HHS Public Access

Author manuscript

Neurosci Biobehav Rev. Author manuscript; available in PMC 2022 March 18.

Published in final edited form as:

Neurosci Biobehav Rev. 2021 December ; 131: 847–864. doi:10.1016/j.neubiorev.2021.09.050.

Factors modulating the incubation of drug and non-drug craving and their clinical implications

Marco Venniro[1,*,#], **Ingrid Reverte**[2,3,*], **Leslie A. Ramsey**[4], **Kimberly M. Papastrat**[1], **Ginevra D'Ottavio**[2,3], **Michele Stanislaw Milella**[5], **Xuan Li**[6,#], **Jeffrey W. Grimm**[7,#], **Daniele Caprioli**[2,3,#]

[1]Department of Anatomy and Neurobiology, University of Maryland School of Medicine, Baltimore, USA

[2]Department of Physiology and Pharmacology, Sapienza University of Rome, Rome, Italy

[3]Santa Lucia Foundation (IRCCS Fondazione Santa Lucia), Rome, Italy

[4]Behavioral Neuroscience Research Branch, Intramural Research Program, Baltimore NIDA, NIH, USA

[5]Toxicology Unit, Policlinico Umberto I University Hospital, Rome, Italy

[6]Department of Psychology, University of Maryland College Park, College Park, USA

[7]Department of Psychology and Program in Behavioral Neuroscience, Western Washington University, Bellingham, USA

Abstract

It was suggested in 1986 that cue-induced cocaine craving increases progressively during early abstinence and remains high during extended periods of time. Clinical evidence now supports this hypothesis and that this increase is not specific to cocaine but rather generalize across several drugs of abuse. Investigators have identified an analogous incubation phenomenon in rodents, in which time-dependent increases in cue-induced drug seeking are observed after abstinence from intravenous drug or palatable food self-administration. Incubation of craving is susceptible to variation in magnitude as a function of biological and/or the environmental circumstances surrounding the individual.

During the last decade, the neurobiological correlates of the modulatory role of biological (sex, age, genetic factors) and environmental factors (environmental enrichment and physical exercise, sleep architecture, acute and chronic stress, abstinence reinforcement procedures) on incubation of drug craving has been investigated. In this review, we summarized the behavioral procedures adopted, the key underlying neurobiological correlates and clinical implications of these studies.

[#]Corresponding authors: Marco Venniro (marco.venniro@som.umaryland.edu), Jeffrey W. Grimm (grimmj@wwu.edu), Xuan Li (annali@umd.edu) and Daniele Caprioli (daniele.caprioli@uniroma1.it).

Author's contributions: MV, IR, LAR, KP, GD, MSM, XL, JWG, DC wrote the manuscript.

[*]These authors equally contributed to the manuscript (MV and IR)

Keywords

self-administration; relapse; craving; contingency management; social community approach; abstinence; incubation; substance use disorders

1. Introduction

A defining feature of substance use disorder (SUD) is drug relapse, that is often triggered by craving, an intense subjective experience of wanting to use a drug (Drummond, 2001; Mendelson and Mello, 1996; O'Brien, 1997; Preston et al., 2018). Now a formal criterion in the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) (Murphy et al., 2014), craving is regarded as a dynamic phenomenon. This is a reason why the large majority of clinical assessments focus on its perceived intensity (Tiffany and Wray, 2012). Notably, craving intensity has been found to predict treatment outcomes (Higley et al., 2011; Tsui et al., 2014). An account of craving dynamicity is exemplified by the incubation of drug craving phenomenon, the progressive increase of cue-induced drug craving during abstinence from drug self-administration (Gawin and Kleber, 1986; Pickens et al., 2011). Incubated craving typically remains elevated for extended drug-free periods followed by a stable decline.

Here we review the biological and environmental factors that modulate (either exacerbate or attenuate) the intensity of drug craving over time. We refer the readers to (Altshuler et al., 2020; Dong and Nestler, 2014; Li et al., 2015b; Pickens et al., 2011; Wolf, 2016) for a thorough analysis of the neurobiological mechanisms of incubation of drug craving per se.

We first describe the biological factors modulating incubation of drug (or food) craving, which include sex, age and genetic factors. We will then review the environmental factors. The latter include environmental enrichment and physical exercise, sleep architecture, acute and chronic stress and abstinence reinforcement procedures. Next, we will review the relevant neurobiological research on the subject. Due to the limited literature available, we discuss incubation of non-drug reward craving separately. We conclude by describing the implications of the reviewed studies to SUD. A comprehensive understanding of the factors that modulate craving intensity, and their interactions, is essential in the management of craving.

1.1. Brief history of incubation of craving (Fig. 1A and Fig. 1B)

In 1986, based on clinical observations, Gawin and Kleber (1986) proposed that cue-induced cocaine craving progressively increases during early abstinence and remains elevated for extended drug-free periods. At the time, this hypothesis was based on limited evidences and was not immediately pursued (Li et al., 2016; Venniro et al., 2016). More than a decade later, Grimm et al. (2001) described a similar phenomenon in rodents, pre-trained to self-administer cocaine, based on observations that time-dependent increases in cue-induced drug seeking occurred after withdrawal from cocaine (Neiswander et al., 2000) and heroin (Shalev et al., 2001a). Specifically, responding for cues associated with cocaine intensified after cessation of drug self-administration. This cocaine "craving" was significantly higher

after 1–2 months than after 1–7 days of abstinence from cocaine. At present, the concept of incubation of craving has been substantiated by several clinical and preclinical studies for both drug and food rewards. Incubation of cue-induced drug craving has been observed in rodents with a self-administration history of heroin (Shalev et al., 2001a), nicotine (Abdolahi et al., 2010), alcohol (Bienkowski et al., 2004), methamphetamine (Shepard et al., 2004), oxycodone (Fredriksson et al., 2020) and fentanyl (Martin et al., 2021). Incubation of drug craving has also been observed in humans with a drug taking history of nicotine (cigarette smoking) (Bedi et al., 2011), methamphetamine (Wang et al., 2013; Zhao et al., 2021), alcohol (Bach et al., 2020; Treloar Padovano and Miranda, 2021) and cocaine (Parvaz et al., 2016). The demonstration of incubation in human studies provides support for the translational potential of therapeutic targets for relapse uncovered through basic research with rodents.

2. Biological factors modulating incubation of drug craving

2.1. Sex

2.1.1. Behavioral findings (Fig. 2A and Fig. 2B)—Several clinical and preclinical studies have investigated sex differences in all stages of SUD [for comprehensive reviews, refer to (Anker and Carroll, 2011; Becker, 2016; Becker and Chartoff, 2019; Becker and Hu, 2008; Becker et al., 2012; Bobzean et al., 2014; Carroll and Anker, 2010; Lynch et al., 2002; Riley et al., 2018)] including drug craving and relapse. The emerging picture is complex, due to the large inconsistencies 1) within clinical or preclinical studies, 2) between clinical and preclinical studies and 3) across drug classes (Fredriksson et al., 2021; Nicolas et al., 2021). Overall, the results of the clinical studies do not support the notion that women are more vulnerable to psychostimulant, opioid, alcohol and nicotine craving. For example, some human studies show that women experience stronger craving to cocaine (Fox and Sinha, 2014; Fox et al., 2013; Kennedy et al., 2013; Li et al., 2005; Potenza et al., 2012; Robbins et al., 1999) and heroin (Moran et al., 2018; Yu et al., 2007) or show a higher smoking cue reactivity than men (Janes et al., 2009, 2010, 2012; Wetherill et al., 2013). In contrast, other reports did not find sex differences in cocaine (Back et al., 2005; Elman et al., 2001; Volkow et al., 2011), opioids (Herbeck et al., 2016; Kennedy et al., 2013) and alcohol (Yarmush et al., 2016) craving. To the contrary, other reports find higher alcohol-primed craving (Willner et al., 1998) and smoking-cue reactivity (Dumais et al., 2017) in men than women.

The few available evidences on incubation of drug craving (Bedi et al., 2011; Li et al., 2014; Parvaz et al., 2016; Wang et al., 2013) have not directly examined sex differences, which may be due to limited sample sizes in each sex.

Preclinical studies provide evidences for sex differences in stress-induced reinstatement and incubation of cocaine craving, but not cue- or cocaine priming-induced reinstatement of cocaine seeking. These studies primarily employed the reinstatement procedure in rats (Alonso-Caraballo et al., 2021; Shaham et al., 2003; Venniro et al., 2016). Drug-associated cues are the most commonly used triggers to study drug seeking after abstinence (Lu et al., 2004b). Female rats, relative to males, show potentiated incubation of cocaine craving after abstinence from short-access (Kerstetter et al., 2008) or intermittent-access

(but not continuous-access) self-administration (Nicolas et al., 2019), and cocaine seeking in females, but not males, stays elevated until 180 days (Kerstetter et al., 2008). Notably, two recent incubation studies revealed no differences between females and males in methamphetamine (Venniro et al., 2018, 2017b), heroin (Venniro et al., 2017b) and oxycodone (Fredriksson et al., 2020) craving after either forced or voluntary abstinence. The dissimilar results in the sex differences between cocaine and methamphetamine, or opioids, in incubated craving have yet to be determined. However, it has been suggested that distinct drugs of abuse feature distinct behavioral and neurobiological determinants that should be taken into considerations (Badiani et al., 2011).

2.1.2. Neurobiological findings (Fig. 3)—What contributes to the sex differences in incubation of cocaine craving? Key factors are ovarian hormones associated with the estrus cycle (Anker and Carroll, 2011). Kerstetter et al. (2008); Nicolas et al. (2019) and Corbett et al. (2021) report that females rats during estrus exhibit stronger incubation of craving than during non-estrus or males, which is consistent with findings in cocaine-induced reinstatement (Feltenstein et al., 2009; Feltenstein and See, 2007; Kippin et al., 2005). The role of the estrus cycle in enhancing cocaine seeking behavior has been linked to ovarian hormones: progesterone and estrogen. Eliminating both progesterone and estrogen by ovariectomy in rats decreases cocaine priming-induced reinstatement, an effect rescued by systemic administration of estrogen (Larson et al., 2005) or estrogen receptor beta agonist (Larson and Carroll, 2007). Lower plasma progesterone levels, on the other hand, are associated with enhanced cocaine priming-induced reinstatement during estrus (Feltenstein and See, 2007). Systemic administration of progesterone (Anker et al., 2007; Feltenstein et al., 2009) or allopregnanolone (the metabolite of progesterone) suppresses cocaine priming-induced reinstatement (Anker et al., 2009). Consistent with animal studies, women report decreased craving for cocaine in the luteal phase (when progesterone level is high) compared with the follicular phase (Evans et al., 2002; Sofuoglu et al., 1999). Progesterone treatment in both men and women decreased subjective effects of cocaine use (Sofuoglu et al., 2002, 2004). Based on these findings, an interesting question for future studies is whether manipulating ovarian hormones also affect incubation of cocaine craving.

2.2. Age

2.2.1. Behavioral findings (Fig. 2A and Fig. 2B)—Another key biological factor that affects incubation of drug craving is age, and adolescence has been a main focus of both clinical and pre-clinical studies (Bernheim et al., 2013; Jordan and Andersen, 2017; Schramm-Sapyta et al., 2009; Spear, 2000, 2016; Stanis and Andersen, 2014). As a critical developmental period, adolescence is characterized by increased risk-taking and sensation/novelty/reward seeking (Galvan, 2010; Jordan and Andersen, 2017; Kreek et al., 2005; Laviola et al., 2003; Spear, 2000, 2016) relative to adults, all of which may contribute to increased vulnerability to drug abuse. Moreover, epidemiological studies show that most individuals diagnosed with SUD initiate drug use as teenagers or young adults (Chen and Kandel, 1995; O'Loughlin et al., 2009), which is associated with increased drug-related problems in later life (Anthony and Petronis, 1995; Clark et al., 1998; Kandel et al., 1992; Palmer et al., 2009). However, it is controversial as to whether adolescents are biologically

more vulnerable to SUD or whether initiation of drug use in adolescents contributes to SUD in adults [see (Bernheim et al., 2013; Schramm-Sapyta et al., 2009) for details].

In animal studies, the age at which drug exposure starts can be precisely controlled and adolescence in rodents is usually referred to a short time window between postnatal day 28–42 (Spear, 2000). However, since behavioral procedures to study animal models of relapse such as incubation usually require 1–2 months (Pickens et al., 2011; Venniro et al., 2016), this short time window presents a challenge to examine relapse behaviors within the adolescence window of rodents. Therefore, preclinical researchers have been focusing on whether adolescent onset drug self-administration leads to potentiated drug seeking in adulthood, compared with adult-onset drug self-administration.

For example, the Frantz laboratory conducted a series of studies to compare incubation of craving after adolescent-onset versus adult-onset drug self-administration and their findings are quite unexpected (Doherty et al., 2013; Doherty and Frantz, 2012; Li and Frantz, 2009, 2017; Li et al., 2018a). In these studies, adolescent or adult rats go through short-access (2 or 3 h/day) drug self-administration and forced abstinence, followed by a single extinction test (Doherty et al., 2013) or a within-session extinction and cue-induced reinstatement test (Doherty and Frantz, 2012; Li and Frantz, 2009, 2017; Li et al., 2018b). Adolescent-onset self-administration rats exhibit both attenuated incubation (assessed during extinction sessions) and cue-induced reinstatement for cocaine (Li and Frantz, 2009, 2017; Li et al., 2018a) and heroin seeking (Doherty et al., 2013; Doherty and Frantz, 2012), compared with adult-onset groups. It is of note that studies above show no differences during drug self-administration (Doherty et al., 2013; Doherty and Frantz, 2012; Li and Frantz, 2009, 2017; Li et al., 2018a). These findings are also in line with a recent nicotine study by Funk et al. (2016) that found an attenuated incubated nicotine craving in adolescent-onset, compared to adult-onset, rats after 2 h nicotine self-administration.

Overall, these findings suggest adolescent onset rats may develop resistance, rather than increase vulnerability, to cue-induced relapse assessed in adulthood. However, in contrast with Frantz group (Li and Frantz, 2009; Li et al., 2018a) and Lê group (Funk et al., 2016) findings, Madsen et al. (2017) evaluated incubation of craving using extended access cocaine self-administration and demonstrate that adolescent- and adult-onset groups exhibit similar incubation of cocaine craving. This finding is supported by a recent study reporting no age differences in incubated oxycodone seeking after extended access oxycodone self-administration, but adolescent rats exhibit decreases seeking during early abstinence (Altshuler et al., 2021).

Two factors may contribute to these conflicting results. One factor is that the incubation of craving after short access self-administration (Li and Frantz, 2009; Li et al., 2018a), is generally less robust (Lu et al., 2004a) relative to that following extended access self-administration (Madsen et al., 2017). Therefore, adolescent-onset groups with short-access self-administration may fail to produce incubation of craving. The other factor is the housing condition. Studies from the Frantz group (Li and Frantz, 2009; Li et al., 2018a) house the rats in pairs, while Madsen's group (Madsen et al., 2017) houses rats individually. The Frantz group has shown that pair housing condition may contribute to the attenuated

incubation of cocaine craving in adolescent-onset rats (Li and Frantz, 2017), possibly due to the developmental significance of social interaction in adolescents (Auger and Olesen, 2009; Burke et al., 2017; Douglas et al., 2004; Panksepp, 1981). However, a recent study using group-housing condition observed no differences in incubation of oxycodone craving after adolescent- and adult-onset oxycodone self-administration. Therefore, it is possible that age differences in cue-induced drug seeking may be more sensitive to different self-administration procedures than housing conditions (Altshuler et al., 2021).

Lastly, the results from incubation studies also contrast with those from the classical reinstatement model: both Anker and Carroll (2010) and Wong and Marinelli (2016) report potentiated stress-induced reinstatement of cocaine seeking in adolescent compared to adult-onset rats, while Cho et al. (2020), report no differences in context-reinstatement of cocaine seeking between adolescent- and adult-onset rats.

For drug priming-induced reinstatement, the current findings are mixed (Anker and Carroll, 2010; Li and Frantz, 2017; Shram et al., 2008), probably due to the differences in behavioral procedures used in each study.

The literature reviewed above conclusively demonstrates that adolescents are not more vulnerable to incubation than adults, providing preclinical evidence that adolescents are not biologically more vulnerable than adults.

Adolescence, in contrast to adulthood, is a sensitive period of brain development and the resulting behavioral flexibility and self-regulatory competence are shaped by the experiences (e.g., social interactions and relationships) (Burke et al., 2017; Westbrook et al., 2018). Based on this consideration, the procedural differences discussed above might reflect distinct “experiences” that might have contributed to the discrepancies between studies in the adolescent behavioral outcome. The same line of reasoning might justify the many controversies highlighted in human studies (Bernheim et al., 2013; Schramm-Sapyta et al., 2009), although to the best of our knowledge, no studies explicitly addressed cue reactivity between adolescents and adults. Because only a minority of adolescents experiencing recreational drugs will later develop SUD (Anthony et al., 1994; Kandel, 1991) we believe that a major aim for future studies will consist in finding endophenotypes (Dalley and Ersche, 2019) along with vulnerability markers of cue-induced relapse.

2.2.2. Neurobiological findings (Fig. 3)—Few studies have addressed the neurobiology of incubation of drug craving after adolescent-onset self-administration. Doherty et al. (2013) compared Fos [a neuronal activity marker (Morgan and Curran, 1991)] induction in medial prefrontal cortex (mPFC; both prelimbic and infralimbic cortex) during heroin seeking tests after 12-days of abstinence from heroin self-administration between adolescent- and adult-onset rats. They found no induction of Fos in adolescent-onset rats, while adult-onset rats showed significant induction of Fos in mPFC during heroin seeking. These data highlight the potential role of mPFC, a brain area that undergoes significant anatomical and functional changes during adolescence (Ernst et al., 2006; Spear, 2000; Tseng and O’Donnell, 2007), in mediating drug seeking behavior after adolescent-onset drug self-administration. In a more recent study from the same group (Li

et al., 2018a), Li et al. explored potential mechanisms underlying attenuated cue-induced reinstatement of cocaine seeking after adolescent-onset self-administration and they found that Arc and brain-derived neurotrophic factor (BDNF) gene expression in PFC and nucleus accumbens (NAc) were overall higher in adolescent-onset than adult-onset rats, suggesting the protective role of Arc and BDNF in adolescent-onset rats against future drug seeking in adulthood. However, these data above are correlational and further functional studies are needed to test causality.

All animal studies described in this section focused exclusively on males. As mentioned above, sex is an important biological factor in incubation of craving and adolescence is indeed the period that animals develop sexual maturity (Spear, 2000). Therefore, an important future direction is to take both sex and age into consideration (Kuhn, 2015) when examining the effect of biological factors on incubation of craving. Additionally, drug abuse in older population has been on the rise recently (Chhatre et al., 2017; Lehmann and Fingerhood, 2019), but largely ignored previously in clinical and preclinical studies. It would be interesting to examine how the effect of aging on incubation of craving in future studies.

2.3. Genetic factors

Genetic prediction efforts in SUD are difficult because of its polygenic, heterogeneous, and multifactorial nature that is heavily influenced by environmental factors (Ducci and Goldman, 2012).

While twin studies suggest that SUD is highly heritable (Agrawal and Lynskey, 2008), only a few genome-wide associations (GWAS) and robust candidate genes studies support genetic heritability of SUD. Among them the most convincing are the polymorphism that affects acetaldehyde and aldehyde dehydrogenases (which influence alcohol metabolism) (Hurley and Edenberg, 2012) and variants of nicotinic acetylcholine receptor subunit (α5, α3, and β4 subunits) (Bierut et al., 2008; Morrow and Flagel, 2016).

It is currently unknown whether specific genes contribute to incubation of craving, but some evidence suggest that genetic factors modulate craving intensity. The alcohol-dependent A allele carriers in the alcohol dehydrogenase gene cluster reported increased alcohol craving and higher alcohol consumption relative to the group of alcohol-dependent individuals homozygous for the C allele (protective factor), which displayed craving values like the control group. Notably, follow-up data indicated that A allele carriers relapsed earlier to heavy drinking compared with individuals with two C alleles (Bach et al., 2019). To a similar extent, the CHRNA5-A3-B4 haplotypes were significantly associated to higher nicotine craving and relapse likelihood relative to control patients (Baker et al., 2009).

3. Environmental factors modulating incubation of drug craving

3.1. Sleep architecture

3.1.1. Behavioral findings (Fig. 2A and Fig. 2C)—In 1883, Emil Kraepelin noted that abnormal sleep patterns and mental health are intrinsically linked (Kraepelin, 1883). This observation gained empirical support from studies that highlighted the connections

between disruption to sleep/circadian rhythms and psychiatric disorders (Wulff et al., 2010). Regarding SUD, human data suggest that drugs of abuse have acute adverse consequences on sleep/circadian rhythms that persist during chronic drug use and are further exacerbated during abstinence (Hasler et al., 2012). Noteworthy, it has been speculated that sleep disturbances during protracted abstinence may lead to an exacerbated drug craving which in turn may foster drug relapse and, in doing so, nurture the vicious cycle of SUD (Roehrs et al., 2004; Teplin et al., 2006).

A recent study by Chen et al. (2015), addressed this general question and more specifically asked how sleep can modulate incubation of cocaine craving. The authors first characterized longitudinal alterations in the sleep architecture [non-rapid eye movement (NREM) and rapid eye movement (REM)] after withdrawal from cocaine self-administration. The authors showed that after protracted abstinence from cocaine self-administration, rats exhibited a reduction in NREM and REM sleep stages, as well as increased sleep fragmentation (repetitive short interruptions of sleep). These findings are particularly relevant from a translational perspective because they mirror the clinical observations in polysomnography studies in people with cocaine use disorder (Kowatch et al., 1992; Valladares and Irwin, 2007). In addition, the authors demonstrated a causal relationship between sleep architecture and craving by experimentally manipulating sleep architecture after withdrawal from cocaine. This manipulation increased the incubation of drug craving. The authors then applied a sleep restriction (SR) procedure during the withdrawal phase to improve the quality of sleep and in an attempt to attenuate incubated cocaine craving. The SR procedure was originally developed by Arthur Spielman et al. (1987) as a treatment for patients suffering from chronic insomnia and is designed to eliminate prolonged nighttime awakenings while not affecting the actual sleep time.

This manipulation preferentially increased daily REM sleep during the light phase without altering the total amount of NREM and REM and total sleep. As expected, exposing rats to this procedure between abstinence days 22–42 prevented the incubated cue-induced cocaine seeking on abstinence day 45. These results, unraveled through a rodent model of drug craving, have several important implications for the role of sleep in individuals with SUD. First, they elucidated the dynamic interplay between sleep, cocaine craving and drug relapse. Abnormalities in sleep timing and sleep architecture play a critical role in cocaine relapse by expediting the development of the incubation of cocaine craving. Second, these findings support the translational potential of sleep-based interventions in the prevention of cocaine relapse. Furthermore, they suggest that an individual’s sleep architecture may be used as a marker for the early detection of cocaine relapse. Consistent with the findings by Chen et al. (2015), several studies have reported that REM sleep disturbances (shortened REM latency, high REM percentages, high REM density) in individuals with alcohol use disorder predict the likelihood of relapse (Roehrs and Roth, 2001). Furthermore, a recent study in individuals with cocaine use disorder revealed that REM time during protracted abstinence is positively correlated with better clinical outcomes and negatively correlated with the amount of drug use (Angarita et al., 2014). Importantly, the work by Chen et al., emphasizes the mechanistic connection between sleep disturbances and cocaine craving. However, it should be noted that sleep is a highly complex state originating from the dynamic interactions between the circadian systems and a homeostatic drive that increases during wakefulness (Hasler et al.,

2012). Chronic cocaine use interferes with this complex system of sleep/circadian cycles by disrupting the delicate balance among several brain regions, neurotransmitter systems and modulatory hormones. Specifically, while Chen et al., demonstrated that sleep can causally affect cocaine craving in a rat model, which itself could be a primary reason for loss of sleep in individuals with SUD, particularly during protracted abstinence, an alternative explanation may be that sleep disturbances (due to pre-existing circadian disturbances) exacerbate cocaine craving and drive subsequent drug use.

3.1.2. Neurobiological findings (Fig. 3)—Chen et al. (2015) explored the Ca2+-permeable AMPA receptors (CP-AMPARs; also called GluA2-lacking AMPARs) accumulation, a key adaptation occurring in the NAc in late abstinence (Loweth et al., 2014), as a putative molecular link through which sleep may influence cocaine craving and relapse. Compared with Ca2+-impermeable AMPARs (CI-AMPARs; also called GluA2-containing AMPARs) CP-AMPARs exhibit calcium permeability, higher conductance, and inward rectification due to voltage-dependent block by endogenous polyamines. Thus, recruiting CP-AMPARs into synapses potentiates synaptic strength (Cull-Candy et al., 2006; Isaac et al., 2007). Previous evidence showed that incubation of cocaine craving is accompanied by an accumulation of CP-AMPARs in NAc synapses and that NAc injection of Naspm, a selective antagonist of CP-AMPARs, blocked the incubation of cocaine craving (Conrad et al., 2008). Drawing on this line of enquiry, Chen et al. used slice electrophysiology and showed that sleep intervention bi-directionally regulates CP-AMPARs in NAc at the late abstinence time points. Specifically, the SR manipulation during the dark phase (leading to improved REM sleep) between abstinence day 22–42 decreased accumulation of CP-AMPARs in NAc on abstinence day 45. Conversely, the sleep fragmentation manipulation between abstinence days 11–17 facilitated accumulation of CP-AMPARs in the NAc on abstinence day 21, when accumulation of CP-AMPARs is yet to emerge (Wolf and Tseng, 2012). Taken together with previous demonstration on the critical roles of CP-AMPARs in incubation of cocaine craving, the authors' findings suggest the accumulation of CP-AMPARs in NAc as a potential mechanism underlying behavioral effects of sleep on incubation of cocaine craving.

3.2. Enrichment and physical exercise

3.2.1. Behavioral findings (Fig. 2A and Fig. 2C)—Environmental Enrichment (EE) is a preclinical procedure for animals in captivity achieved by increasing the complexity of their living environment (Solinas et al., 2021). EE groups are housed in large cages (up to 10 times the size of normal cages) with several objects changed out frequently. In some preparations, running wheels are available, however this introduces a potential confound as physical exercise itself produces some of the beneficial effects of enrichment (Solinas et al., 2021). The final aim of EE is to increase the animal well-being. EE provides enhanced sensory, cognitive, and motor stimulation. These specific aspects led to the hypothesis that an enriched environment can be beneficial in alleviating several psychiatric and neurodegenerative disorders (Laviola et al., 2008), although is still matter of debate which features constitute an enriched environment in humans (Kuhn et al., 2017).

Consistently, a wealth of preclinical studies suggest that EE increases resistance to acquire drug taking and prevents drug relapse (Solinas et al., 2010). Regarding the application of the EE procedure during the abstinence phase, two studies (Thiel et al., 2012, 2010) found a reduced “incubated” cocaine craving in rats housed in large cages equipped with toys and social partners relative to isolated controls (Thiel et al., 2010). A third study by Chauvet et al. (2012) confirmed the anti-incubation of craving effect of EE, but also revealed its transitory effect. Indeed, when the EE was discontinued (for 30 days), the protective effects of EE on incubation of cocaine craving was not evident.

Two more studies focused anti-craving effects of exercise, an enriching activity noted above. Controlled laboratory studies in humans have demonstrated that aerobic exercise decreased alcohol (Ussher et al., 2004), nicotine (Daniel et al., 2004; Prapavessis et al., 2014) and cannabis (Buchowski et al., 2011) craving and preclinical animal model have shown that voluntary wheel running decreased cue-induced cocaine-seeking behavior (Lynch et al., 2010; Thanos et al., 2013). Concerning incubation of cocaine craving, Zlebnik and Carroll (2015) found a robust incubated cocaine craving in female rats with access to a locked running wheel but not to an unlocked running wheel (day 30 vs day 3), indicating that incubation of cocaine seeking was suppressed following access to exercise for 30 days. A second study by Beiter et al. (2016) manipulated the timing of the availability of physical exercise and found that exercise applied during early abstinence (days 1–7) robustly attenuated subsequent cocaine seeking (day 15). In contrast, physical exercise during late abstinence (days 8–14) was not effective and these animals displayed high levels of cocaine seeking similar to that observed in sedentary animals. These results are relevant because, both in humans and rodents, certain exercise conditions enhance rather than decrease SUD related behaviors. This could mean that biological factors are critical (Beiter et al., 2016; Terry-McElrath et al., 2011; Zlebnik et al., 2014). To sum up, these findings support the translational potential of a healthier life/environmental context-based interventions in the prevention of drug relapse. However, at least using the approaches reported thus far, the anti-craving effect of physical exercise and EE appear to be transient.

Solinas et al. (2010) argued that EE and exercise are reinforcing. We speculate that EE or physical exercise decreases cocaine seeking by acting as an alternative and competing non-drug reinforcer. This is an intriguing hypothesis that deserve to be investigated. A possibility would be by exposing rats to a discrete, mutually exclusive, choice procedure between EE (or physical exercise) and the drug.

3.2.2. Neurobiological findings (Fig. 3)—At the neural level, EE is typically associated with increased: 1) dendritic branching, 2) dendritic spines, 3) hippocampal neurogenesis and 4) the integration of these newly born cells into functional circuits (Greenough and Volkmar, 1973; Kempermann et al., 1997; Nithianantharajah and Hannan, 2006). As previously reported, Thiel et al. found a reduced “incubated” cocaine craving in rats housed in large cages equipped with toys and social partners relative to isolated controls (Thiel et al., 2010). Importantly, by manipulating the length of the exposure to the EE the authors found that short exposure (1 day) to EE, but not long (28 days), increased the level of BDNF in the hippocampus. In contrast, long exposure to EE, but not short, prevented central amygdala (CeA) extracellular signal–regulated kinases (ERK) activation at

late abstinence test day (Thiel et al., 2012). These findings are particularly relevant because other findings support the hypothesis that ERK might drive cue-induced enhancement of excitatory neurotransmission by AMPAR insertion into cell membranes (Wolf, 2016). These data further suggest that EE, by attenuating the time-dependent increased sensitivity of the CeA, recently implicated in incubation of methamphetamine craving after forced and voluntary abstinence (Li et al., 2015c; Venniro et al., 2017a), promote the attenuation of drug craving. In support of this hypothesis an earlier study by Thiel et al. (2010) found that EE inhibits incubated cocaine craving and associated Fos expression in CeA after 30 abstinence days. A similar counter-adaptation was observed by Powell et al. (2020) which, using an RNA-seq in the NAc shell, found that the EE-mediated reduction of incubated cocaine craving correlate with a differential regulation of several signaling pathways (which include synaptogenesis and neurogenesis pathways) in isolated versus enriched forced abstinence. Finally, Ma et al. (2016) found that after cocaine abstinence and subsequent maturation of silent synapses by recruitment of CP-AMPARs (Wolf, 2016), the basolateral amygdala (BLA) to NAc projection (Lee et al., 2013) became highly resistant to EE (8 days EE exposure; in this specific experiment rats were single housed in environmentally enriched cages). Indeed, the authors found that in cocaine-exposed rats, 1) silent synapses in the EE group remained at low levels and 2) that Naspm sensitivity of BLA to NAc synapses remained high in the EE group relative to controls. These findings suggest that EE only partially affected the “incubated” synapses. Notably, the authors, by combining EE with an optogenetic long-term depression protocol (LTD) to the BLA to NAc projection in vivo, decreased persistently incubated cocaine craving via a mechanism hypothesized to promote the insertion of Ca2+-impermeable-AMPARs.

3.3. Acute and chronic stress

3.3.1. Behavioral findings (Fig. 2A and Fig. 2C)—Stressor exposure initiates a complex set of neuronal, endocrine and behavioral responses that prepare an organism to cope with this perturbation in homeostasis. Although initiation of these stress responses is typically adaptive, their persistent or inappropriate activation is linked to the pathophysiology of several psychiatric disorders (Bangasser and Valentino, 2014). As far as SUD is concerned, exposure to stress is associated with increase in craving in drug dependents (Sinha, 2001) and in susceptibility to relapse to drug use (Mantsch et al., 2016; Shaham et al., 2000; Stewart, 2000). Most of the pre-clinical literature describes results from studies using the reinstatement model following extinction of drug-seeking behavior. Acute foot-shock reinstates seeking for heroin (Shaham and Stewart, 1995), cocaine (Erb et al., 1996), alcohol (Le et al., 2005), methamphetamine (Shepard et al., 2004) and nicotine (Buczek et al., 1999). Among other stressors, acute food deprivation reinstates cocaine (Highfield et al., 2002; Shalev et al., 2003) and heroin seeking (Shalev et al., 2001b), while both quinine (Twining et al., 2015) and cold swim stress (Conrad et al., 2010) induce reinstatement in rats trained to self-administer cocaine. Reinstatement can also be elicited through pharmacological stressors: yohimbine, the most widely studied, was effective on cocaine (Feltenstein and See, 2006), methamphetamine (Shepard et al., 2004), alcohol (Le et al., 2005) and nicotine seeking rats (Feltenstein et al., 2012), although its stress-like effect has been recently challenged (Chen et al., 2014).

In a variation of the reinstatement model, in which the concept of incubation of craving started to take shape, Shalev et al. (2001a) showed time-dependent changes in stress-induced heroin seeking. With extinction and footshock-induced reinstatement conducted in the same daily session, maximal reinstatement was in fact present on day 6 and day 12 of forced abstinence with negligible drug seeking on day 1. Since then, only a few studies have directly tested the effect of stress on the incubation of craving. Using food restriction as the stressor, the Shalev group demonstrated that chronic (14 days) restriction during abstinence, but not acute food deprivation, enhances heroin seeking post-abstinence in both male and female rats (D'Cunha et al., 2013; Sedki et al., 2015). The Loweth group (Glynn et al., 2018; Munshi et al., 2021) instead explored the phenomenon adopting both acute and chronic restraint procedures during abstinence from cocaine self-administration. In this model, rats are placed in a restraint hemicylinder for 20 min once a day for 5 consecutive days, then for 2 more days following a 2-day break. The study showed that while acute restraint was ineffective, rats exposed to the 1-week chronic restraint during early abstinence showed a greater incubation effect on day 15 compared to unrestricted controls. This regimen did not affect the long-term incubation of craving (day 48). The effect of chronic restraint stress on incubation of cocaine craving was not replicated in another study (Ball et al., 2018). It should be noted, though, that there are important methodological differences between the studies, including the short vs long access drug self-administration and the different length and schedule of the daily restraint sessions.

Finally, to study the incubation of opioid craving under conditions that more closely resemble voluntary abstinence in humans, Fredriksson et al. (2020) introduced the electric barrier-based abstinence model. In this experimental procedure, rats were first trained to self-administer oxycodone. Rats were then required to cross an electrified grid floor to reach and press the lever for drug infusions, mimicking the stressful contingencies often associated with drug seeking in humans. The electric barrier-induced voluntary abstinence potentiated the incubation of craving on day 15 and day 30 compared to rats maintained in forced abstinence. This study highlights the importance of incorporating voluntary abstinence protocols in animal models of drug seeking, achieved in this specific case by introducing adverse consequences to drug seeking.

3.3.2. Neurobiological findings (Fig. 3)—To investigate the neurobiological mechanisms driving chronic stress-induced acceleration of incubation of craving, Munshi et al. (2021) focused on the BLA. Indeed, previous studies have shown that repeated restraint stress exposure increases neuronal excitability in the BLA of adult male rats (Rosenkranz et al., 2010). The authors found that repeated restraint stress during early abstinence produced an additive enhancement in the firing rate of BLA already increased following cocaine craving incubation alone. This is consistent with a possible role for the BLA-NAc pathway in driving cue-induced cocaine seeking during abstinence (Lee et al., 2013) and confirms a critical role for stress as an underlying contributor to relapse.

In fact, a wealth of human literature has identified dysregulation of the stress responses in individuals with SUD on a variety of drugs of abuse (Adinoff et al., 1991; Kreek and Koob, 1998). Persisting into abstinence from the drug, these could contribute to the pathophysiology of craving and vulnerability to relapse (Karoly and Hutchison, 2012). A

few papers have therefore used pharmacological manipulations to assess whether toning down stress signals interferes with the phenomenon of incubation of craving. As antagonism of the CRF receptor 1 (CRFr1) seems to attenuate the behavioral expression of withdrawal from opioids (Iredale et al., 2000), reinstatement of opioid conditioned place preference (Lu et al., 2000) and drug seeking following forced abstinence (Erb et al., 1998; Shaham et al., 1997). Martin et al. (2021) extended these findings to the incubation of fentanyl craving. A CRFr1 antagonist injected in the bed nucleus of the stria terminalis (BNST) blocked the development of incubation of craving for fentanyl measured on day 30 of abstinence. In a second experiment, adopting a procedure to make rats opioid-dependent post self-administration, the same treatment did not differentially affect dependent and nondependent rats. In this case, however, no incubation of craving was evident. More recently, instead, chronic oxytocin administered in early abstinence inhibited the development of incubation of craving in rats with a history of long access to methamphetamine (Everett et al., 2021). Given the putative role for the oxytocin system in both stress regulation (Nylander and Roman, 2012) and susceptibility to develop SUD (Baracz et al., 2020), a possible modulatory action of this peptide in the emotional control of relapse to methamphetamine could be speculated, purportedly through inhibitory activity within the CeA (Li et al., 2015c).

Expanding the set of experiments here presented may help interpret the (as yet limited) human literature where cue-induced craving incubates over time whilst baseline reported craving and withdrawal symptoms show a time-dependent decrease (Bedi et al., 2011; Li et al., 2015a). A history of exposure to a drug could perhaps selectively increase the vulnerability to cues by inducing rapid “phasic” stress that CRFr1 antagonists could therapeutically target, while the “tonic” level of stress inherent to a forced abstinence from a drug, decreases as withdrawal signs/symptoms subside. It should be noted though, that two human translational medicine studies reported negative results in patients with alcohol use disorder on the effect of the CRFR1 antagonists verucerfont and pexacefront on alcohol craving and relapse (Kwako et al., 2015; Schwandt et al., 2016).

Finally, Fredriksson et al. (2020) tested the effect of the dopamine stabilizer (-)-OSU6162 on incubation, using an electric barrier-based abstinence procedure. Females were less sensitive to the systemic administration of (-)-OSU6162, while incubation of oxycodone craving in male rats after either forced or voluntary abstinence was dose-dependently decreased by the treatment. Notably, this effect is in line with previous results where (-)-OSU6162 attenuated alcohol craving in preclinical (Fredriksson et al., 2019) and clinical studies (Khemiri et al., 2015).

3.4. Abstinence reinforcement procedures

For people with SUD, abstinence can be promoted by providing access to alternative nondrug rewards (e.g., vouchers, participation in support groups and job training) in exchange for drug-free tests. For humans, this knowledge is incorporated into treatments such as the contingency management and the community reinforcement approach (Aklin et al., 2014; Azrin et al., 1996; Higgins et al., 2004; Preston et al., 2002; Silverman et al., 2012). From a translational perspective, choice procedures are well-suited to capture this

critical aspect of human SUD (Ahmed, 2018; Fredriksson et al., 2021; Venniro et al., 2020a, 2016, 2019a). In monkeys and rodents, drug self-administration in a choice procedure is reliably decreased by palatable food reward (Cantin et al., 2010; Caprioli et al., 2015; Lenoir et al., 2007; Spragg, 1940) or social rewards (Venniro et al., 2020b; Venniro and Shaham, 2020; Venniro et al., 2018). Below we describe and discuss recent findings using these two models.

3.4.1. Food-based model

3.4.1.1. Behavioral findings (Fig. 2A and Fig. 2C).: The food choice-induced abstinence model (Caprioli et al., 2015) can be used to study drug relapse and mimic some aspects of contingency management in which small prizes or monetary vouchers can maintain abstinence for many months. Notably, when contingency management is discontinued, humans often relapse to drug use (Higgins et al., 2004; Preston et al., 2002). Based on the above-mentioned 'translational' considerations, Caprioli et al. (2015) showed that, independently of training conditions [i.e., drug escalation (Ahmed and Koob, 1998) or DSM-IV-based rodent SUD models (Deroche-Gamonet et al., 2004)], food-sated male rats voluntarily abstain from methamphetamine. This is because of their preference to palatable pellets over methamphetamine in a mutually exclusive choice procedure. However, once the contingencies with the alternative nondrug reward was discontinued, rats showed reliable incubation of methamphetamine craving. In a follow-up study, Venniro et al. (2017b) extended the food choice-induced voluntary abstinence model to female rats reporting no sex differences in either the choice procedure or incubation of methamphetamine seeking. However, the food choice-induced voluntary abstinence prevented the emergence of incubation of heroin seeking in both male and female rats. In a recent paper, Reiner et al. (2020), showed that this effect generalizes to the synthetic opioid fentanyl.

3.4.1.2. Neurobiological findings (Fig. 3).: In an initial study, Caprioli et al. (2015) showed that the novel mGluR2 positive allosteric modulator, AZD8529 (Justinova et al., 2015), decreased incubated methamphetamine seeking after forced or food-based voluntary abstinence. Subsequently, using a variety of approaches including RNAscope, classic pharmacology and chemogenetic Daun02 inactivation with transgenic Lac-Z rats (Koya et al., 2009), Caprioli et al. (2017) showed the role of selectively activated neuronal ensembles in the dorsomedial striatum (DMS) in mediating incubation of methamphetamine craving after food choice-induced voluntary abstinence. These findings extend also to the ventral striatum. Rossi et al. (2020) showed that incubation of methamphetamine seeking after food choice voluntary abstinence is mediated by dopamine transmission through Drd1 and Drd2 in NAc core but not shell.

Using the same model, Venniro et al. (2017a) showed the critical role CeA Drd1- (but not Drd2)-mediated transmission in relapse to methamphetamine seeking after food choice-induced voluntary abstinence. Furthermore, using anatomical tracing approaches in combination with electron microscopy, in vitro electrophysiology, and chemogenetic manipulations the same authors demonstrate the unique role of the monosynaptic glutamatergic projection from the anterior ventral insular cortex (AIV) to CeA

(preferentially the lateral part) for relapse to methamphetamine seeking after discontinuation of successful food choice-induced voluntary abstinence.

Finally, Reiner et al. (2020) showed the critical role of orbitofrontal cortex (OFC), Piriform cortex (Pir) and AIV in relapse to fentanyl seeking after food choice-induced voluntary abstinence in both male and female rats. Additionally, the same authors found that anatomical disconnection of Pir from OFC decreased fentanyl relapse after voluntary abstinence identifying a role of Pir-OFC projections in relapse to fentanyl seeking after food-induced abstinence.

3.4.2. Social-based model

3.4.2.1. Behavioral findings (Fig. 2A and Fig. 2C).: The quality of the social context and the emotional valence of the social experience have a profound impact on mental health and illness (Cohen, 2004). Accordingly, social epidemiological evidences support a strong connection between the severity of SUD and social interaction (Berkman and Kawachi, 2000). In humans, triggers of relapse are often negatively valanced social experiences such as bullying, physical attack, or problems associated with a low socioeconomic status (Havassy et al., 1991; Sinha et al., 2011). Despite the robustness of these clinical findings, and the abundance of preclinical animal models that enquire the neurobiological underpinnings of social interactions on drug relapse, very few studies investigated their interaction [for a few exceptions refer to (Heilig et al., 2016; Mantsch et al., 2016; Miczek et al., 2008)]. A possible reason for why more research is not being done on this topic is the large inconsistency of the findings (Miczek et al., 2008; Neisewander et al., 2012). Indeed, studies investigating the relationship between early or late maternal separation, social defeat and social subordination on drug self-administration vary as a function of the species employed, the procedure adopted and the drug under investigation.

To the best of our knowledge, no preclinical studies investigated the impact of social stressors on time-dependent changes in cue-induced drug seeking. Refer to Section 3.3 for time-dependent changes in footshock-stress-induced reinstatement.

Positively-valanced social experiences can have a protective and restorative effects over drug relapse (Havassy et al., 1991). For humans this is because social interactions, like other rewards, can generate a positive feeling [for review (Trezza et al., 2011) also refer to (Heilig et al., 2016; Miczek et al., 2008; Neisewander et al., 2012)]. Additionally, ideal treatments for SUD should promote a reallocation of behavior towards nondrug activity (Banks and Negus, 2017). In humans, these activities have intrinsic social components (Pickard, 2012, 2017; Stitzer et al., 2011). To implement these translational aspects in the current animal models of drug relapse, Venniro et al. (2018) developed a social choice procedure showing that rats strongly prefer social interaction over drugs (either psychostimulant or opioids), and that this effect was independent of “DSM-IV-based addiction score” [numbers of addiction-like behaviors as in (Deroche-Gamonet et al., 2004)], dose, self-administration procedure, housing conditions (single versus paired housing), sex, and duration of social housing (Venniro et al., 2020b, 2018). Surprisingly, social choice-induced voluntary abstinence prevented incubation of methamphetamine craving, even one month after the last social choice session housing (Venniro et al., 2018). In a follow-up study, Venniro et al. (2021)

showed that social choice-induced voluntary abstinence is protective against incubation of cocaine craving after either prolonged (12 h/d) or intermittent (5 ON – 25 OFF x12 h/day) access to cocaine self-administration. Additionally, Venniro et al. (2019b) showed that incubation of heroin craving is reduced (relative to the reliable heroin incubation observed after forced abstinence) after social choice-induced voluntary abstinence. The reasons for this dissociation between the drug type are unknown. Venniro et al. (2019b) We speculate that the different effect of social choice on incubation of methamphetamine versus heroin craving may be due to the differential impact of social interaction on dissociable behavioral and brain mechanisms controlling opioid versus psychostimulant reward and relapse (Badiani et al., 2011; Caprioli et al., 2009, 2008; 2007; Celentano et al., 2009; De Luca et al., 2019; De Pirro et al., 2018; Paolone et al., 2007).

3.4.2.2. Neurobiological findings (Fig. 3).: Why does social choice-induced abstinence prevent incubation of methamphetamine craving? To explore a possible mechanistic explanation, Venniro et al. (2017a) examined the role of CeA which is involved in incubation of drug craving after forced abstinence (Li et al., 2015c) and in drug seeking after food-choice-induced voluntary abstinence. The reported correlational data demonstrating that the protective effect of social choice-induced abstinence on incubation of methamphetamine seeking was associated with activation (assessed by Fos) of inhibitory protein kinase-Cδ (PKCδ)-expressing neurons in central lateral amygdala (CeL) and decreased activity of output neurons in central medial amygdala (CeM). In contrast, the strong incubation of methamphetamine seeking after forced abstinence was associated with activation of CeL-expressing somatostatin (SOM) neurons and CeM output neurons. In a subsequent study, Venniro et al. (2020b) determined the causal role of CeL PKCδ and SOM in inhibition of incubation of methamphetamine seeking after social choice-induced abstinence and expression of incubation of drug seeking after homecage forced abstinence, respectively. For this purpose, the authors developed short-hairpin RNAs against PKCδ or SOM and, using immunohistochemistry and in slice electrophysiology, they validated the knockdown efficacy of the viruses. In the behavioral experiments, the authors found that viral knockdown of PKCδ enzyme in CeL decreases Fos in CeL PKCδ-expressing neurons, increases Fos in CeM output neurons, and reverses the inhibitory effect of social choice-induced abstinence on incubation of methamphetamine seeking. In contrast, viral knockdown of SOM CeL injections decreased Fos in CeL SOM-expressing neurons, decreased Fos in CeM output neurons, and decreased incubation after forced abstinence. Questions for future research are whether PKCδ and SOM long projections play a causal role, or what afferent and efferent CeL projections contribute to this protective effect.

4. Nondrug rewards and incubation of craving (Fig. 1A and Fig. 1C)

Incubation of craving occurs for non-drug rewards. Thus far, many studies have focused on sucrose in rats where incubation occurs for responding for sucrose cues or for sucrose itself [e.g., (Harkness et al., 2010)]. However, incubation of craving has also been reported for standard or high-fat food pellets (Darling et al., 2016; Dingess et al., 2017; McCue et al., 2019), saccharin (Aoyama et al., 2014), and water (Grimm et al., 2012) (non-deprived rats).

See Grimm (2020) for a detailed review of these findings. Incubation of craving in response to a sucrose-associated discriminative stimulus was not observed (Madangopal et al., 2019).

There are translational implications for incubation of food craving. As with SUD, individuals with eating disorders experience intense cravings that precede diet recidivism (Boswell and Kober, 2016). Very recently in a clinical study, food craving (hunger) was found to incubate (Coutinho et al., 2018). It is therefore possible that for some individuals, the ability to maintain a healthy food plan is compromised by incubation of craving for restricted foods.

There is also a basic science implication for the fact that there is generality of incubation of craving. It could be that incubation is a general phenomenon selected for, as it invigorates the saliency of rewards that have not recently been available (Lu et al., 2004a). For example, consider a valuable nutrient source that is only seasonally available. Over a period of unavailability, an increase in saliency of the nutrient (including saliency of cues that predict it) would more easily attract an individual should it become available again. Abstinence from drugs of abuse and palatable food likely recruit neuroadaptations in the circuitry that underlie this behavior but also in divergent circuits that underlie abstinence-dependent reward class specific effects, such as dysphoria that accompanies cocaine withdrawal (Haake et al., 2019).

A handful of laboratory studies have explored the behavioral and neurobiological substrates of incubation of food craving with focus on a critical role for motivational processes and mesocorticolimbic dopamine signaling. These results may eventually yield a consensus of what incubation of craving “is” or “isn’t” possibly for both incubation of drug and food craving. For example, incubation of sucrose craving following prolonged abstinence is not reduced by overnight devaluation of sucrose with satiation (Haake et al., 2019; Harkness et al., 2016) nor with punishment during abstinence (Krasnova et al., 2014). However, incubation is blocked by devaluation of sucrose with illness (LiCl) only if that devaluation occurs in the days immediately prior to testing (Harkness et al., 2016). From these studies, it is apparent that re-evaluation of the reinforcing value of sucrose is still possible after prolonged abstinence with illness pairing (LiCl results) and perhaps behavioral contrast (EE, see below) but not with sucrose itself or with punishment. These findings indicate that treating sucrose craving with sucrose itself will not satisfy incubated sucrose craving. Furthermore, only some types of negative re-valuation of sucrose reduce incubated sucrose craving. Future studies may reveal whether incubation of drug craving has similar features.

The literature examining incubation of craving of non-drug rewards is smaller than for drug rewards and there are several questions that have only begun to be examined or have not yet been explored with non-drug rewards. The impact of age has received some attention. Counotte et al. (2014) identified age of sucrose self-administration onset specific effects: onset in young adolescence (postnatal day 35, P35) did not result in incubation over 21 days of forced abstinence, while incubation was observed if onset was in adolescence (P42) or early adulthood (P70). Thus far there are no reports of sex, age, sleep, withdrawal factors, chronic stress, or priming and stress-induced incubation of non-drug craving. Sex-related effects are currently being evaluated (e.g., Grimm lab) for incubation of sucrose

craving. In addition, there are only a handful of studies that directly compare incubated drug with non-drug craving. Hopefully, the other factors listed here will be evaluated in future studies, either side-by-side with studies of incubation of drug craving or as stand-alone studies. Below are relevant findings related from evaluation of environmental factors including EE and social housing (social factor). This is followed by a brief review of neurobiological (behavioral pharmacology and molecular biology correlation studies) evaluation of incubation of sucrose craving in rats including findings reported from studies using incubation of food craving as a comparison (or control) in neurobiological studies of incubation of drug craving or as stand-alone investigations into incubation of food craving.

4.1. Enrichment (Fig. 2A and Fig. 2C)

As recently reviewed (Grimm, 2020), EE robustly decreases sucrose seeking in rats (Grimm et al., 2008) whether EE is provided for the duration of 4 weeks of abstinence (chronic EE) or if it is provided overnight (acute EE) in either early or late abstinence (Grimm et al., 2013). Either chronic EE or acute EE just before testing on day 30 of abstinence reduces sucrose seeking (and taking, the next day) to levels similar to non-enriched rats in the first days of abstinence (Grimm et al., 2013). The effect of EE on cue-reactivity is similar to that observed with rats with history of cocaine self-administration (Thiel et al., 2012) and could be interpreted as EE blocking incubation of craving. That being stated, EE-reduced responding on day 30 of abstinence is greater than EE-reduced responding on day 1 of abstinence (although both are less than day 1 controls) so there is still incubation of responding occurring, albeit extremely reduced from control conditions. Factors that mediate the EE effect on sucrose seeking and taking have been parametrically evaluated in some detail. For acute EE, novelty, a social partner, and the enrichment cage all reduce sucrose seeking, but being in the enrichment cage with or without conspecifics is most potent. For chronic EE, the enrichment cage itself was again most critical. Surprisingly, chronic housing with a conspecific did not robustly decrease subsequent sucrose seeking (Grimm et al., 2013). One working hypothesis for why EE reduces craving is by creating a negative behavioral contrast between the EE and the self-administration context (Grimm et al., 2019).

4.2. Parametric considerations

While the incubation of food caving is a robust phenomenon in several laboratories, there are reports of not finding incubation of food craving in rats (Jones et al., 2008; Noye Tuplin et al., 2018; Xi et al., 2013) and, as yet, incubation of food craving has not been observed in mice (Nugent et al., 2017). Several factors might contribute to this, requiring parametric evaluation within a laboratory. For example, food deprived animals will likely have higher response rates for food during training and this could elevate responding in early abstinence. Higher response rates could also be due to the reinforcement schedule (e.g., variable interval vs. fixed ratio), age of subjects, type of food reward, amount of handling, and housing conditions. As an example of parametric evaluation, Terrier et al. (2016) found in mice that by increasing the dose of cocaine self-administered during training, response rate was decreased. This manipulation led to lower responding on day 1 of abstinence followed by incubation on day 30. The importance of measuring reliable incubation for food is especially critical in studies comparing drug vs non-drug incubation of craving.

4.3. Neurobiology of incubation of food craving (Fig. 4)

4.3.1. Pharmacology of dopamine—SCH 23390 (dopamine D1 antagonist) blocked incubated sucrose craving, but only at a dose 25X higher than necessary to reduce sucrose seeking in early abstinence (Grimm et al., 2011). This incubation aspect was not mediated by the NAc core or shell as there was no abstinence-dependence to the anti-craving effect of SCH 23390 when administered directly to these brain regions (Grimm et al., 2011).

4.3.2. Pharmacology of opiates—Naloxone (opiate antagonist) blocks incubated sucrose craving (Grimm et al., 2007).

4.3.3. Pharmacology of glutamate—LY379268 (mGluR2/3 agonist) blocks incubated sucrose craving (systemic and intra-CeA) (Uejima et al., 2007). Incubation of craving resembles the time-dependent increase in locomotor behavior described as psychostimulant sensitization (Kalivas et al., 1988). Indeed, incubated sucrose cue reactivity is accompanied by increased locomotor activity (Grimm et al., 2018). However, results thus far using behavioral pharmacology approaches have not confirmed an overlap between incubation and sensitization. For example, although there is an abstinence-dependent increase in dopamine D1 agonist enhanced sucrose cue-reactivity (Glueck et al., 2017) and a shift in dose-response of cocaine enhanced sucrose cue-reactivity (Grimm et al., 2006), the effects are dissociable from stimulant-induced locomotor activity.

4.3.4. Molecular biology—There are only a few studies correlating molecular markers with incubation of both drug and non-drug craving. In these, either there were no changes in analytes related to either drug or non-drug (e.g., (Grimm et al., 2002): cocaine vs sucrose, TH and DAT in mesolimbic terminals) or correlations reported were only between drug seeking and molecular changes. For example, BDNF levels in ventral tegmental area (VTA), NAc, and amygdala (AMY) incubate with cocaine craving but not sucrose (Grimm et al., 2003). There is less potency of serotonin 2C receptor agonist (WAY 163909) to reduce incubated cocaine seeking, and mPFC serotonin 2C receptors are decreased with incubated cocaine, but not sucrose craving (Swinford-Jackson et al., 2016). There are also no changes in ventromedial prefrontal cortex glutamate or glutamate (microdialysis) associated with incubation of sucrose craving, but neurotransmitter overflow is correlated with incubation of cocaine craving (Shin et al., 2016).

In studies examining incubation of food craving specifically, there are reports both of absence and presence of molecular changes associated with incubation. For example, there was no change in cortical perineuronal net density related to incubation of sucrose craving (Slaker et al., 2016) nor were there associations between Fos immunohistochemistry and incubation of chocolate-flavored pellets craving in cortical regions in rats (Noye Tuplin and Holahan, 2019). In contrast, for sucrose craving, Fos IR (immunoreactivity) “incubated” in prelimbic, infralimbic, anterior cingulate, somatosensory cortices, dorsolateral striatum (DLS), core and shell of the NAc, and CeA (Grimm et al., 2016). There were also abstinence-dependent changes in DARPP32 signaling (phosphorylation at Threonine 34) in VTA, DLS and DMS, and OFC (Grimm et al., 2018). Finally, Counotte et al. (2014) reported incubation of sucrose craving associated with decreased AMPA/NMDA ratio in

NAc (in adult rats). With incubation of high-fat food, McCue et al. (2019) reported that knockdown of neuromedin U receptor 2 in the paraventricular nucleus of the hypothalamus prevents incubation of craving. Dingess et al. (2017) reported spine density changes in NAc and an increase in CP-AMPARs and CI-AMPARs.

To sum up, there are inconsistencies, in the neuroanatomical and neuroanatomical substrates of incubation of craving for drug and non-drug rewards. There are also many comparisons that have not yet been made. Future studies are required to discern whether these substrates are clearly distinguishable, or whether there is a common substrate that is further impacted itself, or by related neurocircuitry, affected by the pharmacological actions of drugs of abuse. A strong example of research aiming to define commonalities of incubation across rewards is a recent study from Roura-Martinez et al. (2019). In this study incubation of heroin, cocaine, and sucrose craving are compared using measures of several genes and related proteins and neurotransmitters in several mesocorticolimbic brain regions. Functional "mapping" revealed common and divergent circuits recruited for incubation of the rewards. A structure common to all was the CeA. This result is especially salient as the CeA was previously identified as being critical to incubation of drug craving [(Lu et al., 2005) and subsequent studies], CeA Fos incubates along with incubation of sucrose craving (Grimm et al., 2016), and intra-CeA mGluR2/3 agonist blocks incubation of both cocaine and sucrose craving (Lu et al., 2007; Uejima et al., 2007).

4.4. Summary

There are inconsistencies, thus far, in the neuroanatomical and neuroanatomical substrates of incubation of craving for drug and non-drug rewards. Future studies examining overlap in the neurobiology [e.g., (Roura-Martinez et al., 2019)] would be valuable, as would studies examining efficacy of potential psychotherapeutics or environmental manipulations aimed at reducing incubation of craving across rewards. These results would inform about the potential applications for treatments and also side-effects (e.g., a decrease in food appetite may be contraindicated for some patients). Even so, the incubation of craving for palatable foods has clear translational implications for diet recidivism. Further research on the incubation of food craving may yield novel treatment approaches for disordered eating that is associated with negative health outcomes such as obesity.

5. Concluding remarks

Drug craving is a dynamic, multidimensional construct of considerable value for predicting the longitudinal trajectory of SUD, and as such a potential target for treatment (Tiffany and Wray, 2012). The preclinical studies here reviewed illustrated the importance of using multiple animal models to better comprehend the biological and environmental determinants of the nature of craving over time (Venniro et al., 2018). This knowledge is essential for a timely comprehension of the neurobiological adaptations occurring in a given individual in a given environment during drug abstinence to estimate the subject's vulnerability to relapse. In turn, we hope that this will allow forward translation of novel medications tailored to the environmental circumstances. A foreseeable option for their timely delivery comes from the mobile/ wearable technology, deployed by researchers to study substance

use “in the moment” (Burgess-Hull and Epstein, 2021), by monitoring both the individual and the environment, to better understand its causes and consequences. Indeed, mobile contingency management already includes technology to alert participants of the need for sample collection, to test samples, and to announce or deliver consequences [reviewed by Kurti et al. (2016)].

Our take home message is also consonant with the reverse translation strategy proposed by Venniro et al. (2020a) whose goal is to develop models that mimic successful treatments. The reverse translation approach capitalizes by the beneficial effect of contingency management, the community-reinforcement approach, environmental enrichment, physical exercise and insomnia interventions and provide an ecologically relevant platform from which to discover new circuits, test new medications and improve translation.

Funding and Disclosure:

The authors declare that they do not have any conflicts of interest (financial or otherwise) related to the text of the paper. The write-up of the review was supported by NIH/NIDA grants: DA047976 (MV) and DA016285-05 (JWG) and DA041350 (XL); by Istituto Pasteur-Fondazione Cenci Bolognetti (DC); by Sapienza University of Rome Fondi di Ateneo RM11715C457665A1 and RM11916B0E316F23 (DC). This research was supported [in part] by the Intramural Research Program of the NIH, NIDA.

Abbreviations

SUD	Substance Use Disorder
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5
GWAS	genome-wide associations
EE	environmental enrichment
REM	rapid eye movement
NREM	non-rapid eye movement
SR	sleep restriction
mPFC	medial prefrontal cortex
NAc	nucleus accumbens
BDNF	brain-derived neurotrophic factor
AMPARs	AMPA receptors
CP-AMPARs	Ca^{2+}-permeable AMPA receptors
CI-AMPARs	Ca^{2+}-impermeable AMPAR receptors
CeA	central amygdala
BLA	basolateral amygdala
ERK	extracellular signal-regulated kinase

LTD	long-term depression
CRFr1	CRF receptor 1
BNST	bed nucleus of the stria terminalis
DMS	dorsomedial striatum
AIV	anterior ventral insular cortex
OFC	orbitofrontal cortex
Pir	piriform cortex
Drd1	dopamine receptor D1
Drd2	dopamine receptor D2
PKCδ	protein kinase-Cδ
CeL	central lateral amygdala
CeM	central medial amygdala
LiCl	lithium chloride
TH	tyrosine hydroxylase
DAT	dopamine transporter
VTA	ventral tegmental area
DLS	dorsolateral striatum
IR	immunoreactivity
pERK	phosphorylated extracellular signal-regulated kinase
AMY	amygdala
NMUR2	neuromedin U receptor 2
PVN	paraventricular nucleus of hypothalamus

References

Abdolahi A, Acosta G, Breslin FJ, Hemby SE, Lynch WJ, 2010. Incubation of nicotine seeking is associated with enhanced protein kinase A-regulated signaling of dopamine- and cAMP-regulated phosphoprotein of 32 kDa in the insular cortex. Eur J Neurosci 31, 733–741. [PubMed: 20384816]

Adinoff B, Risher-Flowers D, De Jong J, Ravitz B, Bone GH, Nutt DJ, Roehrich L, Martin PR, Linnoila M, 1991. Disturbances of hypothalamic-pituitary-adrenal axis functioning during ethanol withdrawal in six men. Am J Psychiatry 148, 1023–1025. [PubMed: 1853950]

Agrawal A, Lynskey MT, 2008. Are there genetic influences on addiction: evidence from family, adoption and twin studies. Addiction 103, 1069–1081. [PubMed: 18494843]

Ahmed SH, 2018. Trying to make sense of rodents' drug choice behavior. Prog Neuropsychopharmacol Biol Psychiatry 87, 3–10. [PubMed: 28965843]

Ahmed SH, Koob GF, 1998. Transition from moderate to excessive drug intake: change in hedonic set point. Science 282, 298–300. [PubMed: 9765157]

Aklin WM, Wong CJ, Hampton J, Svikis DS, Stitzer ML, Bigelow GE, Silverman K, 2014. A therapeutic workplace for the long-term treatment of drug addiction and unemployment: eight-year outcomes of a social business intervention. J Subst Abuse Treat 47, 329–338. [PubMed: 25124257]

Alonso-Caraballo Y, Guha SK, Chartoff EH, 2021. The neurobiology of abstinence-induced reward-seeking in males and females. Pharmacol Biochem Behav 200, 173088. [PubMed: 33333134]

Altshuler RD, Garcia KT, Li X, 2021. Incubation of Oxycodone Craving Following Adult-Onset and Adolescent-Onset Oxycodone Self-Administration in Male Rats. Front Behav Neurosci 15, 697509. [PubMed: 34248518]

Altshuler RD, Lin H, Li X, 2020. Neural mechanisms underlying incubation of methamphetamine craving: A mini-review. Pharmacol Biochem Behav 199, 173058. [PubMed: 33250444]

Angarita GA, Canavan SV, Forselius E, Bessette A, Morgan PT, 2014. Correlates of polysomnographic sleep changes in cocaine dependence: self-administration and clinical outcomes. Drug and alcohol dependence 143, 173–180. [PubMed: 25124303]

Anker JJ, Carroll ME, 2010. Reinstatement of cocaine seeking induced by drugs, cues, and stress in adolescent and adult rats. Psychopharmacology 208, 211–222. [PubMed: 19953228]

Anker JJ, Carroll ME, 2011. Females are more vulnerable to drug abuse than males: evidence from preclinical studies and the role of ovarian hormones. Curr Top Behav Neurosci 8, 73–96. [PubMed: 21769724]

Anker JJ, Holtz NA, Zlebnik N, Carroll ME, 2009. Effects of allopregnanolone on the reinstatement of cocaine-seeking behavior in male and female rats. Psychopharmacology 203, 63–72. [PubMed: 18998113]

Anker JJ, Larson EB, Gliddon LA, Carroll ME, 2007. Effects of progesterone on the reinstatement of cocaine-seeking behavior in female rats. Exp Clin Psychopharmacol 15, 472–480. [PubMed: 17924781]

Anthony JC, Petronis KR, 1995. Early-onset drug use and risk of later drug problems. Drug and alcohol dependence 40, 9–15. [PubMed: 8746919]

Anthony JC, Warner LA, Kessler RC, 1994. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the National Comorbidity Survey. Experimental and Clinical Psychopharmacology 2, 244–268.

Aoyama K, Barnes J, Grimm JW, 2014. Incubation of saccharin craving and within-session changes in responding for a cue previously associated with saccharin. Appetite 72, 114–122. [PubMed: 24161592]

Auger AP, Olesen KM, 2009. Brain sex differences and the organisation of juvenile social play behaviour. J Neuroendocrinol 21, 519–525. [PubMed: 19500222]

Azrin NH, Acierno R, Kogan ES, Donohue B, Besalel VA, McMahon PT, 1996. Follow-up results of supportive versus behavioral therapy for illicit drug use. Behav Res Ther 34, 41–46. [PubMed: 8561763]

Bach P, Weil G, Pompili E, Hoffmann S, Hermann D, Vollstadt-Klein S, Mann K, Perez-Ramirez U, Moratal D, Canals S, Dursun SM, Greenshaw AJ, Kirsch P, Kiefer F, Sommer WH, 2020. Incubation of neural alcohol cue reactivity after withdrawal and its blockade by naltrexone. Addict Biol 25, e12717. [PubMed: 30748046]

Bach P, Zois E, Vollstadt-Klein S, Kirsch M, Hoffmann S, Jorde A, Frank J, Charlet K, Treutlein J, Beck A, Heinz A, Walter H, Rietschel M, Kiefer F, 2019. Association of the alcohol dehydrogenase gene polymorphism rs1789891 with gray matter brain volume, alcohol consumption, alcohol craving and relapse risk. Addict Biol 24, 110–120. [PubMed: 29058369]

Back SE, Brady KT, Jackson JL, Salstrom S, Zinzow H, 2005. Gender differences in stress reactivity among cocaine-dependent individuals. Psychopharamcology 180, 169–176.

Badiani A, Belin D, Epstein D, Calu D, Shaham Y, 2011. Opiate versus psychostimulant addiction: the differences do matter. Nat Rev Neurosci 12, 685–700. [PubMed: 21971065]

Baker TB, Weiss RB, Bolt D, von Niederhausern A, Fiore MC, Dunn DM, Piper ME, Matsunami N, Smith SS, Coon H, McMahon WM, Scholand MB, Singh N, Hoidal JR, Kim SY, Leppert MF, Cannon DS, 2009. Human neuronal acetylcholine receptor A5-A3-B4 haplotypes are associated

with multiple nicotine dependence phenotypes. Nicotine Tob Res 11, 785–796. [PubMed: 19436041]

Ball KT, Stone E, Best O, Collins T, Edson H, Hagan E, Nardini S, Neuciler P, Smolinsky M, Tosh L, Woodlen K, 2018. Chronic restraint stress during withdrawal increases vulnerability to drug priming-induced cocaine seeking via a dopamine D1-like receptor-mediated mechanism. Drug and alcohol dependence 187, 327–334. [PubMed: 29705546]

Bangasser DA, Valentino RJ, 2014. Sex differences in stress-related psychiatric disorders: neurobiological perspectives. Front Neuroendocrinol 35, 303–319. [PubMed: 24726661]

Banks ML, Negus SS, 2017. Insights from Preclinical Choice Models on Treating Drug Addiction. Trends in pharmacological sciences 38, 181–194. [PubMed: 27916279]

Baracz SJ, Everett NA, Cornish JL, 2020. The impact of early life stress on the central oxytocin system and susceptibility for drug addiction: Applicability of oxytocin as a pharmacotherapy. Neurosci Biobehav Rev 110, 114–132. [PubMed: 30172802]

Becker JB, 2016. Sex differences in addiction. Dialogues Clin Neurosci 18, 395–402. [PubMed: 28179811]

Becker JB, Chartoff E, 2019. Sex differences in neural mechanisms mediating reward and addiction. Neuropsychopharmacology 44, 166–183. [PubMed: 29946108]

Becker JB, Hu M, 2008. Sex differences in drug abuse. Front Neuroendocrinol 29, 36–47. [PubMed: 17904621]

Becker JB, Perry AN, Westenbroek C, 2012. Sex differences in the neural mechanisms mediating addiction: a new synthesis and hypothesis. Biol Sex Differ 3, 14. [PubMed: 22676718]

Bedi G, Preston KL, Epstein DH, Heishman SJ, Marrone GF, Shaham Y, de Wit H, 2011. Incubation of Cue-Induced Cigarette Craving During Abstinence in Human Smokers. Biological psychiatry 69, 708–711. [PubMed: 20817135]

Beiter RM, Peterson AB, Abel J, Lynch WJ, 2016. Exercise during early, but not late abstinence, attenuates subsequent relapse vulnerability in a rat model. Transl Psychiatry 6, e792. [PubMed: 27115123]

Berkman LF, Kawachi I, 2000. Social Epidemiology.

Bernheim A, Halfon O, Boutrel B, 2013. Controversies about the enhanced vulnerability of the adolescent brain to develop addiction. Front Pharmacol 4, 118. [PubMed: 24348419]

Bienkowski P, Rogowski A, Korkosz A, Mierzejewski P, Radwanska K, Kaczmarek L, Bogucka-Bonikowska A, Kostowski W, 2004. Time-dependent changes in alcohol-seeking behaviour during abstinence. Eur Neuropsychopharmacol 14, 355–360. [PubMed: 15336295]

Bierut LJ, Stitzel JA, Wang JC, Hinrichs AL, Grucza RA, Xuei X, Saccone NL, Saccone SF, Bertelsen S, Fox L, Horton WJ, Breslau N, Budde J, Cloninger CR, Dick DM, Foroud T, Hatsukami D, Hesselbrock V, Johnson EO, Kramer J, Kuperman S, Madden PA, Mayo K, Nurnberger J Jr., Pomerleau O, Porjesz B, Reyes O, Schuckit M, Swan G, Tischfield JA, Edenberg HJ, Rice JP, Goate AM, 2008. Variants in nicotinic receptors and risk for nicotine dependence. Am J Psychiatry 165, 1163–1171. [PubMed: 18519524]

Bobzean SA, DeNobrega AK, Perrotti LI, 2014. Sex differences in the neurobiology of drug addiction. Exp Neurol 259, 64–74. [PubMed: 24508560]

Boswell RG, Kober H, 2016. Food cue reactivity and craving predict eating and weight gain: a meta-analytic review. Obes Rev 17, 159–177. [PubMed: 26644270]

Buchowski MS, Meade NN, Charboneau E, Park S, Dietrich MS, Cowan RL, Martin PR, 2011. Aerobic exercise training reduces cannabis craving and use in non-treatment seeking cannabis-dependent adults. PLoS One 6, e17465. [PubMed: 21408154]

Buczek Y, Le AD, Wang A, Stewart J, Shaham Y, 1999. Stress reinstates nicotine seeking but not sucrose solution seeking in rats. Psychopharmacology 144, 183–188. [PubMed: 10395000]

Burgess-Hull A, Epstein DH, 2021. Ambulatory Assessment Methods to Examine Momentary State-Based Predictors of Opioid Use Behaviors. Curr Addict Rep, 1–14.

Burke AR, McCormick CM, Pellis SM, Lukkes JL, 2017. Impact of adolescent social experiences on behavior and neural circuits implicated in mental illnesses. Neurosci Biobehav Rev 76, 280–300. [PubMed: 28111268]

Cantin L, Lenoir M, Augier E, Vanhille N, Dubreucq S, Serre F, Vouillac C, Ahmed SH, 2010. Cocaine is low on the value ladder of rats: possible evidence for resilience to addiction. PLoS One 5, e11592. [PubMed: 20676364]

Caprioli D, Celentano M, Dubla A, Lucantonio F, Nencini P, Badiani A, 2009. Ambience and drug choice: cocaine- and heroin-taking as a function of environmental context in humans and rats. Biol Psychiatry 65, 893–899. [PubMed: 19217078]

Caprioli D, Celentano M, Paolone G, Lucantonio F, Bari A, Nencini P, Badiani A, 2008. Opposite environmental regulation of heroin and amphetamine self-administration in the rat. Psychopharmacology 198, 395–404. [PubMed: 18463850]

Caprioli D, Paolone G, Celentano M, Testa A, Nencini P, Badiani A, 2007. Environmental modulation of cocaine self-administration in the rat. Psychopharmacology 192, 397–406. [PubMed: 17297633]

Caprioli D, Venniro M, Zeric T, Li X, Adhikary S, Madangopal R, Marchant NJ, Lucantonio F, Schoenbaum G, Bossert JM, Shaham Y, 2015. Effect of the novel positive allosteric modulator of metabotropic glutamate receptor 2 AZD8529 on incubation of methamphetamine craving after prolonged voluntary abstinence in a rat model. Biol Psychiatry 78, 463–473. [PubMed: 25861699]

Caprioli D, Venniro M, Zhang M, Bossert JM, Warren BL, Hope BT, Shaham Y, 2017. Role of dorsomedial striatum neuronal ensembles in incubation of methamphetamine craving after voluntary abstinence. J Neurosci 37, 1014–1027. [PubMed: 28123032]

Carroll ME, Anker JJ, 2010. Sex differences and ovarian hormones in animal models of drug dependence. Horm Behav 58, 44–56. [PubMed: 19818789]

Celentano M, Caprioli D, Dipasquale P, Cardillo V, Nencini P, Gaetani S, Badiani A, 2009. Drug context differently regulates cocaine versus heroin self-administration and cocaine-versus heroin-induced Fos mRNA expression in the rat. Psychopharmacology 204, 349–360. [PubMed: 19169671]

Chauvet C, Goldberg SR, Jaber M, Solinas M, 2012. Effects of environmental enrichment on the incubation of cocaine craving. Neuropharmacology 63, 635–641. [PubMed: 22634364]

Chen B, Wang Y, Liu X, Liu Z, Dong Y, Huang YH, 2015. Sleep Regulates Incubation of Cocaine Craving. J Neurosci 35, 13300–13310. [PubMed: 26424879]

Chen K, Kandel DB, 1995. The natural history of drug use from adolescence to the mid-thirties in a general population sample. Am J Public Health 85, 41–47. [PubMed: 7832260]

Chen YW, Fiscella KA, Bacharach SZ, Tanda G, Shaham Y, Calu DJ, 2014. Effect of yohimbine on reinstatement of operant responding in rats is dependent on cue contingency but not food reward history. Addict Biol (in press).

Chhatre S, Cook R, Mallik E, Jayadevappa R, 2017. Trends in substance use admissions among older adults. BMC Health Serv Res 17, 584. [PubMed: 28830504]

Cho BR, Gerena J, Olekanma DI, Bal A, Herrera Charpentier AN, Arguello AA, 2020. Correction to: Role of adolescent-formed, context-drug-associations on reinstatement of drug-seeking behavior in rats. Psychopharmacology 237, 3505–3506. [PubMed: 33025025]

Clark DB, Kirisci L, Tarter RE, 1998. Adolescent versus adult onset and the development of substance use disorders in males. Drug and alcohol dependence 49, 115–121. [PubMed: 9543648]

Cohen S, 2004. Social relationships and health. Am Psychol 59, 676–684. [PubMed: 15554821]

Conrad KL, McCutcheon JE, Cotterly LM, Ford KA, Beales M, Marinelli M, 2010. Persistent increases in cocaine-seeking behavior after acute exposure to cold swim stress. Biol Psychiatry 68, 303–305. [PubMed: 20494337]

Conrad KL, Tseng KY, Uejima JL, Reimers JM, Heng LJ, Shaham Y, Marinelli M, Wolf ME, 2008. Formation of accumbens GluR2-lacking AMPA receptors mediates incubation of cocaine craving. Nature 454, 118–121. [PubMed: 18500330]

Corbett CM, Dunn E, Loweth JA, 2021. Effects of Sex and Estrous Cycle on the Time-Course of Incubation of Cue-Induced Craving Following Extended-Access Cocaine Self-Administration. eNeuro.

Counotte DS, Schiefer C, Shaham Y, O'Donnell P, 2014. Time-dependent decreases in nucleus accumbens AMPA/NMDA ratio and incubation of sucrose craving in adolescent and adult rats. Psychopharmacology 231, 1675–1684. [PubMed: 24114427]

Coutinho SR, Rehfeld JF, Holst JJ, Kulseng B, Martins C, 2018. Impact of weight loss achieved through a multidisciplinary intervention on appetite in patients with severe obesity. Am J Physiol Endocrinol Metab 315, E91–E98. [PubMed: 29360396]

Cull-Candy S, Kelly L, Farrant M, 2006. Regulation of Ca2+-permeable AMPA receptors: synaptic plasticity and beyond. Curr Opin Neurobiol 16, 288–297. [PubMed: 16713244]

D'Cunha TM, Sedki F, Macri J, Casola C, Shalev U, 2013. The effects of chronic food restriction on cue-induced heroin seeking in abstinent male rats. Psychopharmacology 225, 241–250. [PubMed: 22864945]

Dalley JW, Ersche KD, 2019. Neural circuitry and mechanisms of waiting impulsivity: relevance to addiction. Philos Trans R Soc Lond B Biol Sci 374, 20180145. [PubMed: 30966923]

Daniel J, Cropley M, Ussher M, West R, 2004. Acute effects of a short bout of moderate versus light intensity exercise versus inactivity on tobacco withdrawal symptoms in sedentary smokers. Psychopharmacology 174, 320–326. [PubMed: 14997270]

Darling RA, Dingess PM, Schlidt KC, Smith EM, Brown TE, 2016. Incubation of food craving is independent of macronutrient composition. Sci Rep 6, 30900. [PubMed: 27485660]

De Luca MT, Montanari C, Meringolo M, Contu L, Celentano M, Badiani A, 2019. Heroin versus cocaine: opposite choice as a function of context but not of drug history in the rat. Psychopharmacology 236, 787–798. [PubMed: 30443795]

De Pirro S, Galati G, Pizzamiglio L, Badiani A, 2018. The Affective and Neural Correlates of Heroin versus Cocaine Use in Addiction Are Influenced by Environmental Setting But in Opposite Directions. J Neurosci 38, 5182–5195. [PubMed: 29760180]

Deroche-Gamonet V, Belin D, Piazza PV, 2004. Evidence for addiction-like behavior in the rat. Science 305, 1014–1017. [PubMed: 15310906]

Dingess PM, Darling RA, Derman RC, Wulff SS, Hunter ML, Ferrario CR, Brown TE, 2017. Structural and Functional Plasticity within the Nucleus Accumbens and Prefrontal Cortex Associated with Time-Dependent Increases in Food Cue-Seeking Behavior. Neuropsychopharmacology 42, 2354–2364. [PubMed: 28294131]

Doherty JM, Cooke BM, Frantz KJ, 2013. A role for the prefrontal cortex in heroin-seeking after forced abstinence by adult male rats but not adolescents. Neuropsychopharmacology 38, 446–454. [PubMed: 23072838]

Doherty JM, Frantz KJ, 2012. Heroin self-administration and reinstatement of heroin-seeking in adolescent vs. adult male rats. Psychopharmacology 219, 763–773. [PubMed: 21773722]

Dong Y, Nestler EJ, 2014. The neural rejuvenation hypothesis of cocaine addiction. Trends in pharmacological sciences 35, 374–383. [PubMed: 24958329]

Douglas LA, Varlinskaya EI, Spear LP, 2004. Rewarding properties of social interactions in adolescent and adult male and female rats: impact of social versus isolate housing of subjects and partners. Dev Psychobiol 45, 153–162. [PubMed: 15505797]

Drummond DC, 2001. Theories of drug craving, ancient and modern. Addiction 96, 33–46. [PubMed: 11177518]

Ducci F, Goldman D, 2012. The genetic basis of addictive disorders. Psychiatr Clin North Am 35, 495–519. [PubMed: 22640768]

Dumais KM, Franklin TR, Jagannathan K, Hager N, Gawrysiak M, Betts J, Farmer S, Guthier E, Pater H, Janes AC, Wetherill RR, 2017. Multi-site exploration of sex differences in brain reactivity to smoking cues: Consensus across sites and methodologies. Drug and alcohol dependence 178, 469–476. [PubMed: 28711813]

Elman I, Karlsgodt KH, Gastfriend DR, 2001. Gender differences in cocaine craving among non-treatment-seeking individuals with cocaine dependence. Am. J. Drug Alcohol Abuse 27, 193–202. [PubMed: 11417935]

Erb S, Shaham Y, Stewart J, 1996. Stress reinstates cocaine-seeking behavior after prolonged extinction and a drug-free period. Psychopharmacology 128, 408–412. [PubMed: 8986011]

Erb S, Shaham Y, Stewart J, 1998. The role of corticotropin-releasing factor and corticosterone in stress- and cocaine-induced relapse to cocaine seeking in rats. J Neurosci 18, 5529–5536. [PubMed: 9651233]

Ernst M, Pine DS, Hardin M, 2006. Triadic model of the neurobiology of motivated behavior in adolescence. Psychol Med 36, 299–312. [PubMed: 16472412]

Evans SM, Haney M, Foltin RW, 2002. The effects of smoked cocaine during the follicular and luteal phases of the menstrual cycle in women. Psychopharmacology 159, 397–406. [PubMed: 11823892]

Everett NA, Turner AJ, Costa PA, Baracz SJ, Cornish JL, 2021. The vagus nerve mediates the suppressing effects of peripherally administered oxytocin on methamphetamine self-administration and seeking in rats. Neuropsychopharmacology 46, 297–304. [PubMed: 32450570]

Feltenstein MW, Byrd EA, Henderson AR, See RE, 2009. Attenuation of cocaine-seeking by progesterone treatment in female rats. Psychoneuroendocrinology 34, 343–352. [PubMed: 18977603]

Feltenstein MW, Ghee SM, See RE, 2012. Nicotine self-administration and reinstatement of nicotine-seeking in male and female rats. Drug and alcohol dependence 121, 240–246. [PubMed: 21945235]

Feltenstein MW, See RE, 2006. Potentiation of cue-induced reinstatement of cocaine-seeking in rats by the anxiogenic drug yohimbine. Behav Brain Res 174, 1–8. [PubMed: 16920204]

Feltenstein MW, See RE, 2007. Plasma progesterone levels and cocaine-seeking in freely cycling female rats across the estrous cycle. Drug and alcohol dependence 89, 183–189. [PubMed: 17240083]

Fox H, Sinha R, 2014. The role of guanfacine as a therapeutic agent to address stress-related pathophysiology in cocaine-dependent individuals. Adv Pharmacol 69, 217–265. [PubMed: 24484979]

Fox HC, Sofuoglu M, Morgan PT, Tuit KL, Sinha R, 2013. The effects of exogenous progesterone on drug craving and stress arousal in cocaine dependence: impact of gender and cue type. Psychoneuroendocrinology 38, 1532–1544. [PubMed: 23374328]

Fredriksson I, Applebey SV, Minier-Toribio A, Shekara A, Bossert JM, Shaham Y, 2020. Effect of the dopamine stabilizer (-)-OSU6162 on potentiated incubation of opioid craving after electric barrier-induced voluntary abstinence. Neuropsychopharmacology 45, 770–779. [PubMed: 31905372]

Fredriksson I, Venniro M, Reiner DJ, Chow JJ, Bossert JM, Shaham Y, 2021. Animal Models of Drug Relapse and Craving after Voluntary Abstinence: A Review. Pharmacol Rev 73, 1050–1083. [PubMed: 34257149]

Fredriksson I, Wirf M, Steensland P, 2019. The monoamine stabilizer (-)-OSU6162 prevents the alcohol deprivation effect and improves motor impulsive behavior in rats. Addict Biol 24, 471–484. [PubMed: 29480646]

Funk D, Coen K, Tamadon S, Hope BT, Shaham Y, Le AD, 2016. Role of central amygdala neuronal ensembles in incubation of nicotine craving. J Neurosci 36, 8612–8623. [PubMed: 27535909]

Galvan A, 2010. Adolescent development of the reward system. Front Hum Neurosci 4, 6. [PubMed: 20179786]

Gawin FH, Kleber HD, 1986. Abstinence symptomatology and psychiatric diagnosis in cocaine abusers. Clinical observations. Arch Gen Psychiatry 43, 107–113. [PubMed: 3947206]

Glueck E, Ginder D, Hyde J, North K, Grimm JW, 2017. Effects of dopamine D1 and D2 receptor agonists on environmental enrichment attenuated sucrose cue reactivity in rats. Psychopharmacology 234, 815–825. [PubMed: 28032125]

Glynn RM, Rosenkranz JA, Wolf ME, Caccamise A, Shroff F, Smith AB, Loweth JA, 2018. Repeated restraint stress exposure during early withdrawal accelerates incubation of cue-induced cocaine craving. Addict Biol 23, 80–89. [PubMed: 27859963]

Greenough WT, Volkmar FR, 1973. Pattern of dendritic branching in occipital cortex of rats reared in complex environments. Exp Neurol 40, 491–504. [PubMed: 4730268]

Grimm JW, 2020. Incubation of food craving in rats: A review. J Exp Anal Behav 113, 37–47. [PubMed: 31709556]

Grimm JW, Barnes JL, Koerber J, Glueck E, Ginder D, Hyde J, Eaton L, 2016. Effects of acute or chronic environmental enrichment on regional Fos protein expression following sucrose cue-reactivity testing in rats. Brain Struct Funct 221, 2817–2830. [PubMed: 26068175]

Grimm JW, Buse C, Manaois M, Osincup D, Fyall A, Wells B, 2006. Time-dependent dissociation of cocaine dose-response effects on sucrose craving and locomotion. Behav Pharmacol 17, 143–149. [PubMed: 16495722]

Grimm JW, Glueck E, Ginder D, Hyde J, North K, Jiganti K, 2018. Sucrose Abstinence and Environmental Enrichment Effects on Mesocorticolimbic DARPP32 in Rats. Sci Rep 8, 13174. [PubMed: 30181585]

Grimm JW, Harkness JH, Ratliff C, Barnes J, North K, Collins S, 2011. Effects of systemic or nucleus accumbens-directed dopamine D1 receptor antagonism on sucrose seeking in rats. Psychopharmacology 216, 219–233. [PubMed: 21318562]

Grimm JW, Hope BT, Wise RA, Shaham Y, 2001. Neuroadaptation. Incubation of cocaine craving after withdrawal. Nature 412, 141–142. [PubMed: 11449260]

Grimm JW, Hyde J, Glueck E, North K, Ginder D, Jiganti K, Hopkins M, Sauter F, MacDougall D, Hovander D, 2019. Examining persistence of acute environmental enrichment-induced anti-sucrose craving effects in rats. Appetite 139, 50–58. [PubMed: 31002852]

Grimm JW, Lu L, Hayashi T, Hope BT, Su TP, Shaham Y, 2003. Time-dependent increases in brain-derived neurotrophic factor protein levels within the mesolimbic dopamine system after withdrawal from cocaine: implications for incubation of cocaine craving. J Neurosci 23, 742–747. [PubMed: 12574402]

Grimm JW, Manaois M, Osincup D, Wells B, Buse C, 2007. Naloxone attenuates incubated sucrose craving in rats. Psychopharmacology 194, 537–544. [PubMed: 17628789]

Grimm JW, Osincup D, Wells B, Manaois M, Fyall A, Buse C, Harkness JH, 2008. Environmental enrichment attenuates cue-induced reinstatement of sucrose seeking in rats. Behav Pharmacol 19, 777–785. [PubMed: 19020412]

Grimm JW, Ratliff C, North K, Barnes J, Collins S, 2012. Nicotine increases sucrose self-administration and seeking in rats. Addict Biol 17, 623–633. [PubMed: 22340200]

Grimm JW, Shaham Y, Hope BT, 2002. Effect of cocaine and sucrose withdrawal period on extinction behavior, cue-induced reinstatement, and protein levels of the dopamine transporter and tyrosine hydroxylase in limbic and cortical areas in rats. Behav Pharmacol 13, 379–388. [PubMed: 12394414]

Grimm JW, Weber R, Barnes J, Koerber J, Dorsey K, Glueck E, 2013. Brief exposure to novel or enriched environments reduces sucrose cue-reactivity and consumption in rats after 1 or 30 days of forced abstinence from self-administration. PLoS One 8, e54164. [PubMed: 23342096]

Gyawali U, Martin DA, Sulima A, Rice KC, Calu DJ, 2021. Corrigendum: Role of BNST CRFR1 Receptors in Incubation of Fentanyl Seeking. Front Behav Neurosci 15, 660759. [PubMed: 34054445]

Haake RM, West EA, Wang X, Carelli RM, 2019. Drug-induced dysphoria is enhanced following prolonged cocaine abstinence and dynamically tracked by nucleus accumbens neurons. Addict Biol 24, 631–640. [PubMed: 29717793]

Harkness JH, Webb S, Grimm JW, 2010. Abstinence-dependent transfer of lithium chloride-induced sucrose aversion to a sucrose-paired cue in rats. Psychopharmacology 208, 521–530. [PubMed: 20039021]

Harkness JH, Wells J, Webb S, Grimm JW, 2016. Extended exposure to environmental cues, but not to sucrose, reduces sucrose cue reactivity in rats. Learn Behav 44, 59–66. [PubMed: 26169836]

Hasler BP, Smith LJ, Cousins JC, Bootzin RR, 2012. Circadian rhythms, sleep, and substance abuse. Sleep medicine reviews 16, 67–81. [PubMed: 21620743]

Havassy BE, Hall SM, Wasserman DA, 1991. Social support and relapse: commonalities among alcoholics, opiate users, and cigarette smokers. Addict Behav 16, 235–246. [PubMed: 1663695]

Heilig M, Epstein DH, Nader MA, Shaham Y, 2016. Time to connect: bringing social context into addiction neuroscience. Nat Rev Neurosci 17, 592–599. [PubMed: 27277868]

Herbeck DM, Jeter KE, Cousins SJ, Abdelmaksoud R, Crèvecoeur-MacPhail D, 2016. Gender differences in treatment and clinical characteristics among patients receiving extended release naltrexone. J. Addict. Dis 35, 305–314. [PubMed: 27192330]

Higgins ST, Heil SH, Lussier JP, 2004. Clinical implications of reinforcement as a determinant of substance use disorders. Annual review of psychology 55, 431–461.

Highfield DA, Mead AN, Grimm JW, Rocha BA, Shaham Y, 2002. Reinstatement of cocaine seeking in 129X1/SvJ mice: effects of cocaine priming, cocaine cues and food deprivation. Psychopharmacology 161, 417–424. [PubMed: 12073170]

Higley AE, Crane NA, Spadoni AD, Quello SB, Goodell V, Mason BJ, 2011. Craving in response to stress induction in a human laboratory paradigm predicts treatment outcome in alcohol-dependent individuals. Psychopharmacology 218, 121–129. [PubMed: 21607563]

Hurley TD, Edenberg HJ, 2012. Genes encoding enzymes involved in ethanol metabolism. Alcohol Res 34, 339–344. [PubMed: 23134050]

Iredale PA, Alvaro JD, Lee Y, Terwilliger R, Chen YL, Duman RS, 2000. Role of corticotropin-releasing factor receptor-1 in opiate withdrawal. J Neurochem 74, 199–208. [PubMed: 10617121]

Isaac JT, Ashby MC, McBain CJ, 2007. The role of the GluR2 subunit in AMPA receptor function and synaptic plasticity. Neuron 54, 859–871. [PubMed: 17582328]

Janes AC, Frederick B, Richardt S, Burbridge C, Merlo-Pich E, Renshaw PF, Evins AE, Fava M, Kaufman MJ, 2009. Brain fMRI reactivity to smoking-related images before and during extended smoking abstinence. Exp Clin Psychopharmacol 17, 365–373. [PubMed: 19968401]

Janes AC, Pizzagalli DA, Richardt S, de BFB, Chuzi S, Pachas G, Culhane MA, Holmes AJ, Fava M, Evins AE, Kaufman MJ, 2010. Brain reactivity to smoking cues prior to smoking cessation predicts ability to maintain tobacco abstinence. Biol Psychiatry 67, 722–729. [PubMed: 20172508]

Janes AC, Smoller JW, David SP, Frederick BD, Haddad S, Basu A, Fava M, Evins AE, Kaufman MJ, 2012. Association between CHRNA5 genetic variation at rs16969968 and brain reactivity to smoking images in nicotine dependent women. Drug and alcohol dependence 120, 7–13. [PubMed: 21764527]

Jones JL, Wheeler RA, Carelli RM, 2008. Behavioral responding and nucleus accumbens cell firing are unaltered following periods of abstinence from sucrose. Synapse 62, 219–228. [PubMed: 18088061]

Jordan CJ, Andersen SL, 2017. Sensitive periods of substance abuse: Early risk for the transition to dependence. Dev Cogn Neurosci 25, 29–44. [PubMed: 27840157]

Justinova Z, Panlilio LV, Secci ME, Redhi GH, Schindler CW, Cross AJ, Mrzljak L, Medd A, Shaham Y, Goldberg SR, 2015. The Novel Metabotropic Glutamate Receptor 2 Positive Allosteric Modulator, AZD8529, Decreases Nicotine Self-Administration and Relapse in Squirrel Monkeys. Biol Psychiatry 78, 452–462. [PubMed: 25802079]

Kalivas PW, Duffy P, DuMars LA, Skinner C, 1988. Behavioral and neurochemical effects of acute and daily cocaine administration in rats. J Pharmacol Exp Ther 245, 485–492. [PubMed: 3130474]

Kandel DB, 1991. The social demography of drug use. Milbank Q 69, 365–414. [PubMed: 1805113]

Kandel DB, Yamaguchi K, Chen K, 1992. Stages of progression in drug involvement from adolescence to adulthood: further evidence for the gateway theory. J Stud Alcohol 53, 447–457. [PubMed: 1405637]

Karoly HC, Hutchison KE, 2012. Does stress contribute to the incubation of craving? Biol Psychiatry 71, e39. [PubMed: 22244359]

Kempermann G, Kuhn HG, Gage FH, 1997. More hippocampal neurons in adult mice living in an enriched environment. Nature 386, 493–495. [PubMed: 9087407]

Kennedy AP, Epstein DH, Phillips KA, Preston KL, 2013. Sex differences in cocaine/heroin users: drug-use triggers and craving in daily life. Drug and alcohol dependence 132, 29–37. [PubMed: 23357742]

Kerstetter KA, Aguilar VR, Parrish AB, Kippin TE, 2008. Protracted time-dependent increases in cocaine-seeking behavior during cocaine withdrawal in female relative to male rats. Psychopharmacology 198, 63–75. [PubMed: 18265959]

Khemiri L, Steensland P, Guterstam J, Beck O, Carlsson A, Franck J, Jayaram-Lindstrom N, 2015. The effects of the monoamine stabilizer (-)-OSU6162 on craving in alcohol dependent individuals: A human laboratory study. Eur Neuropsychopharmacol 25, 2240–2251. [PubMed: 26482910]

Kippin TE, Fuchs RA, Mehta RH, Case JM, Parker MP, Bimonte-Nelson HA, See RE, 2005. Potentiation of cocaine-primed reinstatement of drug seeking in female rats during estrus. Psychopharmacology 182, 245–252. [PubMed: 16001116]

Kowatch RA, Schnoll SS, Knisely JS, Green D, Elswick RK, 1992. Electroencephalographic sleep and mood during cocaine withdrawal. J Addict Dis 11, 21–45. [PubMed: 1486092]

Koya E, Golden SA, Harvey BK, Guez-Barber DH, Berkow A, Simmons DE, Bossert JM, Nair SG, Uejima JL, Marin MT, Mitchell TB, Farquhar D, Ghosh SC, Mattson BJ, Hope BT, 2009. Targeted disruption of cocaine-activated nucleus accumbens neurons prevents context-specific sensitization. Nat Neurosci 12, 1069–1073. [PubMed: 19620976]

Kraepelin E, 1883. Compendium der psychiatrie zum gebrauch fuer dtudierende und aerzte. Abel Verlag, Leipzig,.

Krasnova IN, Marchant NJ, Ladenheim B, McCoy MT, Panlilio LV, Bossert JM, Shaham Y, Cadet JL, 2014. Incubation of methamphetamine and palatable food craving after punishment-induced abstinence. Neuropsychopharmacology 39, 2008–2016. [PubMed: 24584329]

Kreek MJ, Koob GF, 1998. Drug dependence: stress and dysregulation of brain reward pathways. Drug and alcohol dependence 51, 23–47. [PubMed: 9716928]

Kreek MJ, Nielsen DA, Butelman ER, LaForge KS, 2005. Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. Nat Neurosci 8, 1450–1457. [PubMed: 16251987]

Kuhn C, 2015. Emergence of sex differences in the development of substance use and abuse during adolescence. Pharmacol Ther 153, 55–78. [PubMed: 26049025]

Kuhn S, Duzel S, Eibich P, Krekel C, Wustemann H, Kolbe J, Martensson J, Goebel J, Gallinat J, Wagner GG, Lindenberger U, 2017. In search of features that constitute an “enriched environment” in humans: Associations between geographical properties and brain structure. Sci Rep 7, 11920. [PubMed: 28931835]

Kurti AN, Davis DR, Redner R, Jarvis BP, Zvorsky I, Keith DR, Bolivar HA, White TJ, Rippberger P, Markesich C, Atwood G, Higgins ST, 2016. A Review of the Literature on Remote Monitoring Technology in Incentive-Based Interventions for Health-Related Behavior Change. Transl Issues Psychol Sci 2, 128–152. [PubMed: 27777964]

Kwako LE, Spagnolo PA, Schwandt ML, Thorsell A, George DT, Momenan R, Rio DE, Huestis M, Anizan S, Concheiro M, Sinha R, Heilig M, 2015. The corticotropin releasing hormone-1 (CRH1) receptor antagonist pexacerfont in alcohol dependence: a randomized controlled experimental medicine study. Neuropsychopharmacology 40 (5), 1053–1063. [PubMed: 25409596]

Larson EB, Carroll ME, 2007. Estrogen receptor beta, but not alpha, mediates estrogen’s effect on cocaine-induced reinstatement of extinguished cocaine-seeking behavior in ovariectomized female rats. Neuropsychopharmacology 32, 1334–1345. [PubMed: 17133264]

Larson EB, Roth ME, Anker JJ, Carroll ME, 2005. Effect of short- vs. long-term estrogen on reinstatement of cocaine-seeking behavior in female rats. Pharmacol Biochem Behav 82, 98–108. [PubMed: 16111740]

Laviola G, Hannan AJ, Macri S, Solinas M, Jaber M, 2008. Effects of enriched environment on animal models of neurodegenerative diseases and psychiatric disorders. Neurobiol Dis 31, 159–168. [PubMed: 18585920]

Laviola G, Macri S, Morley-Fletcher S, Adriani W, 2003. Risk-taking behavior in adolescent mice: psychobiological determinants and early epigenetic influence. Neurosci Biobehav Rev 27, 19–31. [PubMed: 12732220]

Le AD, Harding S, Juzytsch W, Funk D, Shaham Y, 2005. Role of alpha-2 adrenoceptors in stress-induced reinstatement of alcohol seeking and alcohol self-administration in rats. Psychopharmacology 179, 366–373. [PubMed: 15551068]

Lee BR, Ma YY, Huang YH, Wang X, Otaka M, Ishikawa M, Neumann PA, Graziane NM, Brown TE, Suska A, Guo C, Lobo MK, Sesack SR, Wolf ME, Nestler EJ, Shaham Y, Schluter OM, Dong Y, 2013. Maturation of silent synapses in amygdala-accumbens projection contributes to incubation of cocaine craving. Nat Neurosci 16, 1644–1651. [PubMed: 24077564]

Lehmann SW, Fingerhood M, 2019. Substance-Use Disorders in Later Life. Reply. N Engl J Med 380, 1190. [PubMed: 30893547]

Lenoir M, Serre F, Cantin L, Ahmed SH, 2007. Intense sweetness surpasses cocaine reward. PLoS One 2, e698. [PubMed: 17668074]

Li C, Frantz KJ, 2009. Attenuated incubation of cocaine seeking in male rats trained to self-administer cocaine during periadolescence. Psychopharmacology 204, 725–733. [PubMed: 19326103]

Li C, Frantz KJ, 2017. Abstinence environment contributes to age differences in reinstatement of cocaine seeking between adolescent and adult male rats. Pharmacol Biochem Behav 158, 49–56. [PubMed: 28601602]

Li CS, Kemp K, Milivojevic V, Sinha R, 2005. Neuroimaging study of sex differences in the neuropathology of cocaine abuse. Gend Med 2, 174–182. [PubMed: 16290890]

Li P, Wu P, Xin X, Fan YL, Wang GB, Wang F, Ma MY, Xue MM, Luo YX, Yang FD, Bao YP, Shi J, Sun HQ, Lu L, 2014. Incubation of alcohol craving during abstinence in patients with alcohol dependence. Addict Biol (in press).

Li P, Wu P, Xin X, Fan YL, Wang GB, Wang F, Ma MY, Xue MM, Luo YX, Yang FD, Bao YP, Shi J, Sun HQ, Lu L, 2015a. Incubation of alcohol craving during abstinence in patients with alcohol dependence. Addict Biol 20, 513–522. [PubMed: 24698092]

Li X, Caprioli D, Marchant NJ, 2015b. Recent updates on incubation of drug craving: a mini-review. Addict Biol 20, 872–876. [PubMed: 25440081]

Li X, Venniro M, Shaham Y, 2016. Translational Research on Incubation of Cocaine Craving. JAMA Psychiatry 73, 1115–1116. [PubMed: 27604057]

Li X, Witonsky KR, Lofaro OM, Surjono F, Zhang J, Bossert JM, Shaham Y, 2018b. Role of Anterior Intralaminar Nuclei of Thalamus Projections to Dorsomedial Striatum in Incubation of Methamphetamine Craving. J Neurosci 38, 2270–2282. [PubMed: 29371321]

Li X, Zeric T, Kambhampati S, Bossert JM, Shaham Y, 2015c. The central amygdala nucleus is critical for incubation of methamphetamine craving. Neuropsychopharmacology 40, 1297–1306. [PubMed: 25475163]

Loweth JA, Tseng KY, Wolf ME, 2014. Adaptations in AMPA receptor transmission in the nucleus accumbens contributing to incubation of cocaine craving. Neuropharmacology 76 Pt B, 287–300. [PubMed: 23727437]

Lu L, Ceng X, Huang M, 2000. Corticotropin-releasing factor receptor type I mediates stress-induced relapse to opiate dependence in rats. Neuroreport 11, 2373–2378. [PubMed: 10943688]

Lu L, Grimm JW, Hope BT, Shaham Y, 2004a. Incubation of cocaine craving after withdrawal: a review of preclinical data. Neuropharmacology 47 Suppl 1, 214–226. [PubMed: 15464139]

Lu L, Grimm JW, Hope BT, Shaham Y, 2004b. Incubation of cocaine craving after withdrawal: a review of preclinical data. Neuropharmacology 47 Suppl 1, 214–226. [PubMed: 15464139]

Lu L, Hope BT, Dempsey J, Liu SY, Bossert JM, Shaham Y, 2005. Central amygdala ERK signaling pathway is critical to incubation of cocaine craving. Nat Neurosci 8, 212–219. [PubMed: 15657599]

Lu L, Uejima JL, Gray SM, Bossert JM, Shaham Y, 2007. Systemic and central amygdala injections of the mGluR(2/3) agonist LY379268 attenuate the expression of incubation of cocaine craving. Biol Psychiatry 61, 591–598. [PubMed: 16893525]

Lynch WJ, Piehl KB, Acosta G, Peterson AB, Hemby SE, 2010. Aerobic exercise attenuates reinstatement of cocaine-seeking behavior and associated neuroadaptations in the prefrontal cortex. Biol Psychiatry 68, 774–777. [PubMed: 20692647]

Lynch WJ, Roth ME, Carroll ME, 2002. Biological basis of sex differences in drug abuse: preclinical and clinical studies. Psychopharmacology 164, 121–137. [PubMed: 12404074]

Ma YY, Wang X, Huang Y, Marie H, Nestler EJ, Schluter OM, Dong Y, 2016. Re-silencing of silent synapses unmasks anti-relapse effects of environmental enrichment. Proc Natl Acad Sci U S A 113, 5089–5094. [PubMed: 27091967]

Madangopal R, Tunstall BJ, Komer LE, Weber SJ, Hoots JK, Lennon VA, Bossert JM, Epstein DH, Shaham Y, Hope BT, 2019. Discriminative stimuli are sufficient for incubation of cocaine craving. Elife 8.

Madsen HB, Zbukvic IC, Luikinga SJ, Lawrence AJ, Kim JH, 2017. Extinction of conditioned cues attenuates incubation of cocaine craving in adolescent and adult rats. Neurobiol Learn Mem 143, 88–93. [PubMed: 27614140]

Mantsch JR, Baker DA, Funk D, Le AD, Shaham Y, 2016. Stress-Induced Reinstatement of Drug Seeking: 20 Years of Progress. Neuropsychopharmacology 41, 335–356. [PubMed: 25976297]

Martin DA, Gyawali U, Calu DJ, 2021. Effects of 5-HT2A receptor stimulation on economic demand for fentanyl after intermittent and continuous access self-administration in male rats. Addict Biol 26, e12926. [PubMed: 32458577]

McCue DL, Kasper JM, Hommel JD, 2019. Incubation of feeding behavior is regulated by neuromedin U receptor 2 in the paraventricular nucleus of the hypothalamus. Behav Brain Res 359, 763–770. [PubMed: 30227148]

Mendelson JH, Mello NK, 1996. Management of cocaine abuse and dependence. N Engl J Med 334, 965–972. [PubMed: 8596599]

Miczek KA, Yap JJ, Covington HE 3rd, 2008. Social stress, therapeutics and drug abuse: preclinical models of escalated and depressed intake. Pharmacol Ther 120, 102–128. [PubMed: 18789966]

Moran LM, Kowalczyk WJ, Phillips KA, Vahabzadeh M, Lin JL, Mezghanni M, Epstein DH, Preston KL, 2018. Sex differences in daily life stress and craving in opioid-dependent patients. Am J Drug Alcohol Abuse 44, 512–523. [PubMed: 29641291]

Morgan JI, Curran T, 1991. Stimulus-transcription coupling in the nervous system: involvement of the inducible proto-oncogenes fos and jun. Annu Rev Neurosci 14, 421–451. [PubMed: 1903243]

Morrow JD, Flagel SB, 2016. Neuroscience of resilience and vulnerability for addiction medicine: From genes to behavior. Prog Brain Res 223, 3–18. [PubMed: 26806768]

Munshi S, Rosenkranz JA, Caccamise A, Wolf ME, Corbett CM, Loweth JA, 2021. Cocaine and chronic stress exposure produce an additive increase in neuronal activity in the basolateral amygdala. Addict Biol 26, e12848. [PubMed: 31750602]

Murphy CM, Stojek MK, Few LR, Rothbaum AO, Mackillop J, 2014. Craving as an alcohol use disorder symptom in DSM-5: an empirical examination in a treatment-seeking sample. Exp Clin Psychopharmacol 22, 43–49. [PubMed: 24490710]

Neisewander JL, Baker DA, Fuchs RA, Tran-Nguyen LT, Palmer A, Marshall JF, 2000. Fos protein expression and cocaine-seeking behavior in rats after exposure to a cocaine self-administration environment. J Neurosci 20, 798–805. [PubMed: 10632609]

Neisewander JL, Peartree NA, Pentkowski NS, 2012. Emotional valence and context of social influences on drug abuse-related behavior in animal models of social stress and prosocial interaction. Psychopharmacology 224, 33–56. [PubMed: 22955569]

Nicolas C, Russell TI, Pierce AF, Maldera S, Holley A, You ZB, McCarthy MM, Shaham Y, Ikemoto S, 2019. Incubation of Cocaine Craving After Intermittent Access Self-administration: Sex Differences and Estrous Cycle. Biol Psychiatry.

Nicolas C, Zlebnik N, Farokhnia M, Leggio L, Ikemoto S, Shaham Y, 2021. Sex differences in opioid and psychostimulant craving and relapse: a critical review. medRxiv.

Nithianantharajah J, Hannan AJ, 2006. Enriched environments, experience-dependent plasticity and disorders of the nervous system. Nat Rev Neurosci 7, 697–709. [PubMed: 16924259]

Noye Tuplin EW, Holahan MR, 2019. Exploring time-dependent changes in conditioned place preference for food reward and associated changes in the nucleus accumbens. Behav Brain Res 361, 14–25. [PubMed: 30576721]

Noye Tuplin EW, Lightfoot SHM, Holahan MR, 2018. Comparison of the Time-Dependent Changes in Immediate Early Gene Labeling and Spine Density Following Abstinence From Contingent or Non-contingent Chocolate Pellet Delivery. Front Behav Neurosci 12, 144. [PubMed: 30061817]

Nugent AL, Anderson EM, Larson EB, Self DW, 2017. Incubation of cue-induced reinstatement of cocaine, but not sucrose, seeking in C57BL/6J mice. Pharmacol Biochem Behav 159, 12–17. [PubMed: 28669705]

Nylander I, Roman E, 2012. Neuropeptides as mediators of the early-life impact on the brain; implications for alcohol use disorders. Front Mol Neurosci 5, 77. [PubMed: 22783165]

O'Brien CP, 1997. A range of research-based pharmacotherapies for addiction. Science 278, 66–70. [PubMed: 9311929]

O'Loughlin J, Karp I, Koulis T, Paradis G, Difranza J, 2009. Determinants of first puff and daily cigarette smoking in adolescents. Am J Epidemiol 170, 585–597. [PubMed: 19635735]

Palmer RH, Young SE, Hopfer CJ, Corley RP, Stallings MC, Crowley TJ, Hewitt JK, 2009. Developmental epidemiology of drug use and abuse in adolescence and young adulthood: Evidence of generalized risk. Drug and alcohol dependence 102, 78–87. [PubMed: 19250776]

Panksepp J, 1981. The ontogeny of play in rats. Dev Psychobiol 14, 327–332. [PubMed: 7250521]

Paolone G, Conversi D, Caprioli D, Bianco PD, Nencini P, Cabib S, Badiani A, 2007. Modulatory effect of environmental context and drug history on heroin-induced psychomotor activity and fos protein expression in the rat brain. Neuropsychopharmacology 32, 2611–2623. [PubMed: 17392735]

Parvaz MA, Moeller SJ, Goldstein RZ, 2016. Incubation of Cue-Induced Craving in Adults Addicted to Cocaine Measured by Electroencephalography. JAMA Psychiatry 73, 1127–1134. [PubMed: 27603142]

Pickard H, 2012. The Purpose in Chronic Addiction. AJOB Neurosci 3, 40–49. [PubMed: 22724074]

Pickard H, 2017. Responsibility without Blame for Addiction. Neuroethics 10, 169–180. [PubMed: 28725286]

Pickens CL, Airavaara M, Theberge F, Fanous S, Hope BT, Shaham Y, 2011. Neurobiology of the incubation of drug craving. Trends in neurosciences 34, 411–420. [PubMed: 21764143]

Potenza MN, Hong KI, Lacadie CM, Fulbright RK, Tuit KL, Sinha R, 2012. Neural correlates of stress-induced and cue-induced drug craving: influences of sex and cocaine dependence. Am J Psychiatry 169, 406–414. [PubMed: 22294257]

Powell GL, Vannan A, Bastle RM, Wilson MA, Dell'Orco M, Perrone-Bizzozero NI, Neisewander JL, 2020. Environmental enrichment during forced abstinence from cocaine self-administration opposes gene network expression changes associated with the incubation effect. Sci Rep 10, 11291. [PubMed: 32647308]

Prapavessis H, De Jesus S, Harper T, Cramp A, Fitzgeorge L, Mottola MF, Ussher M, Faulkner G, Selby P, 2014. The effects of acute exercise on tobacco cravings and withdrawal symptoms in temporary abstinent pregnant smokers. Addict Behav 39, 703–708. [PubMed: 24290209]

Preston KL, Kowalczyk WJ, Phillips KA, Jobes ML, Vahabzadeh M, Lin JL, Mezghanni M, Epstein DH, 2018. Exacerbated Craving in the Presence of Stress and Drug Cues in Drug-Dependent Patients. Neuropsychopharmacology 43, 859–867. [PubMed: 29105663]

Preston KL, Umbricht A, Epstein DH, 2002. Abstinence reinforcement maintenance contingency and one-year follow-up. Drug and alcohol dependence 67, 125–137. [PubMed: 12095662]

Reiner DJ, Lofaro OM, Applebey SV, Korah H, Venniro M, Cifani C, Bossert JM, Shaham Y, 2020. Role of Projections between Piriform Cortex and Orbitofrontal Cortex in Relapse to Fentanyl Seeking after Palatable Food Choice-Induced Voluntary Abstinence. J Neurosci 40, 2485–2497. [PubMed: 32051327]

Riley AL, Hempel BJ, Clasen MM, 2018. Sex as a biological variable: Drug use and abuse. Physiol Behav 187, 79–96. [PubMed: 29030249]

Robbins SJ, Ehrman RN, Childress AR, O'Brien CP, 1999. Comparing levels of cocaine cue reactivity in male and female outpatients. Drug and alcohol dependence 53, 223–230. [PubMed: 10080048]

Roehrs T, Greenwald M, Roth T, 2004. Risk-taking behavior: effects of ethanol, caffeine, and basal sleepiness. Sleep 27, 887–893. [PubMed: 15453546]

Roehrs T, Roth T, 2001. Sleep, sleepiness, sleep disorders and alcohol use and abuse. Sleep medicine reviews 5, 287–297. [PubMed: 12530993]

Rosenkranz JA, Venheim ER, Padival M, 2010. Chronic stress causes amygdala hyperexcitability in rodents. Biol Psychiatry 67, 1128–1136. [PubMed: 20378100]

Rossi LM, Reverte I, Ragozzino D, Badiani A, Venniro M, Caprioli D, 2020. Role of nucleus accumbens core but not shell in incubation of methamphetamine craving after voluntary abstinence. Neuropsychopharmacology 45, 256–265. [PubMed: 31422417]

Roura-Martinez D, Ucha M, Orihuel J, Ballesteros-Yanez I, Castillo CA, Marcos A, Ambrosio E, Higuera-Matas A, 2019. Central nucleus of the amygdala as a common substrate of the incubation of drug and natural reinforcer seeking. Addict Biol.

Schramm-Sapyta NL, Walker QD, Caster JM, Levin ED, Kuhn CM, 2009. Are adolescents more vulnerable to drug addiction than adults? Evidence from animal models. Psychopharmacology 206, 1–21. [PubMed: 19547960]

Schwandt NL, Cortes CR, Kwako LE, George DT, Momenan R, Sinha R, Grigoriadis DE, Pich EM, Leggio L, Heilig M, 2016. The CRF1 antagonist verucerfont in anxious alcohol-dependent

women: translation of neuroendocrine, but not of anti-craving effects. Neuropsychopharmacology 41 (12), 2818–2829 [PubMed: 27109623]

Sedki F, Gardner Gregory J, Luminare A, D'Cunha TM, Shalev U, 2015. Food restriction-induced augmentation of heroin seeking in female rats: manipulations of ovarian hormones. Psychopharmacology 232, 3773–3782. [PubMed: 26246318]

Shaham Y, Erb S, Stewart J, 2000. Stress-induced relapse to heroin and cocaine seeking in rats: a review. Brain Res Brain Res Rev 33, 13–33. [PubMed: 10967352]

Shaham Y, Funk D, Erb S, Brown TJ, Walker CD, Stewart J, 1997. Corticotropin-releasing factor, but not corticosterone, is involved in stress-induced relapse to heroin-seeking in rats. J Neurosci 17, 2605–2614. [PubMed: 9065520]

Shaham Y, Shalev U, Lu L, De Wit H, Stewart J, 2003. The reinstatement model of drug relapse: history, methodology and major findings. Psychopharmacology 168, 3–20. [PubMed: 12402102]

Shaham Y, Stewart J, 1995. Stress reinstates heroin-seeking in drug-free animals: an effect mimicking heroin, not withdrawal. Psychopharmacology 119, 334–341. [PubMed: 7675970]

Shalev U, Marinelli M, Baumann MH, Piazza PV, Shaham Y, 2003. The role of corticosterone in food deprivation-induced reinstatement of cocaine seeking in the rat. Psychopharmacology 168, 170–176. [PubMed: 12845419]

Shalev U, Morales M, Hope B, Yap J, Shaham Y, 2001. Time-dependent changes in extinction behavior and stress-induced reinstatement of drug seeking following withdrawal from heroin in rats. Psychopharmacology 156, 98–107. [PubMed: 11465640]

Shalev U, Yap J, Shaham Y, 2001b. Leptin attenuates acute food deprivation-induced relapse to heroin seeking. J. Neurosci 21 (4:RC129).

Shepard JD, Bossert JM, Liu SY, Shaham Y, 2004. The anxiogenic drug yohimbine reinstates methamphetamine seeking in a rat model of drug relapse. Biol. Psychiatry 55, 1082–1089. [PubMed: 15158427]

Shin CB, Serchia MM, Shahin JR, Ruppert-Majer MA, Kippin TE, Szumlinski KK, 2016. Incubation of cocaine-craving relates to glutamate over-flow within ventromedial prefrontal cortex. Neuropharmacology 102, 103–110. [PubMed: 26522436]

Shram MJ, Funk D, Li Z, Le AD, 2008. Nicotine self-administration, extinction responding and reinstatement in adolescent and adult male rats: evidence against a biological vulnerability to nicotine addiction during adolescence. Neuropsychopharmacology 33, 739–748. [PubMed: 17507913]

Silverman K, DeFulio A, Sigurdsson SO, 2012. Maintenance of reinforcement to address the chronic nature of drug addiction. Prev Med 55 Suppl, S46–53. [PubMed: 22668883]

Sinha R, 2001. How does stress increase risk of drug abuse and relapse? Psychopharmacology 158, 343–359. [PubMed: 11797055]

Sinha R, Shaham Y, Heilig M, 2011. Translational and reverse translational research on the role of stress in drug craving and relapse. Psychopharmacology 218, 69–82. [PubMed: 21494792]

Slaker M, Barnes J, Sorg BA, Grimm JW, 2016. Impact of Environmental Enrichment on Perineuronal Nets in the Prefrontal Cortex following Early and Late Abstinence from Sucrose Self-Administration in Rats. PLoS One 11, e0168256. [PubMed: 27977779]

Sofuoglu M, Babb DA, Hatsukami DK, 2002. Effects of progesterone treatment on smoked cocaine response in women. Pharmacol Biochem Behav 72, 431–435. [PubMed: 11900816]

Sofuoglu M, Dudish-Poulsen S, Nelson D, Pentel PR, Hatsukami DK, 1999. Sex and menstrual cycle differences in the subjective effects from smoked cocaine in humans. Exp Clin Psychopharmacol 7, 274–283. [PubMed: 10472516]

Sofuoglu M, Mitchell E, Kosten TR, 2004. Effects of progesterone treatment on cocaine responses in male and female cocaine users. Pharmacol Biochem Behav 78, 699–705. [PubMed: 15301924]

Solinas M, Chauvet C, Lafay-Chebassier C, Jaafari N, Thiriet N, 2021. Environmental enrichment-inspired pharmacological tools for the treatment of addiction. Curr Opin Pharmacol 56, 22–28. [PubMed: 32966941]

Solinas M, Thiriet N, Chauvet C, Jaber M, 2010. Prevention and treatment of drug addiction by environmental enrichment. Prog Neurobiol 92, 572–592. [PubMed: 20713127]

Spear LP, 2000. The adolescent brain and age-related behavioral manifestations. Neurosci Biobehav Rev 24, 417–463. [PubMed: 10817843]

Spear LP, 2016. Consequences of adolescent use of alcohol and other drugs: Studies using rodent models. Neurosci Biobehav Rev 70, 228–243. [PubMed: 27484868]

Spielman AJ, Saskin P, Thorpy MJ, 1987. Treatment of chronic insomnia by restriction of time in bed. Sleep 10, 45–56. [PubMed: 3563247]

Spragg SDS, 1940. Morphine addiction in chimpanzees. . Comp. Psychol. Mono 15, 132.

Stanis JJ, Andersen SL, 2014. Reducing substance use during adolescence: a translational framework for prevention. Psychopharmacology 231, 1437–1453. [PubMed: 24464527]

Stewart J, 2000. Pathways to relapse: the neurobiology of drug- and stress-induced relapse to drug-taking. J. Psychiatry Neurosci. 25, 125–136. [PubMed: 10740986]

Stitzer M, Jones HE, Tuten M, Wong C, 2011. Goal-Based Approaches to Assessment and Intervention with Addiction and Other Problems, in: Cox WM & Klinger E, e. (Ed.), Handbook of Motivational Counseling. John Wiley & Sons, Ltd, Chichester, UK, 2011.

Swinford-Jackson SE, Anastasio NC, Fox RG, Stutz SJ, Cunningham KA, 2016. Incubation of cocaine cue reactivity associates with neuroadaptations in the cortical serotonin (5-HT) 5-HT2C receptor (5-HT2CR) system. Neuroscience 324, 50–61. [PubMed: 26926963]

Teplin D, Raz B, Daiter J, Varenbut M, Tyrrell M, 2006. Screening for substance use patterns among patients referred for a variety of sleep complaints. Am J Drug Alcohol Abuse 32, 111–120. [PubMed: 16450646]

Terrier J, Luscher C, Pascoli V, 2016. Cell-Type Specific Insertion of GluA2-Lacking AMPARs with Cocaine Exposure Leading to Sensitization, Cue-Induced Seeking, and Incubation of Craving. Neuropsychopharmacology 41, 1779–1789. [PubMed: 26585289]

Terry-McElrath YM, O'Malley PM, Johnston LD, 2011. Exercise and substance use among American youth, 1991–2009. Am J Prev Med 40, 530–540. [PubMed: 21496752]

Thanos PK, Stamos J, Robison LS, Heyman G, Tucci A, Wang GJ, Robinson JK, Anderson BJ, Volkow ND, 2013. Daily treadmill exercise attenuates cocaine cue-induced reinstatement and cocaine induced locomotor response but increases cocaine-primed reinstatement. Behav Brain Res 239, 8–14. [PubMed: 23103403]

Thiel KJ, Painter MR, Pentkowski NS, Mitroi D, Crawford CA, Neisewander JL, 2012. Environmental enrichment counters cocaine abstinence-induced stress and brain reactivity to cocaine cues but fails to prevent the incubation effect. Addict Biol 17, 365–377. [PubMed: 21812872]

Thiel KJ, Wenzel JM, Pentkowski NS, Hobbs RJ, Alleweireldt AT, Neisewander JL, 2010. Stimulation of dopamine D2/D3 but not D1 receptors in the central amygdala decreases cocaine-seeking behavior. Behav Brain Res 214, 386–394. [PubMed: 20600343]

Tiffany ST, Wray JM, 2012. The clinical significance of drug craving. Ann N Y Acad Sci 1248, 1–17. [PubMed: 22172057]

Treloar Padovano H, Miranda R Jr., 2021. Incubation of alcohol craving as it naturally occurs in a developmentally diverse sample of dependent and nondependent drinkers. Addict Biol 26, e12934. [PubMed: 32666651]

Trezza V, Campolongo P, Vanderschuren LJ, 2011. Evaluating the rewarding nature of social interactions in laboratory animals. Dev Cogn Neurosci 1, 444–458. [PubMed: 22436566]

Tseng KY, O'Donnell P, 2007. Dopamine modulation of prefrontal cortical interneurons changes during adolescence. Cereb Cortex 17, 1235–1240. [PubMed: 16818475]

Tsui JI, Anderson BJ, Strong DR, Stein MD, 2014. Craving predicts opioid use in opioid-dependent patients initiating buprenorphine treatment: a longitudinal study. Am J Drug Alcohol Abuse 40, 163–169. [PubMed: 24521036]

Twining RC, Wheeler DS, Ebben AL, Jacobsen AJ, Robble MA, Mantsch JR, Wheeler RA, 2015. Aversive stimuli drive drug seeking in a state of low dopamine tone. Biol Psychiatry 77, 895–902. [PubMed: 25442790]

Uejima JL, Bossert JM, Poles GC, Lu L, 2007. Systemic and central amygdala injections of the mGluR2/3 agonist LY379268 attenuate the expression of incubation of sucrose craving in rats. Behav Brain Res 181, 292–296. [PubMed: 17537525]

Ussher M, Sampuran AK, Doshi R, West R, Drummond DC, 2004. Acute effect of a brief bout of exercise on alcohol urges. Addiction 99, 1542–1547. [PubMed: 15585045]

Valladares EM, Irwin MR, 2007. Polysomnographic sleep dysregulation in cocaine dependence. ScientificWorldJournal 7, 213–216. [PubMed: 17982595]

Venniro M, Banks ML, Heilig M, Epstein DH, Shaham Y, 2020a. Improving translation of animal models of addiction and relapse by reverse translation. Nat Rev Neurosci 21, 625–643. [PubMed: 33024318]

Venniro M, Caprioli D, Shaham Y, 2016. Animal models of drug relapse and craving: From drug priming-induced reinstatement to incubation of craving after voluntary abstinence. Prog Brain Res 224, 25–52. [PubMed: 26822352]

Venniro M, Caprioli D, Shaham Y, 2019a. Novel models of drug relapse and craving after voluntary abstinence. Neuropsychopharmacology 44, 234–235. [PubMed: 30206419]

Venniro M, Caprioli D, Zhang M, Whitaker LR, Zhang S, Warren BL, Cifani C, Marchant NJ, Yizhar O, Bossert JM, Chiamulera C, Morales M, Shaham Y, 2017a. The Anterior Insular Cortex-->Central Amygdala Glutamatergic Pathway Is Critical to Relapse after Contingency Management. Neuron 96, 414–427 e418. [PubMed: 29024664]

Venniro M, Panlilio LV, Epstein DH, Shaham Y, 2021. The protective effect of operant social reward on cocaine self-administration, choice, and relapse is dependent on delay and effort for the social reward. Neuropsychopharmacology ahead of print.

Venniro M, Russell TI, Ramsey LA, Richie CT, Lesscher HMB, Giovanetti SM, Messing RO, Shaham Y, 2020b. Abstinence-dependent dissociable central amygdala microcircuits control drug craving. Proc Natl Acad Sci U S A 117, 8126–8134. [PubMed: 32205443]

Venniro M, Russell TI, Zhang M, Shaham Y, 2019b. Operant Social Reward Decreases Incubation of Heroin Craving in Male and Female Rats. Biol Psychiatry 86, 848–856. [PubMed: 31326085]

Venniro M, Shaham Y, 2020. An operant social self-administration and choice model in rats. Nat Protoc 15, 1542–1559. [PubMed: 32203485]

Venniro M, Zhang M, Caprioli D, Hoots JK, Golden SA, Heins C, Morales M, Epstein DH, Shaham Y, 2018. Volitional social interaction prevents drug addiction in rat models. Nat Neurosci 21, 1520–1529. [PubMed: 30323276]

Venniro M, Zhang M, Shaham Y, Caprioli D, 2017b. Incubation of methamphetamine but not heroin craving after voluntary abstinence in male and female rats. Neuropsychopharmacology 42, 1126–1135. [PubMed: 28025975]

Volkow ND, Tomasi D, Wang G, Fowler JS, Telang F, Goldstein RZ, Alia- Klein N, Wong C, 2011. Reduced metabolism in brain “control networks” following cocaine-cues exposure in female cocaine abusers. PLoS One 6 (e16573)

Wang G, Shi J, Chen N, Xu L, Li J, Li P, Sun Y, Lu L, 2013. Effects of length of abstinence on decision-making and craving in methamphetamine abusers. PLoS One 8, e68791. [PubMed: 23894345]

Westbrook SR, Hankosky ER, Dwyer MR, Gulley JM, 2018. Age and sex differences in behavioral flexibility, sensitivity to reward value, and risky decision-making. Behav Neurosci 132, 75–87. [PubMed: 29481101]

Wetherill RR, Young KA, Jagannathan K, Shin J, O’Brien CP, Childress AR, Franklin TR, 2013. The impact of sex on brain responses to smoking cues: a perfusion fMRI study. Biol Sex Differ 4, 9. [PubMed: 23628003]

Willner P, Field M, Pitts K, Reeve G, 1998. Mood, cue and gender influences on motivation, craving and liking for alcohol in recreational drinkers. Behav Pharmacol 9, 631–642. [PubMed: 9862088]

Wolf ME, 2016. Synaptic mechanisms underlying persistent cocaine craving. Nat Rev Neurosci 17, 351–365. [PubMed: 27150400]

Wolf ME, Tseng KY, 2012. Calcium-permeable AMPA receptors in the VTA and nucleus accumbens after cocaine exposure: when, how, and why? Front Mol Neurosci 5, 72. [PubMed: 22754497]

Wong WC, Marinelli M, 2016. Adolescent-onset of cocaine use is associated with heightened stress-induced reinstatement of cocaine seeking. Addict Biol 21, 634–645. [PubMed: 26202521]

Wulff K, Gatti S, Wettstein JG, Foster RG, 2010. Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. Nat Rev Neurosci 11, 589–599. [PubMed: 20631712]

Xi ZX, Li X, Li J, Peng XQ, Song R, Gaal J, Gardner EL, 2013. Blockade of dopamine D3 receptors in the nucleus accumbens and central amygdala inhibits incubation of cocaine craving in rats. Addict Biol 18, 665–677. [PubMed: 22913325]

Yarmush DE, Manchery L, Luehring-Jones P, Erblich J, 2016. Gender and Impulsivity: Effects on Cue-Induced Alcohol Craving. Alcohol Clin Exp Res 40, 1052–1057. [PubMed: 27028602]

Yu J, Zhang S, Epstein DH, Fang Y, Shi J, Qin H, Yao S, Le Foll B, Lu L, 2007. Gender and stimulus difference in cue-induced responses in abstinent heroin users. Pharmacol Biochem Behav 86, 485–492. [PubMed: 17306353]

Zhao D, Zhang M, Tian W, Cao X, Yin L, Liu Y, Xu TL, Luo W, Yuan TF, 2021. Neurophysiological correlate of incubation of craving in individuals with methamphetamine use disorder. Mol Psychiatry.

Zlebnik NE, Carroll ME, 2015. Prevention of the incubation of cocaine seeking by aerobic exercise in female rats. Psychopharmacology 232, 3507–3513. [PubMed: 26159456]

Zlebnik NE, Saykao AT, Carroll ME, 2014. Effects of combined exercise and progesterone treatments on cocaine seeking in male and female rats. Psychopharmacology 231, 3787–3798. [PubMed: 24595506]

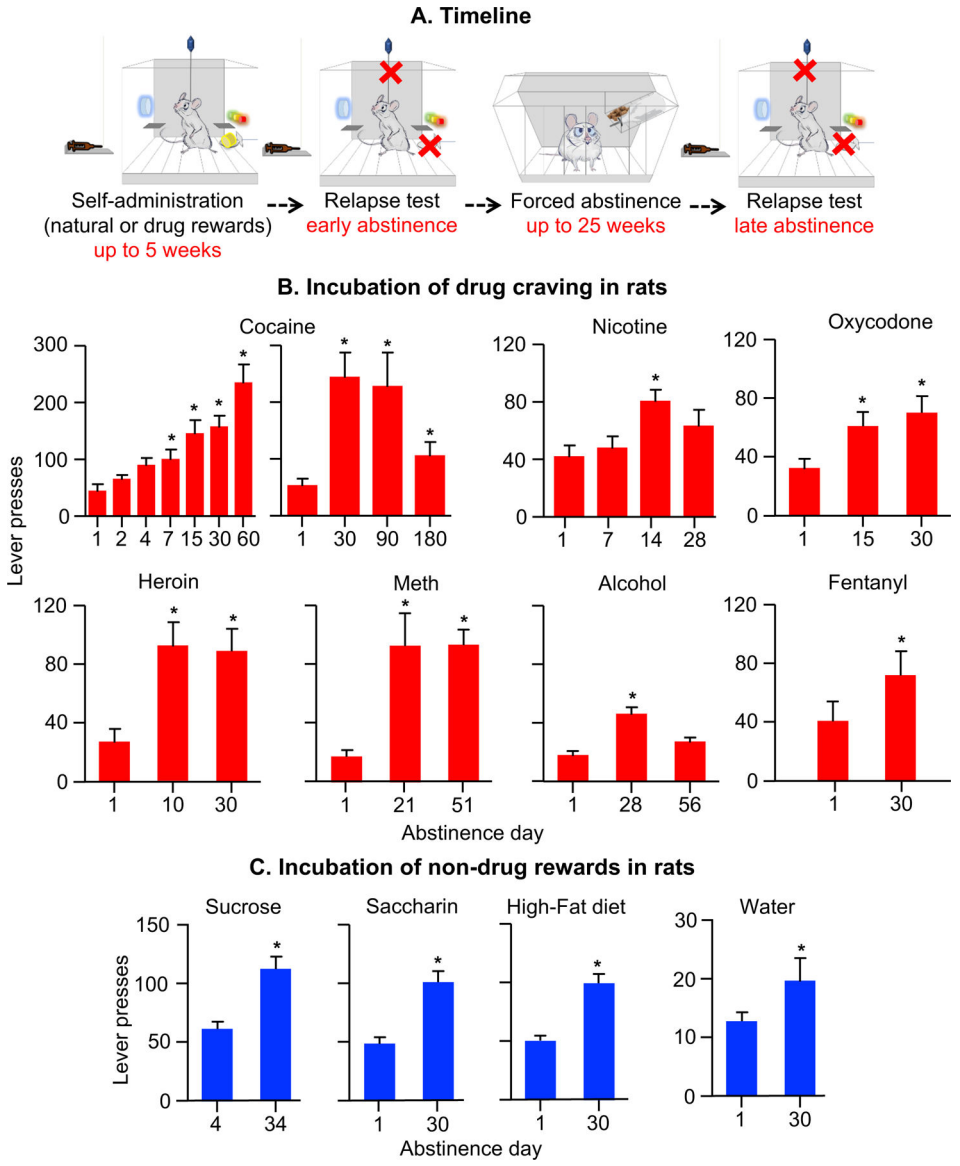

Figure 1.

(A) Timeline. Incubation of drug craving procedure: rats are trained to self-administer a reward (up to 5 weeks) and then relapse is tested in early and late phases of abstinence, between tests rats undergo a forced-abstinence period (up to 25 weeks). During the relapse tests rats are re-exposed to the self-administration chambers and lever presses lead to contingent presentations of a discrete cue previously paired with reward delivery. (B) Incubation of drug craving in rats. Relapse tests: data are Mean±SEM number of non-reinforced lever presses during relapse tests at different days of abstinence from cocaine (Grimm et al., 2001), nicotine (Abdolahi et al., 2010), oxycodone (Fredriksson et al., 2020), heroin (Shalev et al., 2001), methamphetamine (Shepard et al., 2004), alcohol (Shepard et al., 2004) and fentanyl (Gyawali et al., 2021). (C) Incubation of non-drug rewards in rats. Relapse tests: data are Mean±SEM number of non-reinforced lever presses during relapse tests at different days of abstinence from sucrose (Harkness et al., 2010), saccharin (Aoyama

et al., 2014), high-fat diet (Darling et al., 2016), and water (Grimm et al., 2012). *Different from abstinence day 1, $p < 0.05$. Data were redrawn, with permission, from the above cited references.

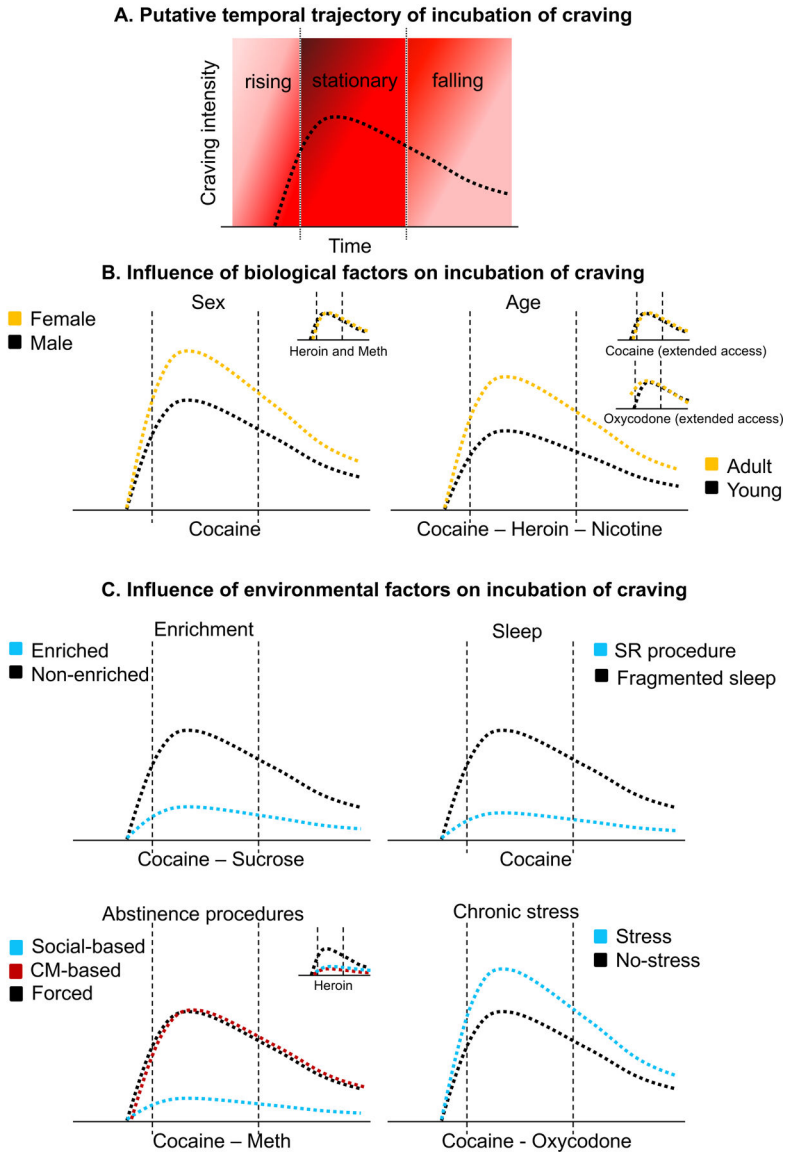

Figure 2.

(A) Putative temporal trajectory of incubation of craving. Drug craving progressively increases during early phases of abstinence, remains stationary for long periods of time and falls after prolonged abstinence periods. (B) Influence of biological factors on incubation of craving. *Sex* (left): incubation of craving is potentiated in female, relative to male rats trained to self-administer cocaine (Kerstetter et al., 2008; Nicolas et al., 2019), but not heroin and methamphetamine (Venniro et al., 2017b). *Age* (right): incubation of craving is potentiated in young, relative to adult rats trained to self-administer cocaine (Li and Frantz, 2009, 2017; Li et al., 2018a), heroin (Doherty et al., 2013; Doherty and Frantz, 2012) and nicotine (Funk et al., 2016), after short access self-administration. While, after extended access cocaine (Madsen et al., 2017) and oxycodone self-administration, incubation of craving is similar between young and adult rats, except that young relative to adult rats exhibit decreased seeking during early abstinence (Altshuler et al., 2021).

(C) Influence of environmental factors on incubation of craving. *Enrichment* (left, top): incubation of cocaine (Thiel et al., 2012; Thiel et al., 2010) and sucrose (Grimm et al., 2013) craving is decreased in rats maintained in enriched, relative to non-enriched environmental conditions. *Sleep* (right, top): incubation of cocaine craving is potentiated by fragmented sleep and decreased with SR procedure (Chen et al., 2015). *Abstinence procedures* (left, bottom): incubation of cocaine (Venniro et al., 2021), heroin (Venniro et al., 2019b), and methamphetamine (Venniro et al., 2018) craving is decreased in rats that undergo to social-based voluntary abstinence, relative to forced; incubation of heroin (Venniro et al., 2017b) craving is decreased in rats that undergo to contingency management (CM)-based voluntary abstinence, relative to forced abstinence. *Chronic stress* (right, bottom): incubation of cocaine (Glynn et al., 2018) and oxycodone (Fredriksson et al., 2020) craving is potentiated in rats exposed to chronic stress, relative to no-stress conditions.

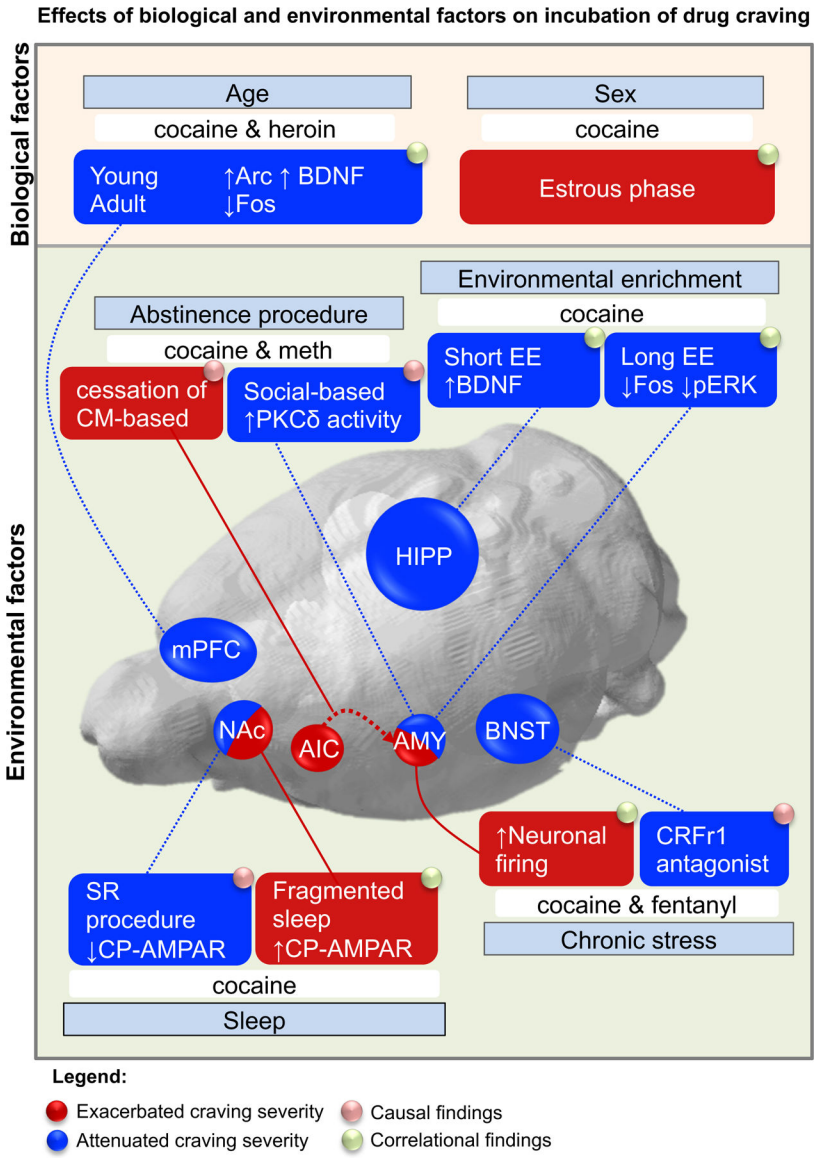

Figure 3. Effects of biological and environmental factors on incubation of drug craving.

Graphic overview of brain regions and molecular mechanisms underlying biological (top box) and environmental (bottom box) factors that exacerbate (Chen et al., 2015; Munshi et al., 2021; Nicolas et al., 2019; Venniro et al., 2017a) or attenuate (Chen et al., 2015; Doherty et al., 2013; Gyawali et al., 2021; Li et al., 2018a; Thiel et al., 2012; Thiel et al., 2010; Venniro et al., 2018) incubation of drug craving. Pink and green balls indicated causal and correlational findings, respectively. Abbreviations: Arc, activity-regulated cytoskeleton-associated protein; BDNF, brain-derived neurotrophic factor; meth, methamphetamine; CM-based, contingency management based voluntary abstinence; EE; environmental enrichment; pERK, phosphorylated extracellular signal-regulated kinase; mPFC, medial prefrontal cortex; HIPP, hippocampus; NAc, nucleus accumbens, AIV, anterior ventral insular cortex; AMY, amygdala; BNST, bed nucleus of the stria terminalis; SR, sleep restriction; CP-AMPARs, calcium permeable AMPA receptors; CRFr1, CRF receptor 1.

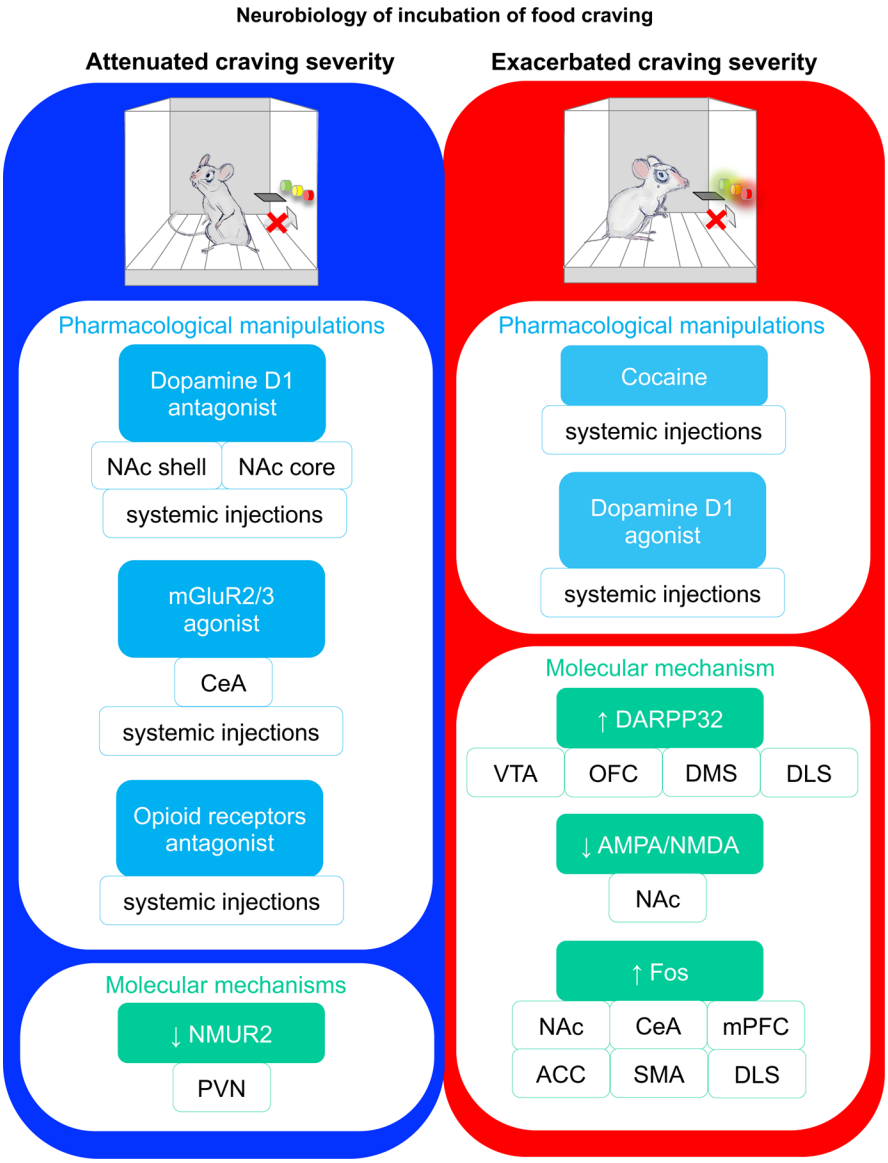

Figure 4. Neurobiology of incubation of food craving.

Graphic overview of pharmacological manipulations and molecular adaptations underling the attenuation (**blue**) (Grimm et al., 2007; Uejima et al., 2007; Grimm et al., 2011; McCue et al., 2019) or the exacerbation (**red**) (Grimm et al, 2002; Grimm et al., 2003; Glueck et al, 2017; Grimm et al., 2006; Cuonotte et al., 2014; Grimm et al., 2016; Grimm et al., 2018) of incubation of food craving. Green indicates the pharmacological manipulations; orange indicate the molecular mechanisms. Abbreviations: NAc, nucleus accumbens, CeA, central amygdala; NMUR2, neuromedin U receptor 2; PVN, paraventricular nucleus of hypothalamus; VTA, ventral tegmental area; OFC, orbitofrontal cortex; DMS, dorsomedial striatum; DLS, dorsolateral striatum; mPFC, medial prefrontal cortex; ACC, anterior cingulate cortex; SMA, somatosensorial cortex.