleyasin H, Flanigan ME, Pfau ML, Menard C, Dumitriu D, Hodes GE, McEwen BS, Nestler EJ, Han MH, Russo SJ, 2017 Establishment of a repeated social defeat stress model in female mice. *Sci. Rep* 7, 12838. [PubMed: 28993631]
- Tatarkiewicz W, 1976 *Analysis of Happiness*. Kluwer Academic Publishers.
- Taylor B, Rehm J, Gmel G, 2005 Moderate alcohol consumption and the gastrointestinal tract. *Dig. Dis* 23, 170–176. [PubMed: 16508280]
- Testa A, Nencini P, Badiani A, 2011 The role of setting in the oral self-administration of alcohol in the rat. *Psychopharmacology (Berl)* 215, 749–760. [PubMed: 21312032]
- Teter CJ, McCabe SE, LaGrange K, Cranford JA, Boyd CJ, 2006 Illicit use of specific prescription stimulants among college students: prevalence, motives, and routes of administration. *Pharmacotherapy* 26, 1501–1510. [PubMed: 16999660]
- Tharp-Taylor S, Haviland A, D'Amico EJ, 2009 Victimization from mental and physical bullying and substance use in early adolescence. *Addict. Behav* 34, 561–567. [PubMed: 19398162]
- Thiel CM, Müller CP, Huston JP, Schwarting RK, 1999 High versus low reactivity to a novel environment: behavioural, pharmacological and neurochemical assessments. *Neuroscience* 93, 243–251. [PubMed: 10430488]
- Thiel CM, 2003 Cholinergic modulation of learning and memory in the human brain as detected with functional neuroimaging. *Neurobiol. Learn. Mem* 80, 234–244. [PubMed: 14521866]
- Thornhill JA, Townsend C, Gregor L, 1989 Intravenous morphine infusion (IMF) to drug-naive, conscious rats evokes bradycardic, hypotensive effects, but pressor actions are elicited after IMF to rats previously given morphine. *Can. J. Physiol. Pharmacol* 67, 213–222. [PubMed: 2743208]
- Tidey JW, Miczek KA, 1996 Social defeat stress selectively alters mesocorticolimbic dopamine release: an in vivo microdialysis study. *Brain Res.* 721, 140–149. [PubMed: 8793094]
- Tidey JW, Miczek KA, 1997 Acquisition of cocaine self-administration after social stress: role of accumbens dopamine. *Psychopharmacology* 130, 203–212. [PubMed: 9151353]
- Timberlake W, Allison J, 1974 Response deprivation: an empirical approach to instrumental performance. *Psychol. Rev* 81(2), 146–164.
- Tizabi Y, Getachew B, Ferguson CL, Csoka AB, Thompson KM, Gomez-Paz A, Ruda-Kucerova J, Taylor RE, 2018 Low Vs. High Alcohol: Central Benefits Vs. Detriments. *Neurotox. Res*, doi: 10.1007/s12640-017-9859-x.
- Tornatzky W, Miczek KA, 2000 Cocaine self-administration “binges”: transition from behavioral and autonomic regulation toward homeostatic dysregulation in rats. *Psychopharmacology* 148, 289–298. [PubMed: 10755742]
- Tsuang MT, 1998 Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. *Arch. Gen. Psychiatry* 55, 967–972. [PubMed: 9819064]
- Tunstall BJ, Kearns DN, 2013 Reinstatement in a cocaine versus food choice situation: reversal of preference between drug and non-drug rewards. *Addict. Biol* 19(5):838–848. [PubMed: 23551949]
- Tunstall BJ, Kearns DN, 2016 Cocaine can generate a stronger conditioned reinforcer than food despite being a weaker primary reinforcer. *Addict. Biol* 21(2), 282–293. [PubMed: 25363637]
- Tunstall BJ, Riley AL, Kearns DN, 2014 Drug specificity in drug versus food choice in male rats. *Exp. Clin. Psychopharmacol* 22(4), 364–372. [PubMed: 24886157]

- Tupala E, Tiihonen J, 2004 Dopamine and alcoholism: neurobiological basis of ethanol abuse. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 28, 1221–1247. [PubMed: 15588749]
- Tupper KW, 2002 Entheogens and existential intelligence: the use of plant teachers as cognitive tools. *Can. J. Educat* 27[4], 499–516.
- Tupper KW, 2003 Entheogens and education: exploring the potentials of psychoactives as educational tools. *J. Drug Educat. Awareness* 1 [2], 145–161.
- Uekermann J, Daum I, 2008 Social cognition in alcoholism: a link to prefrontal cortex dysfunction? *Addiction* 103, 726–735. [PubMed: 18412750]
- Usher M, Cohen JD, Servan-Schreiber D, Rajkowski J, Aston-Jones G, 1999 The role of locus coeruleus in the regulation of cognitive performance. *Science* 283, 549–554. [PubMed: 9915705]
- Uslaner J, Badiani A, Day HE, Watson SJ, Akil H, Robinson TE, 2001a Environmental context modulates the ability of cocaine and amphetamine to induce c-fos mRNA expression in the neocortex, caudate nucleus, and nucleus accumbens. *Brain Res.* 920, 106–116. [PubMed: 11716816]
- Uslaner J, Badiani A, Norton CS, Day HE, Watson SJ, Akil H, Robinson TE, 2001b Amphetamine and cocaine induce different patterns of c-fos mRNA expression in the striatum and subthalamic nucleus depending on environmental context. *Eur. J. Neurosci* 13, 1977–1983. [PubMed: 11403691]
- Vale W, Spiess J, Rivier C, Rivier J, 1981 Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. *Science* 213, 1394–1397. [PubMed: 6267699]
- van Erp AM, Tachi N, Miczek KA, 2001 Short or continuous social stress: suppression of continuously available ethanol intake in subordinate rats. *Behav. Pharmacol* 12, 335–342. [PubMed: 11710748]
- van Erp AM, Miczek KA, 2001 Persistent suppression of ethanol self-administration by brief social stress in rats and increased startle response as index of withdrawal. *Physiol Behav.* 73, 301–311. [PubMed: 11438355]
- Van Overwalle F, Baetens K, Mariën P, Vandekerckhove M, 2015 Cerebellar areas dedicated to social cognition? A comparison of meta-analytic and connectivity results. *Soc. Neurosci* 10, 337–344. [PubMed: 25621820]
- Vandaele Y, Cantin L, Serre F, Vouillac-Mendoza C, Ahmed SH, 2016 Choosing Under the Influence: A Drug-Specific Mechanism by Which the Setting Controls Drug Choices in Rats. *Neuropsychopharmacology* 41(2), 646–657. [PubMed: 26129679]
- Vanderschuren LJM, Everitt BJ, 2004 Drug seeking becomes compulsive after prolonged cocaine self-administration. *Science* 305, 1017–1019. [PubMed: 15310907]
- Veiga MP, Arrondo JL, Goni FM, Alonso A 1999 Ceramides in phospholipid membranes: effects on bilayer stability and transition to nonlamellar phases. *Biophys. J* 76, 342–350. [PubMed: 9876146]
- Vengeliene V, Bilbao A, Molander A, Spanagel R, 2008 Neuropharmacology of alcohol addiction. *Br. J. Pharmacol* 154, 299–315. [PubMed: 18311194]
- Venniro M, Caprioli D, Zhang M, Whitaker LR, Zhang S, Warren BL, Cifani C, Marchant NJ, Yizhar O, Bossert JM, Chiamulera C, Morales M, Shaham Y, 2017 The Anterior Insular Cortex-Central Amygdala Glutamatergic Pathway Is Critical to Relapse after Contingency Management. *Neuron* 96(2), 414–427. [PubMed: 29024664]
- Venniro M, Zhang M, Shaham Y, Caprioli D, 2017 Incubation of Methamphetamine but not Heroin Craving After Voluntary Abstinence in Male and Female Rats. *Neuropsychopharmacology* 42(5), 1126–1135. [PubMed: 28025975]
- Volkow ND, Wang GJ, Fischman MW, Foltin RW, Fowler JS, Abumrad NN, Vitkun S, Logan J, Gatley SJ, Pappas N, Hitzemann R, Shea CE, 1997 Relationship between subjective effects of cocaine and dopamine transporter occupancy. *Nature* 386, 827–830. [PubMed: 9126740]
- Volkow ND, Wang GJ, Fowler JS, Logan J, Gatley SJ, Wong C, Hitzemann R, Pappas NR, 1999 Reinforcing effects of psychostimulants in humans are associated with increases in brain dopamine and occupancy of D(2) receptors. *J. Pharmacol. Exp. Ther* 291, 409–415. [PubMed: 10490931]

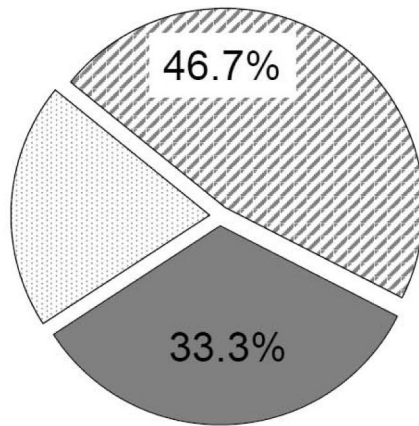
- Volkow ND, Wang G-J, Telang F, Fowler JS, Logan J, Childress A-R, Jayne M, Ma Y, Wong C, 2006 Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. *J. Neurosci* 26, 6583–6588. [PubMed: 16775146]
- Volkow ND, Koob GF, McLellan AT, 2016 Neurobiologic Advances from the Brain Disease Model of Addiction. *N. Engl. J. Med* 374, 363–371. [PubMed: 26816013]
- Von Holst D, 1969 Sozialer Stress bei Tupaia (Tupaia belangeri). *Z. vgl. Physiol* 63, 1–58.
- Von Holst D, 1998 The concept of stress and its relevance for animal behavior In: Møller AP, Milinski M, Slater PJB (eds) *Advances in the Study of Behavior*, Vol. 27: Stress and Behavior. Academic Press, New York, pp 1–131.
- Vonmoos M, Hulka LM, Preller KH, Jenni D, Baumgartner MR, Stohler R, Bolla KI, Quednow BB, 2013 Cognitive dysfunctions in recreational and dependent cocaine users: role of attention-deficit hyperactivity disorder, craving and early age at onset. *Br. J. Psychiatry* 203, 35–43. [PubMed: 23703315]
- Wagner FA, Anthony JC, 2002 From first drug use to drug dependence; developmental periods of risk for dependence upon marijuana, cocaine, and alcohol. *Neuropsychopharmacology*, 26, 479–88. [PubMed: 11927172]
- Waldorf D, Reinerman C, Murphy S, 1991 *Cocaine Changes: the Experience of Using and Quitting*. Temple University Press, Philadelphia.
- Wang B, Shaham Y, Zitzman D, Azari S, Wise RA, You ZB, 2005 Cocaine experience establishes control of midbrain glutamate and dopamine by corticotropin-releasing factor: a role in stress-induced relapse to drug seeking. *J. Neurosci* 25, 5389–5396. [PubMed: 15930388]
- Waterhouse U, Brennan KA, Ellenbroek BA, 2018 Nicotine self-administration reverses cognitive deficits in a rat model for schizophrenia. *Addict. Biol* 23, 620–630. [PubMed: 28497655]
- Weil AT, 1998 *The Natural Mind*. Houghton Mifflin Co.
- Weir E, 2000 Raves: a review of the culture, the drugs and the prevention of harm. *CMAJ* 162, 1843–1848. [PubMed: 10906922]
- Wells BE, Kelly BC, Golub SA, Grov C, Parsons JT, 2010 Patterns of alcohol consumption and sexual behavior among young adults in nightclubs. *Am. J. Drug Alcohol Abuse* 36, 39–45. [PubMed: 20141395]
- White NR, Cagiano R, Moises AU, Barfield RJ, 1990 Changes in mating vocalizations over the ejaculatory series in rats (*Rattus norvegicus*). *J. Comp. Psychol* 104, 255–262. [PubMed: 2225763]
- White NM, 1996 Addictive drugs as reinforcers: multiple partial actions on memory systems. *Addiction* 91, 921–949. [PubMed: 8688822]
- White BP, Becker-Blease KA, Grace-Bishop K, 2006 Stimulant medication use, misuse, and abuse in an undergraduate and graduate student sample. *J. Am. Coll. Health* 54, 261–268. [PubMed: 16539218]
- Williams MJ, Adinoff B, 2008 The role of acetylcholine in cocaine addiction. *Neuropsychopharmacology* 33, 1779–1797. [PubMed: 17928814]
- Wise RA, 1980 The dopamine synapse and the notion of 'pleasure centers' in the brain. *Trends Neurosci.*, 91–95.
- Wise RA, 1994 A brief history of the anhedonia hypothesis In: Legg CR and Both DA (Eds.), *Appetite: Neural and Behavioural Base*, Oxford University Press, Oxford, pp. 234–263.
- Wise RA, 2002 Brain reward circuitry: Insights from unsensed incentives. *Neuron* 36, 229–240. [PubMed: 12383779]
- Wise RA, 2004 Dopamine, learning and motivation. *Nat. Rev. Neurosci* 5, 483–494. [PubMed: 15152198]
- Wolff K, Winstock AR, 2006 Ketamine : from medicine to misuse. *CNS. Drugs* 20, 199–218. [PubMed: 16529526]
- Wolff W, Brand R, 2013 Subjective stressors in school and their relation to neuroenhancement: a behavioral perspective on students' everyday life "doping". *Subst. Abuse Treat. Prev. Policy* 8, 23. [PubMed: 23777577]

- Wolff W, Brand R, Baumgarten F, Losel J, Ziegler M, 2014 Modeling students' instrumental (mis-) use of substances to enhance cognitive performance: Neuroenhancement in the light of job demands-resources theory. *Biopsychosoc. Med* 8, 12. [PubMed: 24904687]
- Wolffgramm J, 1991 An ethopharmacological approach to the development of drug addiction. *Neurosci. Biobehav. Rev* 15(4), 515–519. [PubMed: 1792014]
- Wonnacott S, 1997 Presynaptic nicotinic ACh receptors. *Trends Neurosci.* 20, 92–98. [PubMed: 9023878]
- Wonnacott S, Kaiser S, Mogg A, Soliakov L, Jones IW, 2000 Presynaptic nicotinic receptors modulating dopamine release in the rat striatum. *Eur. J. Pharmacol* 393, 51–58. [PubMed: 10770997]
- Yap JJ, Miczek KA, 2007 Social defeat stress, sensitization, and intravenous cocaine self-administration in mice. *Psychopharmacology* 192, 261–273. [PubMed: 17297635]
- Yap JJ, Miczek KA, 2008 Stress and Rodent Models of Drug Addiction: Role of VTA-Accumbens-PFC-Amygdala Circuit. *Drug Discov. Today Dis. Models* 5, 259–270. [PubMed: 20016773]
- Yap JJ, Chartoff EH, Holly EN, Potter DN, Carlezon WA, Miczek KA, 2015 Social defeat stress-induced sensitization and escalated cocaine self-administration: the role of ERK signaling in the rat ventral tegmental area. *Psychopharmacology* 232,1555–1569. [PubMed: 25373870]
- Young AM, Joseph MH, Gray JA, 1993 Latent inhibition of conditioned dopamine release in rat nucleus accumbens. *Neuroscience* 54, 5–9. [PubMed: 8515846]
- Zacny JP, Lichtor SA, 2008 Nonmedical use of prescription opioids: motive and ubiquity issues. *J. Pain* 9, 473–486. [PubMed: 18342577]
- Zinberg NE, 1984 *Drug, set, and setting: the basis of controlled intoxicant use.* Yale University Press, New Haven.
- Zorrilla EP, Logrip ML, Koob GF, 2014 Corticotropin releasing factor: a key role in the neurobiology of addiction. *Front. Neuroendocrinol* 35, 234–244. [PubMed: 24456850]
- Zuckerman M, 1990 The psychophysiology of sensation seeking. *J. Pers* 58, 313–345. [PubMed: 2198341]
- Zvolensky MJ, Vujanovic AA, Bernstein A, Bonn-Miller MO, Marshall EC, Leyro TM, 2007 Marijuana use motives: A confirmatory test and evaluation among young adult marijuana users. *Addict. Behav* 32, 3122–3130. [PubMed: 17602842]

Highlights

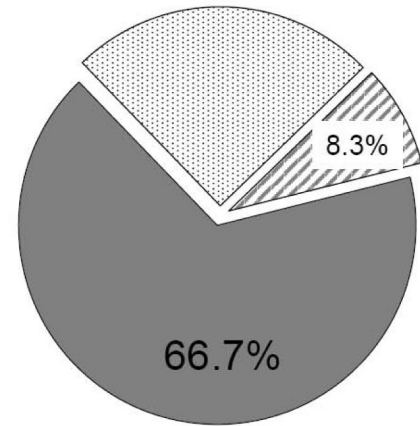
- Non-pharmacological factors modulate pharmacological action of addictive drugs
- We review the neurobiological mechanisms of non-pharmacological influences
- Environmental conditions shape drug search and self-administration
- Social stress is a crucial determinant of drug effects
- Drug instrumentalization allows highly specific drug use in non-addicts
- Behavioral alternatives shape drug choice and consumption patterns

Drug preference at home



Heroin/cocaine preference ratio
 $46.7/33.3 = 1.4$

Drug preference outside the home



Heroin/cocaine preference ratio
 $8.3/66.7 = 0.12$

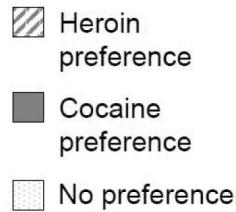


Figure 1.

Drug preferences in rats that were trained to self-administer heroin and cocaine either at home or outside the home on alternate days and were then given the opportunity to choose between the two drugs within the same session, for several daily sessions (see text for details). At home, most rats exhibited a preference for heroin over cocaine. Outside the home, most rats tended to prefer cocaine to heroin. Some rats did not exhibit significant drug preferences; data from: Caprioli et al. (2009). Both the Mann-Whitney test and the Fisher exact probability test indicated significant differences in preference ($p < 0.05$).

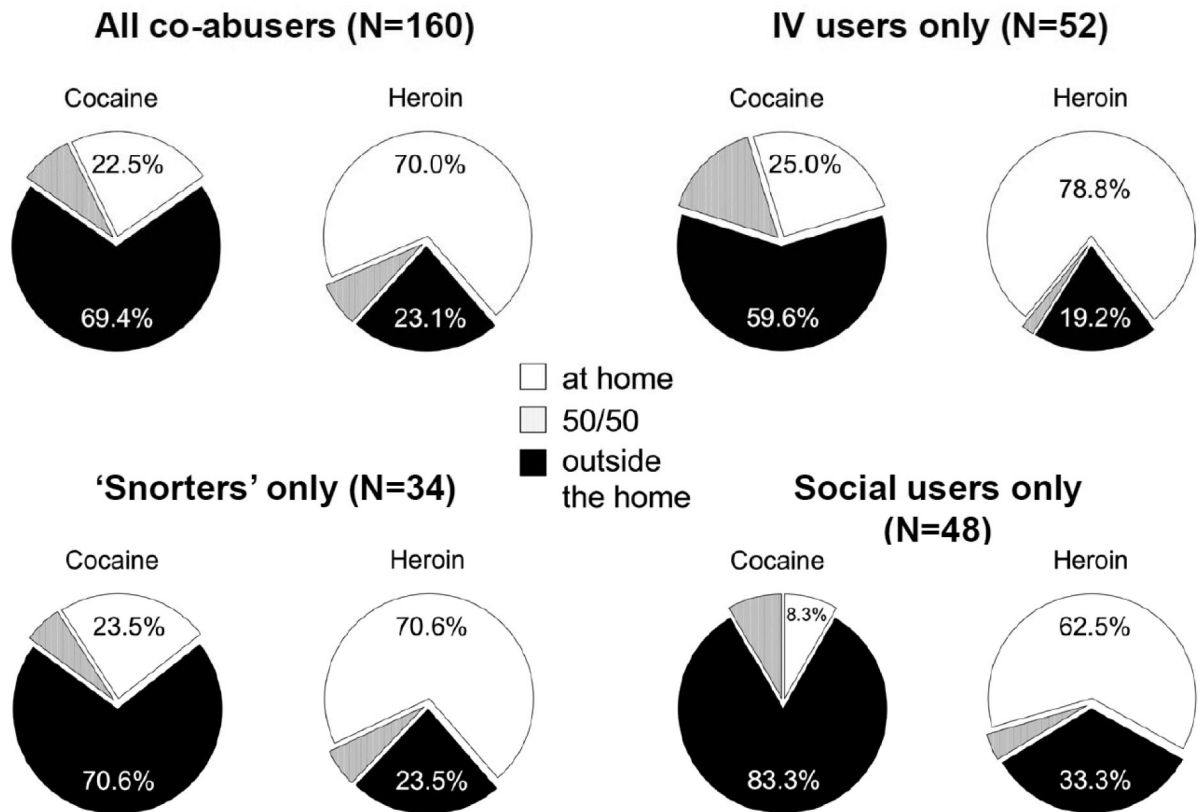


Figure 2.

Setting preferences for heroin versus cocaine use in individuals with substance use disorder in studies using a within-subject design. Most of these individuals reported using heroin exclusively or prevalently at home. In contrast, the same individuals reported using cocaine exclusively or prevalently outside the home. Similar results were obtained in addicts using the intravenous route or the intranasal route for both drugs. Some addicts did not report clear setting preferences. Data from: Caprioli et al. (2009) and Badiani and Spagnolo, (2013). The McNemar's test indicated a significant within-subject shift in the setting for cocaine vs. heroin taking ($p < 0.0001$).

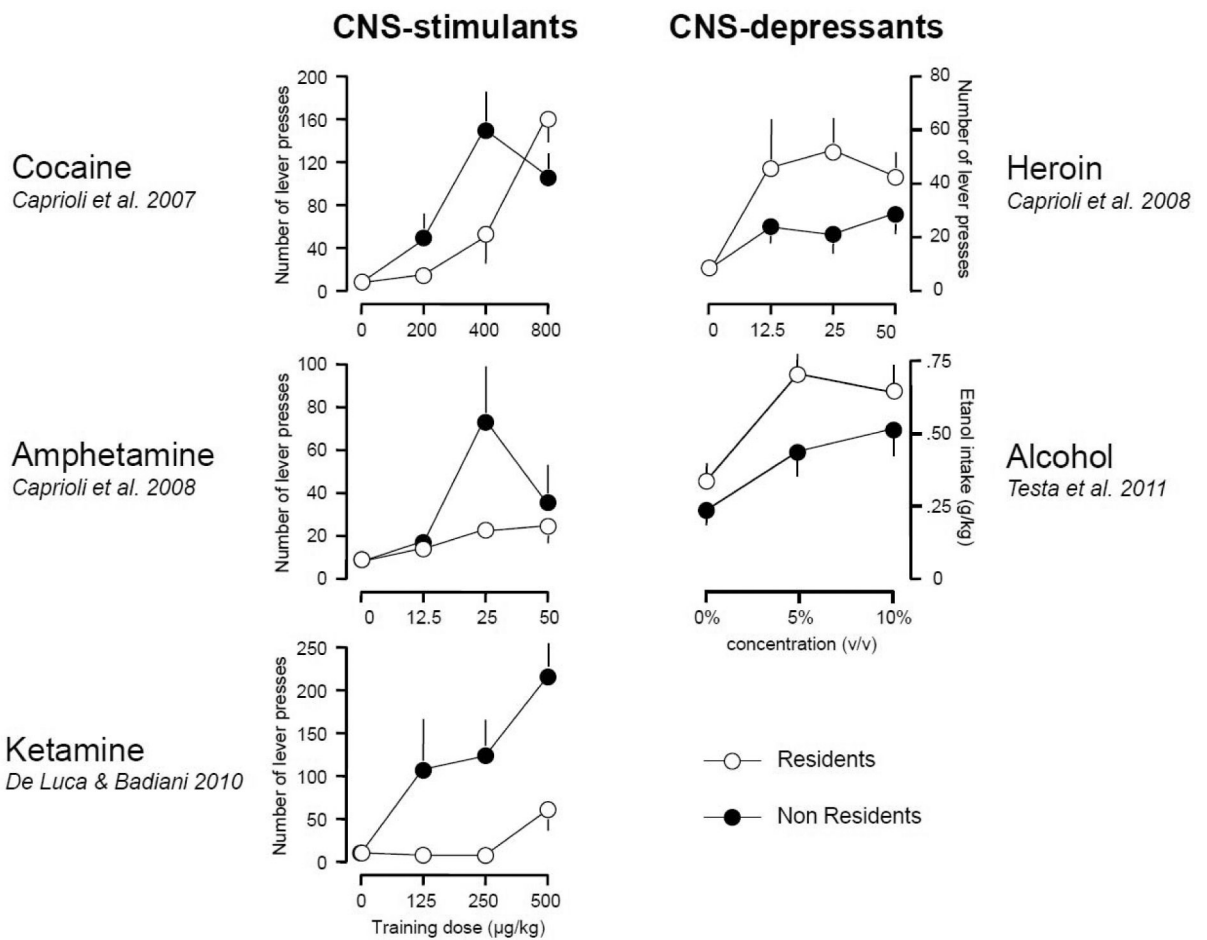


Figure 3. The setting of drug taking affects in opposite directions the intake of drugs that depress the central nervous system (CNS), such as opioid agonists and alcohol, versus drug that have a stimulant effects on the CNS, such as cocaine, amphetamine, and ketamine (data from: Caprioli et al. (2007, 2008), Testa et al. (2011), and De Luca and Badiani (2011)).

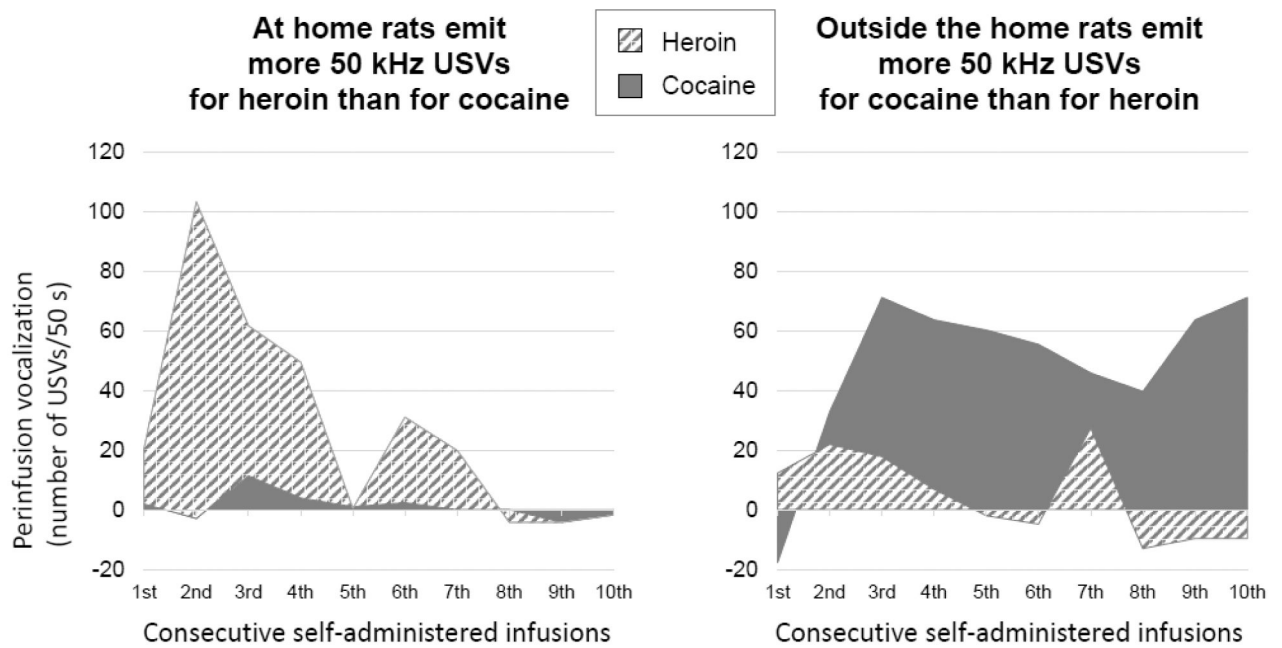


Figure 4. Peri-infusion 50-kHz USVs in the 10 s before and 40 s after each of the ten consecutive self-administered infusions for rats trained to self-administer heroin and cocaine on alternate days, either at home or outside the home. Data were collected on sessions 13 and 14 and were expressed as delta score relative to saline self-administration sessions (sessions 15 and 16); for details see: Avvisati et al. (2016).

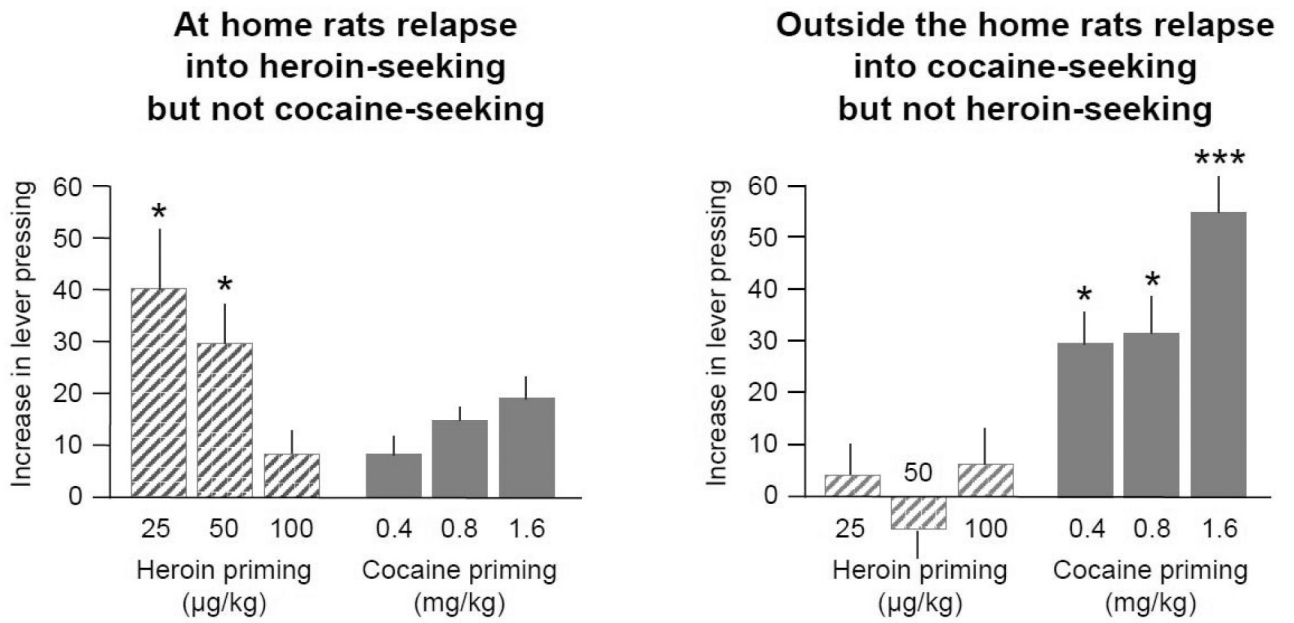


Figure 5.

Increase in lever pressing (means \pm SEM) during a reinstatement session in rats that were trained to self-administer heroin and cocaine on alternate days, either at home or outside the home, and then underwent an extinction procedure. At the beginning of the reinstatement session, independent groups of rats received non-contingent intravenous infusions of one of three doses of cocaine or heroin. At home, rats relapsed into heroin seeking but not into cocaine seeking. Outside the home, the rats relapsed into cocaine seeking but not into heroin seeking. Data were expressed as change in lever pressing relative to the last extinction session. * and *** indicate a main effect of priming (p 0.01 and p 0.0001, respectively); for details see: Montanari et al. (2016)

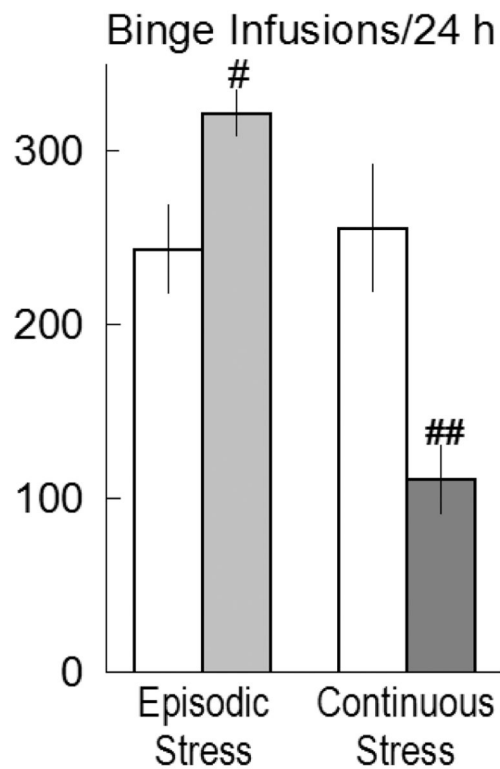


Figure 6. Total number of intravenous cocaine infusions self-administered during a 24 h unrestricted-access binge by rats exposed to 10 d of episodic stress (n = 14; light gray bars) and corresponding controls (n = 14; open bars) or exposed to 36 d of continuous social stress (n = 9; dark gray bars) and corresponding controls (n = 8; open bars). All values are means \pm SEM; #p < 0.05, ##p < 0.01, compared with the relevant control group (data from: Miczek et al. (2011)).

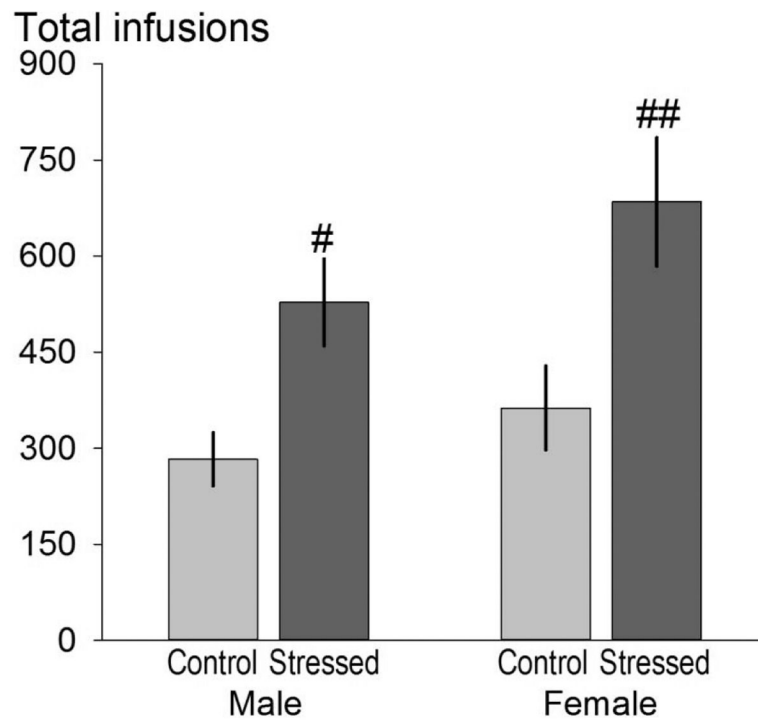


Figure 7. Effects of episodic social defeat stress on total IV infusions self-administered in an unlimited access cocaine “binge” (0.3 mg/kg/infusion, FR1) in male (control n=8, stressed n=8) and female (control n=12, stressed n=10) rats. Self-administration terminated after 120 minutes without a cocaine infusion. Values are means \pm SEM; # p <0.05, ## p <0.01 vs same-sex control (data from: Holly et al. (2012)).

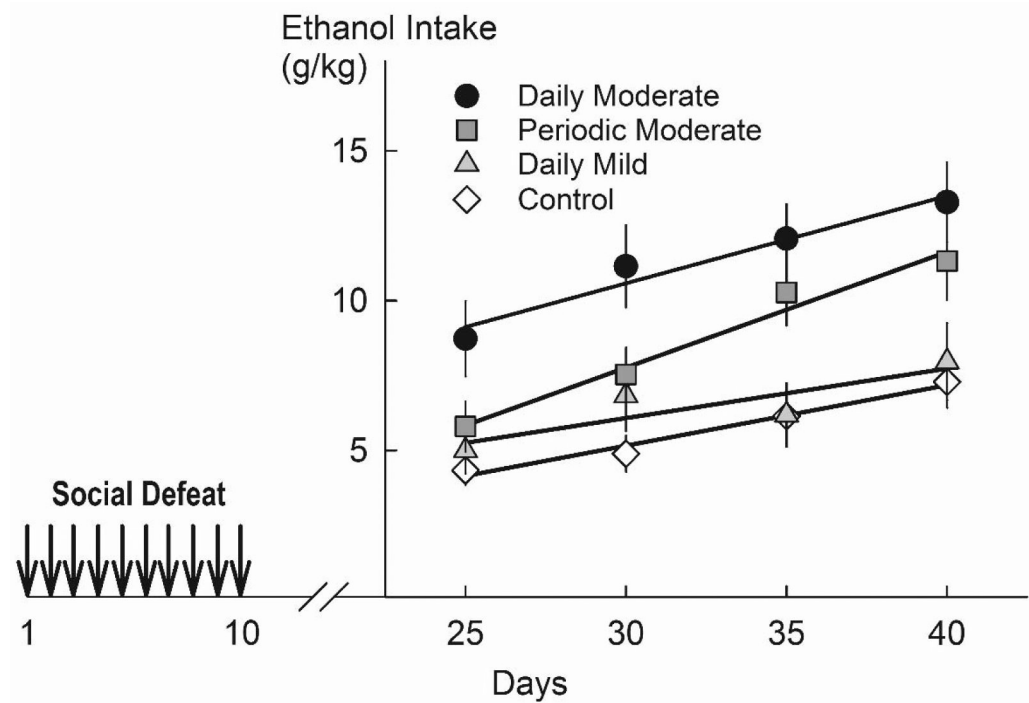


Figure 8.

20% ethanol intake (g/kg/day) during continuous access 2-bottle choice over the course of 20 days, starting 10 days after moderate (n=39) or mild (n=19) social defeat stress (control, n=29). Data points are 5-day averages \pm SEM beginning on the day indicated (i.e. 25 signifies days 25–29); **p<0.001 vs. controls (adapted from: Norman et al. (2015)).

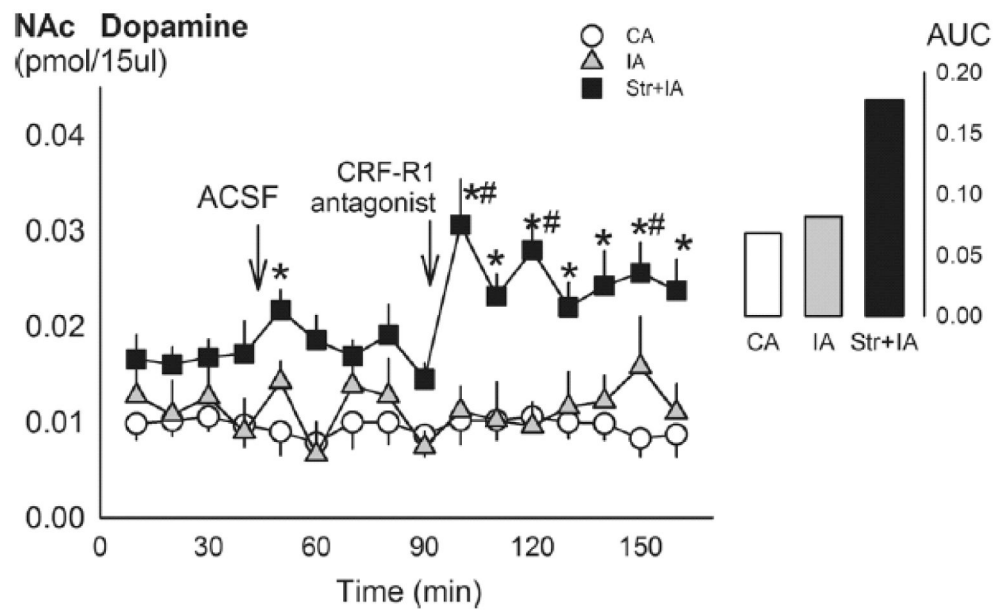


Figure 9. Dopamine levels (pmol/15 μ l) in the nucleus accumbens. White circles are mice with continuous ethanol (EtOH) access (CA; $n = 7$), gray triangles are mice with intermittent EtOH access (IA; $n = 7$), and black squares are socially defeated mice with intermittent EtOH access (Str+IA; $n = 7$). Arrows denote intra-VTA microinjections of aCSF and 0.6 μ g CP376395. Values are means \pm SEM, * $p < 0.05$ vs. CA, # $p < 0.05$ vs. baseline. The bars show area under the curve (AUC) after the CP376395 microinjection (data from: Hwa et al. (2016)).

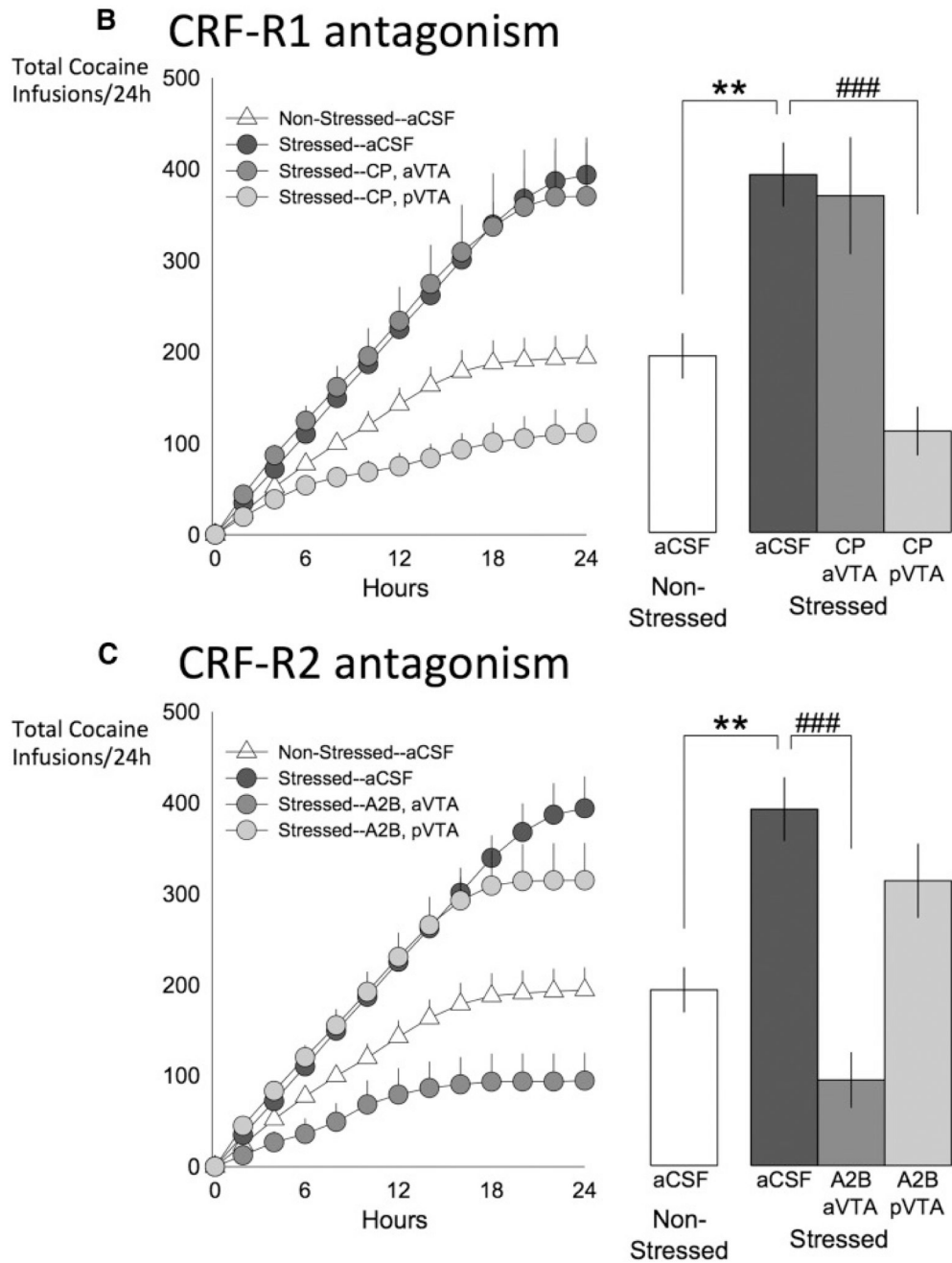


Figure 10.

Role of VTA CRF during stress on later cocaine self-administration. **Top:** Stressed rats pretreated with aCSF before each social defeat (dark gray, n = 11) self-administered significantly more cocaine during a 24 h “binge” compared with aCSF-pretreated nonstressed controls (white, n = 13). This was prevented with intra-pVTA antagonism of CRF-R1 (light gray, CP, n = 4), but not intra-aVTA CRF-R1 antagonism (medium gray, CP, n = 4). Cumulative infusions in 2 h bins are shown on the left, with total infusions shown on the right. **Bottom:** Conversely, intra-aVTA CRF-R2 antagonism (medium gray, A2B, n = 4), but not intra-pVTA CRF-R2 antagonism (light gray, A2B, n = 5), prevented stress escalation

of cocaine self-administration during the 24 h binge. ** $p < 0.01$ vs. aCSF-nonstressed, ### $p < 0.001$ vs. aCSF-stressed (data from: Holly et al. (2016)).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

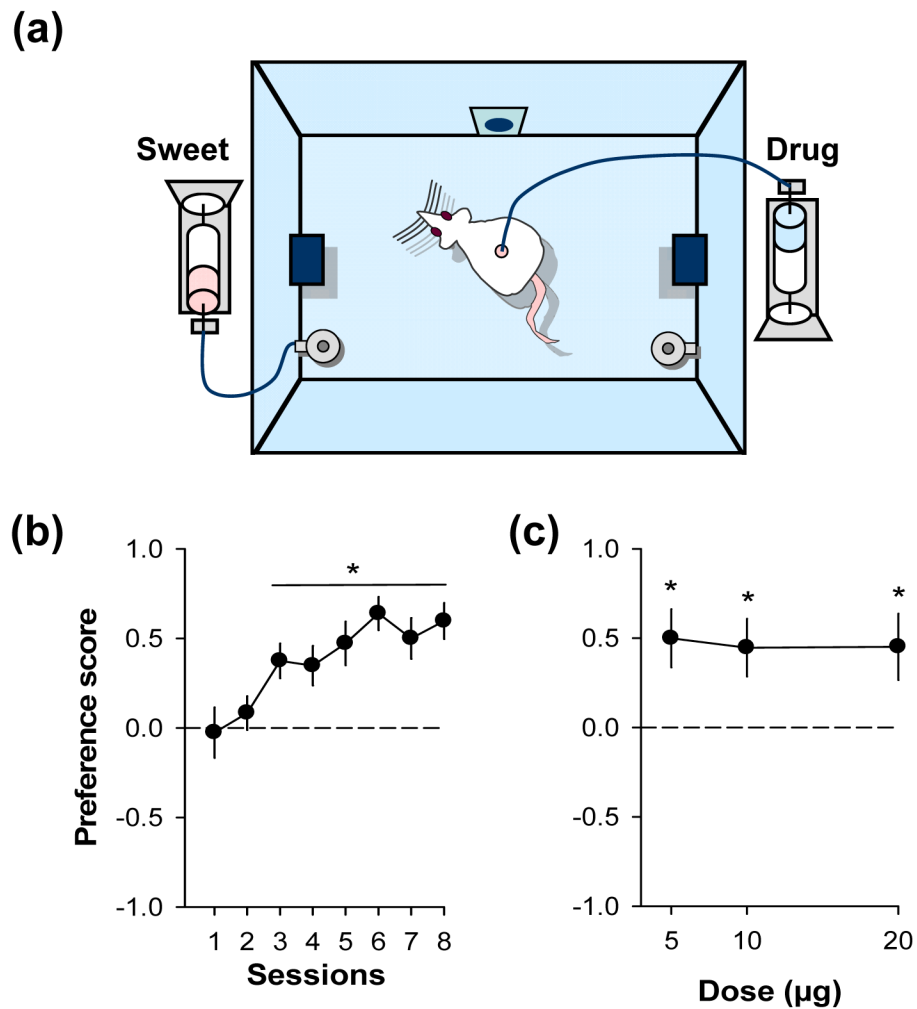


Figure 11. Choice between heroin and a nondrug alternative. (a) Top view of an operant chamber showing a rat choosing between a heroin-paired lever and a sweet water-paired lever. (b) Mean preference scores (\pm SEM) as a function of testing sessions. The horizontal dashed line at 0 represents the indifference level. Values above 0 indicate a preference for water sweetened with saccharin while values below 0 indicate a preference for intravenous heroin. (c) Mean preference scores as a function of i.v. heroin doses. *, different from the indifference level ($p < 0.05$, t-test) (adapted from: Lenoir et al. (2013)).

Substance-specific effects of setting on the rewarding effects of heroin versus cocaine in the rat.

Table 1.

	Heroin	Cocaine
Intake Caprioli et al. 2007, 2008, 2009 Celentano et al. 2009	Rats <i>take more heroin at home</i> than outside the home	Rats <i>take more cocaine outside the home</i> than at home
'Motivation' (PR) Caprioli et al. 2007, 2008 Celentano et al. 2009	Rats are willing to <i>work harder for heroin at home</i> than outside the home	Rats are willing to <i>work harder for cocaine outside the home</i> than at home
Choice: Heroin vs. Cocaine Caprioli et al. 2009	Residents tend to <i>choose heroin at home</i>	Rats tend to <i>choose cocaine outside the home</i>
'Pleasure' (50 kHz USVs) Avvisati et al. 2016	<i>Heroin 'pleasure' is greater at home</i> than outside the home	<i>Cocaine 'pleasure' is greater outside the home</i> than at home
'Craving' after abstinence (Relapse) Montanari et al. 2015	Rats <i>relapse into heroin seeking at home</i> but not outside the home	Rats <i>relapse into cocaine seeking outside the home</i> but not at home