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Sex Differences in Opioid and Psychostimulant Craving and Relapse: A Critical Review [S]

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***Abstract*——A widely held dogma in the preclinical addiction field is that females are more vulnerable than males to drug craving and relapse. Here, we first review clinical studies on sex differences in psychostimulant and opioid craving and relapse. Next, we review preclinical studies on sex differences in psychostimulant and opioid reinstatement of drug seeking after extinction of drug self-administration, and incubation of drug craving (time-dependent increase in drug seeking during abstinence). We also discuss ovarian hormones' role in relapse and craving in humans and animal models and speculate on brain mechanisms underlying their role in cocaine craving and relapse in rodent models. Finally, we discuss imaging studies on brain responses to cocaine cues and stress in men and women.**

The results of the clinical studies reviewed do not appear to support the notion that women are more vulnerable to psychostimulant and opioid craving and relapse. However, this conclusion is tentative because most of the studies reviewed were correlational, not sufficiently powered, and not a priori designed to detect sex differences. Additionally, imaging studies suggest sex differences in brain responses to cocaine cues and stress. The results of the preclinical studies reviewed provide evidence for sex differences in stress-induced reinstatement and incubation of cocaine craving but not cue- or cocaine-induced reinstatement of cocaine seeking. These sex differences are modulated in part by ovarian hormones. In contrast, the available data do not support the notion of sex differences in craving and relapse/reinstatement for methamphetamine or opioids in rodent models.

***Significance Statement*——This systematic review summarizes clinical and preclinical studies on sex differences in psychostimulant and opioid craving and relapse. Results of the clinical studies reviewed do not appear to support the notion that women are more vulnerable to psychostimulant and opioid craving and relapse. Results of preclinical studies reviewed provide evidence for sex differences in reinstatement and incubation of cocaine seeking but not for reinstatement or incubation of methamphetamine or opioid seeking.**

I. Introduction

Substance use disorders are characterized by high *relapse* rates during abstinence (Hunt et al., 1971; Sinha, 2011; SAMHSA, 2016; Marsh et al., 2018). Over the last decades, investigators examined *sex* differences in human drug use and relapse (Griffin et al., 1989). In the early 1990s, Kosten et al. (1993) reported that women have more severe cocaine use problems, more cocaine use days, and shorter abstinence periods. In contrast, women had better outcomes at 6-month follow-up (Kosten et al., 1993). In the early 2000s, Elman et al. (2002) reported that cue-induced cocaine *craving* is higher in women. In parallel, many preclinical studies since the 1990s reported that female rats are more sensitive than males to the reinforcing effects of cocaine, as assessed by *drug self-administration* and *conditioned place preference* models (Lynch et al., 2002; Roth and Carroll, 2004; Lynch, 2006; Becker and Hu, 2008; Quinones-Jenab and Jenab, 2012). For example, female rats acquire cocaine self-administration faster than male rats (Lynch and Carroll, 1999). Additionally, investigators reported sex differences in relapse to cocaine seeking, as assessed by *extinction-reinstatement* and *incubation of drug craving* models (Becker, 2016; Carroll and Lynch, 2016; Becker et al., 2017) (see below). These findings have led to the widely held dogma especially in the preclinical addiction field that across drug classes females are more vulnerable to initiation and escalation of drug use and to relapse to drug use during abstinence (Fattore et al., 2008; Becker, 2016; Carroll and Lynch, 2016; Becker and Chartoff, 2019).

The goal of our review is to critically examine evidence for sex differences in psychostimulant and opioid craving and relapse in humans and in reinstatement of drug seeking and incubation of drug craving in rat models. We refer readers to excellent comprehensive reviews of the preclinical literature on sex differences in initiation and escalation of drug self-administration and withdrawal (Lynch et al., 2002; Roth et al., 2004; Becker and Koob, 2016; Becker and Chartoff, 2019). Notably, our review does not cover sex differences in humans and animal models of legal drugs (nicotine and alcohol). We refer readers to excellent papers and reviews on this topic (Walitzer and Dearing, 2006; Rahman et al., 2016; Goenaga et al., 2020).

ABBREVIATIONS: CRF, corticotropin-releasing factor; Drd2, dopamine receptor 2; fMRI, functional magnetic resonance imaging; NAc, nucleus accumbens; PAG, periaqueductal gray; PET, positron emission tomography; PFC, prefrontal cortex; vmPFC, ventromedial prefrontal cortex; VTA, ventral tegmental area.

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We first review clinical studies on sex differences in psychostimulant (cocaine, methamphetamine) and opioid (heroin) craving and relapse. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for the literature search strategy and searched Embase, PsycINFO, and MEDLINE databases. The details of the search strategy for MEDLINE are provided below, which was adapted for the other two databases using similar terms (see methods of the systematic review in the Supplemental Material for more details):

("craving"[MeSH] OR "craving"[tiab] OR "recurrence"[MeSH] OR "relapse"[tiab] OR "abstinence"[tiab] OR "remission"[tiab]) AND ("analgesics opioid"[Pharmacological Action] OR "Central Nervous System Stimulants"[Pharmacological Action] OR "Cocaine"[MeSH] OR "Amphetamine-Related Disorders"[MeSH] OR "Opioid-Related Disorders"[MeSH] OR "Cocaine-Related Disorders"[MeSH] OR "opioid"[tiab] OR "opiate"[tiab] OR "opium"[tiab] OR "heroin"[tiab] OR "morphine"[tiab] OR "stimulants"[tiab] OR "amphetamine"[tiab] OR "dextroamphetamine"[tiab] OR "methamphetamine"[tiab] OR "Cocaine"[tiab] OR "caffeine"[tiab]) AND ("sex characteristics"[MeSH] OR "sex factors"[MeSH] OR "sex characteristics"[tiab] OR "sex differences"[tiab] OR "gender"[tiab] OR "gender differences"[tiab]). Filters: Humans

Next, we review preclinical studies on sex differences in psychostimulant and opioid (heroin, fentanyl, oxycodone) reinstatement of drug seeking and incubation of drug craving. We also discuss the role of ovarian hormones in cocaine craving and relapse/reinstatement in humans and animal models. As with the clinical search, our preclinical literature search followed PRISMA guidelines, and we searched Embase, PsycINFO, and MEDLINE datasets using keywords and controlled vocabulary terms relevant to our review. Below we provide the details of the research strategy for MEDLINE, which was adapted for the other two databases:

((craving[Title/Abstract] OR relapse[Title/Abstract] OR recurrence[Title/Abstract] OR abstinence[Title/Abstract] OR recovery[Title/Abstract] OR remission[Title/Abstract]) AND ("sex differences"[Title/Abstract] OR "sex difference"[Title/Abstract] OR "gender differences"[Title/Abstract] OR "gender difference"[Title/Abstract])) AND (opioid[Title/Abstract] OR methamphetamine[Title/Abstract] OR estrous cycle[Title/Abstract] OR estradiol[Title/Abstract] OR progesterone[Title/Abstract]). Filters: Other Animals

Next, we propose a mechanistic model of the role of ovarian hormones in mediating sex differences in cocaine relapse in rat models. Finally, we summarize results from several human imaging studies on the brain response to drug cues and stress in men and women. In Supplemental Tables S1–S5 and Figs. 1 and 2, we provide a summary of the studies reviewed. In Table 1, we provide a glossary of terms (*italic font* in the text), and in Table 2, we outline the methodological considerations in studying ovarian hormones in human and rodent models of drug craving and relapse. In the Supplemental Material, we describe the methodological details of the systematic review of both the clinical (Supplemental Fig. 1) and preclinical (Supplemental Fig. 2) literature [note: Our review does not include studies on sex differences in extinction responding 1 day after the last self-administration session because this procedure does not meet the operational definition of *relapse* (resumption of drug-seeking behavior after a period of abstinence)].

II. Sex Differences in Drug Craving and Relapse: Clinical Studies

We review studies on sex differences in psychostimulant and opioid craving and relapse in human laboratory and treatment settings (Fig. 1; Supplemental Table S1). Drug craving is correlated, to some degree, with drug use (Bordnick and Schmitz, 1998; Da Silveira et al., 2006; Paliwal et al., 2008; Preston et al., 2009, 2018) and often predictive of future relapse (Bordnick and Schmitz, 1998; Sinha et al., 2006, 2011). In human laboratory studies, drug craving is measured by psychometric self-report assessments before and after exposure to the drug itself, drug-related cues, or stressors (Jaffe et al., 1989; Sinha et al., 2011). Cue-induced craving is achieved by exposing study participants to videos or pictures showing drug-associated cues (e.g., syringe), handling of drug paraphernalia, standardized scripts, or individualized guided imagery (Bedi et al., 2011). Stress-induced craving is achieved by exposing study participants to psychologic (e.g., personalized imagery, public speaking, mental arithmetic), physical (e.g., cold pressor), or pharmacological (e.g., α-2 adrenoreceptor antagonist yohimbine) stressors (Charney et al., 1983; Sinha et al., 1999, 2011; Stine et al., 2002).

In treatment settings, relapse is defined as resumption of regular drug use during outpatient treatment or after completion of inpatient or outpatient treatment. These studies rely on follow-up interviews at specific time points or ecological momentary assessment, real-time reporting of drug craving, and use in the natural environment (Shiffman et al., 1996; Epstein et al., 2009). We also review cross-sectional studies because they provide additional insight on sex differences in relapse vulnerability.

A. Psychostimulants

1. Craving. Several studies examined sex differences in cocaine craving (Fig. 1; Supplemental Table S1), and although some studies suggest greater craving in women, other studies do not.

2. Spontaneous Drug Craving. Cocaine (Fig. 1A): Elman et al. (2001) reported that when craving is

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Fig. 1. Summary of clinical studies on sex differences in psychostimulant and opioid craving and relapse. Both craving (left) and relapse (right) panels depict the proportion of observations and list the total number of comparisons of sex differences in which F > M, F = M, and F < M for cocaine (A and D), methamphetamine (B and E), and opioids (C and F). Conditions under which craving was measured, and the abstinence period when relapse was assessed is also displayed. F, females; M, males; m, months. Note: The number of comparisons does not equal the number of studies for a given category in Supplemental Table S1 because in some studies investigators assessed more than one dependent measure (e.g., both cue- and stress-induced craving). Spontaneous craving refers to baseline nonprovoked subjective craving.

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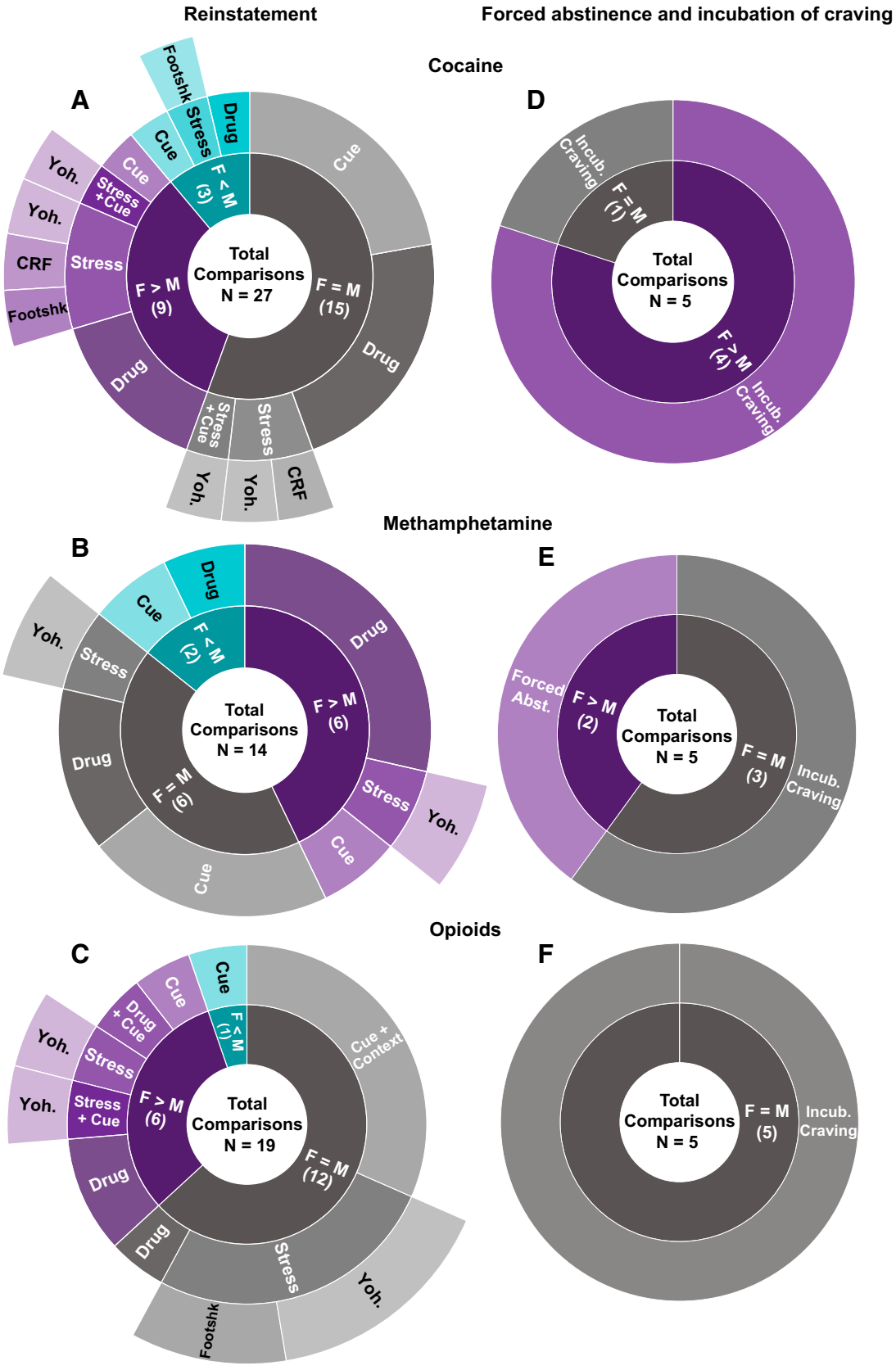

Fig. 2. Summary of preclinical studies on sex differences in psychostimulant and opioid reinstatement and incubation of craving. Both reinstatement of drug-seeking behavior (left) and incubation of craving and drug seeking after forced abstinence (right) panels depict the proportion of observations and list the total number of comparisons of sex differences in which F > M, F = M, and F < M for cocaine (A and D), methamphetamine (B and E), and opioids (C and F). The conditions under which drug seeking was measured are also displayed. F, females; M, males; Yoh, yohimbine. Note: the number of comparisons does not equal the number of studies for a given category in Supplemental Table S2 because in some studies investigators assessed more than one dependent measure (e.g., both cue- and stress-induced reinstatement).

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TABLE 1
Glossary of terms

Behavioral Term	Definition
Conditioned place preference	A Pavlovian conditioning procedure in which one distinct context is paired with noncontingent drug injections while another context is paired with vehicle injections. During subsequent drug-free tests, increased preference for the drug context serves as a measure of the drug's reinforcing effects.
Craving	An affective state described as an urge for drug; it can be induced in human drug users by exposure to the self-administered drug, drug cues and contexts, or stress.
Cue-induced reinstatement	An experimental condition in which laboratory animals are first trained to self-administer a drug or non–drug reinforcer, and each reinforcer delivery is temporally paired with a discrete cue (e.g., tone or light). Operant responses are then extinguished in the absence of the reinforcer and the cue. During reinstatement testing, exposure to the cue, which is earned contingently during testing, reinstates responding.
Discrete cue	An experimental condition in which an environmental cue (e.g., light, tone) is contingently paired with the reinforcer delivery.
Discriminative cue	An experimental condition in which an environmental cue (e.g., light, tone) predicts the availability of a reinforcer.
Drug-induced reinstatement	Resumption of drug seeking after extinction following noncontingent priming injections of the self-administered drug or related drugs immediately prior to the test session.
Drug self-administration	An operant procedure in which laboratory animals lever press (or nose poke) for drug injections or oral drug delivery. Most (but not all) drugs self-administered by humans are self-administered by rodents and nonhuman primates.
Early abstinence	The beginning of abstinence phase when people with substance use disorders experience somatic withdrawal symptoms. In studies using rat models, this term refers to the first several days after cessation of drug self-administration.
Extinction	The decrease in the frequency or intensity of learned responses after the removal of the unconditioned stimulus (e.g., drug) that has reinforced the learning. In studies on incubation of drug craving and relapse after forced or voluntary abstinence, extinction responding (in the presence of the drug-paired contextual and discrete cues) is the operational measure of drug seeking.
Forced abstinence	Experimental conditions in which abstinence after drug self-administration is imposed by the experimenter. In animal models, forced abstinence can be achieved by (1) extinction training in the drug self-administration context or a nondrug context or (2) keeping the experimental animals in their home cage during the abstinence period.
Incubation of drug craving	A hypothetical psychologic process inferred from the findings of time-dependent increases in nonreinforced drug seeking after cessation of drug self-administration in rodents.
Intermittent-access drug self-administration	A drug self-administration procedure in which the drug is repeatedly available for short periods that are separated by long timeout periods (typically 12 cycles of 5-min drug access, 25-min timeout). Exposure to this procedure induces binge-like self-administration behavior and spiking brain drug levels.
Long-access drug self-administration	A drug self-administration procedure in which the drug is continuously available for extended daily sessions (6 h/day or more). This procedure results in escalation of drug intake and high and stable drug concentrations in the brain.
Reinstatement of drug seeking	Postextinction resumption of operant behavior that had previously been maintained by a drug. Reinstatement is induced by a drug priming injection, stressors, contexts previously paired with drug self-administration, or response-contingent presentation of drug-associated cues.
Relapse	Resumption of drug-taking behavior during self-imposed (voluntary) or forced abstinence in humans and laboratory animals.
Sex	Characterization of an individual as female or male from biologic and morphologic features.
Short-access drug self-administration	A drug self-administration procedure in which the drug is continuously available during short daily sessions (3 h/day or less).
Stress-induced reinstatement	Resumption of drug seeking after extinction following exposure to environmental or pharmacological stressors.
Voluntary abstinence	Experimental conditions in which the self-administered drug is available in the self-administration chamber but the laboratory animal either stops or significantly decreases drug self-administration behavior. In animal models, voluntary abstinence can be achieved by introducing 1) mild foot shock punishment after the drug-reinforced operant response, 2) an electric barrier that delivers mild shock near the drug-paired lever, 3) mutually exclusive alternative palatable food reward, and 4) mutually exclusive alternative social reward.

assessed during *early abstinence* (12 hours) with a craving questionnaire of six items measuring aspects of craving, such as current intensity, projected intensity, resistance, and response to drug-associated cue, women reported higher spontaneous (nonprovoked) cocaine craving than men. However, other studies found no sex differences in cocaine craving 2 days into abstinence (Waldrop et al., 2010) or in nonabstaining users (Volkow et al., 2011) when craving was measured with the Craving/Distress/Mood scale or a brief version of the Cocaine Craving Questionnaire. Similarly, when craving is monitored at least a week into abstinence with a brief version of the Cocaine Craving Questionnaire or a 10-point visual analog scale, several studies reported no sex differences in spontaneous craving (Fox et al., 2006, 2013; Paliwal et al., 2008).

Methamphetamine (Fig. 1B): Galloway et al. (2010) reported no sex differences in spontaneous methamphetamine craving measured by a self-reported 0–100 scale (endpoint anchors of "no craving" and "most

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TABLE 2
Methodological considerations in studying the role of ovarian hormones in drug craving and relapse in humans and animal models

Method Used	Limitations	References
	Clinical studies	
Identification of the phases based on self-report of menses onset combined with radioimmunoassay from estradiol and progesterone plasma concentrations	1. Assumption of similar cycle length between women. 2. Does not take in consideration the variation of hormones concentration within each phase. 3. Cycle can be disrupted by drug intake. 4. Only one or two blood samples per participant, which is restricted to a specific time point and does not fully represent estradiol and progesterone concentrations across the full cycle.	(Collins et al., 2007; Evans et al., 2002; Lukas et al., 1996; Sofuoglu et al., 1999)
Saliva sample of estradiol and progesterone	Only one or two blood samples per participant, which is restricted to a specific time point and does not fully represent estradiol and progesterone concentrations across the full cycle.	(Fox et al., 2008)
	Preclinical studies	
Vaginal swab	1. Based on the proportion of leukocytes, cornified and nucleated cells in the vaginal sample, which can be subjective. 2. Some studies pool different phases together based on similar behavior responses, which excludes the role of hormones variations between the different phases. 3. Does not take in consideration the variation of hormone concentration within each phase.	(Bechard et al., 2018; Cox et al., 2013; Feltenstein et al., 2009; Feltenstein and See, 2007; Fuchs et al., 2005; Kerstetter et al., 2008; Kippin et al., 2005; Nicolas et al., 2019)
Radioimmunoassay for plasma levels of estradiol and progesterone	Only one or two blood samples per animal, which is restricted to a specific time-point and does not fully represent estradiol and progesterone concentrations across the full cycle.	(Feltenstein et al., 2009; Feltenstein and See, 2007)

craving ever experienced") during 4 months of abstinence.

3. Drug-Induced Craving. Cocaine (Fig. 1A): During early abstinence (<7 days), craving induced by cocaine injection was either similar in men and women when measured by multidimensional questionnaires (Elman et al., 2002) or higher in men when measured with 10-point visual analog scales (Evans et al., 1999).

4. Cue-Induced Craving. Cocaine (Fig. 1A): No sex differences in cue-induced cocaine craving were observed after 2 days of abstinence (Waldrop et al., 2010) or in nonabstaining users (Volkow et al., 2011). Similarly, Fox et al. (2006) and Potenza et al. (2012) reported no sex differences in cue-induced craving when craving was measured at least a week into abstinence using a 10-point visual analog scale. Additionally, using the same measurement tool, there were no sex differences in cocaine craving in individuals with comorbid substance use disorder undergoing long-term opioid agonist treatment (Avants et al., 1995; Kennedy et al., 2013). However, Fox et al. (2014) and Robbins et al. (1999) reported higher cue-induced cocaine craving measured with a 10-point visual analog scale in women after 14–21 days of inpatient treatment or long-term outpatient treatment, respectively.

Methamphetamine (Fig. 1B): Tolliver et al. (2010) reported no sex differences in cue-induced methamphetamine craving measured with a 10-point visual analog scale during early abstinence.

5. Stress-Induced Craving. Cocaine (Fig. 1A): Waldrop et al. (2010) reported stronger correlation between peak craving and peak response to a social stressor (Trier Social Stress Test) in women after 2 days of abstinence. Similarly, Moran-Santa Maria et al. (2014) reported that within 2–3 days of initiating abstinence, women report greater yohimbine-induced craving measured with a 10-point visual analog scale. In contrast, using the same craving scale method, Back et al. (2005) reported no sex differences in craving induced by psychological (Mental Arithmetic Task) or physical (Cold Pressor Task) stressors. Additionally, Brady et al. (2009) reported that after similar abstinence length, men and women show similar corticotropin-releasing factor (CRF)-induced craving. Finally, no sex differences in craving induced by script-guided stressful situations were observed in participants abstinent for at least 2 weeks using a 10-point visual analog scale (Li et al., 2005).

Together, these studies show that women are more sensitive to stress-induced craving only during early abstinence and that this effect is independent of the

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type of stressor (e.g., physical or psychosocial). However, our conclusion is tentative because of the few studies published, the divergent results, and the low statistical power to measure sex differences.

6. Relapse. Cocaine (Fig. 1D): Kosten et al. (1993) reported that upon entering treatment, women had higher relapse rates. However, they reported that there were no sex differences during the treatment study (desipramine or lithium carbonate), and at 6-month follow-up, relapse rates were lower in women (Kosten et al., 1993). In contrast, Kennedy et al. (2013) reported that in polydrug (cocaine + heroin) users, women undergoing opioid agonist therapy showed higher relapse rates over a 7-month period. However, during 3-month (Burch et al., 2015; Bashiri et al., 2017) and 6-month (Gallop et al., 2007) treatment follow-up, women showed lower relapse rates. Similarly, when relapse was assessed at treatment follow-up, women often exhibited better outcomes. Specifically, women had lower relapse rates at 6-month follow-up from both inpatient (Weiss et al., 1997) and outpatient (Kosten et al., 1993) treatment. In contrast, no sex differences in relapse rates were observed 9 months (Sterling et al., 2004) or 12 months (Negrete and Emil, 1992; McKay et al., 2003) after outpatient treatment. Additionally, during a 2-year period after a randomized clinical trial in polydrug (cocaine + opioid) users, men and women showed similar relapse rates (Schottenfeld et al., 1998).

Methamphetamine (Fig. 1E): Hillhouse et al. (2007) reported higher relapse rates in women during 4-month outpatient treatment but no sex differences in relapse at 6-month or 12-month post-treatment. In contrast, Lanyon et al. (2019) reported higher relapse rates in men at both 12-month and 5-year follow-ups. He et al. (2013) and Brecht et al. (2000, 2004) reported no sex differences in lifetime relapse rates among inpatients or after treatment completion.

B. Opioids

1. Craving. Back et al. (2011) reported greater spontaneous opioid craving in women, and Yu et al. (2007) reported higher cue-induced heroin craving in women during inpatient treatment (Fig. 1C). Additionally, Moran et al. (2018) reported that over 4 months of outpatient opioid maintenance therapy, women showed higher stress-induced opioid craving. However, Herbeck et al. (2016) reported no sex differences in opioid craving during 3 weeks of extended-release naltrexone treatment. Similarly, Kennedy et al. (2013) reported no sex differences in heroin craving during 6 months of outpatient opioid agonist treatment with methadone (100 mg/day).

2. Relapse. Maehira et al. (2013) reported higher relapse rates in women during the first 2 months of abstinence (Fig. 1F). Ignjatova and Raleva (2009) reported more heroin lapses in women during 6 months of opioid agonist treatment with methadone (dose not provided). In contrast, Kamal et al. (2007) and Kennedy et al. (2013) reported no sex differences in heroin relapse during the first 3 (methadone, average 74 mg/day) and 6 (methadone, 100 mg/day) months of opioid agonist treatment.

After more prolonged abstinence periods (>1 year), there is some evidence for lower relapse rates in women. Gordon et al. (2017) reported lower relapse rates for women at 1-year follow-up after buprenorphine treatment (average 8 mg/day). Zimmer-Höfler and Dobler-Mikola (1992) reported similar findings after 2 years of abstinence from different therapeutic programs (e.g., methadone maintenance therapy, therapeutic community program) and prisons. Additionally, during a 2-year follow-up period during opioid agonist treatment (buprenorphine, 4 mg/day) for polydrug (cocaine + opioids) use, women had more drug-free days (Schottenfeld et al., 1998). Within the same longitudinal study of individuals using heroin who were recruited from randomly selected treatment agencies delivering various treatments (e.g., methadone or buprenorphine maintenance treatment, drug-free residential rehabilitation, or detoxification), Darke et al. reported that women were less likely to relapse over 3-year (Darke et al., 2007) and 11-year (Darke et al., 2015) follow-up periods. These results contrast with previous studies reporting no sex differences in relapse at 7-year (Zimmer-Höfler and Dobler-Mikola, 1992) and 8-year (Brunswick and Messeri, 1986) follow-ups. Additionally, several studies reported no sex differences in relapse over 12-month follow-up during methadone treatment [average dose 130 mg/day in Adelson et al. (2018) and 40–70 mg/day in Levine et al. (2015) and Smyth et al. (2012)] and no sex differences in lifetime opioid relapse rates (Zhou et al., 2017; Moradinazar et al., 2020). Importantly, the different outcomes from these studies could be due to the divergent screening of the participants. Indeed, although some studies directly compared drug craving and relapse in men and women after the same opioid agonist treatment (e.g., methadone or buprenorphine maintenance therapy), others compared cohorts of participants with mixed therapy programs (e.g., opioid agonist therapy, detoxification, or drug-free residential rehabilitation), which may increase sample variability and decrease the power to detect sex differences.

C. Conclusions

The studies reviewed do not support the notion of sex differences in drug craving and relapse for either psychostimulants or opioids. However, these studies suggest areas for further examination, including potential sex differences in craving and relapse vulnerability during early abstinence wherein women may be more vulnerable.

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III. Sex Differences in Drug Craving and Relapse: Preclinical Studies

Sex differences in drug relapse were examined using the reinstatement and incubation of drug-craving models (Fig. 2; Supplemental Table S2) (Venniro et al., 2016). In studies using the reinstatement model, investigators determined sex differences in resumption of drug seeking after extinction induced by exposure to the self-administered drug, *discrete cues*, *contextual cues*, and stress. For clarity, we refer to discrete cues as "cues" in the text below. In stress-induced reinstatement studies, the typical stressors investigators used in male rats were intermittent foot shock (Shaham and Stewart, 1995; Shaham et al., 2000; Mantsch et al., 2016) and yohimbine as a pharmacological stressor (Shepard et al., 2004; Mantsch et al., 2016). In opioid users, yohimbine has been shown to induce stress- and withdrawal-like symptoms and opioid craving (Stine et al., 2002). However, interpretation of results from studies using yohimbine in reference to stress-induced reinstatement has been challenged by Chen et al. (2015). They showed that at the dose range yohimbine is used in reinstatement studies, the drug's effect on reinstatement is independent of the history of contingent self-administration and unrelated to the commonly assumed stress-like effects of yohimbine.

A. Psychostimulants

1. Drug-Induced Reinstatement. Cocaine (Fig. 2A): Lynch and Carroll (2000) reported that female rats showed higher drug-induced reinstatement (often termed *drug priming-induced reinstatement*) after *short-access drug self-administration* of cocaine at 1.0 and 3.2 mg/kg but not 0.32 mg/kg. This initial finding of sex differences in cocaine-induced reinstatement was confirmed in subsequent studies (Anker et al., 2009; Smith et al., 2012; Doncheck et al., 2020). In contrast, after *continuous long-access drug self-administration* of cocaine, Zlebnik et al. (2014) and Swalve et al. (2016) reported no sex differences in cocaine-induced reinstatement. Additionally, after *intermittent-access drug self-administration* of cocaine, Kawa and Robinson (2019) reported no sex differences in reinstatement induced by cocaine priming (<1.6 mg/kg, i.v.).

A tentative conclusion from these studies is that females are more sensitive to cocaine-induced reinstatement after short-access but not long-access cocaine self-administration, suggesting that cocaine history (e.g., quantity of drug intake) may be an important contributing factor to sex differences in cocaine-induced reinstatement.

Finally, Jordan and Andersen (2018) reported that after 30 days of short-access self-administration training with a high (0.75 mg/kg) but not low (0.25 mg/kg) cocaine unit dose (training started on P28) followed by 30 abstinence days, cocaine seeking was higher in males than in females after exposure to a noncontingent cocaine injection (10 mg/kg, i.p) immediately prior to a single relapse test session under extinction conditions. The relevance of these results to sex differences in cocaine-induced reinstatement after extinction is unknown because the rats did not undergo extinction training and the authors did not assess the effect of vehicle (saline) injections on drug seeking.

Methamphetamine (Fig. 2B): After both short- and long-access drug self-administration, methamphetamine (1 mg/kg)-induced reinstatement was higher in female rats (Holtz et al., 2012; Reichel et al., 2012; Cox et al., 2013; Cordie and McFadden, 2019). However, using the same dose, others reported either no sex differences in methamphetamine-induced reinstatement (Everett et al., 2020; Zlebnik et al., 2021) or higher reinstatement in males (Everett et al., 2021).

2. Cue-Induced Reinstatement. Cocaine (Fig. 2A): Zhou et al. (2014) reported higher *cue-induced reinstatement* in females after short-access cocaine self-administration. In contrast, under similar training conditions, several studies reported no sex differences in cue-induced reinstatement (Fuchs et al., 2005; Swalve et al., 2016; Bechard et al., 2018; Weber et al., 2018). Similarly, no sex differences in cue-induced reinstatement were observed after long-access (Zlebnik et al., 2014) or intermittent-access (Kawa and Robinson, 2019) cocaine self-administration.

Methamphetamine (Fig. 2B): Five studies examined sex differences in cue-induced reinstatement of methamphetamine seeking, and, as with cocaine, the results are inconclusive. After short-access self-administration, Cox et al. (2013) reported higher cue-induced reinstatement in female rats. In contrast, Bernheim et al. (2017) and

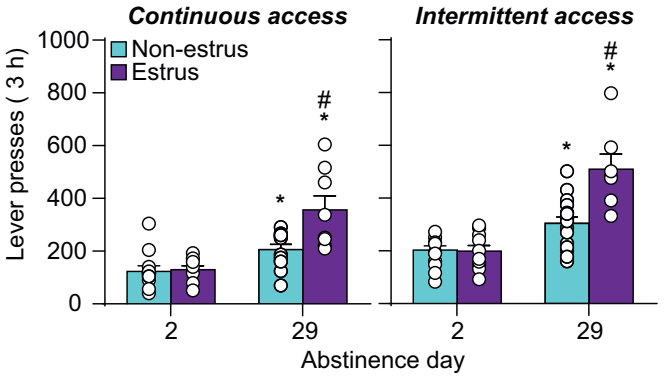

Fig. 3. Effect of estrous cycle on incubation of craving after long-access and intermittent-access cocaine self-administration in female rats. Relapse (incubation) test. Mean ± S.E.M. number of active lever presses per session after continuous (nonestrus: n = 12 for day 2 and 29, estrus: n = 9/8 for day 2/29) and intermittent (nonestrus: n = 13/16 for day 2/29, estrus n = 10/7 for days 2/29) access drug self-administration. * Different from day 2 within each estrous phase, $P < 0.05$; # Different from nonestrus on day 29, $P < 0.05$. Adapted from Nicolas et al. (2019). Figure 3 was reproduced with permission from Elsevier.

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Everett et al. (2020a) reported no sex differences. Additionally, Takashima et al., (2018) reported higher cue-induced reinstatement in male rats after long-access self-administration. Zlebnik et al. (2021) used a methamphetamine self-administration protocol of two 2-hour sessions/day and reported no sex differences in cue-induced reinstatement.

3. Stress-Induced Reinstatement. Cocaine (Fig. 2A): After short-access self-administration, Anker and Carroll (2010b) reported higher yohimbine-induced reinstatement, and Feltenstein et al. (2011) reported higher yohimbine- and cue-induced reinstatement in females. In contrast, Zlebnik et al. (2014) reported no sex differences in either yohimbine-induced or yohimbine- and cue-induced reinstatement. Doncheck et al. (2020) reported no sex differences in restraint stress-induced potentiation of drug-induced reinstatement. However, they reported that intermittent footshock potentiates drug-induced reinstatement in males but not females. In contrast, Connelly et al. (2020) reported higher foot shock–induced reinstatement in females.

In male rats, the effect of intermittent footshock stress on reinstatement of drug seeking is inhibited by extrahypothalamic CRF, and ventricular CRF injections mimic the effect of intermittent footshock on reinstatement (Shaham et al., 2000; Erb et al., 2001; Mantsch et al., 2016). Based on these results, Buffalari et al. (2012) examined sex differences in CRF-induced reinstatement of cocaine seeking after short-access self-administration. The main finding was that although ventricular injections of CRF reinstated cocaine seeking in both sexes, the response to CRF was more variable in females than in males.

Methamphetamine (Fig. 2B): Cox et al. (2013) reported higher yohimbine-induced reinstatement in females, whereas Everett et al. (2020a) reported no sex differences. The reasons for these different results are unclear but may be due to a long abstinence period (21 days) before the extinction phase in the Everett et al. (2020a) study. As discussed above, interpretation of data from yohimbine studies in reference to stress-induced reinstatement is problematic (Chen et al., 2015; Mantsch et al., 2016).

Together, these divergent results across different stressors do not indicate significant sex differences in stress-induced reinstatement of cocaine or methamphetamine seeking.

4. Incubation of Craving and Relapse after Abstinence. Cocaine (Fig. 2D): Kerstetter et al. (2008) reported longer-lasting and higher incubation of cocaine craving (up to 180 days of home-cage *forced abstinence*) in females after long-access drug self-administration. We extended these results and reported higher incubation of cocaine craving on abstinence day 29 in females after both long-access and intermittent-access cocaine self-administration (Nicolas et al., 2019) (Fig. 3). Most recently, Corbett et al. (2021) reported similar results (i.e., higher incubation in females) after both 15 and 48 abstinence days. Johnson et al. (2019) reported similar results with higher cocaine seeking in female rats tested at 1 or 30 abstinence days after short-access cocaine self-administration. However, these results should be interpreted with caution because in both sexes the incubation effect was variable and statistically nonsignificant, likely because of the use of the short-access procedure [incubation is less robust with this procedure (Lu et al., 2004)]. Additionally, Madangopal et al. (2019) reported that incubation of the response to cocaine *discriminative cues* (e.g., light, tone) that predict availability of the drug is more persistent in female rats and lasts for up to 200 abstinence days. However, these results should also be interpreted with caution because the study was not powered to detect sex differences.

In contrast, Venniro et al. (2021) reported that after either long-access (12 hour/day) or intermittent long-access (12 hour/day, 5 minutes ON, 25 minutes OFF 24), there were no sex differences in incubation of cocaine craving after home-cage forced abstinence or after *voluntary abstinence* induced by providing rats with a mutually exclusive choice between cocaine or rewarding social interaction. The different results of Venniro et al. (2021) versus the studies of Kerstetter et al. (2008), Nicolas et al. (2019), and Corbett et al. (2021) may be because of two reasons. The first is that Venniro et al. (2021) trained their rats for 12 hours/day, whereas in the other studies, the session duration was 6 hours/day. The second is that the male and female rats in Venniro et al. (2021) study were first trained to lever press for social interaction for 6 days, whereas the rats in the other studies were not.

Methamphetamine (Fig. 2D): Venniro et al. (2017) (long-access self-administration) and Everett et al. (2020a) (short- and long-access self-administration) reported no sex differences in incubation of methamphetamine craving after either forced abstinence in home cage or voluntary abstinence in the drug self-administration chambers, the latter being achieved by providing rats with mutually exclusive choices between the self-administered drug and an alternative nondrug reinforcer (e.g., palatable food or social interaction) (Caprioli et al., 2015; Caprioli et al., 2017; Venniro et al., 2018; Venniro and Shaham, 2020; Fredriksson et al., 2021). Similarly, Daiwile et al. (2019) reported no sex differences in incubation of methamphetamine craving after forced abstinence after a self-administration protocol of two 3-hour sessions/day. In contrast, Ruda-Kucerova et al. (2015, 2017) reported that in a single relapse test after 15 days of forced abstinence from short-access methamphetamine self-administration, drug seeking was higher in female rats. In the context of sex differences

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in incubation of drug craving, these results are difficult to interpret because the authors did not establish that incubation had occurred under their experimental conditions.

B. Opioids

1. Drug-Induced Reinstatement (Fig. 2C). In an early study, Klein et al. (1997) reported that reacquisition of oral fentanyl self-administration after extinction is higher in female rats. However, these results are difficult to interpret without ruling out potential confounds related to the oral route of drug administration (i.e., sex differences in pharmacokinetics and taste sensitivity). In a recent study, Malone et al. (2021) tested both sexes for fentanyl-induced reinstatement after short- (1 hour) or long- (6 hours) access fentanyl self-administration training. They reported higher fentanyl-induced reinstatement in females after short- but not long-access fentanyl self-administration. Similarly, Smethells et al. (2020) reported higher heroin-induced reinstatement and heroin- and cue-induced reinstatement after short-access self-administration.

2. Cue- and Context-Induced Reinstatement (Fig. 2C). Cue-induced reinstatement: Vazquez et al. (2019) reported higher extinction responding and cue-induced reinstatement of heroin seeking in females after short-access drug self-administration in food-restricted rats. In contrast, Phillips et al. (2020) reported no sex differences in cue-induced reinstatement of oxycodone self-administration after 3 hours oral oxycodone self-administration in mice. Additionally, Smethells et al. (2020) reported no differences in cue-induced reinstatement after short-access heroin self-administration. Bakhti-Suroosh et al. (2021) tested both sexes for cue-induced reinstatement after 6 hours of extinction in a single daily session performed 14 days after intermittent-access fentanyl self-administration (24 hours/day) under two training conditions: fixed ratio 1 reinforcement schedule with or without 1-second timeout. There were no sex differences in either extinction responding or cue-induced reinstatement in the no-timeout training condition. In contrast, sex differences (higher responding in females) emerged in the 1-second timeout training condition for extinction responding but not cue-induced reinstatement. The reasons for the sex-specific effect of the timeout manipulation on extinction responding are unknown. Most recently, Malone et al. (2021) tested both sexes for cue-induced reinstatement after short- (1 hour) or long- (6 hours) access fentanyl self-administration training. They reported lower cue-induced reinstatement in females after long- but not short-access self-administration.

Context-induced reinstatement: Bossert et al. (2020, 2021) reported no sex differences in context-induced reinstatement of oxycodone or heroin seeking after long-access (6 hours/day) drug self-administration training.

Together, there is limited evidence for sex differences in cue- or context-induced reinstatement of opioid seeking. Unexpectedly, under certain experimental conditions, female rats can be either more sensitive [intermittent access (24 hour/day) plus 1-second timeout] or less sensitive [long-access (6 hours/day) drug self-administration] to cue-induced reinstatement of fentanyl seeking.

3. Stress-Induced Reinstatement (Fig. 2C). Smethells et al. (2020) reported no sex differences in extinction responding but higher yohimbine-induced reinstatement in females; they also reported higher yohimbine- and cue-induced reinstatement in females after short-access heroin self-administration. In contrast, Fulenwider et al. (2020) reported no sex differences in footshock–induced reinstatement of oxycodone seeking after short-access oral oxycodone self-administration training. Malone et al. (2021) tested male and female rats for yohimbine-induced reinstatement after short- (1 hour) or long- (6 hours) access fentanyl self-administration training. There were no sex differences in either extinction responding or yohimbine-induced reinstatement; however, independent of the access condition, yohimbine's effect on reinstatement was weak and statistically significant only after injections of the low (1 mg/kg) but not higher (2 mg/kg) dose. In the context of sex differences in stress-induced reinstatement, these data are difficult to interpret because of the weak effect of yohimbine on reinstatement in both sexes. In a follow-up study, the same group studied the effect of systemic injections of the glucocorticoid receptor antagonist PT150 on stress-induced reinstatement of fentanyl seeking (Hammerslag et al., 2021). They reported that PT150 decreased intermittent footshock– but not yohimbine-induced reinstatement in male but not female rats. However, these results should also be interpreted with caution because they are 1) based on post hoc analyses in the absence of a significant interaction between the footshock stress condition and PT150 dose, and 2) the weak effect of yohimbine on reinstatement in both sexes and the weak effect of footshock on reinstatement in females. Finally, the data on the inhibitory effect of glucocorticoid antagonism on stress-induced reinstatement of opioid seeking is unexpected based on previous endocrinological and pharmacological studies showing that the effect of intermittent footshock on reinstatement of drug seeking is independent of activation of the hypothalamic-pituitary-adrenal axis and glucocorticoid systems (Shaham et al., 2000; Erb et al., 2001; Mantsch et al., 2016).

Together, the limited number of studies reviewed above do not support the notion of increased vulnerability to stress-induced reinstatement of opioid seeking in females.

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4. Incubation of Craving and Relapse during Abstinence (Fig. 2F). Unlike the mixed evidence for reinstatement of opioid seeking, there is no evidence for sex differences in incubation of opioid craving after either forced or voluntary abstinence achieved via either providing the rats with alternative non–drug reinforcer in a choice procedure or by introducing an electric barrier of increasing shock intensity near the drug-paired lever (Cooper et al., 2007).

Using a long-access self-administration protocol, Venniro et al. (2017) reported no sex differences in either incubation of heroin seeking after forced abstinence or reversal of incubation of heroin craving after food choice–induced abstinence. Venniro et al. (2019) replicated the findings for forced abstinence and also reported no sex differences in the inhibition of incubation of heroin seeking after social choice–induced abstinence. Reiner et al. (2020) reported no sex differences in relapse to fentanyl seeking after 2 weeks of food choice–induced abstinence. Fredriksson et al. (2020) reported no sex differences in incubation of oxycodone seeking after forced abstinence or potentiation of incubation of oxycodone seeking after electric barrier–induced abstinence. Finally, Bossert et al. (2021) reported no sex differences in incubation of heroin seeking after home-cage forced abstinence. In this study, the authors performed the incubation-related tests after 1 and 8 abstinence days (within-subjects assessment) in a nondrug context because the same rats were also tested for context-induced reinstatement after extinction of the operant response in the nondrug context.

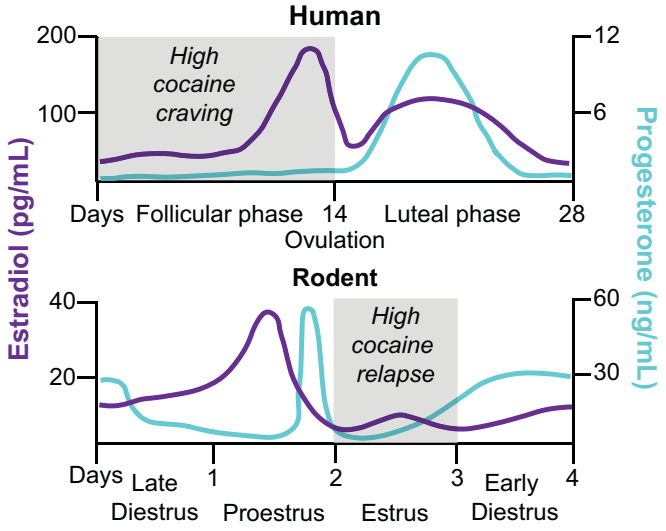

Fig. 4. Schematic comparison of the menstrual cycle in humans and the estrous cycle in rodents and fluctuation of estradiol and progesterone levels across the cycle phases. In humans, the menstrual cycle is divided into the follicular and luteal phases separated by ovulation (Sherman and Korenman, 1975; Anker and Carroll, 2010a). The cycle begins with menses, and the onset of the follicular phase is characterized by high levels of estradiol, with a peak during the preovulation period before decreasing to a moderate level during the luteal phase. Conversely, progesterone is at its lowest level during the follicular phase and starts increasing during the preovulation period to peak at the midluteal phase. In female rodents, the estrous cycle is divided into late diestrus, proestrus, estrus, and early diestrus phases, with ovulation occurring between proestrus and estrus (Cora et al., 2015; Krentzel and Meitzen, 2018). Estradiol peaks twice at the middle of the early diestrus and proestrus phases and drops by ovulation. Progesterone peaks at the end of the early diestrus and proestrus phases, and low stable levels remain for the rest of the cycle. In many studies, investigators pool together early and late diestrus phases to a single phase called diestrus because of similar hormonal and cytologic characteristics. Additionally, when no behavioral differences are observed during proestrus and diestrus, investigators combine these phases and call the combined phase nonestrus. There are major differences in the reproductive cycle of women and female rodents: the duration of the cycle, the cycle pattern of estradiol and progesterone, and the amplitude of hormone level variations. However, when the hormonal ratio over the phases is compared, some analogies are conventionally made: the follicular phase is comparable to the estrus phase (progesterone < estradiol) and the luteal phase to the nonestrus phase (progesterone > estradiol) (Anker and Carroll, 2010a; Krentzel and Meitzen, 2018).

C. Conclusions

The studies reviewed demonstrate sex differences for stress-induced reinstatement of cocaine seeking and incubation of cocaine craving after forced abstinence. In contrast, there is mixed evidence for sex differences in cue- or drug-induced reinstatement of cocaine seeking. In the case of cocaine-induced reinstatement, it appears that females are more vulnerable after short-access but not long-access cocaine self-administration. The literature on sex differences in cocaine pharmacokinetics is mixed, but sex differences in cocaine-induced reinstatement could be at least in part due to sex differences in first-pass cocaine metabolism after intraperitoneal noncontingent cocaine injections (Bowman et al., 1999; Festa et al., 2004). Similarly, the evidence supporting sex differences in reinstatement of methamphetamine and opioid seeking across different reinstating stimuli is mixed at best. Additionally, there is consistent evidence for lack of sex differences in incubation of methamphetamine and opioid craving after forced or voluntary abstinence.

However, these conclusions should be confirmed in future studies considering the relatively small number of sex differences studies, particularly for stress-induced reinstatement, wherein investigators primarily used yohimbine as the stress manipulation. In this regard, the subjects in the first intermittent footshock stress–induced reinstatement study were mostly female rats (Shaham and Stewart, 1995), but with few exceptions (Buffalari et al., 2012; Sedki et al., 2015; Connelly et al., 2020; Doncheck et al., 2020), only males were used in subsequent studies on reinstatement induced by intermittent footshock or other stressors like restraint, food restriction, or forced swim (Mantsch et al., 2016; Reiner et al., 2019). In addition, the studies on sex differences in opioid relapse and craving did not assess opioid dependence by parametric measures of spontaneous or naloxone-precipitated withdrawal symptoms. Consequently, we used the duration of opioid self-administration training as a proxy for nondependent (short-access, 1- to 3-hour daily session) and dependent (long-access, 6 hours or longer daily session) conditions. In this regard, session duration has been

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shown to be a critical factor in determining the magnitude of relapse to opioid seeking (Ahmed et al., 2000; Reiner et al., 2019).

Finally, studies on reinstatement of food seeking also provide little evidence for sex differences. No sex differences were observed for sucrose-, yohimbine-, or cue-induced reinstatement (Cox et al., 2013; Bernheim et al., 2017; Hernandez et al., 2020) after palatable food self-administration. However, Cox et al. (2013) reported higher cue-induced reinstatement of sucrose seeking in female rats.

IV. Role of Menstrual and Estrous Cycle

Several studies examined the role of ovarian hormones and menstrual/estrous cycle (Figs. 3 and 4) in drug (primarily cocaine) craving and relapse in humans and rat models (Supplemental Tables S3–S4). The methodological aspects and limitations of menstrual and estrous cycle tracking are summarized in Table 2.

A. Clinical Studies

Sofuoglu et al. (1999) reported lower cocaine desire (craving) during the luteal than the follicular phase. Evans et al. (2002) reported lower cocaine-induced subjective positive drug effects and craving during the luteal than the follicular phase. These results suggest a protective effect of progesterone (high during luteal phase) on cocaine-induced cocaine craving. In agreement with this idea, several studies reported that women with high endogenous progesterone levels (comparable to luteal phase) are less sensitive to stress- and cue-induced cocaine craving than women with low progesterone levels (Sinha et al., 2007; Moran-Santa Maria et al., 2018; Sherman et al., 2020). Additionally, several studies reported that exogenous progesterone reduces positive subjective cocaine effects and craving in both women and men (Sofuoglu et al., 2002; Sofuoglu et al., 2004; Evans and Foltin, 2006; Fox et al., 2013; Milivojevic et al., 2016), confirming progesterone's protective effects.

In contrast, in occasional intranasal cocaine users, Lukas et al. (1996) reported no effect of the menstrual cycle on cocaine-induced subjective positive drug effects. The results of this negative study agree with those from other studies in cocaine-dependent women (Collins et al., 2007; Potenza et al., 2012). Additionally, Fox et al. (2008) reported no variations in craving over the menstrual cycle during the first month of abstinence from smoked cocaine, but the ratio of estradiol/progesterone was stable across the cycle, which could explain these negative results.

However, both the negative and positive results reviewed above should be interpreted with caution because of relatively small sample sizes and other factors that may play a role in the behavioral outcomes under investigation (e.g., severity of cocaine use disorder, route of administration).

B. Preclinical Studies

The results of studies on the role of estrous cycle and ovarian hormones in reinstatement and incubation of craving are summarized in Supplemental Table S4.

Cocaine: Cocaine-induced reinstatement is higher during estrus than diestrus or proestrus (Kippin et al., 2005 Feltenstein and See, 2007; Kerstetter et al., 2008; Feltenstein et al., 2009). The expression of incubation of cocaine craving is higher during estrus than nonestrus (Fig. 3) (Kerstetter et al., 2008; Nicolas et al., 2019; Corbett et al., 2021). In contrast, evidence for the role of estrous cycle in cue- and stress-induced reinstatement is mixed. Fuchs et al. (2005) reported *lower* cue-induced reinstatement of cocaine seeking in females in estrus than nonestrus. Feltenstein et al. (2011) reported that yohimbine- and cue-induced reinstatement is lower in estrus and diestrus than proestrus. In contrast, they reported that the estrus phase has no effect on yohimbine-induced reinstatement of cocaine seeking. Peterson et al. (2014) and Bechard et al. (2018) also reported similar cue-induced reinstatement of cocaine seeking during different phases of the estrous cycle.

Suppression of ovarian hormones by ovariectomy decreases cocaine-induced reinstatement, whereas chronic estradiol treatment in ovariectomized rats restores this reinstatement to levels similar to those of sham rats (Larson et al., 2005; Anker et al., 2007). Additionally, acute proestrus-level estradiol in ovariectomized rats potentiates cocaine-induced reinstatement (Doncheck et al., 2018). In contrast, exogenous progesterone treatment in free-cycling rats decreases cocaine-induced reinstatement (Anker et al., 2007; Feltenstein et al., 2009). Anker et al. (2007) also reported that exogenous progesterone treatment in ovariectomized rats inhibits the facilitating effect of estradiol on cocaine-induced reinstatement. Together, these results suggest a role of ovarian hormones in cocaine relapse with estradiol increasing relapse vulnerability and progesterone having an opposite effect.

Methamphetamine, heroin, and fentanyl: The role of ovarian hormones in relapse/reinstatement to methamphetamine and opioid seeking is largely unknown. Cox et al. (2013) reported that the estrous cycle has no effect on methamphetamine-induced reinstatement. Vazquez et al. (2019) reported that estradiol or progesterone treatment has no effect on cue-induced reinstatement of heroin seeking. Sedki et al. (2015) reported that food restriction for 2 weeks (a chronic stressor) increases relapse to heroin seeking after home-cage forced abstinence in female rats. This effect is not decreased by ovariectomy, and unexpectedly, in ovariectomized rats, estradiol replacement but not progesterone injections

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decrease the potentiation effect of chronic food restriction on relapse. These results highlight the necessity to better characterize the potential role of the estrous cycle in heroin relapse.

Bakhti-Suroosh et al. (2021) reported higher extinction responding and cue-induced reinstatement of drug seeking after 14 days of forced abstinence from intermittent-access fentanyl self-administration during estrus versus nonestrus. In contrast, Malone et al. (2021) reported that the estrous cycle has no effect on cue-, yohimbine-, and fentanyl-induced reinstatement after short- or long-access fentanyl self-administration training. These different results may be due to the use of the intermittent access self-administration procedure for 23 hours/day and imposing 14 days abstinence before the relapse/reinstatement tests in the study of Bakhti-Suroosh et al. (2021) versus the use of continuous long-access self-administration procedures for 6 hours/day without an abstinence period in the study conducted by Malone et al. (2021).

C. Conclusions

The clinical and preclinical studies reviewed above suggest that under certain conditions, cocaine craving and relapse are dependent on the menstrual/estrous cycle, with higher vulnerability during the follicular/estrus phase. The hypothesis that emerges from the studies reviewed is that progesterone decreases cocaine craving and relapse vulnerability, whereas estradiol has opposite effects. Specifically, the menstrual/estrous cycle influences incubation of cocaine craving and cocaine-induced reinstatement. However, the review of the literature does not provide clear evidence for sex differences in the magnitude of cocaine-induced reinstatement, indicating that the influence of hormonal cycle on relapse-related behaviors in females does not necessarily lead to higher relapse vulnerability in females compared with males.

Many of the studies reviewed were designed to specifically assess the influence of the menstrual/estrous cycle on cocaine relapse and craving with statistical power to detect the effect of hormonal fluctuations and manipulation on relapse-related behaviors if such effect exists. However, some limitations of the methods to identify menstrual and estrous cycles phases need to be taken into consideration in the interpretation of the results. We describe these limitations in Table 2.

Finally, the results of Sedki et al. (2015) described above on the "protective" effect of estradiol suggest that this hypothesis may not generalize to opioid

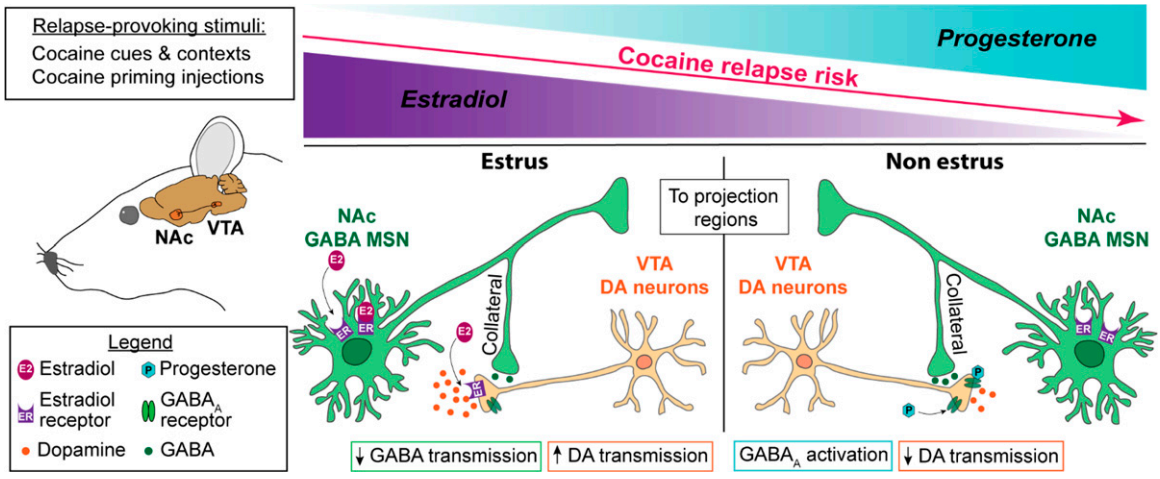

Fig. 5. A proposed brain mechanism model of the role of estradiol and progesterone in cocaine relapse in rodent models. There is evidence that estradiol potentiates striatal and NAc dopamine release by modulating GABAergic neurotransmission of medium spiny neurons (MSNs) through collaterals synapsing on dopamine neurons (Krentzel and Meitzen, 2018; Yoest et al., 2018). This effect is likely mediated by membrane estrogen receptors (ERs) (membrane-associated ERα and membrane-associated ERβ) expressed in MSNs (Almey et al., 2012). ERα and ERβ antagonists prevent estradiol enhancement of amphetamine-induced dopamine release (Xiao et al., 2003), and overexpression of ERα in the striatum increases the effect of estradiol on K+ induced GABA release (Schultz et al., 2009). Additionally, ERα and ERβ are expressed on VTA dopamine neurons terminals in NAc (Yoest et al., 2018), which play a critical role in reinstatement of cocaine seeking (Shaham et al., 2003; Schmidt et al., 2005). Together, these results suggest a role of ERα and ERβ in estradiol regulation of dopamine neurotransmission and, by implication, in reinstatement of cocaine seeking. Additionally, increased dopamine release by estradiol would be at least in part due to its action on dopamine receptors: striatal dopamine receptor 2 (Drd2) affinity decreases during estrus (Di Paolo et al., 1988), and estradiol injections in ovariectomized rats decrease Drd2 binding in striatum (Bazzett and Becker, 1994). In contrast to estradiol, progesterone decreases striatal dopamine release, as shown in estradiol-primed ovariectomized females treated with progesterone (Dluzen and Ramirez, 1984; Becker and Rudick, 1999). Progesterone and its metabolites are positive allosteric modulators of GABA$_A$ receptors (Schumacher et al., 1989; Schumacher and McEwen, 1989; Lambert et al., 1995). Drugs that promote GABA$_A$ function (e.g., imidazenil, diazepam) decrease cocaine-induced increases in dopamine release in NAc shell (Giorgetti et al., 1998). Consequently, progesterone could protect against estradiol-induced increases in cocaine seeking by inhibiting NAc dopamine release via increased GABA$_A$ receptor transmission. Together, we propose that during the estrus/follicular phase, cocaine- or cocaine cue-induced NAc dopamine release is increased by estradiol through its action on ER in GABAergic medium spiny striatal neurons and dopamine neurons terminals, leading to disinhibition of dopamine neurons and directly enhanced VTA dopamine cell firing via decreased Drd2 signaling, resulting in increased cocaine reinstatement/relapse. In contrast, during nonestrus/luteal phase, high progesterone levels may inhibit dopamine release induced by drug or drug cues through its action on GABA$_A$ receptors expressed in VTA dopamine terminals (Brodnik et al., 2019; Lopes et al., 2019), resulting in decreased cocaine relapse. DA, dopamine.

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drugs [but see Bakhti-Suroosh et al. (2021) for results congruent with the notion of opposing roles of estradiol and progesterone in drug relapse].

V. Brain Mechanisms

The brain mechanisms involved in the putative opposite effects of estradiol and progesterone on cocaine craving and relapse are unknown. We speculate that the mesolimbic dopamine system, with its projections from ventral tegmental area (VTA) to nucleus accumbens (NAc), is critically involved. This system plays important roles in both reinstatement of cocaine seeking after extinction (Shalev et al., 2002; Kalivas and McFarland, 2003; Schmidt et al., 2005) and incubation of cocaine craving (Wolf, 2016; Dong et al., 2017). Many studies reported that amphetamine-induced striatal and accumbal dopamine release is increased during estrus in free-cycling females (Becker and Ramirez, 1981; Becker and Cha, 1989; Castner et al., 1993) and by estradiol treatment in ovariectomized rats (Becker, 1990; Thompson and Moss, 1994; Becker and Rudick, 1999; Cummings et al., 2014; Song et al., 2019). In contrast, progesterone has an opposite effect by inhibiting striatal dopamine release in estradiol-primed ovariectomized females (Dluzen and Ramirez, 1984; Becker and Rudick, 1999). Calipari et al. (2017) also reported that dopamine activity in the VTA-to-NAc projection is higher during estrus than nonestrus.

We propose that in females estradiol and progesterone exert opposite effects on dopamine neurotransmission in the VTA-to-NAc projection, leading to increased cocaine craving and relapse by estradiol and decreased cocaine craving and relapse by progesterone (Fig. 5). Other neurobiological mechanisms of reinstatement and incubation of cocaine craving, including mesocorticolimbic glutamate transmission (Cornish and Kalivas, 2000; McFarland and Kalivas, 2001; Kalivas et al., 2009; Wolf, 2016; Dong et al., 2017), may also contribute to the sex differences described above. As discussed elsewhere, there are sex differences in brain glutamate systems and drug-induced neuroadaptations in glutamate transmission that may play a role in this regard (Giacometti and Barker, 2020). To date, no evidence has been provided on the role of estradiol and progesterone in relapse-related behavior in males.

A. Human Imaging Studies on Sex Differences in Response to Cocaine Cues and Stress

During the last several decades, numerous studies have used positron emission tomography (PET) (Volkow et al., 1991) and functional magnetic resonance imaging (fMRI) (London et al., 1999) to identify brain regions activated (or inhibited) during craving induced by exposure to drug injections (Stein et al., 1998), drug cues (Grant et al., 1996), and stress (Sinha et al., 2005). However, with rare exceptions, these studies were either performed only in male participants or included both sexes but were not designed (lacked power) to assess sex differences. Indeed, in our systematic literature search, we only identified six studies that statistically evaluated sex differences in brain activity during cue- or stress-induced cocaine craving (Supplemental Table S5). We describe these studies below. In the Supplemental Material we also describe results from several studies wherein investigators separately analyzed imaging data within each sex. The data from these studies are inconclusive and difficult to interpret without knowing whether the interactions between sex and cue or stress conditions are significant (see Nieuwenhuis et al., 2011).

In the studies described below, cue-induced craving was provoked by either presentation of videos or pictures showing cocaine-associated cues or by standardized or personalized scripts (Kilts et al., 2004; Volkow et al., 2011; Zhang et al., 2020). Stress-induced craving was induced by standardized or personalized scripts (Sinha et al., 1999; Li et al., 2005). Brain activity changes induced by cocaine or stress cues were compared with those induced by neutral cues. Participants in these studies were either abstinent and underwent inpatient or outpatient treatment (Kilts et al., 2004; Li et al., 2005; Zhang et al., 2020) or were non–treatment-seeking active cocaine users (Volkow et al., 2011).

Kilts et al. (2004) used PET with $[^{15}O]H_2O$ to measure regional cerebral blood flow (an index of brain activity) after cue exposure during early abstinence (days 1–14) in eight women. They compared the women to five men from their previous study (Kilts et al., 2001) and three new men. There were no sex differences in cue-induced cocaine craving. Exposure to cocaine cues induced stronger activation (increased glucose utilization) in right amygdala, left insula, right postcentral gyrus, and left caudate nucleus in men. In contrast, women showed increased activation of right precentral gyrus, middle frontal gyrus, and posterior cingulate gyrus. These results should be interpreted with caution because of the low number of participants and the use of male data from a previous study.

Volkow et al. (2011) used PET with 2-deoxy-2[18F]fluoro-D-glucose to measure brain glucose metabolism in response to cocaine cues in 10 women and 16 men. There were no sex differences in cue-induced cocaine craving. In contrast, sex differences were detected in cue-induced whole-brain metabolism (glucose utilization) with significantly decreased activity in women and modest increased activity in men. Additionally, analyses of specific brain areas showed decreased glucose utilization in frontal, cingulate, and parietal cortices, thalamus, and midbrain

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in women. In contrast, men showed increased glucose utilization in right inferior frontal gyrus. Direct comparisons of men and women showed sex by cue (cocaine cue, neutral cue) interaction due to greater decrease in glucose utilization among women in frontal (broca areas 8, 9, 10), anterior cingulate, posterior cingulate, inferior parietal, and dorsomedial thalamus.

The reasons for the different pattern of results in the two aforementioned studies, cue-induced brain activation in women in Kilts et al. (2004) versus cue-induced inhibition in Volkow et al. (2011), are unknown. One potential reason is that participants in the first study (Kilts et al., 2004) were treatment seekers tested during abstinence, whereas those in the second study (Volkow et al., 2011) were non–treatment-seeking tested during active cocaine use.

Kober et al. (2016) investigated fMRI-based changes in brain activity in response to videos depicting cocaine use, gambling, or sad scenarios in participants with cocaine dependence or pathologic gambling. There were no sex differences in cocaine craving or urges between men (n = 18) and women (n = 12) with cocaine-dependence. However, men showed greater dorsomedial prefrontal cortex and superior frontal gyrus activation in response to the cocaine videos.

Joseph et al. (2019) used fMRI to investigate the effects of oxytocin on cocaine craving and cocaine cue-induced activity in right amygdala and dorsomedial prefrontal cortex (PFC) among cocaine-dependent participants with (24 men, 16 women) or without (19 men, 8 women) childhood trauma history. Independent of the trauma condition, there were no sex differences in cue-induced cocaine craving, and in both sexes, oxytocin had no effect on this measure. Independent of the trauma condition, there were no sex differences in the placebo groups for cue-induced activation of dorsomedial PFC, a finding different from that of Kober et al. (2016), and oxytocin decreased this activation in all groups in a sex-independent manner. A different pattern of results was observed for cue-induced activation of right amygdala, wherein sex differences (activation in men but not women) were observed in the trauma but not nontrauma participants. Additionally, in the trauma groups, oxytocin increased cue-induced right amygdala activity in women but decreased this activity in men. In contrast, oxytocin had no effect on cue-induced right amygdala activity in men and women without trauma. The small sample size of women with prior trauma limits the interpretation of the sex-specific effects of oxytocin on amygdala activity in this study.

Zhang et al. (2020) used fMRI to investigate periaqueductal gray (PAG) activity and connectivity between PAG and ventromedial prefrontal cortex (vmPFC) after craving induced by cue exposure during early abstinence (7–10 days) in 10 women and 42 men. The PAG is known for its role in pain, avoidance, and defensive behaviors (Basbaum and Fields, 1984; Graeff, 1994). There were no sex differences in cue-induced cocaine craving, cue-induced PAG activity, or cue-induced increased PAG-vmPFC connectivity. However, PAG-vmPFC connectivity strength was positively correlated with cue-induced craving in men but negatively correlated in women. These results suggest sex differences in the role of PAG-vmPFC connectivity in cue-induced cocaine craving. However, these results should be interpreted with caution because of the low number of women participants and other significant sex differences in the sample (age and depression score).

Li et al. (2005) investigated brain activation using fMRI during stress imagery in 10 women and 17 males who were abstinent for 2–3 weeks. There were no sex differences in stress-induced cocaine craving. Additionally, there were no sex differences in the observed negative correlations between stress-induced craving and activation of the anterior and posterior cingulate. However, sex differences (higher activation in women) were observed for stress-induced activation of left frontolimbic areas, including anterior cingulate, insula, dorsolateral and medial PFC, inferior frontal cortices, and posterior cingulate cortex.

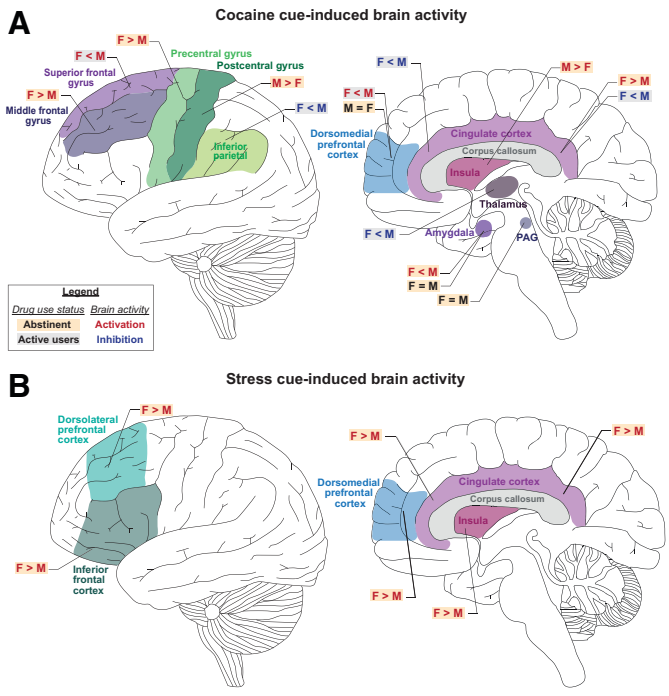

Fig. 6. Sex differences in cue- and stress-induced brain activation in humans who use cocaine. Schematic illustration of sex differences in (A) cocaine cue-induced and (B) stress-induced brain activation (assessed by PET or fMRI). F, female; M, male.

B. Conclusions

The results of the studies reviewed demonstrate strong sex differences in the effect of cue- and stress-induced cocaine craving manipulations on brain activity, with both quantitative (different degrees of activation)

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and, unexpectedly, qualitative (opposite effects) differences (Fig. 6). These differential brain responses occurred despite the consistent lack of sex differences in cue- or stress-induced subjective craving. Thus, a tentative conclusion from these studies is that to the degree that correlational results from imaging studies reflect causes rather than consequences of drug craving, the brain circuits controlling cocaine craving in men and women are likely different. The studies reviewed also suggest that in both sexes the brain mechanisms of cue-induced versus stress-induced cocaine craving are largely dissociable. This conclusion is consistent with results from preclinical studies on differences in brain circuits of cue- versus stress-induced reinstatement of drug seeking (Shalev et al., 2002; Bossert et al., 2013; Reiner et al., 2019). Another observation from the studies reviewed is that cue-induced brain activation versus inhibition is dependent on the substance use disorder phase (active use vs. abstinence) (Kilts et al., 2004; Volkow et al., 2011).

A limitation of the studies reviewed, particularly in reference to an important clinical outcome—relapse after prolonged abstinence—is that they were performed during early abstinence or ongoing cocaine use. Thus, the pattern of brain activation in both sexes in response to drug cues and stress during protracted abstinence is unknown. Finally, for the fMRI studies, a common problem in the studies reviewed was small sample sizes that are well below the recommended number of human participants required for reproducible task-based fMRI studies (Turner et al., 2018). Thus, future research should replicate these studies with larger sample sizes.

Finally, the implications of the sex differences in brain activity during cue- and stress-induced cocaine craving to the development of new medications are unknown, specifically in regard to the general conclusion of lack of sex differences in response to opioid agonist therapy. However, these sex differences in brain activity during cue- and stress-induced cocaine craving could be potentially used as brain markers to predict relapse in men and women.

VI. Conclusion and Clinical Implications

A prevailing notion in the preclinical addiction field is that females are more vulnerable than males to drug self-administration, withdrawal, and relapse across drug classes (Fattore et al., 2008; Becker, 2016; Carroll and Lynch, 2016). Here, we critically reviewed this notion with respect to psychostimulant and opioid craving and relapse in humans and rodent models. Unexpectedly, as our own research was guided by this notion (Zlebnik et al., 2014, 2021; Nicolas et al., 2019), our review does not support ubiquitous female susceptibility to craving and relapse.

Our main conclusion of the clinical literature is that the published studies do not support the idea that women are more vulnerable to psychostimulant and opioid craving and relapse. However, this conclusion is tentative because many of the studies reviewed were either correlational or not sufficiently powered to detect sex differences.

Our main conclusion of the preclinical literature is that there are sex differences in stress-induced reinstatement of cocaine seeking and incubation of cocaine craving, which in the latter case are modulated in part by ovarian hormones. In contrast, there is minimal evidence for sex differences for either cue- or cocaine-induced reinstatement of cocaine seeking. Additionally, the studies with methamphetamine and heroin (and other opioid drugs) do not support the notion of sex differences in reinstatement of drug seeking or incubation of craving for these drugs. However, for reinstatement of methamphetamine and heroin seeking, our conclusion is tentative because only a few studies were published, and the results are mixed.

The reasons for the drug-specific evidence of sex differences in rodent models are unknown. Potential reasons could be the distinct neurobiological mechanisms of relapse between opioids versus psychostimulants and cocaine versus methamphetamine (Badiani et al., 2011; Bossert et al., 2013) and the differential interaction of these drugs with ovarian hormones or organizational sex effects.

Another main conclusion is that fluctuations in ovarian hormones appear to play a role in cocaine craving in humans as well as cocaine-induced reinstatement and incubation of craving in rat models. The hypothesis that emerges from these studies is that progesterone decreases drug craving and relapse, whereas estradiol has an opposite effect (see Fig. 5 for a proposed brain mechanism for these effects).

An issue to consider from a translational perspective is the apparent lack of concordance between preclinical and clinical studies with cocaine, with some evidence supporting sex differences in rat models but not in humans. This discrepancy is not surprising because of the complex social, legal, cultural, and language-related factors that contribute to substance use disorders in humans that cannot be modeled in rodents (Heilig et al., 2016; de Wit et al., 2018; Venniro et al., 2020). However, a close inspection of the human results suggests some similarities, opportunities for future research, and potential treatment implications. Specifically, in some studies women report greater cocaine craving than men during early abstinence (Elman et al., 2001; Waldrop et al., 2010; Moran-Santa Maria et al., 2014). Additionally, several laboratory studies report decreased cocaine craving during the luteal versus follicular phase (Sofuoglu et al., 1999; Evans et al., 2002). Thus, abstinence

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attempts during the luteal phase may be more successful than those during the follicular phase. Indeed, similar approaches have led to favorable cessation outcomes in tobacco smokers (Allen et al., 2008, 2009a,b). Additionally, treatment with exogenous progesterone reduced cocaine craving (Sofuoglu et al., 2002, 2004; Evans and Foltin, 2006; Fox et al., 2013; Milivojevic et al., 2016). Together, these results suggest that in both humans and rodent models, the menstrual/estrous cycle contributes to cocaine seeking and highlights progesterone as a potential adjunct pharmacotherapy to reduce cocaine relapse.

The influence of gonadal hormones on drug craving is an example of how different mechanisms may differentially promote susceptibility to relapse in males and females. Additionally, as discussed above, despite the apparent lack of sex differences in self-reported craving and rates of relapse in humans, neuroimaging studies identified sex differences in regional brain activation associated with cue- and stress-induced cocaine craving (Fig. 6) (Kilts et al., 2004; Li et al., 2005; Volkow et al., 2011; Potenza et al., 2012; Zhang et al., 2020). These results suggest sex differences in brain mechanisms of cocaine (and potentially other drugs) craving and possibly relapse. This conclusion is supported by preclinical studies suggesting sex-specific mechanisms of cocaine-seeking behaviors (Calipari et al., 2017; Doncheck et al., 2020).

Variation in the underlying neurobiology of craving and relapse between men and women may result in differential treatment effects. For example, women experienced a greater reduction in stress- and cue-mediated cocaine craving than men after administration of the α2-adrenergic agonist guanfacine (Fox et al., 2014). Sex differences in "treatment" effects were also demonstrated for drug-seeking behavior in rodent models (Anker et al., 2009; Anker and Carroll, 2010b; Holtz et al., 2012; Zhou et al., 2012; Swalve et al., 2016; Witt and Reissner, 2020). For example, in a recent study Bossert et al. (2020) reported that female rats are less sensitive than males to the effect of the μ opioid receptor partial agonist TRV130 on context-induced reinstatement and reacquisition of oxycodone self-administration.

Finally, our review focused on degree and prevalence of self-reported craving and rates of relapse and found no clear evidence for sex differences. However, the etiology of these phenomena may differ between men and women (Back et al., 2011), and future studies should examine the complex factors that may differentially promote craving and relapse in both sexes.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Nicolas, Zlebnik, Farokhnia, Leggio, Ikemoto, Shaham.

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Supplementary Online Material

Sex differences in opioid and psychostimulant craving and relapse: a critical review

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Methods of the systematic review

Clinical studies

The literature search strategy was developed and executed by Ms. Diane Cooper (an NIH informationist) in consultation with the authors. Consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we searched MEDLINE, Embase, and PsycINFO with no time limits (see below). We included original research studies on sex/gender differences in psychostimulant and/or opioid craving and/or relapse in adults. We excluded the studies if (1) the reports were preclinical studies, review articles, commentaries, case reports, or conference abstracts, (2) the results in women and men were reported without formal statistical comparisons, (3) the breakdown of men versus women was not reported, and/or (4) parametric measures of craving or relapse were not reported. NEZ and MF independently screened the titles/abstracts and filtered the records according to the eligibility criteria described above. They compared the two resulting lists and discussed discrepancies. In case of disagreement, they consulted LL and reached a consensus. Following this initial screen, we retrieved the full texts of potentially eligible records. Using an identical process as the title/abstract stage, we evaluated the full text of these articles for final inclusion in this review (**Figure S1**). We used EndNote X9 to collect, de-duplicate, and manage the records. After screening, 12% of the

papers from the initial search were include in the review, which is consistent with other systematic reviews using PRISMA guidelines (Daurio et al., 2020; Pisanu et al., 2019).

Preclinical studies

The preclinical literature search was consistent with the clinical search and based on methods Shaham and colleagues have used in previous reviews of the preclinical literature of studies using animal models of relapse and craving (e.g., (Bossert et al., 2005; Bossert et al., 2013; Fredriksson et al., 2021; Pickens et al., 2011; Reiner et al., 2019; Shalev et al., 2002; Venniro et al., 2016). In accordance with the PRISMA guidelines, Ms. Diane Cooper searched MEDLINE, Embase, and PsycINFO, using keywords and controlled vocabulary terms relevant to the concept of the review, with no time limits.

Additionally, we performed a manual PubMed search (no time limit) of preclinical studies on sex differences in which rodents were trained to self-administer psychostimulant (cocaine and methamphetamine) or opioid (heroin, oxycodone, and fentanyl) drugs, and investigators used different variations of the extinction-reinstatement model, the incubation of drug craving model, and the relapse after forced abstinence model (Venniro et al., 2016). We used a search strategy that included different combinations of the terms “sex differences” and “rat” or “mouse” and the following terms: “relapse”, “reinstatement”, “extinction”, “craving”, “cocaine”, “methamphetamine”, “heroin”, “opioids”, “estrous cycle”, “estradiol”, and “progesterone.” We limited our search to studies published in English language and excluded reviews and conference abstracts. We also identified relevant articles that were not identified by the formal literature search by screening the reference lists of the identified articles. Finally, we used the PubMed tools “Similar articles” and “Cited by” to identify additional relevant articles. The articles we identified in the systematic and manual searches were combined and screened independently by CN and YS, in consultation with NEZ in cases of disagreement (**Figure S2**). We excluded the studies if (1) the results in females and males were reported without formal statistical comparisons, and (2) the breakdown between females and males was not reported. We used EndNote X9 to collect, de-duplicate, and manage the records.

Figure S1. A flow chart of the clinical literature search and review

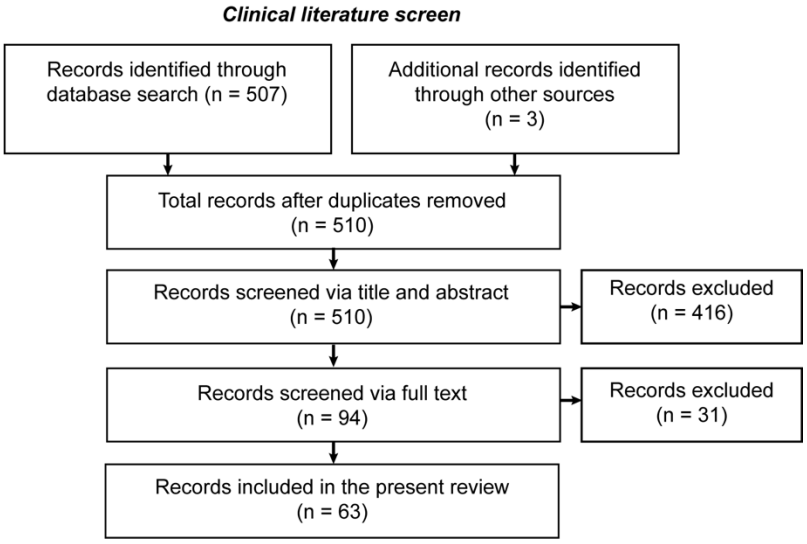
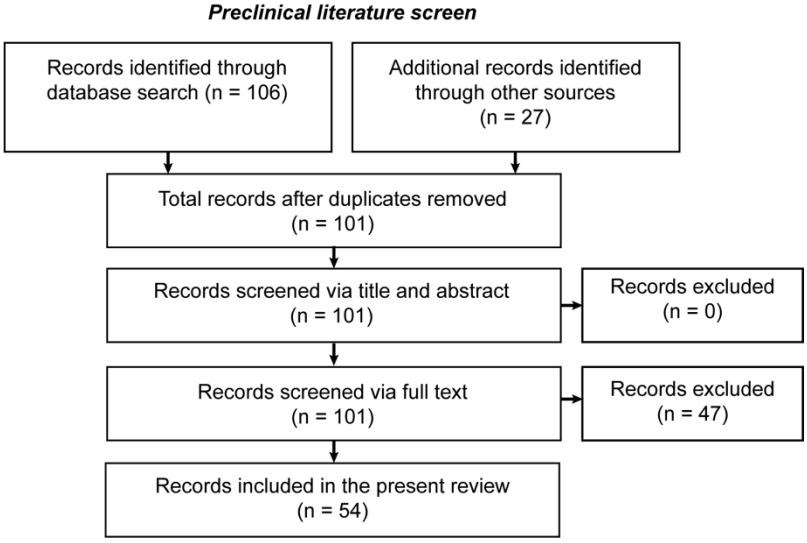


Figure S2. A flow chart of the preclinical literature search and review



Additional human neuroimaging studies on sex differences

Below we describe additional neuroimaging studies that (1) separately analyzed the data within each sex by comparing cue or stress conditions to a neutral cue, or (2) compared, within each sex, brain responses to cocaine cue, stress cue, and neutral cue between cocaine-experienced and drug-naïve control subjects. We provide a summary of these studies in **Table S5**.

Li and Sinha (2006) used data from the same subjects participated in Li et al. (2005b) study. They investigated stress-induced brain activation and its association with alexithymia (decreased capacity to identify and describe one's own feelings). The main finding was that men showed positive correlation between alexithymia scores (Toronto Alexithymia Scale) and stress-induced activation of the right putamen and middle frontal cortex. In contrast, women showed negative correlations between alexithymia scores and stress-induced activation of the right amygdala, thalamus, putamen, and left frontal and bilateral temporal cortices. Thus, stress-induced brain activity during cocaine abstinence appears to interact with alexithymia in a sex-specific manner. However, the result of the two studies should be interpreted with caution because of the small sample size for an imaging study.

Li et al. (2005a) investigated brain activity using fMRI during cue and stress imagery in 6 women and 5 men who were cocaine abstinent for at least two weeks. There were no sex differences in cue- or stress-induced craving. However, men showed higher activation in the left uncus and right claustrum during cue versus stress trials. No brain regions showed higher activation during stress versus cue trials in men. In contrast, women showed higher activation in the right medial and superior frontal gyri during stress versus cue trials, but no brain regions showed higher activation during cue versus stress trials in women. The results of this study suggest both quantitative and qualitative sex differences in stress- vs. cue-induced brain activity. However, these results should be interpreted with caution because of the low number of participants.

Potenza et al. (2012) investigated brain activity using fMRI during cocaine cue and stress cue imagery in inpatient men and women (n=14-16 per sex) who were abstinent from cocaine for at least two weeks. The authors also included a cocaine-naïve control group (n=18 per sex). As previously shown (see above and main text), cocaine and stress cues increased drug craving in both sexes. However, analysis of the neuroimaging data within each sex showed differences in the pattern of brain activation during stress and

drug cue trials. In women, stress-induced craving in cocaine abstinent subjects was associated with increased activity in amygdala, hippocampus, lateral and medial ventral prefrontal cortices, ventral and dorsal striatum, insula, anterior cingulate, temporal and parietal cortices, and dorsomedial and dorsolateral cortices. In contrast, in men, stress-induced craving was associated with a more restricted activation of striatum, thalamus and temporal cortex. Additionally, in women, cue-induced craving was associated with decreased activation of posterior cingulate, dorsal frontal, and parietal. In contrast, in men, cue-induced craving was associated with increased activation of amygdala, hippocampus, ventral and lateral prefrontal cortices, insula, ventral striatum, thalamus, anterior and posterior cingulate, temporal and parietal cortices, and dorsolateral and dorsomedial prefrontal cortices. Finally, in women, cue-induced craving (but not stress-induced craving) was positively correlated with activation of midbrain, hippocampus, ventrolateral prefrontal cortex, temporal cortex, cerebellum and thalamus. In men, cue-induced craving was positively correlated with activation of hippocampus, insula, posterior cingulate, dorsolateral and dorsomedial prefrontal cortices, temporal and parietal cortices, and cerebellum; stress-induced craving was correlated with activation of cerebellum and parietal cortices. No significant effects of the menstrual cycle phases on brain activity were found in this study; however, these results are not conclusive because of the small sample size.

The authors of this comprehensive study interpreted the results to suggest that in cocaine-dependent women corticostriatal-limbic hyperactivity mainly contributes to stress reactivity, while in men corticostriatal-limbic hyperactivity mainly contributes cue reactivity. However, this conclusion should be interpreted with caution for two reasons. First, in both men and women, exposure to the neutral cues also activated corticostriatal-limbic regions. Second, the conclusions are not based on statistical comparisons between men and women but on comparisons within each sex between cocaine-experienced and cocaine-naïve individuals.

Table S1. Psychostimulant and opioid craving and relapse: clinical studies. Abbreviations: METH: methamphetamine, M: Male, F: Female, CRH: corticotropin-releasing hormone, n.s: not significant

Drug	Active drug use status and n per sex	Measure(s)	Effect	*p* value	Reference
Psychostimulant					
Cocaïne					
Human laboratory studies					
Cocaine	Cocaine, 10+ h abstinent F = 5 M = 28	Cocaine-induced cocaine craving (0.2 mg/kg, i.v.)	F = M	n.s.	(Elman et al., 2002)
Cocaine	Cocaine, < 7 d abstinent F = 9 M = 11	Cocaine-induced cocaine craving (up to 6 50-mg doses/session, smoked)	F < M	<0.05	(Evans et al., 1999)
Cocaine	Cocaine, 12+ h abstinent F = 10 M = 11	Cocaine craving questionnaire	F > M	< 0.05	(Elman et al., 2001)
Cocaine	Cocaine, 7-14 d abstinent F = 18 M = 24	Cocaine craving questionnaire	F = M	n.s	(Fox et al., 2013)
Cocaine	Cocaine, 7 d abstinent F = 51 M = 72	Cocaine craving questionnaire	F = M	n.s	(Paliwal et al., 2008)
Cocaine	Cocaine F = 10 M = 16	Cue-induced cocaine craving	F = M	n.s	(Volkow et al., 2011)
Cocaine	Abstinent, confirmed, outpatient, > 1 mo. F = 34 M = 47	Cue-induced cocaine craving	F = M	n.s.	(Sterling et al., 2004)
Cocaine	Cocaine F = 12 M = 18	Cue-induced cocaine craving	F = M	n.s.	(Kober et al., 2016)
Cocaine	Abstinent, 7 d inpatient F = 17 M = 29	Cue-induced cocaine craving	F = M	n.s.	(Milivojevic et al., 2016)
Cocaine	Abstinent, 14 d inpatient F = 16 M = 14	Cue-induced cocaine craving	F = M	n.s	(Potenza et al., 2012)
Cocaine	Abstinent, 14 d inpatient F = 25 M = 25	Baseline cocaine craving Cue-induced cocaine craving	F = M F = M	n.s n.s	(Fox et al., 2006)
Cocaine	Abstinent, 14 d inpatient F = 17 M = 23	Cue-induced cocaine craving	F = M	n.s.	(Fox et al., 2008b)
Cocaine, alcohol, nicotine	Nicotine, 14-21 d inpatient F = 13 M = 27	Cue-induced cocaine craving	F > M	<0.001	(Fox et al., 2014)
Cocaine	Abstinent, unconfirmed, outpatient F = 38 M = 26	Cue-induced cocaine craving	F > M	<0.05	(Robbins et al., 1999)
Cocaine	Cocaine, 2 d abstinent F = 25 M = 28	Cue-induced cocaine craving Stress-induced cocaine craving	F = M F > M	n.s = 0.0015	(Waldrop et al., 2010)
Cocaine	Cocaine, 3 d abstinent F = 21 M = 18	Stress-induced cocaine craving	F = M	n.s	(Back et al., 2005)
Cocaine	Cocaine, 3 d abstinent F = 25 M = 28	Stress-induced cocaine craving following CRH injection (1 µg/kg)	F = M	n.s.	(Brady et al., 2009)
Cocaine	Abstinent, 14+ d inpatient	Stress-induced cocaine craving	F = M	n.s	(Li et al.,

	F = 10 M = 17				2005b)
Cocaine	Cocaine, 3 d abstinent F = 30 M = 32	Cue-induced cocaine craving following yohimbine injections (21.6 mg)	F > M	=0.006	(Moran-Santa Maria et al., 2014)
Cohort studies					
Cocaine	Abstinent F = 39 M = 87	Relapse during treatment (3 mo.)	F < M	<0.0001	(Bashiri et al., 2017)
Cocaine, Opioids	Opioid agonist treatment F = 189 M = 134	Relapse during treatment (3 mo.)	F < M	=0.001	(Burch et al., 2015)
Cocaine	Abstinent F = 104 M = 350	Relapse during treatment (6 mo.)	F < M	=0.015	(Gallop et al., 2007)
Cocaine	Abstinent F = 37 M = 64	Relapse at follow-up (6 mo.)	F < M	<0.02	(Weiss et al., 1997)
Cocaine	Abstinent F = 19 M = 53	Relapse during treatment (21 days) Relapse at follow-up (6 mo.)	F = M F < M	n.s <0.05	(Kosten et al., 1993)
Cocaine, Heroin	Opioid agonist treatment F = 42 M = 72	Relapse during treatment (6 mo.) Cocaine craving during abstinence (6 mo.)	F > M F = M	=0.0003 n.s	(Kennedy et al., 2013)
Cocaine	Abstinent F = 34 M = 47	Relapse at follow-up (9 mo.)	F = M	n.s.	(Sterling et al., 2004)
Cocaine	Abstinent F = 77 M = 244	Relapse at follow-up (12 mo.)	F = M	n.s.	(McKay et al., 2003)
Cocaine	Abstinent F = 10 M = 26	Relapse at follow-up (12 mo.)	F = M	n.s	(Negrete and Emil, 1992)
Cocaine, Opioids	Opioid agonist treatment F = 36 M = 80	Relapse over follow-up period (2 yr.)	F = M	n.s.	(Schottenfeld et al., 1998)
Methamphetamine					
Human laboratory studies					
METH	METH, 1+ d abstinent F = 33 M = 10	Cue-induced METH craving	F = M	n.s	(Tolliver et al., 2010)
Cohort studies					
METH	Abstinent F = 536 M = 329	METH craving during abstinence (4 mo.)	F = M	n.s	(Galloway et al., 2010)
METH	Abstinent F = 225 M = 195	Relapse during treatment (4 mo.) Relapse at follow-up (6, 12 mo.)	F > M F = M	=0.013 n.s	(Hillhouse et al., 2007)
METH	METH, regular use 12 mo.: F = 79 M = 122 5 yr.: F = 43 M = 59	Relapse during follow-up (12 mo., 5 yr.)	F < M	=0.005	(Lanyon et al., 2019)
Cross-sectional studies					
METH	Abstinent F = 279 M = 1185	Rate of relapse	F = M	n.s	(He et al., 2013)
METH	Abstinent F = 154	Rate of relapse	F = M	n.s.	(Brecht et al., 2004)

	M = 196				
METH	Abstinent F = 33 M = 65	Time to relapse	F = M	n.s.	(Brecht et al., 2000)
Opioids					
Human laboratory Studies					
Heroin	Heroin, inpatient F = 23 M = 26	Cue-induced heroin craving	F > M	=0.014	(Yu et al., 2007)
Opioids	Opioids F = 293 M = 599	Opioid craving	F > M	<0.01	(Back et al., 2011)
Cohort studies					
Opioids	Opioid antagonist treatment F = 242 M = 223	Craving during treatment (3 wk.)	F = M	n.s.	(Herbeck et al., 2016)
Opioids	Opioid agonist treatment F = 47 M = 135	Stress-induced opioid craving (4 mo.)	F > M	<0.0001	(Moran et al., 2018)
Cocaine, Heroin	Opioid agonist treatment F = 42 M = 72	Relapse during treatment (6 mo.) Heroin craving during abstinence (6 mo.)	F = M F = M	n.s n.s	(Kennedy et al., 2013)
Heroin	Residential inpatient treatment F = 110 M = 150	Relapse over follow-up period (2 mo.)	F < M	< 0.01	(Maehira et al., 2013)
Opioids	Opioid agonist treatment F = 163 M = 277	Relapse during treatment (3 mo.)	F = M	n.s.	(Kamal et al., 2007)
Heroin	Opioid agonist treatment F = 31 M = 60	Relapse during treatment (6 mo.)	F > M	=0.027	(Ignjatova and Raleva, 2009)
Opioids	Opioid agonist treatment F = 117 M = 173	Relapse during treatment (12 mo.)	F = M	n.s.	(Levine et al., 2015)
Heroin	Opioid agonist treatment F = 54 M = 46	Relapse during treatment (12 mo.)	F = M	n.s.	(Smyth et al., 2012)
Heroin	Opioid agonist treatment F = 215 M = 622	Relapse at follow-up (12 mo.)	F = M	n.s.	(Adelson et al., 2018)
Heroin	Opioid agonist treatment F = 63 M = 148	Relapse at follow-up (12 mo.)	F < M	No p value	(Gordon et al., 2017)
Opioids, Cocaine	Opioid agonist treatment F = 36 M = 80	Relapse over follow-up period (2 yr.)	F < M	< 0.001	(Schottenfeld et al., 1998)
Heroin	Abstinent, different therapeutic programs and prisons F = 70 M = 178	Relapse at follow-up (2 yr.) Relapse at follow-up (7 yr.)	F < M F = M	=0.05 n.s.	(Zimmer-Höfler and Dobler-Mikola, 1992)
Heroin	Heroin, regular use F = 259 M = 277	Relapse over follow-up period (8 yr.)	F = M	n.s.	(Brunswick and Messeri, 1986)
Heroin	Abstinent, different therapeutic programs plus a not in treatment group 3 yr.: F = 151 M = 278	Relapse over follow-up period (3 yr.) Relapse at follow-up (3 yr.) Relapse over follow-up period (11 yr.) Relapse at follow-up (11 yr.)	F < M F = M F < M F = M	No p values	(Darke et al., 2015; Darke et al., 2007)

	11 yr.: F = 155 M = 276				
Cross-sectional studies					
Heroin	Abstinent, different therapeutic programs and prisons F = 241 M = 547	Rate of relapse	F = M	n.s	(Zhou et al., 2017)
Opioids	Opioid agonist treatment F = 95 M = 2581	Rate of relapse	F = M	n.s.	(Moradinazar et al., 2020)

Table S2. Psychostimulant and opioid reinstatement and incubation of craving: preclinical studies**.**
Abbreviations: SA: Self-administration, FR: fixed ratio, FI: fixed interval, inf: infusion, METH: methamphetamine, M: Male, F: Female, n.s: not significant

Drug	SA procedure, n per sex, reinforcement schedule, unit dose	Relapse test	Effect	*p* value	Reference
Psychostimulant					
Cocaïne					
Reinstatement					
Cocaine	2 h/d F = 8 M = 8 FR1 0.2 mg/kg/inf	Cocaine priming (0.32, 1, 3.2 mg/kg)	F > M (1, 3.2 mg/kg) F = M (0.32 mg/kg)	<0.05 n.s	(Lynch and Carroll, 2000)
Cocaine	14 d, 2 h/d F = 57 M = 18 FR1 0.4 mg/kg/inf	Cocaine priming (5, 10, 15 mg/kg)	F > M (5 mg/kg) F = M (10, 15 mg/kg)	<0.05 n.s	(Anker et al., 2009)
Cocaine	14 d, 2 h/d F = 14 M = 14 FR1 0.5 mg/kg/inf	Cocaine priming (15, 30 mg/kg)	F > M	<0.001	(Smith et al., 2012)
Cocaine	30 d, 2 h/d Per dose: F = 7-9 M = 7-12 FR5 0.25, 0.75 mg/kg/inf	Cocaine priming (10 mg/kg)	F < M	< 0.01	(Jordan and Andersen, 2018)
Cocaine	14 d, 2 h/d Cocaine: F = 16 M = 19 Footshock: F = 6 M = 29 FR4 0.2 mg/ml	Cocaine priming (1.25, 2.5 or 5.0 mg/kg) Intermittent footshock	F > M (2.5, 5 mg/kg) F < M	<0.001 <0.01	(Doncheck et al., 2020)
Cocaine	30 d, 6 h/d F = 16 M = 18 FR1 0.4 mg/kg/inf	Cocaine priming (0.2, 0.4, 0.8, 1.6 mg/kg) Cue	F = M F = M	n.s n.s	(Kawa and Robinson, 2019)
Cocaine	10 d, 6 h/d F = 29 M = 22 FR1 0.4 mg/kg/inf	Cocaine priming (10 mg/kg) Cue Yohimbine (2.5 mg/kg) Yohimbine (2.5 mg/kg) + cue	F = M F = M F = M F = M	n.s n.s n.s n.s	(Zlebnik et al., 2014)
Cocaine	10 d, 6 h/d F = 45 M = 43 FR1 0.4 mg/kg/inf	Cocaine priming (10 mg/kg) Cue	F = M F = M	n.s n.s	(Swalve et al., 2016)
Cocaine	10 d, 24 h/d F = 37 M = 34	Cue	F = M	n.s	(Peterson et al., 2014)

	FR1 1.5 mg/kg/inf				
Cocaine	10 d, 2 h/d Per dose: F = 16-18 M = 7-12 FR1 0.25-1 mg/kg/inf	Cue	F = M F < M (for training dose 0.25 mg/kg)	n.s <0.01	(Fuchs et al., 2005)
Cocaine	10 d, 2 h/d F = 7 M = 7 FR1 0.6 mg/kg/inf	Cue	F > M	<0.05	(Zhou et al., 2014)
Cocaine	12 d, 2 h/d F = 32 M = 20 FR1 0.5 mg/kg/inf	Cue	F = M	n.s	(Bechard et al., 2018)
Cocaine	13 d, 2 h/d F = 45 M = 45 FR5 0.5 mg/kg/inf	Cue	F = M	n.s	(Weber et al., 2018)
Cocaine	10/14 d, 2 h/d F = 47 M = 14 FR1 0.5 mg/kg/inf	Cue + Yohimbine (1.25, 2.5 mg/kg)	F > M	< 0.01	(Feltenstein et al., 2011)
Cocaine	14 d, 2 h/d F = 11 M = 8 FR1 0.4 mg/kg/inf	Yohimbine (2.5 mg/kg)	F > M	<0.05	(Anker and Carroll, 2010)
Cocaine	10 d, 2 h/d F = 20 M = 22 FR1 0.5 mg/kg/inf	Corticotropin-releasing factor (2 µg)	F = M (all population) F > M (high responders)	n.s < 0.05	(Buffalari et al., 2012)
Cocaine	10 d, 2 h/d F = 22 M = 22 FR1 0.5 mg/kg/inf	Footshock (0.5 sec, 0.5 mA)	F > M	< 0.05	(Connelly et al., 2020)
Incubation of craving					
Cocaine	10 d, 2 h/d Per condition: F = 14-17 M = 14-16 FR1 0.5 mg/kg/inf	Abstinence day 1, 14, 60 and 180	F > M	<0.05	(Kerstetter et al., 2008)
Cocaine	12 d, 8 h/d Continuous or intermittent: F = 23-24 M = 25-27 FR1 0.75 mg/kg/inf	Abstinence day 2 and 29	F > M	<0.001	(Nicolas et al., 2019)
Cocaine	10 d, 6 h/d F = 60 M = 36	Abstinence days 1, 15, and 48	F > M	<0.05	(Corbett et al., 2021)

	FR1 0.5 mg/kg/inf				
Cocaine	Non-contingent cocaine-cue pairings, 24 pairings, 0.3 mg/kg/inf; Self-admin., 7d, 2 h/d Per condition: F = 4 or 9 M = 9 FR1 0.8 mg/kg/inf	Abstinence day 1 and 30	Trend: F > M	n.s.	(Johnson et al., 2019)
Cocaine	10 d, 3 h x 2/d F = 6 M = 5 FR1 0.75 mg/kg/inf	Abstinence day 1, 21, 60, 120, 200, 300,400	F > M	=0.008	(Madangopal et al., 2019)
Cocaine	8 d, 12 h/d Continuous or intermittant: F = 5-6 M = 5-6 FR1 0.75 mg/kg/inf	Abstinence days 1 and 15	F = M	n.s.	(Venniro, 2021)
Methamphetamine					
Reinstatement					
METH	10 d, 2 h/d F = 9 M = 10 FR1 0.05 mg/kg/inf	METH priming (1 mg/kg)	F > M	<0.01	(Holtz et al., 2012)
METH	7 d, 8 h/d Per condition: F = 7-8 M = 7-8 FR1 0.09-0.12 mg/inf	METH priming (1 mg/kg)	F > M	<0.05	(Cordie and McFadden, 2019)
METH	14 d, 1 or 6 h/d Per condition: F = 9-10 M = 6-8 FR1 17.5-20 ug/inf	METH priming (0.03, 0.1, 0.3,1 and 3 mg/kg)	F > M (0.3 mg/kg for 1 h SA, 1 mg/kg for 6 h SA)	<0.05	(Reichel et al., 2012)
METH	14 d, 2 h/d F = 39 M = 22 FR5 17.5-20 ug/inf	METH priming (1 mg/kg) Cue Yohimbine (2.5 mg/kg)	F > M F > M F > M	<0.05 <0.05 <0.05	(Cox et al., 2013)
METH	12 d, 2 or 6 h/d Per condition: F = 16 M = 16 FR1 0.1 mg/kg/inf	METH priming (0.3, 1.0 mg/kg) Yohimbine (0.625, 1.25 mg/kg)	F = M F = M	n.s n.s	(Everett et al., 2020a)
METH	14 d, 2 h/d F = 20 M = 20 FR1	METH priming (1 mg/kg) Cue	F < M F = M	=0.038 n.s	(Everett et al., 2020b)

	0.1 mg/kg/inf				
METH	5 d, 2x2h/d F = 9 M = 7-8 FR1 0.05 mg/kg/inf	METH priming (1 mg/kg) Cue	F = M F = M	n.s.	(Zlebnik et al., 2021)
METH	14 d, 6 h/d F = 17 M = 22 FR1? 0.05 mg/kg/inf	Cue	F < M	<0.05	(Takashima et al., 2018)
METH	13 d, 2 h/d F = 27 M = 26 FR5 17.5-20 ug/inf	Cue	F = M	n.s	(Bernheim et al., 2017)
Incubation of craving and relapse after forced abstinence					
METH	12 d, 6 h/d Per condition: F = 10 M = 10-11 FR1 0.1 mg/kg/inf	Abstinence day 1 and 21	F = M	n.s	(Venniro et al., 2017)
METH	20 d, 2x3 h/d F = 24 M = 24 FR1 0.1 mg/kg/inf	Abstinence day 3 and 30	F = M	n.s	(Daiwile et al., 2019)
METH	12 d, 2 or 6 h/d Per condition: F = 16 M = 16 FR1 0.1 mg/kg/inf	Abstinence day 2 and 30	F = M	n.s	(Everett et al., 2020a)
METH	14 d, 90 min/d F = 6 M = 6 FR1 0.08 mg/kg/inf	Forced abstinence 14 days, relapse day 15	F > M	=0.006	(Ruda-Kucerova et al., 2015)
METH	14 d, 90 min/d F = 25 M = 16 FR1 0.08 mg/kg/inf	Forced abstinence 14 days, relapse day 15	F > M	=0.012	(Ruda-Kucerova et al., 2017)
Opioids					
Reinstatement					
Heroin	10 d, 2 h/d F = 34 M = 30 FR1 0.015 mg/kg/inf	Heroin priming (0.5 mg/kg) Yohimbine (2.5 mg/kg) Cue Heroin (0.5 mg/kg) + cue Yohimbine (2.5 mg/kg) + cue	F > M F > M F = M F > M F > M	<0.05 <0.05 n.s <0.05 <0.05	(Smethells et al., 2020)
Heroin	12 d, 3 h/d F = 7 M = 7 FR4 0.04 mg/inf	Cue	F > M	<0.05	(Vazquez et al., 2020)
Heroin	14 d, 6 h/d F = 35 M = 25 FI20 0.05-0.1	Context	F = M	n.s.	(Bossert, 2021)

	mg/kg/inf				
Fentanyl	10 d, 24 h/d Per condition: F = 12-15 M = 10-11 FR1 0.25 µg/kg/inf	Cue	F = M	n.s.	(Bakhti-Suroosh et al., 2021)
Fentanyl	21 d, 1 or 6 h/d Per condition: F = 8-9 M = 8 FR1 2.5 µg/kg/inf	Fentanyl priming (10-30 µg/kg) Short access (1 h) Long access (6 h) Yohimbine (1-2 mg/kg) Short access Long access Cue Short access Long access	 F > M F = M F = M F = M F = M F < M	 <0.05 n.s. n.s. n.s n.s. <0.01	(Malone et al., 2021)
Fentanyl	21 d, 6 h/d F = 22 M = 22 FR1 2.5 µg/kg/inf	Footshock (0.5 sec, 0.7 mA) Yohimbine (1 mg/kg)	F = M F = M	ns. ns. (vehicle on no-shock cond.)	(Hammerslag et al., 2021)
Oxycodone	14 d, 6 h/d Per condition: F = 12-13 M = 11-17 FR1 0.05-0.1 mg/kg/inf	Context	F = M	n.s	(Bossert et al., 2020)
Oxycodone	22 d, 3 h/d F = 8 M = 8 FR2 0.05-1 mg/ml, PO	Cue	F = M	n.s.	(Phillips et al., 2020)
Oxycodone	23 d, 1 h/d F = 10 M = 10 FR1 0.1 mg/ml, PO	Footshock (0.5 sec, 0.4-1.0 mA)	F = M	n.s.	(Fulenwider et al., 2020)
Incubation of craving and relapse after forced abstinence					
Heroin	12 d, 6 h/d Per condition: F = 15-16 M = 11-15 FR1 0.1 mg/kg/inf	Abstinence day 1 and 21	F = M	n.s	(Venniro et al., 2017)
Heroin	12 d, 6 h/d: Per condition: F = 16 M = 16-18 FR1 0.1 mg/kg/inf	Abstinence day 1 and 15	F = M	n.s	(Venniro et al., 2019)
Heroin	14 d, 6 h/d F = 35 M = 25 FI20 0.05-0.1 mg/kg/inf	Abstinence day 1 and 8 (test performed in a non-drug context)	F = M	n.s.	(Bossert, 2021)

Fentanyl	12 d, 6 h/d F = 20 M = 22 FR1 2.5 ug/kg/inf	Abstinence day 1 and 14	F = M	n.s	(Reiner et al., 2020)
Oxycodone	14 d, 6 h/d Per condition: F = 12-25 M = 14-28 FR1 0.1 mg/kg/inf	Abstinence day 1, 15 and 30	F = M	n.s	(Fredriksson et al., 2020)

Table S3. Role of menstrual cycle in cocaine subjective effects and craving. Abbreviations: n.s: not significant; F: females

Cocaine status and sample size	Measures	Effect	*p* value	Reference
Single smoked cocaine dose F = 21	Craving Feel high	Follicular > luteal Follicular > luteal	=0.019 =0.03	(Sofuoglu et al., 1999)
Repeated smoked cocaine doses F = 11	Subjective positive drug effects, craving	Follicular > luteal	<0.05	(Evans et al., 2002)
Repeated smoked cocaine doses F = 8	Subjective positive drug effects	Follicular = luteal	n.s	(Collins et al., 2007)
Acute intranasal dose of cocaine F = 7	Subjective positive drug effects	Follicular = luteal	n.s	(Lukas et al., 1996)
Abstinent to smoked cocaine F = 12	Craving	Follicular = luteal	n.s	(Fox et al., 2008a)
Engaged in treatment F = 16	Cue-induced craving	Follicular = luteal	n.s	(Potenza et al., 2012)

Table S4. Role of estrous cycle in cocaine reinstatement and incubation of craving
Abbreviations: SA: Self-administration, FR: fixed ratio, Inf: infusion, E: estrus, D: diestrus, P: proestrus, NE: non-estrus, n.s: not significant; F: females

SA procedure, sample size, reinforcement schedule, unit dose	Relapse tests	Effect	*p* value	References
Cocaine				
Reinstatement				
10 d, 2 h/d F = 73 FR1 0.5 mg/kg/inf	Cocaine priming (5, 10 mg/kg)	E > D, P, male (10 mg/kg)	<0.05	(Kippin et al., 2005)
10 d, 2 h/d F = 30 FR1 0.5 mg/kg/inf	Cocaine priming (5, 10 mg/kg)	E > D, P (10 mg/kg)	<0.05	(Feltenstein and See, 2007)
10 d, 2 h/d F = 61 FR 0.5 mg/kg/inf	Cocaine priming (10 mg/kg)	E > NE, male	<0.05	(Kerstetter et al., 2008)
10 d, 2 h/d F = 60 FR1 0.5 mg/kg/inf	Cocaine priming (10 mg/kg)	E > D, P	<0.05	(Feltenstein et al., 2009)
10 d, 2 h/d Per dose: F = 16-18 FR1 0.25-1 mg/kg/inf	Cue	E < NE (only for SA training with 0.25 mg/kg)	<0.01	(Fuchs et al., 2005)
10 d, 24 h/d F = 37 FR1 1.5 mg/kg/inf	Cue	E = NE	n.s	(Peterson et al., 2014)
12 d, 2 h/d F = 32 FR1 0.5 mg/kg/inf	Cue	E = NE	n.s	(Bechard et al., 2018)
10/14 d, 2 h/d F = 47 FR1 0.5 mg/kg/inf	Cue + Yohimbine (1.25, 2.5 mg/kg)	D, E < P	<0.01	(Feltenstein et al., 2011)
Incubation of craving and relapse after forced abstinence				
10 d, 2 h/d F = 61 FR 0.5 mg/kg/inf	Abstinence day 1, 14, 60 and 180	E > NE, male (day 1, 60 and 180)	<0.05	(Kerstetter et al., 2008)
12 d, 8 h/d Continuous or intermittent: F = 23-24 FR1 0.75 mg/kg/inf	Abstinence day 29	E > NE	<0.05	(Nicolas et al., 2019)
10 d, 6 h/d F = 60 FR1 0.5 mg/kg/inf	Abstinence days 15, and 48	E > NE	<0.05	(Corbett et al., 2021)
Methamphetamine				

Reinstatement				
14 d, 2 h/d F = 39 FR5 17.5-20 ug/inf	Meth priming (1 mg/kg)	E = D, P	n.s	(Cox et al., 2013)
Opioids				
Reinstatement				
Fentanyl 10 d, 24 h/d Per condition: F = 11-16 FR1 0.25 µg/kg/inf	Cue	E > NE	<0.05	(Bakhti-Suroosh et al., 2021)
Fentanyl 21 d, 1 or 6 h/d Per condition: F = 8-9 FR1 2.5 µg/kg/inf	Fentanyl priming (10-30 µg/kg) Yohimbine (1-2 mg/kg) Cue	E = D, P	n.s.	(Malone et al., 2021)

Table S5. Human neuroimaging studies on cocaine cue- and stress-induced brain activity. Abbreviations: F: female, M: male, fMRI: functional magnetic resonance imaging, PET: positron emission tomography, ^{18}FDG: 2-[18F]-fluoro-2-deoxy-d-glucose, PFC: prefrontal cortex, vmPFC: ventromedial prefrontal cortex, PAG: periaqueductal gray, n.s: not significant

Drug	Active drug use status, N per sex, imaging technique	Drug craving	Brain regions	Effects	*p* value	Reference
Cue-induced craving						
Direct comparison between males and females						
Cocaine	Abstinent, ≥ 3 d Cocaine-dependent F = 24 M = 43 fMRI	F = M, n.s.	Dorsomedial PFC Amygdala	F = M F = M	n.s. n.s.	(Joseph et al., 2019)
Cocaine	Abstinent, 1-14 d Cocaine-dependent F = 8 M = 8 PET ([^{15}O]H2O)	F = M n.s.	 Amygdala Insula Postcentral gyrus Caudate nucleus Precentral gyrus Middle frontal gyrus Posterior cingulate gyrus	Activation: F < M F < M F < M F < M F > M F > M F > M	<0.005	(Kilts et al., 2004)
Cocaine	Active cocaine users F = 10 M = 16 PET (^{18}FDG)	F = M n.s.	 Frontal cortex Anterior cingulate cortex Posterior cingulate cortex Inferior parietal Dorsomedial thalamus	Inhibition: F < M F < M F < M F < M F < M	<0.001	(Volkow et al., 2011)
Cocaine	Abstinent, 7-10 d Cocaine-dependent F = 10 M = 42 fMRI	F = M n.s.	PAG PAG-vmPFC connectivity	F = M F = M	n.s. n.s.	(Zhang et al., 2020)
Cocaine	Cocaine-dependent F = 12 M = 18 Controls: F = 22 M = 23 fMRI	F = M, n.s.	 Dorsomedial PFC, Superior frontal gyrus	Activation: F < M F < M	 <0.05 <0.05	(Kober et al., 2016)
Indirect comparison between males and females						
Cocaine	Abstinent, ≥ 14 days Cocaine-dependent: F = 16 M = 14 Controls: F = 18 M = 18 fMRI	F = M, n.s.	F: Posterior cingulate, Dorsal frontal cortex, Parietal cortex Midbrain, Hippocampus, Ventrolateral PFC, Temporal cortex, Cerebellum, Thalamus	Activation: Cocaine F < control F Positively correlated with craving	<0.05 <0.05	(Potenza et al., 2012)
			M: Amygdala, Hippocampus, Ventral PFC, Lateral PFC, Insula,	Activation: Cocaine M < control M	<0.05	

			Ventral striatum, Thalamus, Anterior cingulate, Posterior cingulate, Temporal cortex, Parietal cortex, Dorsolateral PFC, Dorsomedial PFC			
			Hippocampus, Insula, Posterior cingulate, Dorsolateral PFC, Dorsomedial PFC, Temporal cortex, Parietal cortex, Cerebellum	Positively correlated with craving	<0.05	
Stress-induced craving						
Direct comparison between males and females						
Cocaine	Abstinent, 14-21 d Cocaine-dependent F = 10 M = 17 fMRI	F = M n.s.	Frontolimbic areas Anterior cingulate cortex Posterior cingulate cortex Insula Dorsolateral PFC Medial PFC Inferior frontal cortex	Activation : F > M F > M F > M F > M F > M F > M F > M	<0.01	(Li et al., 2005b)
Indirect comparisons between males and females						
Cocaine	Abstinent, ≥ 14 d Cocaine-dependent: F = 16 M = 14 Controls: F = 18 M = 18 fMRI	F = M, n.s.	F: Amygdala, Hippocampus, Lat. ventral PFC, Med. ventral PFC Ventral striatum, Dorsal striatum, Insula, Anterior cingulate, Temporal cortex, Parietal cortex, Dorsomedial cortex, Dorsolateral cortex	Cocaine F > control F	<0.05	(Potenza et al., 2012)
			M: Striatum, Thalamus, Temporal cortex Cerebellum Parietal cortex	Cocaine M > control M Positively correlated with craving	<0.05 <0.05	
Cocaine	Abstinent, ≥ 14 d Cocaine-dependent F = 10 M = 17 fMRI	F = M, n.s.	F : Amygdala Thalamus Putamen Frontal cortex Temporal cortex	Activation negatively correlated with alexithymia score	<0.001	(Li and Sinha, 2006)
			M : Putamen Middle frontal cortex	Activation positively correlated with alexithymia score	<0.001	

Cue vs. stress-induced craving						
Indirect comparisons between males and females						
Cocaine	Abstinent, ≥ 14 d Cocaine-dependent F = 6 M = 5 fMRI	F = M, n.s.	F : Medial frontal gyrus Superior frontal gyrus	Activation: Stress > drug cue	<0.01	(Li et al., 2005a)
			M : Uncus Claustrum	Activation: Drug cue > stress	<0.01	

* For full statistical reporting of the imaging data, see the original papers.

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