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## **Non-pharmacological factors that determine drug use and addiction**

Serge Ahmed <sup>1\*</sup>, Aldo Badiani <sup>2,3\*</sup>, Klaus A. Miczek <sup>4,5\*</sup>, Christian P. Müller <sup>6\*</sup>

<sup>1</sup> Université 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.

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

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

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

<sup>5</sup> Department of Neuroscience, Sackler School of Graduate Biomedical Sciences, Boston, MA, 02111, USA.

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

\* authors are listed alphabetically, as all authors contributed equally

*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  
Email: Christian.mueller@uk-erlangen.de

## **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-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.

*Key words:* drug abuse, drug addiction, drug instrumentalization; social stress, environment

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## 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 –  $\gamma$ -amino-butyrac acid; GHB –  $\gamma$ -hydroxybutyrate; HPA - hypothalamic–pituitary–adrenal; LPS – lipopolysaccharide; LSD - lysergic acid diethylamide; MDMA – methylenedioxymethamphetamine/ ecstasy; MIA - maternal immune activation; NAc - nucleus accumbens; NA – noradrenaline; nAChR - nicotinergetic 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 -  $\Delta$ 9-tetrahydrocannabinol; VTA - ventral tegmental area; WT – wild type

## 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. While 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 addiction-related behaviors all on their own grounds, 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) and 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, but 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  $\gamma$ -amino-butyric acid (GABA)<sub>A</sub> receptors produces sedation and anxiolysis, at home than outside the home (Testa et al., 2011), 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  $\alpha$  - and  $\beta$  - 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), whereas 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 than 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 and into cocaine seeking (but not heroin seeking) outside the home (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 (Tab. 1) and humans depend on dissociable psychological and neural substrates and that therapeutic approaches to addiction should take into account the peculiarities of different drug classes and the settings of drug use. 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



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 dopamine, 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, and 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, III 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. 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-generalty 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, III 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), 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, III 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, III et al. 2005; Covington, III and Miczek 2001; Holly et al. 2012; Quadros and Miczek 2009; Leonard unpublished). Mice self-administer cocaine in a “burst-and-pause” pattern, whereas most rats self-administer with metronome-like 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 potently 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, III 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, III 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, III 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), and 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 dopamine 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 dopamine 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) with 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 that 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; 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 the autonomic and behavioral responses of an organism. 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. depressive). 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. Here we discuss in how far that has been shown for distinct instrumentalization goals and which insights into neurobiological mechanisms this has yielded (Müller, 2018). 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 & Brodsky 2000; Carrigan et al. 2008; Booth & Hasking 2009). These effects occur after lower doses of alcohol and are mediated by multiple mechanisms in the brain (McBride et al. 2002; Tupala & Tiihonen 2004; Harris et al. 2008; Spanagel, 2009). An important mediator is the interaction of alcohol with GABA<sub>A</sub>-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<sub>A</sub>-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 & 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 & Panksepp 1999; Ross & 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 & 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 & 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 & Schuster 1980) and enhance aggression (Emley & 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 & Kuhar 1989; Ritz et al. 1990) by their interaction with respective monoamine transports (Johanson & 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 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 & 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 &

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 & Morelli 2005).

Another widely used legal drug is nicotine, the active compound in tobacco (Le Foll & 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 & Stolerman 2002) and in non-smoking humans (Rezvani & 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 & Markou 2006).

Psychostimulant drugs have been widely used to increase cognitive performance over long periods of time (Grinspoon & Hedblom 2005; Davey et al. 2007; McCabe et al. 2005; Arria & 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 & Schuster 1980). In particular the acute effects on noradrenergic activity may mediate this action (Johanson & 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; 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<sub>A</sub>-receptor (Ito et al. 1996), though at other binding sites than alcohol, and allosterically enhance responses to the inhibitory transmitter GABA (Allison & Pratt

2003). Enhanced GABA<sub>A</sub>-receptor signaling may reduce innate anxiety and conditioned anxiety. By their interaction with neocortical GABA<sub>A</sub>-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 & 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  $\Delta$ 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  $\Delta$ 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-instatement 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,  $\mu$ - and  $\kappa$ -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 compared (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, a first expressed 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 coordinated interaction of sphingolipids with cholesterol results 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).

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 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 culture (Pascual et al., 2003; Saito et al., 2005), 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 the enzyme acid sphingomyelinase, tgASM, which leads to enhanced turnover of sphingomyelin to ceramide, 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 also 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 little 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 psychotropic 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  $\gamma$ -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) and are used for this reason by non-addicts (Boyd et al., 2006; Teter et al., 2006; McCabe et al., 2007; Zacny and Lictor, 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 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 & Imperato 1989; Di Chiara 1995), which is a key structure of the brain's reward circuitry (Olds & 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 & 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 & 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 & Hikosaka 2009). While DA may still have an outstanding role for reinforcement learning, drug use and addiction (Robbins & Everitt 1996; Ikemoto & 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 & 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 & Aghajanian 1997; Koob 1999; Everitt & Wolf 2002; Kalivas & Volkow 2005; Williams & Adinoff 2007; Heilig & Koob 2007; Müller and Homberg, 2015).

Other instrumentalization goals include the ‘Improvement of physical appearance and attractiveness’ (Garattini et al. 1978; Goldstein 1990; Boys et al. 1999, 2000; Boys & Marsden 2003) and the ‘Facilitation of spiritual and religious activities’ (Abel, 1980; Streatfeild, 2001; Jay, 2010). Since they may apply exclusively to humans, no animal models have been developed so far. An important motives for drug self-administration in animals and humans is to self-medicate for physical problems and its indicator, pain (Colpaert et al., 2001). To our

knowledge, no direct demonstration of drug instrumentalization for this goal has been established yet. 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. These may include a.) behaviors directed towards an improvement of physical appearance and attractiveness (e.g. nicotine consumption to reduce appetite and eating), b.) the improvement of physical performance (e.g. sport doping) c.) the facilitation of spiritual and religious activities, and d.) the self-medication to reduce pain (Müller and Schumann, 2011a, 2011b, Müller, 2017). 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.

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## Figure legends

**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 ( $p \leq 0.05$ ).

**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 (in white); 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 ( $p \leq 0.01$  and  $p \leq 0.0001$ , 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  $\mu$ 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 µg CP376395. Values are means ± 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)).

**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 (± 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)).

**Table 1.** Substance-specific effects of setting on the rewarding effects of heroin versus cocaine in the rat.